MECHANISMS OF AIRWAY PROTECTION IN AGEING AND PARKINSON'S DISEASE

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Preface

This PhD thesis conforms to the referencing style recommended by the American Psychological Association Publication Manual (5th ed.) and spelling recommended by the New Oxford Dictionary for Writers and Editors (2005).

The research was carried out between March 2004 and June 2007 at the Canterbury Swallowing Rehabilitation Research Laboratory, Van der Veer Institute for Parkinson's and Brain Research, Christchurch, New Zealand. The research was supervised by Dr Maggie-Lee Huckabee, University of Canterbury and Professor Tim Anderson, Christchurch School of Medicine and Health Sciences. Financial support was provided by Tan Tock Seng Hospital, Singapore.

Preliminary results from the PhD research have been presented at the following local and international conferences:

Dysphagia Research Society annual meetings (Scottsdale, Arizona, USA, 2006, and Vancouver, Canada, 2007);

11th International Congress of Movement Disorders meeting (Turkey, Istanbul, 2007);

27th World Congress of the International Association of Logopedics and Phoniatrics. (Copenhagen, Germany, 2007);

6th International Symposium of the Asian and Pacific Parkinson's Association (Singapore, 2007);

University of Canterbury Showcase for Postgraduates (Christchurch, New Zealand, 2004, 2005, and 2006);

New Zealand Speech-language Therapists' Association Conference (Christchurch, 2006);

Canterbury Conference on Communication Disorders (Christchurch, New Zealand, 2005).

The following publications have also been generated from this research:

Leow, L. P., Huckabee, M.-L., & Anderson, T. A. (2007). Sensory Aspects of Airway Protection in Ageing and Parkinson's disease [Abstract]. *New Zealand Medical Journal, 120*(1252).

Leow, L. P., Huckabee, M.-L., & Anderson, T. A. (2007). Swallowing Efficiency in Parkinson's Disease [Abstract]. *Proceedings of the 11th International Congress of Parkinson's and Movement Disorders*.

Lim, A., Leow, L., Huckabee, M. L., Frampton, C., & Anderson, T. (2007). A Pilot Study of Respiration and Swallowing Integration in Parkinson's Disease: "On" and "Off" Levodopa. *Dysphagia*. DOI: 10.1007/s00455-007-9100-9

Abstract

Safe and efficient swallowing requires integrity of both motor and sensory systems. Prior studies have established that motor impairment in individuals with PD frequently manifests as abnormalities in swallowing biomechanics. In contrast, very few studies have investigated the contribution of sensory impairment towards pharyngeal biomechanics and airway protection in this patient cohort. This area should be addressed in light of evidence that the severity of limb motor dysfunction in PD does not reliably predict severity of dysphagia. Emerging data suggests that dysphagia in PD cannot be solely attributed to motor impairment, but may also be influenced by deficits in sensory aspects of airway protection. As an example, silent aspiration in up to 100% has been reported in individuals with PD due to laryngopharyngeal sensory deficits have. Even so, current research lacks information on the integration of both motor and sensory components that make up the swallowing process.

The aim of this study was to document changes in airway protection with age, in PD and across severity levels of PD. The project was comprised of two parts. In part one, three parallel studies were conducted to assess a series of both motor and sensory airway mechanism (Chapters 4 to 9). In the first study, 16 young (8 males, age range 21.3 - 32.4) and 16 elder adults (8 males, age range 61.5 - 84.7), were assessed to investigate changes in airway protection that accompany ageing. In the second study, data from individuals diagnosed with PD across severity levels (Hoehn-Yahr 1 – 4, age range 64.2 - 84.5) were age and gender-matched to 16 healthy elders in order to examine the effects of PD on airway protection. In the third, the impact of disease severity was studied with data from 16 individuals in the earlier stages (Hoehn-Yahr $\leq$ 2, 13 males, age range 51.3 - 82.5,) compared to 16 individuals in the later stages (Hoehn-Yahr $\geq$ 2.5, 10 males, age range 61.5 - 78.9). In part two of this project, two smaller, pilot studies were completed to probe the influence of pharmacologic and behavioural treatments on airway protection mechanisms. In the first pilot study, the effect of pharmacotherapy on airway protection was investigated in 10 patients ‘on’ and ‘off’ levodopa (Chapter 10). In the second study, 5 patients were assessed before and after completing the Lee Silverman Voice Treatment (LSVT) to document effects of speech rehabilitation on airway protection (Chapter 11).

Multimodality assessment elicited data from all participants on both motor and sensory components of airway protection (Chapter 3). Specifically, breathing-swallowing coordination (BSC) and swallowing apnoea (SA) were captured using simultaneous directional nasal airflow and surface electromyography (sEMG). Standard, closed-loop spirometry was used to assess pulmonary function. Swallowing biomechanics were screened using a validated timed test of swallowing efficiency and further evaluated using fibreoptic endoscopic evaluation of swallowing (FEES). Finally, chemo-sensation of the laryngopharynx was determined with the administration of the inhalation cough challenge while mechano-sensation was examined using FEES.

Results suggest that motor control for airway protection is reasonably robust in PD, although sensory response is impaired. The predominant pattern for swallowing respiratory coordination was mid-expiration for all participants regardless of age and disease severity (Chapter 4). Individuals with PD demonstrated a reduction in average time and volume per swallow, leading to an overall decrease in swallowing capacity (Chapter 5). No difference was found for swallowing efficiency between those in early and later stages of PD. Pulmonary function measures were not significantly different as a function of age, PD or PD severity (Chapter 6). In summary, results from motor assessments contributing to airway protection support the robustness of breathing-swallowing coordination (BSC) and pulmonary function across research groups, but identify a reduction in overall swallowing efficiency in PD.

Results from sensory assessments contributing to airway protection revealed that chemo-sensation was not different between age groups but base of tongue mechano-sensation was diminished in individuals with PD. Natural cough thresholds did not differ between young adults and elders but when asked to stifle coughing, elders were less able to do so compared to young adults (Chapter 7). For the first time, a reduction in mechano-reception at the base of tongue was recorded in individuals with PD (Chapter 8). These patients also demonstrated increased post swallow residual (Chapter 5), which offers an explanation for the complaint of globus in this population. These assessments highlight some compromise to sensory aspects of airway protection in PD. Overall, dysphagia had a negative impact on the quality of life of individuals with PD and even more as disease severity progresses (Chapter 9).

Results from part two of the study looking at the effects of therapeutic interventions on airway protection revealed some unexpected findings. In chapter 10, results showed a reduction in pulmonary function when ‘on’ levodopa, but no differences in swallowing efficiency, BSC, or

laryngopharyngeal chemo- and mechano-reception were observed. These results suggested a reduction in pulmonary function with levodopa without any increase in risk of airway protection compromise[1]. Unexpectedly and documented for the first time, the percentage of post swallow inspiration increased after LSVT (Chapter 11) but as with the levodopa study, this was also not accompanied by any apparent increase in aspiration risk. An increase in submental surface electromyography (sEMG) amplitude across all 5 participants may serve as a proxy measure of improvement in hyolaryngeal excursion. Finally, participants reported an overall improvement in social functioning and communication after LSVT.

In conclusion, this study provided evidence that mechano-sensory aspect of airway protection is diminished in individuals with PD, possibly compromising airway protection. Patients not only demonstrated increased residue but the lack of sensation may prevent clearing or spontaneous multiple swallows. Overall, airway protection is maintained in ageing but swallowing efficiency declines in the presence of PD. This study contributes significantly to current research efforts in PD by expanding on existing reports regarding motor aspects of airway protection. Specifically, BSC, swallowing efficiency and evaluation of biomechanics using FEES research have never before been investigated exclusively in the PD population. Finally, the chemo- and mechano-sensation evaluated in this study are an important addition to the limited evidence that sensory impairment in individuals with PD potentially compromises airway protection. Results of the present study will serve as a platform upon which future studies may compare and expand.

[1] Data from this section of the thesis have been published as Lim, A., Leow, L., Huckabee, M. L., Frampton, C., & Anderson, T. (2007). A Pilot Study of Respiration and Swallowing Integration in Parkinson's Disease: "On" and "Off" Levodopa. *Dysphagia*. DOI: 10.1007/s00455-007-9100-9

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Table of Contents

Abbreviations

AEF	aryepiglottic folds
BOT	base of tongue
BSC	breathing-swallowing coordination
DA	dopamine
EE	expiration-SA-expiration
FEES	fibreoptic endoscopic evaluation of swallowing
FEESST	fibreoptic endoscopic evaluation of swallowing with sensory testing
FET	forced expiratory time
FEV1	forced expiratory volume in 1 second
FIVC	forced inspiratory vital capacity
FVC	forced vital capacity
EI	expiration-SA-inspiration
IE	inspiration-SA-expiration
II	inspiration-SA-inspiration
IPD	idiopathic Parkinson's disease
LSVT	Lee Silverman voice treatment
MMSE	mini mental state examination
PD	Parkinson's disease
PEF	peak expiratory flow
PIF	peak inspiratory flow
PPW	posterior pharyngeal wall
SA	swallowing apnoea
SAD	swallowing apnoea duration
sEMG	surface electromyography
SWAL-QOL	swallowing quality of life questionnaire
UPDRS	unified Parkinson's disease rating scale
VFS	videofluoroscopy

PART I: INTRODUCTION AND LITERATURE REVIEW

Chapter 1. Introduction

This research was undertaken to investigate motor and sensory mechanisms of airway protection in ageing and Parkinson's disease (PD).

A disorder of swallowing (dysphagia) is a common consequence of PD, with reports of 40% to 100% of patients in the later stages experiencing symptoms like coughing, choking and having food stuck at the back of the throat (Bushmann, Dobmeyer, Leeker, & Perlmutter, 1989; Leopold & Kagel, 1997a; Potulska, Friedman, Krolicki, & Spychala, 2003; Stroudley & Walsh, 1991; Volonte, Porta, & Comi, 2002). These symptoms are regarded as disorders in the biomechanics of swallowing, and are frequently investigated in this patient cohort. Aberrations in the biomechanics of swallowing are thought to give rise to symptoms that compromise airway protection.

Assessments of swallowing using instruments such as videofluoroscopy (VFS) revealed that these patients exhibit swallowing impairments in all stages of swallowing: oral preparatory, oral, pharyngeal and oesophageal (Ertekin et al., 2002; Leopold, 1996; Leopold & Kagel, 1997a, 1997b; Logemann, 1983). These valuable studies highlighted that rocking anterior-posterior movements that are inefficient in transporting the bolus into the pharynx are a form of tongue rigidity (Logemann, 1983). Muscle rigidity, along with tremor and bradykinesia are accepted as cardinal signs of PD (Schapira, 1999). Numerous research have highlighted the possibility that these signs are not limited to limbs or mobility (Blumin, Pcolinsky, & Atkins, 2004; Hanson, Gerratt, & Ward, 1984; Perez, Ramig, Smith, & Dromey, 1996; Shill & Stacy, 2002; Smith, Ramig, Dromey, Perez, & Samandari, 1995; Stelzig, Hochhaus, Gall, & Henneberg, 1999). Bradykinesia, another symptom of PD may also manifest as temporal delays in bolus transfer and/or incoordination between pharyngeal swallowing and glottic closure, possibly leading to laryngeal penetration or tracheal aspiration (Curtis & Langmore, 1997; Ren et al., 1994; Shaker et al., 2003; Zamir, Ren, Hogan, & Shaker, 1996). Vocal fold insufficiency from rigidity and tremulous movements (Zhang, Jiang, & Rahn, 2005) may further compromise airway protection. Weakness affecting motor movements of the pharyngeal muscles is also noted in PD, leading to poor pharyngeal stripping and pharyngeal residue after swallowing (Logemann, 1983).

In addition to VFS, swallowing efficiency may be measured using methods that allow clinicians to calculate indices such as volume and time per swallow. One of these, the timed test of swallowing efficiency has been validated, with published normative data from healthy persons ranging from 19 - 91 years old and also patients with neurological disorders (Hughes & Wiles, 1996b). That it is easily conducted without the need for expensive and/or cumbersome instruments makes it a suitable option for clinicians to administer at the patient's bedside as an adjunct to, and to supplant clinical bedside assessment. As normative data for healthy person's are available, data from individuals with PD may be compared to these as a measure of disease influence on swallowing efficiency.

The extrapyramidal system, that which plays an important role in motor movements works with the autonomic nervous system to help with postural stability. Incoordination, together with the loss of postural balance and stability is frequently seen in PD due to lesions in the extrapyramidal tract (Bloem, van Vugt, & Beckley, 2001) yet little is known about whether general incoordination plays a part in airway protection. What is known, however, is that since 1920, researchers have documented that the coordination between respiration and swallowing in a turn-taking manner is essential, since the oropharynx is a conduit for both processes (Clark, 1920; Hiss, Strauss, Treole, Stuart, & Boutilier, 2003; Klahn & Perlman, 1999; Preiksaitis, Mayrand, Robins, & Diamant, 1992; Preiksaitis & Mills, 1996; Selley, Flack, Ellis, & Brooks, 1989a, 1989b). The importance of breathing-swallowing coordination (BSC) is further emphasised with animal models confirming that the primary central nervous system site responsible for coordinating respiration and swallowing lie within the brainstem in close proximity (Saito, Ezure, & Tanaka, 2002) and even though these are controlled by distinct neural networks, these networks also share neurons (Shiba, Satoh, Kobayashi, & Hayashi, 1999). Finely tuned neural transmission for the activation and attenuation of respiratory and swallowing neurons happen in a turn-taking fashion to ensure that these processes do not overlap (Saito et al., 2002). Whether disruptions to BSC occur as a result of a lesion to the extrapyramidal tract is unknown.

Even though much more is known about biomechanics and motoric contributions of swallowing, it can hardly be claimed that research to date has fully elucidated patterns of breakdown in airway protection. This difficulty, at least in part, is demonstrated by the observation that airway protection encompasses more than biomechanics. Miller (1999) stresses that the integration of motor *and* sensory systems of the upper and lower airway during swallowing is paramount in keeping the airway clear of any prandial aspiration.

Although PD may be the best-known and most frequently occurring disease affecting motor movements, sensory deficits are also a frequent complaint (Zucco, Zaglis, & Wambsganss, 1991). Less attention has been given to the contributions of sensory deficits towards airway protection during swallowing (Aviv, 1997a). This is surprising, given that up to 40% - 100% of patients in this patient cohort are found to aspirate silently (Stroudley & Walsh, 1991). The sequalae of chronic aspiration, especially silent aspiration include pneumonia and even more devastating, mortality (Hoehn & Yahr, 1967; Temlett & Thompson, 2006; Wang, You, Chen, & Cai, 2002). The importance of addressing the consequences of aspiration is further emphasised by reports that bronchial pneumonia and shock induced by pulmonary infection account for 73.3% of deaths in PD (Wang et al., 2002).

The loss of the sense of taste and smell may affect the pleasure of eating but while these sensory losses occur in PD (Chaudhuri et al., 2006; Zucco et al., 1991), they have little intrusion or impact on airway protection. The loss of sensation to the laryngopharynx, however, is profound. The inability to sense aspirated food/fluid means that coughing, the most important airway defence mechanism may not ensue. It would be justifiable to state that assessment of airway protection is not complete without evaluating laryngopharyngeal sensation.

Assessments of chemo-reception using citric acid to induce coughing was described in the mid-1950s (Bickerman & Barach, 1954; Bickerman, Cohen, & German, 1956). Since then, authors have refined administration techniques to what is known today as the inhalation cough challenge (Ebihara et al., 2003; Fuller, 2002; Kastelik et al., 2002). Raised sensory threshold during cough challenge testing has been positively correlated to the risk of developing aspiration pneumonia in strokes with different sites of lesion (Addington, Stephens, Gilliland, & Rodriguez, 1999a). Few researchers have established similar sensory loss in the PD, with some documenting significant differences (Ebihara et al., 2003) and others reporting no difference (Fontana, Pantaleo, Lavorini, Benvenuti, & Gangemi, 1998). Whatever, authors agree that deterioration in sensory mechanisms in addition to well-established deterioration in motor function arises, and especially so in the later stages of the disease (Ebihara et al., 2003).

Mechano-sensation plays a substantial part in airway protection so much so that gag reflex testing has been routine in many bedside assessments for swallowing ability (Linden, Kuhlemeier, & Patterson, 1993; Ramsey, Smithard, Donaldson, & Kalra, 2005). The importance of the gag in predicting swallowing ability has been challenged of late (Leder,

1996) and refuted by many (Aviv, 1997b; Davies, Kidd, Stone, & MacMahon, 1995; Leder, 1996; Schulze-Delreiu & Miller, 1997). Nonetheless, mechano-sensation cannot be dismissed entirely due to its important role in airway protection (Bradley, 2000; Widdicombe, 1986b). Fibreoptic endoscopic evaluation of swallowing (FEES) and fibreoptic endoscopic evaluation of swallowing with sensory testing (FEESST) pair nasendoscopy with swallowing evaluation and mechano-sensation respectively. These offer the clinician ways to assess the integrity of swallowing and laryngopharyngeal mechano-reception in a safe way that was not possible before the advent of these tests. Diminished sensation, whether chemical or mechanical, contribute to the development of aspiration pneumonia (Daggett, Logemann, Rademaker, & Pauloski, 2006; Gleeson, Eggli, & Maxwell, 1997; Matsuse, Oka, Kida, & Fukuchi, 1996; Pontoppidan & Beecher, 1960). It would be prudent therefore, to establish whether individuals with PD exhibit raised sensory thresholds in response to chemo- and mechano-stimulation.

The importance of assessing motor and sensory aspects of airway protection is further emphasised with multiple observations that clinical staging does not necessarily predict the occurrence or severity of dysphagia in this patient cohort. Those who report awareness of difficulties swallowing do not exhibit as many physiologic abnormalities when compared to patients who do not complain of dysphagia. Conversely, patients who do not report dysphagia were found to have greater number of dysphagic symptoms (Bushmann et al., 1989; Calne, Shaw, Spiers, & Stern, 1970; Ertekin et al., 1998; Tison et al., 1996; Wintzen et al., 1994). As such, the number and/or severity of motor symptoms are unreliable predictors of airway protection. Authors have acknowledged that it may be possible, or even likely that physiological abnormalities are present before the symptoms are noticed by the patient or the physician.

It is acknowledged that even without disease, and/or before dysphagia is identified or reported in a disease state, subtle changes in the anatomy, physiology and biomechanics are known to accompany healthy ageing (Dejaeger & Pelemans, 1996; Ekberg & Feinberg, 1991; Fucile et al., 1998; Fulp, Dalton, Castell, & Castell, 1990; Gleeson, 1999; Jaradeh, 1994; Logemann, 1990; Martin-Harris et al., 2005; Nagaya & Sumi, 2002; Nilsson, Ekberg, Olsson, & Hindfelt, 1996; Plant, 1998; Ribeiro, Klingler, Hinder, & DeVault, 1998; Robbins, 1996; Robbins, Hamilton, Lof, & Kempster, 1992). It is therefore, of utmost importance for studies that look for aberrations in the PD population to have age- and gender-matched controls in order to truly tease out the effects of disease from the effects of healthy ageing. A second control

group of healthy, young adults matched for gender would be required to investigate age effects.

The overarching aim of this research is to document motor and sensory changes that are central to airway protection as a result of ageing and PD. This study will identify robust risk factors for the development of dysphagia and aspiration pneumonia in this population so that healthcare professionals can identify at-risk patients early in the disease process. Timely implementation of intervention programmes would be possible if airway protection compromise is detected early.

In the chapters following the literature review (Chapter 2), methods employed in this research are described (Chapter 3). Data from 16 healthy elders who were age-and gender-matched to 16 individuals with PD are presented (Chapters 4 - 9). In addition, data from 16 healthy, young adults were compared to that obtained from the healthy elders to look for age effects. Finally, comparisons between 16 patient participants in the early stages of PD were made to 16 patient participants in the later stages of PD. Two further, separate studies were conducted to explore the effects of pharmacotherapy and speech rehabilitation on airway protection mechanisms. Results of these are presented in Chapter 10 and 11 respectively. Key findings from this study and concluding remarks are summarised in Chapter 12.

Chapter 2. Literature Review

2.1 Parkinson's Disease: an Overview

James Parkinson first described the disorder that bears his name 190 years ago. In his manuscript, "An Essay on the Shaking Palsy", Parkinson described in great detail symptoms of this movement disorder in six patients (Parkinson, 1817). Since its first description, Parkinson's disease (PD) continues to be well researched, and we now know it to be a common neurodegenerative disease of the elderly, afflicting approximately 1% of the population over 50 years of age (Stern et al., 1993). Additionally, authors have recognised that early symptoms of the disease may be present in as many as 10% of those over 60 years of age, translating to over 1 million people in North America (Mitchell, Kiely, Kiel, & Lipsitz, 1996; Schoenberg, 1987; Young, 1999). Young onset PD has also been reported and known to affect up to 10% of Parkinson's patients (Calne & Kumar, 2007; Jung, 2004; Louis, Henchcliffe, Bateman, & Schumacher, 2006).

About 900 New Zealanders are diagnosed with PD each year with approximately 8,000 New Zealanders affected at any one time (Neurological Foundation of New Zealand, 2002). Given that age is the single most consistent risk factor in PD (Lang & Lozano, 1998a, 1998b), this ranks PD among the most common neurodegenerative diseases in the 6^{th} and 7^{th} decades of life. With the increasing age of the general population, the prevalence of PD is expected by NFNZ (2002) to rise steadily in the future. In New Zealand, persons aged 65+ currently cost the public health system about 5 times as much as the persons under 65. It is estimated that in the next 50 years, the proportion of the population aged 65+ will double (Bryant, Teasdale, Tobias, Cheung, & McHugh, 2004). The impact of PD is indicated by the finding that mortality is 2 to 5 times higher among affected persons as among age-matched controls, resulting in a marked reduction in life expectancy (Bennett et al., 1996; Louis, Marder, Cote, Tang, & Mayeux, 1997; Morens et al., 1996). In fact, it has been predicted that neurodegenerative diseases like PD, motor neuron disease and dementia are projected to surpass cancer as the second most common cause of death among the elderly by the year 2040 (Lilienfeld & Perl, 1993). Given the ramifications of health and socio-economic impact, greater understanding of the pathophysiology of PD is important to reduce financial and personal costs through effective management and treatment.

2.1.1 Pathophysiology and Clinical Presentation of Parkinson's Disease

Although the aetiology of PD is not fully understood, the condition is thought to result from an interaction of several factors (Schapira, 1999). Ageing is considered the single most important factor for the development of PD (Gibb & Lees, 1991; Koller, 1992). It is estimated that 1% of individuals over the age 50 of will have PD (Stern et al., 1993) but this increases to 10% by the age of 80 (Lang & Lozano, 1998a). Support for environmental causes of PD come from neuroimaging studies that have found that exposure to an environmental neurotoxins such as 1-Methyl-4-phenyl1,2,3,6-tetrahydropyridine (MPTP) and solvent abuse causes symptoms resembling idiopathic PD (Uitti et al., 1994; Vingerhoets et al., 1994).

There is also increasing evidence for a genetic component as the cause of PD. Golbe, (1995) reported a two to three fold increased risk of developing PD in first degree relatives of a PD patient. Several lines of research into genetic causes of PD have uncovered gene and protein mutations that are implicated in PD. These include Ω-synuclein gene on chromosome 4 (Polymeropoulos et al., 1997; Zarranz et al., 2004) and the parkin gene on chromosome 6 in families showing autosomal dominant and recessive parkinsonism respectively (Kitada et al., 1998). Given that PD may result from a conglomeration of factors, it is likely that both genetic and environmental factors interact to result in PD (Schapira, 1999). In addition, some researchers believe that PD is not one disease but several diseases that share clinical, pathological and, possibly, biochemical manifestations (Carlsson, 1993; Joyce & Millan, 2006). Whatever the initial aetiology, researchers agree that the claimed PD symptoms result from dopamine depletion.

Dopamine (DA) is a neurotransmitter that activates dopamine receptors via 4 major pathways: (1) the nigrostriatal pathway, (2) the mesocortical pathway, (3) the mesolimbic pathway, (4) the tuberoinfundibular pathway. Of these, the pathway implicated most heavily in DA transportation is the nigrostriatal pathway (Fearnley & Lees, 1991). This pathway connects the substantia nigra with the striatum and is involved in the production of movement as part of a system called the basal ganglia motor loop. The basal ganglia form part of the extrapyramidal motor system and have five interconnected nuclei, in which different neurotransmitters are active, including DA.

The substantia nigra, or 'black substance', is a midbrain structure that gets its name from the large nigral neurons that exhibit a characteristic black pigmentation. It is considered part of the basal ganglia complex and has classically been divided into two components: the pars

compacta and the pars reticulata. The pars compacta is a cell-rich region that is subdivided into a ventral and a dorsal tier (Francois, Yelnik, Tande, Agid, & Hirsch, 1999). In humans, it contains approximately 450,000 dopaminergic neurons (Lang & Lozano, 1998a). The collateral axons from the neurons of the pars reticulata send inhibiting information to the pars compacta and together, these neurons send their axons along the nigrostriatal pathway to the striatum where DA is released. There is a delicate balance between direct and indirect pathways that are partly maintained by DA release from the substantia nigra to the striatum. DA release excites the direct pathway by stimulating the dopamine D1 (excitatory) receptor and inhibits the indirect pathway by stimulating dopamine D2 (inhibitory) receptors (Aubert et al., 2005; Baas, 2000). This balance helps to maintain the efficiency and smoothness of motor behaviour.

Although the mechanisms responsible for cell death in PD are largely unknown, increasing evidence suggests that neuronal death in the pars compacta of the substantia nigra may occur by means of programmed cell death, known as apoptosis (Burke & Kholodilov, 1998; Novikova, Garris, Garris, & Lau, 2006). Not all dopaminergic projection areas are equally susceptible. Within the pars compacta, the ventrolateral tier experiences the greatest neuronal loss, estimated between 60 to 70% at the onset of symptoms. This is followed by medial ventral tier and dorsal tier neuronal loss (Fearnley & Lees, 1991). This pattern of cell loss is relatively specific to PD; it is the opposite of that seen in normal aging. The end result is a regional loss of striatal DA, the consequence of which is believed to manifest as akinesia and rigidity (Kish, Shannak, & Hornykiewicz, 1988). Striatal DA loss, coupled with the progressive cell death of dopaminergic neurons in other parts of the basal ganglia complex, give rise to the classic symptoms of PD.

Even though striatal DA loss is strongly linked to PD, symptoms of PD may not be evident until 70-80% of striatal DA has been depleted (Bernheimer, Birkmayer, Hornykiewicz, Jellinger, & Seitelberger, 1973; Sandyk, 1988, 1989). Post-mortem data and studies using positron-emission tomography support a latency period of approximately 3 years before PD symptoms emerge (Fearnley & Lees, 1991; McGeer, Itagaki, Akiyama, & McGeer, 1988; Morrish, Sawle, & Brooks, 1996) while some studies suggested a very long preclinical period of up to several decades (Hopfensperger & Koller, 1991; Koller et al., 1991). Animal models using the selective neurotoxin, 6-hydroxydopamine (6-OHDA) to induce PD found that during this prodromal period, the extensive loss of dopaminergic neurons is compensated by increased synthesis and release of DA from remaining DA neurons. A reduced rate of DA

inactivation has been reported as a compensatory process (Zigmond, Abercrombie, Berger, Grace, & Stricker, 1990). Therefore, the initial diagnosis of PD can be challenging in patients who exhibit a long prodromal period with slowly evolving or intermittent symptoms in the early stages (Koller, 1992).

To date, neuropathological examination remains the gold standard for the diagnosis of PD as there are no biological markers that clearly confirm this disease. Physicians look for the classic symptom triad of tremor, rigidity, and bradykinesia in idiopathic Parkinson's disease (IPD). A fourth symptom, the instability of posture has also been deemed one of the cardinal features that points to the diagnosis of PD. The classic symptoms, combined with asymmetry of onset, the presence of a resting tremor, and a good response to levodopa best differentiates PD from other pathologies that mimic Parkinson's. Post mortem autopsies remain the most reliable way of confirming the diagnosis of PD but even so, under-diagnosis has been reported on approximately 24% of patients who had a final diagnosis of PD before death (Rajput, Rozdilsky, & Rajput, 1991).

Studies have also revealed that the formation of neurofibrillary tangles called Lewy bodies in the substantia nigra is a hallmark sign of PD and has been heavily implicated in PD with dementia (Burn, 2006; Hornykiewicz, 2001; McKeith, 2000). Gibb and Lees (1991) found that in the brains of healthy persons between the ages of 60 and 90, the prevalence of Lewy bodies increased from 3.8% to 12.8%. They suggested that these findings of Lewy body disease were not accidental. Rather, these fibrous deposits actually represented a pre-symptomatic stage of PD. Lang & Lozano (1998a) stated that if, in fact, it does represent a preclinical phase of PD, the ramifications of this finding are staggering, since the prevalence of PD in the population over the age of 80 years is 1 in 10.

Neurodegeneration of other brain structures is thought to contribute to other motor and non-motor symptoms in PD. As an example, cognitive impairment has been shown to positively correlate with the density of Lewy neurites in the hippocampus (Churchyard & Lees, 1997), while degeneration in the brainstem serotinergic and noradrenergic nuclei has been linked to behavioural dysfunction, including major depression (Tandberg, Larsen, Aarsland, & Cummings, 1996). Other clinical-pathological correlations include degenerative changes in the olfactory bulb causing anosmia and degeneration in the central nucleus of the amygdala, causing autonomic dysfunction (Braak et al., 1994).

In addition to the above non-motor symptoms, dementia is increasingly recognised as an important feature of PD in the elderly (Aarsland, Andersen, Larsen, Lolk, & Kragh-Sorensen, 2003; Hughes et al., 2000). In a large population-based survey in Norway, 28% of patients with PD presented with dementia (Aarsland, Tandberg, Larsen, & Cummings, 1996). A new diagnosis of dementia occurs 6.6 times more frequently in elderly patients with PD compared to elderly controls, with 65% of surviving members of an initial cohort of patients over the age of 85 having dementia (Mayeux et al., 1990). Dementia with Lewy bodies is now recognised as the second most common cause of neurodegenerative dementia, second only to Alzheimer's dementia (McKeith et al., 1996). Although PD alone may increase mortality slightly, dementia further shortens survival in patients with PD. Compared to non-demented elderly, Louis et al., (1997) found that individuals with PD *and* dementia have a two- to five-fold increased risk of mortality. Further, this risk is strongly related to the presence of severe extra-pyramidal signs, especially bradykinesia (Levy et al., 2002). In an autopsy series of 100 histologically confirmed patients with PD, Hughes, Daniel, Blankson, & Lees, (1993) reported that 44% had dementia in life. Coexisting Alzheimer's disease occurred in 29%. Numerous cortical Lewy bodies were found in 10% and 6% had a possible vascular cause. This leaves 55% with no definite pathological explanation for the dementia other than PD.

Even though marked degeneration of the substantia nigra and loss of striatal DA are necessary before clinical symptoms of motor dysfunction develop, non-motor signs such as depression or sensory changes often precede motor signs by many years. As an example, the loss of smell may be one of the first symptoms of PD (Berendse & Ponsen, 2006; Braak et al., 2002). In the long term, other non-motor complications of the illness become increasingly apparent. Depression, weight loss and cognitive disorders have been well documented (Berendse & Ponsen, 2006; Kashihara, 2006; Lorefalt, Granerus, & Unosson, 2006; Lorefat, Ganowiak, Wissing, Granerus, & Unosson, 2006; Slawek, Derejko, & Lass, 2005). Prominent communication and swallowing disorders further complicate the course of the disease (Miller, Noble, Jones, & Burn, 2006b), with up to 100% of individuals with PD experiencing some form of swallowing difficulty (Bushmann et al., 1989; Leopold & Kagel, 1997a; Potulska et al., 2003; Stroudley & Walsh, 1991; Volonte et al., 2002).

In summary, research has shown that while PD is a disorder primarily of the motor system, sensory deficits and other non-motor signs occur concurrently, or even before motor signs are observed. One of the challenges that face physicians is the knowledge that by the time the patient's symptoms are severe enough to seek help, up to 80% of their dopaminergic neurons

have already depleted. Therefore, the main foci of PD treatment are to protect dopaminergic neurones with the aim of disease prevention, to stop disease progression and provide early identification and treatment in order to "rescue" at risk neurons (Schapira, 1999). As age is considered the most important factor in the development of PD, any studies into PD must also take into account the effects of healthy ageing if proper management of this debilitating disease is to be implemented.

Special consideration is often given to disorders of swallowing in PD. Aside from medical risks like malnutrition and dehydration, pulmonary compromise from prandial aspiration occurs at an alarmingly high rate in this patient cohort. Wang et al., (2002) found repeated pulmonary infections to be the most common complication in individuals with PD, with bronchial pneumonia and shock induced by pulmonary infection accounting for 73.3% of deaths in PD. Pneumonia remains the most likely cause of mortality in this patient cohort (Hoehn & Yahr, 1967). Even though literature lends support to the dangers of aspiration, it is uncertain which patients demonstrating prandial aspiration would develop or succumb to pneumonia. As with the identification or pre-clinical symptoms of PD, it would be important to investigate whether deterioration of swallowing function can be identified before patients or caregivers report swallowing difficulty.

In the sections to follow, an overview of normal anatomy and physiology of swallowing is provided as this is a prerequisite to the understanding of disordered swallowing. This is followed by a detailed review of dysphagia in PD. Comprehensive reviews of current research into the effects of ageing and PD on motor *and* sensory airway protection mechanisms are provided. Finally, under-researched areas and unanswered questions pertaining to airway protection identified.

2.1.2 Functional Anatomy of Normal Swallowing

Swallowing or deglutition is a complex action requiring 5 cranial nerves, 2 cervical nerves and more than 25 paired muscles of the lips, tongue, jaw, pharynx, larynx and upper oesophageal sphincter working in a synchronous and coordinated sequence to transfer food from the mouth to the stomach (Jean, 2001; Miller, 1999). The process of efficient swallowing is dependent on information from both afferent and efferent systems.

In 1836, swallowing was described as consisting of 3 phases: oral, pharyngeal and oesophageal (Magendie, 1836). In more recent years, the oral phase has been further subdivided into oral preparatory and oral transport phase (Figure 2.1), described in detail below (Logemann, 1983; Perlman & Christensen, 1997).

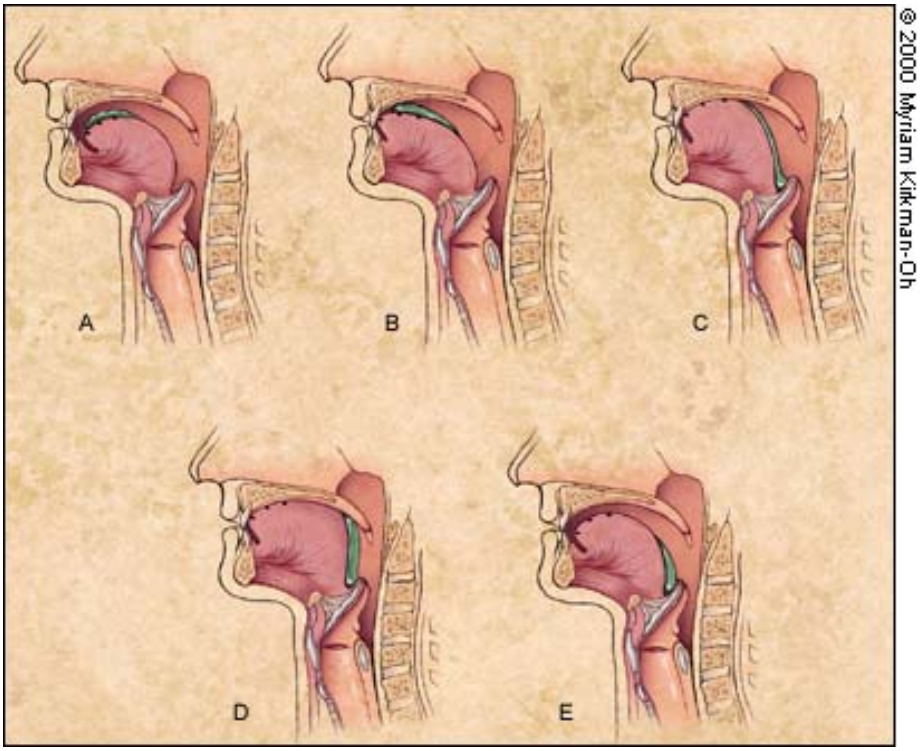


Figure 2.1 Lateral view of the oral propulsive phase of swallowing chewed solid food in a normal person, based on videofluorographic recordings. For the original videofluorographic study, three small radiopaque markers were glued to the surface of the tongue to highlight its movement. *(A)* Food *(shown in green)* has been softened and mixed with saliva and is sitting on the dorsum of the tongue. *(B)* Moving upward and forward, the tip of the tongue comes into contact with the hard palate anteriorly. *(C)* The area of tongue-palate contact expands posteriorly, which pushes food into the oropharynx. *(D)* The area of tongue-palate contact continues to increase as a portion of the food collects in the valleculae (one vallecula [space between the epiglottis and the back of the tongue] on each side of the mouth). *(E)* The jaw reaches its maximum downward position (maximum gape), and the tongue drops away from the palate. A portion of food remains in the valleculae. From Palmer, J. B., Drennan, J. C., & Baba, M. (2000). Evaluation and treatment of swallowing impairments. *American Family Physician, 61*(8), 2453-2462.

The oral preparatory phase involves voluntary manipulation of a bolus and employs the use of the lips, jaw, tongue, soft palate and muscles of mastication. Collectively, these muscles move food between the molars for chewing. Food is mixed with saliva secreted from three pairs of salivary glands. With chewing, the food and saliva are reduced to form a bolus which is manoeuvred onto the tongue surface in preparation for the next phase. In the oral preparatory phase the posterior tongue is elevated to make contact with the velum to form a glossopalatal seal while the front of the tongue is elevated with its tip on the alveolar ridge (Perlman & Christensen, 1997). With the tongue in contact with the velum, respiration can continue without airway compromise. Labial seal is maintained to prevent anterior loss and buccal muscles are tense to prevent lateral pocketing of food.

Duration of the oral preparatory stage is variable and influenced by dentition, taste, temperature, viscosity and size of bolus (Cook et al., 1989; Kendall, Leonard, & McKenzie, 2001; Logemann, 1994; Palmer, Rudin, Lara, & Crompton, 1992; Pereira, Duarte Gaviao, & Van Der Bilt, 2006). Fluids typically have a shorter oral preparation time compared to solids as the latter requires mastication. Palmer and colleagues have reported oral preparatory times as follows: fluids, 1.61 +/-0.55 seconds; muffin, 5.81 +/- 1.12 seconds; peanuts, 10.41 +/- 2.08 (Palmer et al., 1992). Once the bolus is adequately prepared, the oral stage begins.

During the oral phase, the velum elevates, the lips and buccal muscles contract and the posterior tongue depresses, breaking the glossopalatal seal. As the velum is elevated and retracted to the posterior pharyngeal wall, the nasal cavity is sealed off. At this stage, the tongue tip remains in contact with the alveolar ridge (Kahrilas, Lin, Logemann, Ergun, & Facchini, 1993). Movement of the tongue is very important during the oral stage as it propels the bolus into the oropharynx. The bolus is moved to the back of the mouth in an anterior to posterior motion. Transport of the bolus posteriorly takes approximately 0.5 to 1.5 seconds but, as in the oral preparatory stage, this is influenced by bolus variation such as volume and taste (Cook et al., 1989; Tracy et al., 1989).

When the bolus passes the anterior faucial pillars laterally and the base of tongue inferiorly, the oral stage ends as the tongue driving force pushes the bolus into the pharynx (Logemann, 1997). Using videofluoroscopy (VFS), this is anatomically identified as the point where the base of tongue crosses the posterior aspect of the vertical ramus of the mandible (Robbins, Levine, Maser, Rosenbek, & Kempster, 1993; Tracy et al., 1989).

The pharyngeal phase of swallowing is no longer under volitional control. In this pseudo-reflexive stage, the following events happen almost simultaneously: the pharynx constricts, moving medially and anteriorly, the epiglottis deflects vertically, the glottis closes, the hyoid and larynx elevates, the upper oesophageal sphincter (UOS) opens, and the tongue and pharyngeal muscles propel the bolus into the oesophagus (Gates, Hartnell, & Gramigna, 2006). The velum remains elevated during the pharyngeal stage, preventing nasal regurgitation.

On VFS one of the first anatomical movements that can be visualised to signal the onset of a swallow is hyoid and laryngeal elevation (Cook et al., 1989). During nasendoscopy, the very first movement that marks swallowing initiation is the medialisation the arytenoids that is associated with the first in a series of events that facilitate airway closure (Langmore & Aviv, 2001). Van Daele, McCulloch, Palmer, & Langmore (2005) observed that the order of airway closure is as follows: the arytenoids first move medially, then anteriorly to approximate the epiglottis, the epiglottis deflects to cover the arytenoids and the true and false vocal folds fully adduct. Full glottic closure typically occurs late in the process of swallowing, with activation of the thyroarytenoid muscle. This sequential pattern of airway closure is unique to swallowing. Airway closure for swallowing takes approximately 0.6 seconds to complete, suggesting that about half a second after the swallow has begun, the airway is vulnerable to an advancing bolus (Langmore, 2001b). With endoscopy, it is often noted that the bolus may fall into the hypopharynx and arrive at the pyriforms well before the vocal folds adduct (Langmore, 2001b). As such, precise timing of airway closure and bolus movement is central to keeping the airway patent and for the prevention of aspiration.

Hyoid excursion occurs approximately 0.3 seconds after arytenoids medialisation (Perlman & VanDaele, 1993). The hyoid is actively moved by the contraction of submental muscles: mylohyoid, geniohyoid and the anterior belly of the digastric. As these muscles contact, the hyoid is pulled into an anterior-superior position (Perlman & Christensen, 1997). The movement of the hyoid together with thyrohyoid muscle contraction elevates that larynx, causing the epiglottis to invert (Vandaele, Perlman, & Cassell, 1995). For this reason, in endoscopy, the onset of epiglottic deflection is taken to reflect the onset of hyoid elevation (Langmore, 2001a).

Hyolaryngeal excursion and/or epiglottic deflection are more readily seen on VFS. While the hyoid moves about 1.1 cm superiorly and another 0.9 cm anteriorly (Perlman, VanDaele, &

Otterbacher, 1995), superior excursion of the larynx has been documented to be as much as 2.5cm (Sundgren, Maly, & Gullberg, 1993). Even so, the literature on hyolaryngeal excursion is debatable as some authors have found that the anterior excursion is greater than the superior movement by up to 8mm (Ishida, Palmer, & Hiiemae, 2002). Ishida, Palmer, & Hiiemae further reported that the anterior displacement of the hyoid was highly consistent in amplitude regardless of food consistency, suggesting that forward hyoid displacement is an essential part of pharyngeal swallowing. Langmore (2001a) proffers 3 biomechanical effects of hyolaryngeal excursion: (1) the creation of a bigger space in the pharynx for bolus flow, (2) facilitation of airway protection from epiglottal deflection and arytenoid medialisation, (3) increased UOS opening from the anterior pull as a result laryngeal elevation.

Hyolaryngeal excursion is accompanied by pharyngeal shortening and medialisation of the lateral pharyngeal walls due to pharyngeal longitudinal and constrictor muscle contraction. The stylopharyngeus, salpingopharyngeus, and palatopharyngeus form the longitudinal pharyngeal muscles and their actions counterbalance anterior floor of mouth muscles. The posterior suprahyoid muscles (stylohyoid, styloglossus and posterior belly of the digastrics) also directly counterbalance anterior floor of mouth muscle contraction. Sequential contraction of superior, middle and inferior pharyngeal constrictors take place immediately after pharyngeal shortening begins. Combined forces of these muscles shorten and narrow the pharyngeal lumen, which in turn squeezes the bolus through the UOS into the oesophagus.

It is important to note that tongue driving force plays an important role in propelling the bolus through the UOS. Using manofluorography (VFS and pharyngeal manometry), McConnel, Cerenko, Jackson, & Guffin, (1988) found that the pharyngeal constrictors played a lesser part than the tongue for bolus propulsion. Rather, the bolus flow is more dependent on tongue driving pressures than on pharyngeal constrictors. This was further supported by Kahrilas et al., with reports that tongue propulsion is required for larger volume boluses while pharyngeal constrictors are required for smaller volumes, such as during residual clearing (Kahrilas et al., 1993).

The combined action of pharyngeal shortening and constriction plus hyolaryngeal excursion serves to push the bolus into the UOS. The oesophageal phase of swallowing then begins and ends when the tail end of the bolus passes through the lower oesophageal segment. Anatomically, the upper and lower ends of the oesophagus are marked by 2 short segments of tonically contracted muscles called upper and lower oesophageal sphincters (LOS). The UOS

is also known as the cricopharyngeal sphincter (Perlman & Christensen, 1997) and separates the pharynx from the body of the oesophagus. The LOS is also known as the gastroesophageal sphincter and demarcates the distal and of the oesophagus and the stomach. Standard measures of oesophageal transit times have been reported using VFS. Barium sulphate takes approximately 8 - 20 seconds to transverse the oesophagus. For healthy persons, liquids require a shorter transit time of 3 - 10 seconds (Margulis & Koehler, 1976). Semisolids like bagels and gelatine capsules are reported to take 3 – 6 seconds (Chisaka, Matsushima, Wada, Saeki, & Hachisuka, 2006; Curtis, Cruess, & Willgress, 1987).

Three factors have been identified by Curtis et al., (1987) to facilitate bolus movement though the oesophagus. First, sufficient elevation of the larynx with adequate UOS opening is required to ensure free bolus passage into the oesophagus. This is significant, since there appears to be a direct relationship between bolus pressure and the amount of cricopharyngeal opening (Jacob, Kahrilas, Logemann, Shah, & Ha, 1989). Second, timely oesophageal peristalsis is required with reference values proposed by Chisaka et al., (2006), Curtis et al., (1987) and Margulis & Koehler (1976). Finally, adequate acceleration of bolus through the UOS is required to prevent any disruption to bolus flow. Even though food is normally cleared within 3 seconds, this acceleration is heavily influenced by body position. The importance of this is highlighted by Davies et al., (1983). These authors measured oesophageal clearing time in healthy adults when eating a piece of folded white bread with sprinkled barium. When in supine position, approximately half the participants took longer than 2 minutes to clear the bread. Some participants were not able to pass the bread bolus even after 5 minutes and even then, required the assistance of liquids to wash the bolus down.

Events and timing during normal swallowing are summarised in Appendix A. In summary, swallowing remains one of the most complex behaviours involving volitional and reflexive elements. Rightly summarised, ‘Swallowing begins at the lips and ends at the stomach. Hence, dysphagia can result from abnormalities in deglutition that occur anywhere along that path (Massey & Shaker, 1997, p. 1).

2.1.3 Swallowing Disorders in Parkinson’s Disease

Dysphagia is known to be one of the leading causes of aspiration pneumonia after a neurological event such as stroke and head injury, and is associated with complications such as malnutrition, dehydration, morbidity and mortality (Carrau & Murray, 1999; Pirlich &

Lochs, 2001; Smithard, O'Neill, Parks, & Morris, 1996). It is a common complaint of those with PD, with all stages of swallowing likely impaired and reported incidence of up to 100%, especially in the later stages of the disease (Bushmann et al., 1989; Leopold & Kagel, 1997a; Potulska et al., 2003; Stroudley & Walsh, 1991). While dysphagia refers to a difficulty in swallowing, one of the consequences of dysphagia is aspiration. Perlman & Schulze-Delrieu, (1997) defined aspiration as follows:

> The penetration of secretions or ingesta below the level of the true vocal folds. This can interfere with effective air exchange (and lead to asphyxiation, for instance) or cause pulmonary inflammation and infection (so-called aspiration pneumonia). Aspiration may occur prior to the actual swallow though an unguarded larynx, during the pharyngeal stage of swallowing from overflow of residue contained in the pharyngeal re-cesses, or from reflux of gastric contents (Perlman & Schulze-Delrieu, 1997, p. 492).

The aspiration of food, fluid or secretions below the level of the true vocal folds without the elicitation of a cough is known as silent aspiration, an event closely associated with laryngeal anaesthesia (Schulze-Delrieu & Miller, 1997). It has been estimated that the incidence of silent aspiration may be as high as 40% in patients with dysphagia and in PD, this presentation may be as high as 100% (Murry & Carrau, 1999; Stroudley & Walsh, 1991).

Dysphagia is a symptom reported by 20%-40% of patients with idiopathic PD but incidence and prevalence reports in the literature may be not be representative as swallowing abnormalities often go undetected until later stages of the disease (Nagaya, Kachi, & Yamada, 2000; Volonte et al., 2002; Wintzen et al., 1994). As such, the incidence of dysphagia may be under-reported in this patient cohort. Incidences varying from 18.5% to 100% have been published but investigators agree that the true figures lie somewhere in between (Bushmann et al., 1989; Calne et al., 1970; Ertekin et al., 2002; Mutch, Strudwick, Roy, & Downie, 1986; Robbins, Logemann, & Kirshner, 1986; Stroudley & Walsh, 1991). The source of the discrepancy in the reported incidence is highlighted by Coates & Bakheit (1997). These authors stated that lowest prevalence of dysphagia symptoms tended to be reported by authors who used postal surveys and questionnaires whilst those using instruments like VFS were likely to report abnormalities in all patients studied. This observation raises an important issue.

Questionnaires that probe swallowing function and /or difficulty require self awareness but in PD, patients may lack self-awareness for several reasons. These include laryngeal anaesthesia, cognitive deficits, self compensation, or any of these in combination (Aarsland et al., 1996; Aviv, 2000; Zigmond et al., 1990). This claim is further illustrated by Bird, Woodward, Gibson, Phyland, & Fonda (1994), who sought to ascertain whether patients with PD without symptoms of dysphagia have abnormalities of swallowing, and to describe the characteristics as seen on clinical examination and VFS. Patients with stable PD were interviewed for symptoms of dysphagia and 16 who reported no symptoms were enrolled. VFS indicated that all patients had at least one abnormality, ranging from prolonged oral transit times to aspiration. This study demonstrated that individuals with PD may experience widespread abnormalities of swallowing without complaints for the reasons outlined above.

Researchers have acknowledged that it may be possible, or even likely that physiological abnormalities are present before the symptoms are noticed by the patient or the physician (Ali et al., 1996; Potulska et al., 2003). Bushmann et al., (1989) evaluated 23 patients with PD of different severity levels with clinical rating scales and VFS. Although 65% showed symptoms of dysphagia on VFS, only 15% of the patients aspirated. No significant correlation between patient's complaints of dysphagia and the presence of abnormalities on VFS were found. Although some patients identified swallowing problems, their self-reported symptoms did not predict the nature and extent of abnormalities seen on VFS. Eight of 13 patients who denied dysphagia were found to have abnormalities that ranged from motility disorders to silent aspiration in 2 cases. They concluded that clinical staging did not necessarily predict the occurrence of abnormal swallowing.

Studies have found that in this patient cohort, those who reported awareness of swallowing difficulties do not exhibit as many physiologic abnormalities when compared to patients who do not complain of dysphagia, whereas patients who do not report dysphagia were found to have greater number of dysphagic symptoms (Bushmann et al., 1989; Calne et al., 1970; Potulska et al., 2003; Tison et al., 1996). Similarly, Ertekin et al., (1998) found that electrophysiological readings using EMG could not be strongly correlated with the degree of the clinical disability or the clinical score of the disease. Although Coates & Bakheit (1997) found strong correlations between severity and duration of PD and the severity of dysphagia, Wintzen et al., (1994) failed to correspond these measures to the number of signs of dysphagia seen on VFS. Due to the weak correlation between awareness of dysphagia and aspiration events, the symptoms of dysphagia may not be readily noticed by patients and/or

caregivers. This poor correlation, coupled with the entity of silent aspiration, could account for the high incidence of pulmonary compromise in individuals with PD (Fall, Saleh, Fredrickson, Olsson, & Granerus, 2003; Paulson & Tafrate, 1970; Wang et al., 2002). Although PD is traditionally considered a disorder of the motor system, the absence of a sensory response to aspiration is particularly compelling and would certainly warrant further investigation.

It is recognised that a direct comparison across centres investigating dysphagia in PD is seldom possible due differences in the methods of participant recruitment, e.g. questionnaires (Mutch et al., 1986), community notice board (Ali et al., 1996) or clinic attendance (Bushmann et al., 1989). Three other methodological differences make comparisons across studies challenging: terminology, methodology and patient selection.

Previous studies on the nature of swallowing abnormalities in PD have reported highly variable results, possibly due to differences in terminology used. The definition of the term 'laryngeal penetration' and 'aspiration' has changed over the years (Daggett et al., 2006). For example, the term 'vestibular aspiration' in 1989 by Bushmann et al. had the same operational definition as the term 'laryngeal penetration' a decade later (Leopold & Kagel, 1997). 'Aspiration' may be termed 'tracheal aspiration' or 'subglottic penetration'(Linden et al., 1993). Aspiration of material before swallowing and after swallowing has been termed early aspiration and late aspiration respectively (Stroudley & Walsh, 1991). The delineation between 'laryngeal penetration' and 'aspiration' has been better agreed upon recently, with the term 'laryngeal penetration' reserved for entry of materials into the laryngeal vestibule but not below the true vocal folds and 'aspiration' for when material passes below the vocal folds (Perlman & Schulze-Delrieu, 1997; Robbins et al., 1992; Rosenbek, Robbins, Roecker, Coyle, & Wood, 1996). The description of laryngeal penetration and aspiration was also made clearer amongst researchers with the advent of the penetration-aspiration scale by Rosenbek et al., (1996). Still, the reader needs to exercise caution when interpreting data, since the nomenclature in terminology used to describe a given dysphagic symptom varies across investigators.

Other methodological differences in studies investigating dysphagia in PD are evident and may be a potential error source in interpretation (Robbins, Coyle, Rosenbek, Roecker, & Wood, 1999). There is yet to be a standardised procedure for VFS. The consistency of food and fluids, the size of each bolus and the number of trials chosen for investigation during the

procedure are left to the discretion of the investigators. These remain highly variable in the literature, including some that have investigated swallowing in different positions: lying down, sitting upright or sitting with head flexed (Coates & Bakheit, 1997). Insufficient attention has been paid to quantitative means of describing results of VFS studies, with relevant data frequently presented in descriptive terms (Robbins et al., 1999).

Finally, the variability in the inclusion and exclusion criteria across studies requires consideration when interpreting and generalising current literature. Even though many studies have clearly defined stages of PD in their patients (Ali et al., 1996; Leopold & Kagel, 1997b; Potulska et al., 2003), these information were not readily available in other papers (Calne et al., 1970; Stroudley & Walsh, 1991). Nagaya et al., (2000) looked at the effect of single session therapy on swallowing function. Patients with mild, moderate and severe PD were included, as assessed using the 5-point Hoehn and Yahr (H-Y) severity rating scale (Hoehn & Yahr, 1967). Although patients in all stages were recruited, results were only reported for patients in stages 3 and 4. Patients in stages 1 and 2 were excluded on the basis that they had not shown 'abnormalities'. Those in stage 5 with reported dysphagia were excluded due to difficulties following instructions for therapy. Clearly, the exclusion of those in stages 1 and 2 would have inadvertently excluded those who may have subclinical signs of dysphagia while the exclusion of those in stage 5 would have overlooked those who may benefit most from having therapy.

In conclusion, dysphagia is a common disorder in PD, with aspiration and silent aspiration reports of up to 100% (Murry & Carrau, 2001; Stroudley & Walsh, 1991). However, direct comparisons between studies are seldom possible due to methodological differences. Even though aspiration pneumonia is the leading cause of death in this patient cohort, there is insufficient evidence to equate aspiration with the development of aspiration pneumonia. Multiple risk factors other than prandial aspiration may play a part, including non-motor impairments such as laryngeal anaesthesia, dependency for feeding and oral care (Aviv et al., 2000; Langmore et al., 1998). The potential sensory contribution and prevalence of silent aspiration in motor systems disorders such as PD remains largely unexplored, leading to the potential for under-identifcation of dysphagia. It is emphasised that motor *and* sensory mechanisms of airway protection are imperative in keeping the airway clear of food and or fluids. These airway protection mechanisms are described in following sections.

2.2 Mechanisms of Airway Protection

Upper and lower airway protection mechanisms are important in preventing aspiration during swallowing. Both motor and sensory defence mechanisms at structural and cellular levels respond to a variety of different incoming stimuli for this purpose (Curtis & Langmore, 1997). Coordination of breathing and swallowing assures that the airway is patent during respiration but sealed off during swallowing. Sensory driven reflexes of the airway such the glottic reflex (Curtis & Langmore, 1997) and coughing (Pantaleo, Bongianni, & Mutolo, 2002) serve to prevent the intrusion and clear the airway of any aspirate. Coughing may also result from irritation to the lower airways and requires sufficient lung function for pulmonary clearance (Curtis & Langmore, 1997; Sabate, Gonzalez, Ruperez, & Rodriguez, 1996a). However, disease and ageing have been reported to compromise airway protection (Shaker et al., 2003) and may be a result of impairment to any or all of the above.

Special consideration is given to the effects of normal ageing on the mechanisms of airway protection as reduction in strength, stability, coordination and endurance are anatomical and physiological changes associated with ageing (Gleeson, 1999). Slowing of motor responses is characterised by a decline in reaction time, the time necessary for transmission of sensory information, decision making, and motor execution (Nagasawa, Yuasa, Tamura, & Tsuru, 1991; Wilkinson & Allison, 1989). Given these changes in normal ageing, it is not surprising that subtle changes in the early stages of PD are often mistaken for signs of normal ageing, especially since these patient's performance in behavioural tests overlap with healthy adults (Crapo & Morris, 1989). However, delineation of normal and abnormal behaviour must be at least attempted if what is considered abnormal is to be understood and defined. The effects of ageing and PD on biomechanics of swallowing, breathing-swallowing coordination (BSC), lung function, cough and laryngeal sensitivity are described in detail in the following sections.

2.2.1 Biomechanics of Swallowing

As described, oral preparatory, oral, pharyngeal and oesophageal phases make up a swallowing event (Logemann, 1997). As the biomechanics of normal swallowing have been discussed in detail (see section 2.1.2), this section addresses changes in swallowing due to normal ageing and in PD.

2.2.1.1 Effects of Ageing on the Biomechanics of Swallowing

There is no doubt that biomechanical changes are observed in swallowing as a function of the normal aging process. It has been reported that swallowing function starts to decrease as early as 45 years of age and by 70, the total duration of oropharyngeal swallowing times are significantly slower when compared to those under 45 (Robbins et al., 1992). Substantial research has quantified age-related changes in swallowing behaviour (Dejaeger & Pelemans, 1996; Ekberg & Feinberg, 1991; Fucile et al., 1998; Fulp et al., 1990; Gleeson, 1999; Jaradeh, 1994; Logemann, 1990; Martin-Harris et al., 2005; Nagaya & Sumi, 2002; Nilsson et al., 1996; Plant, 1998; Ribeiro et al., 1998; Robbins, 1996; Schindler & Kelly, 2002; Shaker et al., 2003; Sonies, 1992; Wilkinson & de Picciotto, 1999). In addition, radiological findings have found dysphagia symptoms such as laryngeal penetration and silent aspiration in elders with and without neurological diagnoses, but who do not admit to any swallowing problems (Bushmann et al., 1989; Daggett et al., 2006; Ekberg & Feinberg, 1991).

In 257 healthy adults between the ages of 23-88, Baum & Bodner (1983) found significant differences in lip posture, tongue posture and masticatory muscle function between the oldest group (80 years) and the youngest group (39 years). While agreeing that skills required in the oral phase of swallowing such as mastication, tongue mobility, and lip closure have been shown to deteriorate with age, Fucile et al., (1998) studied the functional effects of these changes across a meal in 79 healthy adults aged 60-97 years. Overall results indicted that healthy elders maintained their functional feeding and oral praxis skills, despite increasing difficulty with foods that are hard or fibrous. Good health and natural dentition were excellent indicators of functional feeding ability. In contrast to isolated swallowing patterns, functional drinking in ageing was studied by Daniels et al., (2004) using sequential straw drinking. Results showed that the leading edge of the bolus at swallow onset was found to be deeper in the hypopharynx for elders. Consequently, elders had more instances of laryngeal penetration compared to young adults.

Using the Iowa Oral Performance Instrument to investigate the effect of lingual pressure generation during isometric movements and swallowing, variability in tongue pressure changes have been reported (Robbins, Levine, Wood, Roecker, & Luschei, 1995). Specifically, maximum tongue blade isometric pressures were greater in young adults than for the older group but neither tongue dorsum nor tongue tip isometric pressures were significantly different. Furthermore, there were no significant differences between age groups for peak lingual swallowing pressures. The original aim of the study by Robbins et al. was to

investigate effects of age on lingual pressure generation as a risk factor for dysphagia but found that while elders have difficulty maintaining pressures necessary for swallowing, overall swallow pressure did not decline significantly with age. These data suggest that while elders lose neuromuscular reserves, they maintain functional ability.

Temporal measures in the biomechanics of swallowing also change as a result of ageing. Shaw et al., (1995) reported significant increases in oral transit duration for elders with mean age of 76 (M = 0.67 s) for all volumes of liquid barium when compared to the young group with mean age of 21 (M = 0.47 s) but no differences in pharyngeal transit duration were found between elders and young adults. This finding is in contrast to that of Robbins et al (1992) who reported significantly longer durations for pharyngeal transit in the oldest subject group (> 70 years) but failed to find an age effect for oral transit duration. These differences are likely due to differences in study protocol. Where Robbins et al. administered both liquid and semi-solids, participants in the study by Shaw et al. were only given liquids. Bolus texture was found to influence duration of pharygeal, with longer pharyngeal transit duration for semi-solids compared to liquids (Robbins et al., 1992). Sonies et al., (1988) examined the initiation and termination of tongue and hyoid activity during the oropharyngeal phase in 47 adults and found that total duration of hyoid activity for dry and liquid swallows increased significantly with age. Specifically, duration of hyoid movement from rest to maximum anterior displacement during liquid swallows was significantly longer for the old-age group (M = 1.24 s) than for the young age group (M = 0.59 s). In addition, there was a significant increase in multiple lingual gestures required to complete a swallow in elders. Double or triple hyoid gestures were observed in 80% of elders to complete one swallow, a pattern that was not seen in middle-age participants. In addition to extraneous hyoid movements, a delay in reaching maximal hyolaryngeal excursion was suggested to be the cause of longer swallowing durations with increased age (Robbins et al., 1992).

Laryngeal closure is undoubtedly one of the most important biomechanical actions in airway protection. Substantial anatomical and physiological effects are known to occur at the laryngeal level with age but how these age-dependent alterations impact on swallowing remains under-researched. Atropy, oedema and changes within the layers of the lamina propria such as decreased density of collagenous and elastic fibres, thinning of elastic tissues and thickening of collagenous fibers have been reported in the vocal folds (Hirano, Kurita, & Sakaguchi, 1989; Honjo & Isshiki, 1980; Ishii, Yamashita, Akita, & Hirose, 2000; Kosztyla-Hojna, Rogowski, & Pepinski, 2003; Sato, Hirano, & Nakashima, 2002; Ximenes Filho,

Tsuji, do Nascimento, & Sennes, 2003). In the larynx, the hyaline cartilages have been found to undergo ossification with increasing age (Fatterpekar, Mukherji, Rajgopalan, Lin, & Castillo, 2004; Paulsen, Kimpel, Lockemann, & Tillmann, 2000). The articulating surfaces of the cricoarytenoid joint change such they negatively impact on the ease of cartilage movement and vocal fold adduction (Kahn & Kahane, 1986), but how these impact swallowing has yet to be elucidated.

Through simultaneous nasendoscopy, UOS manometry, respirography and submental sEMG, Ren et al., (1993) studied age affects on the coordination of glottic closure and UOS opening during swallowing in 10 young adults (M= 23years) and 10 elders (M= 73 years). For both groups, vocal cord adduction preceded the onset of UOS relaxation for all water volumes ranging from 5–20 ml. Compared to dry swallows, water swallows also shortened the interval between the onset of glottal closure and UOS relaxation. The authors concluded that coordination between swallowing, glottal closure and UOS relaxation is preserved in the elderly. The shortened period between glottic closure onset and UOS relaxation during liquid swallows was perceived as a contributing factor to airway protection.

Even though technology has improved and more diagnostic studies have become available, research regarding oesophageal function in the aged continues to yield contradictory results. In the aforementioned study by Ren et al., (1993), primary peristaltic amplitude was similar across ages at all sites of the oesophagus, while overall peristaltic wave durations were longer in the elderly population. This finding is further supported by Aly & Abdel-Aty, (1999) who found that the overall mean for oesophageal transit time was up to 10 seconds but this was longer in those over 40 years old. Grande et al., (1999) found that longer peristaltic duration was accompanied by an increase in the number of failed contractions in advanced age. Ren et al's (1993) finding that primary peristaltic amplitude was similar is in contrast to a later study that found decreased peristaltic contraction amplitude in healthy adults above 60 compared to adults below 50 (Nishimura et al., 1996). The discrepancy in results by various authors highlights a wide variation in the performance of healthy elders. Diverse assessment techniques may also yield different results, accounting for the contradiction in findings.

In summary, while changes may negatively impact all phases of the swallowing process as a function of age, equally compelling evidence exists to suggest that normal aging alone does not cause significant functional impairment to the ability to swallow. It can be difficult to distinguish the effect of normal aging from the effects of gradual degenerative changes or

diseases (Ekberg & Feinberg, 1991). There are subtle changes in muscle tension, speed and coordination of swallowing responses across all swallowing phases but these findings do not necessarily indicate oropharyngeal nor oesophageal dysphagia. Instead, dysphagia is more often the direct result of a pathologic condition or illness that may occur more commonly in elderly persons (Sonies, 1992).

2.2.1.2 Effects of Parkinson's Disease on the Biomechanics of Swallowing

As with other complex coordinated muscle activities in patients with PD, swallowing is significantly affected by rigidity and bradykinesia producing aberrations in the oral preparatory, oral, pharyngeal and oesophageal phases (Ali et al., 1996; Johnston, Li, Castell, & Castell, 1995; Potulska et al., 2003). Clinicians have sought to clarify the precise nature of swallowing disorders in PD by investigating the biomechanics of swallowing as abnormalities in the biomechanics are thought to give rise to symptoms of dysphagia and eventual aspiration (Coates & Bakheit, 1997; Stroudley & Walsh, 1991).

Logemann, (1983) writes that patients with PD exhibit impairment in all phases of swallowing. This is supported by several other investigators (Ertekin et al., 2002; Leopold & Kagel, 1996, 1997a, 1997b; Stroudley & Walsh, 1991). In a study using VFS to examine swallowing in 24 patients with PD, Stroudley & Walsh (1991) found oral phase abnormalities in 92% of patients, pharyngeal phase abnormalities in 54% of patients with 8% demonstrating oesophageal phase abnormalities. Aspiration was seen in 46% of their patients, although how the presence/absence of cough was judged was not reported by the authors. Furthermore, none of their patient participants elicited a cough response upon aspiration. However, the investigators reported neither their patient selection criteria nor the severity of PD in their population. As dysphagia may be more apparent in later stages of the disease (Calne et al., 1970), high rates reported may be attributed to the recruitment of patients with severe PD in the late stages of the disease.

In the oral phase of swallowing, patients with PD often demonstrate "typical repetitive, anterior to posterior rolling pattern in lingual propulsion of the bolus" (Logemann, 1983 p. 218). In normal swallowing when the bolus first enters the oral cavity, the tongue base rises to form a seal against the hard palate (Perlman & Christensen, 1997). When the bolus is ready to be swallowed the base of the tongue lowers in preparation for the bolus to be pushed into the pharynx. However, in PD, the tongue may not lower, forcing the bolus back to the anterior of

the oral cavity. This oscillating anterior-posterior movement may repeat many times before the swallow that has sufficient tongue-driving force is triggered (Logemann, 1983). This atypical pattern, according to Logemann, may be attributed to a form of muscle rigidity in PD. Other symptoms of oral phase impairment such as excessive tongue pumping movements, piecemeal anterior to posterior transfer of bolus and anterior loss due to poor lip seal have also been described (Murry & Carrau, 2001).

In a study involving 24 patients with varying severities of dysphagia, Stroudley & Walsh (1991) found oral phase dysphagia in 92%. Poor lip closure resulting in intermittent or continuous anterior loss was described in 29%, whilst 86% had tongue and bolus control abnormalities that resulted in premature spillage into the pharynx. These behaviours were more prevalent in liquid than in semi-solids or solids. As soft palate function was deemed part of the oral phase of swallowing in that study, authors also reported intermittent nasal reflux in 29% of patients. Nagaya et al., (2000) described oral phase dysphagia in PD based on a measure of reaction time called premotor time (PMT), defined as latency of EMG activity from the time a stimulus was given to the time of first detectable change in the EMG measurement. Using submental EMG, patients were commanded to swallow immediately in response to a flashing light. Compared to healthy adults, this latency was found to be significantly longer in those with PD.

The use of VFS has expanded our knowledge of bolus transport during the pharyngeal phase of swallowing. Leopold & Kagel (1997b) examined 71 patients using VFS and found that the most common abnormalities of the pharyngeal phase were impaired pharyngeal motility, valleculae and pyriform sinus stasis, laryngeal penetration, aspiration and deficient epiglottic retroflexion. From the time the bolus entered the pharynx to the time of gastric emptying, bolus transport was normal in only 2 patients. This finding supported earlier studies that reported similar and other biomechanical abnormalities such as pyriform sinus bolus retention and reduced velar movements (Bushmann et al., 1989; Robbins et al., 1986). Weak pharyngeal contraction/squeeze and impaired pharyngeal peristalsis have been reported, along with delays in the triggering of the pharyngeal phase that results in spillage and or pooling of the bolus in valleculae or pyriforms (Murry & Carrau, 2001). Post swallow residue may also be present in the presence of reduced pharyngeal stripping secondary to pharyngeal muscle weakness (Logemann, 1983). With an increase in number of swallows, post swallow residual puts patients at risk for aspiration due to the accumulated residue.

At the laryngeal level, atrophy of the vocal folds leading to vocal fold bowing during phonation in PD has been well documented (Blumin et al., 2004; Hanson et al., 1984; Smith et al., 1995; Stelzig et al., 1999), along with other abnormalities such as resting tremor of arytenoid and supraglottic structures (Perez et al., 1996). However, the relative contribution of vocal fold closure to airway protection and swallowing in PD has not been fully explored even though it was shown to provide airway protection (Medda et al., 2003). Impaired vertical excursion of the larynx has been reported (Bushmann et al., 1989) but research documents that vertical movements of the larynx may not be as important as the anterior excursion of the hyolaryngeal complex, for which anterior movement of the hyoid is greater than vertical movement by up to 8mm (Ishida et al., 2002; Jacob et al., 1989; Logemann, Kahrilas, Begelman, Dodds, & Pauloski, 1989).

In 1997, Leopold and Kagel claimed that although vocal fold adduction helps to define phonation and voice, intrinsic laryngeal movements during swallowing are no less critical. They allege that laryngeal muscle function is defective in PD. Results of their study using VFS revealed that at least one abnormality of laryngeal motility during swallowing was found in 95.8% of patients. There were significant delays in the start of vertical excursion of the larynx, delayed true vocal fold closure, coupled with delayed, incomplete or absent abduction of the true vocal folds. Deficits in the onset of laryngeal movement were also positively correlated with disease advancement.

Even though Logemann (1983) claimed that only the occasional patient exhibits cricopharyngeal (CP) dysfunction, several other studies have suggested that CP dysfunction exists in this patient cohort (Ertekin et al., 2002; Lieberman et al., 1980; Miller, Noble, Jones, & Burn, 2006a; Potulska et al., 2003). Using concentric needle electrodes, Ertekin et al. (2002) observed that even though the CP sphincter in PD was not electrophysiologically different to healthy controls, 21% of patients exhibited incomplete UOS relaxation during swallowing. Similarly, Ali et al., (1996) reported that although individuals with PD and healthy controls demonstrated similar resting pressures at rest, incomplete UOS relaxation and reduced UOS opening during swallowing were prevalent in PD only.

Between 45% to 73% of individuals with PD exhibit manometric abnormalities (Bassotti et al., 1998; Castell et al., 2001), with most frequent symptoms being complete aperistalsis or diffuse oesophageal spasm characterised by multiple simultaneous contractions. In addition, Castell et al., (2001) reported that oesophageal abnormalities were independent of PD severity

or duration, reflecting selective involvement of either the dorsal motor nucleus of the vagus or the oesophageal myenteric plexus. Nonetheless, individuals with PD did not show abnormalities in all measures as normal resting pressures were found to be similar in PD and in healthy controls (Castell et al., 2001). This report is in contrast to a study published in the same year that reported abnormal resting pressures of the UOS (Higo, Tayama, Watanabe, & Niimi, 2001). Despite some conflicting results, all agree that multiple abnormalities of the UOS are present in PD, with the most common being incomplete relaxation of the UOS and delayed peristalsis, stasis, bolus redirection and spastic, tertiary contractions for the oesophagus (Castell et al., 2001; Higo et al., 2001; Higo, Tayama, Watanabe, Nitou, & Ugawa, 2003).

In summary, it is undisputed that biomechanics of swallowing are impaired in PD. Even though studies have suggested that dysphagia does not emerge till the later stages (Coates & Bakheit, 1997; Potulska et al., 2003), growing evidence suggest that subtle signs of dysphagia may be present in the early stages, especially since subjective reports of dysphagia may not correspond to symptoms observed (Bushmann et al., 1989; Volonte et al., 2002). Additionally, emergence of symptoms does not necessarily correlate to duration or severity of PD (Castell et al., 2001). Clearly, future investigations into biomechanical aspects would call for a comparison between severity levels.

2.2.2 Coordination of Breathing and Swallowing

The oropharynx and hypopharynx share the same pathway for respiration and swallowing (Curtis & Langmore, 1997; Hiss, Treole, & Stuart, 2001; Selley et al., 1989a). With each swallow, the prepared bolus is transferred lateral to the larynx from anterior to posterior, while the pathway for expired air passes in the opposite direction into the oral and nasal cavities. Swallowing always interrupts breathing in order to prevent aspiration, and airway protection necessitates a high level of coordination between respiration and swallowing (Klahn & Perlman, 1999).

The dual role of the pharynx as a conduit for food and airway has led to several functional adaptations that serve to protect the airway during swallowing (Preiksaitis & Mills, 1996). Adduction of the vocal folds during swallow is supplemented by the closure of false vocal folds, and epiglottic deflection to direct food away from the larynx into the oesophagus (Hadjikoutis, Pickersgill, Dawson, & Wiles, 2000). The momentary cessation in respiration

during swallowing, termed swallowing apnoea (SA) (Hadjikoutis et al., 2000; Hiss et al., 2001; McFarland & Lund, 1993, 1995; Preiksaitis & Mills, 1996). This biomechanical closure consists of the medialisation of the arytenoids and approximation to the epiglottis, with subsequent closure of the true and false vocal folds (Miller, 2002). Many authors report that the onset of glottic closure in adults may still be one of the earliest airway protection mechanism to occur during swallowing, and has been reported to precede the onset of hyoid movement (Martin-Harris et al., 2005; Shaker, Dodds, Dantas, Hogan, & Arndorfer, 1990). Typically, SA happens before the bolus reaches the hypopharynx and prior to the start of pharyngeal phase. The early cessation of respiration through the biomechanical closure of the airway is thought to prevent aspiration (Palmer & Hiiemae, 2003).

Even though cessation of respiratory efforts during swallowing occurs early in the swallowing process, Langmore, (2001b) highlighted that full glottic closure may not occur till the bolus advances towards the pyriforms. Ohmae, Logemann, Kaiser, Hanson, & Kahrilas, (1995) also report that although arytenoid adduction and contact happen as one of the earliest physiological process, these are highly variable as true vocal fold closure mainly happened *after* the onset of hyolaryngeal elevation. This finding that vocal folds are frequently not fully approximated until after the onset of laryngeal elevation is further supported by Shaker et al., (1990) in a study of 8 healthy young adults using concurrent trans-nasal video laryngoscopy, pharyngeal manometry and submental surface electromyography. In this study, Shaker et al., found that the onset of hyolaryngeal excursion occurred approximately 0.33 seconds after initial vocal fold approximation but full vocal closure only happened after 0.42 seconds.

The use of direction nasal airflow has been used my many as a non-invasive way of determining the onset and offset of SA (Hiss et al., 2003; Hiss et al., 2001; Kelly, Huckabee, & Cooke, 2006; Martin-Harris et al., 2005). However, it is important to note that obstruction of the lower or proximal airways also contribute cessation of respiration. For example, velar closure causes a cessation in nasal airflow and quite often occur simultaneously, or even before SA (Perlman, He, Barkmeier, & Van Leer, 2005). The study by Perlman et al. reiterates that SA and vocal fold adduction are not be inextricably linked and cannot be used synonymously.

Although SA is a biomechanical closing action, there is emerging evidence that a swallowing apnoeic reflex exists (Miller, 1999; Widdicombe, 1986b). Pharyngeal and laryngeal stimulation have been found to induce prolonged apnoea in both animals (Boggs & Bartlett,

1982; Khater-Boidin, Wallois, Toussaint, & Duron, 1994; Miller, 1976; Storey & Johnson, 1975) and humans (Davies, Koenig, & Thach, 1988, 1989; Thach, Davies, Koenig, Menon, & Pickens, 1990). In the kitten's first week of life, stimulation of the lingual nerve (sensory input provided to the anterior 2/3 of tongue) induces apnoea, but not swallowing (Khater-Boidin et al., 1994; Miller, 1976). In the next 3 weeks, apnoea is elicited with swallowing and within a month, the adult pattern emerges, whereby respiration alternates with swallowing. Upon reaching maturity, SA appears robust. Typically, SA begins before the bolus reaches the hypopharynx and ends when the tail end of the bolus has reached the oesophagus (Palmer & Hiiemae, 2003).

The apnoeic reflex that is found during the pharyngeal phase of the swallow is believed to be centrally integrated (Broussard & Altschuler, 2000). Evidence for the central integration of SA comes from human studies of laryngectomised (Hiss et al., 2003) and intubated patients (Nishino & Hiraga, 1991). With the trachea routed to the anterior cervical wall, individuals with laryngectomy are not at risk for aspiration. During swallowing, the bolus passes from the oral cavity through the pharynx without threatening the trachea. Theoretically, these individuals could breathe and swallow simultaneously, since the pharynx is no longer a shared pathway for these two functions. However, Hiss et al., (2003) found that these individuals continued to demonstrate measurable SA in the absence of glottic closure. In a similar study, Charbonneau, Lund, & McFarland, (2005) also reported on the persistence of SA in 12 patients following laryngectomy. Intubated patients with no opportunity for glottic closure also showed SA and changes in breathing-swallowing coordination (Nishino & Hiraga, 1991). In these patients, central mechanisms integrating respiration and swallowing are responsible for changes in breathing patterns during swallowing. Broussard & Altschuler (2000) suggested a neuroanatomical basis for the central integration between swallowing and airway protective reflexes but they concluded that even though swallowing motoneurons are thought to be centrally controlled, the exact coordination and coupling of airway reflexes are yet to be fully elucidated (Broussard & Altschuler, 2000).

Instances of SA relative to respiration are typically classified as occurring in one of four categories: expiration-SA-expiration (EE), inspiration-SA-inspiration (II), inspiration-SA-expiration (IE) and expiration-SA-inspiration (EI). In adults, the majority of SA occurs in the mid expiratory phase of respiration (EE) (Klahn & Perlman, 1999; Preiksaitis & Mills, 1996). SA in mid-expiration is also thought to be a useful mechanism for clearing residue post swallow and preventing subsequent micro-aspiration (Hadjikoutis et al., 2000). Nonetheless,

the reported frequency or percentage of each SA category may differ due to methodological differences. As an example, Hiss et al., (2001) reported more than 62% of SA during mid-expiration, in comparison to Martin, Logemann, Shaker, & Dodds, (1994) who reported similar patterns in 94-100% of healthy young adults. Differences in the reported rates may be attributed to the size of the bolus used and the method of bolus delivery during the assessment. Preiksaitis & Mills (1996) found that the mid-expiratory respiratory pattern was the preferred pattern with all drinking and eating tasks but this was only for single bolus swallows. Inspiration followed SA in less than 5% of single bolus swallows but increased significantly with a 200 ml drink by cup or straw by 23% and 27% respectively. Post swallow inspiration increased to 16% when eating solid textures.

Direct comparison of studies is difficult for 2 further reasons. First, the way bolus was administered and second, the way data was grouped for analyses and subsequently reported. In a study involving 10 healthy adults, Preiksaitis & Mills (1996) found that SA duration (SAD) lasts approximately 1 second and is consistent across different bolus size (5-20 mls), consistency (thickened, thin liquids, soft diet and solids) and mode of bolus presentation (syringe, straw and cup). In a similar study, Hiss et al., (2001) looked at the effects of age, gender, bolus volume and trial on SA and swallow/respiratory phase relationships in 10 males and 10 females across 3 age groups: young (20-39 year olds), middle-aged (49-59 year olds) and elderly (60-83 year olds). Significant effects on SA for age, gender, and bolus volume were reported, in contrast to that reported by Preiksaitis & Mills (1996) who found no effects as a function of volume. Hirst, Ford, Gibson, & Wilson, (2002) chose only to report swallows that preceded expiration while Preiksaitis & Mills (1996) categorised swallows based on whether SA occurred pre- or post swallow.

Despite differences in bolus type and administration and reporting of results, authors are in agreement on the following. First, the timing of swallows in relation to respiration is not random. More than 70% of swallows begin during the expiratory phase of the respiratory cycle. Second, most bolus swallows end with expiration and third, swallowing is associated with a swallow apnoea varying between 1-2 seconds in duration. The consistency of these observations has led to the conclusion that precise coordination of breathing and swallowing is systematic and thus may be an important mechanism in preventing aspiration (Broussard & Altschuler, 2000; Hadjikoutis et al., 2000; Mokhlesi, Logemann, Rademaker, Stangl, & Corbridge, 2002).

In summary, there is sufficient evidence to show that SA may be one swallowing parameter that can be utilised to determine airway protection during swallowing (Hadjikoutis et al., 2000; Hiss et al., 2001; Nilsson, Ekberg, Bulow, & Hindfelt, 1997). The goals of SA research are to "establish data so that normal SA can be compared to abnormal swallowing physiology and potential aspiration. In addition, SA duration may potentially be identified as an invariant that if increased or decreased in duration, is correlated with aspiration" (Hiss et al., 2001 p.129).

2.2.2.1 Effects of Ageing on Coordination of Breathing and Swallowing

In young adults, movement of the bolus towards the pharynx often occurs after the vocal cords have reached maximum adduction (Langmore, 2001a; Ren et al., 1993) with some variability (Ohmae et al., 1995). However, Zamir, Ren, Hogan, & Shaker, (1996) found this to be true in only 20% of elders. In another 20%, the bolus entered the pharynx an average of 0.08 seconds before respiration ceased, with the remaining 60% showing interchanging patterns of timing between bolus transfer and cessation of respiration. Using a water drinking test termed ROSS (Repetitive Oral Suction Swallow), Nilsson, Ekberg, Olsson, & Hindfelt (1996) observed features of incoordination such as increased frequency of multiple swallows, and increased frequency of polyphasic laryngeal movements in their elders. Even though other features, such as decreased peak suction pressure and increased frequency of coughing during or after swallowing were documented, the coordination of various swallowing biomechanical events in the elderly was similar to that in young adults (Nilsson et al., 1996; Zamir et al., 1996).

Breathing-swallowing coordination (BSC) in ageing has received less attention even though anatomical and physiological changes in swallowing and pulmonary functions are expected in healthy elderly (Berend, 2005; Gleeson, 1999; Jaradeh, 1994; Martin-Harris et al., 2005; Plant, 1998; Robbins, 1996; Schindler & Kelly, 2002; Sonies, 1992; Turner, Mead, & Wohl, 1968). Selley et al., (1989a) found that in their study of 33 adults, all exhibited post swallow expiration. Martin-Harris et al., (2005) used simultaneous VFS and nasal respiratory tracings to investigate BSC across the adult lifespan (21 to 81+). The authors reported that the most common respiratory phase category in their cohort of 76 adults as EE (75%), followed by IE (18%), EI (4%) and II (3%). Subsequently, pre-expiratory patterns (EE, IE) were compared to pre-inspiratory patterns (EI, II). A significant age effect was also seen, with a mean age of 56

years for pre-expiratory apnoea and the mean age of 68 years for pre-inspiratory apnoea patterns.

Regarding SAD, when young adults (mean age 21) were compared to elders (mean age 76) in the study by Selley et al, (1989a), SAD increased from 0.6 seconds to 1 second respectively. Similarly, Hiss et al., (2001) report that the overall duration of SA in elderly adults (> 60) was significantly longer than young and middle age adults (< 60). Results from these studies are in contrast to that reported by Nilsson et al., (1996). Although not specifically termed SAD, no significant differences were found in the total duration between onset of vocal cord adduction and their complete reopening between young adults and elders. With SAD operationally defined as 'plateau in respiratory tracing along the abscissa' for the onset and 'departure from plateau in respiratory tracing along abscissa in positive or negative direction' for offset in the study by Martin-Harris et al., (2005), apnoeic durations ranging from 0.5 to 10.02 seconds were found when ingesting 5mL liquid boluses. Outliers were from the oldest ages group (>80). Otherwise, median duration was 1.00 seconds.

In conclusion, subtle alterations occur in the coordination of vocal cord closure and oropharyngeal bolus transit in some elderly individuals (Zamir et al., 1996). Prolonged SAD in the elderly is one change observed with age and may be a compensatory mechanism for compromised airway protection (Selley et al., 1989a) even though the mechanisms underlying gender differences are not yet explained (Hiss et al., 2001). Post-swallowing expiration in BSC seems to be robust in healthy adults (Martin-Harris et al., 2005; Selley et al., 1989a).

2.2.2.2 Effects of Parkinson's Disease on the Coordination of Breathing and Swallowing

Aberrant BSC has been reported in neurological disorders such as stroke, multiple sclerosis, motor neurone disease and spinal cord damage (Selley et al., 1989b). Disruption to the dominant pattern of mid-expiratory swallows may be seen as a possible risk factor for aspiration (Curtis & Langmore, 1997; Hadjikoutis et al., 2000). In those with neurological disorders, 43% (Selley et al., 1989b) to 91% (Hadjikoutis et al., 2000) demonstrated post swallow inspiration regardless of bolus size. Over a period of 12-18 months of follow up, two patients with normal respiratory patterns during swallowing developed post swallow inspiratory patterns. Interestingly, post swallow inspiration did not predict chest infections, coughing/choking episodes or survival rates, which could suggest that post swallow

inspiration may be a non-specific concomitant of disordered breathing-swallowing coordination rather than an important mechanism leading to aspiration.

A limited number of studies have included patients with different neurological disorders but none have investigated SA and BSC specifically in individuals with PD. No literature has been identified that specifically investigated temporal relationships of respiration and swallowing in this patient cohort. Given that PD is a movement disorder, with features that include, tremor, rigidity and bradykinesia at laryngeal levels (Blumin et al., 2004; Hanson et al., 1984; Perez et al., 1996; Smith et al., 1995; Stelzig et al., 1999) and obstructive and/or restrictive patterns at the pulmonary level (Sabate et al., 1996a), it is surprising that no research has looked at the relationship between SA and swallow-respiratory phase relationship in this population.

2.2.3 Pulmonary Function

In the previous section, it was established that respiration and deglutition are two life-sustaining physiological actions that also share crucial anatomical space because the upper airway serves as a common pathway for both air and nourishment. Most research efforts to date have focused on breathing swallowing coordination, emphasising the need for turn taking between the two actions for airway protection (Hiss et al., 2001; Klahn & Perlman, 1999; Preiksaitis & Mills, 1996; Selley et al., 1989a, 1989b). However, Gross, Atwood, Grayhack, & Shaiman, (2003) stress that consideration must be given to a more integrated paradigm whereby the respiratory system and the airflow actively participate in deglutition. It is important for clinicians to have knowledge of the respiratory system as any disruption to the respiratory system can increase the likelihood of respiratory disease or exacerbate acute or chronic respiratory failure conditions (Enright, Kronmal, Higgins, Schenker, & Haponik, 1993; Krumpe, Knudson, Parsons, & Reiser, 1985).

Respiration is critical for sustaining life but also equally important for generating the pressure needed to cough, speak, and swallow (Kim & Sapienza, 2005). Evidence that subglottic pressure changes are crucial enough to make a difference in swallowing originated from observations of altered swallowing function in tracheostomy patients, for whom air pressure below the true vocal folds was modified (Bonanno, 1971; Bone, Davis, Zuidema, & Cameron, 1974; Buckwalter & Sasaki, 1984; Cameron, Reynolds, & Zuidema, 1973). An unoccluded tracheostomy tube eliminates the generation of positive subglottic air pressure. If swallowing

requires an interaction between 4 pressure valves as suggested by Perlman & Christensen (1997), disruption to this system could put the patient at risk of aspiration. Not surprisingly, increased aspiration and dysphagia have been linked to the presence of an open tracheostomy tube (Bonanno, 1971; Bone et al., 1974; Buckwalter & Sasaki, 1984; Cameron et al., 1973; Muz, Mathog, Nelson, & Jones, 1989; Nash, 1988). Conversely, occluding the tracheostomy stoma eliminated or reduced aspiration, possibly due to the restoration of positive subglottic pressure (Dettelbach, Gross, Mahlmann, & Eibling, 1995), even though this claim has been challenged recently by a single research group using nasendoscopy (Leder, Joe, Hill, & Traube, 2001; Leder, Joe, Ross, Coelho, & Mendes, 2005; Leder, Tarro, & Burrell, 1996).

In another study to investigate lung volume effects on pharyngeal swallowing physiology, Gross et al., (2003) recorded swallows using simultaneous VFS (3 pudding consistency boluses), bipolar intramuscular electromyography to the superior pharyngeal constrictor and respiratory inductance plethysmography. Twenty-eight participants swallowed under three randomised lung volumes: total lung capacity, functional residual capacity, and residual volume[2]. EMG results indicated that duration of pharyngeal activity for swallows produced at residual volume was significantly longer than those occurring at total lung capacity or at functional residual capacity. With prior research indicating that prolonged pharyngeal transit times is one of the risk factors for developing aspiration pneumonia (Holas, DePippo, & Reding, 1994), swallowing at low subglottic pressures and/or points in the respiratory cycle when lung volumes are low may result in airway protection compromise (Selley et al., 1989b).

In conclusion, it is clear that pulmonary function plays a significant part in the protection of the airways. Spirometry is a non-invasive method of measuring pulmonary function that has standardised reference values for various population groups (Crapo, Morris, & Gardner, 1981; Gardner & Hankinson, 1988; Gore et al., 1995; Hankinson, Odencrantz, & Fedan, 1999; Miller et al., 2005a; Miller et al., 2005b; Pierce, 2005; Wohlgemuth, van der Kooi, Hendriks, Padberg, & Folgering, 2003) and is readily available to most clinicians. Spirometry measures the rate at which the lungs change volume during forced breathing manoeuvres and is a reasonable test for the measurement of pulmonary function. As it is used in during data

[2] Total lung capacity is the total amount of gas in the lungs after maximum inspiration.
Functional residual capacity is the total amount of gas left in the lungs after a resting expiration.
Residual volume is the volume of gas remaining in the lungs after a complete exhalation.
Defined in Miller, et al. (2005). Standardisation of spirometry. *The European Respiratory Journal, 26*(2), 319-338.

collection in the present study, definitions for measurements taken during spirometry are provided in Appendix 2.

2.2.3.1 Effects of Ageing on Pulmonary Function

The ageing respiratory system undergoes both structural and functional changes. Physiologic and aerodynamic data support the hypothesis that respiratory function declines significantly with advancing age, thereby affecting the communication capabilities of the older individual (Hollien, 1987). Typically, age-related changes in the respiratory system include changes in respiratory volumes and lung capacity. It is well known that spirometry values change with age, with values such as FEV1/FVC ratio decreasing with increasing age (Berend, 2005; Lundback et al., 2003). Other changes include reduction in vital capacity, inspiratory capacity and expiratory reserve volume (Hoit & Hixon, 1987). The loss of elasticity in the lungs have also been reported (Turner et al., 1968). However, there is no evidence that changes in the respiratory system impact day-to-day function of older adults; they may become evident under circumstances when physiologic demand reaches the limits of supply (Zeleznik, 2003). Certainly, the impact of low lung volumes on swallowing in the ageing population is under-explored.

No research to date has been conducted specifically to investigate the effects of ageing on the interaction between lung volumes and swallowing for airway protection. It is well established, however, that age produces changes in lung function parameters (Berend, 2005; Hoit & Hixon, 1987; Lundback et al., 2003). Conceivably, swallowing may be affected in healthy ageing as pulmonary function declines. This needs to be investigated.

2.2.3.2 Effects of Parkinson's Disease on Pulmonary Function

Manifestations of PD like rigidity and bradykinesia are not limited to the extremities and larynx but can affect a broad range of striated muscles, including the upper airway and chest wall (Shill & Stacy, 2002). Conceivably, rigidity and/ or bradykinesia in PD can impair respiratory function, which can have a detrimental impact on airway protection. Several studies have found both restrictive and obstructive ventilatory patterns in this cohort (De Pandis et al., 2002; Herer, Arnulf, & Housset, 2001; Sabate et al., 1996a; Vercueil, Linard, Wuyam, Pollak, & Benchetrit, 1999). In addition, Fontana, Pantaleo, Lavorini, Benvenuti, & Gangemi (1998) found abdominal muscle weakness in PD, as measured by surface EMG of

the abdominal muscles, leading to weak cough strength. EMG activity during cough was always significantly lower in patients compared to healthy elders.

Shill & Stacy (2002) reported that incidence and prevalence of airway obstruction and restriction in PD have decreased in recent years, possibly a reflection of the therapeutic benefits of anti-Parkinson medications on the airway. They cite two similar studies that reported very different rates of upper airway obstruction and/or restriction and found that the major difference in these studies lie in whether lung function tests were done during the 'on' or 'off' phase of the medication. The study in which investigations were done during the 'on' phase of medication Izquierdo-Alonso, Jimenez-Jimenez, Cabrera-Valdivia, & Mansilla-Lesmes, (1994) reported more restrictive patterns and significantly less upper airway obstruction than the study that was carried out during the 'off' phase (Sabate et al., 1996a), where up to 62% of patients exhibited obstructive-patterned spirograms. These studies suggest that airway obstruction may be sensitive to dopaminergic stimulation. Vercueil, Linard, Wuyam, Pollak, & Benchetrit, (1999) observed that studying the effects of levodopa therapy in PD is unique, given that patients may be considered as their own control. Improvements in clinical signs under levodopa therapy during the 'on' phase can be compared to the effects of drug withdrawal during the 'off' phase.

Herer et al., (2001) acknowledged that upper airway obstruction may be present in PD with possible reversibility after levodopa therapy. They conducted a double-blind, placebo-controlled, crossover study to investigate the effects of levodopa on pulmonary function. In 22 patients with idiopathic PD, lung function tests that included spirometry and maximal inspiratory and expiratory flow volumes were performed after a 12 hour withdrawal of levodopa therapy, and 1 hour after oral intake of a placebo or levodopa. Upper airway obstruction was diagnosed if 6 of the a priori criteria for upper airway obstruction were met. In their study, a total of 5 patients were diagnosed with upper airway obstruction. Results show that all patients, regardless of airway obstruction status had a positive response to levodopa with a minimum of 50% improvement in inspiratory and expiratory flow rates. No changes in lung volume were noted for either group. Of the 5 patients initially diagnosed with upper airway obstruction, 3 patients no longer met the criteria for having upper airway obstruction post levodopa. However, 1 patient from the placebo group also no longer fulfilled the criteria for having upper airway obstruction post 'treatment'. The authors suggested that motor disability in PD may be partially reversed with levodopa therapy. The improvement in upper airway obstruction seen in the patient receiving placebo was not further commented on

even though it would further suggest that other factors besides levodopa therapy contributed to the measured improvements.

Despite pharmacological treatment providing clinical benefits and reduced mortality in PD, respiratory dysfunction remains one of the most common causes of death in these patients (Hoehn & Yahr, 1967; Vincken et al., 1984). This high mortality rate from respiratory complications is reported even though patients themselves do not admit to having respiratory complications (Polatli, Akyol, Cildag, & Bayulkem, 2001; Sabate et al., 1996a). Using spirometry, Hovestadt, Bogaard, Meerwaldt, van der Meche, & Stigt, (1989) found that upper airway obstruction was often asymptomatic in PD, even though up to 65% of individuals with PD are known to have obstructive ventilatory defect when tested (Hovestadt et al., 1989; Sabate et al., 1996a; Vincken et al., 1984). This disturbance may remain unnoticed because the physical disability in PD does not lead patients to engage in activities where problems such as ventilatory insufficiency are manifest (Sabate et al., 1996a; Sabate, Rodriguez, Mendez, Enriquez, & Gonzalez, 1996b). Tzelepis, McCool, Friedman, & Hoppin, (1988) further commented that individuals with PD are usually able to perform single motor acts but have difficulties performing more complex, repetitive ones. Consequently, the ability to perform rapid successive movements is impaired in the presence of normal muscle strength. Conceivably, patients may not manifest differences in quiet breathing on or off medication (Gardner, Langdon, & Parkes, 1987) but exhibit abnormal spirograms during forced manoeuvres that demands rapid activation and coordination of contraction of the upper airways and chest wall.

Although prior studies have found improvements in respiratory function with levodopa, this is not a universal finding. Adverse consequences to respiratory function have been documented with the administration of levodopa. Within a few years of the first long term levodopa use (Cotzias, Papavasiliou, & Gellene, 1969), respiratory problems associated with its administration were described (Granerus, Jagenburg, Nilsson, & Svanborg, 1974). Subsequently, many reports of respiratory disturbance induced by levodopa treatment have been reported (De Keyser & Vincken, 1985; Rice, Antic, & Thompson, 2002; Vidailhet, Bonnet, Marconi, Durif, & Agid, 1999; Weiner, Goetz, Nausieda, & Klawans, 1978; Zupnick, Brown, Miller, & Moros, 1990). Irregular breathing with alternating tachypnoea-apnoea (Rice et al., 2002), dyspnoea (De Keyser & Vincken, 1985), and chest discomfort not associated with cardiac/pulmonary disorders (Weiner et al., 1978) were among the symptoms of respiratory dyskinesia experienced during peak ‘on’ phase.

Spirometry data from selected case studies documented deterioration of FVC ranging from 0% to 27% and FEV_1 ranging from 0% to 24% (De Keyser & Vincken, 1985; Zupnick et al., 1990) but greatest deterioration in maximum pressures of up to 57% (Zupnick et al., 1990). In all reports, the temporal relationship of the respiratory disturbance to the administration of levodopa treatment suggested a peak-dose drug effect (De Keyser & Vincken, 1985; Rice et al., 2002; Zupnick et al., 1990) with respiratory symptoms and spirometry values returning to normal by 1-3.5 hours post drug administration (Zupnick et al., 1990). Reducing the titration of L-DOPA (Weiner et al., 1978) or supplementing L-DOPA with Tiapride, a DA agonist (De Keyser & Vincken, 1985) either reduced or abolished respiratory symptoms, further lending support to peak dose respiratory dykinesia.

In summary, respiratory function is altered in PD, especially with advancement of the disease. While motor function improves with pharmacotherapy, it is unclear whether striated muscles of respiration respond in the same manner. One study has demonstrated, at least in part, reversibility of airway obstruction after levodopa administration (Herer et al., 2001). These changes may be monitored objectively and non-invasively using spirometry. The importance of assessing respiratory function is highlighted by prior studies that report that improvement or impairment of respiratory muscles is directly related to the individual's cough strength and airway protection (Ebihara et al., 2003; Fontana et al., 1998).

2.2.4 Cough Reflex and Chemo-sensitivity

Six different types of respiratory responses (apnoea, expiration and cough reflex, spasmodic panting, slowing of breathing and rapid, shallow breathing) have been identified in humans when the tracheal mucosa is stimulated (Nishino, Hiraga, Mizuguchi, & Honda, 1988). Of these, coughing may be the single most effective defence mechanism for airway clearance aimed at removing mucus and or foreign particles from the respiratory tract (Bickerman & Barach, 1954; Bickerman et al., 1956; French, Irwin, Curley, & Krikorian, 1998; Hutchings, Eccles, Smith, & Jawad, 1993a; Hutchings, Morris, Eccles, & Jawad, 1993b; Irwin et al., 1998; Karlsson, 1996; Pantaleo et al., 2002; Shannon, Baekey, Morris, & Lindsey, 1996). An effective cough is dependent on the ability to achieve high gas flows and velocities through the airways in an attempt to eject mucus and/or aspirate (Irwin et al., 1998).

Biomechanically, coughing begins with deep inspiration, followed by glottic closure, respiratory muscle contraction, rapid airflow, glottic opening and expectoration of mucus and foreign material (Shannon et al., 1996). During the inspiratory phase, the posterior cricoarytenoid muscle, innervated by the internal recurrent laryngeal nerves, maximally abducts the vocal folds for wide glottic opening, and lung volume increases rapidly. The next compressive phase is brief, distinguished by the tight closure of true and false vocal folds and the continued contraction of the expiratory muscles (abdominal, chest wall, and pelvic floor muscles), resulting in a dramatic increase in intrathoracic pressure. Normally, dynamic compression is initiated in the trachea and bronchi and extends to the peripheral airways in an attempt to ensure that the whole length of the tracheobronchial tree is engaged during cough. For this to happen, high intrathoracic pressures must be sustained throughout the expiratory effort (Leith, 1986). The final phase of the cough cycle is expulsive, with the high intrapleural pressures developed during glottic closure simultaneously promoting high expiratory flow rates and narrowing the central airways. With the transverse diameter of the trachea narrowed up to 16% of its original size (Comroe, 1974), dynamic compression of the airways during the expiratory phase of cough decreases tracheal cross-sectional area, resulting in a 5-fold increase in the linear velocity of the gas (McCool & Leith, 1987). Flow rates of up to 12 litres per second, or 800 kilometres per hour have been reported (Irwin et al., 1998; McCool & Leith, 1987). The entire cough sequence can be repeated multiple times during a coughing episode without the need for additional inspiration between each cycle, gradually taking the lung volumes down to residual volume.

Neurophysiological studies have been crucial in mapping out the neurophysiology of cough initiation. These studies have confirmed that the cough reflex is elicited by stimulation of central airway receptors belonging to a group of rapidly adapting irritant receptors found within the epithelium throughout respiratory system (Irwin et al., 1998; Sant'Ambrogio & Sant'Ambrogio, 1996). Subserved by the vagus nerve and located throughout the tracheobronchial tree are thin, myelinated, rapidly adapting pulmonary stretch receptors (RARs), and the non-myelinated bronchial C-fibers, both of which are thought to be involved in conducting impulses during cough (Widdicombe, 1995). Animal studies have shown that in dogs, chemical and mechanical receptors are most numerous on the posterior wall of the trachea, at the main carina, and at the branching points of large airways. These reduce in prevalence at the more distal, smaller airways (Tatar, Sant'Ambrogio, & Sant'Ambrogio, 1994) and no nerve endings have been found beyond the respiratory bronchioles in dogs, cats and rats (Karlsson, 1996). As the use of surgical experimental techniques on humans is

unjustified, most of the knowledge concerning cough and other respiratory reflexes has been obtained in anaesthetised animals with questionable applicability to awake humans (Nishino, Tagaito, & Isono, 1996b). Humans have a more evenly distributed pattern of nerve endings that extends throughout the trachea and bronchi (Karlsson, 1996). The study of sleeping or anaesthetised humans may be an acceptable substitute for the study of airway reflexes and defence mechanism since these processes have been shown to either potentiate or attenuate reflexes (Nishino et al., 1996b).

Neurophysiological studies have also been important in clarifying the roles of different receptor types found in the trachea. The reactivity of these nerve endings distributed throughout the trachea depends on the type of sensory nerve ending present. Mechanical receptors that are sensitive to touch and displacement are concentrated in the larynx, trachea and carina, becoming progressively less numerous in the tracheobronchial tree. Chemical receptors that are sensitive primarily to noxious gases and fumes are concentrated more in the larynx and bronchi than in the trachea (Irwin et al., 1998; Karlsson, 1996). In a study involving anaesthetised humans Nishino, Kochi, & Ishii (1996a) reported that airway sensitivity to irritation by small amounts of distilled water was greater at the larynx and trachea than at the more peripheral airways. While vigorous defensive responses including forceful expiratory efforts and apnoea were elicited during tracheal stimulation, the same stimulation to the bronchus caused either little or no response. Of note is the inference that cough and irritant receptors must also exist outside of the lower respiratory tract, since research has shown that mechanical stimulation of the external auditory canals, tympanic membrane, paranasal sinuses, pharynx, diaphragm and pleura have all been reported to cause cough (Clerf, 1947; Ishrat-Husain, 1967; Wolff, May, & Nuelle, 1973).

The vagus nerve plays a crucial role in mediating cough induced in the tracheobronchial tree and larynx as cough receptors are innervated through branches of this nerve (Korpas & Widdicombe, 1991). This is supported by the observation that vagal denervation of the tracheobronchial tree following heart-lung transplant eliminates the cough that is usually provoked by the inhalation of distilled water (Higenbottam, Jackson, Woolman, Lowry, & Wallwork, 1989). Sensory information from receptors in the larynx is primarily carried by the superior laryngeal nerve (SLN) while impulses from irritation of tracheobronchial and pleural receptors are carried by the pulmonary branches of the vagus (Widdicombe, 1964). Of note is that in addition to the vagus nerve, the trigeminal and glossopharyngeal nerves are also

important in relaying afferent information from peripheral receptors that are in the nose and paranasal sinuses.

Sensory information from the periphery is carried to the cough centre, postulated to be situated in a diffused area of the medulla and lower pons, in close proximity to the nucleus tractus solitarious (Jordan, 1996; Shannon et al., 1996). The existence of a discrete central cough centre that is separate from the medullary centres that control breathing is controversial, as pharmacological and electricical stimulation research have reported equivocal evidence for a discrete cough centre (Bolser & Davenport, 2002; Mori & Sakai, 1972; Nishino et al., 1996b; O'Connell, 2002; Sant'Ambrogio & Sant'Ambrogio, 1996). Regardless, these impulses in the putative cough centre are then integrated into a coordinated cough response in the medulla of the brain stem. Here, efferent impulses of the cough reflex are transmitted to the respiratory musculature through the phrenic and other spinal motor nerves and to the larynx through the recurrent laryngeal branches of the vagus (Irwin et al., 1998; Irwin, Rosen, & Braman, 1977). Vagal efferents also mediate bronchial smooth muscle constriction that is thought to assist coughing efforts by narrowing the airways, thereby increasing the velocity of air flow (Widdicombe, 1964).

Even though coughing is normally referred to a reflex mediated by control centres in the respiratory areas of the brainstem, more recent experimental information would indicate that voluntary control of cough is possible and that higher centres such as the cerebral cortex have an important role in initiating and/or inhibiting coughing (Hutchings et al., 1993a; Hutchings et al., 1993b; Lee, Cotterill-Jones, & Eccles, 2002). Evidence for voluntary suppression of coughs comes from 3 types of experiments that compare (1) cough and consciousness, (2) voluntary suppression of cough versus natural cough thresholds and (3) the effectiveness of antitussives on cough suppression.

Unlike the swallowing reflex, there is experimental evidence to indicate that cough can only occur during consciousness. Peripheral stimulation of cough in sleeping animals using small amounts of water have shown that cough was suppressed during rapid eye movement (REM) sleep in cats (Anderson, Dick, & Orem, 1996) and dogs (Sullivan, Kozar, Murphy, & Phillipson, 1979). The stimulation first arouses the animal that then produces cough. Similar patterns of cough depression have also been shown in sleeping humans with coughing only occurring after wakefulness (Power et al., 1984). Further evidence for the need for consciousness during coughing come from the observation that in humans, cough responses

are inhibited during light anaesthesia while completely abolished with increasing depth of anaesthesia (Nishino et al., 1988; Nishino et al., 1996a).

Studies using capsaicin-induced cough have demonstrated that cough may be voluntarily suppressed (Hutchings et al., 1993a; Hutchings et al., 1993b). Participants in the study by Hutchings, Morris et al., (1993b) underwent 2 sessions of cough challenge using 5 increasing concentrations of capsaicin. In one session, participants were allowed to cough freely when shown a green traffic light (non-suppressed condition). In another session, participants were shown a red light asked to try and inhibit cough in a suppressed challenge. In the suppressed cough condition, participants were able to almost completely inhibit the capsaicin induced cough, lending support to cortical control over cough. More recent research continued to provide evidence for cortical modulation of cough (Leow, Huckabee, & Anderson, 2006). In a citric acid cough challenge, young adults were given instructions to inhibit cough after natural cough threshold was identified. Significant differences between natural and suppressed cough thresholds were found when participants were asked to inhibit cough, where participants were able to suppress cough even at the maximum citric acid concentration of 2 Mols (Leow et al., 2006).

It has been shown that in upper respiratory tract infection (URTI), placebo treatment alone can lead to up to a 50% decrease in cough frequency (Lee et al., 2001). Furthermore, codeine, a known antitussive, also failed to provide any antitussive activity beyond that which could attribute to a placebo treatment or rest (Eccles, 1996; Eccles, Morris, & Jawad, 1992). This was clearly demonstrated by Eccles et al., (1992) in a double-blind, placebo-controlled trial involving 91 patients with non-productive URTI. The medication used in the trial was codeine linctus in syrup versus syrup alone. Results demonstrate a highly significant reduction in the severity of cough in both treatment groups, with no significant difference between the codeine and placebo treatment groups. Studies that found strong placebo effect accounted for their findings by proposing that the mind-body interaction may lead to a voluntary suppression of cough, which in turn raises the threshold for reflexive cough via cough control centres in the brainstem (Lee et al., 2001) and which consequently mediates the release of endogenous opioids (Eccles et al., 1992).

Lee et al., (2002) proposed a model of cough that incorporates both voluntary and involuntary cough (Figure 2.2). In this model, irritation of airway receptors at the periphery is relayed to the brainstem cough control area, where cough is reflexively generated (solid line). Such

coughing occurs when a peripheral stimulus has breached the threshold for cough in the brainstem. The sensation of irritation at the periphery may also produce a volitional cough via higher centres such as the cerebral cortex (ascending, broken line). Normally, coughing can also be voluntarily initiated and inhibited. This is done via the cerebral cortex that influences cough by two pathways: via the brainstem, and via a descending pathway to the spinal cord (descending, broken line). Both descending pathways result in coughing. However, cough initiated from the cerebral cortex may also be inhibited within the cerebral cortex, thereby suppressing the urge to cough (short, descending, broken line). Lee et al., (2002, p. 318) summarised the extent of cortical control by stating that "The cortical inhibition of cough can be surmounted when the afferent input from peripheral cough receptors causes the cough threshold to be exceeded despite cortical inhibition. In this instance the cough is uncontrollable and is a reflex type of cough".

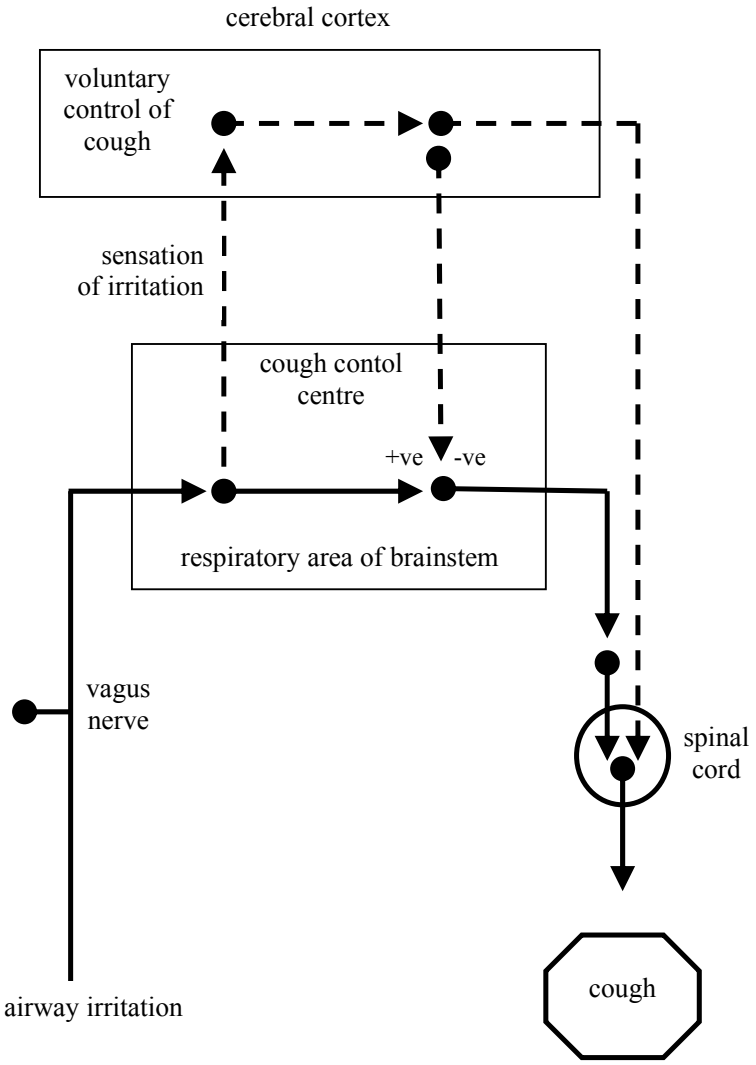


Figure 2.2 Cough model to illustrate reflex and voluntary control mechanisms. Irritation of airway receptors may cause reflex cough via a brainstem cough control area. A sensation of irritation may cause cough via higher centres such as the cerebral cortex. Cough can be voluntarily initiated and inhibited via the cerebral cortex that influences cough by two pathways; via the brainstem; and via a descending pathway to the spinal cord. Cough associated with common cold may be a mixture of both voluntary and reflex cough. Adapted from Lee, P. C., Cotterill-Jones, C., & Eccles, R. (2002). Voluntary control of cough. *Pulmonary Pharmacology & Therapeutics, 15*(3), 317-320..

In 1996, Karlsson acknowledged that even though cough is the most common symptom of airway disease, it is the least studied. Subsequently, Fuller (2002) identified that one of the obstacles to the understanding of cough is the lack of a simple, systematic method of assessing cough objectively. Even though questionnaires that probe type and duration of coughing are valuable, in the absence of an independent objective measure, the subjective nature of questionnaires prevent understanding of inter-patient variation (French et al., 1998). Subjective measures of cough cannot be used as surrogate markers for objective cough frequency measurements (Clare Decalmer et al., 2007). The inhalation cough challenge is one technique that has received wide-scale use in objectively quantifying cough frequency.

Inhalation cough challenge has been used in the investigation of the cough reflex and antitussives for over 50 years (Bickerman & Barach, 1954; Bickerman et al., 1956) Subsequently, refinement of techniques have allowed the administration of inhaled irritants to be honed into a useful epidemiological and pharmacological tool (Auffarth, de Monchy, van der Mark, Postma, & Koeter, 1991; Dilworth, Pounsford, & White, 1990; Higenbottam et al., 1989; Hutchings et al., 1993a; Hutchings et al., 1993b; Morice, Marshall, Higgins, & Grattan, 1994; Pounsford & Saunders, 1985; Prime, 1961).

The cough challenge procedure involves the delivery of tussive agents and the subsequent recording of the number of induced coughs (Morice, Kastelik, & Thompson, 2001). As the sensory nerve endings can be triggered by a number of stimuli, a variety of chemicals can be used to investigate cough reflex. Tussigenic agents that are commonly used include citric acid (Kastelik et al., 2002), capsaicin (Midgren, Hansson, Karlsson, Simonsson, & Persson, 1992) and tartaric acid (Addington, Stephens, & Goulding, 1999b) even though water (Fontana, Lavorini, & Pistolesi, 2002), ammonia, sulphur dioxide and even cigarette smoke have been used (Gravenstein, Devloo, & Beecher, 1954). Of these, only capsaicin and citric acid are considered reliable due to their reproducibility across time (Morice et al., 2001). During cough challenge, the tussigenic agents are delivered as aerosols for inhalation via jet or ultrasonic nebulisers. Simple inspiration method such as vital capacity volume inhalation has been employed but this is less reliable since inspiratory flow rate has been found to influence cough response (Barros, Zammattio, & Rees, 1990). For this reason, more accurate methods using dosimeter-controlled nebulisers that enable standardised doses of the tussigenic agents are preferred (Morice et al., 2001).

Two methods of cough challenge are commonly used, namely single dose and dose response. The former involves the administration of one concentration of the tussive agent. As only one concentration is used, this method is less time consuming when compared to dose response cough challenge, and has acquired wider usage in the studies of the antitussive properties of pharmacological agents (Grattan, Marshall, Higgins, & Morice, 1995). Dose response cough challenge involves the inhalation of incremental concentrations of tussive agents interspersed with placebo inhalations. This method can be further subdivided into single breath or fixed time inhalation challenges. Single breath methods require one inhalation of a given concentration while fixed-time responses may be several inhalations ranging from 15 to 60 seconds (Midgren et al., 1992). However, Morice et al., (2001) pointed out that fixed-time inhalation is associated with difficulties in the delivery of accurate amounts of tussigenic agents due to subject-related differences like lung volume and breathing effort. It also time consuming and involves long inhalation times. As such, single breath method has gained wider usage. Whether single breath or fixed inhalation, results of dose response cough challenge are most often expressed as D2 or D5, defined as the lowest dose concentrations generating 2 or 5 coughs per inhalation respectively.

Several factors have been identified which influence cough sensitivity. There is evidence for the existence of gender differences in cough elicitation, with women having greater sensitivity, hence lower cough thresholds, than men (Dicpinigaitis & Rauf, 1998; Kastelik et al., 2002). Further, there is evidence that children are more sensitive than adults (Chang, Phelan, Roberts, & Robertson, 1996). Heightened sensitivity and/or an artefact of dosing may account for these differences since women compared to men, and children compared to adults, have smaller airways (Dicpinigaitis & Rauf, 1998; Fuller, 2002). Asthma (Chang, Phelan, & Robertson, 1997), gastroesophageal reflux disease (GORD) (Ferrari et al., 1995) and common colds (Empey, Laitinen, Jacobs, Gold, & Nadel, 1976) lead to increased sensitivity of cough receptor sensitivity, while smoking (Dicpinigaitis, 2003) diminishes airway sensitivity. Long term smoke-induced desensitisation of cough receptors within the airway epithelium may account for the increase in cough thresholds in smoking. Even though disease, lifestyle and gender influence cough challenge performance, no support for ethnic differences in cough challenge inhalation has been reported. Dicpinigaitis et al., (2001) explored ethnic differences in three population groups, Caucasian, Indian and Chinese. Results from that study show no support for ethnic differences in capsaicin cough challenge.

Despite the progress made in refining cough challenge techniques, one limitation remains and that is the lack of normal values. This lack of universal norms and standards may be attributed to the several types of cough challenge methods and tussigenic agents used. Consequently, direct comparisons of norms between centres difficult (Morice et al., 2001). That notwithstanding, cough challenge may be a potentially useful tool for the assessment of airway chemo-sensitivity. Although no current standards or norms are available, this test remains one of the few that have received, at least in part, wide use. More research is needed p;db=PubMed&dopt=Citation&list_uids=1954529</URL></MDL>2.2.4.1 Effects

2.2.4.1 Effects of Ageing on Cough Reflex and Chemo-sensitivity

Silent aspiration is considered to be very important in the pathogenesis of aspiration pneumonia in older persons (Daggett et al., 2006; Gleeson et al., 1997; Matsuse et al., 1996; Pontoppidan & Beecher, 1960). As pneumonia may be prevented by defense mechanisms of the upper airway reflexes such as coughing, age-dependent declines of upper airway reflexes may be one of the pathophysiologic features of aspiration pneumonia in elders (Pontoppidan & Beecher, 1960). It has been proffered that elders are slower to clear particles from the airway, possibly due to impaired mucociliary function that accompanies aging (Teramoto, Matsuse, & Ouchi, 1999). In addition, Teramoto et al., (2005) highlights that in elderly patients, it is the cough reflex rather than mucociliary clearance that is most important for preventing aspiration. Significant decreases in cough reflex have been observed in elderly patients with aspiration pneumonia (Sekizawa, Ujiie, Itabashi, Sasaki, & Takishima, 1990).

There are very few published data on the cough reflex in ageing. Pontoppidan & Beecher (1960) demonstrated significant reductions in sensitivity in elders when compared to young adults in a cough challenge using inhaled ammonia. More recently, Newnham & Hamilton (1997) conducted a placebo-controlled, randomised, double-blind crossover study using single-dose, fixed time inhalation method with distilled water. They compared the number of coughs in 20 young adults (mean age 27) and 20 elders (mean age 83). The authors reported that elders demonstrated significantly fewer coughs compared to young adults at the same concentration of administered antitussive, suggesting less sensitivity. No participants coughed on the placebo (isotonic saline).

Only one research group has published data to suggest that elders have normal cough reflexes but failed to provide reasons for this finding (Katsumata et al., 1991). Few researchers have

looked at the effect of age on chemo-sensitivity using cough challenge, even though one of the applications of cough challenge is to compare performance in patient populations such as stroke (Addington et al., 1999a), GORD (Ferrari et al., 1995) and chronic obstructive pulmonary disease (COPD) (Peruzza et al., 2003; Sacco et al., 1997; Smith, Owen, Earis, & Woodcock, 2006). As these diseases are more prevalent in the elderly, this area deserves more research than what is currently available for comparison.

2.2.4.2 Effects of Parkinson's Disease on Cough Reflex and Chemo-sensitivity

Researchers and clinicians have acknowledged the importance of cough reflex in the neurogenic population (Addington et al., 1999a; Ebihara et al., 2003; Smith & Wiles, 1998). Delayed recovery of the cough reflex has been postulated to increase morbidity and mortality (Addington et al., 1999a). In stroke, for example, laryngeal cough reflex may be impaired up to a month or longer with permanent impairment in some (Kobayashi, Hoshino, Okayama, Sekizawa, & Sasaki, 1994). In addition, patients with weak cough have an increased risk of developing aspiration pneumonia (Smith Hammond et al., 2001).

Addington et al., (1999a) were among the first to explore the clinical use of inhalation cough challenge in a neurogenic population with dysphagia. A prospective study of 400 patients who were acutely post stroke was carried out with the aim of using the inhalation cough challenge to identify patients who were thought to be at risk of developing aspiration pneumonia. Depending on the patient's response to 20% tartaric acid in a single dose, single inhalation method, a score of normal, weak or absent cough was assigned. Patients with intact cognition and a normal cough response were fed orally. Patients with absent or weak scores were not allowed food/liquids or recommended restricted diets. A comparison of the incidence of pneumonia was done with a sister hospital whose patients did not receive the cough challenge. Results show a significant difference in pneumonia rates between those who received cough challenge testing (1%) compared to those who did not (13%). A limitation of this study was the failure to disclose why 20% of tartaric acid was chosen over other concentrations. Furthermore, there were no objective definitions for the classification of cough responses, i.e. normal vs. weak, or how these were measured. Based on the description of 'normal' vs. 'weak' in the study by Addington et al., it would not be possible to distinguish between weak cough due to insensitivity or respiratory muscle weakness that can result from neurological event (Fugl-Meyer, Linderholm, & Wilson, 1983). Despite these criticisms, the study by Addington et al., (1999a) remains one of the first to document changes in chemo-sensation

using cough challenge. It lends support to the presumption that cough challenge testing may be a potentially useful tool in helping clinicians to monitor changes in cough sensitivity in patients with neurological impairment.

Despite advances in the treatment of PD, aspiration pneumonia is still the leading cause of mortality (Wang et al., 2002). Weak motor control of coughing has been demonstrated in this population (Fontana et al., 1998) but sensory aspects of coughing cannot be overlooked. Ebihara et al., (2003) compared the motor component of cough efficacy (assessed by monitoring voluntary maximal cough peak flow) and sensory aspects of cough (using fixed-time, dose response cough challenge with citric acid). These authors found that in the early stages of the disease, mainly motor control was impaired with preservation of sensory aspects. In the later stages of the disease, however, both motor and sensory components of cough were affected. Citric acid cough thresholds in individuals with PD were significantly higher when compared to healthy controls, suggesting reduced chemo-sensation. The study by Ebihara et al. makes an important contribution to the understanding of chemo-reception changes in PD, especially since the authors also investigated the effects of disease severity. One weakness of the study by Ebihara et al. was that only female patients were recruited. This is problematic as there are gender differences for chemo-sensitivity (Dicpinigaitis & Rauf, 1998; Kastelik et al., 2002). In addition, there are more males with PD compared to females, with the male:female ratio at 3:2 (Wooten, Currie, Bovbjerg, Lee, & Patrie, 2004). With only female participants, results from the study by Ebihara et al. would not apply to male patients.

Fontana et al., (1998) used distilled water delivered in increasing concentrations of aerosol/fog as the tussigenic agent in a group of 23 patients with idiopathic PD to determine cough threshold. The authors reported that although increased cough thresholds were seen in patients with PD compared to healthy, age-matched controls, the results failed to reach statistical significance. Whether reduced cough sensitivity is a consistent feature in neurogenic population remains to be elucidated. Smith & Wiles (1998) reported that in a group of patients with neurogenic dysphagia of with mixed aetiology, there was a trend towards *enhanced* cough responsiveness to capsaicin when compared to their non dysphagic counterparts; those with abnormal swallowing had a lower cough threshold. Smith and Wiles highlighted that even though this finding was not statistically significant ($p= 0.07$), it approached significance. As such, they were unable to conclude that sensitivity is decreased in all patients with neurogenic dysphagia.

The authors did suggest reasons for their surprising result. In the self-evaluation of their study, the Smith & Wiles admitted that no systematic study of capsaicin responses in healthy adults was undertaken for comparison. A wide range of cough responsiveness was noted between patients with a variety of diagnoses in each group, when a more homogeneous population might have been preferred to show clear differences between groups. Furthermore, the authors recommend that future studies should compare or correlate cough sensitivity to symptoms of dysphagia using an objective instrumentation, e.g. VFS. Finally, they recommend a change in methodology by using dose response, single breath method for future studies to reduce the possibility of tachyphylaxis in the neurogenic population.

In summary, desensitisation of pharyngeal, laryngeal or tracheal mucosa resulting in failure to clear substances from the upper airway is thought to be the result of impairment to the sensory components of the vagus and glossopharyngeal nerves. This may account for the high incidence of silent aspiration and subsequent aspiration pneumonia, the leading cause of mortality in PD. Current literature in cough sensitivity testing is still emerging and thus is equivocal and variable. The influence of reduced cough sensitivity as a consistent feature in neurogenic population remains to be elucidated. Nonetheless, the study by Smith & Wiles (1998) and Ebihara et al., (2003) highlight the importance of assessing cough sensitivity as a possible contributor of dysphagia and/or silent aspiration in PD. Future studies can refine methods for this assessment based on the recommendations by Smith & Wiles, (1998).

2.2.5 Laryngeal Adductor Reflex and Mechano-sensitivity

In addition to chemo-sensitive fibres in the laryngo-pharyngeal region, mechano-receptors that respond to tactile stimulus are also found in abundance in the oral, pharyngeal and laryngeal regions, with most mechano-receptors concentrated over the arytenoids and laryngeal surface of the base of the epiglottis (Storey, 1968a, 1968b). These mechano-sensitive neurons detect static and dynamic touch and pressure, then transmits impulses via the SLN to the brainstem (Aviv, 1997b; Miller, 1999). Miller (1999) suggested that the central neural system is relatively diffusely organised for mechano-sensation since receptors that respond to tactile stimuli and those that respond to airflow are both found in close proximity (Sant'Ambrogio & Mathew, 1986). In addition, Feindel (1956) reported that mechanical stimulation of the epiglottis in humans evokes a poorly localised touch sensation and is often accompanied by pain sensation, suggesting the inadvertent stimulation of other receptors.

The importance of mechano-sensation is its link to protective mechanisms and reflexes that serve to prevent aspiration of food into the upper airway (Aviv et al., 1994; Bradley, 2000). Widdicombe (1986a) writes about a number of protective mechanisms in the upper respiratory tract, including coughing (described in section 2.2.4). In addition to coughing, closure of the vocal folds upon stimulation to the interarytenoid and lateral cricoarytenoid muscles has been observed. Shaker et al., (2003) termed this complete adduction of vocal folds the glottic closure reflex. Aviv et al., (2000) further described the existence of the brainstem driven laryngeal adductor response (LAR), which manifests as brief closure of the true vocal folds in response mechanical stimuli. Literature supports the notion that mechanical stimulation to the laryngopharynx induces airway protection mechanism. If this is true, then mechanical stimulation that does not induce any reaction may suggest a risk to airway protection.

The gag reflex has been described as a "strong contraction of the entire pharyngeal wall and soft palate" in response to a stimulus against the base of the tongue or the posterior pharyngeal wall (Logemann, 1983, p. 110). It has been used in the past as a standard test of laryngopharyngeal sensation used to predict the patient's ability to swallow and risk of airway compromise (Linden & Siebens, 1983) and even more recently, the gag is still described as a measure with high sensitivity (but low specificity) in acute stroke patients (Ramsey et al., 2005). However, there is equally convincing evidence that the gag reflex does not rightly predict the patient's ability to swallow nor offer airway protection (Davies et al., 1995; Leder, 1996, 1997). Many individuals with normal swallowing ability demonstrate variablity in their responsiveness to gag reflexes (Schulze-Delreiu & Miller, 1997) with as many as 37% out of a cohort of 140 healthy adults, young and old, not having a gag reflex (Davies et al., 1995). In addition, (Aviv, 1997a) points out that the gag reflex measures sensory response of the glossopharyngeal nerve and not the superior laryngeal branch of the vagus nerve and it is the SLN that provides sensation to the hypophyarynx and the larynx. It may be summarised that even though the gag reflex may not be a reliable prognosticator of swallowing ability and the glossopharyngeal nerve does not supply sensation the the hypopharynx, the integrity of this nerve is important as it is heavily involved in swallowing process.

Assessment of laryngopharyngeal sensitivity is difficult. As discussed, mechano-stimulation of the oropharynx produces the gag reflex, which is not only uncomfortable, but has been established as having very little predictive value for airway protection. Anatomically, the lower pharynx and larynx are difficult to access (Aviv, 1997b). Nasendoscopy using a

fibreoptic nasendoscope has been used to evaluate swallowing since the late 1980s (Langmore, Schatz, & Olsen, 1988). Fibreoptic endoscopic evaluation of swallowing (FEES) provides direct visualisation of the nasopharynx, oropharynx, larynx and hypopharynx (Langmore & McCulloch, 1997). A light touch to the pharyngeal walls, base of tongue or the epiglottis with the tip of the scope may provide a subjective assessment of pharyngeal sensitivity (Langmore & Aviv, 2001).

In the last decade, a more objective measurement of laryngopharyngeal mechano-sensitivity has been possible with the introduction of fibreoptic endoscopic evaluation of swallowing with sensory stimulation (FEESST) (Aviv, 1997b). FEESST uses a specially designed endoscope with an extra lumen to allow passage of air bursts encased within the endoscope. Air pulses are delivered for 50 milliseconds at pressures that vary between 0-12 mm Hg. The stimuli are directed at the aryepiglottic folds as this region is innervated by the internal branch of the SLN to elicit the laryngeal adductor response (LAR).

Two methods have been used to determine sensory thresholds. In the psyshosocial testing method, patients are asked to indicate the time they first feel the stimulus. The second method consists of delivering air pulses at a constant 50 msec starting at subliminal intensity. In the former, the air pulse is increased in 1mmHg increments until the LAR is observed, in the latter, the intensity is decreased until the LAR is no longer observed. The patient's sensory threshold is defined as the mean of the lowest detected pressures when 6 ascending or descending blocks are completed (Langmore & Aviv, 2001). Because of the involuntary nature of the LAR, the second method adds more objectivity to sensory testing than the use of psychophysical testing alone. To determine whether either or both methods are valid, Aviv et al., (1999) compared patient's sensory thresholds using psychophysical method against stimulus evoked LAR in 100 adults, with and without dysphagia. Results indicated no significant difference in the laryngopharyngeal sensory thresholds for either method. In addition, the correlation between both methods was .999, making the mechano-sensory evoked LAR method a reliable one for assessing mechano-sensitivity.

Endoscopic procedures, with or without sensory testing carry some risks (Aviv, Kaplan, & Langmore, 2001). Aviv et al., (2000) conducted total of 500 consecutive FEESST evaluations on 253 patients with dysphagia from predominantly neurogenic causes. The presence of epistaxis, airway compromise and significant changes in heart rate pre- and post assessment were documented. The authors recorded 3 instances of self-limiting episodes of epistaxis and

no cases of airway compromise. Furthermore, no significant changes in heart rate were recorded post examination. Even though some participants reported discomfort, 71% of patients from Aviv's study rated the FEESST procedure as mildly uncomfortable, and only 3% reported it to be severely uncomfortable. When asked if they would were asked if they would repeat the examination, 98% indicated 'yes'. Other possible risks include mucosal injury, laryngospasm and vasovagal syncope (Langmore & McCulloch, 1997). However, these are minimised when performed by an experienced and competent endoscopist. Current literature would suggest that endoscopy is a safe procedure and may be a viable tool for the assessment of mechano-reception in the laryngopharynx.

In summary, the loss of motor function of the oral cavity, pharynx and larynx leading to the impairment of biomechanics of swallow has been well described. However, this alone would not be able to account for all symptoms of dysphagia, since the act of swallowing is dependent on the inter-relationships between both motor and sensory systems. A complete understanding of swallowing physiology would have to include analysis of both motor and sensory function. Sensory testing using FEESST provides an assessment of mechano-sensation while inhalation cough challenge (described in earlier section) offers a way of assessing chemo-sensitivity. Both tests may be clinically useful in predicting airway protection compromise in the patient population.

2.2.5.1 Effects of Ageing on Laryngeal Adductor Reflex and Mechano-sensitivity

Changes in oral, pharyngeal and laryngeal sensation occur with age (Aviv, 1997a; Aviv et al., 1994; Calhoun, Gibson, Hartley, Minton, & Hokanson, 1992; Shaker et al., 2003). Morphometric techniques using electron-microscopy to examine SLN of human cadavers have shown significant decreases of up to 31% in the number of small myelinated sensory fibres above the age of 60 compared to those below 30 (Mortelliti, Malmgren, & Gacek, 1990). This loss may represent a significant histological correlate to the observed age-related sensory loss in the upper airways commonly observed in the elderly (Mortelliti et al., 1990). In a study involving 60 healthy adults, it has been documented that sensory discrimination thresholds of the lips increase with age, especially after 80 (Calhoun et al., 1992). Aviv et al., (1994) further documented deterioration of sensation in the laryngopharynx in 80 adults aged between 23-87 who underwent laryngopharyngeal sensory discrimination testing using FEESST. Participants were divided into 3 groups according to age: 20-40, 41-60 and 61+. Overall sensory thresholds were 2.3mmHg across all age groups, but increased thresholds

were significantly and positively correlated to age. Specifically, the average thresholds of those aged 20-40, 41-60 and 60+ were 2.06, 2.45 and 3.97 respectively. Thresholds for adults < 60 were significantly different to those > 60. Subsequently, in another study comparing healthy adults to those with dysphagia secondary to stroke, a cut off pressure of ≤ 4mmHg was deemed normal (Aviv et al., 1997b).

Shaker et al., (2003) studied the effects of ageing on the volume thresholds required to elicit swallowing in 9 healthy young adults (mean age 26) and 9 healthy elders (mean age 77). Water was infused to the posterior pharyngeal wall using 2 methods: rapid infusion of 0.1 incremental doses via hand-held syringe, or slow, continuous infusion via infusion pump set at 5.5 ml/min. The pharyngoglottal reflex that induced vocal fold closure was observed, as was the volume of water required to trigger an irrepressible swallow. Results show that for rapid injection, the threshold volume of water for triggering pharyngoglottal closure and pharyngeal swallowing in elders was significantly greater than that for the young adults, suggesting some deterioration of sensation in this age group. Although it could be argued that water is a chemo-rather than mechano-receptor, Miller stated that "water receptors are distributed across the laryngeal mucosa like tactile receptors" (Miller, 1999, p. 25). Since Shaker et al. (2003) compared volumes of water rather than comparing different liquids in triggering these reflexes, it maybe assumed that the authors either took water to be a mechanoreceptor or did not make clear what sensory receptors were involved.

Whatever the reason, this study highlights an issue that has been difficult to reconcile in tests involving sensory testing, and that is the problem of isolating the precise site and reason for the impairments seen. For example, a raised threshold of laryngopharyngeal sensitivity may result from a confluence of different factors, such as a reduction of cortical appreciation of the sensation in the presence of response at the periphery, or the abation of the actual sensory nerve endings. An impairment of the actual motor response that ensue to signal that the sensation had been felt may also be misconstrued as the lack of sensation. Miller, Bieger, & Conklin, (1997) also suggest neural accommodation to a habitual stimulus as a possible reason for reduced sensitivity, such as consistent presence of microaspirate, or gastric refluxate. As the SLN has different afferent nerve endings including mechano-sensitive, chemo-sensitive and themo-sensitive fibres (Bradley, 2000; Miller, 1999; Widdicombe, 1986b), these fibres may respond to many different modalities. As an example, although 4% of SLN sensory fibres responded to chemical stimuli alone, 16% responded to chemical *and*

mechanical stimuli (Miller, 1999). When using FEESST or any other laryngo-pharyngeal testing method, it is impossible to determine the exact type of receptor that elicits the LAR.

2.2.5.2 Effects of Parkinson's Disease on Laryngeal Adductor Reflex and Mechano-sensitivity

Despite the high incidence of silent aspiration in PD to suggest loss of sensation, evidence for the loss of laryngo-pharyngeal sensation in this patient group is lacking. Research has reported the loss of sensation in the pharynx and larynx after a neurological event such as stroke (Aviv et al., 1997a; Aviv et al., 1997b; Kidd, Lawson, Nesbitt, & MacMahon, 1993, 1995), and it would not be surprising if this extends to other neurological disorders such as PD. In a study of 500 FEESST examinations in 253 patients of mixed aetiologies (Aviv et al., 2000), only 13 patients had a diagnosis of PD. The focus of that study was on the safety of the procedure and no reference values were published. Using the same procedure on 15 post stroke patients, with equal numbers of age-matched controls, Aviv et al., (1996) reported that stroke patients only responded at a statistically significantly higher thresholds compared to controls. No patient responded to pressure below 4mmHg, with most responding above 6mmHg. Subsequently, sensory thresholds were defined as normal: < 4mmHg, moderately impaired: 4-6mmHg, or severely impaired: > 6mmHg of air pressure (Aviv et al., 1997b).

Even though these values are specific to stroke patients, it does provide some reference values for patients with neurological disorders. More importantly however, there remains a gap in the knowledge of laryngopharyngeal deficits in the PD population that needs to be addressed. Specifically, there have been no studies that have used FEESST to determine sensory thresholds in PD. It would also be useful to explore the correlation of threshold changes to the severity level of PD. Perhaps, as with ageing, severity of PD would also have a positive correlation to increased laryngopharyngeal sensory thresholds.

2.3 Therapy for Parkinson's Disease

2.3.1 Pharmacotherapy for Parkinson's Disease

Levodopa is an amino acid that is absorbed from the small bowel and subsequently transfers across the blood-brain barrier into the brain where it is decarboxylated to DA (Martin & Wieler, 2003). Since the lack of availability of DA in the striatum is the main deficit in PD,

the logical treatment is to replace this with exogenous DA, or stimulate the same receptors as endogenous DA (Nicholson, Pereira, & Hall, 2002; Savitt, Dawson, & Dawson, 2006). First described by Cotzias, Van Woert, & Schiffer (1967), DA replacement therapy with the precursor levodopa (L-DOPA) remains the single most effective drug in ameliorating signs and symptoms in the early stages of PD and in improving the quality of life and survival of treated patients (Diamond, Markham, Hoehn, McDowell, & Muenter, 1989; Fahn, 2005; Rascol et al., 2003). However, during its systemic conversion to DA, side effects like nausea and vomiting may occur due to the activation of DA receptors in the area postrema (Martin & Wieler, 2003). As such, L-DOPA is normally administered in combination with a peripheral DOPA decarboxylase inhibitor such as carbidopa (Sinemet) to minimise side-effects (Martin & Wieler, 2003; Nicholson et al., 2002). This combination significantly reduces the nausea and vomiting associated with levodopa therapy whilst allowing a greater proportion of levodopa to enter the brain.

In addition to side effects like nausea, prolonged use of L-DOPA, especially in later stages of the disease are complicated mainly by motor fluctuations, dyskinesias, and psychiatric problems (Munchau & Bhatia, 2000; Schapira et al., 2006). Munchau & Bhatia (2000) suggested that wearing off effects may be corrected by increasing standard L-dopa doses, changing standard L-dopa to slow release preparation, changing COMT inhibitors, or changing long lasting DA agonists (described below).

Once absorbed on the small bowel, levodopa is metabolised not only by decarboxylase, but also by catechol-o-methyl transferase (COMT), a ubiquitous enzyme. COMT is sufficiently active so that even when levodopa is administered with a peripheral decarboxylase inhibitor, only about 10% of a given dose reaches the brain intact (Kurth & Adler, 1998). In an effort to stabilise the availability of endogenous DA, COMT inhibitors, which prolong the half-life of levodopa and dopamine, were found to enhance the effect of a given levodopa dose (Roberts et al., 1993). In a double blind, crossover study, Ruottinen & Rinne (1996) found that the COMT inhibitor entacapone (Comtan) inhibited peripheral metabolism of levodopa by COMT, thereby increasing its availability to the brain. COMT inhibitors may reduce fluctuations in DA concentration that cause wearing off, or on-off fluctuations often seen with L-DOPA (Nicholson et al., 2002). Incidentally, the COMT inhibitors commonly prescribed are tolcapone and entacapone but the latter is better tolerated without any evidence of hepatotoxicity associated with tolcapone (Olanow, 2000).

Initial use of L-DOPA may produce early dyskinesias (Nicholson et al., 2002). As L-DOPA has a short half-life of 30–60 minutes, DA receptors are subject to phasic stimulation rather than the tonic stimulation that is thought to occur in normal basal ganglia function (Tuite & Ebbitt, 2001). The pathophysiology of dyskinesia remains poorly understood but the onset may be related to the short half-life of L-DOPA in the striatum (Tuite & Ebbitt, 2001). The development of dopamine agonists that directly stimulate postsynaptic DA receptors has avoided the problem of lack of DA synthesis (Savitt et al., 2006). Dopamine agonists stimulate DA receptors directly, mimicking the endogenous neurotransmitter (Martin & Wieler, 2003; Munchau & Bhatia, 2000). Drugs belonging to this class can be classified into ergoline derivates, e.g. such as bromocriptine, pergolide, lisuride, and cabergoline, and non-ergoline derivates, e.g. apomorphine, pramipexole, and ropinirole (Munchau & Bhatia, 2000). The main advantage of DA agonists is in the prevention or delay of motor complications (Rascol et al., 2003).

In clinical practice DA agonists are commonly used as monotherapy before starting L-dopa or as adjunctive therapy to L-dopa after motor complications have developed (Rascol et al., 2000). In a randomsed control trial by the Parkinson Study Group ("Pramipexole vs levodopa as initial treatment for Parkinson disease: A randomized controlled trial. Parkinson Study Group," 2000) showed that initial pramipexole treatment resulted in significantly less development of wearing off, dyskinesias, or on-off motor fluctuations (28%) compared with levodopa (51%). Even so, patients on DA agonist monotherapy require supplementary L-dopa for relief of symptoms after a varying period of time (Lang & Lozano, 1998b).

In summary, the aim of pharmacological treatment is the restoration of neurotransmitter function in the basal ganglia with the goal of enabling the patient to pursue a normal active lifestyle (Nicholson et al., 2002). L-DOPA, in combination with a peripheral decarboxylase inhibitor or DA agonists remains the single most effective drug to improve parkinsonian symptoms although long term use is associated with motor fluctuations and dyskinesias (Fahn, 2005). DA agonists can be tried before introducing L-DOPA but they are less effective than L-DOPA, and sooner or later supplementary L-DOPA is required (Munchau & Bhatia, 2000).

The effects of pharmacotherapy on swallowing are not well known. In an early double blind, placebo-controlled, randomised study investigating the effects of maximum levodopa dose on the swallow using VFS, Calne et al., (1970) reported that although patients on levodopa

therapy had shorter duration of pharyngeal deglutition, the difference failed to reach statistical significance. In addition, 11 of 19 patients demonstrated 'remarkably normal' swallowing patterns (Calne et al., 1970, p. 457). Only pharyngeal phase of swallowing was reported, with the duration of pharyngeal phase estimated using the number of videofluroscopic frames from the time velopharyngeal seal was observed to the time the epiglottis returned to its original position. The authors failed to report the effects of levodopa on oral or oesophageal phases of swallowing. Given that PD is largely considered a motor disorder (Petajan & Jarcho, 1975), and the oral phase of swallowing is voluntarily and motorically controlled, abnormalities in this phase may be more amenable to pharmacological interventions. Indeed, it has been previously suggested that rigidity and bradykinesia of oral musculature may underlie abnormalities in the oral preparatory phase, which is under volitional control, and it would therefore seem logical for there to be an improvement in this phase post treatment (Robbins et al., 1986).

Tison et al., (1996) examined the effect of the DA agonist apomorphine in combination with domperidone drugs on 8 symptoms of oropharyngeal dysphagia using a qualitative 4 point scale. Duration of swallow was measured from the initiation of posterior bolus movement until the time when the tail of the bolus passed through the upper oesophageal sphincter (UOS). Thirty minutes post-medication, swallowing duration was noted to improve in 5 of the 8 patients (percentage improvement ranged from 13%-69%). Laryngeal penetration was found in 3 patients and improved in 2. The total swallowing duration was improved by apomorphine in 5 patients and this improvement correlated with an improvement of the buccal, lingual and facial muscles. Improvements in total swallow duration were also combined with improvement of pharyngeal transit times. Thus, central dopaminergic stimulation by apomorphine may lend evidence to the therapeutic benefits of pharmacotherapy for dysphagia.

Several studies, however, have reported inconsistent responses of patients' swallowing after levodopa treatment (Bushmann et al., 1989; Fuh et al., 1997; Hunter, Crameri, Austin, Woodward, & Hughes, 1997). Of 15 patients who had symptoms of dysphagia in oral and pharyngeal phases in the study by Bushmann et al., (1989), 7 improved after medication but 1 patient's swallow worsened. Similarly, Fuh et al., (1997) observed that only 50% of their patient cohort with abnormal swallowing showed an improvement while the other half showed no change with treatment. Of those that did improve, one patient showed improvement in the oral phase, but deterioration in the pharyngeal phase. Incidentally, twice

as many patients demonstrated swallowing abnormalities, but only half as many reported it. Hunter et al., (1997) compared walking ability and swallowing function pre- and post-levodopa and apomorphine. They found that while patients responded to medication with increased motor responses for walking, there were fewer benefits for swallowing function. Specifically, although some improvements were observed in the oral preparatory phase, this was not consistent across food consistencies. While there was a reduction in the oral preparatory phase with semisolids (jelly) and thin fluids, the reverse was found for solids (dry System/innervatioral phase time and the total initial swallow time increased after administration of levodopa. Such inconsistencies have led to the conclusion that that unlike the cardinal motor features of PD, swallowing abnormalities may in fact be predominantly resistant to dopaminergic stimulation (Hunter et al., 1997). Degeneration of systems other than the dopaminergic system may be the cause of swallowing difficulty. Dysphagia due to a non-dopamine related disturbance of the central pattern generator for swallowing must be considered (Hunter et al., 1997).

In conclusion, current evidence would suggest that in most instances, the benefits of pharmacotherapy for dysphagia remain unsupported. Differences and inconsistencies indicate the need for greater understanding of mechanisms underlying effect of drugs on swallowing in PD. Emerging evidence that other neurotransmitter systems mat be involved in the neurological control and coordination of swallowing in PD require further investigation.

2.3.2 Speech and Swallowing Rehabilitation for Parkinson's Disease

The role of speech therapy in the rehabilitation of speech and swallowing impairment has been controversial, since one could argue that (1) there is no expectation of recovery or improvement of function and (2) that any improvements will not be maintained in the long term (Hillman, Gress, Haugraf, Walsh, & Bunting, 1990). Individuals with PD have been particularly resistant to speech rehabilitation, with little carry over of improvement observed in the treatment room to daily conversation (Allan, 1970; Sarno, 1968; Weiner & Singer, 1989). As such, although up to 89% of individuals with PD experience speech and voice disorders (Hartelius & Svensson, 1994) only 3-4% actually receive treatment (Ramig, 1998). The lack of treatment and/or referral to speech therapists would, perhaps more likely account for why speech treatments have not been effective for individuals with IPD.

Regarding swallowing rehabilitation, Deane, Whurr, Clarke, Playford, & Ben-Shlomo (2001) conducted a systematic review of the literature to compare the effectiveness of swallowing therapy for dysphagia versus placebo or no intervention for patients with PD. When trials that used pharmacological or surgical approaches were excluded, the extensive literature search did not uncover any randomised control trials. This may be due to the many challenges in conducting randomised trials (Brandt et al., 2006). The first multi-site, randomised behavioural trial in dysphagia evaluated two commonly used treatments (chin tuck posture and thickening fluids) with respect to short-term and long-term management of liquid aspiration and subsequent pneumonia in dysphagic geriatric participants with dementia and/or PD. Although one could argue that these treatments do not qualify as rehabilitation, such compensatory strategies are frequently used in clinical practice (Brandt et al., 2006).

The research team led by Ramig and colleagues has focused on improving speech disorders PD by directing attention to phonation and respiration. This treatment, known as the Lee Silverman Voice Treatment (LSVT), has 5 essential concepts (1) exclusive focus on vocal loudness, (2) high-effort speech productions with multiple repetitions, (3) intensive treatment of 4 individual sessions a week for 4 weeks, (4) enhancing sensory awareness of increased vocal loudness and (5) quantifying improvements (Ramig, Countryman, Thompson, & Horii, 1995). Since its introduction, concurrent research has generated short- and long-term efficacy data for a speech treatment in this population (Ramig, Countryman, O'Brien, Hoehn, & Thompson, 1996; Ramig et al., 2001a; Ramig, Sapir, Fox, & Countryman, 2001b). Improvements subsequent to LSVT treatment have included changes in facial expression (Spielman, Borod, & Ramig, 2003), speech intensity (Ramig et al., 1995), vocal cord adduction (Smith et al., 1995) and sub-glottal air pressure (Ramig & Dromey, 1996).

In 2002, Sharkawi et al. found positive improvements in the motor function of swallowing in eight individuals with PD with mild swallowing disorder following LSVT. Pre-treatment, the most prevalent swallowing motility disorders were oral phase problems including reduced tongue control and strength. Reduced tongue base retraction resulting in residue in the vallecula was the most common disorder, followed by prolonged pharyngeal transit time. Post-LSVT, the approximate amount of oral residue after 3 ml and 5 ml liquid swallows was significantly reduced, with an overall 51% reduction in the number of oral-tongue and tongue-base disorders (Sharkawi et al., 2002). Futhermore, the delayed triggering of the pharyngeal swallow that resulted in prolonged pharyngeal transit time and pre-swallow laryngeal

penetration completely disappeared post-LSVT for liquid swallows. A 25% and 66% reduction in the frequency of this disorder was observed for paste and biscuit respectively.

Although no previous studies have been done to evaluate the effects of LSVT on swallowing, the findings by Sharkawi et al. suggest that LSVT may have important effects on the oral and pharyngeal phases of swallow. Sharkawi et al., (2002) speculated that LSVT may activate neuromuscular control of the entire aerodigestive tract, improving function in both the oral tongue and the tongue base during swallowing. This may also reflect an overflow of effort from the habituated increase in phonatory effort. In addition, with repeated practice of LSVT vocal exercises, the patients' awareness of the overall function of the vocal tract may have also increased. Another reason why LSVT may improve swallowing comes from two studies using positron emission tomography (PET) to examine regional cerebral blood flow during swallowing in healthy adults (Hamdy et al., 1999; Zald & Pardo, 1999). Both studies found that besides the brainstem and the primary sensorimotor cortex, where pharynx and larynx are represented, the other region most strongly activated during voluntary swallowing was the right anterior insular cortex, one of the exact sites that significantly changes with LSVT (Liotti et al., 2003). It is likely that speech and communication share important neurons within the anterior insular, such that improvement is anterior insular function would lead to an improvement in both speech and swallowing.

In conclusion, the literature affirms that interactions between speech, swallowing and respiration cannot be ignored since these functions share the same anatomical space and structures (Curtis & Langmore, 1997; Hiss et al., 2001; Selley et al., 1989a). As the adduction of vocal folds and closure of the glottis is deemed the primary mechanism in the prevention of aspiration (Medda et al., 2003), it is logical that vocal fold bowing seen in PD may place patients at some risk of aspiration (Blumin et al., 2004; Stelzig et al., 1999). LSVT focuses on high vocal intensities and loudness by working on the respiratory subsystem so future studies are needed to clarify the simultaneous effects of LSVT on voice and swallowing of individuals with PD.

2.4 Airway Protection Mechanisms: Unanswered Questions

There is still much to be investigated about mechanisms underlying compromise of airway protection in PD. That notwithstanding, research has shown that motor and sensory impairment in the upper airway happens frequently enough to compromise airway protection. This is highlighted by the finding that the onset and severity of swallowing dysfunction in PD is independent of the degree of motor disturbance (Bushmann et al., 1989; Volonte et al., 2002), leaving the healthcare professional in the difficult position of determining how and when to monitor for compromised swallowing in these patients.

Biomechanically, the loss of coordination in PD may manifest as postural instability but it may also detrimentally affect highly coordinated breathing-swallowing patterns. This has not yet been supported by existing research. A limited number of studies have included patients with different neurological disorders but no research has investigated temporal relationships of respiration and swallowing in individuals with PD. Given that manifestations of PD like tremor, rigidity and bradykinesia are not limited to the extremities and larynx (Blumin et al., 2004; Hanson et al., 1984; Perez et al., 1996; Smith et al., 1995; Stelzig et al., 1999) but can affect striated muscles of the upper airway and chest wall (Shill & Stacy, 2002), the gap in BSC knowledge calls for investigations of this mechanism in this patient cohort.

A decrease in spirometry values such as FEV1/FVC ratio has been documented with increasing age (Berend, 2005; Lundback et al., 2003). Other authors report a reduction in vital capacity, inspiratory capacity and expiratory reserve volume with ageing (Hoit & Hixon, 1987). A decline in lung volumes of individuals with PD has also been reported, with both obstructive and restrictive patterns seen. It would be important to investigate the impact of underlying respiratory function on swallowing and airway protection. This importance is further highlighted in a study that found significantly longer swallows occurring at low lung volumes (Gross et al., 2003). Prior research identified that prolonged pharyngeal transit times are one of the risk factors for developing aspiration pneumonia (Holas et al., 1994). Consequently, swallowing at low subglottic pressures or points in the respiratory cycle when lung volumes are low may compromise airway (Selley et al., 1989b). This requires investigation.

Silent aspiration plays an important part in the pathogenesis of aspiration pneumonia in the elderly, both healthy and with dysphagia (Daggett et al., 2006; Gleeson et al., 1997; Matsuse et al., 1996; Pontoppidan & Beecher, 1960). It has been also been established that delayed and/or slow mucociliary clearance is a consequence of ageing (Teramoto et al., 1999), and that elderly persons with aspiration pneumonia have decreased cough reflex due to loss of sensation (Sekizawa et al., 1990). Although PD is a known disorder of the motor system, silent aspiration resulting from the loss of sensation is reported to be as high as 100%. Even so, the question of the type of sensory loss, whether chemo- or mechano-sensation remains unanswered in this population. The stage of the disease when sensory loss occurs is also largely unknown.

Chemosensitivity of the upper airways may be assessed using inhalation cough challenge to provoke cough but cross-centre comparisons are almost impossible due to methodological differences (Fuller, 2002). To date, very few studies have investigated the effects of ageing on chemosensation using cough challenge. The limited number of studies have yielded conflicting results, with some authors suggesting reduced sensitivity with age and others failing to detect age differences (Katsumata, Sekizawa, Ebihara, & Sasaki, 1995; Katsumata et al., 1991; Newnham & Hamilton, 1997; Pontoppidan & Beecher, 1960). Likewise, while Fontana et al., (1998) and Ebihara et al., (2003) reported decreased cough sensitivity in PD, Smith & Wiles (1998) found *enhanced* cough response in a group of patients with neurogenic dysphagia (including PD). Clearly, the pathophysiology of chemo-sensitivity assessed using cough challenge has not yet been fully elucidated. Not withstanding, cough challenge testing may have clinical use in evaluating this patient population (Addington et al., 1999a).

The importance of mechano-sensation of the upper airway is linked to protective reflexes that prevent aspiration (Miller, 1999). In the last decade, FEESST has been available for the assessment of mechano-sensation. Aviv et al., (1994, 1997a) established that mechano-sensation is reduced, especially after the age of 60. No studies using FEESST have established mechano-sensation in the PD cohort alone, although studies of neurogenic dysphagia have included a small subset of individuals with PD (Aviv et al., 2000). Results of studies using FEESST have almost exclusively been reported by Aviv and colleagues, with one study using FEESST on the paediatric population (Link, Willging, Miller, Cotton, & Rudolph, 2000). The lack of studies outside those reported by Aviv and colleagues may be due to the fact that the FEESST system is expensive and not readily available. In the absence of FEESST, Langmore & Aviv (2001) recommend sensory testing in a qualitative manner

using the tip of the endoscope to very lightly touch various points in the pharynx and larynx, also observing for the LAR and/ or any signs from the patient to indicate presence of sensation e.g. grimacing, coughing or swallowing. Although this method is not easily quantifiable, FEES without the air pulse generator is more readily available to clinicians and may be a viable assessment tool for the evaluation of mechano-sensation. To date, nothing is known about mechano-sensory loss in individuals with PD as there has been no prior research conducted exclusively in this group. Whether silent the high rates of aspiration in PD can be attributed to the loss of mechano-sensation remains unanswered.

Another important question that remains unanswered is whether pharmacotherapy influences the patient's ability to protect their airway. The best known control of PD symptoms by far is by means of pharmaco-therapy. With the discovery of levodopa and the subsequent advent of L-dopa (Cotzias et al., 1967), improvements in motor function, especially in the early stages, have been reported. Even so, current literature is inconsistent in the reported benefits of L-Dopa on swallowing function. As most studies have mainly investigated temporal aspects of swallowing, it would be equally important to know if the benefits of L-Dopa extend to BSC and pulmonary function. Some authors have reported the beneficial effects of L-dopa in improving pain tolerance by increasing pain thresholds but this study investigated how nociception is influenced by L-dopa (Brefel-Courbon et al., 2005). To date, no studies have investigated L-dopa chemo-or mechano-sensation.

To date, only one speech treatment for PD has received Level 1 clinical evidence for efficacy and that is LSVT, first described by Ramig et al (1995). Subsequently, El Sharkawi et al., (2002) reported that the benefits extend beyond speech improvement when a small number of individuals with PD also demonstrated improvements in swallowing function. It is unknown if LSVT would specifically improve airway protection mechanisms; but this would not be surprising, since the aim of LSVT is primarily to improve respiratory and glottic closure function, both of which are central to airway protection.

2.5 Hypotheses

The primary aim of this current research is to investigate motor and sensory aspects of airway protection and document changes due to ageing and PD. This research is important in light of prior research documenting changes in various aspects of airway protection due to ageing and disease. Promising, non-invasive methods of evaluating airway protection are now available to clinicians. Many of these may be useful and practical in a clinical setting, including FEES, FEESST, spirometry, and timed test of swallowing. However, there is limited data describing the applicability of these techniques to evaluate motor and sensory aspects of airway protection compromise that may accompany ageing, and even less in PD. This research uses these tools with the expectation that these will be able to identify distinctive changes and differences in airway protection in young adults, elders and those with PD.

Hypotheses of the present project are presented in this section. This is followed by a detailed description of the methods and procedure used in the present study (Part II, Chapter 3). Mechanisms that are thought to safeguard the airway are presented in Part III (Chapters 4 to 9). Each chapter in Part III contains a brief foundation review of the literature, methods and data preparation that are unique to the research question under investigation, results, discussion and conclusions. A total of 6 self-contained chapters are written for Part III. Assessments of the motor components are first presented (Chapters 4 to 6), followed by sensory aspects (Chapters 7 and 8). Chapter 9 investigated the impact of a swallowing disorder on quality of life.

Part IV contains 2 chapters; both investigating the results of therapy in PD. As in Part III, each are also self-contained chapters. Chapter 10 documents the changes in airway protection with pharmaco-therapy in 10 participants. Chapter 11 details the effect of LSVT in 5 patients. Finally, Part V contains a concluding chapter (Chapter 12), in which information from Parts III and IV are integrated. This final chapter also provides a discussion of key findings, strengths and critique of the present research and future clinical and research applications.

2.5.1 Hypotheses for part III: Airway Protection Mechanisms in Ageing and Parkinson's Disease

Chapter 4: Hypotheses for Breathing-Swallowing Coordination in Ageing and Parkinson's Disease

Hypotheses:

1. There will be significant differences in BSC between young adult and healthy elders. Young adults will demonstrate a higher percentage of EE patterns when compared to healthy elders. However, both groups will demonstrate significantly higher percentage of EE patterns when compared to all other patterns (IE, EI, and II).
2. There will also be significant differences in BSC between healthy elders and those with PD. Individuals with PD will demonstrate significantly greater proportion of post swallow inspiration (EI and II) swallows compared to age and gender matched healthy elders.
3. Finally, there will be significant differences in BSC between those in the earlier stages of PD (H-Y $\leq$ 2) when compared to those in the later stages of PD (H-Y $\geq$ 2.5). Patients in the later stages will demonstrate significantly greater proportion of post swallow inspiration (EI and II) swallows compared to those in the earlier stages.

Study design:

BSC of 16 young adults, 16 healthy elders who were age and gender-matched to 16 individuals with PD were recorded during ingestion of 10 small cupfuls (self-ingestion) containing 10mL of water at room temperature. Submental sEMG were also recorded to assist in identifying swallows. Recordings were also obtained from 16 individuals with PD in the earlier stages (H-Y $\leq$ 2) and 16 individuals with PD in the later stages (H-Y $\geq$ 2.5). Recordings were made within 1/2 hour of their last medication dose for patient participants.

Justification and Implication:

Evidence for the influence of ageing on BSC suggests that healthy adults across the lifespan demonstrate robust BSC patterns with EE being the most common pattern (75%), followed by IE, EI and finally II (3%) (Martin-Harris et al., 2005). However, no research has investigated BSC in PD, although those with other neurological disorders such as stroke are known to demonstrate aberrant BSC patterns, i.e. post swallow inspiration. Given that motor incoordination is a feature of PD, BSC in these patients may be affected, and to a greater level with disease progression.

BSC is vital in the protection of airway as post swallow inspiration increases aspiration risks. BSC data in PD from thus study will be useful as comparison to similar studies in the future. Recordings may also show that aberrant BSC may account for aspiration in these patients.

Chapter 5: Hypotheses for Swallowing Efficiency in Ageing and Parkinson's Disease

Hypotheses for Swallowing Efficiency:

1. There will be significant differences in swallowing efficiency measures (number of swallows, time taken, average volume/swallow, average time/swallow and swallowing capacity) between young adult and healthy elders. Young adults will demonstrate greater swallowing efficiency when compared to healthy elders.
2. There will also be significant differences in swallowing efficiency measures (number of swallows, time taken, average volume/swallow, average time/swallow and swallowing capacity) between healthy elders and those with PD. Healthy elders will demonstrate greater swallowing efficiency when compared to patients.
3. Finally, there will be significant differences in swallowing efficiency measures (number of swallows, time taken, average volume/swallow, average time/swallow and swallowing capacity) between those in the earlier stages of PD (H-Y $\leq$ 2) when compared to those in the later stages of PD (H-Y $\geq$ 2.5). Patients in the earlier stages will demonstrate significantly greater swallowing efficiency compared to those in the later stages.

Hypotheses for Floor of Mouth Muscle Contraction:

1. There will be a significant difference in submental sEMG peak amplitude between young adults and healthy elders. Young adults will demonstrate higher peak amplitudes when compared to healthy elders.
2. There will also be a significant difference in submental sEMG peak amplitude between healthy elders and those with PD. Healthy elders will demonstrate higher peak amplitudes when compared to patients.
3. Finally, there will be a significant difference in submental sEMG peak amplitude between those in the earlier stages of PD (H-Y $\leq$ 2) when compared to those in the later stages of PD (H-Y $\geq$ 2.5). Patients in the earlier stages will demonstrate higher peak amplitudes compared to those in the later stages.

Hypotheses for Swallowing Biomechanics:

1. There will be a significant difference in swallowing function between young adults and healthy elders during FEES. Young adults will demonstrate less symptoms of a swallowing disorder compared to healthy elders.

2. There will also be a significant difference in swallowing function between healthy elders and those with PD. Healthy elders will demonstrate less symptoms of a swallowing disorder compared to patients.
3. Finally, there will be a significant difference swallowing function between those in the earlier stages of PD (H-Y $\leq$ 2) when compared to those in the later stages of PD (H-Y $\geq$ 2.5). Patients in the earlier stages will demonstrate less symptoms of a swallowing disorder compared to those in the later stages.

Study design:

Procedures followed that outlined in Hughes & Wiles (1996b) for the timed test of swallowing. Participants self ingested 150 mls of water after given the instruction to "drink as quickly as is comfortably possible". Submental sEMG were also recorded to assist in identifying swallows while the peak submental sEMG amplitude during swallowing reflected relative hyolaryngeal hyoid movement. Participants also underwent FEES where liquid and food were administered in the following order: 3 trials each of thin and nectar-thick liquid (both 10ml), pudding (10ml), a piece of shortbread biscuit and 90ml water test (straw).

For all 3 assessments of swallowing efficiency, there were 16 young adults, 16 healthy elders who were age and gender-matched to 16 individuals with PD. Recordings were also obtained from 16 individuals with PD in the earlier stages (H-Y < 2) and 16 individuals with PD in the later stages (H-Y > 2.5). Recordings were made within 1/2 hour of their last dose of medication for patient participants.

Justification and implication:

It would be useful to obtain normative data for those with PD since biomechanics of swallowing in these patients are known to be affected. The timed test of swallowing may be useful as a screening test for the biomechanics of swallowing at the bedside. It has been validated on adults up to age 90+ and also in 30 patients with motor neurone disease. However it has not been used in PD. This study will add to the knowledge of swallowing efficiency for studies using the timed test of swallowing in patient populations.

FEES has also provided clinicians a more objective way of assessing swallowing efficiency by providing direct visualisation of the laryngopharynx. It would be important to correlate results from the timed test of swallowing with a more objective evaluation as this would further validate the usefulness of the timed test of swallowing as an adjunct to bedside swallowing assessment.

Chapter 6: Hypotheses for Pulmonary Function in swallowing in Ageing and Parkinson's Disease

Hypotheses:

1. There will be significant differences in lung function values between young adult and healthy elders when measured using spirometry. Young adults will demonstrate significantly higher values for Forced Vital Capacity (FVC), Forced Expiratory Volume 1 sec (FEV1), FEV1/FVC, Peak Expiratory Flow (PEF), Forced Inspiratory Vital Capacity (FIVC) and Peak Inspiratory Flow (PIF) when compared to healthy elders.
2. There will be significant differences in lung function values between elders and patients with PD when measured using spirometry. Healthy will demonstrate higher values for Forced Vital Capacity (FVC), Forced Expiratory Volume 1 sec (FEV1), FEV1/FVC, Peak Expiratory Flow (PEF), Forced Inspiratory Vital Capacity (FIVC) and Peak Inspiratory Flow (PIF) when compared to patients with PD.
3. Finally, there will be significant differences in lung function values between those in the earlier stages of PD (H-Y $\leq$ 2) when compared to those in the later stages of PD (H-Y $\geq$ 2.5). Patients in the earlier stages will demonstrate significantly higher values for Forced Vital Capacity (FVC), Forced Expiratory Volume 1 sec (FEV1), FEV1/FVC, Peak Expiratory Flow (PEF), Forced Inspiratory Vital Capacity (FIVC), and Peak Inspiratory Flow (PIF) compared to those in the later stages.

Study design:

Standard closed-loop spirometry was conducted on 16 young adults, 16 healthy elders who were age and gender-matched to 16 individuals with PD. Recordings were also obtained from 16 individuals with PD in the earlier stages (H-Y $\leq$ 2) and 16 individuals with PD in the later stages (H-Y $\geq$ 2.5). All PD participants were tested within 1/2 hour of their last dose of medication and spirometry procedure met standards and guidelines by the American Thoracic Society (ATS).

Justification and Implication:

Most research efforts to date have focused on BSC with emphasis on the need for turn-taking between breathing and swallowing. Equally important consideration must be given to a more integrated paradigm whereby the respiratory system actively participates in swallowing. The value of spirometry as an adjunct for determining whether airway obstruction and/or restriction compromises airway protection has not been explored. Furthermore, the consequence and influence of obstruction and/or restriction in the airways over airway protection is not fully known, although swallowing at low lung pressures or points in the respiratory cycle are low are thought to compromise airway protection (Selley et al., 1989b).

An FEV1 loss of about 20 to 30 ml/year after the age of 21 in non-smokers is considered normal (Crapo, 1994). In addition to determining lung function, correlations between spirometric values may be made to other biomechanical measurements such as timed test of swallowing and swallowing assessment using FEES, with the expectation that there will be a positive correlation between lung function and swallowing efficiency.

Chapter 7: Hypotheses for Cough Reflex and Chemo-sensitivity in Ageing and Parkinson's Disease

Hypotheses:

1. There will be significant differences in laryngopharyngeal chemo-sensitivity between young adult and healthy elders who undergo citric acid inhalation cough challenge. Young adults will demonstrate significantly higher chemo-sensitivity when compared to healthy elders.
2. There will also be significant differences in laryngopharyngeal chemo-sensitivity between elders and patients with PD who undergo citric acid inhalation cough challenge. Healthy elders will demonstrate significantly higher chemo-sensitivity when compared to patients with PD.
3. Finally, there will be significant differences in laryngopharyngeal chemo-sensitivity between those in the earlier stages of PD (H-Y $\leq$ 2) when compared to those in the later stages of PD (H-Y $\geq$ 2.5) who undergo citric acid inhalation cough challenge. Patients in the earlier stages will demonstrate significantly higher chemo-sensitivity when compared to those in the later stages.

Study design:

Single-breath, dose response inhalation cough challenge using 12 incremental doses of citric acid and 3 randomly interspersed placebo was conducted in 16 young adults, 16 healthy elders who were age and gender-matched to 16 individuals with PD. Cough thresholds were also obtained from 16 individuals with PD in the earlier stages (H-Y < 2) and 16 individuals with PD in the later stages (H-Y >2.5). Recordings were made within 1/2 hour of their last dose of medication for patient participants.

Justification and Implication

Coughing may be the single-most effective way of clearing the upper airways of mucus and other foreign particles including food and fluids. The absence of cough upon aspiration is important in the pathogenesis of aspiration pneumonia in older persons and in those with dysphagia. There is some evidence to suggest that chemo-sensitivity of the mucosa decreases with age (Newnham & Hamilton, 1997; Pontoppidan & Beecher, 1960). The literature is

equivocal regarding changes in laryngopharyngeal chemo-sensitivity in the neurogenic population, although delayed recovery of the cough reflex has been postulated to increase morbidity and mortality in stroke patients (Addington et al., 1999a; Smith & Wiles, 1998) but little is known about what happens in degenerative diseases such as PD when 'recovery' is not possible. It has not been established whether desensitisation of the laryngopharyngeal mucosa or compensation with heightened sensitivity occurs. In light of Smith & Wiles' study, (1998) that documented *increased* sensitivity in a group of patients with neurogenic dysphagia, a study investigating changes in laryngopharyngeal sensitivity in PD is justified. If there is indeed a loss of sensation, identification of early laryngopharyngeal sensory loss would be useful as treatment and/or rehabilitation may be recommended earlier.

Chapter 8: Hypotheses for Laryngeal Adductor Reflex and Mechano-sensitivity in Ageing and Parkinson's Disease

Study design:

The tip of the nasendoscope is used to provide a light touch to bilateral base of tongue (BOT), posterior pharyngeal wall (PPW) and aryepiglottic folds (AEF) in 16 young adults, 16 healthy elders who were age and gender-matched to 16 individuals with PD. Mechano-sensitivity testing was also carried out on 16 individuals with PD in the earlier stages (H-Y $\leq$ 2) and 16 individuals with PD in the later stages (H-Y $\geq$ 2.5). Recordings were made within an hour of the 'on' phase for patient participants

Hypotheses:

1. There will be significant differences in laryngopharyngeal mechano-sensitivity between young adults and healthy elders who undergo mechano-sensory testing. Young adults will demonstrate significantly higher mechano-sensitivity when compared to healthy elders.
2. There will also be significant differences in laryngopharyngeal mechano-sensitivity between elders and patients with PD who undergo mechano-sensory testing. Healthy elders will demonstrate significantly higher mechano-sensitivity when compared to patients with PD.
3. Finally, there will be significant differences in laryngopharyngeal mechano-sensitivity between those in the earlier stages of PD (H-Y $\leq$ 2) when compared to those in the later stages of PD (H-Y $\geq$ 2.5) who undergo mechano-sensory testing. Patients in the earlier stages will demonstrate significantly higher mechano-sensitivity when compared to those in the later stages.

Justification and Implication:

Brainstem-driven LAR in response to mechanical stimulation to the supraglottic areas subserved by the SLN is a reliable indicator of laryngopharyngeal mechano-sensation. This maybe qualitatively tested using FEESST (Aviv et al., 1994) but in the absence of this equipment, qualitative sensory testing may still be completed (Langmore & Aviv, 2001).

The loss of mechano-sensation in neurological disorders may be one of the reasons for the high incidence of silent aspiration. Mechano-sensation decreases with age and in strokes (Aviv, 1997a; Shaker et al., 2003). Despite the high incidence of silent aspiration in PD, evidence for the loss of laryngopharyngeal sensation in this patient group is lacking as no research has been done to specifically assess this in PD. Establishing whether patients with PD also experience loss of mechano-sensation and whether LAR is a robust reflex would allow clinicians to implement timely intervention.

Chapter 9: Hypotheses for Swallowing and Quality of Life (SWAL-QOL) in Ageing and Parkinson's Disease

Hypotheses:

1. There will be no significant difference in SWAL-QOL scores between young adults and healthy elders.
2. There will be a significant difference in SWAL-QOL scores between elders and patients with PD. Healthy elders will demonstrate significantly higher SWAL-QOL scores when compared to patients with PD.
3. There will also be a significant difference in SWAL-QOL scores between those in the earlier stages of PD (H-Y $\leq$ 2) when compared to those in the later stages of PD (H-Y $\geq$ 2.5). Patients in the earlier stages will demonstrate significantly SWAL-QOL scores when compared to those in the later stages.

Study design:

All participants completed the SWAL-QOL questionnaire prior to the commencement of data collection.

Justification and Implication:

The literature reports that elders and individuals with PD with dysphagia have decreased quality of life, and even more so as the disease progresses (de Luis et al., 2006; Hobson, Edwards, & Meara, 2001). In these patients, social isolation, anxiety (Miller et al., 2006b) and depression (Playfer, 1999) associated with mealtimes are commonly reported. Even though

QOL may be reduced in elders with dysphagia, there is insufficient evidence that QOL decreases in healthy elders without dysphagia.

Assessing QOL in patients with dysphagia is importance as those who require diet modifications may accept or reject foods based on its visual appearance (Huckabee & Pelletier, 1999b). Conceivably, limited and/or unappealing food textures may ultimately affect eating desire. As dysphagia is also known to detrimentally affect nutritional status and dietary intake in patients (de Luis et al., 2006; Lorefalt et al., 2006), reduced desire to eat would only exacerbate this problem and would require attention of healthcare professionals involved in the patient's care.

2.5.2 Hypotheses for part IV: Effects of Therapy on Airway Protection in Parkinson's Disease

Chapter 10: Hypotheses for the Effects of Pharmacotherapy on Airway Protection Mechanisms in Parkinson's Disease

Hypotheses:

There will be a significant difference in airway protection mechanisms 'on' and 'off' levodopa. Specifically, BSC, pulmonary function measures, swallowing efficiency and laryngopharyngeal chemo- and mechano-sensation are expected to improve with medication, as will quality of life.

Study design:

10 patients with idiopathic PD were assessed on motor and sensory aspects of airway protection on 2 sessions, spaced at least one week apart. Counterbalancing was done by randomly allocating 5 patients who underwent first session 'on' and second session 'off' and another 5 who underwent first session 'off' and second session 'on'.

Justification and Implication:

Prior research reported that levodopa improves motor function by providing relief from symptoms such as tremor, rigidity and bradykinesia but the efficacy of levodopa for motor and sensory aspects of airway protection has not been fully explored. If pharmacotherapy improves airway protection in PD in addition to motor function, there will justification for patients to undergo swallowing rehabilitation and to time mealtimes with the 'on' phase of medication. Further research needs to address the issue of how much improvement is expected with medication.

Chapter 11: Hypotheses for the effects of Lee Silverman Voice Treatment on Airway Protection Mechanisms in Parkinson's Disease

Hypotheses:

There will be a significant difference in airway protection mechanisms pre- and post LSVT treatment. Specifically, BSC, pulmonary function measures, swallowing efficiency and laryngopharyngeal chemo- and mechano-sensation are expected to improve with after LSVT, as will quality of life.

Study design:

Five participants who were also part of the original study (Part II) underwent LSVT. These patients were assessed on motor and sensory airway protection mechanisms less then a month before commencing therapy and reassessed up to a year post therapy. As the numbers that were recruited for this arm of the study is small, data are mostly presented as a descriptive study.

Justification and Implication:

In 2002, El Sharkawi et al. documented improvements in swallowing function in a small number of patients following LSVT. As the focus of LSVT is on achieving and maintaining a loud voice with increased respiratory effort, increased glottic closure and improved lung function is anticipated. Improvements in both functions would serve to improve airway protection.

If LSVT improves airway protection, it may be considered a treatment option, especially for patients with reduced maximal capacities tested using spirometry. In addition, patients who exhibit poor vocal closure and/or vocal bowing severe enough to compromise airway protection may also benefit from LSVT. It would be important to document changes in airway protection following treatment.

PART II: METHODS

Chapter 3. Methods

3.1 Participants

Following approval from the regional Health Ethics Committee, a total of 68 participants were recruited to the study. Thirty six participants with the diagnosis of Idiopathic Parkinson's Disease (mean age 68.5, range 45.8 - 82.5) were recruited by advertisement from a movement disorders clinic. No patient participant had a history of other neurological or movement disorders (e.g. stroke, progressive supranuclear palsy, Huntington's disease). Medications prescribed for PD were stable, without changes to the regime at least a month prior to participation in the study.

In addition to patient participants, 16 healthy young adults (8 males, mean age 25.1, range 21.3 - 32.4) and 16 healthy elders (8 males, mean age 72.8, range 61.5 – 84.7) were recruited by advertisement. No healthy participant had a history of neurological impairment (e.g. stroke, Parkinson's disease, dementia) or swallowing impairment.

For all participant groups, individuals were excluded for a history of pulmonary disorder (e.g. asthma, chronic obstructive pulmonary disease), head and/or neck injury or surgery. Potential participants on antitussive medication for coughs, colds and hay fever allergies were excluded, as were participants who had current upper/lower respiratory tract infection. Participants with a history of smoking had ceased smoking at least 5 years prior to participating in this study.

3.2 Materials

3.2.1 Mini Mental State Examination (MMSE)

Also known as Folstein's test, the MMSE is a brief, 30 point test used to assess cognitive function. The test takes approximately 10 minutes to administer and samples a variety of functions including orientation and memory. A maximum of 30 points is possible, with scores above 24 considered within normal limits. Scores below 24 points are closely correlated with the presence of dementia. Additional normative values for the MMSE have also been corrected for age and years of schooling as these were found to be inversely related to MMSE

score. Further, allowances have been made for physical disability, e.g. tremor, that may affect performance (Crum, Anthony, Bassett, & Folstein, 1993).

3.2.2 Hoehn-Yhar Scale (H-Y scale)

Hoehn-Yahr first documented the progression of PD in 1967 and the scale used then is still widely used today as a simple tool to stage the progression of the disease (Hoehn & Yahr, 1967). Adapted from the original, the 5 point rating tool scale is as follows:

Stage 1

- Signs and symptoms on one side only
- Symptoms mild
- Symptoms inconvenient but not disabling
- Usually presents with tremor of one limb
- Friends have noticed changes in posture, locomotion and facial expression

Stage 2

- Symptoms are bilateral
- Minimal disability
- Posture and gait affected

Stage 3

- Significant slowing of body movements
- Early impairment of equilibrium on walking or standing
- Generalized dysfunction that is moderately severe

Stage 4

- Severe symptoms
- Can still walk to a limited extent
- Rigidity and bradykinesia
- No longer able to live alone
- Tremor may be less than earlier stages

Stage 5

- Cachectic stage
- Invalidism complete
- Cannot stand or walk
- Requires constant nursing care

3.2.3 Unified Parkinson's Disease Rating Scale (UPDRS)

The UPDRS is the most widely used scale to follow the longitudinal course of PD. The UPDRS is frequently used to supplant the H-Y scale to give a comprehensive assessment of disease progression and severity. Published in 2003, the Movement Disorder Society Task Force for Rating Scales for Parkinson's Disease prepared a critique of the scale. While weaknesses of the UPDRS include some ambiguities of the written text, the absence of important screening questions on non-motor aspects of PD and inadequate instructions for raters, it remains favoured and widely used for its comprehensive coverage of motor symptoms, its reliability and validity (Siderowf et al., 2002). UPDRS scores were found to have excellent test-retest reliability in a sample of 400 patients with early PD rated by academic movement disorder specialists.

For this study, sections II (activities of daily living) and III (motor examination) of the UPDRS was administered for all patient participants.

3.2.4 Swallowing Quality of Life (SWAL-QOL) questionnaire

This questionnaire was developed over a few years but finally published as a tool for measuring the impact of dysphagia on quality of life (McHorney et al., 2000a; McHorney et al., 2000b; McHorney et al., 2002). The SWAL-QOL contains 44 items and assesses 10 quality if life concepts (Appendix C). The SWAL-QOL was validated on 398 patients and showed excellent internal-consistency reliability and short-term reproducibility (McHorney et al., 2002). This questionnaire was administered to all participants

3.2.5 Submental Surface Electromyography (sEMG)

Submental surface electromyography (sEMG) was used to measure submental muscle (mylohyoid, geniohyoid and the anterior belly of the digastric activity) associated with a swallowing event (Palmer, Luschei, Jaffe, & McCulloch, 1999). The skin was first cleaned using alcohol swabs. All men were required to share prior to data collection. Triode patch electrodes (Thought Technology Triode™) was placed at midline on the under surface of the chin and overlying the submental muscles (Figure 3.1).

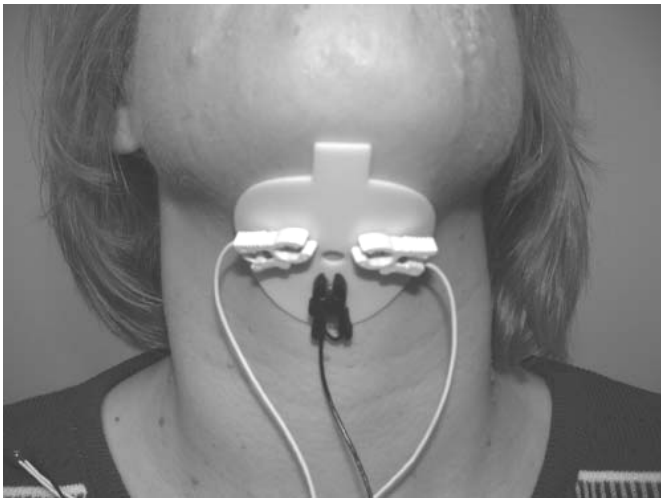


Figure 3.1 Anterior view of electrode placement on anterior neck. Center point on the electrode patch was placed in the midline neck slightly inferior to the hyoid bone. Recording electrodes were oriented toward the chin (white leads). The ground electrode (black lead) was oriented toward the larynx. From Crary, M. A., Carnaby Mann, G. D., & Groher, M. E. (2006). Biomechanical correlates of surface electromyography signals obtained during swallowing by healthy adults. *Journal of Speech, Language, and Hearing Research, 49*(1), 189.

Each patch contained 2 recording electrodes and 1 ground electrode in a triangle configuration and a thin layer of electrolyte conductivity gel (Pharmceutical Innovations, Inc. Newark, NJ) was applied to the electrodes to assure good electrode to skin conductance. The sEMG electrode cable was attached to the single channel sEMG component of the Kay Swallowing Signals Lab which interfaced with the Digital Swallowing Workstation (DSW) Model 7200 (Kay Elemetrics Corp. Lincoln Park, NJ). The raw signal was amplified, bandpass filtered (50–220 Hz), lowpass filtered at 3Hz and digitised at a sampling rate of 250 Hz. The electrodes remained in situ during data collection for the entire duration of the study. The electrode cable was attached to the single channel sEMG component of the Digital Swallowing Workstation (DSW) Model 7200 (Kay Elemetrics Corp. Lincoln Park, NJ.

3.2.6 Nasal Cannula

A 7ft, adult-sized nasal cannula was used to measure the direction of nasal airflow. Nasal prongs placed at the entrance of each nostril monitored the respiratory phase cycle in which a swallowing event occurred and also to determine the duration of swallowing apnoea. The distal end of the nasal cannula was attached to the nasal component of the DSW. Nasal

airflow was calibrated as per requirement of the workstation system prior to data collection. The signal was sampled at 250 Hz.

Simultaneous time-locked recordings for the nasal airflow and sEMG determined the breathing-swallowing coordination and respiratory phase cycle during swallowing for all participants.

3.2.7 Spirometer

A Sensormedic Vmax dry rolling seal spirometer (SensorMedic Corp. Yorba Linda, CA) was used to obtain participant's lung volume and flow rates. ATS standards were met for during spirometry (Miller et al., 2005b). The accuracy of the spirometer was assured with the graduated 3 litre calibration syringe (ATS, 1987).

3.2.8 Nebuliser

The PulmoMate Compressor/Nebuliser by deVilbiss (model 4650I) with a predetermined flow output of 8 litres per minute was used to deliver different concentrations of citric acid in the inhalation cough challenge (Figure 3.2). Citric acid was the choice tussigenic agent as it has been used for over 60 years (Bickerman & Barach, 1954), readily available and known to have good reproducibility over test sessions (Morice et al., 2001).

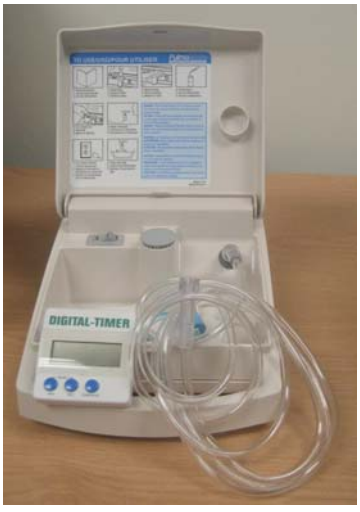


Figure 3.2 De Vilbiss nebuliser (model 4650 I)

3.2.9 Fibreoptic Endoscopic Evaluation of Swallow (FEES)

Nasendoscopy was used to provide an objective evaluation of swallowing function and a subjective evaluation of pharyngeal sensitivity (Langmore, 2001a). A 3.5mm Welch Allyn® RL-150™ nasendoscope connected to the DSW captured and stored entire swallowing evaluations for off-line analyses. Simultaneous images of Fibreoptic Endoscopic Evaluation of Swallowing (FEES) time-locked to sEMG enabled the distinction between actual swallowing of bolus (white out and sEMG peak) and submental muscle movement without swallowing (sEMG peak without/with poor white out).

3.3 Study Protocol and Procedure

Participants were invited to come to a swallowing research laboratory for a single visit assessment session of airway protection mechanisms (Appendix D). As patient participants were assessed during the 'On' phase of their medication, the studies were scheduled round the time of their best performance; generally within 1/2 hour of their last dose of medication.

Prior to the scheduled assessment, participants were sent the SWAL-QOL (McHorney et al., 2002). Participants brought the completed questionnaire with them on the day of the study. After providing written consent, (Appendix F), the completed questionnaire was collected from the participant.

All participants were then administered the Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), administered by the primary investigator (LP). Those with a score of < 24 were excluded from further participation in the study. Parts II and III of the Unified Parkinson's Disease Rating Scale (UPDRS) were used to assess motor and daily living functions in patient participants prior to the study. Patient participants were subsequently staged using the Hoehn-Yahr Scale (Hoehn & Yahr, 1967).

Upon completion of the SWAL-QOL, MMSE and UPDRS, all participants underwent evaluation of airway protection mechanisms in the order presented below. Each participant took approximately 1½ -2 hours to complete all assessments. All but 2 participants were able to complete the tests in one session. Two participants reported a wearing off effect of their medication and were rescheduled to complete the assessments within 3 days.

3.3.1 Breathing-Swallowing Coordination during Timed Test of Swallowing

Participants were comfortably seated on a chair facing away from the swallowing workstation computer monitor, preventing any form of visual feedback. After the skin was cleansed using alcohol swab, sEMG electrodes were placed in midline and longitudinally underneath the chin and overlying the collective anterior suprahyoid muscles. A nasal cannula was carefully secured at the entrance of each nostril. Participants were asked to perform two saliva swallows as practice. Following that, participants were handed a small cup with 8ml of tap water and instructed to 'drink as you (they) normally would'. Participants were able to self administer the water with little help required. Inspiration and expiration immediately preceding and following 10 swallows of 8ml were recorded. Participants then underwent the timed test of swallowing by Hughes and Wiles, (1996) with continued recording of sEMG and nasal airflow. When ready, they were asked to cup drink 150ml of plain tap water 'as quickly as is comfortably possible'.

3.3.2 Pulmonary Function Testing

Pulmonary function testing using standard closed-loop spirometry was performed to standards set out by the American Thoracic Society (Crapo et al., 1981; Gardner & Hankinson, 1988). Participants were seated comfortably in front of the spirometer with a nose clip placed to inhibit nasal respiration. With the participant's mouth forming a seal over the mouthpiece, they were instructed to forcefully inspire to full inhalation and immediately, forcefully exhale for at least six seconds before being instructed to perform a second full inhalation to close the respiratory loop. Participants were coached during the manoeuvre to increase compliance to the task. In keeping with ATS criteria, this manoeuvre was repeated so that at least three comparable results were obtained. Participants performed the manoeuvre no more than 8 times in a session.

3.3.3 Swallowing Evaluation with Qualitative Sensory Testing

After lubricating the endoscope with K-Y Jelly® the endoscope was inserted into the patient's nostril, with the choice of nostril left to the participant. Two qualified Speech-Language Therapists were present in the room for endoscopy, with the primary investigator performing the procedure. FEES was carried out according to recommendations by Langmore (2001). As far as possible, the endoscope followed the inferior turbinate of the nasal cavity. Once the posterior pharyngeal wall was in view, with the scope still in the nasal cavity, participants

were asked to phonate the syllables ‘duh-nuh’ several times and to perform a saliva swallow to assess velar elevation. They were instructed to breathe through the nose whilst the endoscope was advanced into the hypopharynx.

Most laryngeal structures are visible with the scope just above the epiglottis, (Figure 3.3). Participants were instructed to perform a cough, a swallow and to vocalise /i:/ for 2-3 seconds as an assessment of voluntary vocal fold adduction. The integrity of vocal folds was further made with observation for any signs vocal fold bowing during adduction as individuals with PD do exhibit vocal fold bowing (Blumin et al., 2004). Assessment of swallowing function was completed with the participants self-administering, in the following order: 3 trials of 8mls thin fluids and 3 trials of 8mls nectar-thick fluid (kiwifruit juice) from a small cup, 3 trials of 8mls chocolate pudding on a spoon and a shortbread biscuit. A few drops of blue food colouring were added to the fluids to provide contrast. Further, the Burke’s 3oz (90mls) water swallow test (DePippo, Holas, & Reding, 1992, 1994) was administered with participants self-ingesting 3oz of water through a straw.

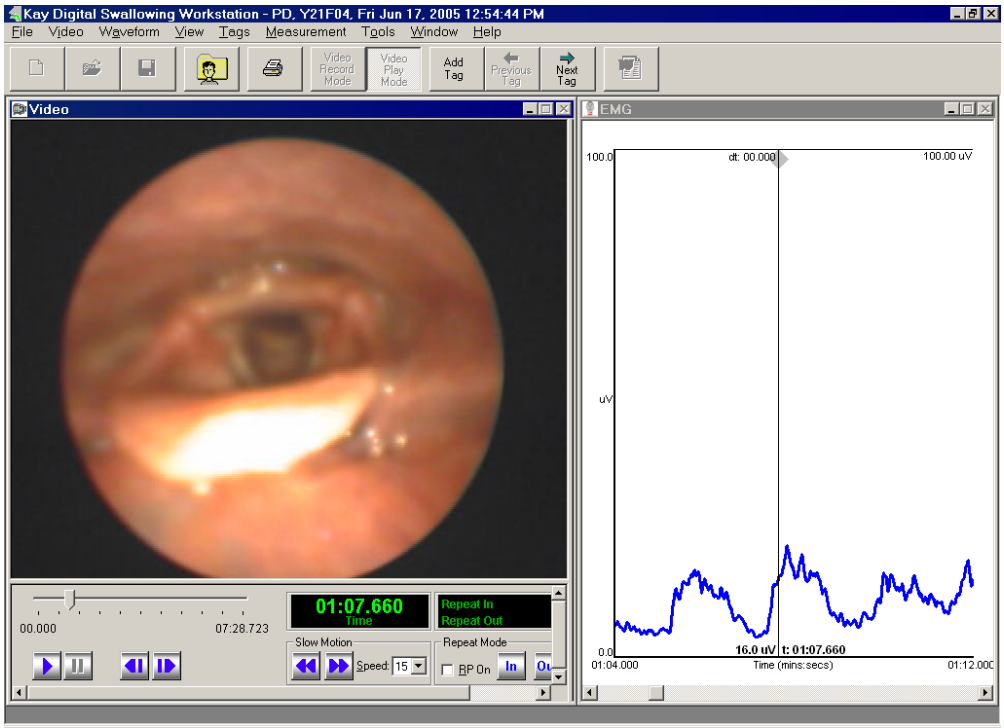


Figure 3.3 The position of nasendoscope during FEES (left window). Right window shows online recording of sEMG.

In addition to online tagging of each swallowing event, sEMG recordings and the swallowing videos were time-locked to enable precise identification of swallowing during off-line analyses.

Qualitative sensitivity testing of the pharynx was completed using a protocol described by Langmore and colleagues (Langmore & McCulloch, 1996; Langmore et al., 1988). Using this method, the tip of the endoscope was used to provide light touch on the left and right side of the base of tongue, posterior pharyngeal wall and aryepiglottic fold. In a subgroup of 10 participants with PD, sensory testing was conducted using the FEESST® procedure. FEESST® a quantitative assessment with the delivery of discrete air pulses at a set duration. Both qualitative and quantitative assessments of laryngopharyngeal mechano-sensitivity procedure allowed for assessment of the LAR, a brief, brainstem mediated adduction of the vocal folds (Aviv et al., 2000). Other responses such as facial grimacing, participant feedback, cough and/or swallow are also taken to be positive responses for pharyngeal sensitivity (Langmore, 2001a).

3.3.4 Inhalation Cough Challenge

Inhalation cough challenge was completed using a method similar to that described by Morice et al., (2001). In that study, citric acid was diluted in 0.9% sodium chloride to obtain ½ log concentrations of citric acid ranging from 1mM to 1M. This translated to concentrations of 1mM, 3mM, 10mM, 30mM, 100mM, 300mM and, 1M. A small pilot study on 6 healthy participants prior to conducting this study showed that no participants coughed at 1 or 3mM. In order to obtain concentrations that were more evenly spaced and that would eliminate floor or ceiling effects without unnecessarily extending the testing time, citric acid was diluted in 0.9% sodium chloride to obtain concentrations of 10mM, 30mM, 100mM (½ log), 177.83mM, 316.23mM, 562.34mM (¼ log), 1M, 1.2M, 1.4M, 1.6M, 1.8M and 2M (linear).

Participants were told that they were participating in a cough challenge, and that the vials contained different concentrations of citric acid. Some of the inhalations may make them cough and some would not. They were initially asked to ‘cough when you (they) feel the need to cough, not to cough if you (they) do not feel the need to cough’. This was to identify the natural cough threshold. The natural cough threshold was identified when participants coughed at least twice within the first 10 seconds in at least two out of the four inhalations (50%) of that dose. When the natural cough threshold was identified, participants were then

told that the test would continue with new instructions. From that time forth, they were asked to ‘try to suppress the cough as much as you (they) can’. The suppressed cough threshold was reached when participants coughed at least twice in at least two out of four inhalations (50%) of that dose.

Delivery of citric acid employed the full exhalation-full inhalation method (Pounsford & Saunders, 1985). With a nose clip in place, participants were instructed to place the mouthpiece of the nebuliser kit into their mouths to form a good seal. When the nebuliser was turned on, they were asked to fully exhale to residual volume then fully inhale to total lung capacity. The DeVilbiss nebuliser had a constant flow rate of 8L/min. Participants were coached on a placebo (0.9% NaCl) dose until proper technique was obtained. Citric acid was administered in incremental concentrations with 3 placebo vials randomly interspersed to increase challenge blindness. Each dose was administered 4 times, with a 30 second interval between each inhalation to prevent tachyphylaxis. The number of coughs in the first 10 seconds after each inhalation was recorded manually. The entire cough challenge study was recorded on an audio-visual system.

3.4 Data Analysis

3.4.1 Breathing-Swallowing Coordination during Timed Test of Swallowing

For the 10 trials of 8ml of water, swallows were identified by observation of the time-locked recordings of sEMG activity paired with a cessation of nasal airflow during swallowing apnoea. Peak sEMG and duration of the pharyngeal swallow was recorded for all 10 swallows (Figure 3.4).

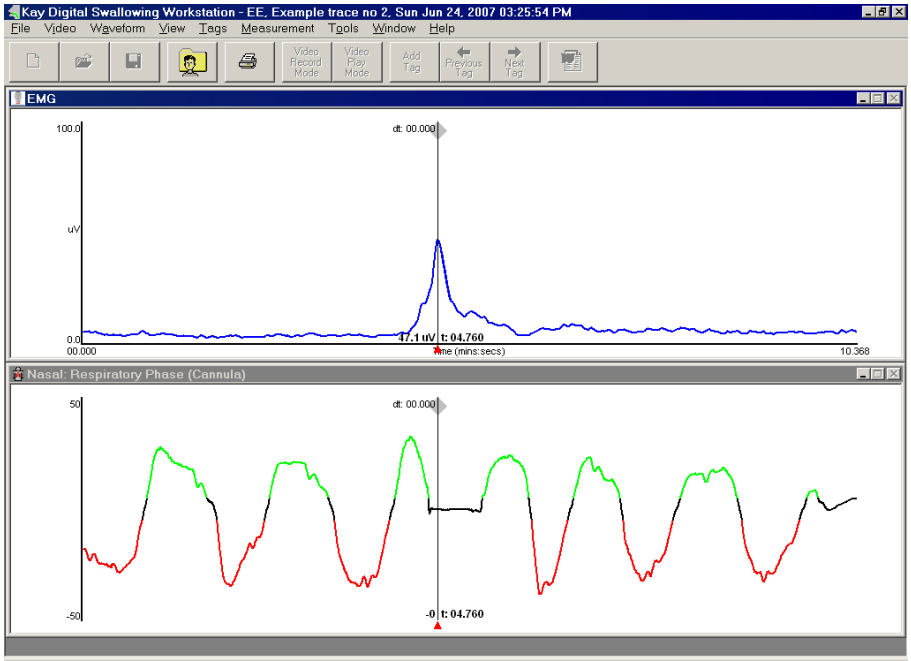


Figure 3.4 Timed-lock recording of sEMG (top window) and directional nasal airflow recordings (bottom window) during swallowing tasks. Black vertical line shows peak sEMG amplitude.

All swallows were also categorised into 1 of 4 respiratory patterns: Expiration-apnoea-Expiration (EE), Expiration-apnoea-Inspiration (EI), Expiration-apnoea-Inspiration (EI) and Inspiration-apnoea-Inspiration (II), (Figures 3.5 a-d). As there were 10 swallows for each participant, the frequency of occurrence in each respiratory pattern was converted into a percentage.

During swallowing a black flat line on the abscissa of the respiratory recording was taken to represent swallowing apnoea. Peak sEMG amplitude within the apnoeic period was considered the maximal submental muscle contraction associated with a swallowing event (Figure 3.5). If participants had two swallows within a single apnoeic period, the second swallow was considered a clearing swallow and excluded from analysis. For each participant, peak sEMG (μv) was recorded and subsequently averaged across all 10 swallows to represent average sEMG amplitude during ingestion of small cupfuls (8mls) of water.

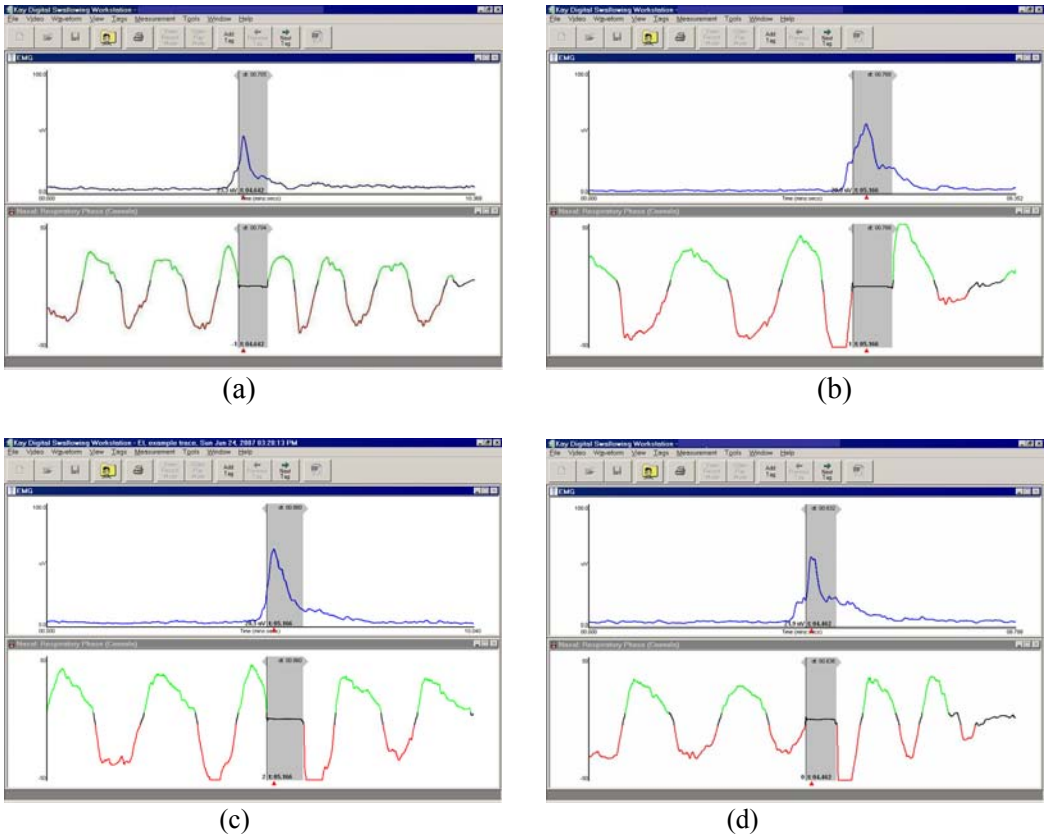


Figure 3.5 Trace examples of 4 possible respiratory patterns during swallowing. Green , upward excursion denotes expiration and red, downward excursion denotes inspiration.
EE respiratory phase category (a), IE respiratory phase category (b), EI respiratory phase category (c) and II respiratory phase category (d). Shaded area represents swallowing apnoea, during which swallowing occurs.

For the timed test of swallow (Hughes & Wiles, 1996b), recording commenced when the water first touched the bottom lip and was completed when the sEMG readings returned to the baseline. The number of swallows we tagged online and time in seconds taken to finish drinking 150 mls of water was recorded. The average volume per swallow (ml/number of swallows), average time per swallow (time taken/number of swallows) and swallowing capacity (ml per second) were calculated.

3.4.2 Pulmonary Function Testing

Following standard close loop spirometry protocols, reports generated by the Vmax software included: Forced Vital Capacity (FVC), Forced Expiratory Volume 1 sec (FEV1), FEV1 over FVC (FEV1/FVC), Peak Expiratory Flow (PEF), Forced Expiratory Time (FET), Forced Inspiratory Vital Capacity (FIVC) and Peak Inspiratory Flow (PIF).

3.4.3 Swallowing Evaluation with Qualitative Sensory Testing

Binary, absent/present decisions were made for all swallows and across all food/fluid consistencies. Pre swallow pooling resulting in the valleculae and/or pyriforms were noted. Pre-swallow pooling was operationally defined as bolus hold, either in the valleculae of pyriforms resulting from premature spillage or delayed pharyngeal swallowing of fluids. Instances of laryngeal penetration and/or aspiration pre-, during, or post swallow were also charted. Observations of coughing or throat clearing were made if aspiration was present. If post swallow residual was observed, it was noted whether participants spontaneously attempted to clear the residual. As there were 3 trials of each fluid consistency, thin, nectar and pudding, the absence/presence of the swallowing behaviour was converted into percentages, where 0 = no occurrence, 33% = present in 1 of 3 swallows, 66% = present in 2 of 3 swallows, 100% = present in 3 of 3 swallows. As expected, patients varied in the number of swallows it took to drink 3 fluid ounces (90ml) of water and to eat a piece of biscuit. Rather than to analyse each swallow for biscuit and 3 ounce water swallow test, an overall decision was made for the swallowing behaviours. 'Yes' was assigned as long as spillage, pooling, laryngeal penetration and/or aspiration was observed, regardless of the number of times it occurred. Thus, only binary yes/no decisions were made for biscuit and 3oz water test.

During sensory testing, the endoscopist (LP) and another Speech-Language Pathologist (MLH) agreed on whether the LAR was present or absent for bilateral base of tongue (BOT), posterior pharyngeal wall (PPW) and aryepiglottc folds (AEF).

3.4.4 Inhalation Cough Challenge

Natural cough was noted when participants coughed at least twice in 50% of the trials after being instructed to cough as needed. Suppressed cough was noted when participants coughed at least twice in 50% of the trials after being instructed to suppress the cough was far as possible. For ease of calculation, numbers 1 to 12 were assigned to 12 of the concentrations administered, where 1 = 10mM, 2 = 30mM, 3 = 100mM, 4 = 178mM, 5 = 316mM 6 = 562mM, 7 = 1M, 8 = 1.2M, 9 = 1.4M, 10 = 1.6M, 11 = 1.6M and 12 = 2M.

3.5 Data Processing, Preparation and Statistical Analysis

The original intent of the study was to obtain data from 48 patient participants. Using an α of 0.05, and power of 80%, 16 participants in each severity groups (early, mid, late) and 16 age

healthy elders controls were required to detect an effect size of ≥ 1.0. In addition 16 young healthy adults were recruited as a further control group to ensure that differences were not due to normal ageing. This would have resulted in a total sample size of 80 research participants. However, due to challenges in recruiting patient participants in the late stages of PD beyond the investigators' control, only a total of 4 patients in the late stage of PD (H-Y stage 4+) participated in this study, reducing the total sample size to 68. Figure 3.6 shows the re-grouping of participants for subsequent analyses.

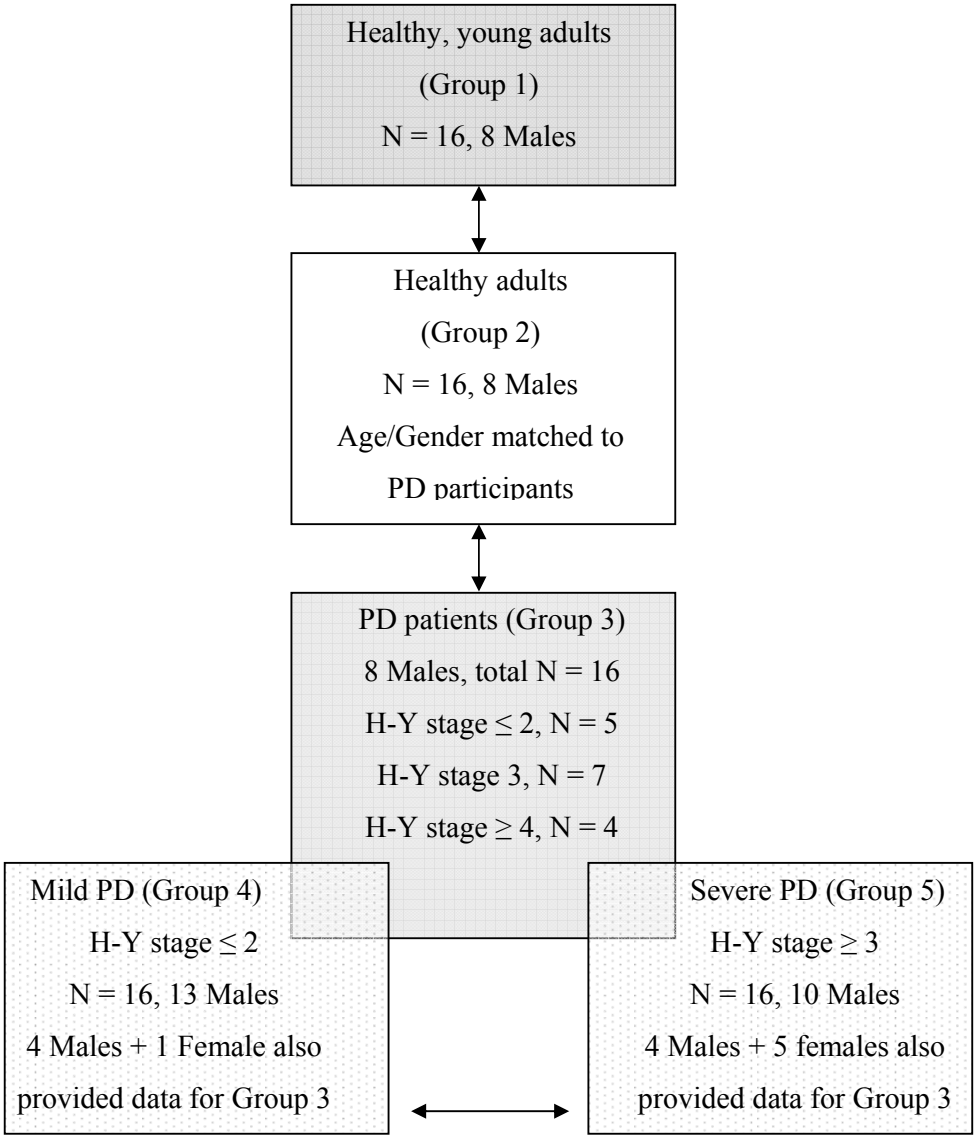


Figure 3.6 Chart showing participant grouping for subsequent statistical analyses. Double-ended arrows denote subsequent statistical analyses between groups. Note no overlaps between participants in Groups 1 to 3 but some overlap of patients in Group 3 with those in Groups 4 and 5.

All statistics were performed using Statistical Package for the Social Sciences (SPSS Release 14). A p-value of < 0.05 was considered to be statistically significant. Levene's test for equality of variance was calculated for all groups in the t-tests. For all comparisons, if Levene's test was significant, i.e. the values for both groups are variable, adjusted p-value and degree of freedom (df) were used. The use of these adjusted values compensated for any inequality of variance in the data set.

Eta squared was used to calculate the effect size in order to provide an indication of the magnitude of the differences between groups. This study adopted guidelines proposed by Cohen (1988) when interpreting eta squared values, where 0.01 = small effect, 0.06 = moderate effect and 0.14 = large effect.

Where results were statistically significant at $p < 0.05$, it was decided *a priori* that no Bonferroni adjustment would be applied to any significant results. It is acknowledged that by setting more stringent p values, Bonferroni adjustments would protect against Type 1 errors of falsely rejecting null hypotheses. As such, Bonferroni adjustments would be needed for studies that have an overall general hypothesis so as to prevent false rejection of the null hypothesis (Perneger, 1998). However, this study investigated a variety of variables that are novel but specific to the PD population, applying Bonferroni adjustments would over-correct any significant differences and nullify possible areas that may warrant further investigation (Perneger, 1998; Rothman, 1990). As such, no Bonferroni adjustments were made to significant findings.

Data preparation, processing and analyses are described in detail in the following chapters.

PART III: AIRWAY PROTECTION MECHANISMS IN AGEING AND PARKINSON'S DISEASE

Chapter 4. Breathing-Swallowing Coordination in Ageing and Parkinson's Disease

4.1 Introduction

The dual role of the pharynx as a conduit for food and respiratory airflow has led to several functional adaptations that serve to protect the airway during swallowing (Preiksaitis & Mills, 1996). Airway protection necessitates a high level of coordination between respiration and swallowing (Klahn & Perlman, 1999), with the act of swallowing interrupting respiration (McCulloch & Daele, 2001). The onset of glottic closure in adults is one if the earliest airway protection mechanism to occur during swallowing (Martin-Harris et al., 2005; Shaker et al., 1990). Airway protection is assured with complete glottic closure during a swallow resulting in a momentary cessation in respiration (Hadjikoutis et al., 2000; Hiss et al., 2001; McFarland & Lund, 1993, 1995; Preiksaitis & Mills, 1996). The initial medialisation of the arytenoids to the epiglottis and subsequent closure of the true vocal folds help to protect the airway (Miller, 2002). Airway protection is further supplemented by the closure of false vocal folds and epiglottic deflection to direct food away from the larynx and into the oesophagus (Hadjikoutis et al., 2000). Swallowing apnoea (SA) is a term reserved for the cessation of respiration during swallowing and may occur as a result of vocal fold closure, and or proximal or lower airway closure (Perlman et al., 2005).

There is evidence to suggest that SA matures post natally (Khater-Boidin et al., 1994) and once developed, remains a robust, centrally integrated biomechanical action (Miller, 1999; Widdicombe, 1986b). Prolonged apnoea may be elicited within pharyngeal and laryngeal regions in animals as young as 3 weeks old (Khater-Boidin et al., 1994; Storey & Johnson, 1975). Further evidence for the robust nature of SA come from human studies where laryngectomised (Hiss et al., 2003) and intubated patients (Nishino & Hiraga, 1991) for whom glottic closure is not possible, continued to demonstrate measurable SA.

In healthy adults, the phase of respiration in which SA occurs is also predictable, with mid expiratory phase of expiration-SA-aspiration (EE) being the most common over 3 other phases: inspiration-SA-expiration (IE) and after expiration-SA-inspiration (EI) and inspiration-SA-inspiration (II) (Hiss et al., 2001; Klahn & Perlman, 1999; Preiksaitis & Mills,

1996). SA in mid-expiration is thought to be a useful mechanism for clearing residue post swallow and preventing subsequent micro-aspiration (Hadjikoutis et al., 2000). Despite this consensus, the precise frequency of SA occurring before, during, and after expiration differs greatly between studies. Hiss et al., (2001) reported more than 62% of swallows during mid expiration, in comparison to (Martin et al., 1994) who reported similar patterns in 94 - 100% of healthy young adults. Differences in the reported rates may be attributed to the size of the boli used and the method of bolus delivery during the assessment. Preiksaitis & Mills, (1996) found that EE respiratory pattern was the preferred pattern with all drinking and eating tasks but this was only for single bolus swallows. Inspiration followed SA in less than 5% of single bolus swallows but increased significantly with a 200 ml drink by cup or straw by 23% and 27% respectively. Post swallow inspiration increased to 16% when eating a sandwich meal.

Direct comparison of studies is difficult due to differences in the way the bolus was administered (self-fed vs. researcher-fed, via syringe, straw or cup), consistency of bolus (thickened, thin liquids, soft diet and solids), the way data was acquired (directional airflow vs. nasal thermistors) and grouped for subsequent analyses. Despite these differences, authors are in agreement that the timing of swallows in relation to respiration is not random, with more than 70% of swallows beginning during the expiratory phase of the respiratory cycle. Most bolus swallows also end with expiration and finally, SA varies between 1-2 seconds regardless of bolus type. The consistency of these observations has led to the conclusion that precise coordination of breathing and swallowing is not only robust, but an important mechanism in preventing aspiration (Broussard & Altschuler, 2000; Hadjikoutis et al., 2000; Mokhlesi et al., 2002).

Hiss et al,, (2001) stated that the goals of SA research are to “establish data so that normal SA can be compared to abnormal swallowing physiology and potential aspiration” (p.129). Although there is sufficient evidence to show that SA may be one swallowing parameter that can be utilised to evaluate airway protection during swallowing (Hadjikoutis et al., 2000; Hiss et al., 2001; Nilsson et al., 1997), there is surprisingly little known about the effects of ageing and disease on breathing-swallowing coordination (BSC). Three studies to date, Hiss et al., (2001), Kelly, Huckabee, & Cooke, (2006) and Martin -Harris et al., (2005) studied the effects of ageing on BSC. While Hiss et al. (2001) were unable to find age differences, Martin -Harris et al. (2005) reported that ageing affected BSC such that non-EE patterns are more prevalent in elders (mean age 68) compared to EE patterns (mean age 56). Kelly et al., (2006) reported significantly less EE swallows in elders (67%) compared to young adults (76.2%)

but no such difference was found for other respiratory phase categories. The literature to date appears equivocal as to whether BSC changes accompany ageing.

Aberrant BSC has been reported in neurological disorders such as stroke, multiple sclerosis, (Selley et al., 1989b), motor neurone disease, and spinal cord damage. Disruption to the dominant pattern of EE swallows giving way to increases in post swallow inspiration may be seen as a possible risk factor for aspiration (Curtis & Langmore, 1997; Hadjikoutis et al., 2000). In those with neurological disorders, between 43% (Selley et al., 1989b) to 91% (Hadjikoutis et al., 2000) demonstrated post swallow inspiration regardless of bolus size. A limited number of studies included patients with different neurological disorders but none have investigated BSC in patients with PD. Given that PD is a movement disorder, with symptoms that affect laryngeal (Blumin et al., 2004; Hanson et al., 1984; Perez et al., 1996; Smith et al., 1995; Stelzig et al., 1999) and respiratory function (Sabate et al., 1996a), it is surprising that no research has looked at the relationship between SA and swallow-respiratory phase relationship in this population. If finely tuned turn-taking between swallowing and respiration is crucial for airway protection, then there is strong justification to investigate BSC in ageing and PD. In this chapter, the effects of BSC in ageing and PD are presented.

4.2 Hypotheses

1. There will be significant differences in BSC between young adults and healthy elders. Young adults will demonstrate a higher percentage of EE patterns when compared to healthy elders. However, both groups will demonstrate significantly higher percentage of EE patterns when compared to all other patterns (IE, EI, and II). It is also hypothesised that SAD will be longer for young adults compared to elders.
2. There will also be significant differences in BSC between healthy elders and those with PD. Individuals with PD will demonstrate significantly greater proportion of post swallow inspiration (EI and II) swallows compared to age and gender matched healthy elders. It is further hypothesised that SAD will be longer for individuals with PD compared to healthy elders.
3. Finally, there will be significant differences in BSC between those in the earlier stages of PD (H-Y $\leq$ 2) when compared to those in the later stages of PD (H-Y $\geq$ 2.5). Patients in the later stages will demonstrate significantly greater proportion of post swallow inspiration (EI and II) swallows compared to those in the earlier stages. In addition, it is

hypothesised that SAD will be longer for those in the later stages of PD compared to earlier stages.

4.3 Data Processing and Preparation

Data were collected as described in Chapter 3. From these data, each swallow was first identified by simultaneous sEMG onset, peak and offset paired with a cessation in directional nasal airflow by the primary rater (LP). All swallows were then classified into 4 categories: EE, IE, EI and II. SAD values were also determined for each swallow for all participants. Inter- and intra-rater reliability was estimated with a random 25% of the original data set re-analysed by the primary rater (LP) and independent raters (SD and ES).

Independent samples t tests were conducted to compare SAD and breathing-swallowing patterns between healthy young adults and elders. Paired samples t test were conducted to compare SAD and swallowing-breathing patterns between those with PD and healthy elders as these two groups were matched for age and gender. Independent samples t tests were also conducted to compare SAD and breathing-swallowing patterns between early stage PD and later stage PD. Group (Young, Elders, PD) was entered as the independent variable and 4 respiratory phase category (EE, IE, EI, II) with % of swallows for each category were entered as dependent variables.

Levene's test for equality of variance was calculated for all groups in the t-tests. For all comparisons, if Levene's test was significant, i.e. the values for both groups are variable, adjusted p-value and degree of freedom (df) were used. The use of these adjusted values compensated for any inequality of variance in the data set.

Eta squared was used to calculate the effect size in order to provide an indication of the magnitude of the differences between groups. This study adopted guidelines proposed by Cohen (1988) when interpreting eta squared values, where 0.01 = small effect, 0.06 = moderate effect and 0.14 = large effect.

4.4 Results

A total of 640 swallows (10 swallows, 64 participants) were recorded, categorised and analysed. Intraclass correlation coefficient showed high intra- and inter-rater for respiratory

phase categorisation (r = .984 and .998 respectively). Intraclass correlation coefficient also showed high intra- and inter-rater for SAD (r = .847 and .992 respectively).

There were no significant differences in respiratory phase patterns for all categories between young healthy adults and healthy elders: EE [t(30) = .458, p = .651], IE [t(30)=.105, p = .907], EI t(16)= -.137, p = .201] and II [t(15)=1.46, p = .164]. The magnitude of differences in the means was small to moderate (eta squared 0.01 to 0.09). There were also no significant differences in respiratory phase patterns for all categories between elders and those with PD: EE t(15) = .744, p = .469], IE ; [t(15) = - .716, p = .485], EI [t(15) = 1.35, p= .196] and II [t(15) = -1.82, p = .089], even though the effect sizes were moderate to large (eta squared 0.04 to 0.18). Finally, there was no significant difference in respiratory phase patterns between those with earlier PD and those with later PD: EE [t(30) = 1.07, p = .295], IE t(27)= -1.18, p = .249], EI t(30)= -.655, p = .518] and II [t(30) = .359, p = .722]. Effect size calculation showed small differences in the means (eta squared 0.001 to 0.04).

Means and standard deviations of the percentage frequency occurrence of swallows showed similar respiratory patterns across groups (Table 4.1). EE was the most frequent pattern for all groups, regardless of age, disease, or disease severity, ranging from 60.63% to 76.25%. This was followed by followed by IE, with percentage ranging from 18.13 to 31.88%. Swallows that preceded expiration (sum of EE and IE) was dominant in all groups: young adults (97.5%), healthy elders (90.63%) and those with PD (90.01%). This pattern remained when patient participants were re-grouped into early stage PD (91.88%) and later stage PD (92.51%). While this small sample of healthy elders did not demonstrate any II respiratory patterns, they exhibited the greatest percentage of swallows that preceded inspiration (9.38%), even higher than patient participants.

Table 4.1 Percentage of swallows occurring in each respiratory-phase category for all groups

Respiratory Phase Category	Young Adults Frequency (%)		Elders Frequency (%)*		PD Frequency (%)*		Earlier PD Frequency (%)**		Later PD Frequency (%)***	
	M	SD	M	SD	M	SD	M	SD	M	SD
EE	76.25	33.44	70.63	36.1	60.63	37.32	73.75	35	60.63	34.73
IE	21.25	34.03	20	33.47	29.38	26.1	18.13	26.39	31.88	38.51
EI	1.25	3.42	9.38	24.08	1.25	5	1.25	3.42	2.5	6.83
II	1.25	3.42	0	0	8.75	19.28	6.88	17.78	5	11

Note: EE = expiration-SA-expiration, IE = inspiration-SA-inspiration, EI = expiration-SA-inspiration, II = inspiration-SA-inspiration, M = mean, SD = standard deviation

* Elders age- and gender-matched to PD across severity levels

** Earlier PD = Hoehn-Yahr ≤ stage 2

*** Later PD = Hoehn-Yahr ≥ stage 2.5

Independent t test revealed that SAD was not different between young adults (M = 1.302, SD = 0.84) and healthy elders [M = 1.143, SD = .50; t(30) = .648, p = 0.552]. During off line analysis, it was noted that 2 of the young healthy participants has SAD of up to 7.92 seconds, which would skew the overall mean for the healthy young adults. When SAD data from these 2 outliers were removed from analyses, independent t test revealed that the mean and standard deviations for healthy young adults and elders were 1.030 (0.43) and 1.145 (.50) respectively. Differences in SAD remained non-significant after removal of outlier data [t(28) = -0.660, p = 0.515].

Paired samples t test revealed that SAD was also not different between healthy elders (M = 1.143, SD = 0.50) and patients with PD [M = 1.785, SD = 1.13; t(15) = -2.021, p = 0.062]. There was a significant difference for SAD between patients in the earlier stages of PD (M = 1.122, SD = 0.47) and those in the later stages [M = 1.932, SD = 1.20, t(20) = -2.513, p = .021) with patients in the later stages demonstrating longer SAD.

4.5 Discussion

An average of 68% of swallows occurred in mid expiration and an average of 93% occurred before expiration regardless of age, disease and disease severity. This is consistent with prior research also indicating that mid expiration and/or swallows before expiration is the most common pattern in healthy adults (Hirst et al., 2002; Hiss et al., 2001; Kelly et al., 2006;

Klahn & Perlman, 1999; Martin et al., 1994; Martin-Harris et al., 2005; Preiksaitis & Mills, 1996). When compared to other studies where participants self-administered 10 ml boluses (Hiss et al., 2001; Preiksaitis et al., 1992) results from this study further confirm that swallows happen most in mid expiration, ranging from 62% (Hiss et al., 2001) to 78.2% (Preiksaitis et al., 1992).

Even though elders demonstrated less swallows preceding expiration and more swallows preceding inspiration, this did not reach statistical significance. As such, no age effects were found in all respiratory phase categories between healthy young adults and healthy elders. This is contrary to that results of Martin-Harris et al., (2005) who reported that the mean age of healthy adults with EE respiratory phase patterns was 56, compared to those with non-EE patterns with mean age of 68. While the study by Martin-Harris et al. demonstrated age effects, this was only seen for adults who are in their 50s. The mean age of healthy elders in this study was 72.8, yet age effects were not demonstrated. This could be because of smaller sample of participants (N = 16 in each group; healthy young adults and elders) in this study compared to 76 in the study by Martin-Harris et al., (2005). Future studies with larger sample sizes would be valuable to establish BSC differences in ageing.

While almost 9% of individuals with PD in this study exhibited II respiratory pattern, none of the healthy elders did. It is intriguing to note that the II pattern reduced in those with earlier stage (6.88%) and even more so in later stage PD (5%). Post swallow expiration serves as a useful mechanism for clearing residual and preventing aspiration while post swallow inspiration has been associated with an increased risk of aspiration in other neurological disorders (Hadjikoutis et al., 2000). In healthy ageing, post swallow inspiration may not have any negative repercussions but in the presence of PD this may also lead to eventual aspiration. It is plausible that even though II patterns are more pronounced in PD, as disease progresses, airway protection mechanisms increase due to patient's self compensation, and with the corresponding decreasing trend of II category in later stages of PD.

The increased SAD in the later stages is an interesting finding. Prior research has established that swallowing apnoea begins even before the bolus reaches the hypopharynx and ends only when the tail end of the bolus has reached the oesophagus (Palmer & Hiiemae, 2003). The increase of SAD in later stage PD patients may reflect prolonged closure of the glottis, thus offering added airway protection. If this is so, this additional mechanism may be very important in light of research suggesting a positive correlation between disease duration, stage

and swallowing impairment (Coates & Bakheit, 1997). In the absence direct visualisation of the thyroarytenoid, it is questionable whether increased SAD is due to prolonged vocal fold closure as the closure of the velopharyngeal port itself would cause a cessation of respiration (Perlman et al., 2005). In PD, and increased in SAD duration may also be a result of laryngeal dyskinesia (Blumin et al., 2004).

The absent age effect on SAD in this study is in agreement with some (Kelly et al., 2006) but not others (Hiss et al., 2001). As the magnitude of differences in the means (eta squared) for SAD was small, a larger sample size in future studies may be warranted to establish true age effects.

This is the first study to assess the contribution of BSC in overall airway protection in PD and to further evaluate the effects of disease severity. Results indicate neither effects of PD nor effects of severity, suggesting that BSC is not only preserved the 6th or 7th decade of life but also stable in PD. Most authors have found that mid-expiratory swallows occur preferentially in mid expiration during awake, bolus swallows (Hirst et al., 2002; Hiss et al., 2001; Klahn & Perlman, 1999; Martin et al., 1994; Martin-Harris et al., 2005). Results from the present study support these studies and suggests that BSC is robust in the presence of ageing and PD.

Rigidity and bradykinesia of the larynx have been reported during volitional closure of the vocal folds in the PD population (Blumin et al., 2004; Hanson et al., 1984; Perez et al., 1996). It is difficult to extend findings from volitional tasks to vocal fold closure during SA as the precise neural controls for BSC is still unclear. Although cortical influence on BSC has been demonstrated (Kelly et al., 2006), its influence on SA is still inexplicit.

4.6 Conclusion

Age did not have a significant influence over BSC. Furthermore, neither PD nor severity of PD influenced BSC. For all groups, mid-expiration swallows were the most frequently seen, which suggests that BSC shows a stable respiratory pattern in relation to swallowing. This study adds value to existing research on breathing during swallowing in neurological disorders by highlighting that unlike strokes and motor neurone disease, pathophysiology of PD may not exert any significant influences over BSC.

Chapter 5. Swallowing Efficiency in Ageing and Parkinson's Disease

5.1 Introduction

Swallowing is a complex action requiring 5 cranial nerves, 2 cervical nerves and more than 25 paired muscles of the lips, tongue, jaw, pharynx, larynx and upper oesophageal sphincter muscles working in a synchronous and coordinated sequence to transfer food from the mouth to the stomach (review in Jean, 2001; Miller, 1999). Changes to the swallowing process that accompany ageing are expected, with overall swallowing times decreasing by as early as 45 years of age. By 70, Robbins et al., (1992) reported that swallowing times are significantly slower when compared to those under 45. Many authors have quantified changes in swallowing behaviour and/or described changes in the different stages of swallowing in healthy ageing (Dejaeger & Pelemans, 1996; Ekberg & Feinberg, 1991; Fucile et al., 1998; Fulp et al., 1990; Gleeson, 1999; Jaradeh, 1994; Logemann, 1990; Martin-Harris et al., 2005; Nagaya & Sumi, 2002; Nilsson et al., 1996; Plant, 1998; Ribeiro et al., 1998; Robbins, 1996; Schindler & Kelly, 2002; Shaker et al., 2003; Sonies, 1992; Wilkinson & de Picciotto, 1999).

Oral (Shaw et al., 1995), pharyngeal (Robbins et al., 1992) and oesophageal transit times (Aly & Abdel-Aty, 1999) are prolonged, in addition to increased duration of hyoid movement (Sonies, Parent, Morrish, & Baum, 1988) during swallowing. A decrease in peak amplitude of submental electromyographic (sEMG) recordings further suggests the reduction of relative hyolaryngeal excursion. In a study of 98 healthy participants ranging from 20-98 years old, Daggett, Logemann, Rademaker, & Pauloski, (2006) found that laryngeal penetration of fluid was more frequent after the age of 50 and with larger bolus size.

At a cellular level, decreased density of collagenous and elastic fibres, thinning of elastic tissues and thickening of collagenous fibres of the vocal folds (Hirano et al., 1989; Honjo & Isshiki, 1980; Ishii et al., 2000; Kosztyla-Hojna et al., 2003; Sato et al., 2002; Ximenes Filho et al., 2003), plus ossification of hyaline cartilages of the larynx (Fatterpekar et al., 2004; Paulsen et al., 2000) negatively impact on the ease of cartilage movement and vocal fold adduction (Kahn & Kahane, 1986).

While changes may negatively impact the swallowing process with age, it is often difficult to distinguish the effect of normal aging from the effects of gradual degenerative changes of disease (Ekberg & Feinberg, 1991). Subtle changes in muscle tension, speed and coordination of swallowing responses are expected in healthy ageing but do not necessarily indicate oropharyngeal or oesophageal dysphagia. According to Sonies (1992), dysphagia in the elderly is more often the direct result of a pathologic condition or illness that may occur more commonly in elderly persons. Parkinson's disease (PD) is one example.

As with other complex coordinated muscle activities in patients with PD, swallowing is significantly affected by rigidity and bradykinesia producing abnormalities in the oral preparatory, oral transport, pharyngeal and oesophageal phases (Ali et al., 1996; Johnston et al., 1995; Potulska et al., 2003). This is supported by several other investigators (Ertekin et al., 2002; Leopold & Kagel, 1996, 1997a, 1997b; Stroudley & Walsh, 1991). Poor lip closure resulting in intermittent or continuous anterior loss were described in 29% whilst 86% had tongue and bolus control abnormalities that resulted in premature spillage into the pharynx (Stroudley & Walsh, 1991). The most common abnormality of pharyngeal phase were impaired pharyngeal mobility, valleculae and pyriforms stasis, laryngeal penetration, aspiration and deficient epiglottic retroflexion affecting up to 97% of patients (Leopold & Kagel, 1997b). These authors also assert that intrinsic laryngeal movements during swallowing are no less critical. In PD, significant delays to the start of vertical excursion of the larynx, delayed true vocal fold closure, coupled with incomplete or absent abduction of the true vocal folds were expected. Subsequently, results of their study using VFS showed least one abnormality of laryngeal motility during swallowing in 95.8% of patients. Multiple abnormalities of the UOS are present in PD, with the most common being incomplete relaxation for UOS and delayed peristalsis, stasis, bolus redirection and spastic, tertiary contractions for the oesophagus (Bassotti et al., 1998; Castell et al., 2001; Higo et al., 2001).

Clinicians have sought the precise nature of swallowing disorders in PD by investigating the biomechanics, as abnormalities in biomechanics are thought to give rise to symptoms of dysphagia and eventual aspiration (Coates & Bakheit, 1997; Stroudley & Walsh, 1991). Swallowing assessments using equipment such as videofluoroscopy and endoscopy has been instrumental in increasing our understanding of dysphagia (Langmore & Aviv, 2001). Even though technology has improved and more diagnostic studies have become available, the clinician's first and oftentimes only assessment relies on his/her skills when evaluating swallowing at the bedside (Mann & Hankey, 2001; Ramsey, Smithard, & Kalra, 2003).

Hughes & Wiles (1996a) published a timed test of swallowing where indices of swallowing efficiency may be calculated when participants were given 150ml of water: number of swallows, time taken, average volume per swallow (ml), average time (s) per swallow and swallowing capacity (ml/s). Results were validated on adults up to age 90+ and also in 30 patients with motor neurone disease. This test requires participants to drink 150mls of water from a cup, reflecting a more natural way of drinking compared to assessments that use single swallows. Furthermore, the test does not require tools/equipment beyond a timing device e.g. stop watch and a calculator, making it an assessment that may be quick to administer in a busy clinic. An easy instruction for this assessment to drink "as quickly as is comfortable possible" does not place high cognitive loads on patients. Finally, measures of swallowing efficiency may still be obtained for participants who are unable to ingest the full 150ml cup of water by subtracting the amount left in the cup from 150ml. It would be useful to obtain data from individuals with PD as biomechanics of swallowing in these patients are known to be affected.

The usefulness of this timed test has been demonstrated by Clarke et al., (1998), who reported that in a group of 63 patients with idiopathic PD, VFS was no better than the clinician's assessment using a combination of the timed test of swallowing efficiency, a simple questionnaire and a novel rating scale for dysphagia. While this does not suggest that the timed test of swallowing could replace objective instrumental assessments, this test may be useful as a screen for biomechanical changes and/or abnormalities associated with ageing and disease. It would be important to compare performances on the indices of timed test of swallowing with swallowing ability as measured with instrumental assessment such as fibreoptic endoscopic evaluation of swallowing (FEES).

In this section, 3 data sets obtained from assessments that investigate overall swallowing efficiency are presented. The timed test of swallowing efficiency was conducted as per Hughes and Wiles (1996) with the inclusion of individuals with PD to form a reference for future studies using this test in this patient cohort. Peak sEMG amplitude of submental muscles was collected for single liquid swallows. Finally swallowing efficiency was also assessed using FEES.

5.2 Hypotheses

5.2.1 Hypotheses for Timed Test of Swallowing

1. There will be significant differences in swallowing efficiency measures (number of swallows, time taken, average volume/swallow, average time/swallow and swallowing capacity) between young adults and healthy elders. Young adults will demonstrate greater swallowing efficiency when compared to healthy elders.
2. There will also be significant differences in swallowing efficiency measures (number of swallows, time taken, average volume/swallow, average time/swallow and swallowing capacity) between healthy elders and those with PD. Healthy elders will demonstrate greater swallowing efficiency when compared to patients.
3. Finally, there will be significant differences in swallowing efficiency measures (number of swallows, time taken, average volume/swallow, average time/swallow and swallowing capacity) between those in the earlier stages of PD (H-Y $\leq$ 2) when compared to those in the later stages of PD (H-Y $\geq$ 2.5). Patients in the earlier stages will demonstrate significantly greater swallowing efficiency compared to those in the later stages.

5.2.2 Hypotheses for sEMG Amplitude

1. There will be a significant difference in average sEMG peak amplitude between young adults and healthy elders. Young adults will demonstrate higher peak amplitudes when compared to healthy elders.
2. There will also be a significant difference in average sEMG peak amplitude between healthy elders and those with PD. Healthy elders will demonstrate higher peak amplitudes when compared to patients.
3. Finally, there will be a significant difference in average sEMG peak amplitude between those in the earlier stages of PD (H-Y $\leq$ 2) when compared to those in the later stages of PD (H-Y $\geq$ 2.5). Patients in the earlier stages will demonstrate higher peak amplitudes compared to those in the later stages.

5.2.3 Hypotheses for Fibreoptic Endoscopic Evaluation of Swallowing

1. There will be significant differences in swallowing function between young adults and healthy elders during FEES. Young adults will demonstrate less symptoms of a swallowing disorder compared to healthy elders.

2. There will also be significant differences in swallowing function between healthy elders and those with PD during FEES. Healthy elders will demonstrate less symptoms of a swallowing disorder compared to patients.
3. Finally, there will be significant differences in swallowing function between those in the earlier stages of PD (H-Y $\leq$ 2) when compared to those in the later stages of PD (H-Y $\geq$ 2.5) during FEES. Patients in the earlier stages will demonstrate less symptoms of a swallowing disorder compared to those in the later stages.

5.3 Data Processing and Preparation

For all 3 sets of data, Levene's test for equality of variance was calculated for all groups in the t-tests. For all comparisons, if Levene's test was significant, i.e. the values for both groups are variable, adjusted p-value and degree of freedom (df) were used. The use of these adjusted values compensated for any inequality of variance in the data set.

Eta squared was used to calculate the effect size in order to provide an indication of the magnitude of the differences between groups. This study adopted guidelines proposed by Cohen (1988) when interpreting eta squared values, where 0.01 = small effect, 0.06 = moderate effect and 0.14 = large effect.

5.3.1 Timed Test of Swallowing Efficiency

Data were collected as described in Chapter 3. From these data, each swallow was identified by the primary rater (LP) using the peak sEMG recording and the number of swallows recorded by counting the number of sEMG peaks. Total time for the test was taken as the time the water first touched the participant's lips until the time when sEMG tracing retuned to baseline (Figure 5.1). Average time per swallow was calculated using total time (s)/number of swallows. Average volume per swallow was calculated using total volume swallowed (ml)/number of swallows. Swallowing capacity was calculated using total volume (ml)/total time (s).

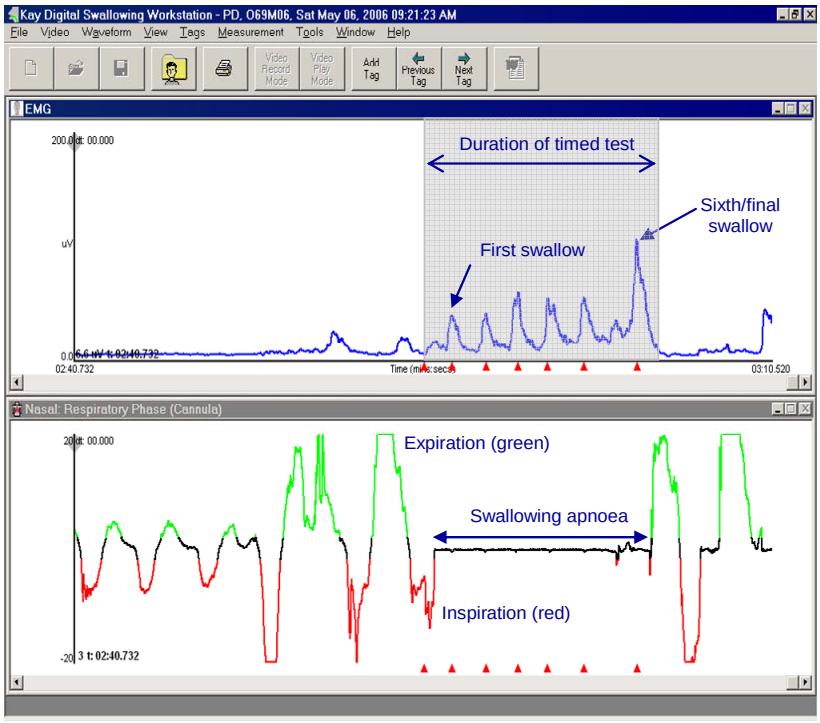


Figure 5.1 Upper window: Measuring the duration of the timed test of swallowing (shaded area) and number of swallows. Lower window: Time-locked directional nasal airflow to confirm swallowing event.

A random 25% of the data was reanalysed by the primary rater (LP) and an independent rater (SD) to calculate intraclass correlation-coefficients for intra- and inter-rater reliability estimation. Independent samples t test was conducted to compare the indices obtained from the timed test of swallowing between healthy young adults and elders. Paired samples t test was conducted to compare the indices obtained from the timed test of swallowing between elders and individuals with PD who were matched for age and gender. Group (Young, Elders, PD) was entered as independent variable and indices obtained form the timed test of swallowing (time taken, number of swallows, average time per swallow, average volume per swallow and swallowing capacity) were entered as dependent variables.

5.3.2 Peak Submental sEMG Amplitude

Peak sEMG amplitude was identified for 10 trials of 8ml single liquid swallows. The identification of a swallowing event was further assured with the use of direction nasal airflow and on-line tagging during swallowing (Figure 5.2).

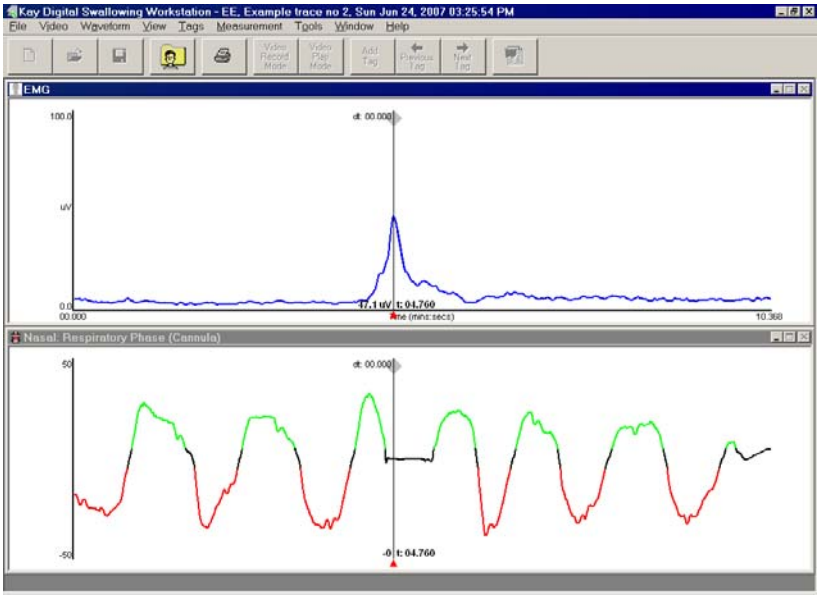


Figure 5.2 Example tracing of a single liquid swallow. Top window shows peak submental sEMG. Bottom window shows directional nasal airflow. Note that swallowing occurs during a period of swallowing apnoea, depicted by the black, flat line during which there is a complete cessation of respiration.

5.3.3 Fibreoptic Endoscopic Evaluation of Swallowing

Swallows for 3 trials of chocolate pudding, nectar and thin fluids (all 8mls), one piece of shortbread biscuit and 90ml of water were identified by the primary rater (LP). Percentage frequency occurrence for pre-swallow pooling (defined as the brief bolus hold in the pharynx prior to pharyngeal swallowing), laryngeal penetration, aspiration, silent aspiration, presence of residue (defined as visible residual in the pharynx) and spontaneous clearing were noted.

As with the timed test of swallowing, a random 25% of the data were reanalysed by the primary rater (LP) and an independent rater (SD) to calculate intraclass correlation-coefficients for intra- and inter-rater reliability estimation. Independent samples t tests were conducted to compare the swallowing symptoms between healthy young adults and elders. Independent samples t tests were also conducted to compare the swallowing symptoms between PD patients in the early stages (Hoehn-Yahr ≤ 2) and patients in the later stages (Hoehn-Yahr ≥ 2.5) Paired samples t tests were conducted to compare the swallowing symptoms between healthy young adults and elders as they were matched for age and gender. Group (young adults, elders, PD patients) was entered as independent variable and

swallowing symptoms (pre-swallow pooling, laryngeal penetration, aspiration, silent aspiration, presence of residue and spontaneous clearing) were entered as dependent variables.

5.4 Results

5.4.1 Swallowing Efficiency Measured by the Timed Test of Swallowing

Intraclass correlation coefficient revealed high intra- and inter- rater reliability, r = .997 and r = .999 respectively for each measure. The means and standard deviations for each group on each swallowing efficiency index are shown in Table 5.1.

Table 5.1 Swallowing Efficiency Indices for All Groups as Measured by the Timed Test of Swallowing Efficiency

Swallowing efficiency measures	Average number of swallows		Average time taken (s)		Average volume per swallow (ml)		Average time per swallow (s)		Swallowing capacity (ml/s)	
Groups	M	SD	M	SD	M	SD	M	SD	M	SD
Young Adults	7.4	2.9	9	4.6	23.6	10.5	1.2	0.29	21.1	10.9
Healthy Elders*	**7.8**	1.6	**11.2**	5	**20.1**	4.1	**1.4**	0.04	**15.5**	5.3
PD Patients*	**10.5**	3.8	**19.8**	14.9	**15.2**	4.01	**1.8**	6.7	**10.1**	4.6
Earlier PD**	9.7	4.5	15.9	15.4	18.3	7.7	1.5	0.5	13.9	6.5
Later PD***	9.6	2.7	17	10.7	16.6	4.8	1.67	.7	12.4	7.3

Note: s = seconds, ml = millilitres, M = mean, SD = standard deviation

In **bold** = significance reached, $p < .05$

* Elders age- and gender-matched to PD across severity levels

** Earlier PD = Hoehn-Yahr ≤ stage 2

*** Later PD = Hoehn-Yahr ≥ stage 2.5

Although elders demonstrated reduced swallowing capacity compared to healthy young adults, this difference did not reach statistical significance [$t(30) = 1.84$, $p = 0.08$]. The magnitude of difference in the means was moderate to large (eta squared 0.10). No other

swallowing efficiency indices reached significance when young adults were compared to healthy elders: average number of swallows [t(30) = -3.8, p = 0.704], average time taken [t(30) = -1.2, p = 0.224], .average volume per swallow t(30)= -1.22, p = 0.239], average time per swallow [t(30) = -1.7, p = 0.106].

Paired samples t test did, however, reveal a significant difference in swallowing capacity between healthy elders and those with PD [t(15) = 4.18, p = 0.001]. In addition, significant differences were found between healthy elders and those with PD for all other swallowing efficiency indices: average number of swallows [t(15) = -2.54, p = 0.023], average time taken [t(15) = -2.4, p = 0.03], .average volume per swallow [t(15) = 3.44, p = 0.004], average time per swallow [t(15)= -2.51, p = 0.024].

When patient participants with mild PD symptoms were compared to those in the later, more severe stages, no differences in any swallowing efficiency measures were found: swallowing capacity: [t(30) = .617, p = 0.542], average number of swallows [t(30) = 0.095, p = 0.925], average time taken [t(30) = -.225, p = 0.823], .average volume per swallow [t(30) = .775, p = .444], average time per swallow [t(30) = -.832, p = 0.412]. The magnitude of differences in the means were very small (eta squared 0.001 to 0.02).

As this study employed timed test described by Hughes & Wiles (1996b), comparison of swallowing indices between males and females obtained from this study to Hughes & Wiles' are presented in Table 5.2

Table 5.2 Comparison of Swallowing Efficiency Indices between that Published by Hughes & Wiles (1996) and that of Healthy Participants in the Current Study

	Age range	Volume/ swallow	Range	Time/ swallow	Range	Swallow Capacity	SD
Young Male	**18.9-34.1**	**37.5**	**25-50**	**1.2**	**1-1.3**	**31.9**	**9.5**
This study	22.3-26.9	29.4	13.6-50	1.1	0.8-1.5	26.6	11.8
Young Female	**18.9-34.1**	**18.8**	**15-30**	**1.1**	**1-1.3**	**18.7**	**6**
This study	21.3-32.4	17.7	10.7-21.4	1.3	0.7-1.6	15.5	6.6
Elder Male	**56.5-73**	**23.2**	**20.8-30**	**1.3**	**1.2-1.4**	**18.7**	**5.2**
This study	67.6-80.2	21.9	18.8-25	1.3	1-1.6	16.3	4.4
Elder Female	**55.4-74.9**	**16.7**	**13.6-21.4**	**1.5**	**1.1-2.1**	**12.3**	**4.9**
This study	61.5-84.7	19.1	15-25	1.5	1-2.5	14.7	6.3

Note: SD= standard deviation

In **bold** = Published norms by Hughes & Wiles (1996b)

5.4.2 Peak Submental sEMG Amplitude

Peak sEMG amplitude failed to reach significance for any comparison. An independent samples t test showed no significant differences in peak sEMG amplitude for healthy young adults (M = 82.1, SD = 52.8) and elders [M = 56, SD = 28.8; t(30) =1.74, p = 0.09]. Paired samples t test revealed no significant differences in sEMG amplitude for healthy elders (M = 56.0, SD = 28.8) and those with PD [M = 48.8, SD = 23.2; t(15) = 0.827, p = 0.421]. Finally, an independent samples t test showed no significant differences in sEMG amplitude for early stage PD (M = 55.2, SD = 30.16) and those with later stage PD [M = 53.0, SD = 21.6; t(30) = 0.236, p = 0.815].

5.4.3 Fibreoptic Endoscopic Evaluation of Swallowing

An independent samples t test revealed a significant increase in frequency pudding residue in elders (M = 64.5, SD = 46.3) compared to healthy young adults [M = 22.75, SD = 33.6; t(30) = -2.9, p = 0.007]. There were no further differences in the frequency of swallowing symptoms between healthy young adults and elders across other textures.

Paired samples t test revealed 2 differences for comparisons between healthy elders and individuals with PD. Specifically, there was an increase in frequency of laryngeal penetration for thin fluids in patients (M = 8.8, SD = 15.1) compared to healthy elders none of whom experienced laryngeal penetration [t(14) = -2.26, p = 0.041). In addition, there was also a significant increase in frequency of residue for thin fluids in those with PD (M = 39.9, SD = 42.1) compared to healthy elders [M = 15.53, SD = 35.33; t(14) = -2.274, p = 0.016). No further differences in the frequency of swallowing symptoms were found for other textures.

Finally, independent samples t test showed no difference in the frequency of swallowing symptoms between early stage PD and later stage PD for all textures with only one exception. No patients in the early stage of PD demonstrated laryngeal penetration on thin fluids while patients in the later stages demonstrated this finding on 8.25% of swallows [t(30) = -2.23, p = .033)].

5.5 Discussion

The key finding in this study is that swallowing efficiency declines in PD remains stable in healthy ageing. In contrast, many studies have demonstrated that decreases in overall swallowing efficiency accompanying ageing with some reporting deterioration as early as 45 (Robbins et al., 1992). This study investigated swallowing efficiency and capacity using a methods described by Hughes and Wiles (1996). Hughes and Wiles reported ‘a clear decline’ in average volume per swallow and swallowing capacity with age without information on whether this decline was statistically significant. This was not reflected in results of our study, and three methodological differences may account for this.

First, although prior studies were important in establishing spatial and temporal norms, most studies have focused on single and isolated bolus volumes (Martin-Harris et al., 2005; Rademaker, Pauloski, Colangelo, & Logemann, 1998; Robbins et al., 1992; Shaw et al., 1995; Tracy et al., 1989). Isolated swallows are not typical of normal swallowing when ingesting

fluids and differences in swallowing biomechanics have been documented during ingestion of fluids in a sequential manner (Daniels et al., 2004; Daniels & Foundas, 2001; Martin et al., 1994). Using sequential straw drinking of thin liquid barium for 10 second duration, Daniels et al., (2004) reported that elders age between 60 and 83 were up to 8.8 times more likely to exhibit airway invasion i.e. laryngeal penetration compared to healthy young adults (age range 25-35). Our study employed a method comparable to Daniels et al. by using sequential drinking from a cup to ensure a more natural behaviour of fluid ingestion.

Compared to the study by Daniels et al., one reason this present study failed to find detect significant age effects despite using natural, sequential drinking may be because of different task instructions. Participants in Daniel et al's study were told, 'When I say go, start drinking. Continually drink until I say to stop' (Daniels et al, 2004, p. 35), without being encouraged to drink quickly as was the instructions to participants in our study. It is possible that age differences may be reflected in normal speed of drinking (Daniel et al's study) but when elders are asked to drink quickly, this difference in speed may no longer be large enough to be significant. After all, elders in this study were all healthy, had normal cognitive status and able to perform tasks that required maximum effort upon request.

Second, some studies recruited participants who were above 60, example, mean age of 83 in Ekberg & Feinberg (1991) and age range of 60 - 97 in Fucile et al., (1998). If the assertion by Robbins et al. that overall swallowing process deteriorates from 45 onwards is true, then direct comparisons for any age effects cannot be made for studies that only include participants above 45. The lack of a control group is problematic and Robbins et al., (1992) rightly highlighted that past studies have not controlled for age effects by comparing young adults with elders. Our study compared healthy young adults (mean age 25.1, range 21.3-32.4) to healthy elders (mean age 72.8, range 61.5 –84.7). A direct comparison of results of this study to those with participants who were similar in age (examples include Daniels et al., 2004; Rademaker et al., 1998; Robbins et al., 1992) is not possible as measurements under investigation were different even though all were investigating biomechanics. Most other studies used frame-by-frame videofluoroscopic analysis for analysis while this study employed the use of a validated, swallowing assessment that could be administered at the bedside and did not require instruments beyond a stop watch. An extension of the present study would be to correlate findings from the timed test of swallowing to videofluoroscopic studies.

The third methodological difference is in the procedure employed. The importance of studies that look into functional swallowing activity, e.g. eating a complete meal (Fucile et al., 1998), or analysing normal, non effortful, isolated (Martin-Harris et al., 2005; Robbins et al., 1992; Shaw et al., 1995) or sequential (Daniels et al., 2004; Daniels & Foundas, 2001) swallows has contributed to our understanding of how age affects swallowing. Clearly, there are age effects in normal swallowing behaviour. Participants in this study were instructed to drink 'as quickly as is comfortably possible'. Inevitably, this drinking style encourages maximum effort to minimise time taken to ingest fluid. Subsequently, results show that when healthy elders put in extra effort, their performance did not differ from young adults, further support the notion that biomechanics of swallowing may be preserved in health.

As reflected in Table 5.2, our results show that swallowing efficiency measured using the timed test of swallowing is comparable to published results by Hughes and Wiles (1996b), regardless of age. In addition, our results demonstrate preservation of swallowing efficiency in health, again, regardless of age. This does not hold true for those with PD, since all indices of swallowing efficiency show significant differences compared to age-gender-matched healthy elders. Results of the present study further supports Clarke et al., (1998) also found significant differences for speed and volume indices of timed test of swallowing.

On a whole, even with the instruction to drink as quickly as possible, those with PD took 2.7 more swallows to drink 150mls of water compared to healthy adults of similar age and gender. Functionally, this meant that patients would take longer to complete eating/drinking compared to healthy adults. It has been reported that patients with PD may be able to perform single motor acts but fail in repetitive motor tasks due to bradykinesia and rigidity (Tzelepis et al., 1988). Conceivably, repetitive and quick swallows during cup drinking placed demands on motor function that are greater than normal, leading to more obvious consequences of bradykinesia and rigidity.

Not only did patient participants take more swallows, they also took almost twice as long to ingest 150 mls of water compared to healthy adults (19.9 seconds and 11.2 seconds respectively). Although bradykinesia and rigidity may account for some slowing down, other reasons may also account for this finding. Intuitively, fear of choking may have caused participants to slow drinking rate. This is not unlike findings in other areas of PD, such as the relationship between fear of falling and/or fall experiences and subsequent fear of walking in case of further falls (review in Bloem, Hausdorff, Visser, & Giladi, 2004). It is plausible that

patients also took significantly smaller sips and longer time per swallow to further prevent aspiration, thus reducing overall swallowing capacity. Fatigue may also have contributed to the longer time it took to drink.

Disease severity did not significantly alter swallowing efficiency indices even though some authors have reported that symptoms of dysphagia are seen in only in the late stages of PD (Calne et al., 1970). This finding did not support the results by Clarke et al., (1998) who reported that the time it took to drink 150 mls of water and the volume per swallow declined with disease progression. This difference could be due to our small sample size, as reflected by our eta squared calculations. It would be worthwhile for future studies to have a larger sample size in both groups (early and late stage PD).

Peak submental sEMG results from this study revealed that relative floor of mouth muscle contraction during single, non-effortful liquid swallows were not different across any groups. This finding is expected, as authors have reported no age effects in peak pharyngeal pressure amplitudes during single, non-effortful swallows (Robbins et al., 1992). However, it is also possible that in this study, small sample size in each group was not sufficient to adequately demonstrate age and disease effects. Indeed, effect size calculations showed very small differences in the means of analyses between elders and PD, as well as between early and late stage PD patients.

Comparisons to FEES did little to support the hypotheses that changes with age and disease are apparent, with no differences found for most measures,. A few exceptions were noted. Pudding residual was observed more frequently in elders compared to young adults. Individuals with PD exhibited increased frequency of laryngeal penetration and notable residue for thin fluids without increased aspiration risk for thin or any other fluid/food consistencies. Finally we were able to demonstrate frequency of laryngeal penetration for thin fluids were evident only in patients in the later stages of PD.

5.6 Conclusion

This study highlights that age alone does not negatively impact swallowing efficiency as measured by a maximal speed sequential swallowing and non-effortful single swallow task. Much of the effects of age and disease on swallowing efficiency were not apparent during FEES with few exceptions. While results do not support existing studies that have found

differences due to ageing, future studies should aim to confirm (or refute) age related differences by instructing participants to ‘drink as you normally would’, akin to instructions given by Daniels et al., (2004). While PD and accompanying bradykinesia and/or rigidity may decrease swallowing efficiency longer times taken and smaller volumes per swallow may also be reflective of self-compensation to decrease possible choking and increase airway protection.

Chapter 6. Pulmonary Function in Ageing and Parkinson's Disease

6.1 Introduction

Respiration and deglutition are two life-sustaining physiological actions that share crucial anatomical space; the upper airway serves as a common pathway for both air and nourishment. Most research efforts to date have focused on breathing swallowing coordination, emphasising the need for turn taking between the two actions for airway protection (Hiss et al., 2001; Klahn & Perlman, 1999; Preiksaitis & Mills, 1996; Selley et al., 1989a, 1989b). However, Gross et al., (2003) stress that consideration must also be given to a more integrated paradigm whereby the respiratory system and airflow actively participate in deglutition.

Research has confirmed that subglottic pressure receptors exist (Adzaku & Wyke, 1979; Widdicombe, 1986a), although their function is not clear (Baer, 1979). Conceivably, the purpose of these receptors may be related to deglutition by providing internal biofeedback on the timely execution of pharyngeal swallowing. If so, stimulation of these subglottic mechanoreceptors during respiration may have an affect on the neuroregulation of swallowing function (Gross et al., 2003). Gross et al. recorded swallows using simultaneous VFS, bipolar intramuscular electromyography of the superior pharyngeal constrictor and respiratory inductance plethysmography in 28 participants under three randomised conditions of lung volume: total lung capacity, functional residual capacity, and residual volume (see Appendix 2). EMG results indicated that duration of pharyngeal activity for swallows produced at residual volume was significantly longer than those occurring at total lung capacity or at functional residual capacity. This measure is assumed to be highly correlated with prolonged pharyngeal transit time. With prior research indicating that prolonged pharyngeal transit time is one of the risk factors for developing aspiration pneumonia (Holas et al., 1994), swallowing at low subglottic pressures and/or points in the respiratory cycle when lung volumes and are low may result in airway protection compromise (Selley et al., 1989b).

Further evidence that subglottic pressure changes are crucial for swallowing originated from observations of altered swallowing function in tracheostomy patients, for whom air pressure

below the true vocal folds was greatly modified (Bonanno, 1971; Bone et al., 1974; Buckwalter & Sasaki, 1984; Cameron et al., 1973). An unoccluded tracheostomy tube eliminates the generation of positive subglottic air pressure. If swallowing requires an interaction between 4 pressure valves as suggested by Perlman & Christensen, (1997), disruption to this system could put the patient at risk of aspiration. Not surprisingly, increased aspiration and dysphagia have been linked to the presence of an open tracheostomy tube (Bonanno, 1971; Bone et al., 1974; Buckwalter & Sasaki, 1984; Cameron et al., 1973; Muz et al., 1989; Nash, 1988). Conversely, occluding the tracheostomy stoma eliminated or reduced aspiration, possibly due to the restoration of positive subglottic pressure (Dettelbach et al., 1995; Logemann, Pauloski, & Colangelo, 1998), even though this claim has been challenged recently by other researchers using nasendoscopy (Leder et al., 2001; Leder et al., 2005; Leder et al., 1996).

Additional evidence that respiratory and pulmonary function influence swallowing ability stems from research into chronic obstructive pulmonary diseases (COPD). Patients with COPD such as chronic bronchitis and emphysema are known to have forced expiratory volume (FEV1) that is only 65% of what is predicted for their age, height and gender, in comparison to healthy individuals without COPD (Mokhlesi et al., 2002). Individuals with COPD are also said to have reduced respiratory strength with diminished capacity to clear the larynx of aspirate, putting them at risk of further exacerbating their COPD (Coelho, 1987). In a group of a78 patients with COPD, Good-Fratturelli, Curlee, & Holle, (2000) reported that almost 85% of these patients evidenced some degree of dysphagia, seen on videofluoroscopy. Laryngeal penetration or aspiration was observed for various food textures in 56% of patients, lending support to the claim that changes in pulmonary function negatively affects airway protection. Since there is close anatomical and physiological relationship between swallowing and respiration, it is reasonable to expect this relationship to be disrupted when respiratory function is compromised (Mokhlesi et al., 2002).

Available physiologic and aerodynamic data using spirometry support the hypothesis that respiratory function declines significantly with advancing age, thereby affecting the communication acts of the older individual (Hollien, 1987). Typically, age-related changes in the respiratory system include changes in respiratory volumes and lung capacity. It has been established that spirometry values change with age, with values such as FEV1/FVC ratio decreasing with increasing age (Berend, 2005; Lundback et al., 2003). Other changes include reduction in vital capacity, inspiratory capacity, and expiratory reserve volume (Hoit &

Hixon, 1987). Despite these findings, no research to date has been conducted to specifically investigate the effects of ageing on the interaction between lung volumes and swallowing for airway protection. Conceivably, swallowing may be affected in healthy ageing as pulmonary function declines.

A decline in the pulmonary function of patients with PD is well documented as manifestations of PD associated rigidity and bradykinesia are not limited to the extremities and larynx but can affect striated muscles of the upper airway and chest wall (Shill & Stacy, 2002). Studies have found both restrictive and obstructive ventilatory patterns in this cohort (De Pandis et al., 2002; Herer et al., 2001; Sabate et al., 1996a; Vercueil et al., 1999). In addition, Fontana, Pantaleo, Lavorini, Benvenuti, & Gangemi, (1998) found abdominal muscle weakness in PD, as measured by EMG of the abdominal muscles involved in expiration. EMG activity during cough was always significantly lower in patients compared to healthy elders. This may have further implications for airway protection as coughing is one of the most important mechanisms of airway protection.

In summary, spirometry has been used extensively as standard lung function assessment. It has been well established that respiratory function is altered in ageing and PD but the consequence and influence of obstruction and/or restriction in the airways on airway protection is not fully known. In this chapter, data comparing spirometry values in young healthy adults, healthy elders and those with PD are presented. In addition, correlations between spirometry values are made to other assessments of swallowing with the intent to investigate the implications of pulmonary function on airway protection.

6.2 Hypotheses

1. There will be significant differences in lung function values between healthy young adults and healthy elders when measured using spirometry. Healthy young adults will demonstrate significantly higher values for Forced Vital Capacity (FVC), Forced Expiratory Volume 1 sec (FEV1), FEV1/FVC, Peak Expiratory Flow (PEF), Forced Inspiratory Vital Capacity (FIVC) and Peak Inspiratory Flow (PIF) when compared to healthy elders.
2. There will be significant differences in lung function values between healthy elders and individuals with PD when measured using spirometry. Healthy elders will demonstrate higher values for Forced Vital Capacity (FVC), Forced Expiratory Volume 1 sec (FEV1),

FEV1/FVC, Peak Expiratory Flow (PEF), Forced Inspiratory Vital Capacity (FIVC) and Peak Inspiratory Flow (PIF) when compared to individuals with PD.

3. There will be significant differences in lung function values between those in the earlier stages of PD (H-Y $\leq$ 2) when compared to those in the later stages of PD (H-Y $\geq$ 2.5). Individuals in the earlier stages will demonstrate significantly higher values for Forced Vital Capacity (FVC), Forced Expiratory Volume 1 sec (FEV1), FEV1/FVC, Peak Expiratory Flow (PEF), Forced Inspiratory Vital Capacity (FIVC), and Peak Inspiratory Flow (PIF) compared to those in the later stages.
4. There will be significant positive correlations between lung function values and peak surface sEMG across all participants.
5. Finally, there will be significant positive correlations between lung function values and swallowing capacity measured by the timed test of swallowing across all participants.

6.3 Data Processing and Preparation

Customised reports for all participants were generated using the Sensormedic VMax software to include measurements of Forced Vital Capacity (FVC), Forced Expiratory Volume 1 sec (FEV1), FEV1/FVC, Peak Expiratory Flow (PEF), Forced Inspiratory Vital Capacity (FIVC) and Peak Inspiratory Flow (PIF). Definitions of these are presented in Appendix 2. Spirometry measurements obtained from all participants were referenced, as a percentage value, against predicted values (FVC % predicted, FEV1 % predicted and PEF % predicted), developed from a group of 7429 participants (Caucasians, African-Americans, and Mexican-Americans 8 to 80 years of age) who participated in the third National Health and Nutrition Examination Survey (NHANES III) (Hankinson et al., 1999). The NHANES III are the most widely used reference values for spirometry testing and have been shown to be most applicable to the population studied in this research (Swanney, Wallace, Beckert, Wilson, & Frampton, 2005).

Independent samples t-tests were conducted to compare spirometry values between healthy young adults and elders. Paired samples t-tests were conducted to compare spirometry values between elders and those with PD. Group (Young, Elders, PD) was entered as independent variable and spirometry values (FVC, FEV1, FEV1/FVC, PEF, FIVC and PIF) were entered as dependent variables.

The relationship between spirometry values and swallowing function was investigated using Pearson's product-moment correlation coefficient. Specifically, two swallowing assessments were chosen. The first was the average surface electromyography (sEMG) amplitudes obtained from 10 trials of 8ml, single liquid swallows. The second was the swallowing capacity calculated by dividing the volume per swallow by time per swallow when participants drank 150mls of water. These assessments were chosen to represent to diverse conditions of swallowing: single swallows and consecutive drinking.

6.4 Results

Young adults differed significantly from healthy elders in four spirometry measurements (Table 6.1). Expiratory measurements (FVC, FEV1, FEV1/FVC and PEF) were significantly larger in young adults. Closer inspection of the percentage predicted values revealed that percentage predicted values for FVC, FEV1 and PEF for young adults and elders exceeded the normal values. As previously highlighted, these normal values were referenced to a large healthy population of same gender, similar height and weight (Hankinson et al., 1999).

Table 6.1 Means and Standard Deviations for Spirometry for Healthy, Young Adults and Healthy Elders

Spirometry values	Young Adults		Elders		T (df = 30)	P-value
	M	SD	M	SD		
FVC	4.9	1.2	3.7	1	3.2	.003*
FVC % Predicted	102.9	15.5	126.8	14.3	-.724	.475
FEV1	4.2	0.8	2.7	0.7	5.3	.001*
FEV1 % Predicted	106.8	14.4	107.2	18.1	-.076	.940
FEV1/FVC	87	5.4	74.3	8.1	5	.001*
PIF	4.8	3	4.7	1.7	1.1	.291
PEF	9	2.2	7.4	1.8	2.3	.029*
PEF % Predicted	104.6	17.5	113.9	19.9	-1.4	.171
FET	6	1.9	10.8	3.1	-5.3	.001*
FIVC	4	1	3.4	1.1	1.1	.106

* significant at $p \leq 0.05$

M = Mean, SD = Standard Deviation, df = degrees of freedom

FVC = Forced Vital Capacity, FEV1 = Forced Expiratory Volume in 1 second, FEV1/FVC = Forced Expiratory Volume in 1 second over Forced Vital Capacity, PIF = Peak Inspiratory Flow, PEF = Peak Expiratory Flow, FET = Forced Expiratory Time, FIVC = Forced Inspiratory Vital Capacity

A significant difference was found in PEF between healthy elders and PD individuals (Table 6.2). The percentage predicted PEF showed a difference of 18% in PEF between these two groups, with individuals having PD performing worse than their healthy counterparts. Nonetheless, percentage predicted PEF was within normal limits for both groups. Elders exceeded the normal values by 13.9%, while PD individuals performed slightly worse (4.1%) compared to reference values from NHANES III.

Table 6.2 Means and Standard Deviations for Spirometry for Healthy Elders and PD Patients

Spirometry values	Elders		PD Patients		T (df = 15)	P-value
	M	SD	M	SD		
FVC	3.7	1	3.62	0.83	.234	.818
FVC % Predicted	106.8	14.3	103	14.4	.884	.391
FEV1	2.7	0.7	2.77	0.62	-.573	.575
FEV1 % Predicted	107.2	18.1	106.5	17.5	.133	.896
FEV1/FVC	74.3	8.1	76.5	5.1	-.838	.415
PIF	1.4	0.04	3.77	1.44	1.91	.075
PEF	7.4	1.8	6.4	1.81	2.67	.017*
PEF % Predicted	113.9	19.9	95.9	18.6	3.1	.008*
FET	10.8	3.1	9.46	3.38	1.05	.312
FIVC	3.4	1.1	3.2	1.22	.595	.561

* significant at $p \leq 0.05$

M = Mean, SD = Standard Deviation, df = degrees of freedom

FVC = Forced Vital Capacity, FEV1 = Forced Expiratory Volume in 1 second, FEV1/FVC = Forced Expiratory Volume in 1 second over Forced Vital Capacity, PIF = Peak Inspiratory Flow, PEF = Peak Expiratory Flow, FET = Forced Expiratory Time, FIVC = Forced Inspiratory Vital Capacity

Significant differences were observed between earlier and later stage PD patients for FEV1/FVC and FET measurements (Table 6.3). Individuals with PD presented with significantly higher FEV1/FVC ratio and reduced FET compared to later stage PD, pointing towards a reduction in respiratory muscle activity causing low lung volumes and borderline restrictive spirometry patterns. No other significant differences were found.

Table 6.3 Means and Standard Deviations for Spirometry for Patient Participants with Earlier PD and Later PD

Spirometry values	Earlier PD		Later PD		T (df = 30)	P-value
	M	SD	M	SD		
FVC	4.33	1.07	3.8	0.88	.55	.132
FVC % Predicted	104.4	18	102.1	12.3	.426	.673
FEV1	3.15	0.64	2.9	.79	.620	.540
FEV1 % Predicted	104.3	21.7	107.3	13.1	-.473	.640
FEV1/FVC	73.5	7.88	78.56	5.45	-2.11	0.043*
PIF	4.26	1.61	4.23	1.4	.042	0.967
PEF	7.35	1.54	6.8	2.08	.851	0.402
PEF % Predicted	95.6	19.6	93.8	16.8	.280	.781
FET	11.8	2.76	8.84	2.8	3	0.005*
FIVC	4.17	1.07	3.33	1.29	2	0.054

* significant at $p \leq 0.05$

M = Mean, SD = Standard Deviation, df = degrees of freedom

FVC = Forced Vital Capacity, FEV1 = Forced Expiratory Volume in 1 second, FEV1/FVC = Forced Expiratory Volume in 1 second over Forced Vital Capacity, PIF = Peak Inspiratory Flow, PEF = Peak Expiratory Flow, FET = Forced Expiratory Time, FIVC = Forced Inspiratory Vital Capacity

The correlation of spirometry values to performance on swallowing assessments across all participants are provided in Table 6.4. Cohen, (1988) proposed the following guidelines for interpreting the strength of correlation: small correlation r = .10 to .29 or r = - .10 to - 2.9, medium correlation r = .30 to .49 or r = - .30 to - 4.9 and large correlation r = .50 to 1.0 or r = - .50 to – 1. Results that were statistically significant indicate medium correlation strength between swallowing capacity and most spirometry values. Specifically, there was a moderate, positive correlation between FVC, FEV1, PEF, FIVC and PIF and swallowing capacity. In addition, there is a small, positive correlation between FEV1/FVC and average sEMG amplitude.

There were also small, positive correlations between FEV1 and average sEMG (r = .111) and FEV1/FVC and swallowing capacity (r = .131). Despite these small correlations, statistical significance was not reached. Pallant, (2005) highlighted that the significance is strongly influenced by sample size so that in small sample sizes, small correlations may not reach statistical significance at the traditional p = .05. This explanation may hold true for the present study, since and N of 68 is not considered large for studies that investigate pulmonary function.

Table 6.4 Correlation of spirometry values for all participants to average sEMG and swallowing capacity

Spirometry values		FVC	FEV1	FEV1/ FVC	PEF	FIVC	PIF
Average sEMG [a]	Pearson Correlation	.048	.111	.246*	.058	.033	.009
	p value	.696	.366	.043	.638	.79	.945
Swallow-ing capacity [b]	Pearson Correlation	.374**	.410**	.131	.430**	.344**	.465**
	p value	.002	.001	.286	0	.004	0

N = 68. * Correlation is significant at the 0.05 level, ** Correlation is significant at the 0.01 level, determined by Pearson's product-moment correlation coefficient

[a] average sEMG amplitude (μ) obtained from 10 single, liquid swallows of 8ml

[b] Swallowing capacity calculated from the timed test of swallowing by Hughes & Wiles, (1996b)

6.5 Discussion

We sought to evaluate changes in pulmonary function as a result of ageing, PD and severity of PD. Results revealed that young adults had significantly larger FVC, FEV1, FEV1/FVC when compared to healthy elders (Table 6.1). When values within each group were compared expected values for persons of the same height, weight and gender (Hankinson et al., 1999) both young adults and elders were within the percentage of predicted values. Results also showed that PEF values between young adults and elders were significantly different (Table 6.1) but again, this was within predicted values. These findings support prior authors who documented that after the age of 21, an FEV1 loss of about 20 to 30 ml/year in non-smokers is considered normal (Crapo, 1994). As such, even though results were statistically significant, they were not clinically significant since both groups had normal values. Results of this study reflect normal biology of the ageing lung. Spirometry results were referenced to the NHANES III values, which were not only widely used but more importantly reproducible in the population included in this study (Swanney et al., 2005). This increased the validity of our measurements when comparing results from healthy adults against results from individuals with PD.

FET is a measure of the length of expiration in seconds and results revealed significant differences between young adult and elders (Table 6.3). This is expected, as the resistance of small airways increase with age (Svartengren, Falk, & Philipson, 2005) such that elders would require longer to fully expel the volume of air in their lungs. Even so, it must be highlighted that some authors believe that when compared to FEV1 and PEF, FET is not sufficiently robust as a test for small airways disease due to its variability when tested over 5 days (Macdonald, Cole, & Seaton, 1975). No significant differences were found for inspiratory measures: FIVC, PIF, suggesting that age alone does not affect forced inspiration manoeuvres and inspiratory flow rates in healthy persons, regardless of age.

PEF and percentage predicted PEF differed significantly between healthy elders and PD patients. Despite this, at 95.9%, the predicted PEF for PD patients were within the normal range, indicating no airway obstruction in this group. It is proposed that the difference seen was more likely due to the finding that healthy elders exceeded the predicated reference values by 13%.

In this study, the influence of disease severity was limited to FEV1/FVC and FET measurements (Table 6.3). The predicted normal FEV1/FVC in the general population is 70%, which means that healthy individuals are able to exhale at least 70% of their VFC in the first second (Wilkins, Stoller, & Scanlan, 2003). In obstructive disorders, the FEV1/FVC ratio may be as low as 20-30% due to low FEV1. In restrictive disorders, both FEV1 and FVC are low, leading to a normal, or even higher than normal FEV1/FVC ratio. Individuals with later stage PD demonstrate increased FEV1/FVC ration and reduced FET. The results of our study would point towards a restrictive spirometry pattern in later stage PD.

The FIVC was one measure that almost reached significant difference between early and later PD (Table 6.3). This deserves further exploration, as forced inspiratory measures are utilised clinically to demonstrate abnormalities in the larynx and proximal trachea such as laryngeal and tracheal obstruction or stenosis since the 1960s (Clark, 1970; Engstroem, Grimby, & Soederholm, 1964; Miller & Hyatt, 1973). Furthermore, the finding that forced vital capacity (FVC), slow vital capacity (SVC) and inspiratory vital capacity (IVC) were not significantly different in a small sample of healthy adults would suggest that any of these 3 vital capacity values may be used as a reliable indicator of vital capacity (Chhabra, 1998). Clark (1970) found it useful to distinguish patients with lesions of the trachea and larynx with healthy persons using FEV1/FEV1 ratio. As vocal fold insufficiency such as tremor contributes to vocal symptoms in PD (Holmes, Oates, Phyland, & Hughes, 2000), it would be useful for future studies to investigate whether inspiratory measures would be more useful than expiratory measures for this patient population. This would be particularly useful as our results show no difference between early and later stage PD for forced expiratory measure (FEV1) but a trend towards significance for inspiratory measure (FIVC).

One important contribution of the study was the attempt to correlate spirometry values to swallowing function. Several lines of research have reported that patients with neurological and pulmonary diseases present with impaired swallowing (Dettelbach et al., 1995; Logemann et al., 1998; Mokhlesi et al., 2002; Selley et al., 1989b). Results of the present study confirm a positive correlation between spirometry performance and swallowing function; larger spirometry measurements are directly associated with increased swallowing capacity and higher sEMG amplitude. In the same vein, one can speculate that impaired muscular function observed in later stage PD causing restrictive spirometry is correlated with reduced swallowing capacity. Future longitudinal studies may continue to see a parallel trend between

swallowing capacity, sEMG amplitude and performance of patients in spirometry. As yet, the small sample size in this study do not permit generalisation of results.

6.6 Conclusion

Despite earlier studies documenting obstructive respiratory patterns in PD cohort, (De Pandis et al., 2002; Herer et al., 2001; Sabate et al., 1996a; Vercueil et al., 1999) our results were unable to support this claim despite adhering strictly to guidelines by the ATS. Results of the present study did reveal a restrictive type respiratory pattern in later stages that is worthy of further investigation with a larger group of participants. For most spirometry measures comparing healthy young adults and healthy elders, we are confident that our results were able to support the normal age effects. Of interest for further exploration is the possibility that inspiratory manoeuvres may be more sensitive in detecting obstruction to the upper airways than forced expiratory manoeuvres in the PD cohort. Finally, the positive correlation between spirometry measures and swallowing capacity has important implications for swallowing safely in individuals with PD with respiratory dysfunction but would need to be confirmed with larger sample sizes.

Chapter 7. Cough Reflex and Chemo-sensitivity in Ageing and Parkinson's Disease

7.1 Introduction

Six different types of respiratory responses have been identified in humans when the tracheal mucosa is stimulated (Nishino et al., 1988) but it is undisputed that of these, coughing may be the single most important defence mechanism for airway clearance (Bickerman & Barach, 1954; Bickerman et al., 1956; French et al., 1998; Hutchings et al., 1993a; Hutchings et al., 1993b; Irwin et al., 1998; Karlsson, 1996; Pantaleo et al., 2002; Shannon et al., 1996). Coughing is aimed at removing mucus and or foreign particles from the respiratory tract and presents as the commonest respiratory symptom (Fuller & Jackson, 1990; Morice et al., 2001).

Despite the importance and prevalence of cough, the assessment of cough has lacked a systematic approach. One of the obstacles is the lack of a simple means of assessing it objectively. Cough challenge testing is a technique adapted from bronchial provocation tests involving the delivery of tussigenic agents and subsequent observation for cough responses. Figure 7.1 depicts different methods of cough challenge, reviewed by Morice et al., (2001).

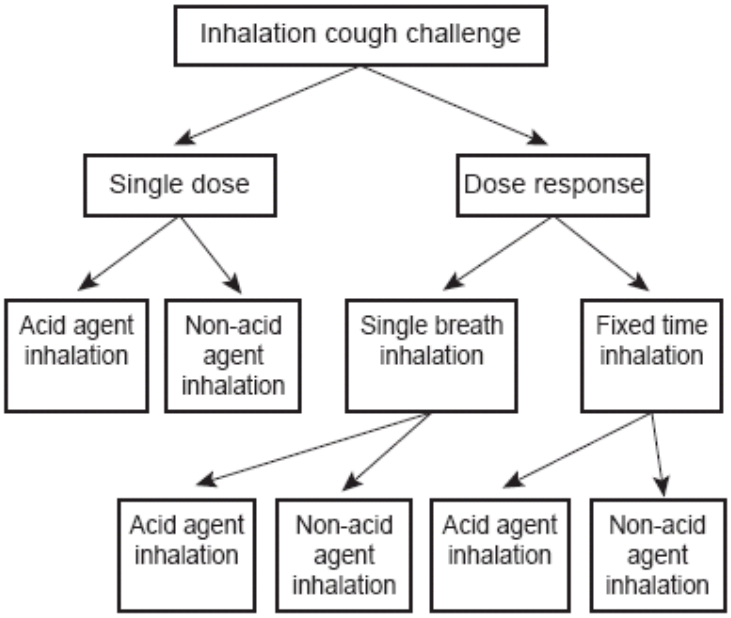


Figure 7.1 An overview of methodology of inhalation cough challenge. From Morice, A. H., Kastelik, J. A., & Thompson, R. (2001). Cough challenge in the assessment of cough reflex. British Journal of Clinical Pharmacology, 52(4), 365-375.

In brief, there are two main methods of cough challenge, namely single dose and dose-response. The former involves the administration of one concentration of tussigenic agent while the latter involves the administration of incremental doses. In the dose-response method, single or fixed time inhalation of 15 to 60 seconds may be employed. For both methods, however, either acid agents such as citric acid or non-acid agents such as capsaicin may be used.

Inhalation cough challenge is a means of evaluating laryngopharyngeal chemo-sensation (Addington et al., 1999a) and has been used in the investigation of the cough reflex and antitussives for over 50 years (Bickerman & Barach, 1954; Bickerman et al., 1956). Subsequent refinement of techniques have allowed the administration of inhaled irritants to be honed into a useful epidemiological and pharmacological tool (Auffarth et al., 1991; Dilworth et al., 1990; Higenbottam et al., 1989; Hutchings et al., 1993a; Hutchings et al., 1993b; Morice et al., 1994; Pounsford & Saunders, 1985; Prime, 1961). Despite this progress, two problems persist.

First, the cough reflex can be consciously suppressed or modified depending on instructions given instructions given. Evidence comes from a study by Hutchings et al., (1993b) where

participants underwent 2 sessions of cough challenge using 5 increasing concentrations of capsaicin. In the non-suppressed condition, participants were allowed to cough freely when shown a green traffic light. In another session, participants were shown a red light instructed to inhibit the urge to cough. In the suppressed cough condition, participants were able to almost completely inhibit the capsaicin induced cough, lending support to cortical control over cough. Even though researchers into the physiology of cough postulate that coughing is a reflex (Irwin et al., 1998; Irwin et al., 1977; Shannon et al., 1996), recent experimental information has indicated that voluntary control of cough is possible and that higher centres such as the cerebral cortex have an important role in initiating and/or inhibiting coughing (Hutchings et al., 1993a; Hutchings et al., 1993b; Lee et al., 2002). As such, whether the cough 'reflex' is truly reflexive is questionable. For studies that only document natural cough responses (example, Choudry & Fuller, 1992), the finding that individuals vary greatly in their sensitivity to tussigenic agents may be attributed to the fact that some participants may inhibit coughing without the investigator's knowledge.

More recently, Davenport (2007) continued to provide evidence for the cortical control of cough with the detailed description of the urge-to-cough (detailed in Davenport, 2007). The urge-to-cough was identified as a component of the brain that mediates cognitive responses to cough stimuli. Thus urge can be studied by measuring the sensations elicited by a cough stimulus. Results suggest that the urge increases with increasing cough stimulus, and that there is a correlation between the urge-to-cough and cough intensity. In addition, there is a threshold for eliciting the sensation of the urge that precedes the motor cough behavior. Participants were able to voluntarily produce coughs of varying magnitudes, depending on the intensity of the cough stimulus.

The second persisting problem is that the precise nature and clinical relevance of each individual type of cough challenge remains uncertain as there are no agreed universal standards. Normal values of the cough response to a particular tussive agent have not been established, making comparisons between centres difficult (Morice et al., 2001). The lack of universal standards and norms in cough challenge is unsurprising given the wide variety of tussigenic agents, concentrations and delivery methods. Despite this, authors are in agreement that inhalation cough challenge may be a potentially useful tool in the clinical setting as chemo-sensitivity is imperative for the generation of a reflexive cough (Addington et al., 1999a; Fuller, 2002; Hutchings et al., 1993b; Lee et al., 2002; Morice, 1996; Morice et al., 2001).

Silent aspiration is considered to be very important in the pathogenesis of aspiration pneumonia in older persons (Daggett et al., 2006; Gleeson et al., 1997; Matsuse et al., 1996; Pontoppidan & Beecher, 1960). Pontoppidan & Beecher (1960) stressed that pneumonia may be prevented by defence mechanisms of the upper airway reflexes such as coughing. As such, age-dependent declines of coughing may contribute to the development of aspiration pneumonia in elders. It has been proffered that elders are slower to clear particles from the airway, possibly due to impaired mucociliary function that accompanies aging (Teramoto et al., 1999). In addition, Teramoto et al., (2005) highlights that in elderly patients, the cough reflex, rather than mucociliary clearance, is most important for the prevention of pneumonia. Significant decreases in cough reflex were observed in elderly patients with aspiration pneumonia (Sekizawa et al., 1990).

There are very few published data on the cough reflex in ageing. One study almost half a decade ago (Pontoppidan & Beecher, 1960) demonstrated significant reduction in sensitivity in elders when compared to young adults in a cough challenge using inhaled ammonia. More recently, Newnham & Hamilton (1997) compared the number of coughs in 20 young adults (mean age 27) and 20 elders (mean age 83) using distilled water. Authors reported that elders demonstrated significantly less coughs compared to young adults, suggesting less sensitivity. Although it may be reasonable to expect decreased sensitivity as a function of age, one research group published data to suggest that elders have normal cough reflexes (Katsumata et al., 1991). These disparate results further suggest that the physiology underlying cough reflex is yet to be fully understood.

Notwithstanding, the importance of cough reflex in the neurogenic population cannot be underestimated. Delayed recovery of the cough reflex has been postulated to increase morbidity and mortality (Addington et al., 1999a; Ebihara et al., 2003; Smith & Wiles, 1998). Stroke patients with weak cough have an increased risk of developing aspiration pneumonia (Smith Hammond et al., 2001). Addington, Stephens, & Goulding, (1999b) administered cough challenge in 400 acute stroke patients with the aim of using this assessment to identify patients who were thought to be at risk of developing aspiration pneumonia. Depending on the patient's response to a single dose of tartaric acid, a score of normal, weak or absent was assigned. Patients with absent or weak scores were nil by mouth or recommended restricted diets while patients with a normal cough response and cognizant were fed orally. A comparison of the incidence of pneumonia was done with a sister hospital whose patients did

not receive the cough challenge. Results show that 1% of those who received cough challenge developed pneumonia compared to 13% of those who did not. The reported morbidity rates as a result of pneumonia were more severe in those who did not have the cough challenge.

Unfortunately, the study did not reveal how cognitive status was determined or why 20% of tartaric acid was chosen over other concentrations. Furthermore, there were no objective definitions for the classification of cough responses, i.e. normal vs. weak. It would be erroneous to assume that a weak cough response is due to laryngeal insensitivity alone as it is possible for weak cough responses to be due to respiratory muscle weakness secondary to a neurogenic event (Fugl-Meyer et al., 1983). No correlations to motor control of cough were made in the Addington et al study. It would be important to have clear definitions for cough responses (weak vs. strong) and cognitive status. It would also be helpful to speculate on the reasons of raised threshold in acute stroke. These were not adequately addressed.

In Parkinson's disease (PD), aspiration pneumonia is still the leading cause of mortality despite advances in the treatment of PD symptoms (Wang et al., 2002). Weakness in muscles involved in coughing has been demonstrated in this population (Fontana et al., 1998) but sensory aspects of coughing cannot be overlooked, as the loss of sensation for coughing plays a part in the development of aspiration pneumonia (Niimi et al., 2003). When the motor component of cough efficacy was compared to sensory aspects of cough using citric acid, Ebihara et al., (2003) found that in the early stages of the disease, mainly motor control was impaired with preservation of sensory aspects. In the later stages of the disease, however, both motor and sensory components of cough were affected. Citric acid cough thresholds in individuals with PD were significantly higher when compared to healthy controls, suggesting reduced sensation, especially in the later stages of PD.

Fontana et al., (1998) used distilled water delivered in increasing concentrations of aerosol/fog as the tussigenic agent in a group of 23 patients with idiopathic PD to determine cough threshold. The authors reported that although increased cough threshold in patients was seen in PD, results failed to reach statistical significance when compared to healthy, age-matched controls. Whether reduced cough sensitivity is a consistent feature in neurogenic population remains to be elucidated, since Smith & Wiles (1998) reported that in a group of patients with neurogenic dysphagia of mixed aetiology, cough responsiveness to fixed-time, dose response capsaicin cough challenge was *enhanced* when compared to their non dysphagic counterparts: those with abnormal swallowing had a lower cough threshold.

In summary, there is equivocal evidence that cough sensitivity is impaired in the neurogenic population, including PD. Desensitisation of pharyngeal, laryngeal or tracheal mucosa resulting in failure to clear substances from the upper airway is thought to be the result of impairment to the sensory components of the vagus and glossopharyngeal nerves. This may account for the high incidence of silent aspiration and subsequent aspiration pneumonia, the leading cause of death in this cohort. Even so, current literature in cough sensitivity testing is equivocal. Direct comparisons between studies are impossible due to methodological differences. Nonetheless, the study by Smith & Wiles (1998) and subsequently Ebihara et al., (2003) highlight the importance of assessing cough sensitivity as a possible contributor of dysphagia and/or silent aspiration in PD. Future studies can refine methods for this assessment based on the recommendations by Smith & Wiles, (1998).

7.2 Hypotheses

1. There will be significant differences in laryngopharyngeal chemo-sensitivity on citric acid inhalation cough challenge thresholds between young adult and healthy elders. Young adults will demonstrate significantly higher chemo-sensitivity when compared to healthy elders.
2. There will also significant differences in laryngopharyngeal chemo-sensitivity on citric acid inhalation cough challenge thresholds between elders and patients with PD. Healthy elders will demonstrate significantly higher chemo-sensitivity when compared to patients with PD.
3. Finally, there will be significant differences in laryngopharyngeal chemo-sensitivity on citric acid inhalation cough challenge thresholds between those in the earlier stages of PD (H-Y $\leq$ 2) when compared to those in the later stages of PD (H-Y $\geq$ 2.5). Patients in the earlier stages will demonstrate significantly higher chemo-sensitivity when compared to those in the later stages.

7.3 Data Processing and Preparation

The inhalation cough challenge test sessions were video-recorded and the number of natural and suppressed coughs was recorded by manually counting the number of coughs generated. A random 25% of the entire data set were reanalysed by the primary rater (LP) and independent raters (IS and AL) in order to determine the intraclass correlation coefficients for intra- and inter-rater reliability. Mann-Whitney U-tests were conducted to compare

concentrations at which natural and suppressed cough occurred between healthy young adults and elders. Wilcoxon signed-rank tests were conducted to compare concentrations at which natural and suppressed cough occurred between elders and those with PD. Group (Young, Elders, PD) was entered as the independent variable and Citric Acid Concentration (where 1 = 10mM, 2 = 30mM, 3 = 100mM, 4 = 178mM, 5 = 316mM, 6 = 562mM, 7 = 1M, 8 = 1.2M, 9 = 1.4M, 10 = 1.6M, 11 = 1.8M, 12 = 2M) for natural and suppressed cough was entered as the dependent variable.

7.4 Results

For both healthy young adults and elders, normal cough threshold (M = 4.9, SD = 2.7) was always significantly lower than the suppressed cough threshold [(M = 8.2, SD = 3.5), Z = -4.7, p = .001]. Detailed analysis comparing young adults and elders using Mann Whitney test showed no difference between healthy young adults and elders for natural cough thresholds (Z = -1.7, p = .102), but a significant difference in suppressed cough thresholds (Z = -2.4, P = .021) (Figure 7.2), with youngers demonstrating greater ability to inhibit cough.

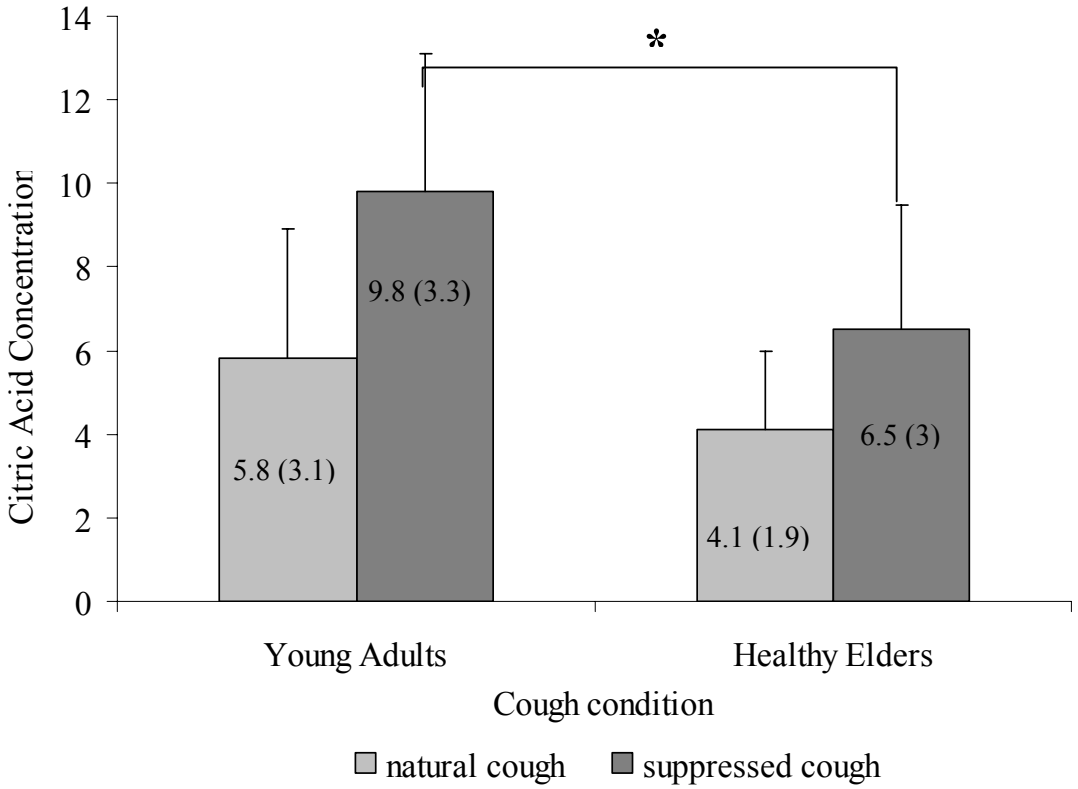


Figure 7.2 Means and Standard Deviations for Natural and Suppressed Cough Challenge for Healthy, Young Adults and Healthy Elders.

Note: * = Significant difference (p = .021) determined by Mann Whitney test

The Wilcoxon signed-ranks test showed no difference for natural cough thresholds between healthy elders (M = 4.06, SD= 1.88) and those with PD [(M = 4.81, SD=2.51), Z = -1.03, p = .306]. There was also no difference for suppressed cough thresholds between healthy elders and those with PD (Z = -.475, p = .635) (Table 7.1).

For patients in the earlier and later stages of PD, normal cough threshold (M=4.69, SD=2.25) is always significantly lower than the suppressed cough threshold [(M= 5.97, SD=2.51), Z=-3.87, p=.001]. In addition, Mann Whitney test showed no difference between those with earlier PD (M = 4, SD 1.2) and those with later PD (M = 5.4, SD = 2.8) for natural cough thresholds (Z=-1.427, p=.171 and suppressed cough (Z=-1.071, P=.305) (Table 7.1).

Table 7.1 Means and Standard Deviations for Natural and Suppressed Cough Threshold Concentrations for Each Group

Groups	Young Adults		Healthy Elders $^{\Delta}$		PD Patients $^{\Delta}$		Earlier PD^{O}		Later PD$^{\square}$	
	M	SD	M	SD	M	SD	M	SD	M	SD
Natural cough threshold	5.8	3.1	4.1	1.9	4.8	2.5	4	1.2	5.4	2.8
Suppressed cough threshold	9.8	3.3	6.5	3	6	2.6	5.5	2.3	6.4	2.7

Note: M = mean, SD = standard deviation

$^{\Delta}$ Elders age- and gender-matched to PD across severity levels

^{O} Early PD = Hoehn-Yahr ≤ stage 2

$^{\square}$ LAter PD = Hoehn-Yahr ≥ stage 2.5

When Wilcoxon signed-ranks test was conducted to investigate the distance between natural and suppressed cough, results did show a significant difference in the distance between cough thresholds (natural and suppressed) for elders and those with PD. Specifically, there was a greater distance between natural and suppressed cough for elders (M = 2.44, SD = 1.79) compared to those with PD [(M = 1.19, SD =1.22), Z = -1.97, p = .049], suggesting greater ability to suppress cough. Mann-Whitney U showed no statistical difference in the distance between cough thresholds for young adults and elders (Z = -1.66, p = .098). Finally, Mann-

Whitney U showed no difference in the distance between cough thresholds for patients with earlier PD and later PD ($Z = -1.13$, $p = .259$).

7.5 Discussion

Most prior research suggests desensitisation of cough reflex in ageing and disease (Ebihara et al., 2003; Fontana et al., 1998; Newnham & Hamilton, 1997; Niimi et al., 2003; Pontoppidan & Beecher, 1960), with fewer studies reporting increased sensitivity (Katsumata et al., 1991; Smith & Wiles, 1998). Results of this study supported latter studies by Katsumata et al., (1991) and Smith and Wiles (1998), where natural cough responses were not significantly increased by age, disease and disease severity. There was a trend toward lower natural cough thresholds in healthy elders compared to healthy young adults.

Although it may be hypothesised that patients who are in the later stages of PD may have decreased cough sensitivity due to disease progression, results of the present study did not support this hypothesis. Even individuals with PD with more severe symptoms and hence, implicit aspiration risk have similar natural cough responses compared to those with less severe symptoms. A single study has reported a significant difference in early and late stage individuals (Ebihara et al., 2003) but that study was methodologically different from this study in three ways. First, early stage patients in Ebihara et al's study consisted of patients in Hoehn and Yahr (H-Y) stages 2 and 3 while patients allocated to the late stage group were in H-Y stage 4. By comparison, this study dichotomised severity level by categorising H-Y stage ≤ 2 as early stage and those in H-Y stage ≥ 3 as late stage. Non significant trends between those in the earlier and later stages in our study may be accounted for by the inclusion of stage 3 patients in the later group, who may not be as insensate as those in stage 4.

Second, the Ebihara study used fixed-time inhalation challenge of 1 minute per citric acid concentration. The present study followed the published protocol by Morice (1996) using single inhalation dose-response method. It is possible that individuals with PD require more citric acid particles to be deposited before cough sensory thresholds are breached, which would only be possible with extended inhalation periods.

Finally, only females were assessed in Ebihara et al's study, whereas the present study included male participants. Although there is justification for limited assessment to one gender due to known gender differences in cough sensitivity (Dicpinigaitis et al., 2001;

Fujimura et al., 1996; Rostami-Hodjegan, Abdul-Manap, Wright, Tucker, & Morice, 2001), it is equally important for males and females to be represented especially when there is a greater preponderance of males with PD (Wooten et al., 2004). This study, included 65% and 35% of males and females respectively, comparable to literature that report 61% and 39% males and females with PD (Van Den Eeden et al., 2003).

For all participants regardless of age, disease and disease severity, suppressed cough response was always significantly higher than natural cough response, lending strong support for the voluntary control of cough described by Hutchings, Morris et al., (1993b). These authors counterbalanced two cough challenges 5 minutes apart with the instructions to cough or to suppress cough. Participants in this study underwent only one session of cough challenge, with similar instructions. The method employed in this study presents a novel way of assessing natural and suppressed cough. With the need for only 1 session, participants do not repeat the concentrations that they no not naturally cough at e.g. lowest concentration. The reduced time required also makes this way of testing more feasible in a clinical setting.

This study revealed that young adults demonstrate significantly higher suppressed cough threshold compared to healthy elders (Figure 7.1), reflecting a greater capability to voluntarily suppress coughing when required. The capability to suppress cough may be further assessed by measuring the distance from the time natural cough happens to the time that cough can no longer be suppressed. When this was calculated, results revealed significantly greater distance between natural and suppressed cough for elders compared to those with PD. In other words, those with PD were not able to suppress cough as well as their counterparts without PD. Cognitive influences may have influenced the ability to follow instructions to suppress cough in individuals with PD but all patient participants had cognition within normal limits (Mini Mental State Examination Score $\geq$ 24). It is more likely that in patients, the need to protect that airway from noxious stimuli supersedes any instruction to suppress cough.

7.6 Conclusion

We were unable to conclude that natural cough sensitivity decreases with age and disease. This research provided evidence for voluntary control of cough. Thus, the importance of assessing suppressed cough thresholds in future studies cannot be underestimated in light of the finding that coughing may be voluntarily suppressed. When instructed to suppress cough, elders demonstrated significantly lower suppressed cough threshold when compared to young

adults. Those with PD are less able to suppress cough compared to their age/gender-matched counterparts, based on the significantly smaller distance between natural and suppressed cough. It is plausible that the need for airway protection is more important than the call to stifle coughing. This hypothesis, in addition to the finding that elders demonstrate a trend toward heightened natural cough sensitivity, may suggest increased airway protection with age and disease.

Chapter 8. Laryngeal Adductor Reflex and Mechano-sensitivity in Ageing and Parkinson's Disease

8.1 Introduction

Laryngopharyngeal mechano-sensation is linked to protective mechanisms and reflexes that serve to prevent aspiration of food into the upper airway (Aviv et al., 1994; Bradley, 2000; Miller, 1999). The complete adduction of vocal folds just prior to diaphragmatic contraction for the cessation of breathing has been termed glottic closure reflex (Curtis & Langmore, 1997), pharyngoglottal reflex (Ren et al., 1994; Shaker et al., 1998; Shaker et al., 2003), and laryngeal adductor reflex (LAR) (Aviv et al., 2000). Despite different terminology, authors agree that this reflex results in brief closure of the true vocal folds in response to mechanical stimulation to the mucosa of the interarytenoid and lateral cricoarytenoid muscles. Aviv et al., (2000) add that glottic closure is a brainstem driven response that precludes conscious control.

Assessment of laryngopharyngeal sensitivity poses difficulties as mechano-stimulation of the oropharynx produces the gag reflex, which is uncomfortable for the patient and has been established as having very little predictive value for airway protection (Davies et al., 1995; Leder, 1996, 1997). Furthermore, the pharynx and larynx are anatomically difficult to access (Aviv, 1997b). Since the late 1980s, fibreoptic nasendoscope has been used to evaluate swallowing (Langmore et al., 1988). Fibreoptic endoscopic evaluation of swallowing (FEES) provides direct visualisation of the nasopharynx, oropharynx, larynx and hypopharynx using a standard nasendoscope (Langmore & McCulloch, 1997). This examination can be augmented to assess mechano-sensation by providing light touch to the pharyngeal walls, base of tongue or the epiglottis with the tip of the scope (Langmore & Aviv, 2001). Observable patient reactions that suggest sensitivity may include the laryngeal adductor response (LAR), eye blinking, tearing, throat clearing, swallowing and coughing (Langmore & Aviv, 2001).

It is acknowledged that sensitivity testing using the tip of the endoscope offers a coarse, qualitative test that may uncomfortable for the patient. In the last decade, Aviv (1997b) described a new method for sensory testing using a modified endoscope that houses an extra lumen for the delivery of discrete air puffs ranging from 2 to10mmHg. This method, known as fibreoptic endoscopic evaluation of swallowing with sensory testing (FEESST) has proven

to be a safe (Aviv et al., 2002) and fairly reliable (Aviv et al., 1999) method of testing laryngopharyngeal mechano-sensation.

Aviv et al., (1994) documented deterioration of sensation in the laryngopharynx in 80 adults aged between 23-87 using FEESST. It was reported that average sensory thresholds were 2.3mmHg across all ages, with increased thresholds significantly and positively correlated with age. Specifically, average air pressures of those aged 20-40, 41-60 and 60+ were documented at 2.06, 2.45 and 2.97mmHg respectively. Thresholds for adults < 60 were significantly different to those > 60. Previous research has reported the loss of sensation in the pharynx and larynx after a neurological event such as stroke (Aviv et al., 1997a; Aviv et al., 1997b; Kidd et al., 1993, 1995); it would not be surprising if this extends to other neurological disorders such as PD. However, evidence for a reduction in laryngopharyngeal sensation is lacking in PD despite the high incidence of silent aspiration in this patient cohort, which suggests deterioration in sensation.

In a study of 500 FEESST examinations in 253 patients of mixed aetiologies (Aviv et al., 2000), only 13 patients had a diagnosis of PD. The focus of that study was on the safety of the procedure and no reference values were published. Using the same procedure on 15 post stroke patients, with equal numbers of age-matched controls, Aviv et al., (1996) reported that stroke patients responded at significantly higher thresholds compared to controls. No patient responded to pressure below 4mmHg, with most responding above 6mmHg. Subsequently, sensory thresholds were defined as normal: < 4mmHg, moderately impaired: 4-6mmHg, or severely impaired: > 6mmHg of air pressure (Aviv et al., 1997b).

Even though these values are specific to a small sample of stroke patients, it does provide some reference values for patients with neurological disorders. More importantly however, there remains a gap in the knowledge of laryngopharyngeal deficits in the PD population that needs to be addressed. Although research using FEESST has been invaluable in providing information regarding age and disease effects on laryngopharyngeal sensation, the need for specialised equipment such as an air pulse generator and modified endoscope makes the complete set up for FEESST expensive and largely unavailable. No research has evaluated the qualitative method described by Langmore & Aviv (2001) to compare mechano-sensitivity in age and disease, which may prove to be the more clinically available technique. Binary decisions as to the presence or absence of sensation would also provide important information

that may help to guide treatment plans. In this chapter, data using the qualitative method of sensory testing are presented.

8.2 Hypotheses

1. There will be significant differences in laryngopharyngeal mechano-sensitivity between young adults and healthy elders who undergo mechano-sensory testing. Young adults will demonstrate significantly higher mechano-sensitivity when compared to healthy elders.
2. There will also be significant differences in laryngopharyngeal mechano-sensitivity between elders and patients with PD who undergo mechano-sensory testing. Healthy elders will demonstrate significantly higher mechano-sensitivity when compared to patients with PD.
3. Finally, there will be significant differences in laryngopharyngeal mechano-sensitivity between those in the earlier stages of PD (H-Y $\leq$ 2) when compared to those in the later stages of PD (H-Y $\geq$ 2.5) who undergo mechano-sensory testing. Patients in the earlier stages will demonstrate significantly higher mechano-sensitivity when compared to those in the later stages.

8.3 Data Processing and Preparation

Binary 'yes' or 'no' choices were entered as positive response or negative response to tactile stimulation using the tip of the endoscope. Bilateral base of tongue (BOT), posterior pharyngeal wall (PPW) and aryepiglottic folds (AEF) were assessed by the primary rater (LP) and responses were coded using the agreed consensus of two speech-language therapists familiar with endoscopy (LP and MLH). Chi-square test for independence was used to analyse observed and expected counts for the presence or absence of sensation. Group (Young adults, elders and PD) and sensitivity (yes or no) were used as the categorical variables. Due to the small sample size, p values from Fisher's exact test (Fisher, 1922) were used to determine significance.

8.4 Results

Chi-square analysis results are presented in Table 8.1. No significant difference in laryngopharyngeal mechano-sensitivity was identified between healthy young adults and healthy elders at all 6 test sites (Table 8.1). There was a significant difference in response to mechano-sensation at bilateral BOT between healthy elders and those with PD. Specifically,

those with PD demonstrated significantly reduced sensation compared to their age and gender-matched counterparts. No significant differences were found between those with earlier PD and those with later PD.

Even though no other significant main effects were obtained, closer inspection of the raw data in Table 8.1 shows some trends towards decreased sensation for all other test sites in PD compared to healthy elders. Specifically, a further decrease of sensation ranging from 10% at the left aryepiglottic fold to 34% (at the right posterior pharyngeal wall was seen in individuals with PD.

Table 8.1 Percentage Positive and Negative Responses for Laryngopharyngeal Sensitivity

	Fisher's Exact	Site of Test	Group	Positive Response (%)	Negative Response (%)
Healthy, Young adults and Healthy Elders	.484	Right BOT	Young	87.5	12.5
			Elders	100	0
	1	Left BOT	Young	93.8	6.3
			Elders	100	0
	1	Right PPW	Young	93.8	6.3
			Elders	87.5	12.5
	.333	Left PPW	Young	93.8	6.3
			Elders	75	25
	.484	Right AEF	Young	100	0
			Elders	87.5	12.5
	1	Left AEF	Young	100	0
			Elders	93.8	6.3
Age and Gender Matched Elders and those with PD [o]	**.004***	Right BOT	Elders	100	0
			PD	53.8	46.2
	.004*	Left BOT	Elders	100	0
			PD	53.8	46.2
	.092	Right PPW	Elders	87.5	12.5
			PD	53.8	46.2
	.270	Left PPW	Elders	75	25
			PD	53.8	46.2
	.624	Right AEF	Elders	87.5	12.5
			PD	75	25
	.560	Left AEF	Elders	93.8	6.3
			PD	83.3	16.7
Earlier PD and Later PD [□]	.707	Right BOT	Earlier	62.5	37.5
			Later	50	50
	1	Left BOT	Earlier	50	50
			Later	50	50
	.459	Right PPW	Earlier	50	50
			Later	66.7	33.3
	.705	Left PPW	Earlier	56.3	43.8
			Later	66.7	33.3
	.092	Right AEF	Earlier	87.5	21.5
			Later	53.8	46.2
	.632	Left AEF	Earlier	87.5	12.5
			Later	76.9	23.1

[o] Elders age- and gender-matched to PD across severity levels

[□] Earlier PD = Hoehn-Yahr ≤ stage 2, Later PD = Hoehn-Yahr ≥ stage 2.5

BOT = base of tongue, PPW = posterior pharyngeal wall, AEF = aryepiglottic fold

Note: * significant at $p \leq .05$, determined by McNemar Chi-Square test

8.5 Discussion

This is the first study to use qualitative sensory testing as described by Langmore & Aviv (2001) for the assessment of laryngopharyngeal mechano-sensation. Key findings from this analysis would support the conclusion that sensation remains intact as long as there was no evidence of neurological disease, as is the case with healthy participants in this study. Individuals with PD, however demonstrate sensory loss at the base of tongue compared to their healthy counterparts.

Afferent nerves for general sensation to the posterior 1/3 of the tongue and the posterior pharyngeal wall are subserved by the glossopharyngeal nerve (GPN) while the aryepiglottic folds are innervated by the internal branch of the superior laryngeal nerve (SLN). Even though significant decreases to the number of human superior laryngeal nerve (SLN) fibres have been documented due to ageing (Mortelliti et al., 1990), this change was not reflected in the loss of mechano-sensation to the AEF of healthy participants in this study.

Sensory loss was significant at BOT of those with PD, which may account for the common finding of valleculae residue (Leopold & Kagel, 1997b). The finding that sensory loss was not evident in elders but present in individuals with PD illustrates a point of discussion offered by Murray & Sullivan (2006). These authors speculate that the body of a healthy person includes several safety margins to prevent the body from failing when it is overloaded by episodes like disease or injury. Only 30% of normal capacity is used to perform activities of daily living. With 70% in reserve, this unused potential is harvested when required to cope with disease, injury or infections.

There is evidence that the model provided by Murray & Sullivan (2006) holds true in motor control. It is plausible that healthy elders accommodate physiologic decline and use available strength more efficiently as they age. For example, Nicosia et al., (2000) demonstrated age-related changes in isometric lingual pressure generation and in peak lingual pressures used in swallowing by comparing young adults and elders. When elders were asked to give a maximum effort by pressing their tongue against a manometric array, peak pressures were lower when compared with a younger group. However, peak swallowing pressures between young adults and healthy elders remained roughly equivalent. This study demonstrated that although a reduction in functional reserve is expected in healthy elders, the pressure needed to

perform the task of swallowing was still within their range of strength. However, when an overlying disease process is present in an elder, the fine gap between available reserve and minimum necessary strength can be compromised, leading to poor outcome (Barczi, Sullivan, & Robbins, 2000).

By the same analogy, it maybe hypothesised that the sequalae of nerve fibre loss was not sufficient to manifest as sensory loss in healthy ageing, hence no significant age differences found, but is enough to do so in the presence of PD (difference in BOT sensation between healthy elders and patients with PD). Elders with muscle weakness but intact sensation might compensate by increasing strength to accommodate the bolus but in PD, because of decreased sensation, there is no compensation for weakness, accounting for post swallowing residual. No one has investigated the functional reserve in terms of sensation, therefore this hypothesis remains speculative. A manometric study comparing pharyngeal sensation and pharyngeal weakness may be useful to investigate whether patients with lower pharyngeal pressures and sensory loss exhibit more valleculae residual compared to those without sensory loss.

From the results of this study, it maybe hypothesised that tongue pumping behaviour seen in PD may also be related to sensory loss. Individuals with PD may repetitively pump the tongue to attempts to advance the bolus from anterior to posterior in an attempt to trigger sensory receptors for pharyngeal swallowing.

It may be argued that sensory testing with FEES alone in the absence of a means to quantify sensation or sensory loss is not a valid test of sensation. It is acknowledged that FEES with qualitative sensory testing may not be sensitive enough to detect small sensory changes. Not withstanding, it may be useful to detect larger or gross sensory loss. Even though mechano-desensitisation may be expected and has been documented with age (Aviv, 1997a; Aviv et al., 1994) using FEESST, it is of note that the difference between the youngest group (age 20-40) and the eldest group ($\geq$ 61) was less than 1mmHg. There were not attempts to correlate age-accompanied sensory changes to swallowing processes in Aviv's study, making it difficult to establish if sensory loss of less than 1mmHg between young adults and elders also translated to airway protection compromise.

Our study demonstrated that a differentiation between healthy adults and those with PD was still possible using qualitative sensory testing, supporting other findings using quantitative means (FEESST) in neurological disorders (Aviv et al., 2000; Aviv et al., 1996). It is further

acknowledged that there is no means of quantifying sensory loss using the method in this study. However, similar criticism may be applied to FEESST. As the highest limit of deliverable pressure is 10mmHg, there is also no quantification of severe sensory loss above 10mmHg. In a different study, Phua, McGarvey, Ngu, & Ing, (2005) demonstrated that those with cough and reflux disease have impaired laryngopharyngeal mechano-sensitivity and many patients did not respond to air pulse stimulation even at the highest pressures (10mmHg), illustrating that quantification of sensory loss beyond 10mmHG is not possible.

The clinical importance of assessing reduced laryngopharyngeal sensation is heightened by the suggestion that sensory loss may be associated with an increased risk of aspiration pneumonia (Aviv et al., 1996; Kidd et al., 1995; Langmore, 1998). Thus, one might predict that patients with reduced sensation would often be silent aspirators. However, Aviv et al., (1997a) reported that 9 out of 10 patients who aspirated on VFS had bilateral laryngopharyngeal sensory deficits but only 1 of these 9 patients demonstrated silent aspiration. From this observation, Langmore (1998) rightly highlighted that this is because silent aspiration implies subglottic insensitivity (recurrent laryngeal nerve), whereas FEESST assesses the integrity of the supraglottic region innervated by the SLN. Perhaps this is the reason why a direct comparison between mechano-sensation and silent aspiration has yielded poor correlations. Although supraglottic sensation may not directly relate to silent aspiration and risk of prandial airway compromise, decreased sensitivity in the laryngopharynx may still impact airway protection indirectly. Patients with post swallow residual may not be able to respond to pharyngeal residual, thereby risking post swallow aspiration.

8.6 Conclusion

This study was the first to document that FEES with qualitative sensory testing was sensitive enough to detect differences between healthy adults and those with PD. This may have implications for the perception of residual in this patient cohort. BOT desensitisation seen in PD may account for the frequent vallecular residue and complaints of food sticking in the throat. It is acknowledged that qualitative sensory testing may not be sensitive enough to detect other differences. There is a need for future studies to correlate the use of qualitative sensory testing to FEESST. In addition, future studies would need to correlate mechano-sensation and swallowing function to establish and quantify how much mechano-sensation contributes to overall airway protection.

Chapter 9. Swallowing and Quality of Life (SWAL-QOL) in Ageing and Parkinson's Disease

9.1 Introduction

The social and psychological consequences of dysphagia are under-researched despite many reports that social isolation from having dysphagia can have a profound impact on a person's quality of life (QOL) (Ekberg, Hamdy, Woisard, Wuttge-Hannig, & Ortega, 2002; Gustafsson, 1995; Jacobsson, Axelsson, Osterlind, & Norberg, 2000; Lai, Studenski, Duncan, & Perera, 2002; Langmore, 1999). Mealtimes are social opportunities and normally a pleasurable experience for healthy persons but it has been reported that dysphagia can devastate the social opportunities and enjoyment associated with mealtimes. From a multi-site study of 360 of elderly patients, detailed interviews uncovered that even though 84% felt that eating should be a pleasurable experience, only 45% found that to be true. 41% admitted to feelings of panic and anxiety during mealtimes, with 35% avoiding meals in the presence of company because of dysphagia (Ekberg & Feinberg, 1991). In addition to social isolation, depression may result from having to live with the consequences of dysphagia (Langmore, 1999).

Prior research has also shown that elders (de Luis et al., 2006) and patients with PD (Hobson et al., 2001) with dysphagia have decreased quality of life. Social isolation and depression are also commonly reported in PD (Miller et al., 2006b; Playfer, 1999). Although quality of life related to dysphagia has been researched, these have either combined several medical diagnoses (Ekberg & Feinberg, 1991), used subjective evaluations of dysphagia (Miller et al., 2006a) and/or administered questionnaires that assess overall QOL without specific regard for swallowing impairment (de Luis et al., 2006; Hobson et al., 2001; Slawek et al., 2005). As such, health-related QOL in PD using generic measures that are biased towards physical signs are unable to fully investigate the independent effect of dysphagia on QOL. Furthermore, most studies have not included matched controls to healthy persons. Although QOL may be reduced in elders with dysphagia (de Luis et al., 2006), there is insufficient evidence that QOL decreases in healthy elders without dysphagia. Nonetheless, it would be important to rule out any influences of healthy ageing and look for pre-symptomatic signs that may alert healthcare professionals to future problems.

The purpose of this study was to assess the impact of dysphagia on quality of life in ageing and PD using the SWAL-QOL, a 44 item, validated questionnaire (McHorney et al., 2002). Full SWAL-OQL questionnaire is found in Appendix C. Furthermore, as disease severity has been associated with further decrease in general QOL (Hobson et al., 2001) with an increase in dysphagia symptoms (Coates & Bakheit, 1997), it expected that this will be reflected as a decrease in SWAL-QOL scores.

9.2 Hypotheses

1. There will be no significant differences in SWAL-QOL scores between young adults and healthy elders.
2. There will be significant differences in SWAL-QOL scores between elders and patients with PD. Healthy elders will demonstrate significantly higher SWAL-QOL scores when compared to patients with PD.
3. There will also be significant differences in SWAL-QOL scores between those in the earlier stages of PD (H-Y $\leq$ 2) when compared to those in the later stages of PD (H-Y $\geq$ 2.5). Patients in the earlier stages will demonstrate significantly SWAL-QOL scores when compared to those in the later stages.

9.3 Data Processing and Preparation

Analysis for this present study followed the outline described by McHorney et al., (2000b) the authors of the SWAL-QOL. McHorney et al. constructed each scale using the Likert method (Likert, 1932). Briefly, in this method of summated ratings, each item is equally weighted and summed into an overall scale score. This allowed each question was linearly transformed to a 0–100 metric, with 100 indicating the most favorable state, 0 the least favorable, and scores in between representing the percentage of the total possible score achieved. The Likert method of scaling assumes that each item correlates substantially with the scale it is hypothesised to represent, that is, each item on the SWAL-QOL correlates positively with quality of life with dysphagia.

Independent samples t tests were conducted to compare the subsection total and overall total scores obtained from the SWAL-QOL between healthy young adults and elders. Paired samples t tests were conducted to compare the subsection total and overall total scores obtained from the SWAL-QOL between healthy elders who were age and gender-matched to patients with PD. Group (Young, Elders, PD) was entered as independent variable. Scores for

each subsection (Food selection, Burden, Mental Health, Social Functioning, Fear, Eating Duration, Eating Desire, Communication, Sleep, Fatigue and Symptom Frequency) and overall total SWAL-QOL score were entered as dependent variables.

Levene's test for equality of variance was calculated for all groups in the t-tests. For all comparisons, if Levene's test was significant, i.e. the values for both groups are variable, adjusted p-value and degree of freedom (df) were used. The use of these adjusted values compensated for any inequality of variance in the data set.

9.4 Results

There were no significant differences in scores for young adults and elders for all subsets of the SWAL-QOL with the exception of symptom frequency, where there was a significant difference in scores for young adults and elders (Figure 9.1). Specifically, elders experience significantly greater frequency of physical symptoms associated with swallowing difficulties compared to healthy, young adults. The means and standard deviations of all subsets and total SWAL-QOL score for young adults and healthy elders are presented in Table 9.1.

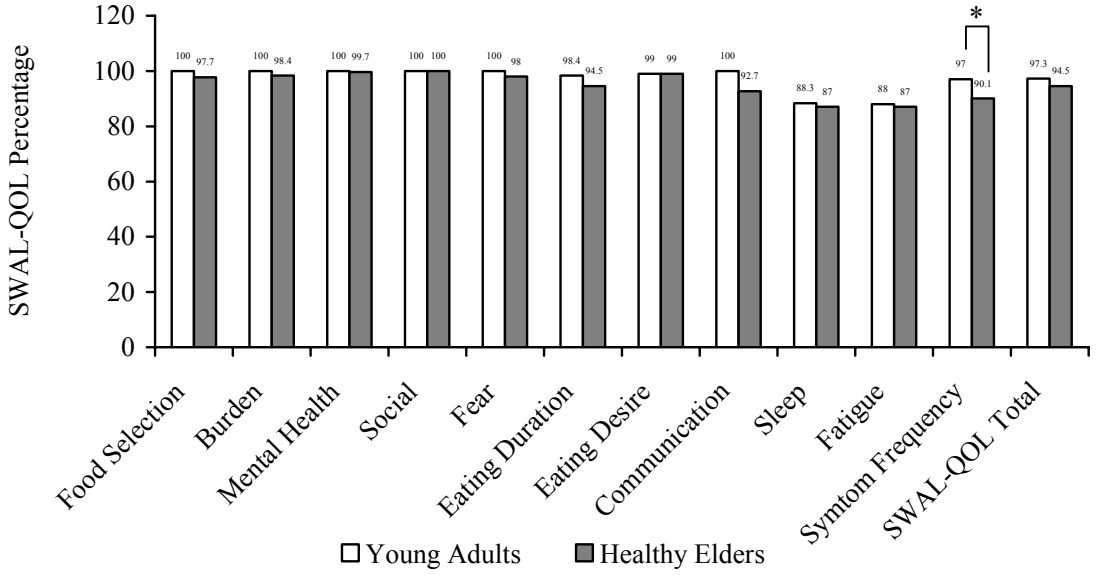


Figure 9.1: Mean scores for subsections of SWAL-QOL and total SWAL-QOL for healthy, young adults and healthy elders

Note: * significant at $p \leq .05$, determined by independent samples t test

Table 9.1 Means and Standard Deviations of SWAL-QOL Subsections and Total SWAL-QOL for Young Adults and Healthy Elders

SWAL-QOL Subsections	Young Adults (%)		Healthy Elders (%)		p value
	M	SD	M	SD	
Food Selection	100	-	97.7	6.8	.188
Burden	100	-	98.4	6.3	.333
Mental Health	100	-	99.7	1.3	.333
Social Functioning	100	-	100	-	-
Fear	100	-	98.1	7.8	.333
Eating Duration	98.4	4.3	94.5	13.7	.290
Eating Desire	99	4.2	99	2.8	.996
Communication	100	-	93	14.4	.070
Sleep	88.3	16.8	81.3	24.6	.352
Fatigue	88	11.4	87	14.3	.821
Symptom Frequency	97	4.2	91	10.4	**.045***
SWAL-QOL TOTAL	97.3	2.5	94.5	6.5	.119

* Significant at $p \leq .05$, determined by independent samples t test

Paired samples t tests were conducted to compare the subsets of SWAL-QOL items for healthy elders and those with PD. There were significant differences in scores for elders and those with PD for all subsets of the SWAL-QOL at $p < 0.05$, with the exception of Sleep (Figure 9.2). The means and standard deviations of all subsets and total SWAL-QOL score for individuals with PD and age- and gender-matched healthy elders are presented in Table 9.2.

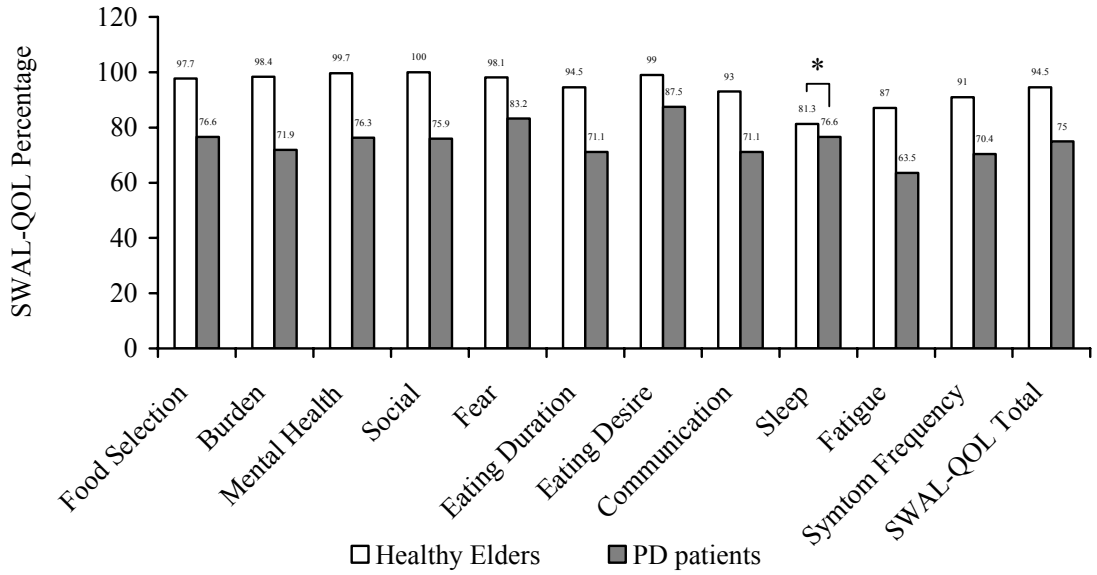


Figure 9.2: Mean scores for subsections of SWAL-QOL and total SWAL-QOL for healthy elders and patients with PD.

Note: All subsets are significant at $p \leq .05$, determined by paired samples t test with the exception of * 'Sleep' where $p \geq .05$.

Table 9.2 Means and Standard Deviations of SWAL-QOL Subsections and Total SWAL-QOL Score for PD Patients and Age- and Gender Matched healthy Adults.

SWAL-QOL Subsections	Healthy Elders (%)		PD Patients (%)		p value
	M	SD	M	SD	
Food Selection	97.7	6.98	76.6	20.9	**.002***
Burden	98.4	6.3	71.9	20.2	**.001***
Mental Health	99.7	1.3	76.3	18.5	**.001***
Social Functioning	100	-	75.9	26.1	**.002***
Fear	98.1	7.8	83.2	15.1	**.007***
Eating Duration	94.5	13.7	71.1	26.9	**.005***
Eating Desire	99	2.8	87.5	14.3	**.01***
Communication	93	14.4	71.1	19.2	**.004***
Sleep	81.3	24.6	76.6	20.9	.65
Fatigue	87	14.3	63.5	17.2	**.002***
Symptom Frequency	91	10.4	70.4	17.3	**.001***
SWAL-QOL TOTAL	94.5	6.5	74.9	12.8	**.001***

* Significant at $p \leq .05$, determined by paired samples t test

Independent samples t tests were conducted to compare the subsets of SWAL-QOL items between those with early PD and those with later PD. There were significant differences in scores for these 2 groups for ‘Food Selection’, Eating Duration’ and ‘Eating Desire’ (Figure 9.3). The means and standard deviations of all subsets and total SWAL-QOL score for early stage PD patients and later stage PD patients are presented in Table 9.3.

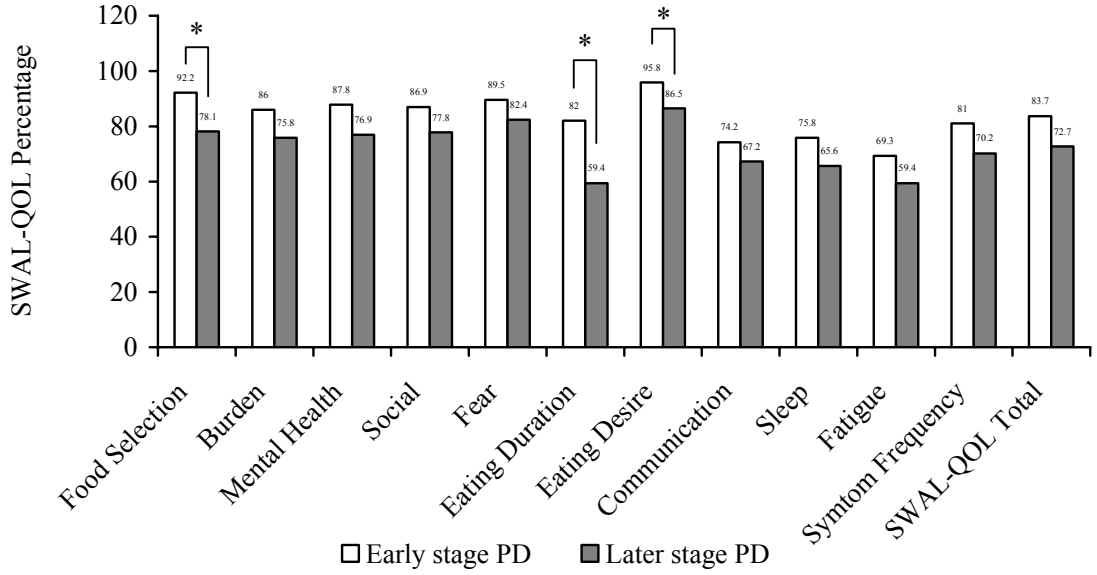


Figure 9.3: Mean scores for subsections of SWAL-QOL and total SWAL-QOL for patients with Early PD and patients with later stage PD

Note: * significant at $p \leq .05$, determined by independent samples t test

Table 9.3 Means and Standard Deviations of SWAL-QOL Subsections and Total SWAL-QOL for Early Stage PD Patients and Later Stage PD Patients

SWAL-QOL Subsections	Early Stage PD^{O} (%)		Later Stage PD$^{\square}$ (%)		p value
	M	SD	M	SD	
Food Selection	92.2	14.3	78.1	16.1	**.014***
Burden	85.9	16.4	75.8	19.6	.122
Mental Health	87.8	14.6	76.9	20.1	.087
Social Functioning	86.9	14.1	77.8	27.6	.251
Fear	89.5	12.4	82.4	15.8	.173
Eating Duration	82	16.4	59.4	28	**.010***
Eating Desire	95.8	8.1	86.5	14.9	**.037***
Communication	74.2	28.7	67.2	22.8	.448
Sleep	75.8	22.6	65.6	21.7	.204
Fatigue	69.3	22.3	59.4	18.2	.181
Symptom Frequency	81	13.4	70.2	19	.072
SWAL-QOL TOTAL	83.7	10.8	72.7	14	.018

* Significant at $p \leq .05$, determined by independent samples t test

^{O} Early Stage PD = Hoehn-Yahr ≤ stage 2, $^{\square}$ Later Stage PD = Hoehn-Yahr ≥ stage 2.5

9.5 Discussion

The impact of swallowing disorders on quality of life has not been adequately addressed as most available assessments and prior research have administered generic questionnaires, used subjective assessment of swallowing, and/or combined several different diagnostic categories. In this study, PD participants who were age and gender-matched to healthy adults completed a validated quality of life questionnaire, the SWAL-QOL. Further comparisons were made to healthy young adults in order to investigate the influence of ageing on QOL.

For most subsections of the SWAL-QOL, as hypothesised, age did not play a significant part in influencing QOL as along as the individuals were in good health. There was however, a difference in 'Symptom Frequency', were elders experienced significantly greater frequency of symptoms such as coughing, food sticking in throat and having excess phlegm and saliva (A full list of symptoms is available in Appendix C, Question 3). Healthy elders with no complaints of dysphagia nonetheless experienced significantly greater frequency of these symptoms. Elders may consider coughing, problems chewing and/or having to throat clear a natural process of ageing and not raise any concerns.

The main finding in this study is that swallowing disorders experienced by individuals with PD greatly reduce QOL (Table 9.2). Patients reported it difficult to select the food textures that they could safely eat. Patients also had significantly greater difficulties in finding foods that they both liked as well as could manage safely. The most significant difference between healthy adults and patients was for the 'Burden' that a swallowing difficulty carried. The burden of having dysphagia may affect 'Mental Health' where there was a significant difference between elders and patients (Table 9.2).

No healthy elders expressed fear of socialising over a meal while almost a quarter of patients reported that having a swallowing problem was detrimental to socialising. Taking a long time to eat may be a part of the overall bradykinesia experienced by patients and this was reflected by significantly longer eating durations reported by patients. Consequently, this may have affected patients' eating desire, which was also significantly lower than their counterparts. Feelings of weakness, tiredness and exhaustion with trouble falling and staying asleep were also significantly different, with patients reporting more of these compared to healthy elders.

Hobson et al., (2001) reported that as disease severity progresses, patients' QOL would deteriorate further. This was true for our patients but not across all subsets. Finding suitable

foods was increasingly difficult, eating desire and eating duration was further reduced. It has been noted that patients that require diet and texture modifications may accept or reject foods based on its visual appearance (Huckabee & Pelletier, 1999b), which would suggest that very limited and/or unappealing food textures may ultimately affect eating desire. The ramifications of dysphagia and reduced desire to eat are broad, since recent research has shown that weight loss, motor symptoms and recumbency increased in individuals with PD who avoid solid foods, compared to their healthy counterparts (Lorefalt et al., 2006). As dysphagia is known to detrimentally affect nutritional status and dietary intake in patients (de Luis et al., 2006; Lorefalt et al., 2006), reduced desire to eat would only exacerbate this problem and would require attention of healthcare professionals involved in the patient's care.

9.6 Conclusion

Healthy ageing does not appear to affect QOL as long as elders did not report having any difficulties swallowing. This is in light of the finding that elders experience symptoms of swallowing problems more frequently than young adults. As to whether coughing, food being stuck and having excess saliva (among other symptoms listed in Appendix C, Question 3) are part of normal ageing or pre-clinical symptoms would require further investigation. With the exception of 'Sleep', patients had reduced scores across all SWAL-QOL subsets, suggesting that the consequence of having a swallowing difficulty was severe enough to significantly affect QOL. Not all subsets of the SWAL-QOL were reduced as a function of disease severity but reductions in eating desire in the presence of significant difficulties in food selection would require careful attention as this has repercussions on weight loss issues.

PART IV: EFFECTS OF THERAPY ON AIRWAY PROTECTION IN PARKINSON'S DISEASE

Chapter 10. The Effects of Pharmacotherapy on Airway Protection Mechanisms in Parkinson's Disease[3]

10.1 Introduction

James Parkinson's first description of Parkinson's disease (PD) in 6 patients included difficulty eating food, impaired muscles of swallowing and sialorrhea (Parkinson, 1817). The disease affects 1/1000 of the population, and life expectancy with current treatment is only 1.5 years less than the general population (Morgante et al., 2000). However, there is a higher risk of pneumonia as a cause of death in PD that is up to six times the normal population (Morgante et al., 2000). A combination of swallowing impairment, bronchial pneumonia and shock induced by pulmonary infection and chronic immobilization are other reasons that are known to shorten survival rates in these patients (Fall et al., 2003; Morgante et al., 2000; Wang et al., 2002).

As the lack of availability of dopamine (DA) in the striatum is the main deficit in PD, current treatment is to replace this loss with exogenous DA, or stimulate the same receptors as endogenous DA (Nicholson et al., 2002; Savitt et al., 2006). DA replacement therapy with the precursor levodopa (L-DOPA) was first described by Cotzias, Van Woert, & Schiffer (1967). Physiological studies show that levodopa is an amino acid that is absorbed from the small bowel and subsequently crosses the blood-brain barrier into the brain where it is decarboxylated to DA (Martin & Wieler, 2003). Levodopa remains the single most effective drug in ameliorating signs and symptoms in the early stages of PD, and in improving the quality of life and survival of treated patients (Diamond et al., 1989; Fahn, 2005; Rascol et al., 2003).

Despite the progress of pharmacotherapy in improving motor function and providing relieve from PD symptoms such as tremor, rigidity and bradykinesia, the effects of levodopa on airway protection are not well known. The problem still remains that swallowing impairment is frequently reported in PD, with 31%-100% of patients experiencing dysphagia (Edwards,

[3] Data from this chapter has been published as Lim, A., Leow, L., Huckabee, M. L., Frampton, C., & Anderson, T. (2007). A Pilot Study of Respiration and Swallowing Integration in Parkinson's Disease: "On" and "Off" Levodopa. *Dysphagia*. DOI 10.1007/s00455-007-9100-9

Quigley, & Pfeiffer, 1992; Johnston et al., 1995; Stroudley & Walsh, 1991; Volonte et al., 2002). Of those with dysphagia, 30% have signs of aspiration (Johnston et al., 1995).

Several studies have reported inconsistent responses of patients' swallowing after levodopa treatment (Bushmann et al., 1989; Fuh et al., 1997; Hunter et al., 1997). Of 15 patients who had symptoms of dysphagia in oral and pharyngeal phases in the study by Bushmann et al., (1989), 7 improved after medication but 1 patient's swallow worsened. Similarly, Fuh et al., (1997) observed that only 50% of their patient cohort with abnormal swallowing examined showed an improvement while the other half showed no change with treatment. Of those that did improve, one patient showed improvement in the oral phase, but deterioration in the pharyngeal phase. Such inconsistencies have led to the conclusion that improvement in other parkinsonian signs from levodopa therapy is not a good indicator of improvement in dysphagia (Ali et al., 1996; Nilsson et al., 1996). Swallowing abnormalities may, in fact, be predominantly resistant to dopaminergic stimulation and degeneration of systems other than the dopaminergic system may be the cause of swallowing difficulty (Hunter et al., 1997).

Pulmonary function is an area where dopaminergic medications have been beneficial. Pulmonary dysfunction in PD is usually due to upper airway obstruction, restrictive defects, or problems with ventilatory control (Brown, 1994; Shill & Stacy, 2002). Pulmonary function testing in patients with PD has shown a decreased FVC, reduced FEV1 and reduced PIF and PEF (Definitions are found in Appendix B) (Hovestadt et al., 1989; Sabate et al., 1996a; Sathyaprabha, Kapavarapu, Pall, Thennarasu, & Raju, 2005). Upper airway obstruction was present in 24% – 37% of patients with PD, most of whom were asymptomatic (Herer et al., 2001; Hovestadt et al., 1989; Sabate et al., 1996a). Other studies have shown mostly restrictive patterns (Sathyaprabha et al., 2005), these being ascribed to rigidity of respiratory muscles (Shill & Stacy, 2002).

There is nothing known about the efficacy of levodopa for sensory improvement in the laryngopharynx. No studies have been undertaken to assess the effects of dopaminergic effects on chemical and mechano-sensitivity in the PD population. As such, it remains unclear whether levodopa offers improvements beyond motor functions. In this chapter, a pilot study was undertaken to clarify the effect of levodopa on swallowing function, pulmonary function and the coordination between breathing and swallowing. In addition, chemo- and mechano-sensation were assessed to investigate the difference in laryngeal sensitivity in PD 'On' (within ½ hour of the last dose) and 'Off' levodopa (medications withheld overnight).

10.2 Hypotheses

There will be significant differences in airway protection mechanisms ‘on’ and ‘off’ levodopa. Specifically, BSC, swallowing efficiency, pulmonary function measures, and chemo- and mechano-sensation of the laryngopharyngeal are expected to improve with after levodopa administration.

10.3 Study Design

10 patients (6 males, mean age 63.5) with idiopathic PD were assessed on motor and sensory aspects of airway protection during 2 sessions: ‘on’ and ‘off’ medication, spaced at least one week apart. Patients were classified within Hoehn and Yahr stages 1 to 4 with an average PD duration of 8.5 years. Further patient details are summarised in Table 10.1. To avoid a sequence affect, counterbalancing was done by allocating 5 patients who underwent first session ‘on’ and second session ‘off’ medication, and another 5 who underwent first session ‘off’ and second session ‘on’.

Paired t tests and McNemar tests were conducted to determine if there were significant differences between any of the key variables in the ‘On’ and ‘Off’ states.

Table 10.1: Details of 10 participants in this study

Patient Number	Gender	Age	Years with PD	Levodopa dose (mg/day)	Years on Levodopa	Hoehn and Yahr	Medications for Parkinson's disease
1	Female	51	3	700	0.4	1	levodopa/carbidopa, ropinirole, orphenadrine
2	Male	67	10	300	1.5	3	Levodopa/carbidopa, pergolide, selegiline, amantadine
3	Female	66	2	400	0.5	3	levodopa/carbidopa, pergolide
4	Male	66	2	400	0.2	1	levodopa/carbidopa, pergolide, amantadine
5	Male	69	8	300	6.0	3	levodopa/benserazide, pergolide
6	Female	67	16	600	6.0	3	levodopa/carbidopa, orphenadrine
7	Male	59	11	600	2.0	1	Levodopa/carbidopa, pergolide, benztropine, selegiline, amantadine
8	Male	69	13	650	10.0	4	levodopa/carbidopa, levodopa/benserazide
9	Male	57	9	550	0.8	2	levodopa/carbidopa, ropinirole, orphenadrine
10	Female	64	11	300	1.0	2.5	levodopa/carbidopa, pergolide, orphenadrine
Mean	**-**	**63.5**	**8.5**	**480**	**2.8**	**2.4**	

10.4 Method

Methods and details of data processing and preparation are available in Chapter 3, the only difference being that Flexible Endoscopic Evaluation of Swallowing with Sensory Testing (FEESST) was available during data collection for this arm of the study. FEESST was performed similar to the method described by Aviv (1997b). However, the currently available instrumentation differed from the one originally used. In the study, a disposable Slide-On™ sheath containing the air delivery channel was placed on a standard nasendoscope (Welch Allyn RL-150) and connected to an air-pulse stimulator (Vision Sciences AP-4000). A continuous air-pulse was demonstrated on the back of the participant's hand to orient them to the task and the nature of the stimulus. The nasendoscope was inserted into the patient's nostril and advanced until the tip rested approximately 2mm above the aryepiglottic folds. Both the psychophysical and laryngeal adductor reflex (LAR) methods were performed.

For the psychophysical method, participants were instructed to raise their hand immediately if they felt an air-pulse. As the air-pulse generator produces a distinctive and loud noise upon discharge, ear-plugs and placebo noise were used to increase task reliability by masking this auditory input. The psychophysical threshold was defined as the lowest pressure of air-pulse that could be detected by the participant. The LAR threshold was defined as the lowest pressure that was immediately followed by a brief, rapid adduction of the vocal cords (Perez et al., 1996). Sets of three 50 millisecond air-pulses were delivered, starting at 2mmHg increasing in 1mmHg increments until both thresholds for LAR and psychophysical methods were reached, to a maximum of 10mHg. This ascending block was repeated two more times on the same side, and then on the opposite side for each patient. Median psychophysical and LAR thresholds were determined for each side.

10.5 Results

Analysis consisted of data collected from ten participants. Table 10.2 summarises the results of the study where paired t tests were used to compare performances 'on' and 'off' levodopa. Of these participants, one participant did not perform the assessment of swallowing using FEES but completed all other assessments (Table 10.3). As individuals with PD may experience asymmetrical onset of symptoms, median LAR thresholds are reported according to whether the air pulses were delivered to the ipsilateral or contralateral of the more affected side.

Table 10.2: Means and Standard Deviations of tests on 10 patient participants comparing performances 'on' and 'off' levodopa

Measure	Mean value 'Off' (Standard Deviation)	Mean value 'On' (Standard Deviation)	Mean difference 'Off'–'On' (95% Confidence Interval)	p-value
Unified Parkinson's Disease Rating Scale (UPDRS)				
Section II (Activities of daily living)	12.90 (6.79)	12.30 (6.58)	0.60 (-1.46, 2.66)	0.526
Section III (Motor examination)	25.30 (13.05)	21 (10.68)	4.30 (0.02, 8.58)	**0.049**
Breathing-Swallowing Coordination				
Percent of swallows preceding expiration	91.00 (25.14)	100.00 (0.00)	-9.00 (-26.99, 8.99)	0.287
Average sEMG amplitude (uV)	64.40 (44.91)	66.04 (47.06)	-1.64 (-17.61, 14.34)	0.822
Variance in sEMG amplitude	120.14 (167.59)	196.53 (294.84)	-76.39 (-294.77, 142.00)	0.449
Timed-Test of Swallowing Efficiency				
Number of swallows	9.50 (3.78)	9.90 (2.69)	-0.40 (-1.37, 0.57)	0.373
Time taken (seconds)	14.70 (8.68)	16.01 (9.46)	-1.31 (-4.76, 2.15)	0.414
Average volume per swallow (milliliters)	17.67 (5.55)	15.95 (3.35)	1.72 (-0.39, 3.82)	0.098
Average time per swallow (seconds)	1.50 (0.433)	1.55 (0.60)	-0.05 (-0.36, 0.25)	0.690
Swallowing capacity (milliliters/second)	13.03 (5.88)	11.75 (4.84)	1.28 (-0.65, 3.21)	0.168

In bold, significant at $p \leq .05$, as determined by paired samples t-test

Table 10.2: Continued

Measure	Mean value 'Off' (Standard Deviation)	Mean value 'On' (Standard Deviation)	Mean difference 'Off'–'On' (95% Confidence Interval)	p-value
Lung Function Testing				
FVC (L)	4.19 (0.86)	4.03 (0.83)	0.15 (0.07, 0.23)	**0.002**
FEV1 (L)	3.29 (0.76)	3.19 (0.75)	0.10 (0.01, 0.20)	**0.035**
FEV1/FVC	78.2 (3.39)	78.9 (4.46)	-0.70 (-2.61, 1.21)	0.428
PEF (L/s)	7.58 (1.79)	7.21 (1.73)	0.37 (-0.24, 0.98)	0.202
PIF (L/s)	5.13 (2.36)	4.93 (1.62)	0.20 (-1.93, 2.32)	0.840
Flexible Endoscopic Evaluation of Swallowing with Sensory Testing (mmHg)				
Median ipsilateral[a] LAR threshold	4.86 (4.22)	6.71 (4.03)	-1.86 (-4.55, 0.84)	0.129
Median contralateral[a] LAR threshold	5.86 (3.72)	5.86 (3.34)	0.00 (-1.31, 1.31)	1.000
Average LAR threshold	5.22 (3.66)	6.06 (3.31)	-0.84 (-1.94, 0.26)	0.113
Median ipsilateral[a] psychophysical threshold	3.67 (3.61)	6.00 (4.29)	-2.33 (-7.99, 3.32)	0.338
Median contralateral[a] psychophysical threshold	4.57 (3.82)	6.71 (4.35)	-2.14 (-6.53, 2.24)	0.277
Average psychophysical threshold	4.50 (3.84)	6.43 (4.08)	-1.93 (-6.46, 2.61)	0.338
Inhalation Cough Challenge (mM)				
Natural cough threshold	358.46 (228.39)	266.96 (200.39)	91.50 (-148.98, 331.97)	0.412
Suppressed cough threshold	537.56 (429.23)	532.47 (901.45)	5.10 (-588.11, 598.30)	0.985
Difference between cough thresholds	378.90 (413.64)	565.21 (711.61)	-186.30 (-682.24, 309.64)	0.417

In bold, significant at $p \leq .05$, as determined by paired samples t-test

[a] Comparison made to the side most affected by PD as determined by the UPDRS

There was a significant increase in motor examination section of the UPDRS, indicating that as expected, the participants showed more severe motor signs of PD 'off' levodopa. For the timed test of swallowing, there was a non-significant trend to lower volume per swallow when 'on' the medication ($p = 0.098$). No differences were found in other measures of the timed test of swallowing. Lung function testing showed significant improvements when 'Off' medication in FVC and FEV1 but no significant changes in FEV1/FVC, peak inspiratory or expiratory flows. No statistically significant differences were observed in breathing-swallowing coordination, laryngeal sensitivity (FEESST) and inhalation cough challenge.

One participant (Number 7) reported discomfort during nasendoscopy and was unable to participate in the swallowing assessment during FEESST. Mc Nemar Chi Square test showed no significant changes or apparent trends in the assessment of swallowing for the remaining 9 patients (regardless of food/fluid consistency). Two patients exhibited spillage of feeds 'on' medication but this increased to 3 patients 'off' medication. Laryngeal penetration was observed in 2 patients regardless of medication status while aspiration was seen in 1 in 9 patients, also regardless of medication status. Residue was noted in 7 patients 'on' medication and 8 patients 'off' levodopa. Table 10.3 details the consistencies of food and/or fluids for each participant.

Table 10.3: Details of Food and/or Fluid Consistencies for each Participant during Swallowing Assessment

Participant	Spillage		Penetration		Aspiration		Residue		Vocal Fold Bowing
Number	'Off'	'On"	'Off'	'On"	'Off'	'On"	'Off'	'On"	
1	Pudding	-	-	-	-	-	Pudding	Solid	Yes
2	Water	-	-	Solid	-	-	Nectar and Solid	Nectar and Solid	No
3	-	-	-	-	-	Water	-	-	No
4	-	-	Water, Nectar, Pudding	Water	Water, Nectar, Solid	-	Solid	Solid	No
5	-	-	-	-	-	-	Solid	-	No
6	Water	Water and Nectar	-	-	-	-	Solid	Pudding and Solid	No
7	Could not be performed due to discomfort								No
8	-	-	-	-	-	-	Pudding and Solid	Pudding and Solid	No
9	-	-	-	-	-	-	Solid	Solid	No
10	-	Nectar	Solid	-	-	-	Water and Solid	Solid	Yes

10.6 Discussion

It has been repeatedly demonstrated that levodopa improves overall motor function, evidenced by the improvement in UPDRS scores (Bejjani et al., 2000; Bonnet, Loria, Saint-Hilaire, Lhermitte, & Agid, 1987; Cutson, Laub, & Schenkman, 1995). Results of this study also revealed that overall motor function in individuals with PD were significantly worse when 'off' levodopa than when 'on' (Table 10.2). Despite this improvement, results of this study found that this improvement in motor function 'off' medication was not accompanied by improvements in other aspects of airway protection mechanisms.

Although previous studies have found improvements in axial signs that affect coordination and stability of posture (Bejjani et al., 2000), these did not translate to improvements in the coordination between breathing and swallowing, suggesting that improvements in coordination may be specific to selective muscles, not overall coordination. This pilot study revealed that the coordination between breathing and swallowing remained unchanged, whether 'on' or 'off' medication. All swallows were preceded by expiration (Expiration-apnoea-Expiration and Inspiration-apnoea-Expiration) during the 'on' phase with a slight, non-significant decrease when 'off' medication (Table 10.2).

No differences were observed between other measures in the timed-test of swallowing, including time per swallow and swallowing capacity. This is inconsistent with prior research which suggests that swallowing efficiency may improve with levodopa (Hunter et al., 1997). Using videofluoroscopy, Hunter and colleagues (1997) detected fewer swallows to clear solid boluses after levodopa, although they did find an increase in oral phase and total swallowing times with the medication. These authors concluded that swallowing efficiency may improve but inconsistently and not for all food/fluid textures (Hunter et al., 1997).

Interestingly, results of this study show that key measures of pulmonary function significantly declined when 'On' levodopa. Nine of the 10 participants had reduced function with levodopa medication. However, all the changes in measures were small and did not meet clinical significance based on ATS/ERS standardisation of lung function testing (Pellegrino et al., 2005). Nonetheless, this is still contrary to expectation, as previous studies have shown improvements with levodopa (Hovestadt et al., 1989; Sabate et al., 1996a; Sathyaprabha et al., 2005). Whilst no studies have found a decline in pulmonary function with levodopa, some

studies describe respiratory dysfunction as a levodopa side-effect, possibly due to restrictive or dyskinetic respiratory muscles (Brown, 1994; Shill & Stacy, 2002). Our findings may be explained by side-effects of levodopa, chance or unidentified flaws in our method. Dyskinesis was not measured during our assessments of the participants but it is recommended that future studies note dyskinesis to help clarify this. It is possible that a change in pulmonary function could be a marker of dyskinesis before it is otherwise clinically evident in peripheral skeletal muscles. This remains to be investigated.

Finally, this study revealed no significant differences in any measurements of laryngeal sensation and inhalation cough challenge when 'on' levodopa suggesting that levodopa may not affect chemo- and mechano- laryngopharyngeal sensation. This finding taken in conjunction with the observation that there were no differences in rates of laryngeal penetration or tracheal aspiration in the endoscopic assessment of swallowing, suggest that the risk of laryngeal aspiration remains unchanged whether 'on' or 'off' levodopa. However, only a small number of participants were studied, and further investigation with greater numbers of participants and long-term follow-up need to be performed assessing the difference in laryngeal sensation, cough reflex and aspiration 'on' and 'off' levodopa to investigate whether or not there truly is no difference.

This pilot project identified several methodological issues that should be addressed in future research. During the FEESST procedure, many participants reported receiving cues as each air-pulse was delivered. Auditory cues were reduced by the use of ear-plugs and placebo noises. However, unlike the endoscope that was previously used by Aviv (1997b), where air pulse channel is encased within the endoscope, current commercially available FEESST equipment requires the placement of an external sleeve housing the air channel over the endoscope. As such, participants were able to see the sleeve expand and feel the pulse travelling through the nasal passage on its way to the larynx. Placebo or sham air pulses described by Aviv (1997b) to increase blindness did not help, since participants could associated that failure of the sleeve to expand would signal no air pulse into the laryngopharynx. Even with clear instructions to only rise their hand when they could feel the pulse at the back of the throat, biasing of the responses cannot be ruled out. This may also explain why variance was higher in the psychophysical method (Table 10.2). For the current FEESST setup, we deem that laryngeal adductor reflex method is therefore a more reliable method than the psychophysical method. By use of an air channel within the endoscope

instead of a sleeve, many cues of air-pulse delivery will be eliminated, increasing reliability of both methods.

10.7 Conclusion

In conclusion, this pilot study found no association between levodopa and measures of motor and sensory function within the pharynx, although there was an unexpected decline in pulmonary function. Current evidence, including this study, would suggest that in most instances the benefits of pharmacotherapy for dysphagia remain unsupported. Differences and inconsistencies indicate the need for greater understanding of mechanisms underlying effect of drugs on swallowing in PD. Emerging evidence that other neurotransmitter systems mat be involved in the neurological control and coordination of swallowing in PD require further investigation. Further studies comprising larger numbers of patients are needed to ascertain whether there really is no difference in risk of aspiration between ‘on’ and ‘off’ states of levodopa. Finally, peak dose dyskinesia may account for the decline of pulmonary function ‘on’ levodopa and would need to be addressed in future studies.

Chapter 11. The Effects of Lee Silverman Voice Treatment on Airway Protection Mechanisms in Parkinson's Disease

11.1 Introduction

Atrophy of the vocal folds leading to vocal fold bowing during phonation (Blumin et al., 2004; Hanson et al., 1984; Smith et al., 1995; Stelzig et al., 1999), along with other abnormalities like resting tremor of arytenoid and supraglottic structures (Perez et al., 1996) have been well documented in PD. However, the relative contribution of vocal fold closure to airway protection and swallowing in PD has not been explored fully even though it is known to provide airway protection (Medda et al., 2003). It has been reported that glottal closure constitutes the primary mechanism for prevention of aspiration (Medda et al., 2003). If this claim is true, then individuals with PD, especially those with vocal fold bowing would be at higher risk of airway compromise.

Insufficient attention has been paid to improving vocal fold function in this patient cohort with no systematic controlled trials for the efficacy of dysphagia therapy (Deane et al., 2001). Slightly more attention has been paid to the improvement of speech, with these reports focused on the effects of Lee Silverman Voice Treatment (LSVT). First described by Ramig and colleagues in the mid 1990s, LSVT focuses on improving speech production disorders in PD by emphasising improvement in phonation and respiration. LSVT has 5 essential concepts, which are: (1) exclusive focus on vocal loudness, (2) high-effort speech productions with multiple repetitions, (3) intensive treatment of 4 individual sessions a week for 4 weeks, (4) enhancing sensory awareness of increased vocal loudness and (5) quantifying improvements (Ramig et al., 1995).

Since the introduction of LSVT, research has generated short- and long-term efficacy data for speech treatment in individuals with PD (Ramig et al., 1996; Ramig et al., 2001a; Ramig et al., 2001b). Improvements in facial expression (Spielman et al., 2003), speech intensity (Ramig et al., 1995), vocal cord adduction (Smith et al., 1995), and sub-glottal air pressure (Ramig & Dromey, 1996) after LSVT have been reported. In 2002, El Sharkawi et al., found positive improvements in the motor function of swallowing in 8 individuals with PD and mild dysphagia following LSVT. Reduced tongue control and strength with weak tongue base

retraction resulting in residue in the valleculae was the most common disorder before LSVT. In addition, authors report prolonged oral and pharyngeal transit times in these patients. Post treatment, however, clearance of oral residue was significantly reduced for 3 ml and 5 ml liquid boluses, with an overall 51% reduction in the number of oral-tongue and tongue-base disorders (Sharkawi et al., 2002).

The interaction between respiration, speech and swallowing cannot be ignored since these functions share the same anatomical space and structures (Curtis & Langmore, 1997; Hiss et al., 2001; Selley et al., 1989a). The focus of LSVT is on achieving and maintaining a loud voice, increased respiratory effort, increased glottic closure and improved lung function. As such, it is anticipated that improvements in these functions may also improve airway protection. The effects of LSVT on sensation has also not been explored. In animal studies, it has been shown that the contraction of the thyroarytenoid muscle (vocal fold adductor) is enhanced by upper airway pressure during expiration (Stella & England, 2001). It is plausible that with increased airflow though the vocal folds during high respiratory and speech tasks, sensation provided to the mucosa of the vocal folds may also improve airway protection. LSVT may result in higher airflow through the larynx to further enhance vocal fold adduction, resulting in a louder voice.

The finding that LSVT improves swallowing is important. If LSVT improves airway protection, clinicians may be able to develop swallowing treatments based on the information from LSVT data. No research has documented changes in airway protection following LSVT so studies are needed to clarify the simultaneous effects of LSVT on swallowing of individuals with PD. This chapter provides a description of the effects of LSVT on airway protection mechanisms in a small cohort of individuals with PD.

11.2 Hypotheses

There will be significant differences in airway protection mechanisms pre and post LSVT treatment. Specifically, BSC, pulmonary function measures, swallowing efficiency and laryngopharyngeal chemo- and mechano-sensation are expected to improve with after LSVT, as will quality of life.

11.3 Study Design

This pilot study follows a pre and post test experimental design. Five male participants who were also part of the larger research cohort (Part II) underwent LSVT. LSVT consisted of intensive, daily therapy lasting an hour each session, over 4 weeks. These patients were assessed on motor and sensory airway protection mechanisms (detailed in Chapter 3) less than a month before commencing therapy. All patients were tested during the 'on' phase of their PD medication, within 1/2 hour of their last medication dose. Particulars of patients are summarised in Table 11.1. As the number of participants recruited for this arm of the study is small, results and data are presented as a descriptive study.

Table 11.1: Details of 5 participants in this study

ID	CC	JC	BM	NN	GW
Gender	M	M	M	M	M
Age pre LSVT	72.3	70.7	68.9	60.5	65.8
Age post LSVT	72.8	71.6	69.4	61.6	66.8
Number of months Between completion of LSVT and reassessment	6	11	6	12	12
Number of years with PD	4	4	8	11	1
Hoehn-Yahr Stage	2	2	3	3	1

11.4 Results

11.4.1 Y-H Stage, UPDRS and MMSE

There were minimal differences in overall mean scores for H-Y stage pre and post LSVT (stage 2.1 and stage 2.2 respectively). There were also minimal differences for UPDRS section II + III pre and post LSVT (41.6 and 43.4 respectively). Finally, there was a minimal difference in mean MMSE score pre and post LSVT (28.8 and 29.4 respectively) across all 5 participants.

11.4.2 Swallowing Quality of Life (SWAL-OQL)

Mean scores for subsections of the SWAL-QOL for all 5 participants are summarised in Figure 11.1. Eight subsections showed improvements post treatment. The largest improvements were in the 'Social Functioning' and 'Communication' subsections with an improvement of 40% and 15% respectively. There was no change in 'Burden' of having a swallowing disorder, with small decreases in 'Eating Duration' (10%) and 'Eating Desire' (3.3%).

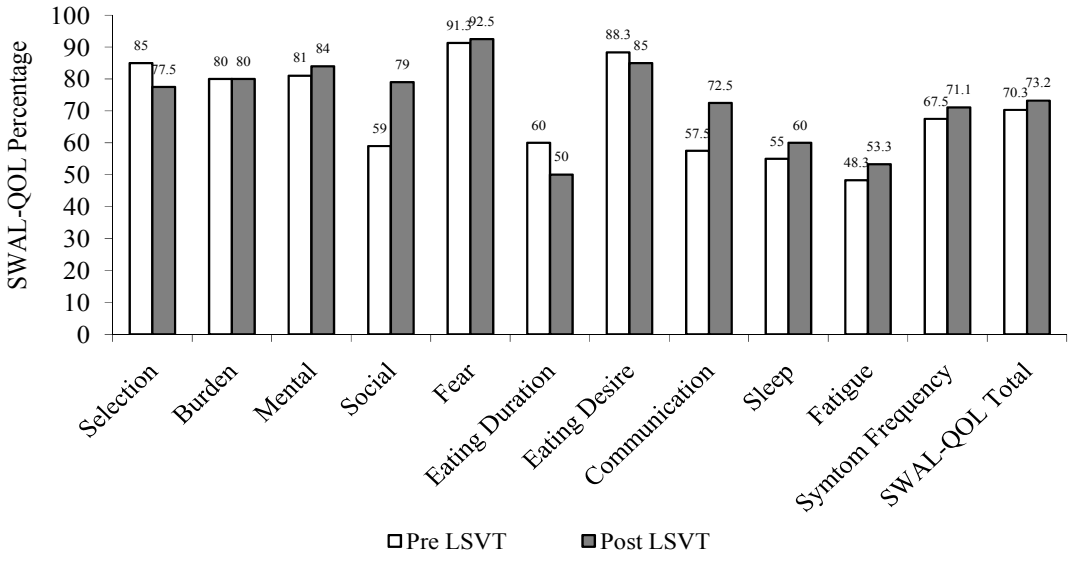


Figure 11.1: Scores for subsections of SWAL-QOL across 5 participants pre and post LSVT

Mean scores for subsections of SWAL-QOL for each participant is summarised in Table 11.2. No specific patterns across participants were noted for any subsection of the SWAL-QOL, suggesting inter-subject variability in the changes in swallowing QOL post treatment.

Table 11.2: Mean scores for SWAL-QOL subsections for each participant

Participant	CC	JC	BM	NN	GW
Tests	Mean	Mean	Mean	Mean	Mean
Pre Food Selection	75.0	100.0	75.0	75.0	100.0
Post Food Selection	100.0	87.5	25.0	75.0	100.0
Pre Burden	87.5	87.5	37.5	87.5	100.0
Post Burden	87.5	87.5	37.5	87.5	100.0
Pre Mental Health	90.0	100.0	75.0	45.0	95.0
Post Mental Health	100.0	100.0	55.0	70.0	95.0
Pre Social Functioning	75.0	80.0	50.0	60.0	75.0
Post Social Functioning	100.0	100.0	25.0	70.0	100.0
Pre Fear	93.8	100.0	93.8	100.0	68.8
Post Fear	100.0	100.0	68.8	100.0	93.75
Pre Eating Duration	87.5	87.5	37.5	12.5	75.0
Post Eating Duration	75.0	87.5	12.5	0	75.0
Pre Eating Desire	91.7	83.3	66.7	100.0	100.0
Post Eating Desire	100.0	83.3	50.0	91.7	100.0
Pre Communication	75.0	87.5	50.0	50.0	25.0
Post Communication	100.0	75.0	62.5	75.0	50.0
Pre Sleep	50.0	62.5	62.5	75.0	25.0
Post Sleep	100.0	62.5	62.5	62.5	12.5
Pre Fatigue	58.3	58.3	58.3	41.7	25.0
Post Fatigue	75.0	75.0	50.0	41.7	25.0
Pre Symptom Frequency	82.1	73.2	53.6	46.4	82.1
Post Symptom Frequency	94.6	71.4	48.2	51.8	89.3
Pre Total	78.7	83.6	55.9	63.0	70.1
Post Total	93.8	84.5	45.2	65.9	76.4

11.4.3 Breathing-Swallowing Coordination

Mean scores for percentage of respiratory phase category across 5 participants are summarised in Figure 11.2. A 20% decrease in EE swallows with a corresponding increase of 10% each in IE and II swallows were noted post treatment.

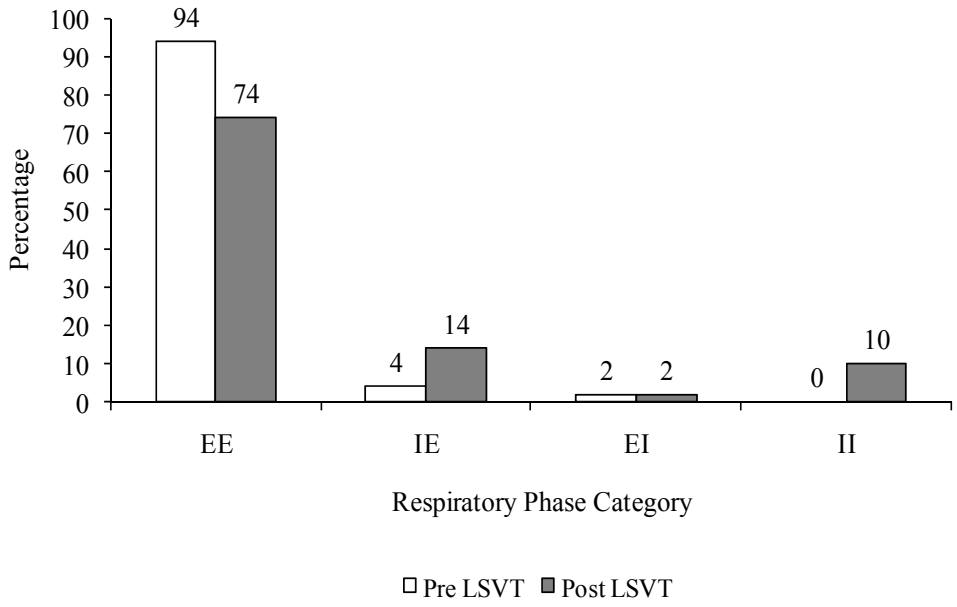


Figure 11.2: Mean scores for percentage of respiratory phase category across 5 participants

Scores for percentage of respiratory phase category for each participant is summarised in Table 11.3. The coordination of breathing and swallowing remained unchanged in 3 patients. Two patients (BM and NN) showed decreased EE swallows and increased IE swallows after treatment. Of note is the finding that in one patient (NN), swallows that precede and follow inspiration (II) increased from 0% to 50% while EE swallows decreased from 80% to 0%.

Table 11.3: Mean percentage of respiratory phase category for each participant

Participant	CC	JC	BM	NN	GW
Tests	Mean	Mean	Mean	Mean	Mean
Pre LSVT EE (%)	100	100	90	80	100
Post LSVT EE (%)	100	100	70	-	100
Pre LSVT IE (%)	-	-	10	10	-
Post LSVT IE (%)	-	-	30	40	-
Pre LSVT EI (%)	-	-	-	10	-
Post LSVT EI (%)	-	-	-	10	-
Pre LSVT II (%)	-	-	-	-	-
Post LSVT II (%)	-	-	-	50	-

11.4.4 Swallowing Efficiency

Three measurements of swallowing efficiency were assessed. These were sEMG amplitude, the timed test of swallowing and FEES.

Results indicate an increase in sEMG amplitude across all participants. Specifically, mean sEMG amplitudes across 10 trials of single 8mL swallow before and after LSVT for each participants are: CC 64.2μv and 65.7μv respectively, JC 33.7μv and 58.7μv respectively, BM 86.8μv and 103.3μv respectively, NN 45.9μv and 159.1μv respectively and GW 40.7μv and 51.1μv respectively.

Table 11.4 shows the swallowing efficiency indices during the timed test of swallowing across 5 participants and for each participant. There was an average increase of 5 seconds in the time taken to drink 150 mls of water after LSVT. There were little changes in other swallowing efficiency indices. Closer inspection of individual patients revealed no consistent changes in any swallowing efficiency measurements with one patient almost doubling their overall swallowing capacity (JC) while another deteriorated by more than half (BM).

Table 11.4: Overall mean across 5 participants and individual scores for each participants for timed test of swallowing efficiency

Timed Test Indices	Group Mean	Patient				
		CC	JC	BM	NN	GW
Pre Number of Swallows	**8.2**	11	11	8	5	6
Post Number of Swallows	**9**	13	5	15	7	5
Pre Time Taken (s)	**12.9**	25	14.3	11	7.3	7.2
Post Time Taken (s)	**17.6**	36.5	7.4	30.3	8.7	5.3
Pre Average Volume/swallow (ml)	**20.2**	13.6	13.6	18.8	30	25
Post Average Volume/swallow (ml)	**20.6**	11.5	30	10	21.4	30
Pre Average Time/swallow (s)	**1.5**	2.3	1.3	1.4	1.4	1.2
Post Average Time/swallow (s)	**1.7**	2.8	1.5	2	1.2	1.1
Pre Swallowing Capacity (ml/s)	**14.4**	6	10.5	13.7	20.8	20.9
Post Swallowing Capacity (ml/s)	**15**	4.1	20.2	5	17.3	28.5

Note: Overall group means are presented in bold, for ease of comparison to the individual patients

Table 11.5 details swallowing function for each participant during FEES. Results show no consistent patterns for swallowing symptoms for individual patients across food and fluid textures.

Table 11.5: Percentage (of 3 trials) of occurrence for each swallowing feature for each patient pre and post LSVT

Patient	CC		JC		BM		NN		GW	
Thin fluids	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Pooling	66	0	100	0	100	66	66	100	0	0
Penetration	0	0	0	0	33	0	0	0	0	0
Aspiration	0	0	0	0	0	0	0	0	0	0
Silent aspiration	0	0	0	0	0	0	0	0	0	0
Residue	66	0	33	66	33	0	66	100	0	0
Residue Clearance	100	NR	100	50	100	NR	100	100	NR	NR
Nectar	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Pooling	100	33	66	0	100	100	100	100	0	0
Penetration	0	0	0	0	0	0	0	0	0	0
Aspiration	0	0	0	0	0	0	0	0	0	0
Silent aspiration	0	0	0	0	0	0	0	0	0	0
Residue	66	33	0	0	0	0	100	100	0	0
Residue Clearance	100	100	NR	NR	NR	NR	100	100	NR	NR
Pudding	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Pooling	33	0	100	33	66	0	33	100	0	0
Penetration	0	0	0	0	0	0	0	0	0	0
Aspiration	0	0	0	0	0	0	0	0	0	0
Silent aspiration	0	0	0	0	0	0	0	0	0	0
Residue	33	66	66	100	0	0	100	100	0	33
Residue Clearance	100	0	33	66	NR	NR	100	100	NR	100
Biscuit	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Pooling	Y	N	Y	Y	N	N	N	Y	N	N
Penetration	N	N	N	N	N	N	Y	N	N	N
Aspiration	N	N	N	N	N	N	N	N	N	N
Silent aspiration	N	N	N	N	N	N	N	N	N	N
Residue	Y	Y	Y	Y	Y	Y	Y	Y	N	N
Residue Clearance	N	N	N	N	N	Y	N	Y	NR	NR
90ml water	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Pooling	N	N	Y	Y	Y	Y	N	Y	N	N
Penetration	N	N	N	N	N	Y	N	N	N	N
Aspiration	N	N	N	N	N	Y	N	N	N	N
Silent aspiration	N	N	N	N	N	Y	N	N	N	N
Residue	Y	N	N	Y	N	Y	N	Y	N	N
Residue Clearance	Y	NR	NR	Y	NR	Y	NR	Y	NR	NR

Note Y = Yes, N = No, NR = Not relevant as no residue noted

11.4.5 Pulmonary Function

Mean scores for pulmonary function indices across 5 participants are summarised in Figure 11.3. Values for each pulmonary function index did not change substantially as a function of treatment. FVC increased but this was mainly due to one patient (GW), since all other patients demonstrated a slight decrease in FVC after treatment (Table 11.6).

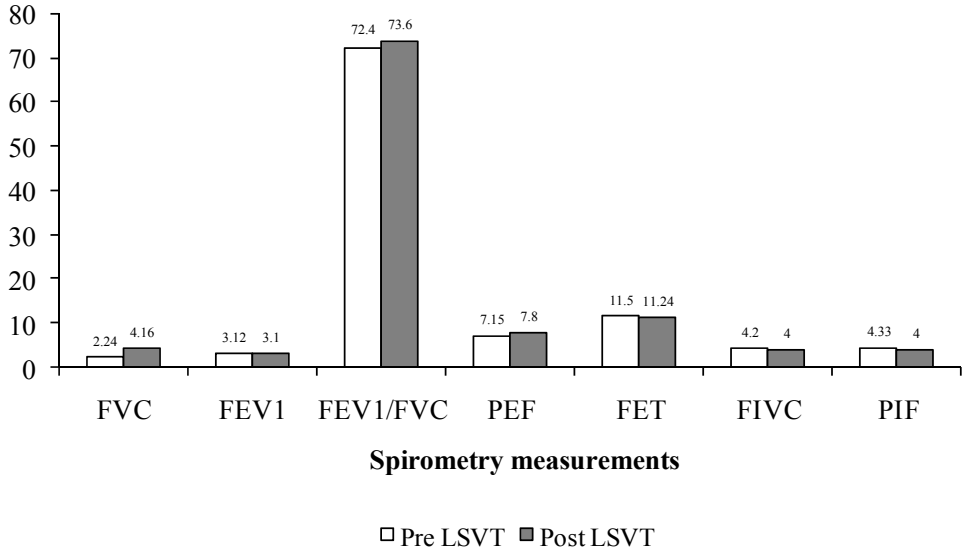


Figure 11.3: Mean scores for pulmonary function indices across 5 participants

Scores for pulmonary function indices for each participant is summarised in Table 11.6. Pre treatment, the percentage predicted scores for FVC for all but one participant (GW) fell within the normal values. After treatment, however, the same 4 participants whose % predicted scores for FVC was within the norm demonstrated lower scores. GW, whose % predicted score for FVC was the lowest was the only participant who had increased % predicted FVC. There was minimal change in FEV1/FVC value for all participants. The PEF scores for all but one participant (CC) increased post treatment. No other consistent patterns were seen for the other pulmonary function indices.

Table 11.6: Scores for pulmonary function indices for each participant

Participant	CC	JC	BM	NN	GW
Spirometry indices					
Pre Forced Vital Capacity	4.42	4.49	4.18	5.04	3.08
Pre Forced Vital Capacity % Predicted	93	101	120	102	67
Post Forced Vital Capacity	4.27	4.37	3.68	4.94	3.53
Post Forced Vital Capacity % Predicted	88	99	106	92	77
Pre Forced Expiratory Volume in 1 second	3.18	3.28	3.36	4.02	1.76
Post Forced Expiratory Volume in 1 second	3.06	3.34	2.91	4.12	2.04
Pre Forced Expiratory Volume in 1 second % Predicted	91	100	130	108	51
Post Forced Expiratory Volume in 1 second % Predicted	86	104	115	102	60
Pre Forced Vital Capacity/ Forced Expiratory Volume	72	73	80	80	57
Post Forced Vital Capacity/ Forced Expiratory Volume	72	76	79	83	58
Pre Peak Expiratory Flow	7.64	9.32	7.32	6.83	4.62
Pre Peak Expiratory Flow % Predicted	88	111	101	72	52
Post Peak Expiratory Flow	6.7	9.58	8.24	8.95	5.54
Post Peak Expiratory Flow % Predicted	76	116	116	90	63
Pre Forced Expiratory Time	13.07	14	7.93	8.26	14.26
Post Forced Expiratory Time	12.73	10.32	9.91	8.05	15.18
Pre Forced Inspiratory Vital Capacity	4.24	4.63	4.22	4.71	3.18
Post Forced Inspiratory Vital Capacity	4.39	4.35	3.08	4.74	3.51
Pre Peak Inspiratory Flow	2.79	6.85	4.67	3.09	4.24
Post Peak Inspiratory Flow	5.18	3.77	5.01	1.57	4.53

11.4.6 Laryngopharyngeal Chemo-sensitivity

Natural and suppressed coughs pre and post LSVT for each participant is summarised in Figure 11.4. Results show a wide variation in natural cough thresholds across participants before treatment. In addition, in 3 participants (CC, BM, NN), natural cough thresholds increased after treatment. Regarding the ability to suppress cough, for 3 participants (CC, BM and NN), suppressed cough thresholds were higher than natural cough thresholds. The remaining 2 participants (JC and GW) were unable to suppress coughing when instructed to do so. No consistent patterns were noted for ability to suppress cough post treatment. Three participants (JC, BM and GW) were able to suppress coughing post treatment, hence the higher suppressed cough thresholds, but 2 participants (CC and NN) were unable to do so, hence the same thresholds for natural and suppressed coughs.

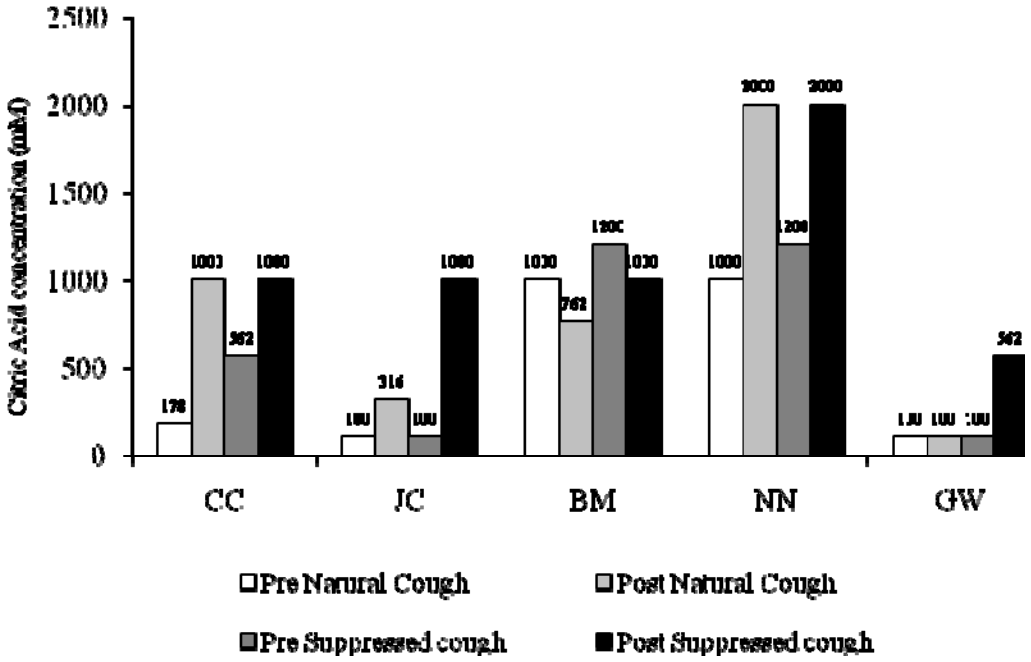


Figure 11.4: Natural and Suppressed Coughs Pre and Post LSVT for each participant

11.4.7 Laryngopharyngeal Mechano-sensitivity

Table 11.7 summarises patients' responses for sensitivity testing at 6 test sites pre and after LSVT. Results show no consistent increase or decrease in laryngopharyngeal sensitivity for the 6 test sites after treatment.

Table 11.7: Individual responses for mechano-sensitivity testing of 6 sites pre and post LSVT

Participant		CC	JC	BM	NN	GW
Right Base of Tongue	Pre LSVT	Y	N	Y	Y	Y
	Post LSVT	Y	N	N	Y	Y
Left Base of Tongue	Pre LSVT	N	N	N	Y	Y
	Post LSVT	Y	N	Y	Y	Y
Right Posterior Pharyngeal Wall	Pre LSVT	Y	N	N	Y	Y
	Post LSVT	Y	N	Y	Y	Y
Left Posterior Pharyngeal Wall	Pre LSVT	Y	N	N	Y	Y
	Post LSVT	Y	N	N	Y	Y
Right Aryepiglottic Fold	Pre LSVT	Y	Y	N	Y	Y
	Post LSVT	N/A	N	N	Y	Y
Left Aryepiglottic Fold	Pre LSVT	Y	Y	Y	Y	Y
	Post LSVT	Y	Y	N	Y	Y

Note: Y = Yes, sensation present, N = No, sensation absent. N/A = unable to advance scope beyond base of tongue as that triggered gag and swallowing.

In conclusion, Table 11.8 summarises the improvement or decline in all the measures taken for the 5 participants after LSVT. For convenience, only key measures from each assessment are provided. Results show a consistent increase in sEMG amplitude after treatment. There was a consistent decline in chemo-sensitivity, determined by the finding that natural cough thresholds increased after treatment. Mechano-sensitivity remained relatively unchanged across all participants. No consistent patterns of improvement or decline were found for other assessments.

Interestingly, Table 11.8 also revealed that 2 patients (JC and GW) benefitted most from LSVT. In all post treatment measures, the performances of these participants were either unchanged, or improved.

Table 11.8 Performance for each participant after LSVT treatment

Participant	CC	JC	BM	NN	GW
SWAL-QOL total after LSVT	↑	↑	↓	↑	↑
Breathing-Swallowing Coordination [a]	—	—	↓	↓	—
sEMG Amplitude	↑	↑	↑	↑	↑
Swallowing Capacity [b]	↓	↑	↓	↓	↑
FEES [c]	↑	↑	↑	↓	—
From spirometry – FEV1/FVC	—	↑	↓	↑	↑
Laryngopharyngeal Chemo-sensitivity [d]	↓	—	↓	↓	—
Laryngopharyngeal Mechano-sensitivity [e]	—	—	—	—	—

↑ = improvement in performance, ↓ = decline in performance, — = unchanged performance

[a] a decline resulting from an increase in II and or EI swallowing pattern

[b] Swallowing capacity from the timed test of swallowing

[c] an improvement or decline in at least of the swallowing symptom: pre-swallow pooling, laryngeal penetration, aspiration, residual as seen on FEES

[d] a decline resulting from an increase in the natural cough threshold

11.5 Discussion

This study set out to examine the effects of LSVT on airway protection. Disease severity staging using the H-Y scale, in conjunction with UPDRS and MMSE were administered to demonstrate that overall disease progression did not change substantially between assessment sessions.

There was a slight increase in mean total SWAL-QOL across patients after LSVT but not all subsections within the questionnaire showed improvement. Eight subsections showed improvements (Figure 11.1), with the largest improvements in the 'Social Functioning' and 'Communication' subsections. Analysis of individual patients showed that for these subsections, all but one (different) patient indicated improvement post LSVT. Presumably, the gains after LSVT allowed for increased communication ability including intelligibility and loudness, with subsequent improvements in social functioning. This particular benefit has been supported by previous studies (Ramig et al., 2001a; Ramig et al., 2001b). There was no change in 'Burden' of having a swallowing disorder, with small decreases in 'Eating Duration' and 'Eating Desire'.

The coordination of breathing-swallowing changed in 2 patients (Table 11.3). Swallows preceding expiration are claimed to be robust and the most common pattern (Martin-Harris, Brodsky, Price, Michel, & Walters, 2003; Selley et al., 1989a) and thought to be helpful in preventing post swallow aspiration. Interestingly, but disconcertingly, both patients had reduced EE swallows and increased IE swallows. In one patient (NN), swallows that precede and follow inspiration (II) increased from 0% to 50% while EE swallows decreased from 80% to 0%. Improved phonatory sufficiency would necessitate coordination between phonation and respiration and this has been reported (Dromey, Ramig, & Johnson, 1995; Ramig et al., 2001a; Stelzig et al., 1999) but exactly how LSVT influences coordination of respiration and swallowing is yet to be explained. One explanation may be that although phonation and swallowing share some laryngeal and pharyngeal structures anatomically, the pathways that generate these two are different so an improvement of breathing-phonation coordination would not automatically improve breathing-swallowing coordination. Our small sample showed that 2 patients had increased post swallow inspiration but 3 of 5 patients had no change in BSC. As yet, the sample size is too small to draw any firm conclusions about the

effects of LSVT on BSC. However the potential, albeit small, for increased post swallow inspiration, necessitates further study of this phenomenon.

One consistent change after LSVT is in the average sEMG across 10 trials of single liquid swallows, during which BSC was recorded. All participants showed increased average sEMG. Of specific interest is patient NN, who, despite having an increase of 50% of swallows preceded and following inspiration post LSVT, demonstrated the largest average peaks during swallows. It is possible that NN had involuntarily increased muscle contraction as an airway defence mechanism. Bearing in mind that sEMG reflects a relative measure of hyolaryngeal excursion (Huckabee & Pelletier, 1999a) increased sEMG may be required to provide added airway protection in the presence of aberrant BSC. It is important to highlight that submental sEMG is a relatively imprecise measurement of collective floor of mouth muscle contraction. As such it is heavily influenced by the contraction of the tongue (genioglossus) muscle. The contraction of genioglossus may also account for the change seen in sEMG amplitude.

There were no consistent changes in the indices of timed test of swallowing following LSVT (Table 11.4). As a group, the overall mean swallowing capacity was marginally increased but this encompassed increased capacity in 3 participants and decreased capacity in 2. In addition, there was no consistent pattern or trend during FEES evaluation, although there appeared to be a trend towards reduced frequency of pooling per bolus given, and increased clearing of residue for thin fluids and nectar thick fluids post LSVT (Table 11.5). Reduced frequency of pre-swallow pooling observed in this study supports a previous report by El Sharkawi et al., (2002), who also found significantly reduced oral and pharyngeal transit times for liquid boluses. In addition, these authors also report a 50% reduction in the frequency of residual in their patients after treatment without reporting whether the patients also spontaneously cleared residue. Results of our small study support the claim that LSVT may improve swallowing, especially in motility aspects of swallowing. In addition, we demonstrated that LSVT may have increased sensation in the pharynx such that patients were clearing residue more frequently.

Of interest is the observation that participant BM demonstrated silent aspiration when drinking 90ml of water sequentially after LSVT. This is a rare occurrence in this group of participants. On closer inspection, however, it is noted that he was at a later stages of PD (H-Y stage 3). The loss of sensation resulting in silent aspiration illustrates a point by Ebihara et al., (2003) who said that patients in the earlier stages of PD experience motor dysfunction but

would also experience sensory loss in the later stages. As reassessment times post LSVT in this study was variable, up to one year post treatment, patient BM may have begun to show evidence of sensory loss between assessments.

One study had documented and followed-up on a single aspect of pulmonary function, the forced vital capacity (FVC) before and after LSVT in a group of 22 individuals with PD (Ramig et al., 1996) and found no significant difference before and up to 12 months after treatment. In our study, 4 of the 5 patients had FVC that were within the normal limits prior to LSVT, as reflected by the % predicted FVC (Table 11.6) but in these patients, % predicted FVC had reduced post treatment. The remaining patient (GW) had increased FVC post treatment but he was also the patient that had FVC outside of the % predicted for his age and gender, as per NHANES III reference values. In addition to FVC, of interest in this study is the PEF (Table 11.6). PEF refers to the maximum flow generated during expiration performed with maximal force and started after a full inspiration (Quanjer, Lebowitz, Gregg, Miller, & Pedersen, 1997). All but one patient had greater PEF. It is of interest that PEF increased despite a mild decline in FVC. Even though patients exhibited a mild decline in volume change of the lung between a full inspiration to total lung capacity and a maximal expiration to residual volume (definition of FVC), they exhibited improvements in maximum flow during expiration. This may suggest that LSVT improved expiratory function that is required during phonatory and speech tasks.

There were no consistent differences across participants for laryngopharyngeal chemo- and mechano-sensitivity (Figure 11.4, Table 11.7). Three participants had increase natural and suppressed cough thresholds post LSVT, one (GW) demonstrated increased thresholds only for suppressed cough and only one (GW) demonstrated decrease in natural and suppressed cough thresholds after treatment. Although one main aim for LSVT is to ‘calibrate’ the patient, a process similar to helping the patient to get use to the sensation of the newly-learnt phonatory patterns for speech, the increased sensory feedback did not play an obvious part in changing the chemo- and mechano-sensation of the laryngopharynx. The implies that patient ‘calibration’ is a cognitive process of linking sensory input to perception of sensory changes rather than changing sensation.

Table 11.8 revealed that 2 patients (GW and JG) benefitted most from LSVT. In post treatment measures, the performances of these participants were either unchanged, or improved. This would suggest that LSVT may benefit some, but not patients. GW and JC

were in H-Y stages 1 and 2 respectively. LSVT may benefit those in the earlier stages more than patients in the later stages of PD but further research would need to confirm this. As yet, no research has compared the long term efficacy of LSVT across severity levels of PD.

Of interest is the finding that none of our participants who underwent LSVT had vocal fold bowing during nasendoscopy, even though vocal fold incompetence is a common and contributing factor to reduced loudness in PD. This is possibly due to the instrumentation used in this study. Research has shown that videostroboscopy with rigid endoscopy provides superior view of the vocal structures and may change first diagnosis in up to 18% of patients (Fortes, Imamura, Tsuji, & Sennes, 2007). It is plausible that vocal fold incompetency may still be present but not detected using flexible nasendoscopy.

11.6 Conclusion

This study is the first to investigate the effect of LSVT in several aspects of airway protection. It is acknowledged that conclusions cannot be drawn from a small sample size. Nonetheless, results yield many interesting trends that warrant further investigation. One limitation of this study was the reassessment time. Due to circumstances beyond the control of the primary researcher, post-test assessment was conducted at variable times post LSVT, up to one year post treatment (Table 11.1). Participants may have advanced further in the disease, which may account for the increased in aspiration during sequential drinking in participant BM. Nonetheless, the benefits of LSVT has been seen to last up to 2 years post treatment (Ramig et al., 2001a).

The ‘Communication’ and ‘Social Functioning’ subsections of the SWAL-QOL improved post treatment, suggesting that as expected, with phonatory efficiency and clarity, LSVT may have provided patients with increased communication opportunities within a social context. This needs to be confirmed in future studies. Other positive changes are improved sEMG amplitudes during normal, non-effortful liquid swallows. Of concern are changes in BSC patterns following LSVT indicating increases in post swallow inspiration but as one patient demonstrated, this may be compensated by increased sEMG amplitudes. Future studies with larger sample sizes are required to see if this trend is significant.

The trend of reduced frequency of pooling and post swallow residual clearing as seen on FEES lends further support to a previous small study documenting improvements in oral and

pharyngeal transit times. LSVT may have advantages beyond improvements in phonation and respiration. Regarding the latter, our study demonstrated in 4 of 5 patients, expiratory flow rates improved after treatment, even in the presence of decreased vital capacity. Finally, our study was unable to support any consistent changes in laryngopharyngeal sensitivity after LSVT. In conclusion, our results did show some areas in assessments of airway protection that are worthy of further exploration.

PART V: MECHANISMS OF AIRWAY PROTECTION IN AGEING AND PARKINSON'S DISEASE: CONCLUDING REMARKS

Chapter 12. Discussion of Airway Protection Mechanisms in Ageing and Parkinson's Disease

12.1 Main Findings of the Project

The protection of the airway during deglutition is crucial for preventing prandial aspiration, and is assured by a range of motor and sensory mechanisms that serve to keep the airway clear of food/fluids. The present study aimed to investigate how ageing, Parkinson's disease (PD) and disease severity affect airway protection by assessing both motor and sensory aspects. In this final chapter, the main effects of age and disease are discussed in turn. Findings for the study on airway protection 'on' and 'off' levodopa and the effects of speech rehabilitation (LSVT) are also summarised.

12.1.1 The Effects of Ageing on Airway Protection

The coordination between breathing and swallowing remains robust in ageing with young adults and elders exhibiting the majority of swallows in mid-expiration (Chapter 4). The duration of SA also remains unchanged in this study despite some studies reporting increased SAD in elders (Hiss et al., 2003; Selley et al., 1989a). The present study supports Nilsson et al (1996) who found several changes in other aspects of airway protection but no age effect on the total duration between the onset of vocal cord adduction to its complete reopening. Conceivably, prolonged SAD may be observed in the presence of potential threat to the airway such as during laryngeal penetration but as this study did not observe for vocal fold adduction during swallowing, SAD cannot be considered synonymous as vocal fold adduction.

In chapter 5, it was documented that elders and young adults did not differ in the frequency of laryngeal penetration for any fluid consistencies trialled. The finding that young adults and healthy elders do not differ in SAD may also account for the low frequency of laryngeal penetration and aspiration in both groups.

Several lines of evidence suggest that subtle changes to various aspects of swallowing occur as early as age 45 onwards (Robbins et al., 1992). In a measurement of swallowing efficiency, the present study found no age difference for drinking rate, swallowing capacity and average volume and time per swallow (Chapter 5) in a task requiring maximal effort to drink quickly.

Closer inspection of data revealed that our data do not differ significantly from the norms reported by Hughes & Wiles (1996b). Prior studies have indicated that although elders may experience significant changes to oral and pharyngeal swallowing (Baum & Bodner, 1983; Daniels et al., 2004; Dejaeger & Pelemans, 1996; Shaker et al., 2003), healthy elders generally maintained functional feeding and swallowing (Fucile et al., 1998).

Peak amplitude submental sEMG in this study further illustrates this with trends towards decreased peak amplitude for elders without significant impact on swallowing function measured during FEES (Chapter 5). Only one age difference was found for swallowing function, where elders were observed to have increased residual for pudding consistency trials on FEES (Chapter 5). This may account for why elders also reported more frequent symptoms of a swallowing problem compared to young adults (Chapter 7). Overall results from the present study support other authors who report that biomechanical changes may accompany some, but not all aspects of swallowing (Daggett et al., 2006; Fucile et al., 1998; Robbins et al., 1992).

In chapter 6, it was noted that young adults and elders demonstrated percentage predicted values for pulmonary function testing that were within the range of normal, even though statistical differences were found between these two groups. As spirometry measures, such as FEV1, are known to decline at a rate of 20-30mls each year after the age of 30 (Jedrychowski, Krzyzanowski, & Wysocki, 1986), it is unsurprising that although statistically significant, results were not *clinically* significant. For both groups, results suggest neither pulmonary obstruction nor restriction.

Cortical, or voluntary, control of cough was supported with differences between natural and suppressed cough thresholds for both groups (Chapter 8). Elders were less able to suppress cough compared to young adults which may suggest that the need for airway protection by coughing supersedes any instruction to inhibit coughing. Laryngopharyngeal mechano-sensation was not different at any of the 6 test sites. Taken together, laryngopharyngeal chemo- and mechano-sensation remain intact with ageing.

Two prior studies have documented decreased chemo-sensation to ammonia (Pontoppidan & Beecher, 1960) and distilled water (Newnham & Hamilton, 1997) but a direct comparison of the present study to these studies is not possible due to methodological differences. As yet, no research has looked at the effect of ageing on chemo-sensation using the methods employed

in this study. As with chemo-sensitivity, a comparison of our results on mechano-sensitivity to other studies is also difficult. Most work evaluating mechano-sensation has been carried out using FEESST, and work by the same group of researchers reported an effect of ageing on mechno-sensation (Aviv, 1997a). The present study is the first to document mechano-sensory changes using a qualitative approach.

In summary, this study demonstrated that healthy elders were able to protect their airway well, with very few exceptions. While elders experienced increased frequency of dysphagia and post swallow residual, this did not did not compromise overall airway protection. There were even changes in favour of airway protection, such as coughing over-riding instructions to suppress cough.

12.1.2 The Effects of Parkinson's Disease on Airway Protection

Our results show many differences in the ability to protect the airway in individuals with PD. One main finding is that swallowing efficiency declines in PD (Chapter 5), with all indices of the timed test of swallowing showing significant deterioration. Bradykinesia, a major symptom in PD may have been reflected in this task requiring maximum effort to drink quickly. Complaints of slowness when eating and drinking are frequent in PD, which holds true even when patients try to minimise drinking time (Chapter 5). Consequently, a reduction in swallowing efficiency impairs patients' quality of life (Chapter 9) with all but one subset of the SWAL-QOL reflecting significant changes compared to their healthy counterparts.

As with comparisons between young adults and elders, BSC did not differ between elders and age-and gender-matched individuals with PD (Chapter 4). Mid expiratory swallows remained the most frequent pattern in patients, contrary to reports that post swallow inspiration may increase to 91% in patients with neurological disorders (Hadjikoutis et al., 2000). No research to date has examined BSC in PD but results of this present study would suggest that the coordination between respiration and swallowing may be spared in PD. Broussard & Altschuler (2000) stress that the exact neurophysiology of BSC is not entirely clear although it is well accepted that the brainstem and to some extent, the cortex exerts significant influence over the coordination of breathing and swallowing (Kelly et al., 2006). While these sites may be detrimentally affected in neurological disorders such as stroke, they are not affected in extrapyramidal disorders thus sparing the neural networks that control BSC.

Pulmonary function was not significantly different in individuals with PD compared to healthy elders (Chapter 6) even though prior research documented both obstructive and restrictive patterns in these patients. Some authors argue that pulmonary disturbance may go unnoticed as patients tend not to engage in activities where ventilatory insufficiency may be manifest (Sabate et al., 1996a; Sabate et al., 1996b), yet, in this study, patients neither exhibited evidence of airway obstruction nor restriction. The heterogeneous PD severity may account for why no differences were noted.

No apparent changes to laryngopharyngeal chemo-sensation were detected in PD using citric acid cough challenge (Chapter 7), suggesting that at least in this patient population, chemo-sensation is not affected. Similar to the findings of the present study, several authors also failed to detect differences in their patients (Fontana et al., 1998; Smith & Wiles, 1998). Ebihara et al., (2003) found that in H-Y stages 2 and 3, cough thresholds in patients were not different to healthy counterparts but in Stage 5, patients exhibited increased cough thresholds. Patients in the present study were of mixed severity levels and any late stage effects may have been masked by having a variable severity level.

Mechano-sensation to the base of tongue was diminished in patients when compared to normals, which may account for why thin fluid residual are more frequently observed. Residual for other consistencies were not observed possibly due to the added 'weight' of thickened and semi-solid consistencies, which in turn prompt clearing swallows. Small amounts of tin liquid residual may not exert enough pressure to trigger the deeper mechanoreceptors required to initiate clearing swallows (Miller, 2002).

12.1.3 The Effects of Disease Severity on Airway Protection

The increasing severity of PD did not alter BSC although significantly longer apnoea duration was observed in later stage PD. Prolonged apnoea has been previously reported as a means of additional airway protection in ageing (Hiss et al., 2001) but the present study is the first to demonstrate longer SAD in individuals with PD. Conceivably, in later stages of disease where aspiration risk is greater (Coates & Bakheit, 1997) patients exhibit prolonged SAD for added airway protection. Whether extended SAD is voluntary (cortical) or involuntarily driven remains unanswered since there is evidence that SA is both reflexive with own separate, neural control (Hiss et al., 2003; Shaker et al., 2003) and cortically influenced (Kelly et al., 2006).

This study revealed that progressively, the quality of life in later stages of PD is further reduced when they find it increasingly difficult to select foods they can safely eat. Consequently, this task may be so challenging that their desire to eat is also reduced (Chapter 9). It is intriguing to note that even though individuals in the later stages claimed to take longer at mealtimes than those in the earlier stages, this slowness was not reflected in the timed test of swallowing, where no differences were found for any indices (Chapter 5). When asked to drink quickly, individuals in the later stages perform just as well as those in the early stage yet they claim to take longer normal mealtimes. This observation is interesting as it suggests that unwittingly, patients may be deliberately slowing down for fear of choking. Patients may also experience fatigue over a course of a meal, which may not be revealed in the timed test of swallowing of a short duration.

Statistical, but not clinical, significance was found for some measures of spirometry between earlier and later stage individuals with PD (Chapter 6). When asked to perform respiratory tasks requiring maximum force, even individuals with PD in later stages were able to demonstrate pulmonary function that was within normal limits. Upper airway obstruction is indicated by a reduction in peak inspiratory flow (Sabate et al., 1996a) and this is one measure in the present study that was close to being statistically lower in later stage PD. Rigidity of the vocal folds that prevent full adduction have been supported (Clark, 1970; Engstroem et al., 1964; Miller & Hyatt, 1973) and would account for the suggestion of upper airway obstruction in later stages. Weakness of respiratory muscles, leading to a restrictive spirometry pattern was also indicated in later stages (Chapter 6).

Individuals in the later stages of PD are known to have higher cough thresholds compared to those in the early stages (Ebihara et al., 2003) but this is not reflected in the present study (Chapter 8). Instead of concluding that there was truly no difference, this discrepancy was most likely due to the categorisation of patient participants. Early stage patients in the study by Ebihara et al were in H-Y stages 2 and 3 while late stage participants were in H-Y stage 5. In contrast, the present study categorised early stages as H-Y 1 to 2 and later stages as H-Y 2.5 and above. There were no participants in stage 5 in the present study. If chemo-sensory loss is a feature of later stage PD, it would account for why no changes were seen in later stage patients in this study.

No studies to date have investigated laryngopharyngeal mechano-sensation exclusively in PD, although in other neurological disorders such as stroke, it is well-documented that mechano-

sensory thresholds increase post injury (Aviv et al., 1996; Aviv et al., 1997a; Aviv et al., 1997b). This study is also the first to evaluate mechano-sensation using a qualitative method described by Langmore & Aviv (2001), which may prove to be the more clinically available technique. Despite the high incidence of silent aspiration in PD to suggest sensory loss, the present study found no changes to mechano-sensation as the disease progresses. A direct comparison between mechano-sensation and silent aspiration has yielded poor correlations because of distinct neural innervations to the laryngopharynx. Whilst FEESST assesses the integrity of the supraglottic region innervated by the superior laryngeal nerve (SLN), Langmore (1998) highlighted that silent aspiration implies *sub*glottic insensitivity, which is innervated by the recurrent laryngeal nerve (RLN). As with chemo-sensory loss, mechano-sensory also may also be a feature of later stage PD.

12.1.4 The Effects of Pharmacotherapy and Speech Rehabilitation on Airway Protection

Ten participants from the original study underwent repeated the assessments to evaluate the effects of levodopa therapy on airway protection (Chapter 9). Results support prior studies to show that levodopa improves motor function in individuals with PD, measured by overall improvement in the Unified Parkinson's Disease Rating Scale (UPDRS) score (Bejjani et al., 2000; Fahn, 2005). Beyond that, no associations were found between levodopa and BSC, swallowing biomechanics as seen in FEES, swallowing efficiency, chemo- and mechno-sensitivity of the laryngopharynx. There was a significant decrease in FEV and FEV1, contrary to reports that levodopa improves pulmonary function (Hovestadt et al., 1989; Sabate et al., 1996a; Sathyaprabha et al., 2005). It was concluded that respiratory dyskinesia, a possible side effect of levodopa (Brown, 1994), may have accounted for the worsening of pulmonary function 'on' levodopa. Further studies are needed to ascertain whether peak dose dyskinesia affects pulmonary function.

Chapter 10 was a small study of 5 individuals with PD at different stages of the disease progression. Even so, it was the first to investigate the effects of LSVT on airway protection. Results uncovered several aspects interesting aspects of note that warrant further investigation. The increased phonatory efficiency and clarity after LSVT may account for an increased in quality of life, reflected in the increase in 'Communication' and 'Social Functioning' subsections of the SWAL-QOL. Conceivably, LSVT provided these individuals with increased communication opportunities. Another positive improvement is the finding that for all 5 participants, sEMG amplitudes increased after LSVT. This provides additional

support to a prior study documenting improved symptoms of dysphagia after LSVT (El Sharkawi et al., 2002). Of concern were changes in BSC patterns demonstrating an increase in post swallow inspiration. However, no firm conclusion may be drawn as this was not consistent across all participants. No other consistent trends were noted for pulmonary function, chemo- and mechano-sensitivity of the laryngopharynx post treatment. While no consistent trends were found for a few of the assessments, an interesting observation was made on closer inspection of individual patients. The performance of two patients either improved or remained unchanged during reassessment across all tests. This observation suggests that certain patients may benefit from LSVT more than other patients. An interesting future study would be to evaluate patient characteristics and the efficacy of LSVT.

12.2 Mechanisms of Airway Protection: Concluding Remarks

In conclusion, results of the present study indicate that overall, elders are capable of airway protection to the same degree as their younger counterparts. This was evidenced by the non-significant changes in most of the motor and sensory assessments of airway protection. Healthy elders do experience more frequent residual on heavier textures like pudding compared to young adults but are aware that they experience symptoms of dysphagia more frequently, such as food getting stuck in throat (Appendix 3). In addition, their decrease in the ability to suppress cough in elders suggests that the need for airway protection over-rides any instruction to suppress coughing.

Airway protection in PD is affected most substantially by changes in motor function. Biomechanical changes that detrimentally affect the efficiency of swallowing, plus increased aspiration risk on thin fluids were severe enough to decrease quality of life in these patients. With the exception of decreased mechano-sensation in bilateral BOT, laryngopharyngeal sensation remained intact. The advancement of the disease resulted in additional airway protection with the prolongation of SAD in later stage patients. However, difficulties in food selection and the extended times required during mealtimes was associated with a reduced eating desire. Consequently, the quality of life declined further for later stage patients.

The effects of levodopa and speech rehabilitation (LSVT) on the mechanisms of airway protection uncovered many interesting results that warrant further investigation. Example, the finding that pulmonary function worsens during the ‘on’ phase is unexpected, and may have implications for airway protection since swallowing and respiration are closely linked. It

would important for future studies comprising larger numbers of patients to seek true effects of pharmacotherapy and speech rehabilitation.

12.3 Strengths and Critique of Present Research

A key strength of the present research is the comprehensive evaluation of both motor and sensory mechanisms of airway protection in PD. Short of conducting a longitudinal study with repeated measures design documenting changes in airway protection, this cross sectional design looking at the severity affects across individuals with PD was the most appropriate.

Much of what is known about BSC has been obtained from infants (Kelly, Huckabee, Jones, & Frampton, 2007), healthy adults (Hiss et al., 2001; Selley et al., 1989a) and some neurological populations (Hadjikoutis et al., 2000; Selley et al., 1989b). BSC data in PD from this present study adds to the knowledge of BSC in patient populations. Prior research has shown that compensation in PD occurs at behavioural levels (Countryman, Hicks, Ramig, & Smith, 1997) and although speculative, increased SAD in later stage PD may also imply a type of compensatory mechanism for increased aspiration risk.

Much more is known about motoric aspects and biomechanics of swallowing in PD compared to the contribution of sensation towards airway protection yet silent aspiration has a significant role in the pathogenesis of pneumonia, the main cause of mortality in these patients (Wang et al., 2002). The present research is the first to document chemo-sensory changes to the laryngopharynx in PD using single-inhalation, dose-response method. This method has not been previously reported in PD. The extension of citric acid concentrations from 1 mole to 2 moles enabled a more comprehensive assessment of chemo-sensation. Data AUTHOR>Sethi, K.</AUTHOR><AUTHOR>Odin, P.</AUTHOR><AUTHOR>Brown, R. G.</AUTHOR><AUTHOR>Koller, W.</AUTHOR><AUTHORluence on coughing may be made.

For the first time, the detrimental effects of dysphagia on the QOL in individuals with PD have been documented. This adds to the substantial evidence that PD negatively impacts upon many aspects of patient's life (Playfer, 1999; Slawek et al., 2005). Findings from this present study would serve as an indication to healthcare professionals that dysphagia in individuals with PD may also signal depression (de Luis et al., 2006; Ekberg et al., 2002; Miller et al., 2006a).

One methodological challenge of the present research was the difficulty in recruiting participants in the later stages of PD (H-Y >4). At the request of the regional health ethics committee, patients with mini mental state examination score of ≤ 26/30 were excluded. A few participants were unable to participant on that basis. Dementia is known to present in approximately 30% of individuals with PD (Aarsland et al., 1996) and plays a role in treatment options in PD patients with dysphagia (Bine, Frank, & McDade, 1995).The exclusion of patient with dementia in this study invariably precluded some patients in the later stages.

12.4 Future Research

Results from the present study uncovered several areas that could be improved in future research. The inhalation cough challenge was carried out using the full exhalation followed by full inhalation method (Pounsford & Saunders, 1985). Same instructions were given to all participants the present study but in the absence of a dosimeter, neither inhalation rate nor dose was tightly controlled. The rate of inhalation has been known to affect the deposition of the tussigenic agent, and subsequently cough threshold. Specifically, cough thresholds were lower at a slower inhalation rate (Barros et al., 1990). It would be important for future studies to use a dosimeter to control the rate and dose of tussigenic agents.

Based on results from the present study, it would appear that individuals with PD did not have airway obstruction or restriction, contradicting many authors who reported both respiratory patterns (De Pandis et al., 2002; Sabate et al., 1996a; Vercueil et al., 1999). A reduction in maximal inspiratory and expiratory flows as well as maximal inspiratory and expiratory pressures are findings characteristic of individuals with PD (Bogaard, Hovestadt, Meerwaldt, vd Meche, & Stigt, 1989). The inability to generate a rapid rise in peak expiratory flow is consistent with hypokinesia typical of PD, and may have implications for generating a maximally effective cough. Nonetheless, Tzelepis et al., (1998) argue that respiratory muscle impairment in individuals with PD may only show up in repetitive tasks but not in tasks requiring single respiratory efforts. As such, patients may have normal spirograms but still show aberrations in respiratory muscle function. Certainly, for the purposes of airway protection, a correlation of spirometry data to peak cough flow and other maximal pressures such as maximal expiratory and inspiratory pressures would also be useful.

Sensory testing using the qualitative method is problematic for 2 reasons that are interlinked. First, no objectively measurable pressure is possible using this method so whether the delivered pressure was consistent across patients remains questionable. Second, the quantification of sensory loss is not feasible. Although the loss of mechano-sensation may be graded in terms of severity using FEEST (Aviv, 1997b, 2000), the qualitative method is unable to quantify this change.

Nonetheless, quantitative sensory testing using FEESST *also* poses its own challenge. In Chapter 10, it was highlighted that the currently available FEESST system provided extra visual, audio and tactile cues as air puffs were delivered via an external sleeve. This is different from the previous FEESST set up where the air channel for air pulse delivery was encased within the scope. Most of the work on FEESST to date has been conducted using the prior FEESST scope. While over 80% of Aviv et al's participants reported little or no discomfort (Aviv et al., 2000), anecdotally, most of our participants reported severe discomfort on the new scope and sleeve. Future studies would need to validate the normative pressures described by (Aviv, 1997b) using the new FEESST setup before data can be compared to their normative values.

One of the key questions that remain unsolved is the link between the loss of sensory function and the loss of ability to respond to sensory stimuli due to motor dysfunction. Example, if no laryngeal adduction was seen upon mechano-stimulation at a particular pressure, it unclear whether it was due to the real loss of sensation or the loss of ability to adduct the vocal folds secondary to hypoadduction. It may be argued that if LAR is absent but the patient acknowledges the sensory of the air puffs, this would signal loss of motor responses in the presence of preserved sensation. Conversely, the absence of LAR plus the failure to acknowledge air puffs would signal total sensory loss. These hypotheses however, remain speculative. Assessment of sensation in animals also uncovered similar challenges. Martinez-Arizala (2003) concluded that a delay in response times in an animal with spinal cord injury may be a delay secondary to motor paralysis and not from sensory dysfunction. In the absence of neuroimaging and mapping studies, it may is extremely difficult to differentiate between these two components. Although beyond the scope of the current study, studies that examine the neurophysiology of sensory pathways and sensory loss are likely to be of value.

Finally, variable effect sizes for some of the assessments in the present study would suggest that for some measures, at least, the sample size was too small. The original intent of the

study was to compare patients across three PD stages, (early, mid and late) with 16 participants in H-Y stage ≤ 2, 3 and ≥4 respectively. With only 4 participants in H-Y stage 4, re-grouping of participants meant that comparisons were made between earlier and later stages (H-Y stage ≤ 2 and ≥ 2.5 respectively). With this dichotomous grouping where there is not a lot of differences in H-Y stages, any differences in patients' performance may have been too minimal to be reflected in the assessments conducted. As some deterioration in function may not be seen till H-Y stage 5 (Ebihara et al., 2003), cross-sectional comparisons between patients in early (H-Y stage 1), mid (H-Y stage 3) and late (H-Y stage 5) stages would be recommended for future studies.

APPENDICES AND REFERENCES

Appendices

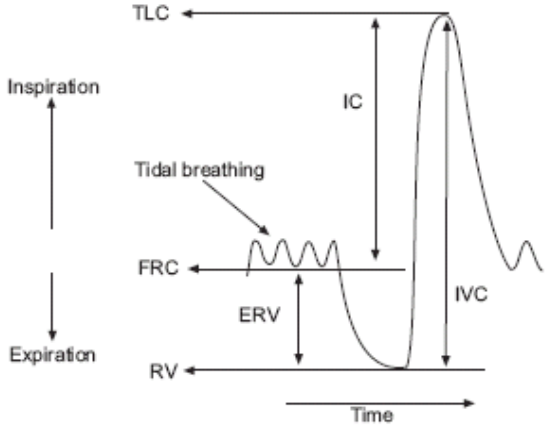
Appendix A. Normal Sequence and Timing of Structural Movements during Swallowing

Onset Of Swallow Event	*Approximate time (s)*	*Standard Deviation*
Arytenoids medial, then forward	0	[-- Endoscopy [a,b,c,d]
Arytenoids contact medially	0.60	0.04 Endoscopy [c]
	0.246	0.292, Endoscopy [d]
Nasopharyngeal closure	(before hyoid elevation)	
	Dua et al., (1997)	
Base of tongue movement	0.31	0.04, Fluoroscopy [a]
	1.08	0.01, Fluoroscopy [c]
	0.15 (liquids)	0.06, Submental EMG [e]
	0.21 (solids)	0.17 Submental EMG [e]
Hyoid elevation/epiglottic inversion	0.33	0.04, Fluoroscopy [a]
	0.341	0.151, Ultrasound [b]
	0.88	0.00 , Fluoroscopy [c]
	0.464	0.194, EMG [d]
UES relaxation	0.517	0.292, EMG [d]
Pharyngeal shortening	0.522	0.370, EMG [d]
Whiteout (pharynx closes)	0.621	0.64, Endoscopy [b]
	0.547	0.280, Endoscopy [d]
TVC actively adduct	0.42	0.04, Endoscopy [a]
	0.74	0.05, Endoscopy [c]
	0.567	0.293, EMG [d]
Arytenoids touch epiglottis	0.71	0.04, Fluoroscopy [a]
	1.10	0.01, Fluoroscopy [c]
UES opens	1.10	-- Fluoroscopy [c]
	0.806	0.259, Endoscopy [d]
UES closes	1.368	0.376, EMG [d]
View returns (pharynx reopens)	1.090	0.82, Endoscopy [b]
	1.499	0.362, Endoscopy [d]
Epiglottis returns to rest	1.174	0.63, Endoscopy [b]
	1.424	0.286, Endoscopy [d]

EMG = electromyography, TVC = true vocal cord, UES = upper oesophageal sphincter
[a] dry swallows, 8 subjects, 40 swallows (Shaker et al., 1990)
[b] unmeasured volumes, 5 subjects, 25 swallows (Perlman & VanDaele, 1993)
[c] 5 ml swallows, 8 subjects, 24 swallows (Ohmae, Logemann, Kaiser, Hanson, & Kahrilas, 1996)
[d] 10 ml swallows, 4 subjects, 24 swallows (Van Daele et al., 2005)
[e] uncontrolled volumes, 15 subjects, 670 swallows (Dua et al., 1997)
Adapted from Langmore, S. E. (2001). Normal swallowing: The endoscopic perspective. In S. E. Langmore (Ed.), *Endoscopic Evaluation and Treatment of Swallowing Disorders*. New York: Thieme.

Appendix B. Common Terminology used in Spirometry

Definition of Common Lung Volumes	



Tracing of tidal breathing followed by an expiratory manoeuvre to residual volume (RV), followed by a full inspiration to total lung capacity (TLC) to record inspiratory vital capacity (IVC) and inspiratory capacity (IC). FRC: functional residual capacity; ERV: expiratory reserve volume. Adapted from Miller, et al. (2005). Standardisation of spirometry. *The European Respiratory Journal, 26*(2), 319-338.

Abbreviation	***Definition***
RV	Residual volume is the volume of gas remaining in the lungs after a complete exhalation
TLC	Total lung capacity is the amount of gas in the lungs after a maximum inspiration
IVC	Inspiratory vital capacity is the maximal volume of air inhaled from the point of maximal exhalation, achieved by a slow expiration from end-tidal inspiration
IC	Inspiratory capacity is the maximum amount of air that can be exhaled from resting end-expiratory level or FRC; the sum of the tidal volume and inspiratory reserve volume
FRC	Functional residual capacity is the total amount of gas left in the lungs after a resting expiration
ERV	Expiratory reserve volume is the total amount of gas that can be exhaled from the lungs following a quiet exhalation
Definition of Common Lung Volumes used in Spirometry	
FVC	Forced vital capacity is the maximum volume of gas that the subject can exhale as forcefully and as quickly as possible
FEV1	Forced expiratory volume, 1 sec is the maximum volume of gas that the patients can exhale during the first second of the forced vital capacity manoeuvre
FEV1/FVC	Forced expiratory volume in one second ratio is the percentage of the measured forced vital capacity that can be exhaled in one second
PEF	Peak expiratory flow is the maximum expiratory flow achieved from a maximum forced inpiration, starting without hesitation from the point of maximal lung inflation
PIF	Peak inspiratory flow is the maximum inspiratory flow achieved from a maximum forced expiration, starting without hesitation from the point of maximal lung deflation
FIVC	Forced inspiratory vital capacity is the volume of gas that the subject can inhale as forcefully and as quickly as possible

Adapted from Douce, F. H. (2003). Pulmonary Function Testing. In R. L. Wilkins, J. K. Stoller & C. L. Scanlan (Eds.), *Egans Fundamentals of Respiratory Care, Eighth Edition*. St. Loius, Missouri: Mosby.

Appendix C. Swallowing Quality of Life (SWAL-QOL) Survey

Instructions for Completing the SWAL-QOL Survey

This questionnaire is designed to find out how your swallowing problem has been affecting your day-to-day quality of life.

Please take the time to carefully read and answer each question. Some questions may look like others, but each one is different.

You do not need to answer all questions.

Here's an example of how the questions in the survey will look.

1. In the last month how often have you experiences each of the symptoms below.

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
Feel weak	1	2	3	4	5

Thank you for your help in taking part in this survey!

1. Below are some general statements that people with ***swallowing problems*** might mention. Please indicate **how true** each of the following are for you.

(circle one number on each line)

	Very much true	Quite a bit true	Somewhat true	A little true	Not at all true
Dealing with my swallowing problem is very difficult.	1	2	3	4	5
My swallowing problem is a major distraction in my life.	1	2	3	4	5

2. Below are aspects of day-to-day eating that people with ***swallowing problems*** sometimes talk about. In the last month, **how true** have the following statements been for you?

(circle one number on each line)

	Very much true	Quite a bit true	Somewhat true	A little true	Not at all true
Most days, I don't care if I eat or not	1	2	3	4	5
It takes me longer to eat than most people.	1	2	3	4	5
I'm rarely hungry anymore	1	2	3	4	5
It takes me forever to eat a meal	1	2	3	4	5
I don't enjoy eating anymore	1	2	3	4	5

3. Below are some physical problems that people with ***swallowing problems*** sometimes experience. In the last month, **how often** you have experienced each problem as a result of your swallowing problem?

(circle one number on each line)

	Almost always	**Often**	**Sometimes**	**Hardly ever**	**Never**
Coughing	1	2	3	4	5
Choking when you eat food	1	2	3	4	5
Choking when you take liquids	1	2	3	4	5
Having thick saliva or phlegm	1	2	3	4	5
Gagging	1	2	3	4	5
Drooling	1	2	3	4	5
Problems chewing	1	2	3	4	5
Having excess saliva or phlegm	1	2	3	4	5
Having to clear your throat	1	2	3	4	5
Food sticking in your throat	1	2	3	4	5
Food sticking in your mouth	1	2	3	4	5
Food or liquid dribbling out of your mouth	1	2	3	4	5
Food or liquid coming out of your nose	1	2	3	4	5
Coughing food or liquid out of your mouth when it gets stuck	1	2	3	4	5

4. Next, please answer a few questions how about your ***swallowing problem*** affects your diet and eating.

(circle one number on each line)

	Strongly agree	**Agree**	**Uncertain**	**Disagree**	**Strongly disagree**
Figuring out what I can and can't eat is a problem for me.	1	2	3	4	5
It is difficult to find foods that I both like and can eat.	1	2	3	4	5

5. In the last month, **how often** have the following statements applied to you because of your ***swallowing problem***?

(circle one number on each line)

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
People have a hard time understanding me.	1	2	3	4	5
It's been difficult for me to speak clearly.	1	2	3	4	5

6. Below are some concerns that people with ***swallowing problems*** sometimes mention having. In the last month, **how often** have you experienced each feeling?

(circle one number on each line)

	Almost always	Often	Sometimes	Hardly ever	Never
I fear I may start choking when I eat food	1	2	3	4	5
I worry about getting pneumonia.	1	2	3	4	5
I am afraid of choking when I drink liquids.	1	2	3	4	5
I never know when I am going to choke.	1	2	3	4	5

7. In the last month, how often have the following statements **been true** for you because of your ***swallowing problem***?

(circle one number on each line)

	Always true	Often true	Sometimes true	Hardly ever true	Never true
My swallowing problem depresses me.	1	2	3	4	5
Having to be so careful when I eat or drink annoys me.	1	2	3	4	5
I've been discouraged by my swallowing problem.	1	2	3	4	5
My swallowing problem frustrates me.	1	2	3	4	5
I get impatient dealing with my swallowing problem.	1	2	3	4	5

8. Think about your social life in the last month. How strongly would you agree or disagree with the following statements?

(circle one number on each line)

	Strongly agree	**Agree**	**Uncertain**	**Disagree**	**Strongly disagree**
I do not go out to eat because of my swallowing problem.	1	2	3	4	5
My swallowing problem makes it hard to have a social life.	1	2	3	4	5
My usual work or leisure activities have changed because of my swallowing problem.	1	2	3	4	5
Social gatherings (like holidays or get-togethers) are not enjoyable because of my swallowing problem.	1	2	3	4	5
My role with family and friends has changed because of my swallowing problem.	1	2	3	4	5

9. In the last month, **how often** have you experienced each of the following physical symptoms?

(circle one number on each line)

	All of the time	**Most of the time**	**Some of the time**	**A little of the time**	**None of the time**
Feel weak?	1	2	3	4	5
Have trouble falling asleep?	1	2	3	4	5
Feel tired?	1	2	3	4	5
Have trouble staying asleep?	1	2	3	4	5
Feel exhausted?	1	2	3	4	5

10. Do you take any food or liquid through a feeding tube?

(circle one)

No 1

Yes.....2

11. Please circle the letter of the one description below that best describes the consistency or texture of the food you have been eating most often in the last week.

Circle one:

A. Circle this one if you are eating a full normal diet, which would include a wide variety of foods, including hard to chew items like steak, carrots, bread, salad, and popcorn.

B. Circle this one if you are eating soft, easy to chew foods like casseroles, canned fruits, soft cooked vegetables, ground meat, or cream soups.

C. Circle this one if you are eating food that is put through a blender or food processor or anything that is like pudding or pureed foods.

D. Circle this one if you take most of your nutrition by tube, but sometimes eat ice cream, pudding, apple sauce, or other pleasure foods.

E. Circle this one if you take all of your nourishment through a tube.

12. **Please circle the letter** of the one description below that best describes the consistency of liquids you have been drinking most often in the last week.

Circle one:

A. Circle this if you drink liquids such as water, milk, tea, fruit juice and coffee.

B. Circle this if the majority of the liquids you drink are thick, like tomato juice or apricot nectar. Such thick liquids drip off your spoon in a slow and steady stream when you turn it upside down

C. Circle this if the majority of liquids you drink are thick milkshake or smoothie. Such moderately think liquids are difficult to such through a straw, like a very thick milkshake, or drip off your spoon slowly drop by drop when you turn it upside down, such as fresh honey.

D. Circle this if your liquids very thick, like pudding. Such very thick liquids will stick to a spoon when you turn it upside down, such as pudding.

E. Circle this if you did not take any liquids by mouth or if you have been limited to ice chips.

13. In general, would you say your health is:

(circle one)

Poor 1

Fair 2

Good 3

Very Good 4

Excellent 5

Appendix D. Participant Recruitment Form

Research Participants needed:

The University of Canterbury Swallowing Rehabilitation Research Laboratory is looking for participants for a study to investigate

Mechanisms of airway protection in ageing and Parkinson's disease

We are looking for 3 groups of participants:

1) Persons who have Parkinson's disease

2) Healthy men and women between 20 and 35 years

3) Healthy men and women 60+ years

This study will take place at the Van der Veer Institute for Parkinson's and Brain Research located at 16 St Asaph Street, Christchurch. The session will take approximately five hours of your time. You will be reimbursed for your travel cost to the research location.

If you are interested and would like more information please contact

Li Pyn Leow

Phone: 378 6098 or 351 1533 (evenings)
Email: lpl17@student.canterbury.ac.nz

*This project has been reviewed and approved by the Canterbury Health Ethics Committee

Appendix E. Participant Information Sheet

INFORMATION SHEET

Research Title: Mechanisms of airway protection in ageing and Parkinson's disease

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Introduction and aims of the project:

You are invited to participate in a research project that investigates how a person protects their airway during swallowing. Your participation is entirely voluntary (your choice). You may have a friend, family or whanau member to support and help you to understand the information provided. We would appreciate a decision regarding your participation within one week. You have the right not to participate in the study, or subsequently withdraw from this study at any time. Any decision not to participate will not affect your current, continuing or future health care at this or any other health care facility.

Difficulties in swallowing frequently occur at late stages of Parkinson's disease. However recent research has shown that the deterioration of swallowing may indeed occur earlier in the disease process. The aim of this project is to contribute to current research regarding the factors that help to predict swallowing difficulties in Parkinson's disease. This will be done by assessing the mechanisms that protect the airway during swallowing. Assessments will include a screening test of swallowing, a series of tests to determine the sensitivity of the throat, cough sensitivity, lung function and the coordination between the swallowing and breathing. These tests will be carried out on a total of 48 people with Parkinson's disease (PD). There will also be two groups of healthy adults, one age range from 20 to 35 and another aged 60+ participating in this study. These participants will serve as 'controls'. Participants in the control group help to ensure that any abnormal measurements are not due to normal ageing. The study will include a total of 48 participants with Parkinson's disease, 16 healthy young adults and 16 healthy elderly adults.

This study involves people with Parkinson's of different severity levels. Including people with different severity levels will enable us to monitor and chart the deterioration of airway protection in the early, middle and late stages of the disease. The outcome of this study will allow physicians and clinicians to be aware of swallowing impairment and to start rehabilitation early in the disease.

Participant selection:

This study requires the participation of three different groups of people. These are

1. Persons diagnosed with Parkinson's disease
2. Healthy elderly adults who are aged 60+
3. Healthy young adults aged between 20 and 35

You may be eligible for this study if you fall into one of the three groups of persons above.

There are certain conditions that would prevent your participation in this study as they influence a person's performance in the tests. If you have had any of the following conditions, you will not be able to participate in the study: stroke, asthma, chronic obstructive pulmonary disease (COPD) and /or other breathing disorder, head/neck surgery, other neurological disorders (e.g. multiple sclerosis). You will also not be able to participate if you are on medication for coughs and colds as this will affect your responses to some of the tests. In addition, you must not have smoked for the last 5 years in order to participate in his study. Finally, if you are on medication for Parkinson's disease, your medication should not have been changed in the last month.

What does the research involve?

If you agree to participate in the study, you will go to the University of Canterbury Swallowing Research Laboratory for the following assessments:

1. Swallowing questionnaire

You will be asked to complete a questionnaire regarding your perception of your own swallowing abilities. If you have difficulty swallowing, the questionnaire will help us to find out how your swallowing problem has been affecting your day-to-day life.

2. Swallowing and breathing

All participants will undergo a swallowing and breathing screen. You will be asked to drink 150 ml of water out of a cup to allow us to determine the average volume per swallow, the average time per swallow and the swallowing capacity. You will also be asked to swallow 10 tablespoons of water delivered by a spoon. Each tablespoonful is 8mls. Your swallows will be monitored using equipment called surface electromyography (sEMG). sEMG consists of an electrode patch that is placed over the muscles under your chin to record muscle activity during each swallow. Your breathing will be recorded using a nasal cannula that is similar to those used in oxygen delivery. This two-pronged nasal cannula will be placed at the entrance of your nose as you swallow. The sEMG and the nasal cannula will be connected to a workstation that allows for later data analysis.

3. Lung function

You will undergo standard spirometry testing. Spirometry is a method of assessing lung function by measuring the volume of air that a person is able to breathe out from the lungs after a big breath in. You will be asked to inhale as deeply as you can and exhale into a

mouthpiece as hard and as fast as possible until there is nothing left to exhale. This is repeated until the volume of air for each trial is more or less the same. To determine the strength of your cough, you will be asked to cough into a mouth piece that is attached to a flow sensor. This voluntary cough is repeated three times.

4. Cough challenge

The inhalation cough challenge is a test to assess how sensitive you are to a chemical that makes people cough. The chemical chosen for use in this study is citric acid. Citric acid is the acid found in citrus fruits such as lemons and oranges. It is also used in baking and making fizzy drinks. It is widely used for cough challenges. In this test, you will be given a breathing mask to wear. This mask is similar to the one used during oxygen delivery. Next, a predetermined concentration of citric acid will be delivered though the mask in the form of tiny water droplets (aerosol) and we will record whether or not you cough. Normally, low concentrations of citric acid do not cause a person to cough. The higher the concentration, the more likely it is to cause coughing. In this test, we are looking for the concentration that makes you cough 5 times in a row. Your *cough threshold* is identified when you cough 5 times in response to that particular concentration. For this test, different concentrations of citric acid will be delivered in a random sequence in order to determine your cough threshold. This test uses citric acid to cause you to cough. We are aware that coughing can be uncomfortable. Excessive coughing may result in chest tightness and breathlessness. To minimise this, as soon as your cough threshold is identified, the test is stopped.

5. Swallowing screen

A test will be completed that involves passing a 3.5mm flexible tube through a nostril. This tube is called an endoscope. It has a camera that enables us to obtain a view of your throat structures and vocal folds (voice box). Once in place, you will be asked to repeat the vowel “ee” three times and the word “duh-nuh” three times. You will also be asked to cough three times. This allows an assessment of how well your vocal folds open and shut.

To assess your swallowing ability you will be asked to drink some water of different thickness from small medicine cups. Each small cupful is 8 ml. You will be asked to have 3 cupfuls of normal, plain water and 3 cupfuls of slightly thickened water. A commercial food thickener is used to thicken the water to the consistency of fruit nectar. In order to obtain a clear contrast, one drop of blue food dye will be added into the water. This does not change the taste of the water and juice. You will also be given three spoonfuls of Dairy Maid pudding. Finally, you will be given 90 ml of plain water to sip from a cup and a piece of biscuit to eat. The

examiner may not complete the full swallowing test if you are unable to swallow well. The test may also be terminated at anytime if you do not with to continue.

Following the swallowing screen, the examiner may also test the sensation of your throat. This is done by providing a slight touch, once, on either side of your throat using the endoscope. Depending on the sensitivity of your throat, this may cause you to clear your throat, swallow or cough. Using this technique, the sensitivity of your throat can be established.

How long do the tests take?

The tests above will take approximately 4-5 hours of your time, on one visit. Following the assessments, you may be advised to see a Speech-Language Therapist. As your participation in this project is strictly confidential, a referral will only be made by Prof Tim Anderson with your agreement.

You may receive speech therapy known as the "Lee Silverman Voice Treatment" programme. Recent research has suggested that this treatment programme also helps to improve swallowing. If you are a participant of the Lee Silverman Voice Treatment programme, you would be asked to repeat the tests upon of completion of treatment.

What are the risks and benefits of the study?

By participating in this study you will contribute important information to the understanding of airway protection in the healthy population and in Parkinson's disease. Specifically, this research will help to determine the patterns of breakdown in swallowing ability as the disease advances. By identifying the mechanisms that give rise to swallowing difficulties, the appropriate treatment can be recommended. If you have been diagnosed with Parkinson's disease and demonstrate swallowing impairment in one or more of the tests, you will be referred to a Speech-Language therapist. Ultimately, your participation in this research will contribute to existing knowledge of treatment options and treatment effectiveness for persons with Parkinson's disease.

There are some risks associated with participation in this research study. Citric acid is a widely used substance in cough challenges because it is known to make people cough. Chest tightness, breathlessness and rarely, fainting have occurred when citric acid has caused excessive coughing. To minimise discomfort associated with coughing, the cough challenge will be stopped as soon as the level of citric acid that causes 5 coughs is observed. There are

no reported long term adverse effects, as coughing normally ceases as soon as the cough challenge is stopped. The researcher performing the cough challenge will monitor you closely for any adverse effect during the test. A medically qualified personnel will be present during the test.

The insertion of the endoscope through your nose does not pose any physical risk beyond a slight risk of nose bleeding and minor discomfort. In a study of 500 consecutive procedures, 3 nose bleeds that stopped by themselves were observed. There were no instances of breathing difficulties during testing and 81% reported no discomfort or only mild discomfort as a result of the examination, 15% reported moderate discomfort and 3% severe discomfort. To further minimise the discomfort, the endoscope will be lubricated with KY Jelly.

You will be monitored very carefully by the researchers for any negative outcomes arising from your participation in this study. Facilities for emergency medical management are available at the Van Der Veer institute where the study is completed. Further medical help will be available from the patient care wards and the Emergency Cardiac Response team at The Christchurch Hospital should any complications arise.

Will ACC cover me in the event of an injury?

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators. If you have any questions about ACC, contact you nearest ACC office or the investigator.

Can I withdraw from the study?

Your participation is entirely voluntary (your choice). If you do agree to take part in this study, you are free to withdraw at any time, without having to give a reason. Any decision not to participate will not affect your current, continuing or future health care at this

or any other health care facility. Your participation in the study will be stopped should any harmful effects appear or if you feel it is not in your best interest to continue.

Who will know of my participation in this study?

Research findings will be presented at International Research Meetings and will be submitted for publication in relevant peer reviewed journals. Additionally, research findings will be made available to the local Canterbury Medical Community through research presentation and regional forums. However, no material which could personally identify you will be used in any reports on this study. Consent forms will be kept in a locked filing cabinet in the locked swallowing research laboratory or will be stored on password protected laboratory computers. Research data will be stored for a period of ten years after data collection is complete, at which time they will be destroyed.

Will I know the result of the tests I undergo?

You will be offered copies of the final manuscript. However, you should be aware that a significant delay may occur between completion of data collection and completion of the final report. Alternatively, or in addition, you can choose to have the results of the study discussed with you personally by the lead investigator.

Who do I contact if I need further information?

You can contact the lead investigator if you require any further information about the study. The lead investigator, Li Pyn Leow, can be contacted at (03) 378 6098 or at (03) 351 1533.

If you may have a friend, family of whanau member to support and help you understand the risks and /or benefits of this study and any other explanation you may require. If you need an interpreter, this can and will be provided.

If you have any queries or concerns regarding your rights as participant in this study, you may wish to contact a Health and Disability Services Consumer Advocate, telephone:

(03) 377 7501 in Christchurch or 0800 377 766 outside Christchurch.

Statement of approval

This study has received ethical approval from the Canterbury Ethics Committee.

Appendix F. Participant Consent Form

Mechanisms of airway protection in ageing and Parkinson's disease

English	I wish to have an interpreter.	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.	Ae	Kao
Samoan	Oute mana'o ia iai se fa'amatala upu.	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea.	Io	Ikai
Cook Island	Ka inangaro au i tetai tangata uri reo.	Ae	Kare
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai

I, _____, have read and I understand the Information Sheet dated _____ for volunteers taking part in the study designed to evaluate airway protection mechanisms as predictors of swallowing impairment in ageing and Parkinson's disease. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

I have had this project explained to me by _____.

I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my current, continuing or future health care. I understand that if I choose to withdraw from the study, I may also withdraw all information that I have provided.

I understand that the information obtained from this research may be published. However, I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study.

Mechanisms of airway protection in ageing and Parkinson's disease

I am aware that information from the proposed study will be stored on computer or in a locked cabinet for 10 years, after which, it will be deleted from computer files and or shredded. I consent to such storage and disposal of data.

I understand that the investigation will be stopped if it should appear harmful to me and I know who to contact if I have any side effects to the study or have any questions about the study.

I understand the potential risks of participation in the study as explained to me by the researcher.

I understand the compensation provisions for this study.

I have had time to consider whether to take part.

I wish to receive a copy of the results. YES / NO

I, _____ hereby consent to take part in this study.

Date

Signature _____

Signature of researcher_____ Name of researcher_____

Name of primary researcher and contact phone numbers:

Name: Li Pyn Leow
Work: 03 378 6098
Home: 03 351 1533

(Note: A copy of the consent form to be retained by participant and (in the case of patients) a copy to be placed in the medical file.)

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