An examination of the modifiable technical factors of ESWL on effective and efficient urinary stone fragmentation

A thesis submitted in partial fulfilment of the requirements for the

Degree of Master of Health Science

in the University of Canterbury

by James M. Hayes

University of Canterbury

2015

Table of Contents

List of Figures

Figure 7-1 The intensity transmission coefficient from water to a second medium, as a second of the impedance of the second medium (Smith, 2007) 84

List of Tables

Acknowledgements

Although writing up the thesis might be the effort of one person, the reason that person even gets as far as starting to write up is thanks to a number of others. I am grateful for everyone who has been there to support my journey towards the finished thesis.

I'm indebted to and grateful for the following persons...Foremost, I would like to express my deepest thanks to my two supervisors, Professor Ann Richardson and Associate Professor Ray Kirk. Their patience, encouragement, and immense knowledge were key motivations throughout my thesis.

I would also like to thank Dr Stuart Gowland for offering thorough and excellent feedback together with funding throughout this project. Stu has been selflessly involved with both my personal and academic development and I consider him a mentor and a friend.

A special mention for Professor Chris Frampton who persuasively conveyed an interest in my work. And for our insightful and detailed discussions about stone fragmentation models many years ago.

Thank you to the New Zealand Urologists who encouraged and critiqued my stone fragmentation theories, in particular Dr Stephen Mark for his explanation of the need to focus the science to a clinical setting.

The generous support of my colleagues and fellow researchers in the Department of Health Sciences and Allied Health at CPIT and the School of Health Sciences at the University of Canterbury.

Finally, this particular copy of my thesis belongs to the library where you are reading it. Every copy, however, belongs to my parents. Because I am dedicating it to them. I'm doing that because unless the sun incinerates the earth in the next few decades, this thesis will outlast me. And I want something that will be around longer than me to show that there was once a couple from Dublin who loved their son very much and set him on his path with a beautifully wrought map and the fullest of toolkits. I love them very much and you would too if you met them.

Abstract

There are pressures from the medical community to reduce total shock numbers during extracorporeal shockwave lithotripsy (ESWL) to reduce renal damage. This in vitro study looked at the modifiable factors of the technique to increase the effectiveness and efficiency. This is important as faster, more efficient, stone elimination would reduce symptom duration and limit the adverse effects of an acute episode of renal colic. Furthermore this would reduce the likelihood of incomplete fragmentation of the stones leading to readmission.

An in vitro model for the kidney was designed. This enabled the systematic scientific study of fragmentation and its relationship with the parameters studied: shock rate, shock power[1], power ramping[2], and coupling gel consistency to discover which technical factor settings allow the most effective and efficient urolith fragmentation. Mathematical models, theories and hypotheses pertaining to these phenomena were employed. Each effect was tested individually by setting up the model kidney and using the ESWL machine to fragment a mock kidney stone.

The results of 534 completed tests showed that shock rate had less impact on stone fragmentation than power in this model. The rate experiments showed no statistical difference between the rates tested; however our observational evidence showed that stone fragments after ESWL to be smaller and more dust-like at the lower rates (60 and 70 shockwaves per minute (SW/min)) than the larger more sand-like particles when the testing was completed at faster rates (90 and 100 SW/min). This may be of clinical significance. While examining power, the most effective and efficient power was 80%, however again the clinical significance of using higher powers may outweigh the time savings. The requirement of a gas free coupling cannot be stressed enough as the tests conducted without gas in the coupling medium required both fewer shocks and lower powers ($p<0.001$).

---

[1] Throughout this thesis "power" is mentioned. Altering the ESWL intensity alters the input voltage to the EMSE (electromagnetic shockwave emitter) coil which alters the intensity of the EMSE electromagnetic field. This in turn alters the intensity of the shockwave. In a clinical environment this is called increasing/decreasing the power.

[2] Ramping is the term used to describe shock waves which are first delivered at a low power setting before the power is gradually increased.

In conclusion, the results showed that diligent care during the ESWL procedure to choose the most effective and efficient shock rate and power, and the conscientious removal of gas from the coupling medium before treatment, improved the results of stone fragmentation.

Glossary

Amplatz Sheaths - firm renal sheaths designed to allow smooth passage of surgical instruments into the nephrostomy tract.

Collimation - is the process of restricting and confining an x-ray beam to a given area. It is achieved by electronically moving a lead diaphragm. Use of such minimises a patient's exposure to unnecessary radiation.

CT/U– Computed tomography/Urography.

Empiricism - a philosophy describing the theory that regards experience as the source of knowledge.

ESWL – Extracorporeal shockwave lithotripsy.

Fench (Fr) - The diameter of a round scope or catheter in millimetres can be determined by dividing the French size by 3. For example, a 12 Fr scope has a diameter of 4mm.

Fluoroscopy - a type of medical imaging that shows a continuous X-ray image on a monitor.

Gating - used when the shockwave from the ESWL machine is coordinated with the patient's ECG tracing.

Haematuria - the presence of blood or red blood cells in the urine.

Hydrophilic guide wires - enhances catheter tracking with their lubricious coating and smooth surface.

Iatrogenesis - inadvertent and preventable induction of disease or complications by the medical treatment or procedures of a physician or surgeon, from the Greek "brought forth by the healer".

kJ - Kilojoule, an International System of Units unit of energy equal to 1000 joules

Multiplaner - a technique used in two-dimensional imaging to generate oblique views.

Nephroscope - an instrument inserted into an incision in the renal pelvis for viewing the inside of the kidney.

Percutaneous nephrolitholapaxy - a procedure which punctures the skin to create a tract which can be widened and used for the introduction of a nephroscope. Smaller calculi are removed with forceps which is simply called nephrolithotomy. Larger calculi are shattered with electro-hydraulic shock waves.

Power - Altering the ESWL intensity alters the input voltage to the EMSE (electromagnetic shockwave emitter) coil which alters the intensity of the EMSE electromagnetic field. This in turn alters the intensity of the shockwave. In a clinical environment this is called increasing/decreasing the power.

Ramping - the term used to describe shock waves which are first delivered at a low power setting before the power is gradually increased.

Shadowgraphy - an optical method that reveals non-uniformities in transparent media.

Ureteroscopy – the procedure where a ureteroscope is passed into the urethra through the bladder and the ureter and possibly up to the kidney.

Urolith - a calculus in the urine or the urinary tract. Also called a kidney/urinary stone depending on its location.

Ventricular Tachycardia (VT) - a dysrhythmia (three or more consecutive ventricular ectopic beats) can progress to ventricular fibrillation, cardiovascular collapse and death.

Volt (V) - the derived unit for electric potential.

Watt (W) - a derived unit of power.

Chapter 1

Introduction

1.1 Development of extracorporeal shock wave lithotripsy

Extracorporeal Shock Wave Lithotripsy is the name given to an acoustic pulse used to fragment kidney stones (uroliths). The idea of ESWL is to use shockwaves (SWs) generated outside the body (extracorporeal) to fragment the kidney stone ("lithos" is Greek for stone and "tripis" is Greek for breaking). Once the stone is broken down into a sand-like state, it can be passed naturally without the need for surgery. ESWL is unique in medical technology though it appears to have deteriorating outcomes over time. What has changed since the Dornier Human ESWL machine 3 (HM-3) ruled the stone kingdom? The shock wave generator in the HM-3 was quite crude, the machine was bulky, and the imaging was rudimentary. However, despite more up to date imaging, a sleeker design, and increasingly sophisticated generators, the stone-free results have not improved. This could simply be due to improved imaging modalities following ESWL. A CTU, which is frequently used after ESWL, will display stone fragments less than 1mm in size. These were harder to diagnose on standard film imaging modalities which were used after ESWL when it was first introduced. Or perhaps second and third generation ESWL machines are not as effective as the first generation machines? To analyse the problem we must look at the features of the original 'gold standard' HM3. The main difference is that the patients were partially submerged in a large bath of water. The water ensured that the shockwave transmitted from the ellipsoid reflector contained no barriers until it entered the patient. Also, as it was unclear what effect the shockwave would have on the patient's cardiac rhythm, the SW were synchronised to the patient's heart rate. Electrocardiography (ECG) gated shockwave trigger speed[3], therefore resulting in a shockwave frequency of between 60 to 90/minute. Second and third generation lithotripters do not

---

[3] Gating is the term used when the shockwave from the ESWL machine is coordinated with the patient's ECG tracing. It will only give a shock wave during the R wave of the ECG, instead of later in the cardiac cycle (absolute refractory period). It is used to avoid R on T phenomenon causing a dangerous arrhythmia; ventricular tachycardia (VT).

incorporate a water bath and are certainly more user-friendly. However this required the transmission of the shockwave through several membranes and transmission media. By the time of their commercial release, it had been noted that ECG gating was not needed in all but very rare occasions. As a result, shock rates of up to 120/minute were used in order to speed up the treatment.

In 1969, two German physicists, Dr Guenter Hoff and Armin Behrendt from Dornier Systems, an aircraft manufacturer, discussed ideas on the technological use of SW (Gravenstein & Peter, 1986). One idea was that SW could be useful for medical purposes. The in vitro studies by Hoff and Behrendt showed that renal stones could be fragmented by these SW (Gravenstein & Peter, 1986). This led to a collaborative study with Dr Manfred Ziegler, a urologist.

The early studies were concerned with the potential issue of SW causing tissue damage in surrounding organs and if so, the extent and nature of the damage. Chaussy et al. (1980) developed a canine model to implant human renal stones and test the performance of ESWL under conditions similar to clinical situations (Chaussy, Brendel & Schmiedt, 1980; Gravenstein & Peter, 1986). In addition to Chaussy, Brendel from Dornier was very involved with technical development and experimental testing. One of the major problems was locating the urolith on a three-dimensional basis. Ultrasound did not prove successful and therefore x-rays intersecting the target were used to locate the uroliths. Imaging accuracy is now an important part of ESWL as, without correctly imaging the stone, it cannot be targeted successfully (Tailly, 2013).

The first patient was referred for ESWL surgery by the Department of Urological Surgery at the University of Munich. The patient was treated successfully on February 7, 1980 (Gravenstein & Peter, 1986; Hayes & Ding, 2012). The first one hundred patients to receive treatment with ESWL were treated by members of the Department of Urology Surgery. The clinical results of the first 21 patients were published in 1980 (Chaussy et al., 1980; Gravenstein & Peter, 1986). The experience with this novel treatment proved so effective that there was a rapid growth of the indications and many more Dornier HM3 lithotripters were fitted worldwide (Tailly, 2013).

1.2 Current state

About 10% of the total population of New Zealand will experience the formation of a kidney stone at least once in their lives (Davidson, Sheerin & Frampton, 2009a). This is similar but slightly higher than the rest of the Western world, where the lifetime prevalence of kidney stones is 8.8%. Internationally, the prevalence of stones among men was 10.6% compared with 7.1% among women (Scales, et al., 2012). Unfortunately, kidney stones have been observed in many cases to recur (Moe, Pearle & Sakhaee, 2010; Sakhaee, Maalouf & Sinnott, 2012a; Srisubat, et al., 2009). Surgically removing each occurrence can possibly place the kidney in jeopardy and increase morbidity for the patient (Srisubat et al., 2009). ESWL is non-invasive, yet a number of reports have shown that this process can cause substantial acute side effects (Davidson, et al., 1991; Doran & Foley, 2008; Tuteja, et al., 1997). This damage includes:

- Bleeding within and around the kidney, as shown by a loss of image contrast between the inner and outer kidney in magnetic resonance imaging (MRI), perhaps due to a release of fluids throughout the kidney or a decrease in blood flow through the kidney.
- Destruction of red and white blood cells in the blood system.
- Injury to surrounding organs, including the liver, skeletal muscle tissue, pancreas and gastrointestinal systems.
- Bruising of the skin where the shock wave enters and exits.
- Blockage of the ureter by fragments of a kidney stone (Gravenstein & Peter, 1986; Polat et al., 2012; Tuteja et al., 1997).
- Hypertension has also been reported as a possible sequela of ESWL (Lingeman, Woods & Toth, 1990). The long-term significance of this change in diastolic blood pressure following ESWL is unknown, but no evidence has been found to suggest this is a problem.

Extracorporeal shock wave lithotripsy proved to be a major breakthrough in urology (Delius, 2002; McConnell, 2001). It is the procedure by which SW are generated at a point external to the body (F1 point) and focused on a kidney stone in the body (F2 point) (see Figure 1-3, p.11). A key issue is the ability to focus the SW so that they damage only the stone and not the body. SWs are relatively weak at their source and can traverse the body without many undesirable effects (skin bruising and hematuria being the most common) (Handa & Evan, 2010). However, as the SWs are focused on a small single point (the focus), they are sufficiently powerful to fragment a kidney stone. This is guided by fluoroscopy or ultrasound to achieve accurate targeting. Fragmenting almost any stone

13

can be attempted with this technique, but success varies greatly depending on the size and location of the stone. Generally, for stones in the upper and inter-polar calyces and the renal pelvis, the upper size limit is 2 cm diameter, and for stones in the lower pole, the size limit is 1 cm diameter (Turk, Knoll & Petrik, 2014). Most stones in the upper ureter can be fragmented as well. The larger the stone, the higher the likelihood there will be a need for a second procedure. Contraindications to this procedure include active urinary tract infection, uncontrolled bleeding diathesis, poorly controlled hypertension and pregnancy. Relative considerations that may prohibit use of ESWL are obesity, deformity of body habitus, suspected anatomic obstruction, stones in a calyceal diverticulum and renal failure (Chaussy & Schmiedt, 1983; American Urological Association University, 2014; Turk et al., 2014).

ESWL remains a primary treatment for urinary tract stones (Urology, 2012). However despite its success, ESWL has problems. The complications can be divided into two separate categories: obstructive problems caused by stone passage through the urinary tract, and tissue damage. Steinstrausse (literally German for 'stone street') is when a collection of stone fragments accumulate in the ureter and appear on a radiograph like a stone street. This occurs when the foremost fragment becomes lodged, causing subsequent fragments to become trapped behind it. Roughly two-thirds of steinstrausse will resolve spontaneously. For those that do not, placement of a percutaneous nephrostomy tube can encourage the passage of stone fragments by restoring ureteral peristalsis, or repeat ESWL to the foremost fragment can resolve the problem. However, if an infection develops associated with an obstruction, emergency decompression of the urinary system with nephrostomy drainage is necessary (Ramsey et al., 2010). Furthermore, the destructive forces generated when cavitation bubbles collapse (discussed in Section 1.4, p.7) are responsible for the ultimate stone fragmentation. However, they can also cause trauma to thin-walled vessels in the kidneys and adjacent tissues (McAteer & Evan, 2008), which result in haemorrhage, release of cytokines/inflammatory cellular mediators and infiltration of tissue by inflammatory response cells (Handa & Evan, 2010).

Within ESWL, misconceptions regarding fragmentation mechanisms, as well as treatment parameters such as dose, applied energy and focal area are still common (Loske, 2010). The European Urological Society and the American Urology Association have some broad suggestions (American Urological Association, 2014; Turk et al., 2014; Urology, 2012) and these are followed along with urologist and patient preferences. ESWL machines focus SW to strengths needed to

fracture concrements. Side effects, some of them acute, have resulted from this procedure, including injury to soft tissue, hypertension and renal trauma (Lingeman et al., 1990). If the renal trauma is severe, it can lead to the permanent loss of functional renal volume (Krestin et al., 1993; McAteer & Evan, 2008; Neri et al., 2000). The focusing of SW through various layers of tissue is a complex process which stimulates many bio-mechano-chemical responses. A number of considerations, described below, are necessary for an optimal result of ESWL.

The precise solution to some clinical stone problems requires proper understanding of the relationship between the SW path, anatomy and the position and composition of the stone (Tiselius & Chaussy, 2012). Initially, treatment rate for ESWL was set to match the patient's heart rate as it was believed that the SW may cause heart arrhythmia (Ramsey et al., 2010). This was discovered to be the case rarely, so SW were no longer synchronised with heart rate. In order to speed up treatment, faster shock rates were used as it was thought that the more shocks administered, the greater the fragmentation would be (Chaussy et al., 1980; Chaussy & Schmiedt, 1983; Jansson, Bengtsson & Carlsson, 1988). Given the recent improved understanding of the physics of ESWL, this upward trend may have been counterproductive as an inverse relationship between shock rate and stone fragmentation rates is likely (Gravenstein, 2000; Nguyen et al., 2015; Salem et al., 2014).

Much research has gone into understanding how ESWL can be made more efficient and safe. The research to date has tended to focus on the two extremes of the shock rate – 1Hz versus 2Hz. It has been concluded that slower treatment shock rates (1 Hz) improve efficiency of ESWL by decreasing the number of SW used, the number of treatment sessions needed, and often the clinical complications associated with the treatment (Bhojani & Lingeman, 2013; Chen, 2012; Honey et al., 2009; Ng et al., 2012; Riehle, Fair & Vaughan, 1986; Semins, Trock & Matlaga, 2008). Those shock rates are the two extremes of the scale (Hayes, 2011) and testing of rates more commonly used in clinical practice would be of benefit (Argyropoulos & Tolley, 2007; Chacko et al, 2006; Pace et al., 2005). Though outcomes of ESWL have been deteriorating, there are two methods that could lead to improvement: reinvention of the lithotripter, or rediscovery regarding how to use it. The most pragmatic approach is to rediscover how to use it.

1.3 Efficiency and effectiveness of extracorporeal shockwave lithotripsy

Two concepts that add an economic aspect to healthcare are effectiveness and efficiency. These acknowledge that there are priorities to be considered in human, physical and financial resources. A complication arises because it is not possible to only take into consideration measured improvements in health, but also negative impacts such as side effects or any iatrogenesis (Madore, 1993).

In its unadulterated form, measuring effectiveness compares two things that have an identical effect or the same purpose. If two drugs are each used to treat a particular illness, the more effective drug will be the one that treats the illness faster and with fewer or less severe side effects. This would be called the more clinically effective drug. With ESWL, the rate at which the least SW required to fragment the urolith, at the lowest power, so as to prevent unwanted adverse side effects, would be the most effective rate. The economic element of effectiveness introduces the idea of cost and refers to cost-effectiveness and cost reduction (Koo, Beattie & Young, 2010). For example, if two shock rates have the same effects (complete stone fragmentation with the same side effects), the more economically effective rate is the one that costs less; this would usually be a time cost. This introduces the concept of efficiency.

Efficiency is a much broader concept and is the association between the level of resources invested in the health care system and the health improvements achieved (Hutubessy, Chisholm & Edejer, 2013; Madore, 1993; Martini, Berta, Mullahy & Vittadini, 2014). Instead of measuring the shortest time for a given effect (stone fragmentation), efficiency tries to achieve the greatest effect per unit of cost (Brent, 2004). British clinical epidemiologist Archie Cochrane defined three concepts related to testing healthcare interventions (Cochrane, 1972): efficacy is the degree to which an intervention does more benefit than harm under ideal conditions ("Can it work?"); effectiveness measures whether an intervention provides a greater benefit than harm when provided under typical circumstances of healthcare practice ("Does it work in practice?"); and efficiency measures the result of an intervention in relation to the means it consumes ("Is it worth it?"). Trials of efficacy and effectiveness have also been described as explanatory and management trials respectively, while efficiency trials are more often called cost effectiveness or cost benefit studies. Cost-benefit analysis is a systematic approach to gauging the economic worth of a procedure. This is done by quantifying, in monetary terms, the costs of a project and comparing them with the benefits, also

expressed in monetary figures. Like cost-benefit analysis, the cost-effectiveness approach calculates the monetary value of all the procedure costs. The difference is that cost-effectiveness considers the outputs produced by a project, which are not measured in monetary terms, according to the Centers for Disease Control and Prevention (2014). Health-care research often uses cost-utility analysis to analyse the cost of health-care interventions in terms of lives saved, illnesses prevented or years of life gained. The resulting measure in cost-effectiveness analysis then is the cost per case prevented or cost per year of life gained. The purpose of efficiency is to effectively make the most of the results given a specific budget (Haynes, 1999). According to this concept, each service must be supplied at the lowest possible cost and make best use of the assets invested. Efficiency is different from effectiveness in that it considers costs in relation to benefits. With ESWL this would relate to the time the procedure lasts. However, if the most efficient shockwave rate appeared to be 120 SW a minute and many patients treated in this manner required a further treatment as the initial treatment did not work, could it really be called efficient? The time of the theatre staff and patient are initially reduced but this reduced time could then be doubled or tripled. Furthermore, this does not take into account the morbidity and discomfort associated with a subsequent ESWL treatment: fasting prior to the anaesthetic, blood tests, possible risks associated with stopping regular medications, bruising on the skin from the shockwave, among other things (Koo et al., 2010).

Greater effectiveness and efficiency require proper use of resources, appropriate delivery of treatment and sound management of health care funds (Madore, 1993). It seems difficult, if not impossible, to determine the optimum level of expenditure that should be allocated to ESWL; however, by using quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs), it is possible to ensure that the budget is allocated in the most effective manner (Sassi, 2006). It is then up to the individual surgeon, using evidence-based guidelines, to decide on the clinical risks and benefits and agree on the patient's clinical pathway.

1.4 Physics

Despite the success of ESWL, the mechanism of stone fragmentation and accompanying tissue injury due to focused waves needs to be better understood (Kaude et al., 1985). To correctly use ESWL, a basic understanding of the physics is required (Rassweiler et al., 2011). The properties of each lithotripter differ slightly from one to another, however the principle remains the same.

Whichever device is used, the primary role is to transfer and focus SW power from the lithotripter to a cigar-shaped volume along the lines of the shockwave path. This volume is often referred to as F2 and the shock generator as F1. The transfer of energy from F1 to F2 is described in detail in Section 1.5, p.10.

Sound waves in medicine are well established, ultrasound for diagnostic imaging being the most prominent. SWs share numerous properties with conventional ultrasound, but there are differences that have a bearing on their clinical use.

Fragmentation of kidney stones using focused SW forms the basis of ESWL. Non-medical research opened up the possibilities of breaking stones by subjecting them to high energy SW. Initially, a limiting factor was the expense and clinical suitability of generating the SW. Once a technique was found of producing the shockwave (through a spark discharge across an underwater gap) the wave could be viewed with clinical possibilities (Chaussy & Schmiedt, 1983).

Fundamental differences in the properties of SW and ultrasound waves need to be considered. Figure 1-1 displays a pressure-time diagram of a shock wave.
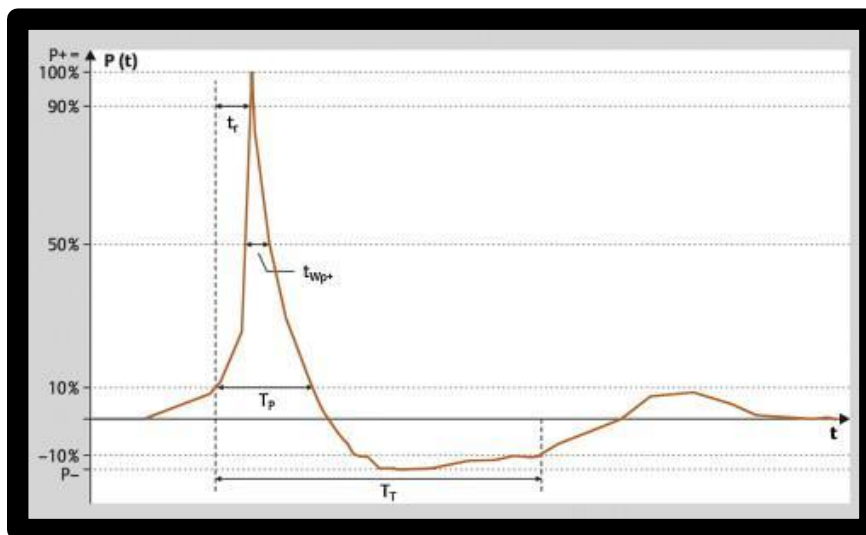
Figure 1-1 Time pressure graph of a shockwave (Rassweiler et al., 2011)

Graph reproduced with permission from Professor Dr. med. Dr. Jens Rassweiler, Chairman EAU-section of Urotechnology, Klinikdirektor Urologie.

Figure 1-2, p.9 displays the same for an ultrasound wave. The shockwave consists of a single pressure pulse with a steep start and slow fall off, ultrasound waves display a more sine-wave like quality with trains of compressions and rarefactions. Also, the two types of waves display different frequency patterns. Ultrasound has well-defined frequency characteristics, SW does not. In both waves, a highly spatial concentration of acoustic energy is produced that is able to be focused to volumes of cubic centimetres or less. As a result both waveforms should have the ability to fracture certain concrements. However when transported over distance, the energy of the ultrasound waves is reduced by the surrounding tissue. To calculate the fragmentation ability of the waveforms it is possible to transform the pressure-time distribution into the frequency domain (Gravenstein & Peter, 1986). Squaring the result shows spectral densities for both wave types. As the attenuation coefficient increases roughly with the square of the frequency, ultrasound waves are inappropriate for fracturing kidney stones as their power is decreased as they travel through the body (Zagsebski, 1996).

Several thousand SW are administered during treatment so as to attain a desirable fragmentation of the stone (fragments ≤ 4mm), which can then be passed naturally. This treatment has been generally effective for stone removal in most cases, eliminating the need for surgery (Chen, 2012).
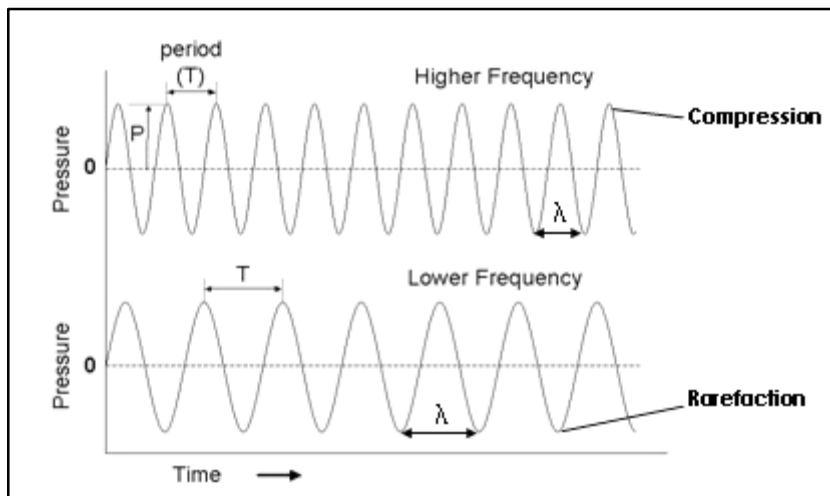
Figure 1-2 Time pressure graph of an ultrasound wave (Toronto Western Hospital, 2008)

As mentioned, shockwave patterns are not the same as ultrasound waves which are typically biphasic and have a peak pressure of 0.5 bar (Zagsebski, 1996). A shockwave pattern is uni-phasic with the peak pressures as high as 500 bars (Ogden, Toth-Kischkat, & Schultheiss, 2001). Therefore the peak pressure of a shockwave is approximately 1,000 times that of an ultrasound wave. These SW are short bursts of energy pulses of about 5 μs duration. There are two main effects of the SW. The primary effect is the direct mechanical forces that result in the maximal useful pulse energy concentrated at the target point where treatment is provided; and the secondary lesser effect is the indirect mechanical forces by cavitation. The importance of this, as shown in Figure 1-1, p.8 is if a second SW is administered before the first wave has completed its cycle. A certain portion of the primary wave will be affected in a negative manner by the second wave. Furthermore a portion of the second shockwave will be affected in a negative way by the primary wave. In other words, the principle of this positive and negative wave, which may affect how effective the wave is, relates to the time between positive and negative peaks. If the rate is too quick and the second positive peak is occurring at the same time that the previous wave's negative pressure, they will cancel some of their respective destructive effect. If, however, the rate is too slow, treatment is less than ideal as the patient may remain under a general anaesthetic for longer than is necessary. This also has an effect on theatre turnaround time, which is an important financial consideration.

To improve the destructive effects of ESWL, it is important to understand the mechanisms of the shock wave. Shock waves are high-energy amplitudes of pressure created in water by an abrupt release of energy in a small space. They multiply according to the physical laws of acoustics and are transmitted through media of similar densities ± water and soft tissue ± with very little attenuation, See Figure 7-1, The intensity transmission coefficient from water to a second medium, as a second of the impedance of the second medium (Smith, 2007), p.84. However when a shock wave encounters an acoustic boundary (stone), the energy is used to overcome the tensile strength of the stone. As a result, the stone begins to fragment (Smith, 2007). Stone fragmentation principles are detailed in Section 3.3 Stone fragmentation theories, p. 50.

The wave begins with an immediate jump to a peak positive pressure of about 40 MPa (Rassweiler et al., 2011). This is referred to as a "shock" or compressive phase. The transition is faster than can

be measured and is less than 5 ns in duration. The pressure then falls to zero about 1 μs later. Following that is a region of negative pressure that lasts around 3 μs and has a peak negative pressure around –10 MPa; this is known as the rarefaction phase. The amplitude of the negative pressure is less than the peak positive pressure, and the negative phase of the waveform generally does not have a shock in it; in other words, there is no abrupt transition. Together the 5 μs pulse is generally referred to technically as a shock wave, shock pulse or pressure pulse. However, it is only the sharp positive pressure that is a shock (Preminger, Badlani, Kavoussi, & Smith, 2011).

1.5 Focusing of the shock wave

ESWL requires very precise focusing in order for a successful treatment. To focus the SW on the stone, lithotripters use different methods. Point source generators (electrohydraulic) use ellipsoid reflectors to direct the wave to the stone. Line source generators use an acoustic lens (electromagnetic) or a dome shaped dish (piezoelectric). This thesis concentrates on the electrohydraulic lithotripter because this is the most commonly used in New Zealand.
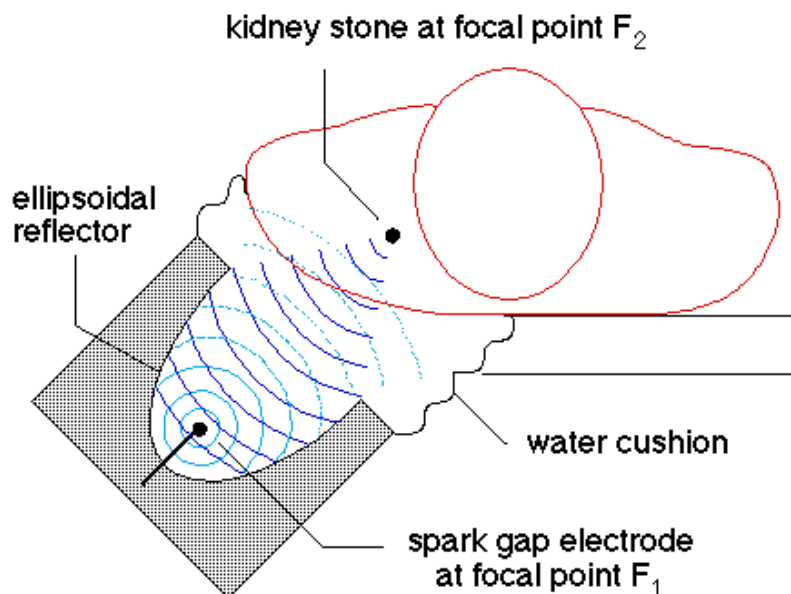
Figure 1-3 A schematic of a lithotripter and patient. The view is of the patient lying supine on the treatment table. (Frantz, 2015)

The patient is positioned on the lithotripsy table supine, as shown in Figure 1-3 and a soft water-filed balloon is placed in contact with their abdomen. The patient's body is positioned so that the stone can be targeted precisely with the shockwave. As mentioned above the shockwave comes from outside the body and how the shockwave is targeted on the stone is discussed here.

Part of each wave produced never hits the reflector, (light blue waves in Figure 1-3), and this part spreads out and eventually weakens. However, the part of the wave that does hit the reflector (dark blue in Figure 1-3) congregates on the other focus and its intensity causes the fragmentation of the stone. The important mechanism is the focusing property of ellipses and ellipsoids. Flanders (1968) provides us with a proof. The reflector is an ellipsoid of revolution about the major axis, so we only need to consider its profile - the ellipse. In addition, we must think of each little part of a wave as reflected ray (Smith, 1992).

Figure 1-4, p.13 shows that if a ray leaves focus F1 (with position vector p) and strikes the ellipse at point A, then it will be reflected to focus F2 (with position vector q). The ellipse is given by a smooth parameterization r = r (t) where r is the position vector of A and t is time. Then the velocity vector d$\mathbf{r}$/dt and its opposite -dr/dt are parallel to the tangent line at A, and by the law of reflection (angle of incidence = angle of reflection), we must prove that $\alpha = \beta$. Since α and β are each less than 180 degrees, this is equivalent to showing that cos α = cos β (Flanders, 1968).

Frantz (2003) explains that if w=w (t) is a function of time t, then we can use the definition of vector magnitude and the dot product rule to compute:

$$\frac{d}{dt} \parallel w \parallel = \frac{d}{dt} (w \cdot w)^{1/2}$$

$$= \frac{1}{2} (w \cdot w)^{-\frac{1}{2}} (\frac{dw}{dt} \cdot w (t) + w (t) \cdot \frac{dw}{dt})$$

$$= \frac{dw}{dt} \cdot \frac{w}{\parallel w \parallel} \qquad (*)$$

The standard definition of an ellipse is $\parallel p - r \parallel + \parallel q - r \parallel = (constant)$

p and q are also constant (time derivative 0). Take derivatives of both sides, using equation (*), and we get

$$-\frac{dr}{dt} \cdot \frac{p-r}{\|p-r\|} - \frac{dr}{dt} \cdot \frac{q-r}{\|q-r\|} = 0$$

which is the same as $\| \frac{dr}{dt} \| \cos \alpha = \| \frac{dr}{dt} \| \cos \beta$

therefore $\cos \alpha = \cos \beta$.

This proof establishes the focussing accuracy of the lithotripter used in this thesis (Frantz, 2003, 2015; Smith, 1992).
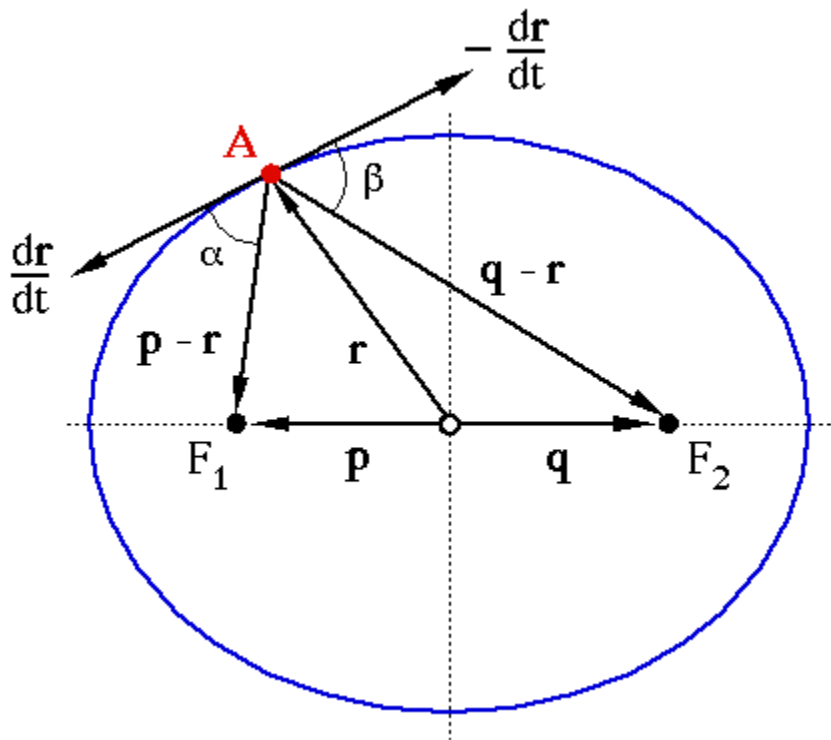
Figure 1-4 The focusing property of an ellipse (Frantz, 2015)

Image reproduced with permission from The Mathematical Association of America.

As shown the basic geometric principle used in electrohydraulic ESWL is that of an ellipse. SW are created at one focal point, F1, and converge on the second focal point, F2. The target zone is the 3D area at F2 where the energy is concentrated and fragmentation occurs.

The target zone (F2) represents the area into which the waves are concentrated. A larger focal zone correlates to larger peak pressures and greater stone fragmentation potential[4]. This comes with an adverse effect of increased tissue damage. This study focuses on the Dornier electrohydraulic style. See Figure 2-4 Electrohydraulic generator (Pearle, 2012), p. 29.

---

[4] The large focal zone increases fragmentation potential as respiration is less likely to move the stone out of the focal zone. This is especially important with smaller stones.

1.6 Coupling

To limit energy loss a coupling agent, (often ultrasound gel) is used in the acoustic interface between the ESWL machine and the patient. During the coupling process air pockets are inevitably trapped in the coupling areas, which subsequently remain invisible to the operator as this area is pressed against the patient's skin. As SW need a medium through which to travel and cannot travel through air, these bubbles are thought to decrease the efficiency of the shockwave (Pishchalnikov, Neucks, et al., 2006).

During the transmission of a wave, energy is lost at interfaces with differing densities (Tipu & Jamalullah, 2011). A coupling medium is therefore necessary. This reduces attenuation and enables more of the shock wave power to reach its target – the stone. The original lithotripter submerged patients in a bath of degassed water which has acoustic impedance similar to soft tissue of the human body (Smith, 2007). The water bath was abandoned for a variety of reasons; that patients had to be anaesthetised while partially submerged in water was a driving factor. Some of the effects caused by the partial submersion were:

- Haemodynamic changes – increase in central blood volume, stroke volume and cardiac output.
- Increases in central venous pressure and pulmonary artery pressure.
- Hydrostatic pressure on the chest and abdomen which decreases functional residual capacity and vital capacity.
- Intrapulmonary pressure and the work of breathing increased due to altered compliance (Paul, 2006).

Furthermore, there was always the electrical hazard to be aware of.

Newer generations of 'dry lithotripters' were produced, a large water-filled balloon onto which ultrasound gel, or similar, was applied was used to act as a transmission devise. This replaced the large water-filled tank. Water and ultrasound gel have similar densities to those of the soft tissues of the patient, see Figure 7-1, p.84 (Tipu & Jamalullah, 2011). This has been a major advancement in some respects (Jain & Shah, 2007). Dry lithotripters are more convenient and allow for greater flexibility for patient positioning, as the patient can assist with much of the initial positioning.

Importantly, the coupling agent used in dry lithotripsy can affect the stone fragmentation rate and should not be considered inert. Ultrasound gel is probably the optimum agent available for use as an ESWL coupling agent (Cartledge, Cross, Lloyd, & Joyce, 2001). Regardless of the transmission agent used, it is imperative that there are no air pockets and that the agent is applied in a manner that covers the entire shock wave head. Tiselius and Chaussy (2012) indicate that careful attention to this factor cannot be over-emphasized, as was noted during in vitro testing in the late 1980s by Coleman, Saunders, Crum, and Dyson (1987). At present there is no mechanism for removing gas bubbles from the coupling medium. Perhaps evidence from cementing operations - casing support and zonal isolation – will provide the answers as the cement industry continues to look at gas migration, its causes, consequences and solutions (Bonett & Pafitis, 1996).

Chapter 2

Clinical Problem

Having seen how the stone can be fragmented we need to look at how this can happen in practice. The first known uroliths were discovered in Egyptian mummies – a bladder urolith was discovered by English Archaeologist E. Smith from a 4500-5000 year old mummy in El Amrah, Egypt (Sandison & Tapp, 1998). The first known mention of surgery to treat uroliths was in the 8th century B.C by a surgeon named Sushruta in India. He provided detailed descriptions on uroliths and urinary anatomy, along with information on surgery (Shah & Whitfield, 2002). In the 4th century B.C., Hippocrates (ca 460 – 370 B.C.E) mentions uroliths in his Hippocratic Oath:

"I will not use the knife, not even on sufferers from the stone, but will draw in favour of such men as are engaged in this work" (Edelstein, 1943 p.4)

This suggests that the treatment of calculi was to be the province of specialised surgeons.

Usual presentation is with loin pain, nausea, fever, and gross or discreet haematuria. However kidney stones may also be asymptomatic (Scales et al., 2012). Standard assessment includes a detailed medical history, physical examination, medical imaging, blood analysis and urinalysis (Reynard, Brewster, & Biers, 2013). Principal imaging techniques are ultrasound and unenhanced CT with judicial use of contrast medium enhancement and plain abdominal x-ray (Rule, Krambeck, & Lieske, 2011). Secondary imaging techniques include excretory urography, magnetic resonance imaging, and antegrade or retrograde pyelography (Turk et al., 2014).

Urolithiasis (the process of developing stones in the urinary system) typically occurs between thirty to sixty years of age. Its incidence is increasing exponentially and the current lifetime risk of developing a kidney stone is about 10% (15% of men and 6% of women) in New Zealand (Davidson et al., 2009a; Hayes, 2011). Kidney stones are not life-threatening in most cases, but can cause severe pain and increased morbidity for the patient, which can lead to hospitalisation and time off work (Abate, Chandalia, Cabo-Chan, Moe, & Sakhaee 2004; Meschi, Nouvenne, & Borghi, 2011;

Morton & Iliescu, 2004; Pak, 1998). For these reasons, together with the exponential increase in diagnosed kidney stones, research into the most effective method to treat these stones is not only warranted but perhaps overdue.

In addition, kidney stones are associated with considerable costs to health services. The annual mean cost of a urolith in 2002 in New Zealand was $4274 (Davidson et al., 2009a). Twenty four per cent of the cost was for emergency visits, twenty three per cent for hospitalisations, twenty one per cent for operative procedures and eleven per cent accounted for patient workdays lost (Davidson, Sheerin, & Frampton, 2009b). Other sundry costs made up the remaining twenty one per cent. Therefore, economic information is of interest to health professionals involved in the diagnosis and treatment of Urolithiasis, in addition to those who plan and manage health services. Renal stone disease creates an economic burden on the community, not only through the direct costs of medical care and lost income, but also through the social cost of lost opportunity. The prevalence of renal stone disease is increasing, as is the cost of looking after patients with stones (Davidson et al., 2009a; Turney, Reynard, Noble, & Keoghane, 2012). One reason for the increase in the production of stones is believed to be the increasing 'westernisation' of the world diet. Eating a high protein((i.e., protein content of more than 25% of energy or more than 2 g/kg body weight per day), sodium, and sugar diet can increase a person's likelihood of developing some types of kidney stones (Marckmann, Osther, Pedersen, & Jespersen, 2015). This is more pronounced with a diet high in sodium than one high in protein and sugars. Too much sodium in the diet increases the amount of calcium the kidneys must filter and increases the risk of kidney stones developing. Another reason for the increase in uroliths development is a population having a high Body Mass Index (BMI) (Meschi et al., 2011; Taylor, Stampfer, & Curhan, 2005; Wang, Chen, Song, Caballero, & Cheskin, 2007). Mean BMI in New Zealand adults has been increasing since 1997 (Hayes, Richardson, & Frampton, 2013).

2.1 Imaging

In order to treat the stone, it must first be visualised. This can be done using either fluoroscopy or ultrasound imaging. The fluoroscopy used is multiplaner in order to judge the depth of the target. This can be used with either antegrade or retrograde contrast media for difficult-to-visualise calculi, although use of contrast media is rare as it typically only shows a filling defect which indicates a large stone. Large stones are rarely a problem to visualise (Lucas, Zheng, & Gravenstein, 2014). Ultrasound can be used, and it has been incorporated into some machines. Ultrasound uses no ionising radiation and allows the treatment of radiolucent stones, which fluoroscopy does not (Hayes, 2011). Ultrasound use requires considerable skill and experience of the operator and, due to the interference and location of skeletal structures such as ribs, not all stones in the renal collecting system can be visualised. Furthermore it can be difficult to judge the degree of fragmentation during the ESWL treatment as a collection of crushed sand and gravel will appear remarkably similar to a solid stone on ultrasound whereas on fluoroscopy this can be better identified (Tiselius & Chaussy, 2012).

To reduce the radiation dose received by the patient during an ESWL treatment, strict collimation must be used. Only during the localisation and positioning of the patient should the collimator ever remain wide. A reduction of up to twenty times the absorbed dose is possible if a tight square of 7cm x 7 cm is used to monitor the stone's progress. However, it must be remembered that stones can move from one area of the collecting system to another during the treatment, sometimes by kinetic energy from the shockwave; these are colloquially referred to as 'jumping stones' (Chang et al., 2001). For this reason frequent monitoring of the treatment is advised and, in the case of a jumping stone, a reduction in power is recommended (Tiselius & Chaussy, 2012). Urinary tract stones have affected humans since civilisation began: they were first reported in the Aphorisms of Hippocrates and are still an important health problem. Aetiology is multifactorial and is discussed in Section 2.2, p. 18. Recent advances in diagnosis and treatment have proved significant and the urologist now has many options for treating urinary stones (Shung, Smith, & Tsui, 2012).

2.2 Aetiology

As shown above, kidney stones are a problem and their incidence is rising (Coe, Evan, & Worcester, 2005). A precise causative factor is not identified in most cases (Abate et al., 2004; Parmar, 2004) and numerous authors have conducted studies involving fluid intake, as intermittent super saturation or dehydration is thought to be one cause of uroliths (Chae et al., 2013; Curhan, Willett, Rimm, Spiegelman, & Stampfer, 1996; Curhan, Willett, Speizer, & Stampfer, 1998; Ferraro, Taylor, Gambaro, & Curhan, 2014, Ferraro, Taylor, Gambaro, & Curhan, 2013; McCauley, Dyer, Stern, Hicks, & Nguyen, 2012). The pathogenetic mechanisms of kidney stone formation are complex and involve both metabolic and environmental risk factors (Sakhaee et al., 2012a). As kidney stones are often idiopathic in nature, several theories have been proposed about lithogenesis. Recent evidence suggests a primary interstitial apatite crystal formation that secondarily leads to CaOx stone formation (Knoll, 2010). Also lifestyle and dietary choices may be important contributing factors but the pathogenesis and pathophysiology of Calcium Oxalate (CaOx) stones are still not completely understood (McCauley et al., 2012).

Other scientific theories suggest the stones may form because the urine becomes too saturated with salts from excessive sweating and that can lead to the formation of stones, or that the urine lacks the normal inhibitors of stone formation (Frassetto & Kohlstadt, 2011; Tamošaitytė et al., 2013). These factors can lead to the formation of renal stones (Caballero & Molinari, 2011). Citrate is one inhibitor because it normally binds with the calcium that is often involved in forming stones (Ando et al., 2013; Chutipongtanate & Thongboonkerd, 2011; Frąckowiak et al., 2010; Khan, 2013a, 2013b; Rabinovich et al., 2006; Rodgers & Lewandowski, 2002; Semins & Matlaga, 2013; Sorensen et al., 2012). Other inhibitors include magnesium, pyrophosphate, and certain enzymes (Tamošaitytė et al., 2013). There have been no large prospective controlled studies of citrate therapy to prevent renal stones, although some studies suggest a link between citrate therapy and the prevention of reforming stones post-ESWL (Sarica, Erturhan, Yurtseven, & Yagci, 2006; Soygür, Akbay, & Küpeli, 2002). In a multivariate analysis, Goldberg et al (1989) reported that the most clearly established method that citrate prevents stone formation is to concentrate urine calcium, thereby decreasing the saturation of calcium oxalate (Goldberg, Grass, Vogl, Rapoport, & Oreopoulos, 1989). In addition citrate is an important blocker of calcium phosphate stone formation. However it is too simple to suggest that stone formation can be prevented by administering citrate to stone formers. A

disadvantage of administering citrate is that it increases the saturation of calcium phosphate. This increases urine pH and favours the forming of the less soluble brushite stones.

A theory that was not well received for many years was developed by Dr Randall (Evan, Lingeman, Coe, & Worcester, 2006) who theorized that the areas of apatite plaque on the renal papillae are an excellent location for an overgrowth of CaOx to develop into a calculus (Matlaga, Coe, Evan, & Lingeman, 2007). This became known as the Randall plaque. On the other hand, many other types of stone formers do not demonstrate the classic Randall plaques (Blaschko, Chi, Miller, Fakra, & Stoller, 2013; Semins et al., 2008).

Coe, Evan, Worcester, and Lingeman (2010) suggest that there is no single theory of pathogenesis which can properly account for urolithiasis. Using human tissue biopsies, intraoperative imaging and physiology data from ten different stone forming groups, they identified at least three pathways that lead to stones (Coe et al., 2010). The first and most common pathway is overgrowth on an interstitial apatite plaque as seen in idiopathic calcium oxalate stone formers; this is also noted in stone formers with primary hyperparathyroidism, ileostomy, and small bowel resection, together with brushite stone formers. In the second pathway, there are crystal deposits in renal tubules that are seen in all stone forming groups except the idiopathic calcium oxalate stone formers. The third pathway is free solution crystallization. Examples of this pathway are those patient groups with cystinuria or hyperoxaluria associated with bypass surgery for obesity (Blaschko et al., 2013). Although the final products (uroliths) may be very similar, the ways of creation are very different. This is of utmost importance for urologists when trying to predict which of their patients will form or re-form stones. However, this is not so important at the end of the patient journey when stones need to be removed.

What we do know from epidemiological evidence is that despite their often unknown origin, stones are more common among people with certain disorders (for example, hyperparathyroidism, dehydration, and renal tubular acidosis) (Curhan, 2007). Other risk factors are, as mentioned, people whose diet is very high in animal-source protein or vitamin C or who do not consume enough water or calcium. People who have a family history of stone formation are more likely to have calcium stones and to have them more often (Sakhaee, Adams-Huet, Moe, & Pak, 2002), however little information is available regarding whether the increased risk is attributable to genetic factors, environmental exposures, or some combination (Curhan, 2007). Racial and ethnic

differences are seen in kidney stone disease, occurring most often in Caucasian males and least often in African-American females. The prevalence in Asian and Hispanic ethnicities is midway between the two (Sakhaee, Maalouf, & Sinnott, 2012b). One randomised controlled trial (RCT) found no evidence that recommendations to follow a low protein, high fibre diet protected people with single calcium oxalate stones from recurrent kidney stones (Hiatt et al., 1996). Worth noting though is that the population in this RCT had already had one episode of urinary stones. Furthermore the authors were so surprised by this result that they wondered whether the subjects actually followed the diet.

Finally, people who have had surgery for weight loss (bariatric surgery) may also be at increased risk of stone formation, which is thought to be due to fat malabsorption (Curhan, 2007; Romero, Akpinar, & Assimos, 2010; Scales Jr, Smith, Hanley, & Saigal, 2012; Whitson, Stackhouse, & Stoller, 2010).

2.3 Classification of stones

Uroliths are made up of crystals that separate from the urine within the urinary tract (Khan, 1992). Correct classification of stones is important since it can affect treatment decisions and therefore outcome (Okhunov et al., 2013). Stones can be classified according to the following aspects: stone size, stone location, X-ray characteristics of stone, aetiology of stone formation, stone composition (mineralogy), and risk group for recurrent stone formation (Türk et al., 2011). Broadly, stones can be categorised into calcium-containing stones which are radio-opaque, and non-calcareous stones which are radiolucent. (Parmar, 2004). This is an important classification as it will dictate which image modality is used during treatment, See Table 2 –1 A classification of urinary stones (Parmar, 2004).

Table 2 –1 A classification of urinary stones (Parmar, 2004)

Composition	Causative factors	Frequency (%)
Calcium oxalate, phosphate or combination	Underlying metabolic abnormality Idiopathic	60-80 25
Struvite (triple phosphate)	Infection	10-15

Cystine	Renal tubular defect	1
Other (indigo, xanthine, indinavir, brushite)		1

2.4 Management of the problem and future directions

The natural course of untreated calculi has not been defined as clinically urinary stones require treatment of some sort. The decision for an active treatment is based on stone composition (if known), stone size, and symptoms.

In the last decades of the previous century the treatment for kidney stones underwent some impressive changes. Prior to 1980 open surgery was common and the majority of kidney and ureteral stones were removed this way—often via challenging procedures with considerable risk of complications, and frequently involving a long stay in hospital for recovery (Lingeman, McAteer, Gnessin, & Evan, 2009). Considering that stone disease is typically recurrent, stone formers often underwent multiple, highly invasive surgeries over time. ESWL offered an entirely new and noninvasive means to remove stones and held the promise of eliminating virtually any stone without injury to the kidney or urinary tract.

It is thought that ESWL may be suitable for more than 90% of uroliths in adults, but success depends on a number of factors:

a. The size and location of the stone (ureteral, pelvic, or calyceal) (El-Assmy, El-Nahas, Abou-El-Ghar, Awad, & Sheir, 2013; Hwang et al., 2014).

b. The composition of the stone (see Table 2 –1 A classification of urinary stones (Parmar, 2004) although this can be difficult to predict preoperatively (Cortes, Motamedinia, & Gupta, 2011).

c. Patient's habitus – obesity, rather than a simply a high BMI, can cause a lower success rate after ESWL, as ESWL success depends on where the excess fat is situated. This is partly due to the difficulty in visualizing the urolith on ultrasound or fluoroscopy and also the skin to stone distance may exceed that recommended

for the lithotripter (Monga, 2011; Tsang, Fu, Wong, Ho, & Yiu, 2013; Wiesenthal, Ghiculete, Honey, & Pace, 2010).

    d.   The efficacy of the lithotripter and the factors chosen by the operator.

Each of these factors is influential on the success rate (stone free status) of ESWL.

Extracorporeal shock wave lithotripsy in addition to the revolutionary advances in other minimally invasive and non-invasive management of stone disease e.g., ureterorenoscopy, percutaneous nephrolitholapaxy, have all played a major part in stone disease treatment. There are now numerous methods of treating kidney stones, as shown in Figure 2-1. Renal stone treatment options.
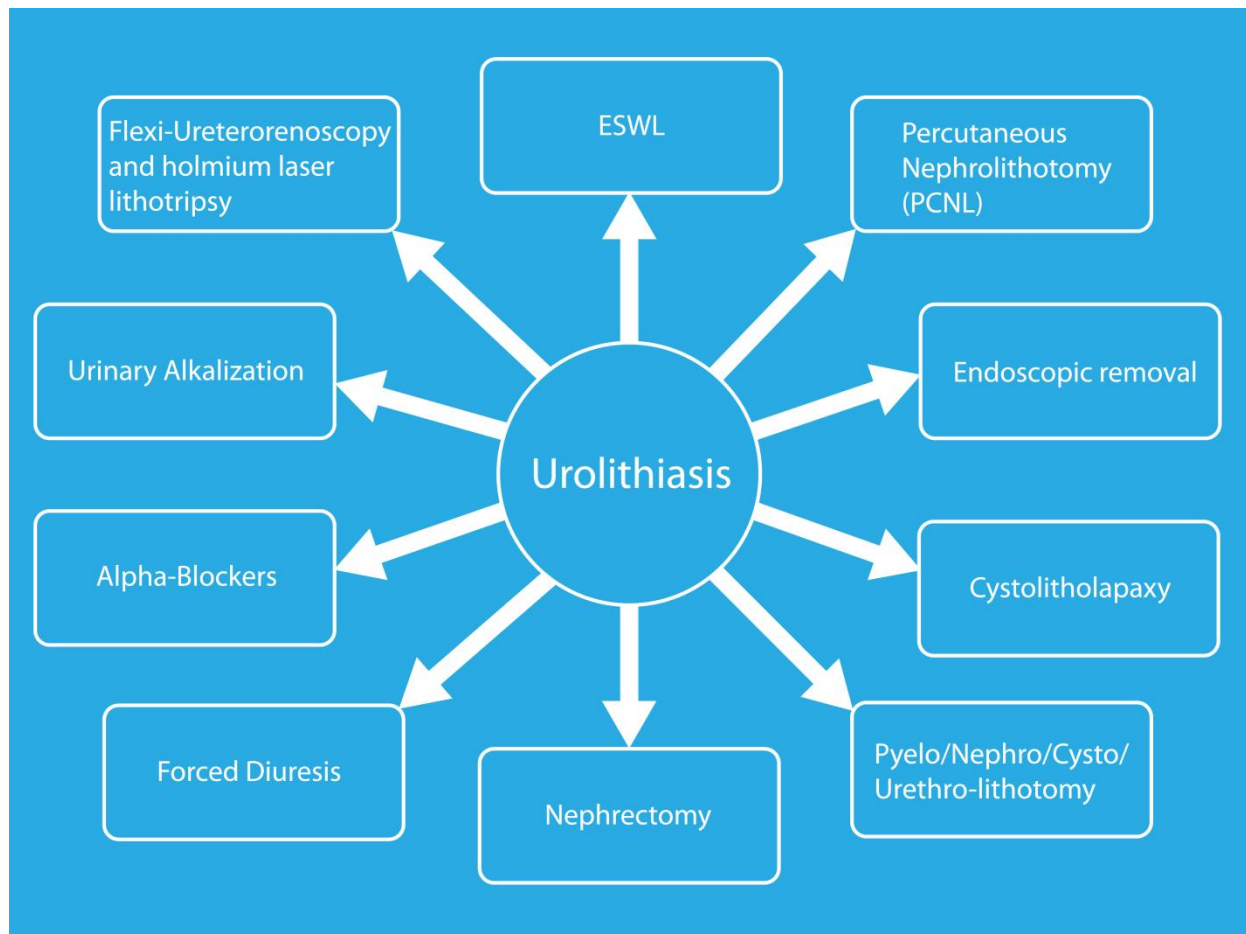
Figure 2-1. Renal stone treatment options.

Of the stone treatment styles showed in Figure 2-1, the following procedures are of interest as they compete with ESWL to be the first choice of treatment or the reference standard:

2.4.1 Surgical Options

Percutaneous nephrolithotomy

Percutaneous nephrostomy (PCNL) is a procedure that has been used since 1955 (Goodwin, Casey, & Woolf, 1955). However it was not until 1976 when it was first used for the specific purposes of removing a kidney stone (Fernström & Johansson, 1975). The procedure is mostly done under epidural, spinal or general anaesthesia (Agarwal & Agrawal, 2014), but can also be done under conscious sedation. There are several similar techniques used to puncture through the flank with a needle into the pelvi-calyceal system of the kidney at the point where access is desired, this access point is determined with fluoroscopy after previous imaging with CTU. A hydrophilic guide wire[5] is passed into the collecting system through the needle. The tract is enlarged by passing serial or telescopic Teflon or metal dilators co-axially over the guide wire (Agarwal & Agrawal, 2014; Lipsky, Shapiro, Cha, & Gupta, 2013).

Dilatation proceeds under fluoroscopic control to 24 - 30 French Gauge (Fr)[6] and an Amplatz sheath[7] is passed over the last dilator, to provide direct access to the collecting system. The nephroscope[8] (size 21-26 Fr) is passed through the sheath to visualize the inside of the collecting system (Agarwal & Agrawal, 2014; Lipsky et al., 2013). Small stones (up to 8-10 mm in size) can be removed intact with forceps or basket (Agarwal & Agrawal, 2014). Larger stones need to be fragmented by intracorporeal-lithotripsy into removable fragments. Some studies (although these could not be pooled) that compare PCNL to ESWL show the stone clearance rate at three months to be statistically higher for PCNL (RR 0.39, 95% CI 0.27 to 0.56) in the lower pole of the kidney. Furthermore, retreatment rates and the use of additional procedures such as stenting were less

---

[5] A hydrophilic guide wire enhances catheter tracking with its lubricious coating and smooth surface.
[6] The diameter of a round scope or catheter in millimetres can be determined by dividing the French size by 3. For example, a 12 Fr scope has a diameter of 4mm.
[7] Amplatz Sheaths are firm renal sheaths designed to allow smooth passage of surgical instruments into the nephrostomy tract.
[8] A nephroscope is an instrument inserted into an incision in the renal pelvis for viewing the inside of the kidney.

with PCNL when compared with ESWL (RR 9.06, 95% CI 1.20 to 68.64). Mean duration (MD) of the treatments was less for ESWL (MD -36.00 minutes, 95% CI -54.00 to -17.90), as were complication rates and hospital stays (MD -3.30 days, 95% CI -5.45 to -1.15) (Srisubat et al., 2009). Many of these studies had low methodological quality and low patient numbers and were clinical reports. Large RCTs have been recommended to investigate the effectiveness and compare the effectiveness of ESWL and PCNL (Srisubat et al., 2009). What is suggested in these studies though is that PCNL may have a superior outcome when used to manage stones over 20mm in size (Resorlu et al., 2012; Srisubat, Potisat, Lojanapiwat, Setthawong, & Laopaiboon, 2014; Wiesenthal, Ghiculete, Honey, & Pace, 2011a).

Endoscopic surgery or Flexible ureteroscopy

This plays an important role in the treatment of renal calculi, especially for the more complex cases. Recent advancements have improved the efficacy of procedures. Endoscopic removal is associated with up to >90% calculus clearance rates. This is true for both retrograde and percutaneous approaches (Fuchs & Yurkanin, 2003; Srisubat et al., 2009). Most procedures are performed on an outpatient basis or a <23 hour inpatient basis (Akman et al., 2012).

Over the past twenty years there has been a substantial advance in technology used in this procedure. Previously urologists had used blind basket techniques. Endoscopy under direct vision has decreased the complication rate associated with the procedure and currently occurs in less than 1% of all procedures (Pickens & Miller, 2013; Rajamahanty & Grasso, 2008). This had been as high as 6.6% for significant complications (Harmon, Sershon, Blute, Patterson, & Segura, 1997).

The procedure includes the following steps: (a) preoperative ureteral stenting; (b) placement of hydrophilic wires; (c) semi rigid ureteroscopy prior to the procedure; (d) the use of a large access sheath (14F-16F) if multiple ureteral passages are expected; (e) the use of a two-working channel flexible endoscope; (f) an active flushing system (Miernik et al., 2012).

Holmium lasers

These have also been introduced as an energy source to fragment the stones. The narrow fibre of <1mm diameter allows use with mini- and micro- instruments, as well as flexible instruments (Zhang, Yu, & Yang, 2013). It also minimizes any accidental firing on the renal mucosa.

Cystolitholapaxy is also an effective and safe technique (Hofmann, Olbert, Weber, Wille, & Varga, 2002; Singh & Kaur, 2011). However as the name suggests this is a procedure used to break up bladder stones. It is now rare for ESWL to be used for bladder stones so there is infrequently a choice to be made between ESWL and cystolitholapaxy.

2.4.2   Medical options

Forced diuresis

This had been used in practice for the management of renal colic caused by renal stones, although it is now very rare. Intravenous fluid administration is a standard therapy for obstructing stones, but a Cochrane systematic review found no evidence to support the use of this treatment (Teichman, 2004). It is also possible that giving saline could exacerbate renal colic if stone passage is not facilitated (Coe, Parks, & Asplin, 1992; Micali et al., 2006; Worster & Richards, 2005).

Alpha blockers

Alpha blockers given daily can reduce the number of recurrent colic episodes. At the time of writing, Tamsulosin has been the most commonly used alpha blocker in studies to aid the spontaneous passage rate (Cakıroglu, Sinanoglu, & Uraz, 2013; Dellabella, Milanese, & Muzzonigro, 2003; Falahatkar et al., 2011; Ye et al., 2011). Caution is advised that when using conservative management of stones, the patient should have no associated signs of infection, uncontrollable pain, or renal failure (Lipkin & Shah, 2006; Micali et al., 2006). Tamsulosin has also been reported to help in the treatment of all ureteral stones after ESWL (Cakıroglu et al., 2013).

The various options must be weighed against each other to determine which is the most suitable for a particular stone and patient (Urology, 2012) whilst taking into account patient wishes (Abate et al., 2004; Aronne, Braham, Riehle Jr, Vaughan Jr, & Ruchlin, 1988; Bader, Eisner, Porpiglia, Preminger, & Tiselius, 2012; El-Nahas et al., 2012; Hyams & Matlaga, 2013; Kim et al., 2005; Lotan & Pearle, 2007; Molimard et al., 2010; Parks & Wike, 2010; Patel, Blacklock, & Rao, 1987; Taylor & Curhan, 2008; Wang, Huang, Routh, & Nelson, 2012)

2.5 History of Extracorporeal shock wave lithotripsy

An accidental discovery of the effect of a shockwave was made in 1966 by an engineer, Claude Dornier, at the Dornier System GmbH. Dornier was working as a scientific advisor at Dornier and his early findings laid the cornerstone for the evolution of metal aircraft. During Dornier's research in aerospace technology, he discovered a previously unexplained phenomenon. Pitting was occurring on the exterior of the aircraft as it neared the sound barrier – a unique event caused by the shock wave created in front of a droplet of vapour (Dornier MedTech, 2015).

The phenomenon was initially explored by the Dornier Company, and later in partnership with the University of Munich. Following extensive experimental testing on animals which had proved the safety and reproducibility of an in vivo shock wave, on the 2nd February 1980 in Munich, Germany, the first clinical application of ESWL was performed (Alder, 1987; Chacko et al., 2006). This human prototype, the HM1 (human machine 1) was produced by Dornier.

The HM3 became available in 1984 and since then several generations of lithotripters have been introduced. They differ in their means of shock wave generation and other minor areas such as table design. All modifications have been in an effort to improve the success rates of the stone fragmentation, decrease the patient morbidity and improve ease of use.

2.6 Principles of action

A lithotripter needs three parts: a shock wave generator, a method of focussing the SW to a point, and a medium to allow the waves to travel from the source to the patient without attenuation. In addition to these, an imaging modality is needed. For this, fluoroscopy or ultrasound is used (Bach, Karaolides, & Buchholz, 2012).

2.7 Shockwave generation

Lithotripters differ from one another in the method used to generate the SW. There are three types of lithotripters on the market that generate SW by different methods. These are shown in Figure 2-2 Electromagnetic generator, p28, Figure 2-3 Piezoelectric generator, p. 28; and Figure 2-4

Electrohydraulic generator, p. 29 (Matin, Yost, & Streem, 2001; Pearle, 2012). In the current study, an electromagnetic shock wave generator was used. This machine was chosen to replicate a modified Dornier model HM-3, which is by far the most widely used and effective in renal stone operations (Albino & Marucco, 2012; Lingeman & Bhojani, 2013). The detailed design of the research lithotripter machine will be discussed in the next chapter.

The electromagnetic generator consists of a magnetic coil surrounded by a shock tube containing a metallic membrane. When an electrical charge is applied to the coil, the metallic membrane is repelled due to its opposite charge. This creates a shock wave that is focussed by means of an acoustic lens. This style of generator has a large skin entry zone and small focus point, which is associated with less pain than electrohydraulic lithotripters (Lingeman, 2013).

Electrohydraulic generators (also known as spark gap) were the original method of shockwave generation and used in the HM3. Their shock is generated from a single source (the electrode) discharging underwater. The gas explosion around the high voltage electrode causes vaporisation of water in a bubble. This rapid expansion and immediate collapse creates a shock wave that diverges from the point of origin. This can be focussed onto a point with an acoustic lens (Lukeš et al., 2012; Singh & Kaur, 2011).
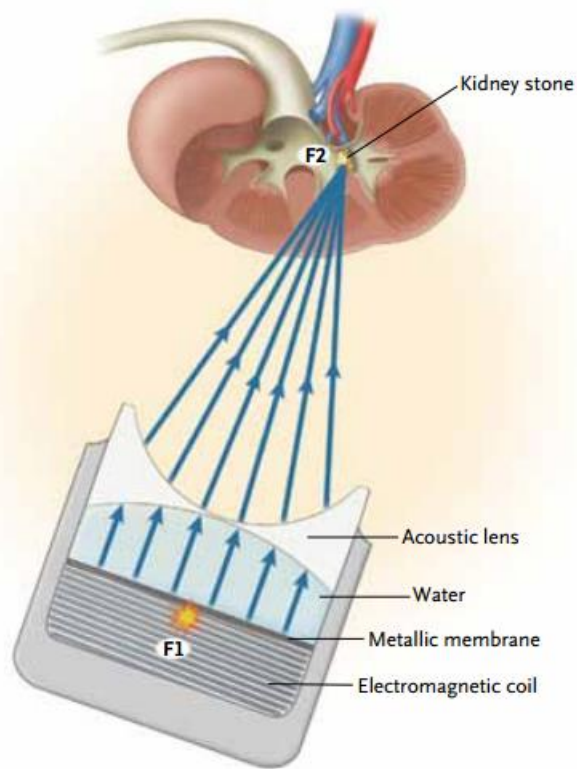
Figure 2-2 Electromagnetic generator (Pearle, 2012)
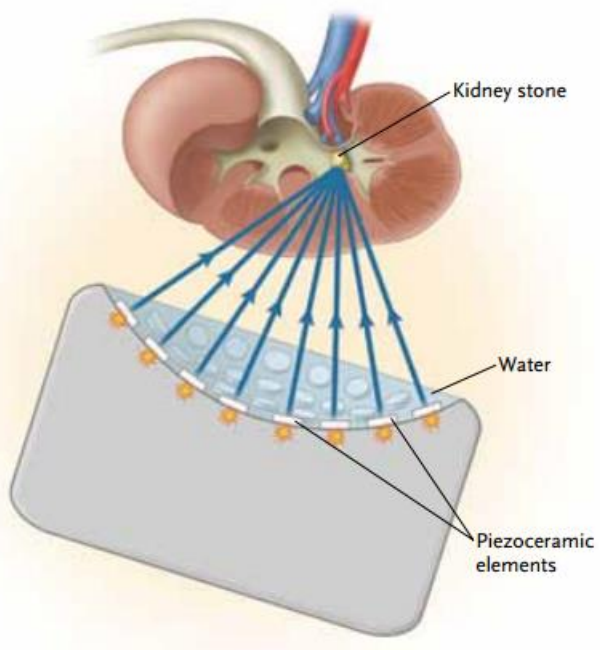
Figure 2-3 Piezoelectric generator (Pearle, 2012)
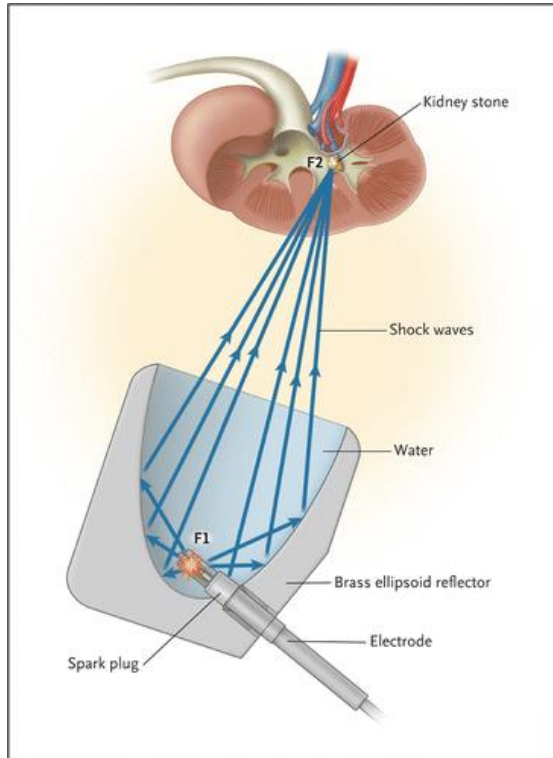
Figure 2-4 Electrohydraulic generator (Pearle, 2012)

Piezoelectrical generators comprise a series of polarized polycrystalline ceramic elements that line a hemispherical dish and produce electricity via application of mechanical stress. The alternating stress/strain changes in the material and resulting simultaneous expansion when a high voltage charge is applied produces a shock wave (Singh & Kaur, 2011).

Regardless of the type of lithotripter, the operator has the ability to control a limited, but nonetheless important number of factors. These may affect the success rates and are explored here. Currently there are guidelines but no set protocols for ESWL nor standardized parameters to characterize SWs physically or to define their optimal configuration (Rassweiler et al., 2011; Turk et al., 2014). It is widely known that treatment 'practice pattern' for ESWL differs depending on the

clinical setting and urologist. Practice patterns are affected by factors such as access to facilities and the proficiency and preference of the individual urologist. ESWL is not performed the same way at all institutions, or at all sites even within New Zealand. It is understandable that variations in patterns exist, but local practice often deviates from what is recognized as 'best practice' (Lingeman et al., 2009). This thesis aims to design a protocol to offer urologists the modifiable technical factor settings which allow the most efficient urolith fragmentation.

Predominantly there is some discussion about the size of focal zone and the energy flux within it. Most urologists have their own theory on ideal treatments from their own subjective analysis from previous treatments. Shock wave rates range from 70 per minute to 110 per minute in New Zealand (Hayes, 2011). Generally speaking the power is kept low (8kJ) for the first 100-300 shocks and rises to 12-14kJ by around 1000 shocks in a near-linear fashion to improve stone fragmentation and reduce the risk of kidney trauma (Handa et al., 2009; Köhrmann & Rassweiler, 2011; Logarakis, Jewett, Luymes, & Honey, 2000; Ng, Lu, Yuen, & Gohel, 2014).

Chapter 3

Literature Review

The first step in answering my research question about improving the modifiable technical factors of ESWL, is to find out more of the history of the procedure and why we need this technology. In the last chapter, I explained the history of the technology and the need for improvements to be made.

In this chapter I will examine and report on research that has been previously carried out in order to improve this procedure. This is crucial in order to ensure as little duplication as possible.

3.1   Method

In medical research, experimentation is always restricted to the availability of patients or specimens as subjects. In the particular case of ESWL, the literature exhibits an abundance of works reporting the practical experience of medical doctors. However, there is still a lack of information that might help to understand and to improve the fragmentation of kidney stones.

I reviewed the pathophysiology and possible improvement measures of ESWL. See Appendix A; p. 124 for search strategy. A thorough literature search was performed with the Medline, Science Direct and PubMed databases on ESWL between 1980 and 2015. Keywords relevant to the review were grouped into two categories to maximise the search results. The first group contained any key words relating to "urinary tract" ("kidney," "renal," "calyx," "ureter"). The second group contained any key words within the category of "extracorporeal shockwave" (related terms: "extracorporeal," "shockwave," "shock wave," "ESWL," and "ESWT"). Wild cards and truncation symbols were used where appropriate. Then the articles were manually screened to ensure that none of the returned articles fell within the exclusion criteria (See Appendix A). The "find similar" function in Medline and the reference lists in extracted articles were used to identify other articles that were potentially overlooked by the electronic searches. Inclusion criteria were RCTs, observational series,

experimental studies, case studies, and reviews providing significant information. Based on this information, we were able to include the expert opinions of participating urologists, physicists, and lithotripter manufacturers. The date range was from 1980 to present because ESWL was first reported in the early 1980s.

As mentioned previously, there are unwanted renal and extra renal side effects that can occur as a result of ESWL, in addition to the possibility of the modifiable technical factors not being at their peak. Most of this research comes from research on animals and the work has shown that there are a variety of risk factors such as age, size of the kidney, the presence or absence of renal disease but, most importantly for this study, side effects are also dependent on the number of SW administered, the rate at which they are delivered and the power settings of the lithotripter (McAteer, Evan, Williams Jr, & Lingeman, 2009).

3.1.1 Studies regarding shockwave rate

There have been on-going efforts to improve treatment outcome since the introduction of ESWL in the early 1980s. One of the basic well-documented mechanisms discussed above well documented is cavitation. ESWL has been shown to cause cavitation[9] erosion at the anterior surface of the urolith due to the implosion of the bubbles. However this only occurs when the bubbles are in contact with the stone (Greenstein & Matzkin, 1999; Li et al., 2013). When the bubbles are not in contact with the stone, they may act as a barrier to effective stone fragmentation. Transmitted energy would decrease when the next wave arrived due to the bubble acting as an impenetrable barrier. When the frequency increases, there is not enough time for these bubbles to disperse and they can form bubble piles by joining with others. Therefore, decreasing the frequency allows bubbles to dissipate and support better cluster bubble dynamics on the stone surface to promote superior fragmentation. For this reason, many studies have attempted to ascertain the ideal shock rate, not only to effectively fragment the urolith but to prevent renal damage (Semins et al., 2008).

Busy Urology facilities will face time constraints and it is likely that most patients are treated at a rate in order to deliver the required number of shocks in the least amount of time rather than at an

---

[9] Cavitation is the pitting of a solid surface as a result of the forces of repeated formation and collapse of bubbles in a surrounding liquid. These bubbles are caused by the shockwave (Simpson & Weiner, 1989).

ideal rate (McAteer et al., 2009; Neisius et al., 2013). This is where stone fragmentation efficiency may differ from stone fragmentation effectiveness. See Section 4.2 on page 5.

Many animals have been used in experimental models but the similarities of a pig's kidney with that of a human (size, shape, and morphology) make the pig the most suitable (Connors et al., 2000; Delius et al., 1988; Paterson et al., 2002; Ryan et al., 1991). In one study with pigs, however, it was shown that the choice of rate can affect the severity of the renal injury (Evan, McAteer, Connors, Blomgren, & Lingeman, 2007). This discovery was a chance finding during investigations to characterize the performance of a low pressure wide focal-zone lithotripter, the Xinin XX-ES .A limitation of studying pigs' kidneys is that, compared with human kidneys, they are hyper-mobile as they have very limited perinephric fat. The renal pelvis of the pig is also vertically longer than in humans, which may make stone fragment passage more difficult. However the calicies are shallower which may encourage fragment passage (Lazo, Vlatko, Florina, Nikola, & Dobrila, 2012). It is also possible to damage any kidney stones that are handled before being implanted into an animal which could result in micro-cracks developing prior to the ESWL procedure. Therefore manually inserting uroliths into a kidney may result in a false indication of effective fragmentation if the urolith had been damaged prior to the ESWL.

A follow up study by the same authors with the HM3 demonstrated a significant reduction in renal damage when the pig's kidneys were treated at 30 shocks per minute when compared to 120 shocks per minute (Evan et al., 2008). In reality most urologists would find it difficult to treat their patients at the lower end of the scale (30 shocks per minute) as the treatment time would far exceed what is common now (Neisius et al., 2013). Furthermore the added risk of having a patient under an anaesthetic for this extended period must also be considered; therefore it is promising that solid laboratory data and some clinical studies show that injury is also reduced at 60 shocks per minute when compared to 120 (Connors et al., 2012). In the follow up study, the left kidneys of female anaesthetised pigs were treated with 2000 or 4000 shock waves at 120 SWs/min, or 2000 SWs at 60 SWs/min. Measures of renal function (glomerular filtration rate and renal plasma flow) were collected before and 1 h after ESWL and the kidneys were harvested for histological analysis and morphometric quantitation of haemorrhage in the renal parenchyma, with lesion size expressed as a percentage of functional renal volume (Connors et al., 2012). Data from this study were compared with data from a previously published study (Evan et al., 2008) in which pigs of the same age (7–8 weeks) were treated (2000 SWs at 120 or 60 SWs/min) using an unmodified

Dornier HM3 lithotripter. Although lithotripter manufacturers were different in the studies, all other aspects were matching. The authors concluded that reduced tissue injury to the kidney and surrounding tissues was seen with these two machines because they were operated at a slow SW rate. A limitation of these comparisons is that in the first study the aim was not to look at tissue damage and rate but focal width. A further slight limitation is that the machines could not be set at the same SW rate, the XX-ES used 27 SW/min and the Dornier HM3 30 SW/min. These rates, 27 or 30 SW/min, would not be used in a clinical setting.

Greenstein and Matzkin (1999) evaluated the effect of the rate of shock wave delivery on stone fragmentation. They discovered that in an in vitro model ESWL is most effective when the SW are delivered at 60 shocks/min. Furthermore they reported higher energy levels than lower are more efficient for stone fragmentation. The in vitro model used was a net-like basket submerged in water, with the stone placed in the basket. The model is an established one but the size of the basket holes in this study were just 2.2mm in diameter. This allows a much smaller fragment to pass through rather than using a mesh diameter of 4mm, which is the diameter of the average human ureter (Tortora & Derrickson, 2008). Furthermore the research used so many shock rates (30, 60, 90, 120, and 150), powers (15, 20, and 22.5kV), and so few stones (n=118) that only a relatively large effect (of about the standard deviation) could be shown. The mean time to stone destruction was used as the outcome which represents a clinically accurate result (Canseco, de Icaza-Herrera, Fernández, & Loske, 2011). They recommended a clinical study verifying their laboratory findings. Also reported is a pronounced decrease in particle size when the shock rate is reduced from 120 to 30 SW/min. This result can lead to clinically superior outcomes as fewer particles are inclined to become trapped in the ureter which is perhaps why they chose a smaller basket mesh diameter.

Paterson, Lifshitz, and Lingeman (2002) were concerned that treatment rates had increased to 120 s/per minute with no obvious benefit in clinical outcome and in vitro studies were showing the opposite, a reduction in stone fragmentation success, to be true. Therefore, they tested the effect of the shock wave rate on stone fragmentation in an animal model. Again, a pig's kidney was used with the benefits and pitfalls listed above being true. Model stones were placed via percutaneous access into the lower pole calix of the kidneys of pigs. ESWL was performed (400 SW uninterrupted at 20 kV and a rate of either 30 or 120 SW /min) 2 hours later using a HM3 lithotripter. After en bloc excision of the urinary tract, stone fragments were collected and sieved through 2 mm mesh. The particles were weighed and surface area was determined. Results showed that stones treated at 30

SW per minute broke more completely (smaller fragments) than stones treated at 120 SW per minute. Limitations of this study include how difficult and therefore inaccurate it can be to determine the surface area of fragments of a kidney stone. Any error in measurement would reduce the rigour of the study.

In another pig model, Gillitzer et al. (2009) compared fragmentation rates for renal stones treated with 60 vs. 120 SW/min at the same energy settings, using standardized validated artificial stones. In this instance the pigs were alive but anaesthetised. ESWL was applied using an electromagnetic lithotripter at 60 and 120 SW/min; 3000 shocks were applied to each kidney with the same energy settings. Stone fragments were collected after nephrectomy, passed through calibrated test sieves, and weighed. Fragment size categories were stratified according to the sieve hole size as set by the manufacturer. Fragments of ≤4.75 mm were defined by the authors as capable of spontaneous passage although no critique is offered as to where this size came from and it appears a little larger than most similar studies. For each pig the number of stone fragments of the respective size categories was counted and weighed. Gillitzer et al. (2009) concluded that ESWL fragmentation with equal energy application yields significantly smaller fragments at 60 than at 120 SW per min. Again this would indicate superior clinical results. Having live animals increases the external validity of this research study. A functioning kidney and ureter can pass the stone fragments as they are broken and shattered thereby removing them from the path of subsequent SW and allowing further damage to be done to the stone. If a kidney was non-functioning, the stone fragments would stay in situ and prevent the full power of the wave from shattering the stone.

Pishchalnikov, McAteer, Williams, Pishchalnikova, and Vonderhaar (2006), tested the hypothesis that stones break more effectively when the rate of shockwave delivery is slowed. A series of gypsum stones held in a 2-mm mesh basket were exposed to 200 SW at 30 or 120 s/min from a research electrohydraulic lithotripter (HM3 clone). Waveforms were collected using a fibre-optic probe hydrophone. High-speed imaging was used to observe cavitation bubbles in the water and at the stone surface. Their results showed that stone breakage was considerably improved at 30 SW per min than at 120 SW per min. A limitation of not allowing the stone to fragment fully before analysis is that often fragmentation is a process whereby micro cracks are formed in the internal structure of the urolith for the first part of the treatment (Lokhandwalla & Sturtevant, 2000). Towards the end of the treatment the stone simply shatters due to the stone lattice no longer having the strength to keep the stone together. Uroliths are crystal aggregates, most commonly

containing calcium oxalate monohydrate (COM) crystals as the primary constituent (Sheng, Ward, & Wesson, 2003). Stopping the treatment before this tipping point would give an inaccurate reflection of how the treatment would have progressed as the fragmentation is not linear.

Vallancien et al. (1989), inserted solitary kidneys into plastic containers and used 3000 shocks at frequencies of 75, 150, 300, and 600 shocks/minute. They concluded that the lower frequencies of 75 and 150 shocks/minute achieved a better quality fragmentation (finer particles) but at the cost of treatment time. Again a limitation of this study is that the kidney was non-functioning and therefore would not accurately represent the level of power delivered, especially towards the end of the procedure as the concrement was plentiful. Another limitation of this study is the low numbers; only nine stones were tested, separated into five fragments of similar size. It is also unknown whether the stone lattice was damaged during the separation of the initial stones. If it was, this study would have little rigour. The ESWL unit used in this study was a piezoelectric generator model so it is difficult to compare with the more common electromagnetic ESWL units.

To determine the optimal frequency of ESWL, in terms of efficacy and duration, 170 patients between the ages of 18 and 69 years with radiopaque kidney stones were studied by comparing three different shock wave frequencies (Yilmaz et al., 2005). The patients were randomly divided into three groups. Group 1 (n = 56) received 120 SW per minute, group 2 (n=57) received 90 SW per minute, and group 3 (n=57) received 60 SW per minute. Also recorded for each operation were the duration, analgesic or sedative requirement, and any complications. The patients were reviewed in terms of successful treatment or otherwise, by radiography of the kidneys, ureters, and bladder and abdominal ultrasonography 10 days after the single-session therapy. This follow up time is at the shorter end of the scale, with most follow up imaging done at four weeks post-surgery (Freifeld et al., 2014). In this study Yilmaz et al. (2005), concluded that the efficacy of lithotripsy is dependent on the interval between the shock wave. If the frequency increases, the rate of lithotripsy success decreases. Therefore, lithotripsy efficiency is inversely proportional to the frequency, however they stop short at specifying the limits. Yilmaz et al. (2005), studied other factors too, such as tissue damage and added that when using a low frequency, tissue damage in the kidney, the repeat ESWL rate, and the requirement for analgesics or sedatives will decrease. However, the reduction in frequency results in a longer duration. Therefore, they concluded that performing ESWL at 90 SW per minute appears to be the optimal frequency. This is thought to be a trade-off between success and efficient use of theatre time.

Chacko et al. (2006), compared the efficacy of a slow rate (70 to 80 shocks per minute) and a fast rate (120 shocks per minute) for ESWL for solitary stones less than 2 cm located in the kidney or proximal ureter. Three hundred and forty-nine patients with a single, radiopaque kidney or ureteral stone underwent ESWL on a DoLi® 50 lithotripter. Patients were grouped based on stone size, stone location and whether a slower or faster treatment was used. Of the 349 patients 135 had a renal stone over 1 cm but under 2 cm, 137 had a renal stone less than 1 cm and 77 had a proximal ureteral stone with a surface area of between 30 and 90 mm². Stone free rates were determined after approximately 1 month by a radiograph of the kidneys, ureters and bladder (Chacko et al., 2006). Their results showed that in comparison to the fast rate groups, the slow rate groups required fewer shocks and needed lower power levels. Of patients with renal stones between 1 and 2 cm 24 of 52 (46%) in the fast rate group were stone-free compared to 56 of 83 (67%) in the slow rate group (p <0.05) (Chacko et al., 2006). For stones with a surface area of 30 to 90 mm² located in the kidney or proximal ureter there was a trend toward an improved stone free rates in the slow rate group but differences between the slow rate and fast rate groups were not statistically significant. A limitation of this study is with the difficulty of measuring such small surface areas accurately; any miscalculations could put the result out significantly.

One hundred and fifty six patients were studied in prospective randomised trial to receive either slow (60 shocks per minute) or fast wave (120 shocks per minute) by Madbouly et al. (2005). Inclusion criteria included patients with a solitary radiopaque renal or ureteral stone. This ensured all the ESWL treatments could use fluoroscopy rather than ultrasound, eliminating the problem of different imaging methods. Also patients had a stone size limit of 30mm in diameter. No critique of the stone size is offered and this appears a large size as one treatment of ESWL is recommended and has excellent results for stone sizes up to 20 mm (Pearle et al., 2005; Pearle et al., 2001; Turk et al., 2014). The study included 114 men (73%) and 42 women (27%) with a mean age of 42 years, which is an over-representation of men despite the predominance usually associated with male nephrolithiasis in this age group. Stones occur more frequently in men as they enter their 40s and continue to rise into their 70s. For women the prevalence of kidney stones peaks in their 50s (Gault & Chafe, 2000; Scales Jr et al., 2007). However ESWL treatment does not favour one gender (El-Nahas, El-Assmy, Mansour, & Sheir, 2007; Pareek, Armenakas, Panagopoulos, Bruno, & Fracchia, 2005). The patients were randomly allocated to slow or fast rate and the groups were of similar size and had similar characteristics at baseline. The male to female ratio was comparable in each group.

The slow rate was used in 49% of patients and the fast with 51%. The total number of shocks required for stone fragmentation (seen during the procedure) was significantly higher in the fast group (p < 0.004) and the treatment time significantly longer (p < 0.001). The authors defined success as being completely stone-free or having fragments less than 2mm in size visible on radiological follow up. The success rate was significantly higher with the slow rate (p = 0.034) and, as this style of treatment used less ESWL pulses overall, it can be expected that less tissue damage would also occur.

Unconvinced that that there was one rate to suit all stones, a systematic review and meta-analysis was performed by (Li et al., 2013). The search included MEDLINE, Web of Science, and the Cochrane library. All RCTs that compared the effects for different rates (60, 90, and 120 per minute) were included in the analysis. They identified nine RCTs which involved 1572 cases. This analysis looked to compare success rates on different stone sizes (using the binary classification of above and below 10mm). Overall, success rates for larger stones were significantly lower in the 120 shocks per minute group than the 60 shocks per minute group (p < 0.001) and in the 120 shocks per minute than the 90 shocks per minute group (p<0.001). However the results were very similar in the 90 and 60 shocks per minute group. Treatment time was significantly shorter in the 120 shocks per minute group vs all other rate groups (p<0.001). Interestingly in the small stone groups, there was no significant difference among the three.

On the basis of these data, it seems realistic that a slower treatment rate improves both the safety and the efficiency of ESWL.

3.1.1 Studies regarding power

The efficacy, safety, feasibility, and outcome of a treatment must all be considered when deciding which parameters to use. The goals are to avoid auxiliary procedures and provide high clearance rates in the shortest possible time (McAteer, Evan, Williams, and Lingeman (2009). However patient safety is of utmost importance and some trading between stone clearance and patient safety may be needed. As shown, optimization of the pulse sequence of ESWL can significantly improve stone comminution while simultaneously decreasing the propensity for tissue injury.

To determine the disintegration capacity of the shock wave various studies have been carried out, however, there is not as large a volume of published studies describing the role of shockwave

power as shockwave rate. The power is another parameter which can be controlled by the operator by adjusting the generator voltage. Disintegration capacity is defined as fragmented volume in µl/pulse (Forssmann, 2006). The relationship between disintegration capacity and effective energy is not as linear as expected and, due to the potential negative side effects of using high powered SW on a kidney, the optimum and least destructive (to the surrounding tissues) power must be ascertained (Madbouly, Sheir, Elsobky, Eraky, & Kenawy, 2002). The European Association of Urology Guidelines on ESWL (Turk et al., 2014) state that starting ESWL using a lower energy setting with step-wise power ramping prevents renal injury. This is thought to occur from vasoconstriction during treatment (Handa et al., 2009; Lingeman et al., 2009). However a safe maximum power is not given. This is discussed in Section 3.1.4 p.44 Studies regarding power ramping.

Permanent renal damage following ESWL has not been reported to occur, although several studies have shown temporary acute functional and morphologic changes immediately after treatment (Littleton, Melser, & Kupin, 1988; Tiselius & Chaussy, 2012). For example, shock wave therapy has been directly associated with intrarenal haematomas, interstitial oedema, and temporary tubular dysfunction (Tiselius & Chaussy, 2012).

In a paper by Auge and Preminger (2002) the clinical indications and efficacy of ESWL is reviewed and the authors discuss the potential adverse events associated with different ESWL machines at that time. They found no specific reasons why ESWL should not be used and why it should not continue to expand beyond the initial intended usage; indeed, they discussed how the clinical efficacy of ESWL was approaching or exceeding that of other modalities of minimally invasive surgery. They still advised caution and the need to be aware that high power could cause tissue damage. Although many studies regarding ESWL side effects, especially the long term side effects such as the link to developing diabetes mellitus and hypertension (Dhar, Thornton, Karafa, & Streem, 2004; Krambeck et al., 2006; Sato et al., 2008) have produced no concrete evidence, enough suggestions exist to require caution and further examination. Cardiac premature ventricular complexes (PVC) are a well-known side effect of ESWL and, as a result, ECG gated treatments are common, especially among younger aged patients and right-sided treatments (Bergsdorf, Thueroff, & Chaussy, 2004). Individuals predisposed to developing cardiac dysrhythmia (CD) during ESWL need careful ECG monitoring during treatment (Skinner & Norman, 2012).

Ventricular Tachycardia (VT)[10] during ESWL is a rare but potentially fatal adverse effect of ESWL (Skinner & Norman, 2012) and as a result the nature, duration, and treatment of these dysrhythmias have been studied (Mathers, Harding, Smeulders, Davies, & Hume-Smith, 2014). Evidence shows multifactorial causes of CD during ESWL, such as direct mechanical stimulation of the myocardium or a neurohumoral response to treatment or both (Skinner & Norman, 2012). Severe, life-threatening CD during treatment is exceedingly rare (Skinner & Norman, 2012). However the fact that CD occurs during ESWL and does not progress to significant physiologic events, and that they cease promptly with ECG-gating, warrants further investigation into understanding these phenomena (Mathers et al., 2014; Skinner & Norman, 2012).

ECG-gating uses the QRS complex of the heart wave[11]. Gating ensures the lithotripter senses this heart wave through the ECG leads and can be programmed to sense the R or S wave of the QRS complex. The shockwave is delivered 20ms after this sensation. Furthermore there is a refractory period that prevents further shocks from being delivered within 500 ms of each other. The reason for this delay in subsequent shocks is to avoid an R on T phenomenon causing VT (Shafquat, 2012; Skinner & Norman, 2012; Zanetti et al., 1999).

One question that needs to be answered, however, is whether there is a threshold power which, once exceeded, means any increase in power will not affect stone fragmentation. Rassweiler et al. (2011) suggests that any energy above a threshold Positive Pressure (P_+) plays a minor role in stone disintegration, indicating that an overestimation has been placed on P_+ in the past (Eisenmenger, 2001; Sapozhnikov, Maxwell, MacConaghy, & Bailey, 2007a). Granz and Köhler (1992) had previously discovered that focal shock wave energy represents the relevant parameter for fragmentation. They proposed Energy dose (E_{dose}) as a method of measuring the power delivered to the stone:

---

[10] VT is a dysrhythmia (three or more consecutive ventricular ectopic beats) can progress to ventricular fibrillation, cardiovascular collapse and death (Bergsdorf et al., 2004; Gravenstein & Peter, 1986; Ötünçtemur et al., 2012).

[11] This is the name given to the graphical deflections seen on the ECG and corresponds to the depolarization of the left and right ventricles.

"$E_{dose}(12\text{ mm}) = n\, E_{eff}(12\text{ mm})$ where n is the number of applied shocks and $E_{eff}(12\text{ mm})$ is the effective energy—that is, the acoustic energy in the focus per shock wave delivered to an area 12 mm in diameter." (Granz & Köhler, 1992).

The power index (shock wave intensity × impulses), is often quoted as a dose, but this equation does not capture the width of the focal zone (Rassweiler et al., 2011). The concept of effective energy dose (E_{eff} at intensity level × impulses) accounts for spatial dependence of the focal spot. The energy delivered to the stone enables comparison of treatment strategies and the effectiveness of lithotripters, the success of ESWL at different intensity levels remains the same when the number of shots delivers an equivalent energy dose (Rassweiler et al., 2011).

Caballero and Molinari (2011), describe a numerical approach to fragmenting the kidney stones by direct impact. Their results show that there are two important delimiting levels of energy; an activation and a saturation limit. Their work studied different energy levels applied directly to a test stone and they assumed full energy transmission. The first delimiting energy level is the minimum energy to be transmitted to the test stone in order to create a significant number of fractures. The second, the saturation level, indicates the power level beyond which any higher energy supplied would not create significantly more damage to the stone and might start to cause problems for a patient. Their activation energy was 0.08J and saturation energy 0.12J, although it must be remembered that this energy was directly applied to the stone and was therefore more aligned with intracorporeal shock wave lithotripsy. For ESWL, some energy is dissipated at the interface of the therapy head and the patient's skin and also as the wave propagates through the soft tissue structures towards the kidney stone. This is why much research has considered a patient's BMI when discussing ESWL success rates (Takahara et al., 2012; Wiesenthal, Ghiculete, Ray, Honey, & Pace, 2011b). The greater the amount of soft tissue the shockwave must travel through, the less likely the therapy is to be successful (Olivi, Védrine, Costilles, Boiteux, & Guy, 2011). Caballero and Molinari (2011), further commented on a wave reflection phenomenon which lasts until the excess of the energy supplied at the impact is dissipated in terms of fracture energy. This is described as fragmentation at the rear surface of the urolith where the reflection of the compression pulse creates negative or tensile waves that travel backwards through the calculi. This is shown in the following video:

The blue circle represents the urinary stone and the red pressure wave is the P+ sent from the ESWL machine. As you can see, once the wave has passed through the stone, some of the energy returns (blue wave). The passage of time (in microseconds (μs)) can be seen at the top of the diagram.

3.1.2   Studies regarding coupling

Acoustic coupling with "dry" lithotripters is not as efficient as the original HM3 where a water bath was used (Becker et al., 1999). Patient movement can further deteriorate the coupling as air pockets can arise (McAteer et al., 2009; Pishchalnikov, Neucks, et al., 2006). Clinically the problem of inefficient coupling is three-fold: inefficient coupling necessitates the delivery of more shocks than would otherwise be needed to fragment the urolith; the increased shocks increase the likelihood of adverse side effects; thirdly, the high variability of coupling, as shown by (Pishchalnikov, Neucks, et al., 2006), leads to a high variability in clinical outcomes, and diminishes the effectiveness of the treatment. This problem is made more difficult as there is currently no clinical way to measure the coupling interface during treatment. Tests have shown that there are some practical techniques that can be used to improve the quality of the acoustic coupling (Neucks et al., 2008). These included how the gel is handled, how it is dispensed, how it is applied, and whether the gel is applied only to the ESWL machine or also to the patient. Neucks (2008) demonstrated that the efficiency of stone fragmentation was significantly superior when gel was applied from a large (5l) stock jug than from a smaller squeeze bottle (p<0.006). Inefficient coupling was also reduced by using the inflation feature of the ESWL balloon. Reduced handling of

the gel can also improve the quality of coupling, as can applying the gel as a bolus to the ESWL treatment head alone and allowing it to spread upon contact with the patient.

Although studies had recognized that gas free coupling is essential for optimal energy transmission and efficient stone fracture, the fact that the coupling interface remains invisible still posed a practical problem in locating and removing air bubbles. In order to observe the coupling area during ESWL and continuously monitor the coupling zone in 30 routine treatments, Bohris (2012) installed a video camera in the therapy head and observed 30 routine shock wave lithotripsy treatments. The machine used was a DoLi SII lithotripter (Dornier MedTech®, Wessling, Germany) (Bohris et al., 2012). However, in this case it was not shown to the blinded operator which would resemble the standard clinical situation. The authors used three coupling gels, LithoClear®, Sonogel® and a custom-made gel of low viscosity. The ratio of air in the relevant coupling area was measured. Lithotripter disintegration efficiency was evaluated by in vitro model stone tests at an air ratio of 0%, 5%, 10% and 20%. In only 10 of the 30 treatments was a good coupling achieved (the authors considered less than 5% of air in the gel to be a good coupling). In eight treatments the ratio was greater than 20%. The best coupling conditions (least gas) were achieved with low viscosity gel. The mean ± SD number of SW needed for complete fragmentation in the model stone tests was 100 ± 4 for bubble-free coupling, and 126 ± 3 for 5%, 151 ± 8 for 10% and 287 ± 5 for 20% air bubbles. A further advantage with this study was that treatment times were reduced by 25%.

A possible limitation of this study is that, as viscosity was the independent variable and the tests were not all carried out at the same time, a possible rise or fall in temperature could have influenced the viscosity (Doolittle, 1951). The precise dependence of the viscosity of liquids on temperature is complicated; however generally speaking, and in everyday working temperatures, a rise in temperature will decrease the viscosity of the liquid.

In a similar study into "dry" lithotripters, Lopez, Chen, Deiling, Iames, and Young (2013) designed a coupling interface video camera which was installed in the therapy head of a Dornier Gemini lithotripter. This enabled all air bubbles observed in the coupling zone to be removed under visual control. The effect of this was tested for one year on treatment results (01/10/12 – 30/09/13) and compared to the results obtained in a "blind" coupling mode (01/04/11 – 30/04/12). The results showed that removal of air bubbles with the video camera from the coupling area reduced the

number of SW required by 25.4% for renal stones and 25.5% for ureteral stones (Lopez et al., 2013). The energy level was reduced by 23.1% for renal stones and by 22.5% for ureteral stones. For renal stones the total applied energy was reduced by 42.9% (Lopez et al., 2013). Lopez concluded that controlled air bubble removal with a video camera proved significant in the realisation of bubble-free coupling. Bubble-free coupling significantly reduced the total energy needed to obtain comparable treatment results. Theoretically this should also lead to a reduced incidence and severity of shockwave-induced adverse effects (discussed in Section 3.1.2 p.38) (Lopez et al., 2013).

As mentioned above, an in vitro study published in 2006 (Pishchalnikov, Neucks, et al., 2006) explored the effect of air bubbles confined in the coupling interface on the transmission of SW and stone fragmentation. Air in the coupling area reduced conduction of acoustic energy to the focal zone leading to a decrease in ESWL efficiency for stone fragmentation. They showed a near-linear correlation between stone fragmentation and air trapped in the coupling area: when only 2% of the coupling area was covered with air bubbles, efficiency of stone fragmentation decreased by 20% to 40%. This undesirable effect was most noticeable after a coupling-decoupling-recoupling sequence, which can happen in the clinical situation after patient movement. Their data also showed that uniformity in coupling is hard to achieve. According to the authors this inconsistency in coupling quality could also pose a safety hazard: a higher shockwave dose than necessary could be delivered when by chance fewer air pockets are present than usual, resulting in conceivable injury to the kidney.

Knowing that gas bubbles at the coupling interface occur and that these hinder the transfer of shockwave energy into the body and reduce the effectiveness of the treatment, Li, Williams Jr, Pishchalnikov, Liu, and McAteer (2012), explored whether the size and location of gas bubbles affect the stone fragmentation. In their research gas was deliberately introduced in the coupling gel between the therapy head and the 'skin' of a phantom. Using a fibre-optic probe hydrophone to measure acoustic pressures and also to chart the dimensions of the focal zone of the lithotripter the effect of different coupling conditions (+/- gas) on stone fragmentation was assessed. Similar to Pishchalnikov, Neucks, et al. (2006), the results showed that stone fragmentation decreased in proportion to the area of the gas bubble in the gel. A centrally positioned gas bubble blocking 18% of the transmission lowered stone fragmentation by an average of 30% compared to when coupling was unobstructed. As expected, the effects on stone fragmentation was greater for gas more

centrally located than for more laterally located bubbles. An 18% gas pocket located 2cm off axis reduced the fragmentation by 15%. However these off-axis gas pockets could affect the symmetry of the acoustic field. This may affect the focal width.

Other research has been conducted into determining which coupling medium is preferable (Jain & Shah, 2007). Ultrasound gel and silicon oil were compared in a 2007 in vivo study. Destruction of the uroliths was greater in all cases where the gas had been removed from the coupling medium; however, it was significantly greater ($p<0.001$) when ultrasound gel with no gas bubbles was used.

3.1.3 Studies regarding power ramping

Operator technique in ESWL is critically important, and it is promising that simple, practical steps can be taken which appear to improve the safety and efficacy of the treatment (Lingeman, 2012).

In 2010 Lambert et al. published a paper in which they described that an escalating power treatment strategy produces better stone comminution than a fixed strategy. The study suggests that there may be a protective effect against damage caused by ESWL with an escalating treatment strategy (Lambert, Walsh, Moreno, & Gupta, 2010), however the paper does not give suggested power levels. At a similar time Honey, Ray, Ghiculete, and Pace (2010), investigated immediate vs. delayed power escalation during ESWL and how efficiency is affected by the energy setting of the lithotripter, the consumption level of the electrode, and the rate of shock wave administration. They concluded that delayed power escalation might not provide superior stone fragmentation compared with conventional, immediate power escalation (Honey et al., 2010). Similarly Berwin et al. (2009), writes that it is also extremely important for the operator to increase the power in gradual increments to aid the development of pain tolerance without giving any suggested powers. This paper assumes that patients are not under a general anaesthetic and caution must be advised when comparing these results to any study where the patients have been treated with ESWL under a general anaesthetic as there have been studies that show that general anaesthesia is associated with a statistically significantly more successful treatment outcome (Grobler, Hayes, Frampton, & English, 2014; Sorensen, Chandhoke, Moore, Wolf, & Sarram, 2002). It is further discussed that tolerance has long been identified as a factor influencing successful treatment of renal calculi by ESWL. Their retrospective analysis (n=179) of patients who had received their first treatment of a solitary kidney stone showed that young women with a normal Body Mass Index (BMI) had a lower

pain tolerance. It must be noted, however, that this does not include patients who receive general anaesthetic sedation for their treatment (Sorensen et al., 2002).

To investigate the idea that a brief pause (3 minutes) in the delivery of SW shortly after the beginning of the ESWL treatment provides a protective effect on the kidney; Handa et al. (2012) tested ESWL on pigs with and without this pause. Three ESWL protocols were used that did not involve a 3 minute pause in shock delivery (2000 SW at 24kV, 100 SW at 12kV plus a 10 second pause followed by 2000 SW at 12kV, and 500 SW plus a 10 second pause followed by 2000 SW at 24kV). The shockwave rate was 120/minute and a Dornier HM3 was used for all experiments. Renal function was measured before and after ESWL and following ESWL the kidneys were examined for ESWL-induced lesions. The data from these studies were compared to similar studies which included a 3 minute pause. The primary function of this research was to investigate the undesirable effects of ESWL rather than stone fragmentation. If ESWL is linked with adverse outcomes, especially the more severe side effects, it would raise concerns about the long term safety of ESWL. Therefore these experiments are important, as developing ESWL treatment protocols that could reduce or prevent these side effects would help to mitigate these concerns (Handa & Evan, 2010; Janetschek et al., 1997; Krambeck et al., 2006; Willis et al., 2006).

Handa et al. (2012) also showed that a ramped treatment protocol initiates renal protection, certainly with regards to mean lesion size and that this reduction was greatest when treatment included a 3 minute pause or when using various power- ramping protocols.

A RCT (n= 50) at an outpatient urology clinic aimed to evaluate the results of conventional and ramped ESWL (Demirci et al., 2007). Twenty five patients were treated in each group with no differences observed between the two groups as to the localisation of uroliths. No differences were shown, either, in the number of ESWL treatments the patients needed for stone clearance. However there were slight differences between groups with respect to age (conventional group 39.9 and ramped group 41.4 p>0.05) and also stone size (mean stone size for conventional group 0.70+/- 0.41cm and 0.83 +/- 0.51cm for the ramped group p>0.05). The results were compared eight weeks after treatment and the stone free results were significantly higher in the ramped group (stone free 96% vs 72% p<0.05). No increase in morbidity was shown despite the superior outcome (Demirci et al., 2007).

3.2 Stone fragmentation outcomes

Following Chaussy in 1980, over 500,000 ESWL treatments have been reported worldwide. Success rates and retreatment rates have ranged from 44 to 90% and from 3 to 30%. See Table 3-1 Stone fragmentation outcomes and Table 3-2, p.48 Success rates for second and third generation lithotripters, and Table 3-3, p.49 Success rates for second and third generation lithotripters.

Table 3-1 Stone fragmentation outcomes

Authors	Number of patients	Stone free	Retreatment
Chaussy and Schmiedt (Chaussy & Schmiedt, 1983)	498[1]	90%	12% [8]
Drach (Drach, Dretler, & Fair, 1986)	2112[2]	66%	16%
Lingeman (Lingerman, Newman, & Mertz, 1986)	982[3]	72%	20%
Palfrey (Palfrey, Bultitude, & Challah, 1986)	654[4]	44%	14%
Riehle (Riehle et al., 1986)	467[5]	75%	5%
Das (Das, Dick, & Bailey, 1987)	1000[4]	85%	4%
Politis (Politis & Griffith, 1987)	1060	74%	8%
Mays (Mays, Challah, & Patel, 1988)	933[6]	45%	4%
Rigatti (Rigatti, Francesca, & Montorsi, 1989)	2557[7]	72%	20%
Cass (Cass, 1995)	3121	70%	4%
Total	13384	70%	14%

[1] Includes 32 patients with ureteral stones

[2] Includes 14% with staghorn stones

[3] Includes 194 ureteral stones

[4] Includes patients with ureteral stones

[5] Includes ureteral stones and staghorn stones

[6] Includes 112 patients with staghorn and 20 patients with ureteral stones

[7] Includes staghorn and ureteral stones but stone free rate only includes renal stones.

[8] Stone free percentage shown indicates clinical status after one or more treatments.

The outcomes for second and third generation lithotripters often appear inferior to the original HM3 and are listed in Table 3-2 Success rates for second and third generation lithotripters. This inferior success rate may in fact relate to more sophisticated imaging systems (such as Computed Tomography Urograms (CTU)) which enable more accurate viewing of stone fragments after the procedure than a plain radiograph would, and perhaps those treatments labelled as successful prior to CTU examinations being commonplace would not be labelled as such now.

Another possible reason for the inferior success rates could be due to the early success and rapid growth of ESWL technology. As mentioned in the Introduction, due to the early success of the ESWL procedure there was a rapid uptake of the original Dornier HM3. However this was a large, expensive, machine and only suited urology clinics and hospitals with a large urinary stone throughput. The shortcomings included:

- High capital investment was needed.
- Large space required to house the machine.
- Treatments required general anaesthesia.
- Lower ureter stones were difficult/impossible to treat.

These issues prompted several companies to manufacture second generation ESWL units. These remedied many of the shortcomings:

- Less capital investment required.
- Less theatre space needed.
- Various types of anaesthesia could be considered.
- Versatile targeting allowed the entire urinary tract to be targeted and treated.

This is discussed in more detail on p.49.

Furthermore the second generation machines were constructed to allow the urologists to perform auxiliary endourological procedures, such as inserting a urological stent to aid the passage of stone fragments (Tailly, 2013).

Table 3-2 Success rates for second and third generation lithotripters

Author	Number of patients	Stone free	Retreatment
Electrohydraulic			
Graff (Graff, Benkert, Pastor, & Senge, 1989)	265	68%	14%
Talati (Talati, Shah, & Memon, 1991)	464	73%	46% [1]
Cass (Cass, 1991)	480	64%	6%
Swanson (Swanson et al., 1992)	281	58%	9%
Simon (Simon, 1995)	500	75%	-
Elhilali (Elhilali et al., 1995)	169	73%	13%
Lalak (Lalak, Moussa, Smith, & Tolley, 2002)	467	68%	-
Totals	2626	68.43%	17.6%
Electromagnetic			
Wilbert (Wilbert et al., 1987)	698	65%	12%
Clayman (Clayman, McClenn, Garvin, Densted, & Andriole, 2009)	266	71%	7%
el-Damanhoury (el-Damanhoury, Schärfe, Rüth, Roos, & Hohenfellner, 1991)	2117	65%	12%
el-Damanhoury (el-Damanhoury et al., 1991)	25	100%	20% [1]
Köhrmann (Köhrmann, Potempa, & Rassweiler, 1991)	185	83%	19% [1]
Psihramis (Psihramis, Jewett, Bombardier, Caron, & Ryan, 1992)	1000	52%	19%
Liston (Liston, Montgomery, Bultitude, & Tiptaft, 1992)	500	78%	32% [1]
Mobley (Mobley, Myers, Grine, Jenkins, & Jordan, 1993)	11516	69%	16%
Coz (Coz et al., 2000)	828	87%	21% [1]
Total	171135	74.44%	17.56%

Table 3-3 Success rates for second and third generation lithotripters

Author	Number of patients	Stone free	Retreatment
Piezoelectric			
Vallancien (Vallancien G et al., 1988)	386	74%	14%
Bowsher (Bowsher, Carter, & Philip, 1989)	398	53%	62%
Rassweiler (J. Rassweiler et al., 1989)	378	72%	45%
Miller (Miller et al., 1989)	461	51%	-
Tan (Tan, Tung, & Foo, 1990)	180	64%	40% [1]
Cope (Cope, Middleton, & Smith, 1991)	220	75%	51% [1]
Laugani (Laugani, Grunberger, & Godec, 1991)	600	61%	23%
Mykulak (Mykulak, Grunberger, & Macchia, 1992)	130	57%	21%
Total	2753	63.38%	36.57%

Stone free is considered the gold standard for determining success of ESWL treatment. However there is no uniformity in the literature as to what defines a successful treatment. Some studies use the term "clinically insignificant fragments" (CIF). However, a number of authors (Osman et al., 2005; Osman et al., 2013; Rebuck, Macejko, Bhalani, Ramos, & Nadler, 2011; Streem, Yost, & Mascha, 1996) have shown that this term is inappropriate as these fragments do not always remain clinically insignificant. Streem (1996) studied 160 patients left with CIF (stone fragments less than 4mm). Only 24% ultimately became stone free. 42% of the patients showed no change and 18% actually showed an increased stone burden. Furthermore, 43% of patients experienced an episode of renal colic or required intervention. Khaitan (2002) and colleagues report similar findings and as a result ESWL outcomes should be reported as either stone free or not (Khaitan et al., 2002).

These newer machines, despite their ease of use and lower costs, may have proved to be a double-edged sword, though, and many urologists have experienced and realized that successful stone

disintegration does not come automatically. The less desirable consequences which accompanied the second generation models were:

- Some stone centres invested in low cost technology, especially in regards to the imaging. As we saw in the previous chapter, without adequate imaging the stone cannot be treated successfully.
- The rapid expansion of the technology resulted in a dilution of clinical experience.
- Less investment in suitable training of urologists or other staff operating lithotripters.
- The above resulted in poorer results with ESWL than could have been achieved.
- Still no developed protocols for the new machines, for instance no suggested power or shock rate.

A number of considerations are necessary for an optimal result (Tiselius & Chaussy, 2012). Selection of appropriate treatment variables in terms of shockwave number, power and frequency, is an important requirement for accurate disintegration and prevention of complications. Good understanding of these factors in addition to the physics of SW is necessary for a successful application of this treatment concept. Fragmentation theories are investigated and explained in the following section.

3.3   Stone fragmentation theories

ESWL repeatedly focuses SWs on kidney stones to disintegrate them. Numerous studies have attempted to explain the mechanism of stone fragmentation (Chaussy et al., 1980; Rassweiler et al., 2011; Zhong, Xi, Zhu, Cocks, & Preminger, 1999). The ideal scenario is an ability to exploit the difference between the stone and tissue physical properties, in order to make stone fragmentation more effective without increasing tissue damage. Initial fragmentation occurs similar to the fracture of any brittle object, during a process where cracks begin as a result of stresses generated by applied SW. Cracks form in areas where shock wave–induced stress exceeds a critical value (Chaussy et al., 1980; Rassweiler et al., 2011). Further disintegration occurs as a result of growth and coalescence of these cracks under repetitive loading and unloading (Zhong et al., 1999). Besides established mechanisms which detail initial fragmentation-like tear and shearing forces (Lokhandwalla & Sturtevant, 2000), spallation (Zhong et al., 1999), cavitation (Crum, 1988), and quasi-static squeezing (Eisenmenger, 2001), further insight was gained by the studies of

Sapozhnikov et al. (2007a) and Sapozhnikov, Maxwell, MacConaghy, and Bailey (2007b) who introduced the theory of dynamic squeezing. These theories are driven by the lithotripter-generated shock wave and possibly also by cavitation effects in the surrounding fluid (Lokhandwalla & Sturtevant, 2000).

3.3.1 Tear and shear forces

These are unaligned forces pushing one part of the stone in one direction, and another part of the stone in the opposite direction (Nash & Potter, 1998). When the length of the pulse is shorter than the stone, then, due to the geometry of the stone surface and its internal structure, the compressive phase of the shock wave will produce pressure gradients. This can result in shear and tensile stresses in the stone (Rassweiler et al., 2011). These stresses can fragment the stone (Chaussy et al., 1980). In this model, shock wave reflection from the stone–water interface, together with pressure inversion and cracking off of concrements by the tensile stress of the reflected wave, is emphasised (Rassweiler et al., 2011).

3.3.2 Spalling

This is a process in which fragments of material (spall) are ejected from the stone due to impact or stress. In this context of impact mechanics, it refers to the ejection or vaporization of stone fragments from the stone during impact by a shockwave. The fluid of the distal stone surface represents an acoustically soft interface, and the leading compressive phase will be reflected as a tensile wave. The power of the tensile stress depends on the difference in acoustic impedance and the shape of the stone surface. Using high-speed shadowgraphy[12] to image stress waves in translucent model calculi, Rassweiler et al. (2011) observed maximum tension occurs within the distal part, which results in a fracturing about a third of the way from the distal end (Sapozhnikov et al., 2007b; Zhong et al., 1999). The mechanism is not unlike freezing water inside a brittle material.

3.3.3 Quasi-static squeezing

If the focal spot is broader than the stone, then pressure waves travel in the fluid around the stone's surface. The front compressive phase can create circular stresses, which act on the stone by quasi-

---

[12] Shadowgraphy is an optical method that reveals non-uniformities in transparent media.

static squeezing, inducing a binary fragmentation with the first cleavage surfaces parallel or perpendicular to the axis of shock wave propagation (Hernandez, 2003; Sapozhnikov et al., 2007b). This process assumes that the shock wave velocity in the surrounding fluid is much lower than the elastic velocities within the stone (Rassweiler et al., 2011). The longitudinal shock wave moves through the stone, leaving the thinner waves in the fluid encircling and squeezing the stone (Eisenmenger, 2001; Sapozhnikov et al., 2007b). For squeezing to be effective, the focal width of the lithotripter must be wider than the stone; this is an important clinical consideration when choosing a lithotripter model. High fragmentation efficiency will be promoted by large focal diameters up to 20 mm, and it is not necessary for a steep shock front to exist. Data suggest that positive pressure (P_+) could be reduced to 10–30 MPa—sufficient to overcome fracture thresholds (2–10 MPa) (Rassweiler et al., 2011). This hypothesis has started discussions about the importance of larger focal sizes and lower pressures compared with small focal sizes with high pressures in large-aperture sources (Fuchs, Miller, Rassweiler, & Eisenberger, 1984; Rassweiler et al., 1990).

3.3.4 Cavitation

In addition to the direct shock wave forces mentioned, cavitation generated by the negative pressure phase of SW occurs in the fluid surrounding stones and within micro cracks or cleavage interfaces (P-). Numerous individual bubbles form on the surfaces of stones, but the bubbles do not remain independent but instead combine to form groups. These groups of bubbles form before collapsing to a narrow point of impact (Pishchalnikov et al., 2003). For initial fragmentation, cavitation is less relevant as there are fewer micro cracks but becomes increasingly important as stone fragments become smaller. Cavitation-induced erosion is especially observed at the anterior surface of stones (Crum, 1988; Delius, Brendel, & Heine, 1988). Cavitation damage to stones is attributable not to the action of individual bubbles, but to the growth and collapse of bubble clusters (Pishchalnikov et al., 2003). Suppression of cavitation using highly viscous media, hyper pressure, or overpressure significantly reduces disintegrative shock wave efficacy (Delius et al., 1988). Their tests may explain some of the reasons why stones in the common bile duct are more difficult to destroy and why, after the initial clinical uses with gastroenterology, ESWL is no longer used for gall stones. As the gall stones in the bile duct are surrounded by tissue, this prevents cavitation from destroying them. Identifying the role of cavitation in stone fragmentation has led to efforts to improve the action of cavitation bubbles, such as dual SW generated using a piezoelectric source fitted to an electrohydraulic system, with an additional discharge circuit to produce the

second pulse. This novel concept and associated technologies may be used to upgrade other existing lithotripters and to design new shock wave lithotripters for improved performance and safety (Zhou, Cocks, Preminger, & Zhong, 2004b). However, cavitation can be somewhat disadvantageous for fragmentation: if the produced gas bubbles last for many seconds, they can attenuate the following SW (Pishchalnikov et al., 2003).

3.3.5   Dynamic squeezing

In dynamic squeezing, fragmentation occurs by shear waves created inside the stone driven by squeezing waves from the lateral stone borders, which in turn are created by the quasi-static squeezing forces (Rassweiler et al., 2011). The theory is based on a model that accounts for all acoustic phenomena inside and outside of the calculus, including transmission, reflection, mode conversion, and diffraction, and shows that peak loading induced in kidney stones is generated by constructive interference from shear waves launched from the outer edge of the stone with other waves in the stone (Cleveland & Sapozhnikov, 2005). Following predictions from this numerical model, Sapozhnikov et al (2005) presented experimental evidence of dynamic squeezing (Sapozhnikov et al., 2007b), demonstrating that shear waves initiated at the corners of the stone and driven by squeezing waves along the calculus led to the greatest stress, whereas reflected longitudinal waves at the posterior surface had less influence.

3.3.6   Dynamic fatigue

Stone disruption inflicted by ESWL accumulates during the course of treatment, leading to eventual fragmentation of the stone configuration (Lokhandwalla & Sturtevant, 2000). Therefore, stone comminution is described as a gradual process consisting of a beginning (based on dynamic squeezing), growth (associated with cavitation), and coalescence (because of increasing fragility). Once the stone's molecular structure is destroyed, the mechanical stresses of the shockwave produce micro-cracks, which result in sudden break-off of particles of the calculus. This theory relates physical stone properties (fracture toughness, acoustic speed, density, void dimensions) to shock wave parameters (peak pressure, pulse width, pulse profile) (Köhrmann & Rassweiler, 2011; Lokhandwalla & Sturtevant, 2000).

This chapter described how other researchers have reported their work in order to improve this procedure and looked at the theories on stone fragmentation. We have seen that the rate of the SW

has been studied and that there is evidence that a slower rate of between 60 and 90 SW/min offers a more effective stone fragmentation than a faster rate of 120 SW/min. Although there are far fewer reports on the relationship between shock power and stone fragmentation we have also seen that the power of the SW can alter the success of the fragmentation of the stone. However, in the clinical trials the researchers advised against using very high powers as care must be taken with the kidney tissue and surrounding organs when using high powered SWs. Other theories such as SW power ramping and gas free coupling were shown to be important when using ESWL.

The reasons SWs fragment stones were also discussed and the evolution of the ESWL machines have been described with reasons for this development. In the following chapter I will discuss my own experiments of the modifiable factors that can improve stone fragmentation.

Chapter 4

Research Design

This chapter discusses the approach used for the in vitro experiments used to answer the research question. Different machine parameters which can easily be adjusted by the ESWL operator were selected and systematically tested to ascertain which provided the most efficient and effective fragmentation result. Our own experiments differ from the research summarised in the previous chapter as it looks at all the modifiable factors, In particular we tested the effect of SW rate and power simultaneously and concentrated on the SW rates and power levels that are commonly used in the clinical environment.

4.1   Methodology

Different authors have measured fragmentation of stones in a variety of ways. For this study an empirical method[13] was chosen. This approach has a number of attractive features: it can produce results that can be summarised, compared, and generalised. A simulation model for the kidney was designed. This enabled the systematic scientific study of a quantitative property (fragmentation) and its relationships with the parameters studied: mathematical models were then applied to these phenomena. Two methods were available. The first was a kidney harvested from a pig with a plaster ball inserted and then fragmented using ESWL. However a problem with this model is that the kidney does not have any dynamic drainage as it would if the pig were alive. This would leave the plaster fragments in the line of the SW and in so doing absorb some of their power. A more realistic model was chosen. This was a mock kidney suspended in water with a wire mesh basket used to catch the stone fragments. The drainage is provided by gravity as, when the fragments are

---

[13] Empiricism is a philosophy describing the theory that regards experience as the source of knowledge. Empirical methods try to answer research questions by obtaining direct, observable information. This information is called data and is used to test ideas (Punch, 2013)

broken from the stone, they fall from the basket and are out of the way of the following shocks. Although this model will typically promote faster clearance of fragments than a kidney[14] draining to the ureter it is closer to reality than a non-draining model (Cui, Thomee, Noble, Reynard, & Turney, 2013; Mustafa, 2012).

4.2   Aim

According to research findings summarised in the literature (in Chapter 3, p.31) there are some conditions of ESWL that may give better outcomes.

1.   Treat at a slower rate.
2.   Use lower powers than previously thought.
3.   Ensure the patient remains motionless throughout the treatment (through anaesthesia).
4.   Ensure the coupling medium allows transfer of the shockwave.
5.   Use a power ramping technique.

The aim of this research was to see which modifiable technical factors give the most efficient stone fragmentation. Due to the clinical nature of 3, this aspect is beyond the scope of this thesis.

4.3   Method

In some recent studies, stone fragmentation is measured in vitro and the fragmentation efficiency is defined in terms of the per cent weight loss of the stone following shock wave therapy. The mass of the fragments that do not fall through a standardized sieve is used to determine fragmentation success (Canseco et al., 2011). Canseco et al. (2011) use a method that requires a fixed number of shocks to be applied to each model stone and the remaining stone mass is weighed to indicate how much fragmentation occurred. Our study measured the stones until complete fragmentation had occurred, as observational evidence indicates that stone fragmentation does not follow a linear path

---

[14] Within the kidney three angles are prominent. The inner angle between the axis of the lower pole infundibular and ureteropelvic axis (1); the inner angle between the lower pole infundibular axis and main axis of pelvis-ureteropelvic (UP) junction point (2) and the inner angle between the lower pole infundibular axis and perpendicular line (3). This model best demonstrates a urolith in either angle two or three.

but rather the urolith gets weakened and damaged by the first shocks and fragmented by the latter ones. Therefore Canseco et al's. (2011) method was not suitable for this research. This observation was backed up by our own experiments. Furthermore despite this research being in vitro, we attempted to mimic clinical conditions, therefore complete fragmentation of the urolith is the desired result.

The experimental protocol used in this study was carried out in accordance with Dornier Medtech® protocols for calibrating their lithotripter. The initial sample consisted of five hundred and fifty three identical calcium sulphate dehydrate (plaster) balls of 300mg each sourced from Dornier, Germany which were used to mimic kidney stones. Their constituents were checked at the Canterbury Health Laboratory in Christchurch and found to be as described. For a detailed analysis of the similarity between the plaster balls and various kidney stones, please see Figure 5-9, p.66. Eleven of the stones did not get used due to operator error and a further eight were excluded from the analysis due to experimental error[15].

---

[15] The reason for these exclusions is discussed in detail in the Results chapter.

Chapter 5

Model Stone Test

In the previous chapters we have seen how other authors have reported their findings in both in vitro and in vivo studies and looked at the science behind the phenomena. This chapter describes the in vitro experiments used in this research.

5.1 Set up

1. Water circuit of the Lithotripter inspected to check it complied with the Dornier® values before performing the Model Stone Test.
2. One litre of distilled water was boiled 'whirling' for five minutes.
3. Water was cooled fast to 35 ^{0}C (by putting the container with the boiling water into another container with cold water)
4. One stone at a time was soaked for 20 minutes in the water.

5.1.1 Performance of model stone test for rate and power.

1. Therapy head moved into the treatment position.
   a. The therapy head must be positioned so that it is at 90° to the vertical.
2. Dornier apparatus is then bolted to the treatment head. See Figure 5-1 Bolts to hold kidney apparatus in place, p.60 and Figure 5-2 ESWL head with test kidney bolted to it, p. 60
3. Ultrasound gel was applied in an even fashion to the coupling bellows.
   a. Gel was inspected visually for bubbles of gas and removed by smearing if necessary.
4. The test container was filled with the water at 35^{0}C (a temperature chosen to mimic the condition of the human body (Houdas & Ring, 1982)) See Figure 5-3 Testing apparatus being filled with heated water, p.61.

5. The basket (silicone mesh[16]) was screwed into the apparatus (mesh diameter 4mm). See Figure 5-4 Mesh basket ready to be screwed into place. p. 61.
6. One soaked model stone at a time was placed in the basket, ensuring the stone was below the water level. See Figure 5-5 Stone left soaking below the water level. p. 62.
7. The bellows was set to pressure 6 to ensure complete contact with kidney apparatus.
8. Trigger mode (rate) was set at the following speeds 60, 70, 80, 90, and 100 SW/min[17].
9. Power was set for 40%, 50%, 60%, 70%, and 80% of maximum power, chosen to mimic the two clinical extremes. See Table 5-1 Explanation of machine settings for an explanation of these percentages.
10. 5 stones were treated at each power level for each rate.
11. The shockwave was started and left to run continuously until the fragments of the model stone had completely fallen through the basket. See Figure 5-6 Remaining stone fragments at conclusion of one stone test. p. 62.
12. The number of SW which were needed for the complete disintegration of the model stones was recorded.

Table 5-1 Explanation of machine settings

Shockwave intensity (kV)	Machine setting (Power) %
12	10
12.8	20
13.5	30
14.2	40
15.1	50
16	60
16.9	70

---

[16] It is not thought that the silicone mesh attenuated any shockwave power due to its silicone composition being identical to the silicone membrane of the bellows. However, if it did, the effect would have been the same for each stone tested.

[17] The rates and power levels were chosen based on the clinical extremes of the scales and what is reported in the international literature.

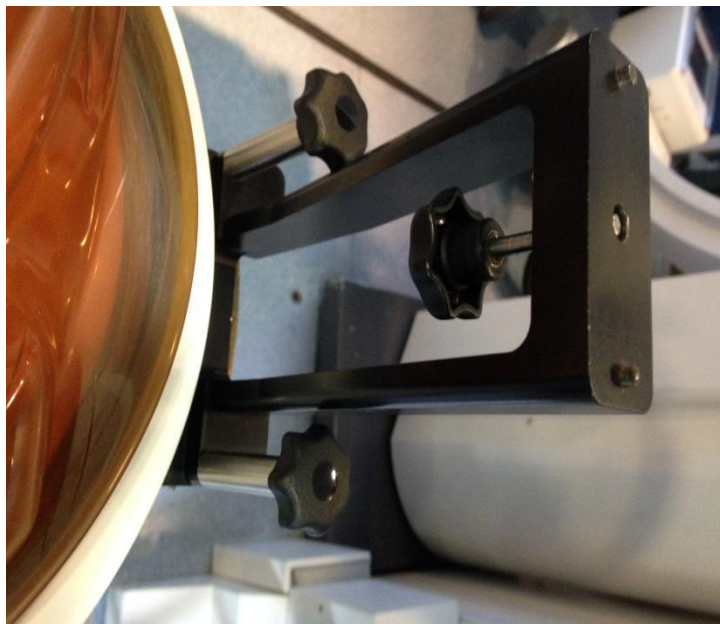| 17.8	80
18.9	90
20	100

Figure 5-1 Bolts to hold kidney apparatus in place

Figure 5-2 ESWL head with test kidney bolted to it

Balloon not inflated.

Figure 5-3 Testing apparatus being filled with heated water

Balloon now inflated to correct pressure.

Figure 5-4 Mesh basket ready to be screwed into place.

Wire basket containing mock kidney stone below the water level.

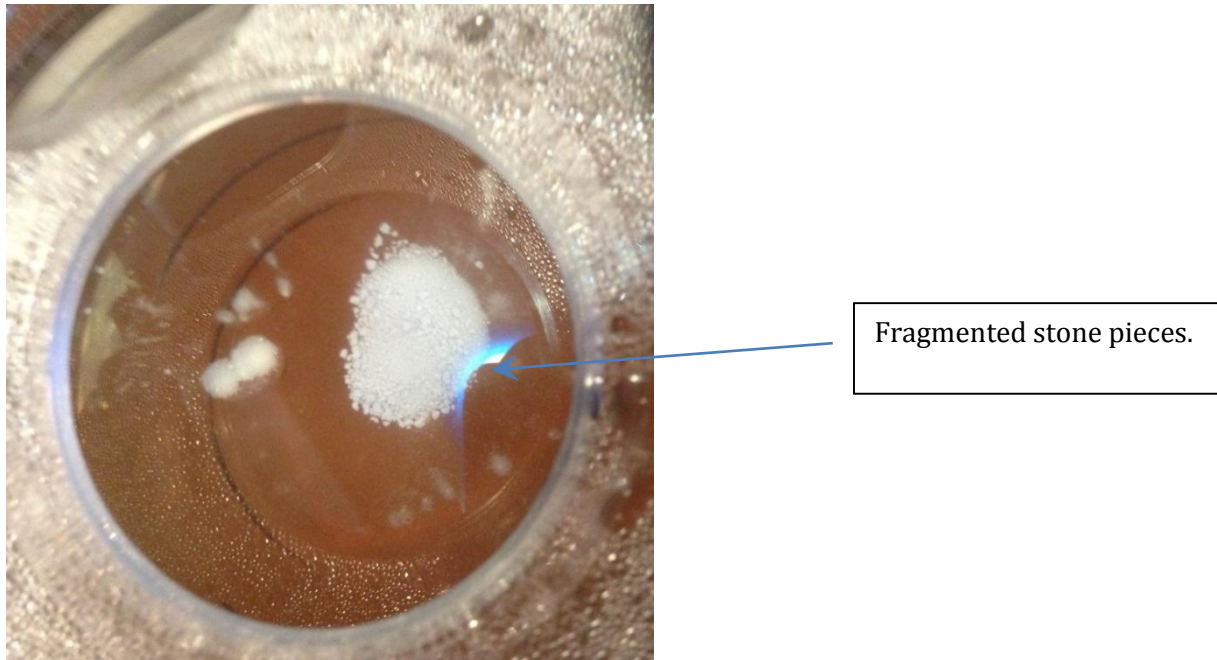Figure 5-5 Stone left soaking below the water level.

Figure 5-6 Remaining stone fragments at conclusion of one stone test.

5.1.2 Performance of model stone test for power ramping.

1. Set up procedure shown in 5.1, p.58.

2. Model Stone Test on p.58 followed.

3. Steps 1-7 as shown in rate and power tests followed.

4. Trigger mode set to 100 shocks per minute.

5. 65 stones treated in this manner to act as a control at power levels 40%, 50%, 60%, 70%, and 80%. See Table 5-1: Explanation of machine settings, p.62.

6. 65 stones treated in a power ramping technique.

    a. Power started at 40%

    b. 100 shocks given

    c. Power increased to 50% for 100 shocks

    d. Power increased in 10% increments for 100 shocks until power level 80%

    e. Shockwave continued at 80% power until complete stone fragmentation.

7. The number of SWs which were needed for the complete disintegration of the model stones was recorded.

5.1.3   Performance of model stone test for gas in the coupling medium.

1. Set up procedure shown in Section 5.1, p.58.
2. Model Stone Test on p.58 followed.
3. Steps 1-7 as shown in rate and power tests followed.
4. 72 model stones fragmented in this manner to act as a control.
5. 20 ml of air deliberately injected into coupling medium. See Figure 5-7: Injection of air into coupling gel, p.64. Figure 5-8: View from the top to show visible bubbles of air in gel, p.64 shows the apparatus sitting on top of the coupling gel with gas bubbles visible.[18]
6. 72 model test stones treated with air in the coupling medium.
7. The number of SWs which were needed for the complete disintegration of the model stones was recorded.

---

[18] It was observed that occasionally some of the gas migrated out of the gel leaving less than the injected 20ml in situ.
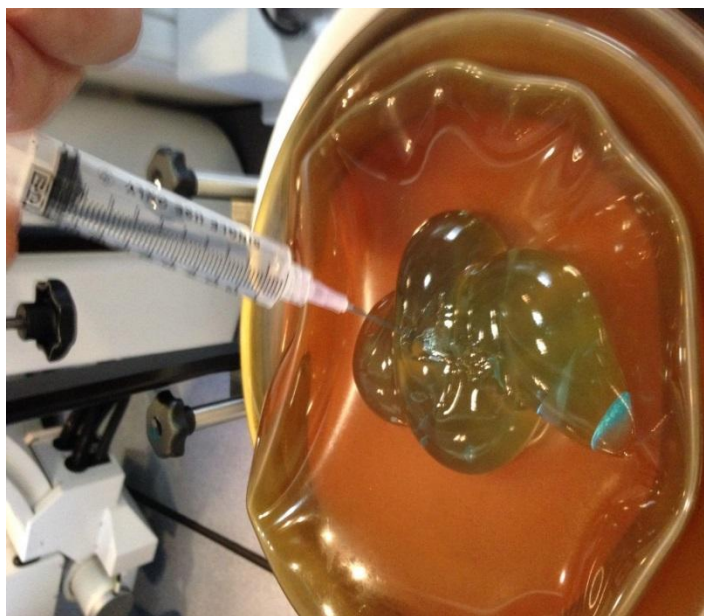
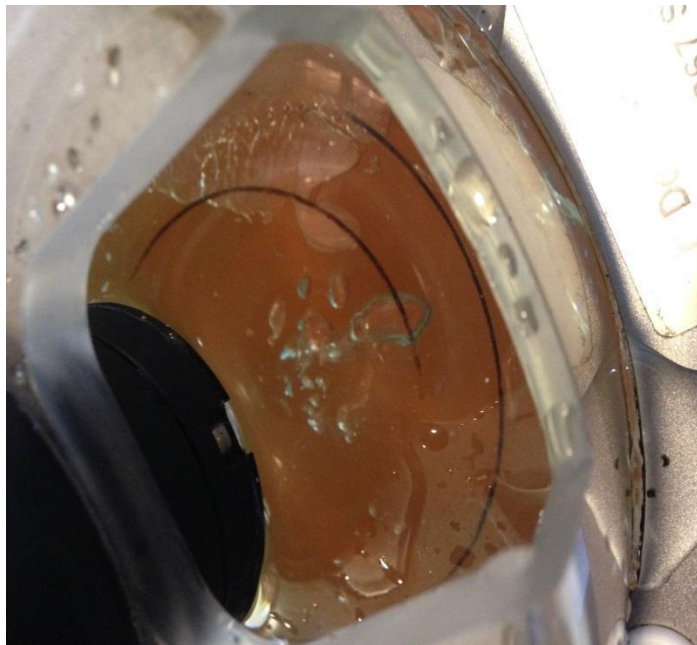Figure 5-7 Injection of air into coupling gel.

Figure 5-8 View from the top to show visible bubbles of air in gel.

As discussed, coupling gel is needed between the lithotripter head and the apparatus in order for the SW to pass from the lithotripter to the stone without an acoustic barrier. For all the studies, except for the studies where air was deliberately introduced, the coupling gel was visually inspected to ensure no air bubbles affected the procedure. Efficacy of ESWL is significantly correlated to air bubbles within the coupling gel and can be improved significantly by eliminating the bubbles from the coupling medium (Jain & Shah, 2007; Lopez et al., 2013).

As the entire experiment could not be completed in one session, a calibration plaster stone was fragmented at the beginning of each experimental session to ensure the ESWL machine had a consistent output.

The ideal case of a single spherical stone immersed in water was chosen for simplicity. We believe that our model is valid because the main objective of our study was to provide a comparison between the effects (rate, power, power ramping, and gas bubbles in the coupling medium) on stone fragmentation caused by conventional ESWL.

Revealing the association between the parameters of SW and their ability to fragment stones is the first step. The next step needs to include an investigation of the mechanism of the process.
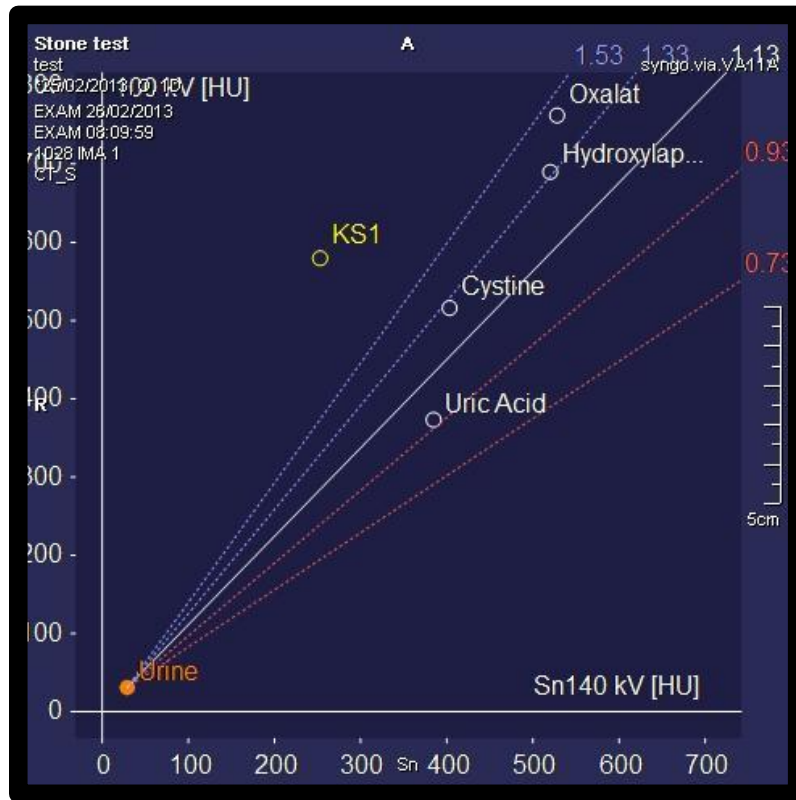
Figure 5-9 Analysis of mock stone.

5.1.4 Explanation of Figure 5-9 *Analysis of mock stone*

As mentioned before in this document (Classification of stones. Section 2.3, p.21), there are a large variety of kidney stones with very different mechanical properties requiring different powers to break up. This makes our test stone (KS1) the most suitable type of stone to focus our simulations on as it is slightly harder to break than the common forms of kidney stones.

Radiographic techniques are the main non-invasive method used to determine the composition of kidney stones. Dual Energy CT enhances regular CT as the stone graph plots the energy ratio of the stone against the known energy ratio of the different compounds.

The energy ratio (see numbers in the ROI box) is simply the Hounsfield Unit (HU) density of the stone at 100kV over the HU density of the stone at 140kV (There will always be slight differences between these two figures due to x-ray photon energy)

The white slope line (ratio) is the predetermined differentiation between calcified and uric acid stones based on a study performed on a large number of known composition stones.

This chapter has explained how the experiments were conducted and why this particular method was chosen. In the following chapter the results of the experiments are presented, which will show what modifiable factors can affect the efficiency and effectiveness of ESWL.

Chapter 6

Results

The aim of this thesis is to investigate the effectiveness and efficiency of stone fragmentation using ESWL.

Efficiency and effectiveness of extracorporeal shockwave lithotripsy are described on p.5. But for simplicity the effectiveness is described as the least number of shocks needed to cause stone fragmentation and the efficiency is the least amount of time needed until stone fragmentation.

The estimated marginal means of the shock numbers were analyzed as this gave us the mean response for each factor, adjusted for any other variables in the model. Estimated marginal means is a term used in the Statistical Package for the Social Sciences (SPSS) programme referring to un-weighted means. This is necessary when comparing means of unequal sample sizes, where it was necessary to take into consideration each mean in proportion to its sample size. The reason for the different sample size was that, prior to each set of stone tests, one calibration stone was fragmented at a fixed rate and power (rate: 100, power 80%). This was to ensure the shockwave produced by the generator was identical at the start of each test session. Therefore more mock stones were fragmented at these power and rate settings than any other. As these calibration tests were consistent and showed that for the same SW power and rate settings the lithotripter achieved very similar fragmentation rates, it was decided to include these results in the analysis as the additional tests would reduce the standard error of the mean (SME). When all the categorical predictors were manipulated, these factors remained independent. This is the only situation where the estimated marginal means will be the same as the straight means from descriptive statistics. Means were compared using a binomial logistic regression analysis that simultaneously tested the effects of the number of shocks administered at each shock rate on success.

Two sets of results are presented for the shock rate and power to show which modifiable machine settings can achieve the most effective and efficient urolith fragmentation. The results aim to show

which power level and rate should be used in clinical practice to achieve the most effective and efficient stone fragmentation differ slightly from one another. The first set (Results with no post hoc outliers removed, p.69) includes all test results completed. The second set (Results with outliers removed. p.73) excludes eight of the 138 test stones for rate and power as they appeared to be outliers. The eight stones excluded had a fragmentation shock result greater than 1000. The mean fragmentation shock number was 577.46 with a std. deviation of 248.71 as shown in Figure 6-1. The reasons for the outliers are discussed in Section 6.2 p.73.
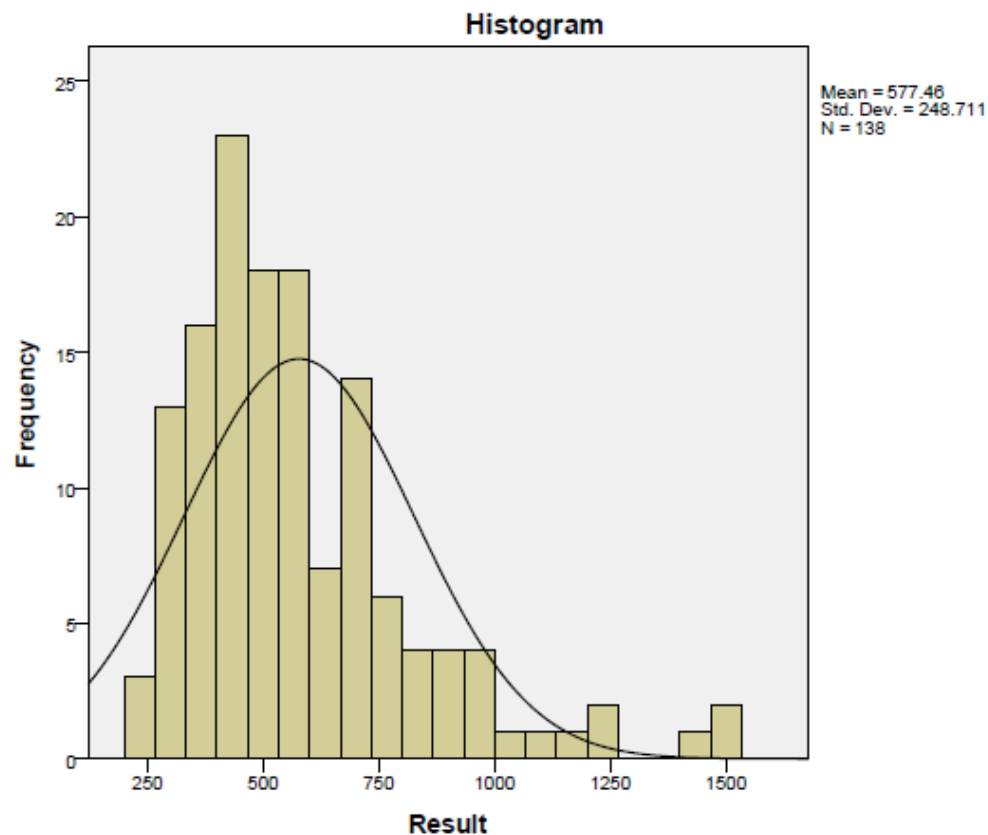
Figure 6-1 Histogram of all shock results completed for shock rate and shock power. Frequency refers to the number of times a test stone was fragmented at the rate shown. Result refers to the shock number when complete fragmentation was achieved.

6.1   Results with no post hoc outliers removed

Figure 6-2 shows the relationship between power and the total number of shocks. The rate is shown using different colours. In this analysis it can be seen that at a rates of 70, 80, and 90 SW/min, the power at which fragmentation occurs with the least number of shocks is 80% power,

84

which is not surprising in this model. There is not a statistically significant difference between these three rates. This is the most effective power and rate combination.
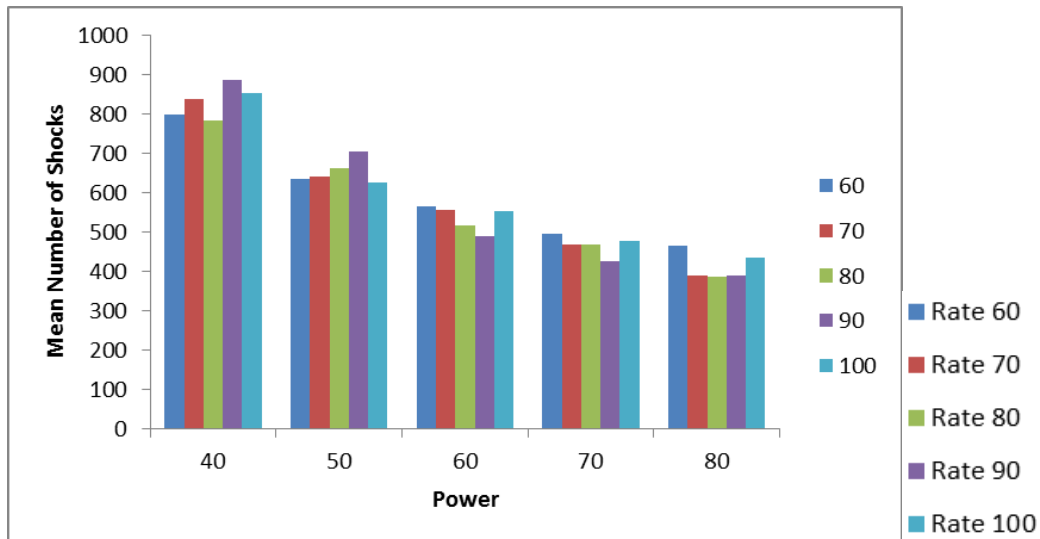
Figure 6-2 The relationship between power and rate and the total number of shocks needed to fragment the test stones.

As shown in Figure 6-3, Relationship between mean number of shocks needed to break the stone and rate, p.71 in this experiment model rate has less to do with stone fragmentation than power. Although a rate of 80 SW/min does fragment the renal stone with the greatest effectiveness, the result is not statistically significant.
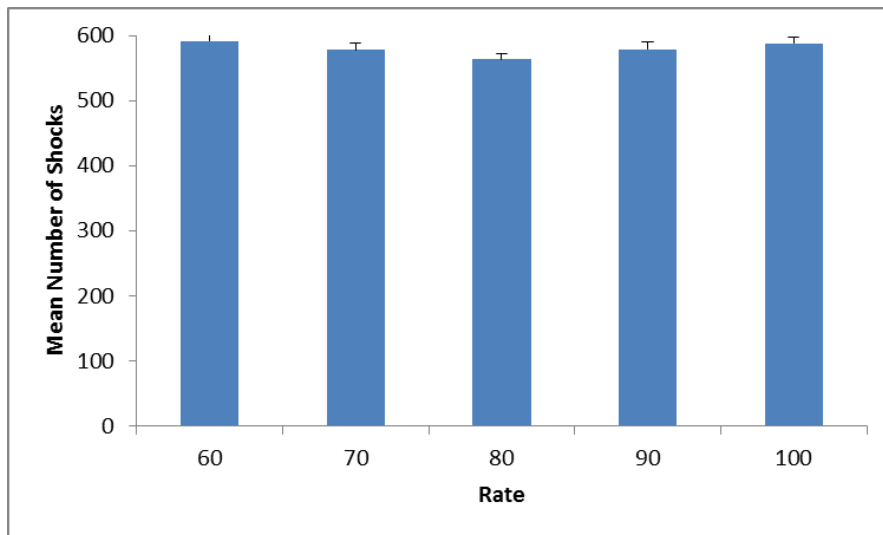
Figure 6-3 Relationship between mean number of shocks needed to break the stone and rate. These results are the mean result of all the test stones and therefore incorporate all power levels tested.

Figure 6-4 shows the relationship between the mean number of shocks required to fragment the mock stone and the power of the shocks. As can be seen the higher power settings require fewer SWs to fragment the stone. However the relationship is not linear with the decrease in mean number of shocks from 70% to 80% power being about a third of that seen for a decrease from 40% to 50%. This is shown in Figure 6-5 Negative exponential of mean number of shocks required for fragmentation and power, p.72.

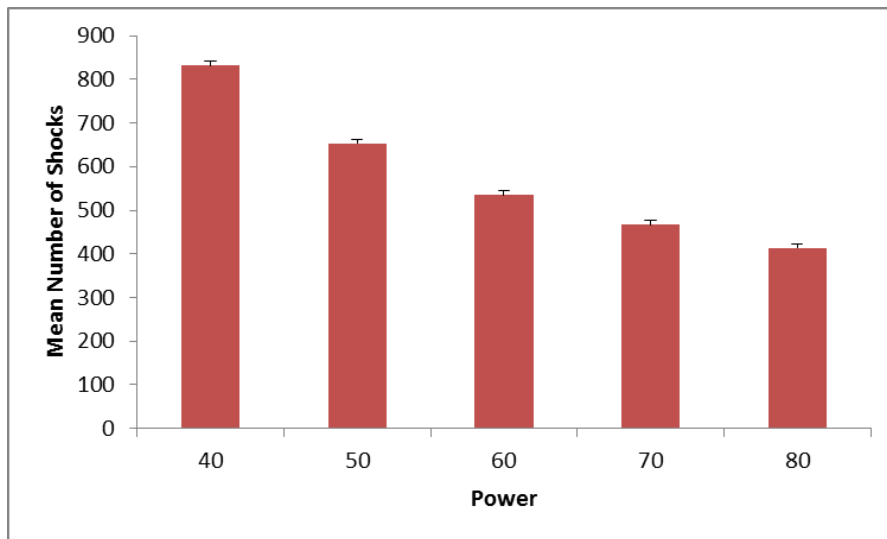Figure 6-4 The relationship between the mean number of shocks required to fragment the stone and the power of the shocks
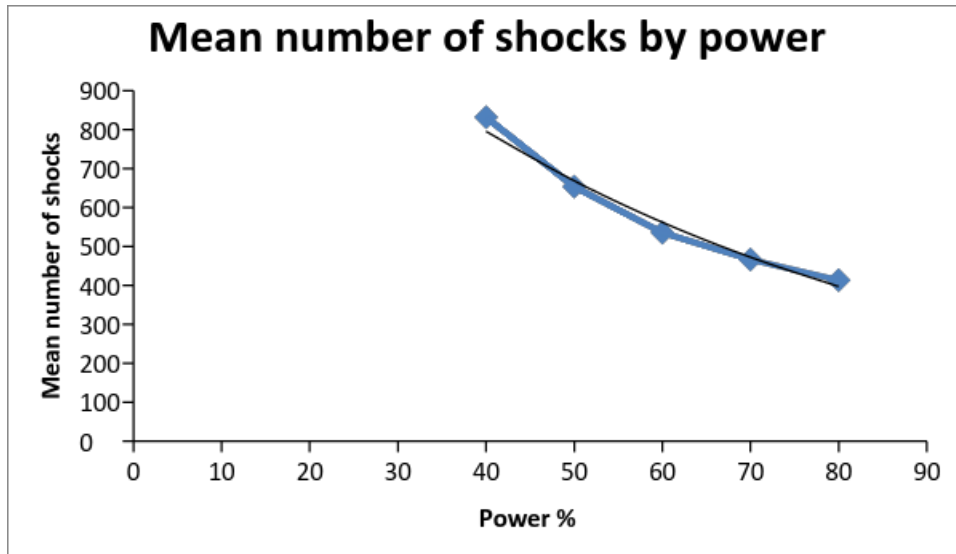

Figure 6-5 Negative exponential of mean number of shocks required for fragmentation and power

6.2   Results with outliers removed.

There are two reasons for presenting a second set of results. Firstly, initially this project was solely testing the modifiable factors of rate and power. During one or two experiments I noticed that the shock number was much greater than in previous tests with the same or similar machine settings. This is when I discovered the effect that gas in the coupling medium has on the efficacy of ESWL. This led to further tests being conducted on stone fragmentation with or without gas in the coupling medium, as described in Section 5.1.3, p. 63.

Furthermore, often during the experiments of shock rate and shock power the kinetic energy of the SW knocked the mock stone out of the direct line of the following waves. The stone would usually roll back to the correct position due to gravity. However occasionally it would remain in the new position for a few shocks and even more occasionally it would get stuck there for the duration of the treatment. As shockwaves act like other sound waves, the further the mock stone was away from the focal zone, the less power the stone would have received, see Inverse square law, p.74. Interestingly this can happen in the clinical situation (Steinholt, 2013) where it is estimated that up to 50% of SWs miss the target stone due to either stone movement from kinetic energy or respiratory motion. For this reason only the results below 1000 were used for the analysis. This excluded eight mock stones.

6.2.1 Inverse square law

A SW like other sound waves behaves in accordance with the inverse square law. This law states that the intensity, I, is related to the distance, r, from the source by the relation

$$I \propto \frac{1}{r^2}$$

S = shock wave source

$r = 3$ units
$r = 2$ units
$r = 1$ unit
S
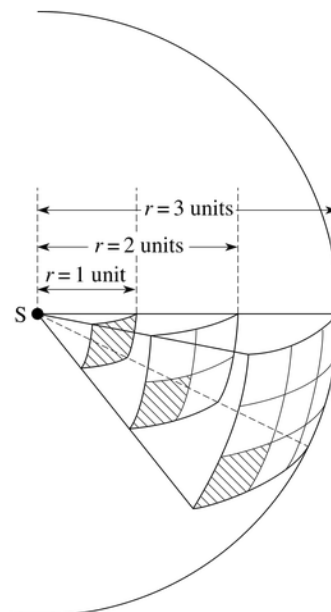
(The Open University, 1996 p.5.7)

Therefore if a stone was moved out of the correct position, all shockwaves thereafter would only be delivered with a decreased effectual power. This resulted in a far greater number of SWs needed for stone fragmentation.

The following graphs are for the test results excluding those eight which were affected by either the gas in the coupling gel or the inverse square law power issue.

As shown in Figure 5-6 the most effective power with which to fragment a mock stone using this model is again 80% power and there is no statistically significant difference between a SW rate of 70, 80, and 90.
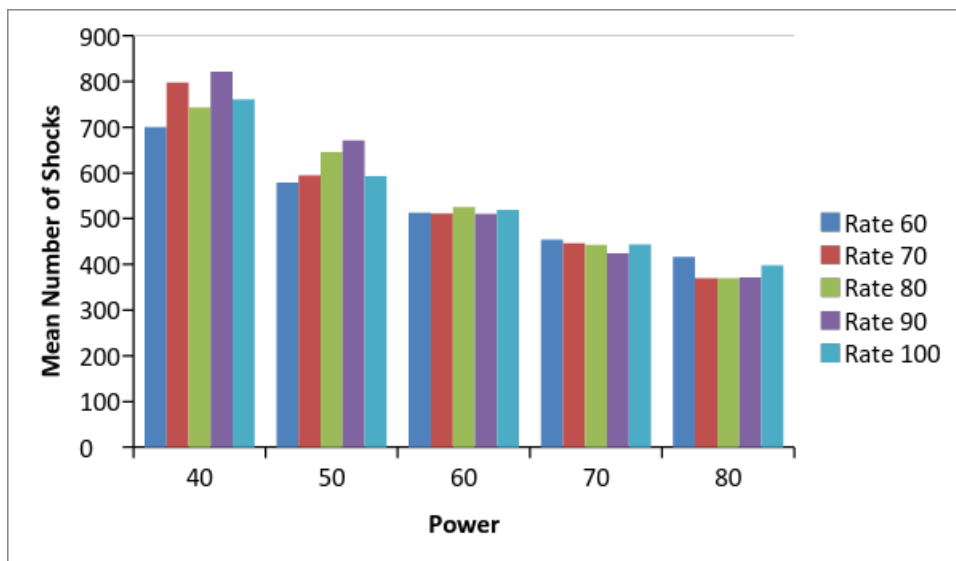
Figure 6-6 The relationship between power and rate and the total number of shocks needed to fragment the test stones.

Figure 6-7, p.76 shows that in this experimental design, rate has far less to do with stone fragmentation than shock power. I was expecting a greater difference between the 60 and 100 SW/min results as explained by the shock or compression phase and the rarefaction phase. See Figure 1-1 Time pressure graph of a shockwave (Rassweiler et al., 2011), p. 8. Each wave needs time to complete both the compression and rarefaction phase in order to provide ideal stone fragmentation. If the time is not sufficient to allow both phases of the wave to complete, the rarefaction of the second wave affects the compression of the first wave and so on. This effectively

reduces the amplitude or power of each SW. However as the most destructive part of the wave is the initial P+, the negative pressure of the wave (P-) may have a lesser role than thought, especially at higher powers. This adds weight to the theory of a P+ threshold developed by Rassweiler et al. (2011) discussed above in Studies regarding power on p.38.
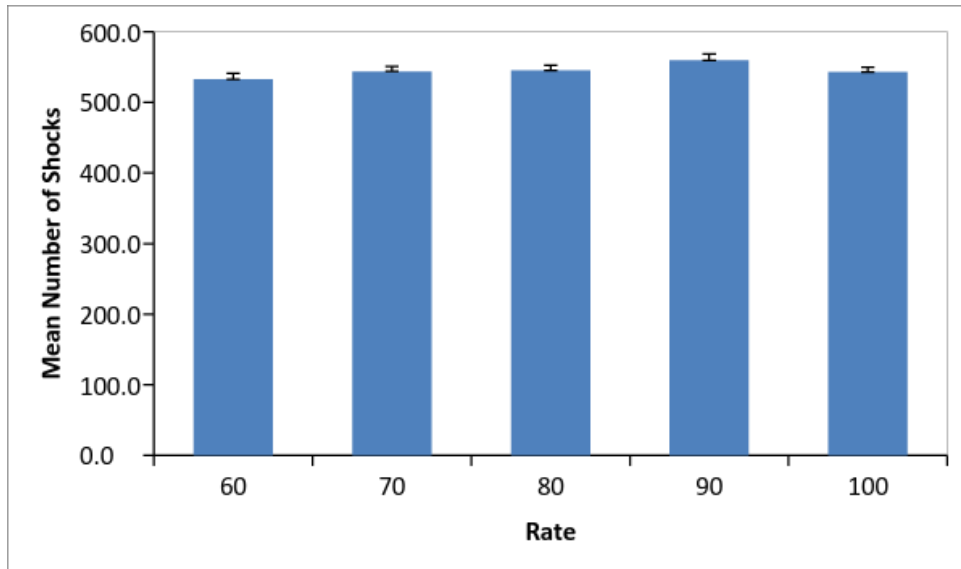
Figure 6-7 Relationship between the mean number of shocks needed to fragment the stones and rate.
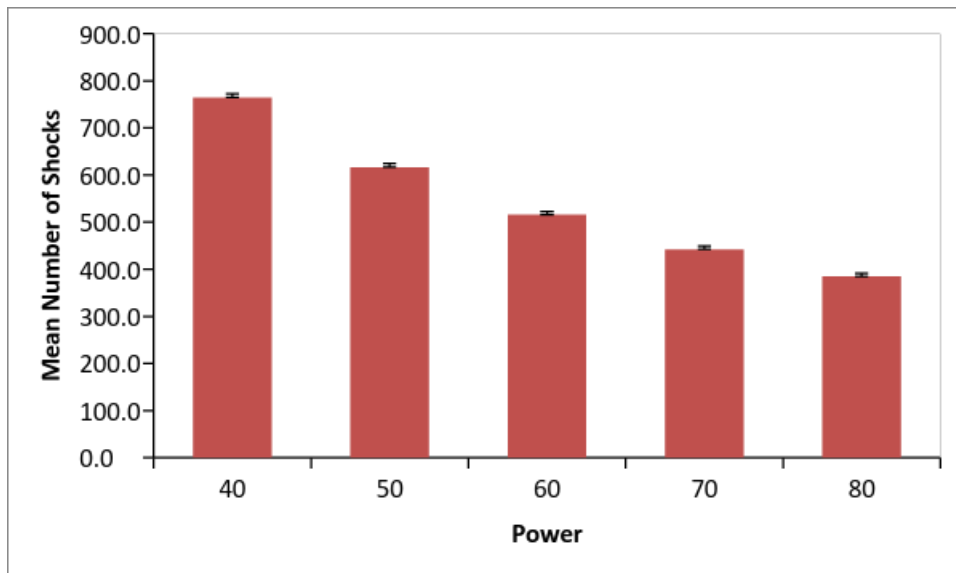
Figure 6-8 Mean number of shocks required to fragment the stone and power of the shocks

Again we can see that in this model, the higher power SWs fragment the mock stones more effectively and again the relationship is not linear. See Figure 6-9 Negative exponential graph, p.77 showing the relationship between power and mean number of shocks.
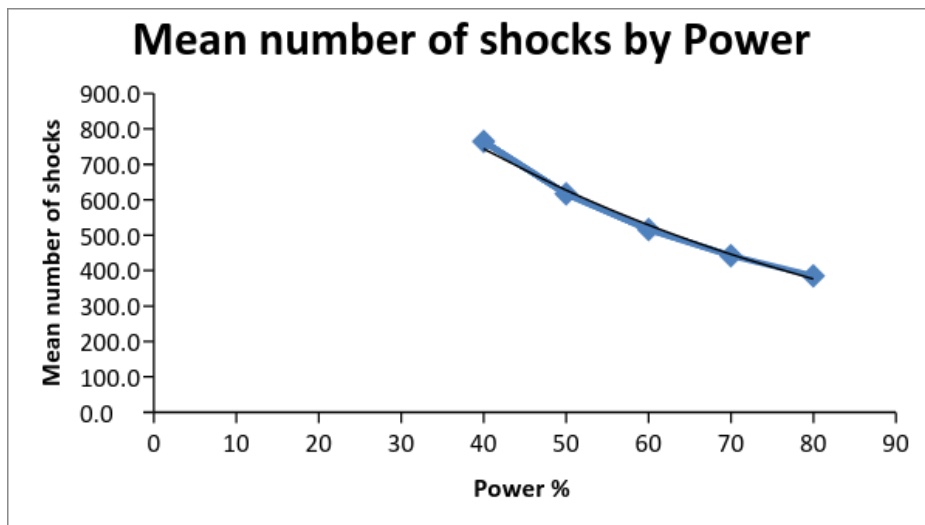

Figure 6-9 Negative exponential graph showing the relationship between power and mean number of shocks.

As can be seen in Figure 6-8, p.76 and Table 6-1 the mean number of shocks needed to fragment the stone does not decline in a linear manner, with the decrease from 70 to 80 being about 1/3 of that seen from 40-50, so there is a diminishing reduction with increasing power.

Table 6-1 Mean number of shocks needed to fragment the stone

Power	Mean	Change
40	764.7	
50	616.6	-148.063
60	515.9	-100.71
70	442.2	-73.722
80	385.1	-57.085

Figure 6.10 and Table 6-2, p.78 show the effect on the number of shocks required when a ramping technique was used. In these studies tests were completed at a fixed shock rate of 90 SW/min and 40, 50, 60, 70, and 80% power and then similar tests were completed using a fixed rate. In this instance, the power was started at a low level (10%) and every 100 shocks was increased by one machine unit (See Table 5-1 Explanation of machine settings, p.59) until either the stone fragmented or power level 80% was reached. As expected when using very low power (40%), the shocks needed for fragmentation were much greater (22%) than the power ramping tests. However, at the other power levels a fixed power level proved to be more effective than ramped power. This is likely as a result of the very low powers that the ramped experiments started at and the number of shocks used at these low powers. These figures must also be traded against the clinical evidence that shows a power ramping technique can help the patient tolerate the procedure (unless a general anaesthetic is used, in which case patient compliance is not an issue (Sorensen et al., 2002)) and also that protocol initiates renal protection certainly with regards to mean lesion size that can develop on the kidney during treatment. This reduction was greatest when treatment included a 3 minute pause or when using various power ramping protocols (Handa et al., 2012).
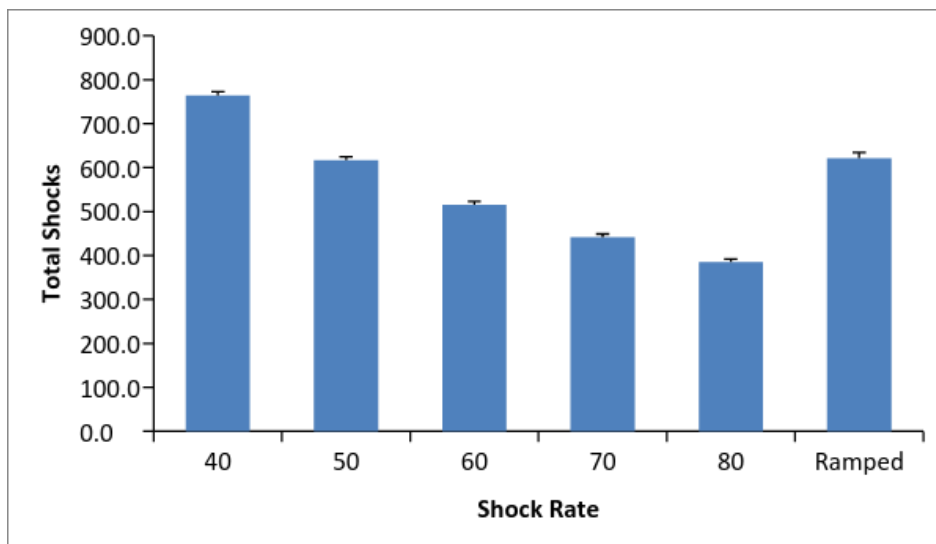
Figure 6-10 The effect on the number of shocks required when a ramping technique was used.

Table 6-2. The effect on the number of shocks required when a ramping technique was used.

Shocks

Power	Mean	Std. Error of Mean	% relative to Ramp
40	764.7	7.8	-23.12%
50	616.6	7.7	0.72%
60	515.9	6.8	16.93%
70	442.2	6.8	28.80%
80	385.1	6.8	37.99%
Ramped	621.1	13.1	0.00%

Figure 6-11 and Table 6-3 show that having a coupling medium free from gas results in a 22% reduction in the number of shocks needed to fragment the stone. In these experiments it was not possible to always have exactly the same amount of air in the coupling gel as some would occasionally bubble out of the gel; however the binary of gas or no gas provided a considerably different result. These results suggest that poor coupling in ESWL acts as a substantial barrier to the transmission of shockwave energy to the stone. As stone breakage was sensitive to air pockets at the coupling interface it seems reasonable that variability in the quality of coupling could contribute to variability in clinical outcomes (Pishchalnikov, Neucks, et al., 2006).
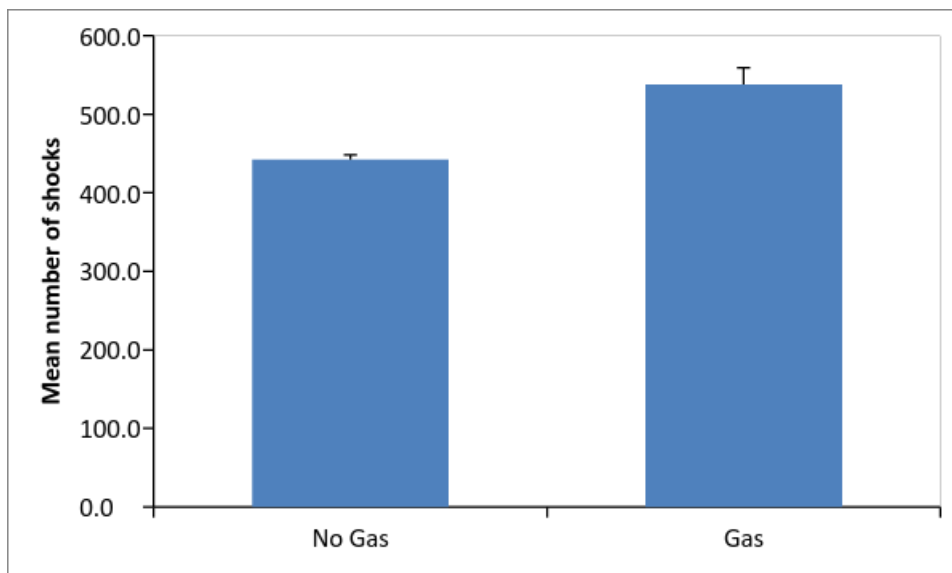
Figure 6-11 Difference in the number of shocks needed when the coupling medium (gel) has gas introduced.

Table 6-3 Difference in the number of shocks needed when the coupling medium (gel) has gas introduced.

Gas In Gel	Mean	Std. Error of Mean
No gas	442.2	6.2
Gas	537.7	21.2

Gas worse by 21.60%

As can be seen in Figure 6-12, when time is looked at by itself a rate of 90 and 100 SW/min and 80% power is the most efficient and Figure 6-13 displays a graph of the time taken to fragment the stone at different power levels. We can see here that as the power increases the time decreases although this is not a linear decrease.

When specifically looking at the efficiency of the SW, the following can be seen:
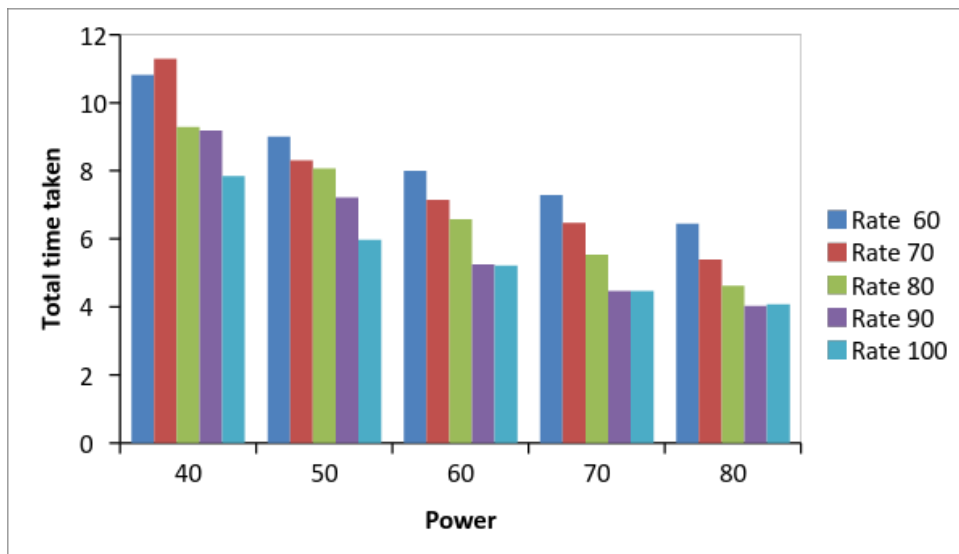
Figure 6-12 Time taken to fragment stone
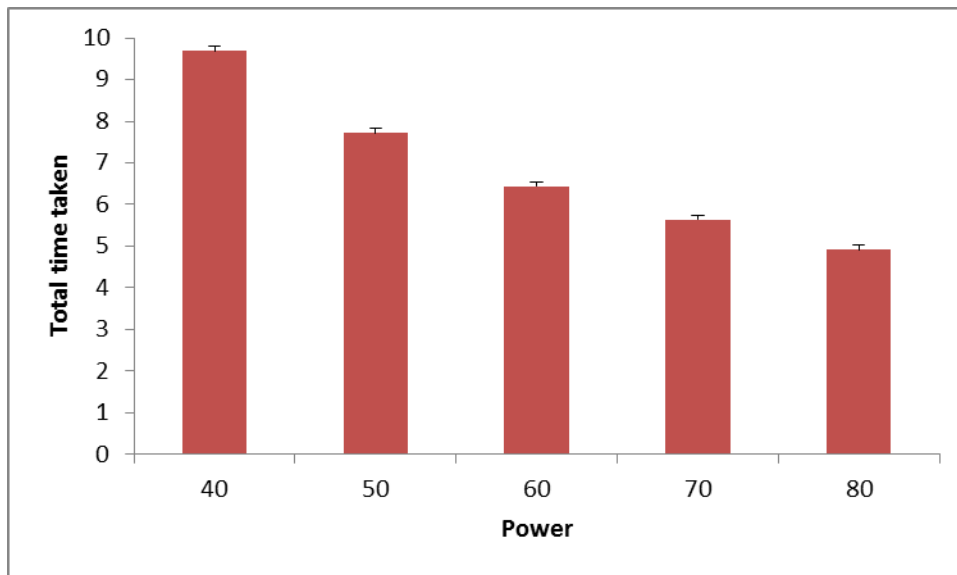
Figure 6-13 Time to fragment the stone in relation to power

Figure 6-14 shows that similar to effectiveness, the efficiency of ESWL improves with higher powers and similar again is the non-linear improvement in stone fragmentation with increasing power.
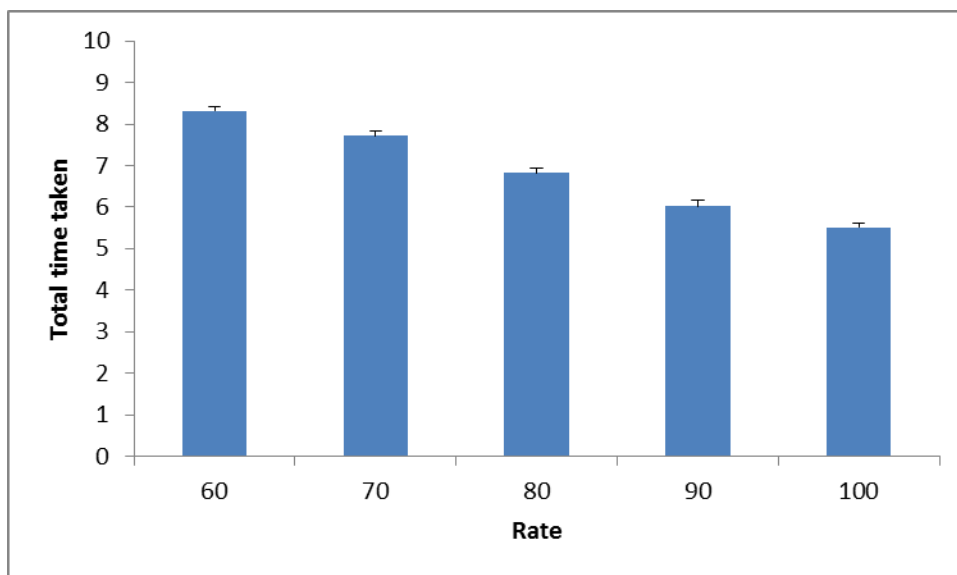
Figure 6-14 Time to fragment the stone and rate

Figure 6-7, p. 76 showed that a 60 SW/min was the most effective rate to fragment a mock stone although the result was not statistically significant. Figure 6-14 shows that despite a rate of 60SW/min having a greater effectiveness, a rate of 100 SW/min has a greater efficiency.

Chapter 7

Discussion

Over the last thirty years various technical improvements in shock wave lithotripsy have been introduced by different lithotripter manufacturers. However the overall performance of modern shock wave lithotripters has not reached the standard that was set by the original Dornier HM3 (Gerber, Studer, & Danuser, 2005; Lingeman, Kim, Kuo, McAteer, & Evan, 2003). The fact remains that the technical improvements made have led to providing greater user convenience and device multi-functionality rather than greater stone fragmentation and less tissue injury in ESWL (Lingeman et al., 2003). Therefore, the need for a better understanding of the technical factors that can be controlled is clearly warranted in order to use these second and third generation lithotripters.

Research in recent years suggests that stone fragmentation by ESWL is multifaceted and a progressive procedure. A number of forces are at play including stress waves, cavitation and squeezing (Zhong, Zhou, Zhu, Cocks, & Preminger, 2003; Zhu, Cocks, Preminger, & Zhong, 2002). The experimental design described in this thesis considers all of these factors but cannot, due to its in vitro method, assess the effect on tissue injury. Zhu et al. (2002) propose two mechanisms that may be responsible for ESWL-induced surrounding tissue injury, namely shear stress (Howard & Sturtevant, 1997) and, more importantly, intraluminal cavitation (Zhu et al., 2002). Therefore, a rational strategy to improve ESWL technology should be the optimization of these critical factors (stress waves and cavitation) for maximal fragmentation gain with minimal side effects. Encouragingly, laboratory studies show that tissue damage, such as cavitation, which can form from bubbles within the blood, does not readily occur within patent vessels, otherwise ESWL would cause vascular damage frequently. The mechanisms of action involved in the effect of shockwave rate are different for stone fragmentation and tissue injury. With stone fragmentation, cavitation

bubbles collapse on the stone surface and erode fragments that are too small to be affected by internal shear stresses (Lingeman et al., 2009).

There are many ways to improve the stone fragmentation results with ESWL. The modifiable technical factors discussed here can facilitate a greater success rate when attention is paid to the methods that have been shown to work well. There is no evidence that slowing the shock rate improves the effectiveness of the stone fragmentation. There is strong evidence that increasing the power of the shockwave increases the fragmentation effectiveness and efficiency, however the benefits to a power ramping technique are less clear in vitro. Measures to ensure adequate and bubble free coupling, including at a minimum visual inspection before the ESWL treatment is started and following any movement by the patient should be used as there is strong evidence to show that having gas in the coupling medium reduces the effectiveness of the shockwave.

7.1 Rate

As shown in Figure 6-7, p.76, a rate of 60 SW/min enhances fragmentation effectiveness at all power levels used, but the result is not statistically significant. However from observational evidence, the stone fragments appeared smaller and more dust-like at lower rates (60SW/min and 70SW/min) than the larger sand-like particles produced at the faster rates (90Sw/min and 100Sw/min). This is likely to lead to enhanced clearance as the smaller fragments can pass more easily in the urine. This is consistent with the literature. However Figure 6-14, p.81 shows us that a faster rate (100SW/min) can lead to a faster treatment. As discussed in Section 1.2.

7.2 Power

The higher power levels allow more effective and efficient fragmentation. However as also shown the increase in efficiency and effectiveness does not increase in a linear fashion with increasing ESWL power. Therefore a power setting of 70% is recommended as international literature recommends power levels to be as low as reasonably achievable to prevent tissue damage. 70% is an appropriate level due to the fragmentation achieved at this level and the lower increases in fragmentation achieved by increasing the power.

7.3   Coupling

Air pockets within the coupling gel dramatically decrease stone fragmentation effectiveness by 22%. See Figure 6-11 Difference in the number of shocks needed when the coupling medium (gel) has gas introduced, p.79. The experiments in this project used 20ml of air injected into the coupling gel. In some experiments, some of this gas would bubble out leaving me unsure of how much remained. For this reason the studies with gas have a higher std. error than those without gas. However of the two categories it was clear that any extra gas in the coupling gel resulted in a significantly greater number of shocks needed to fragment the stone. Of all the modifiable factors investigated, the gas in the coupling gel has proven to be the most important. This makes sense when the graph for the intensity transmission coefficient for an acoustic wave traveling from water to another medium with different impedance is viewed, see Figure 7-1 The intensity transmission coefficient from water to a second medium, as a second of the impedance of the second medium (Smith, 2007), p.84. As shown the transmission from water to tissue (as would occur when the shockwave leaves the therapy head) is very efficient, the water to stone transmission is also very efficient with between 75% and 95% of the energy transmitted into the kidney stones. However the water to air transmission has an extremely small coefficient and less than 0.1% of the energy of a shockwave in water will pass into air. This further establishes the need for great care when using a dry lithotripter to ensure that air pockets are removed in the coupling gel.
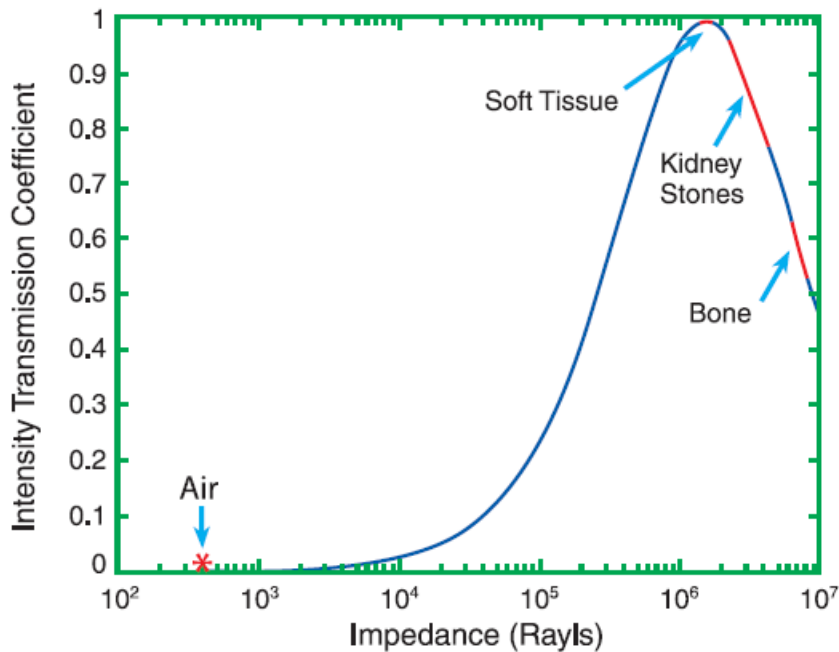
Figure 7-1 The intensity transmission coefficient from water to a second medium, as a second of the impedance of the second medium (Smith, 2007)

7.4 Ramping

Using an in vitro system that mimicked stone fragmentation Zhou, Cocks, Preminger, & Zhong, (2004a) exposed mock kidney stones to 1500 shocks at a shock rate of 60 per minute. They concluded that to progressively ramp the lithotripter power produced the best overall stone fragmentation. This is discordant to my own results, see Figure 6-11 Difference in the number of shocks needed when the coupling medium (gel) has gas introduced, p.79. One reason is likely to be the extended number of overall shocks they applied to the stones. In my experiments many hundred shocks were administered at very low power levels before the ramping technique brought the power to a level where treatment might be given clinically. As I used, on average, a third of the number of shocks that Zhou et al. (2004a) used, it is likely that they had more shocks delivered at the higher powers and therefore achieved greater fragmentation. The clinical need for power ramping is discussed by (Maloney et al., 2006) and is beyond the scope of this thesis.

The final conclusions are presented in Conclusion and Implications of Research on p.88. Recommendations are given from the results above.

7.5 Advantages of this study

Randomised controlled trials are often presumed to serve as the reference standard to assess medical procedures. However, in the early stages of investigation, in vitro studies play an extremely useful role. There are benefits in terms of reduced costs, reduced ethical considerations, and a more straightforward ability to assess the dependent variables.

With regard to ethical considerations, there is a universal belief that no unnecessary human testing should be undertaken (Niazi, 2014). This experimental design has produced guidelines which can be used in clinical practice or tested further, perhaps in the form of an RCT. However as some shock rates and powers have been eliminated, the amount of human testing has been reduced.

Furthermore, having identical test stones of known size and composition reduced the variables tested. There were no confounding factors in our study such as age, gender, or stone composition. The internal validity, as shown in the similar results for each test level, was high. The same ESWL machine was used for all test stones and only one person completed all the testing. Therefore the reliability was excellent.

Our in vitro model kidney is limited by an artificial environment: in contrast the kidneys in vivo are surrounded by fat and tissue, but shockwaves are known to pass through these tissues nearly unchanged, see Figure 7-1, and the focal zone area is the area of highest energy density.

7.6 Limitations of this study

7.6.1 Stone microstructure

The kidney stone in this model is a sphere of 10mm radius. Although it is known that renal stones have a shell-like microstructure (i.e. the microstructure consists of concentric thin layers with different mechanical properties), for the present study the stone is assumed to be homogeneous and amorphous. The present work has simplified the microstructure of the stone to a homogeneous

material. As mentioned above, uroliths have a shell-like microstructure. The existence of such a microstructure which contains components/material properties would introduce internal reflection points to the tensile/compression stress waves. In addition to these effects, particles within the stone with different stiffness's would help the crack initiation into the urolith. While failure would occur at an earlier time, it is not clear to assess if material heterogeneity would reduce or increase the energy absorption capacity of the stone. To this end, the model could be improved by incorporating a microstructural shell to the stone.

7.6.2 Stone shape

In the presented work KS1 stones are modelled as spherical particles. However, genuine renal stones will exhibit different random external shapes which may have some influence on the results. In particular, an irregular stone shape might lead to a different initiation and saturation limit values although it would not preclude the existence of both limits.

7.6.3 Stone size

The present study has considered a fixed stone size, i.e. 10mm, and therefore the values of the presented energy levels and shock rates are directly related to this stone size. Although proposing a universal scaling law representing the absorbed energy as a function of stone size would be of great interest, it was left out of this thesis because some factors complicate the scaling behaviour.

7.6.4 Lithotripter used

There are numerous commercial lithotripters available, manufacturers include: Dornier®, Wolf Piezolith®, Siemens Lithostar®, Technomed Sonolith®, XiXin XX-ES® (Köhrmann & Rassweiler, 2011). All of these tests were run on a Dornier Doli II® which has an electromagnetic generator and a focal zone of 12mm^2. For lithotripters with a different focal zone areas or different style of generator, further research is advised.

Chapter 8

Conclusion and Implications of Research

This study identifies areas for education to improve efficient stone fragmentation guidelines. Effective communication of the most up-to-date evidence and current recommendations for ESWL will be important in assuring that optimal treatment patterns are followed. The results shown in this in vitro study will lead to further research where clinical results can be analysed using the guidelines developed here. A major goal of future ESWL research would continue to be optimisation of ESWL treatment protocols to achieve superior stone comminution but also include minimal tissue injury. This must be closely linked with a cost effectiveness analysis; however, it must be remembered that economic analyses don't always include costs outside the health sector. If poor delivery of the ESWL treatment necessitates a patient undertaking many additional sessions, this would increase the costs [19] to the individual and their family. If a health system perspective is taken in the economic sense these costs will not be looked at, however if a societal perspective is taken then they should be included. It must also be stressed that any pressure to increase efficiency in the ESWL setting may lead hospitals to lower effectiveness and therefore an ultimately lower efficiency. This must be looked at with more than an econometric model; however this extension is left for future research.

8.1   Advance in knowledge

ESWL is the only non-invasive means to treat uroliths, which makes this technique particularly valuable. The severity of the negative effects of ESWL, such as soft tissue injury depends on multiple factors and it typically takes thousands of SWs to treat a urolith. Due to the immediate success and apparent ease of applying this treatment little has been done to define the limits of ESWL. Patients may therefore be receiving more SWs than necessary to remove their stones. Simultaneous and

---

[19] Costs include pain and suffering, time off work, and transport etc.

dedicated application of the ideal ESWL modifiable factors results in a more effective efficient fragmentation of the renal stone which is likely to cause less injury and improve stone fragmentation.

This study has shown the following protocol should be adopted in clinical practice if the desired result is a more efficient urolith fragmentation. These modifications are easily adopted by the operator of the ESWL unit and, if followed, are likely to result in more efficient urolith fragmentation.

- The most effective shockwave rates are 70 - 90 shocks per minute. However the most efficient rate is 100 SW/min so, taking both results into consideration, a rate of 90 SW/min is recommended.
- The most effective and efficient power is 80% power. However from the literature it can be seen that the higher power shockwaves can cause clinical problems and as shown in Section 6.2 p.73, shock power does not increase stone fragmentation in a linear way. Therefore the lower of the most advantageous shock rates is advised, 70%.
- Gas free acoustic coupling between the water cushion of the treatment head and the patient's skin is paramount. This is crucial for effective shock wave transportation.
- Maintain careful imaging monitoring during the procedure. If the urolith moves from the target zone, the treatment should be stopped and re focussed. Movement can occur through stone movement and/or patient movement.

8.2   Implications for patient care

Improving the renal stone fragmentation and lowering the number and duration of further treatments or adjunct therapies reduces patient morbidity.

References

Abate, Nicola, Chandalia, Manisha, Cabo-Chan, Alberto V, Moe, Orson W, & Sakhaee, Khashayar. (2004). The metabolic syndrome and uric acid nephrolithiasis: novel features of renal manifestation of insulin resistance. *Kidney International, 65*(2), 386-392.

Agarwal, Ketan, & Agrawal, Madhu S. (2014). Place of percutaneous nephrolithotripsy (PCNL) in the management of renal calculi. *Sri Lanka Journal of Surgery, 31*(3), 41-47.

Akman, Tolga, Binbay, Murat, Ozgor, Faruk, Ugurlu, Mesut, Tekinarslan, Erdem, Kezer, Cem, . . . Muslumanoglu, Ahmet Yaser. (2012). Comparison of percutaneous nephrolithotomy and retrograde flexible nephrolithotripsy for the management of 2–4 cm stones: a matched-pair analysis. *British Journal of Urology International, 109*(9), 1384-1389.

Albino, G, & Marucco, EC. (2012). Comparison of ESWL outcome between Wolf Piezolith 3000 vs. storz Modulith Slk. it is the man who makes efficient the machine. *Archivio italiano di urologia, andrologia: organo ufficiale [di] Societa italiana di ecografia urologica e nefrologica/Associazione ricerche in urologia, 84*(4), 268-271.

Alder, Henry C. (1987). ESWL Management Issues. *Principles of Extracorporeal Shock Wave Lithotripsy*, 225.

American Urological Association University. (2014). Advancing Urology Retrieved 6th April, 2015, from https://www.auanet.org/education/aua-guidelines.cfm

Ando, Ryosuke, Nagaya, Teruo, Suzuki, Sadao, Takahashi, Hidekatsu, Kawai, Makoto, Okada, Atsushi, . . . Kohri, Kenjiro. (2013). Kidney Stone Formation is Positively Associated with Conventional Risk Factors for Coronary Heart Disease in Japanese Men. *The Journal of Urology, 189*(4), 1340-1346. doi: http://dx.doi.org/10.1016/j.juro.2012.11.045

Argyropoulos, Athanasios N., & Tolley, David A. (2007). Optimizing Shock Wave Lithotripsy in the 21st Century. *European Urology, 52*(2), 344-354. doi: http://dx.doi.org/10.1016/j.eururo.2007.04.066

Aronne, Louis J., Braham, Robert L., Riehle Jr, Robert, Darracott Vaughan Jr, E., & Ruchlin, Hirsch S. (1988). Cost-effectiveness of extracorporeal shock-wave lithotripsy. *Urology, 31*(3), 225-230. doi: http://dx.doi.org/10.1016/0090-4295(88)90146-X

Auge, Brian K, & Preminger, Glenn M. (2002). Update on shock wave lithotripsy technology. *Current Opinion in Urology, 12*(4), 287-290.

Bach, Christian, Karaolides, Theocharis, & Buchholz, Noor. (2012). Extracorporeal shock wave lithotripsy: What is new? *Arab Journal of Urology, 10*(3), 289-295.

Bader, Markus J., Eisner, Brian, Porpiglia, Francesco, Preminger, Glen M., & Tiselius, Hans-Goran. (2012). Contemporary Management of Ureteral Stones. *European Urology, 61*(4), 764-772. doi: http://dx.doi.org/10.1016/j.eururo.2012.01.009

Becker, Armin, Stief, Christian, Truss, Michael, Oelke, Matthias, Machtens, Stefan, & Jonas, Udo. (1999). Petroleum jelly is an ideal contact medium for pain reduction and successful treatment with extracorporeal shock wave lithotripsy. *The Journal of Urology, 162*(1), 18-22.

Bergsdorf, T, Thueroff, S, & Chaussy, C. (2004). 265 ESWL induced ventricular arrhythmia, in fact an "exogenous parasystoly". *European Urology Supplements, 3*(2), 69-69.

Berwin, James Theo, El-Husseiny, Tamer, Papatsoris, AG, Hajdinjak, Tine, Masood, Junaid, & Buchholz, Noor. (2009). Pain in extracorporeal shock wave lithotripsy. *Urological Research, 37*(2), 51-53.

Bhojani, Naeem, & Lingeman, James E. (2013). Shockwave Lithotripsy–New Concepts and Optimizing Treatment Parameters. *Urologic Clinics of North America, 40*(1), 59-66.

Blaschko, Sarah D, Chi, Thomas, Miller, Joe, Fakra, Sirine, & Stoller, Marshall L. (2013). Micro Architecture of Randall Plaques Using Advanced Imaging Techniques. *The Journal of Urology, 189*(4), e849-e850.

Bohris, Christian, Roosen, Alexander, Dickmann, Martin, Hocaoglu, Yasmin, Sandner, Stefan, Bader, Markus, . . . Walther, Sebastian. (2012). Monitoring the coupling of the lithotripter therapy head with skin during routine shock wave lithotripsy with a surveillance camera. *The Journal of Urology, 187*(1), 157-163.

Bonett, Art, & Pafitis, Demos. (1996). Getting to the root of gas migration. *Oilfield Review, 8*(1), 36-49.

Bowsher, W.G, Carter, S, & Philip, T. (1989). Clinical experience using the Wolf device at two British stone centers. *Journal of Urology, 142*, 679.

Brent, Robert J. (2004). *Cost-benefit analysis and health care evaluations*: Edward Elgar Publishing.

Caballero, Antonio, & Molinari, Jean-Francois. (2011). Optimum energy on the fragmentation of kidney stones by direct impact. *Engineering Computations, 28*(6), 747-764.

Cakıroglu, Basri, Sinanoglu, Orhun, & Uraz, Mahmure. (2013). The Effect of Tamsulosin on Pain and Clearance According to Ureteral Stone Location After Shock Wave Lithotripsy. *Current Therapeutic Research, 74*, 33-35.

Canseco, Guillermo, de Icaza-Herrera, Miguel, Fernández, Francisco, & Loske, Achim M. (2011). Modified shock waves for extracorporeal shock wave lithotripsy: A simulation based on the Gilmore formulation. *Ultrasonics, 51*(7), 803-810.

Cartledge, JJ, Cross, WR, Lloyd, SN, & Joyce, AD. (2001). The efficacy of a range of contact media as coupling agents in extracorporeal shockwave lithotripsy. *British Journal of Urology International, 88*(4), 321-324.

Cass, AS. (1991). Equivalence of mobile and fixed lithotriptors for upper tract stones. *Journal of Urology, 146*, 290-293.

Cass, AS. (1995). Comparison of first generation (HM3) and second generation (Medstone STS) lithotriptors: treatment results with 13684 renal and ureteral calculi *Journal of Urology, 153*, 588-592.

Centers for Disease Control and Prevention. (2014). HIV Cost-effectiveness Retrieved 10/3/15, 2015, from http://www.cdc.gov/hiv/prevention/ongoing/costeffectiveness/

Chacko, Job, Moore, Michael, Sankey, Noel, & Chandhoke, Paramjit S. (2006). Does a Slower Treatment Rate Impact the Efficacy of Extracorporeal Shock Wave Lithotripsy for Solitary Kidney or Ureteral Stones? *The Journal of Urology, 175*(4), 1370-1374. doi: http://dx.doi.org/10.1016/S0022-5347(05)00683-X

Chae, Ji Yun, Kim, Jong Wook, Kim, Jin Wook, Yoon, Cheol Yong, Park, Hong Seok, Moon, Du Geon, & Oh, Mi Mi. (2013). Increased fluid intake and adequate dietary modification may be enough for the successful treatment of uric acid stone. *Urolithiasis, 41*(2), 179-182.

Chang, Chien-Chen, Liang, SM, Pu, YR, Chen, CH, Chen, I, Chen, TS, . . . Chu, ZF. (2001). In vitro study of ultrasound based real-time tracking of renal stones for shock wave lithotripsy: part 1. *The Journal of Urology, 166*(1), 28-32.

Chaussy, C, Brendel, W, & Schmiedt, E. (1980). Extracorporeally induced destruction destruction of kidney stones by shock waves. *Lancet, 2*, 1265-1268.

Chaussy, C, & Schmiedt, E. (1983). Shockwave treatment for stones in the upper urinary tract. *Urological Clinics of North America, 10*, 743-750.

Chen, Yung-Tai. (2012). Urolithiasis update: Evaluation and management. *Urological Science, 23*(1), 5-8. doi: http://dx.doi.org/10.1016/j.urols.2011.12.002

Chutipongtanate, Somchai, & Thongboonkerd, Visith. (2011). Ceftriaxone crystallization and its potential role in kidney stone formation. *Biochemical and Biophysical Research Communications, 406*(3), 396-402. doi: http://dx.doi.org/10.1016/j.bbrc.2011.02.053

Clayman, R, McClenn, B, Garvin, T, Densted, J, & Andriole, G. (2009). Lithostar: An Electromagnetic Acoustic Shock Wave Unit for Extracorporeal Lithotripsy *Journal of Endourology, 3*(3), 307-313.

Cleveland, Robin O, & Sapozhnikov, Oleg A. (2005). Modeling elastic wave propagation in kidney stones with application to shock wave lithotripsy. *The Journal of the Acoustical Society of America, 118*, 2667.

Cochrane, AL. (1972). Effectiveness and efficiency: Random reflections on health services. *London: Nuffield Provincial Hospitals Trust.*

Coe, Fredric L, Evan, Andrew P, Worcester, Elaine M, & Lingeman, James E. (2010). Three pathways for human kidney stone formation. *Urological Research, 38*(3), 147-160.

Coe, Fredric L, Parks, Joan H, & Asplin, John R. (1992). The pathogenesis and treatment of kidney stones. *New England Journal of Medicine, 327*(16), 1141-1152.

Coe, Fredric L., Evan, Andrew, & Worcester, Elaine. (2005). Kidney stone disease. *The Journal of Clinical Investigation, 115*(10), 2598-2608. doi: 10.1172/jci26662

Coleman, Andrew J, Saunders, John E, Crum, Lawrence A, & Dyson, Mary. (1987). Acoustic cavitation generated by an extracorporeal shockwave lithotripter. *Ultrasound in Medicine & Biology, 13*(2), 69-76.

Connors, Bret A, Evan, Andrew P, Willis, Lynn R, Blomgren, Philip M, Lingeman, James E, & Fineberg, Naomi S. (2000). The effect of discharge voltage on renal injury and impairment caused by lithotripsy in the pig. *Journal of the American Society of Nephrology, 11*(2), 310-318.

Connors, Bret A, McAteer, James A, Evan, Andrew P, Blomgren, Philip M, Handa, Rajash K, Johnson, Cynthia D, . . . Lingeman, James E. (2012). Evaluation of shock wave lithotripsy injury in the pig using a narrow focal zone lithotriptor. *British Journal of Urology International, 110*(9), 1376-1385.

Cope, RM, Middleton, RG, & Smith, JA. (1991). A 2-year experience with the Wolf piezoelectric lithotripter: impact of repeat treatment on results and complications. *Journal of Urology, 145*, 1141-1144.

Cortes, Janice A Santos, Motamedinia, Piruz, & Gupta, Mantu. (2011). Update on technological and selection factors influencing shockwave lithotripsy of renal stones in adults and children. *Current Opinion in Urology, 21*(2), 134-140.

Coz, F, Orvieto, M, Bustos, M, Lying, R, Stein, A, Hinrichs, A, & I, San Francisco. (2000). Extracorporeal Shockwave Lithotripsy of 2000 Urinary Calculi with the Modulith SL-20: Success and Failure According to Size and Location of Stones *Journal of Endourology, 14*(3), 239-246.

Crum, Lawrence A. (1988). Cavitation microjets as a contributory mechanism for renal calculi disintegration in ESWL. *The Journal of Urology, 140*(6), 1587-1590.

Cui, Helen, Thomee, Eeke, Noble, Jeremy G, Reynard, John M, & Turney, Benjamin W. (2013). Efficacy of the lithotripsy in treating lower pole renal stones. *Urolithiasis, 41*(3), 231-234.

Curhan, Gary C. (2007). Epidemiology of stone disease. *Urologic Clinics of North America, 34*(3), 287-293.

Curhan, Gary C, Willett, Walter C, Rimm, Eric B, Spiegelman, Donna, & Stampfer, Meir J. (1996). Prospective study of beverage use and the risk of kidney stones. *American Journal of Epidemiology, 143*(3), 240-247.

Curhan, Gary C, Willett, Walter C, Speizer, Frank E, & Stampfer, Meir J. (1998). Beverage use and risk for kidney stones in women. *Annals of Internal Medicine, 128*(7), 534-540.

Das, G, Dick, J, & Bailey, MJ. (1987). Extracorporeal shock wave lithotripsy: first 1000 cases at the London stone clinic. *British Medical Journal, 295*, 891-893.

Davidson, Peter J, Sheerin, Ian G, & Frampton, Chris. (2009a). Renal stone disease in Christchurch, New Zealand. Part 1: presentation and epidemiology. *Journal of the New Zealand Medical Association, 122*(1297).

Davidson, Peter J, Sheerin, Ian G, & Frampton, Chris. (2009b). Renal stone disease in Christchurch, New Zealand. Part 2: a community study on the burden of renal stone disease. *Journal of the New Zealand Medical Association, 122*(1297).

Davidson, T, Tung, K, Constant, O , & Edwards, L. (1991). Kidney rupture and psoas abscess after ESWL. *British Journal of Urology, 68*(6), 657-658.

Delius, M, Brendel, W, & Heine, G. (1988). A mechanism of gallstone destruction by extracorporeal shock waves. *Naturwissenschaften, 75*(4), 200-201.

Delius, Michael, Jordan, Michaela, Eizenhoefer, Harald, Marlinghaus, Ernst, Heine, Gerold, Liebich, Hans-Georg, & Brendel, Walter. (1988). Biological effects of shock waves: kidney haemorrhage by shock waves in dogs—administration rate dependence. *Ultrasound in Medicine & Biology, 14*(8), 689-694.

Delius, Michael. (2002). Twenty years of shock wave research at the Institute for Surgical Research. *European surgical research, 34*(1-2), 30-36.

Dellabella, Marco, Milanese, Giulio, & Muzzonigro, Giovanni. (2003). Efficacy of tamsulosin in the medical management of juxtavesical ureteral stones. *The Journal of Urology, 170*(6), 2202-2205.

Demirci, Deniz, Sofikerim, Mustafa, Yalçin, Engin, Ekmekcioglu, Oguz, Gülmez, Ibrahim, & Karacagil, Mustafa. (2007). Comparison of conventional and step-wise shockwave lithotripsy in management of urinary calculi. *Journal of Endourology, 21*(12), 1407-1410.

Dhar, Nivedita Bhatta, Thornton, Julie, Karafa, Matthew T, & Streem, Stevan B. (2004). A multivariate analysis of risk factors associated with subcapsular hematoma formation following electromagnetic shock wave lithotripsy. *The Journal of Urology, 172*(6), 2271-2274.

Doolittle, Arthur K. (1951). Studies in Newtonian flow. I. The dependence of the viscosity of liquids on temperature. *Journal of Applied Physics, 22*(8), 1031-1035.

Doran, Owen, & Foley, Bernard. (2008). Acute complications following extracorporeal shock-wave lithotripsy for renal and ureteric calculi. *Emergency Medicine Australasia, 20*(2), 105-111.

Dornier MedTech. (2015). Our History. Retrieved 7th April, 2015, from http://www.dornier.com/unitedstates/about-us/history/

Drach, GW, Dretler, S, & Fair, W. (1986). Report of the United States cooperative study of extracorporeal shock wave lithotripsy. *Journal of Urology, 135*, 1127-1133.

Edelstein, Ludwig. (1943). The Hippocratic oath, text, translation and interpretation.

Eisenmenger, Wolfgang. (2001). The mechanisms of stone fragmentation in ESWL. *Ultrasound in Medicine & Biology, 27*(5), 683-693.

El-Assmy, Ahmed, El-Nahas, Ahmed R, Abou-El-Ghar, Mohamed E, Awad, Bassam A, & Sheir, Khaled Z. (2013). Kidney stone size and hounsfield units predict successful shockwave lithotripsy in children. *Urology, 81*(4), 880-884.

El-Damanhoury, H, Schärfe, T, Rüth, J, Roos, S, & Hohenfellner, R. (1991). Extracorporeal shock wave lithotripsy of urinary calculi: experience in treatment of 3,278 patients using the Siemens Lithostar and Lithostar Plus. *Journal of Urology, 145*(3), 484-488.

El-Nahas, Ahmed R, El-Assmy, Ahmed M, Mansour, Osama, & Sheir, Khaled Z. (2007). A prospective multivariate analysis of factors predicting stone disintegration by extracorporeal shock

wave lithotripsy: the value of high-resolution noncontrast computed tomography. *European Urology, 51*(6), 1688-1694.

El-Nahas, Ahmed R., Eraky, Ibrahim, Shokeir, Ahmed A., Shoma, Ahmed M., El-Assmy, Ahmed M., El-Tabey, Nasr A., . . . El-Kenawy, Mahmoud R. (2012). Percutaneous nephrolithotomy for treating staghorn stones: 10 years of experience of a tertiary-care centre. *Arab Journal of Urology, 10*(3), 324-329. doi: http://dx.doi.org/10.1016/j.aju.2012.03.002

Elhilali, MM, Stoller, ML, McNamara, TC, Morehouse, DD, Wolf, JS Jr, & Keeler, LL Jr. (1995). Effectiveness and safety of the Dornier compact lithotriptor: an evaluative multicenter study. *Journal of Urology, 155*(3), 834-838.

Evan, A, Lingeman, J, Coe, FL, & Worcester, E. (2006). Randall's plaque: pathogenesis and role in calcium oxalate nephrolithiasis. *Kidney International, 69*(8), 1313-1318.

Evan, Andrew P, McAteer, James A, Connors, Bret A, Blomgren, Philip M, & Lingeman, James E. (2007). Renal injury during shock wave lithotripsy is significantly reduced by slowing the rate of shock wave delivery. *British Journal of Urology International, 100*(3), 624-628.

Evan, Andrew P, McAteer, James A, Connors, Bret A, Pishchalnikov, Yuri A, Handa, Rajash K, Blomgren, Philip, . . . Gao, Sujuan. (2008). Independent assessment of a wide-focus, low-pressure electromagnetic lithotripter: absence of renal bioeffects in the pig. *British Journal of Urology International, 101*(3), 382-388.

Falahatkar, Siavash, Khosropanah, Iradj, Vajary, Anahita Doustkhah, Bateni, Zhoobin Heidari, Khosropanah, Darya, & Allahkhah, Aliakbar. (2011). Is there a role for tamsulosin after shock wave lithotripsy in the treatment of renal and ureteral calculi? *Journal of Endourology, 25*(3), 495-498.

Fernström, I, & Johansson, B. (1975). Percutaneous pyelolithotomy. A new extraction technique. *Scandinavian Journal of Urology and Nephrology, 10*(3), 257-259.

Ferraro, Pietro Manuel, Taylor, Eric N, Gambaro, Giovanni, & Curhan, Gary C. (2013). Soda and other beverages and the risk of kidney stones. *Clinical Journal of the American Society of Nephrology, 8*(8), 1389-1395.

Ferraro, Pietro Manuel, Taylor, Eric N, Gambaro, Giovanni, & Curhan, Gary C. (2014). Caffeine intake and the risk of kidney stones. *The American Journal of Clinical Nutrition*, ajcn. 089987.

Flanders, Harley. (1968). The optical property of the conics. *American Mathematical Monthly*, 399-399.

Forssmann, Bernd. (2006). *25 Years of ESWL—From the Past to the Future.* Paper presented at the Innovations in nonlinear accoustics: 17th International Symposium on Nonlinear Acoustics including the International Sonic Boom Forum.

Frąckowiak, Anna, Skibiński, Przemysław, Gaweł, Wiesław, Zaczyńska, Ewa, Czarny, Anna, & Gancarz, Roman. (2010). Synthesis of glycoside derivatives of hydroxyanthraquinone with ability to dissolve and inhibit formation of crystals of calcium oxalate. Potential compounds in kidney stone therapy. *European Journal of Medicinal Chemistry, 45*(3), 1001-1007. doi: http://dx.doi.org/10.1016/j.ejmech.2009.11.042

Frantz, Marc. (2003). Drawing with Awareness Retrieved 5th April, 2015, from http://www.mathaware.org/mam/03/essay6.html

Frantz, Marc. (2015). Medical Lithotripsy. Retrieved 01 February, 2015, from American Mathematical Monthly

Gerber, R, Studer, U, & Danser, H. (2005). Is newer always better? A comparative study of 3 lithotriptor generations. *The Journal of urology, 173*(6), 2013-2016.

Graff, J, Benkert, S, Pastor, J, & Senge, T. (1989) A new multifunctional lithotriptor, the Dornier MFL 5000, results of 415 treatments. *Journal of Endourology, 3*, 315-319.

Granz, B, & Köhler, G. (1992). What makes a shock wave efficient in lithotripsy? *The Journal of Stone Disease, 4*(2), 123-128.

Gravenstein, Dietrich. (2000). Extracorporeal shock wave lithotripsy and percutaneous nephrolithotomy. *Anesthesiology Clinics of North America, 18*(4), 953-971.

Gravenstein, J.S., & Peter, K. (1986). *Extracorporeal Shock-Wave Lithotripsy for Renal Stone Disease: Technical and Clinical Aspects*: Butterworths.

Greenstein, Alexander, & Matzkin, Haim. (1999). Does the rate of extracorporeal shock wave delivery affect stone fragmentation? *Urology, 54*(3), 430-432. doi: http://dx.doi.org/10.1016/S0090-4295(99)00176-4

Grobler, C, Hayes, J, Frampton, C, & English, S. (2014). *Is extra corporeal shockwave lithotripsy more effective when conducted under general anaesthetic compared with conscious sedation? A retrospective review.* Paper presented at the BJU international.

Handa, Rajash K, Bailey, Michael R, Paun, Marla, Gao, Sujuan, Connors, Bret A, Willis, Lynn R, & Evan, Andrew P. (2009). Pretreatment with low-energy shock waves induces renal vasoconstriction during standard shock wave lithotripsy (SWL): a treatment protocol known to reduce SWL-induced renal injury. *British Journal of Urology International, 103*(9), 1270-1274.

Handa, Rajash K, & Evan, Andrew P. (2010). A chronic outcome of shock wave lithotripsy is parenchymal fibrosis. *Urological Research, 38*(4), 301-305.

Handa, Rajash K, McAteer, James A, Connors, Bret A, Liu, Ziyue, Lingeman, James E, & Evan, Andrew P. (2012). Optimising an escalating shockwave amplitude treatment strategy to protect the kidney from injury during shockwave lithotripsy. *British Journal of Urology International, 110*(11c), E1041-E1047.

Harmon, William J, Sershon, Peter D, Blute, Michael L, Patterson, David E, & Segura, Joseph W. (1997). Ureteroscopy: current practice and long-term complications. *The Journal of Urology, 157*(1), 28-32.

Hayes, J. (2011). Extracorporeal Shockwave Lithotripsy. Does Success Corelate to Shock Rate? [Review]. *New Zealand Journal Medical Radiation Technology, 3*(2), 1-6.

Hayes, J, Richardson, A, & Frampton, C. (2013). Population attributable risks for modifiable lifestyle factors and breast cancer in New Zealand women. *Internal medicine journal, 43*(11), 1198-1204.

Hayes, James M, & Ding, Steven L. (2012). Pancreatic stone and treatment using ERCP and ESWL procedures: a case study and review. *Journal of the New Zealand Medical Association, 125*(1361).

Haynes, Brian. (1999). Can it work? Does it work? Is it worth it? *British Medical Journal, 319*(7211), 652-653.

Hernandez, Gonzalo. (2003). Two-dimensional model for binary fragmentation process with random system of forces, random stopping and material resistance. *Physica A: Statistical Mechanics and its Applications, 323*(0), 1-8. doi: http://dx.doi.org/10.1016/S0378-4371(03)00032-3

Hiatt, Robert A, Ettinger, Bruce, Caan, Bette, Quesenberry, Charles P, Duncan, Debra, & Citron, John T. (1996). Randomized controlled trial of a low animal protein, high fiber diet in the prevention of recurrent calcium oxalate kidney stones. *American Journal of Epidemiology, 144*(1), 25-33.

Hofmann, R, Olbert, P, Weber, J, Wille, S, & Varga, Z. (2002). Clinical experience with a new ultrasonic and LithoClast combination for percutaneous litholapaxy. *British Journal of Urology International, 90*(1), 16-19.

Honey, R John D'A, Ray, A Andrew, Ghiculete, Daniela, & Pace, Kenneth T. (2010). Shock wave
lithotripsy: a randomized, double-blind trial to compare immediate versus delayed voltage
escalation. *Urology, 75*(1), 38-43.

Honey, R. J. D. 'A, Schuler, T. D., Ghiculete, D., & Pace, K. T. (2009). A Randomized, Double-Blind Trial
to Compare Shock Wave Frequencies of 60 and 120 Shocks per Minute for Upper Ureteral
Stones. *The Journal of Urology, 182*(4), 1418-1423. doi:
http://dx.doi.org/10.1016/j.juro.2009.06.019

Houdas, Yvon, & Ring, EFJ. (1982). *Human body temperature*: Springer Science & Business Media.

Howard, Danny, & Sturtevant, Bradford. (1997). In vitro study of the mechanical effects of shock-
wave lithotripsy. *Ultrasound in medicine & biology, 23*(7), 1107-1122.

Hutubessy, R, Chisholm, D, & Edejer, TT. (2013). Generalized cost-effectiveness analysis for
national-level priority-setting in the health sector. *Cost Effectiveness and Resource
Allocation, 1*(8), 1-13.

Hwang, Insang, Jung, Seung-Il, Kim, Kwang Ho, Hwang, Eu Chang, Yu, Ho Song, Kim, Sun-Ouck, . . .
Park, Kwangsung. (2014). Factors influencing the failure of extracorporeal shock wave
lithotripsy with Piezolith 3000 in the management of solitary ureteral stone. *Urolithiasis,
42*(3), 263-267.

Hyams, Elias S., & Matlaga, Brian R. (2013). Cost-effectiveness Treatment Strategies for Stone
Disease for the Practicing Urologist. *Urologic Clinics of North America, 40*(1), 129-133. doi:
http://dx.doi.org/10.1016/j.ucl.2012.09.010

Jain, Arun, & Shah, Tariq K. (2007). Effect of air bubbles in the coupling medium on efficacy of
extracorporeal shock wave lithotripsy. *European Urology, 51*(6), 1680-1687.

Janetschek, Gunter, Frauscher, Ferdinand, Knapp, Rudolf, Hofle, Gunter, Peschel, Reinhard, &
Bartsch, Georg. (1997). New onset hypertension after extracorporeal shock wave

lithotripsy: age related incidence and prediction by intrarenal resistive index. *The Journal of Urology, 158*(2), 346-351.

Jansson, Lars, Bengtsson, Mats, & Carlsson, Christer. (1988). Heart-synchronized ventilation during general anesthesia for extracorporeal shock wave lithotripsy. *Anesthesia & Analgesia, 67*(7), 706-709.

Kaude, Jun V, Williams, Clyde M, Millner, Michael R, Scott, Katherine N, & Finlayson, Birdwell. (1985). Renal morphology and function immediately after extracorporeal shock-wave lithotripsy. *American Journal of Roentgenology, 145*(2), 305-313.

Khaitan, A, Gupta, NP, Hemal, AK, Dogra, PN , Seth, A, & M, Aron. (2002). Post-ESWL, clinically insignificant residual stones: reality or myth? *Urology, 59*(1), 20-24.

Khan, Saeed R. (1992). Structure and development of calcific urinary stones. *Calcification in biological systems. CRC Press, Boca Raton*, 345-363.

Khan, Saeed R. (2013a). Chapter 21 - Animal Models of Calcium Oxalate Kidney Stone Formation. In P. Michael Conn (Ed.), *Animal Models for the Study of Human Disease* (pp. 483-498). Boston: Academic Press.

Khan, Saeed R. (2013b). Reactive Oxygen Species as the Molecular Modulators of Calcium Oxalate Kidney Stone Formation: Evidence from Clinical and Experimental Investigations. *The Journal of Urology, 189*(3), 803-811. doi: http://dx.doi.org/10.1016/j.juro.2012.05.078

Kim, Samuel C, Matlaga, Brian R, Kuo, Ramsay L, Watkins, Stephanie L, Kennett, Katie M, Gilling, Peter J, & Lingeman, James E. (2005). Holmium laser enucleation of the prostate: a comparison of efficiency measures at two institutions. *Journal of Endourology, 19*(5), 555-558.

Knoll, Thomas. (2010). Epidemiology, Pathogenesis, and Pathophysiology of Urolithiasis. *European Urology Supplements, 9*(12), 802-806. doi: http://dx.doi.org/10.1016/j.eursup.2010.11.006

Köhrmann, KU, Potempa, DM, & Rassweiler, J. (1991). A detailed analysis of the clinical efficacy of the Modulith SL20 *Journal of Endourology, 5*(S), 54.

Köhrmann, Kai Uwe, & Rassweiler, Jens. (2011). Extracorporeal Shock Wave Lithotriptors *Urinary Tract Stone Disease* (pp. 263-277): Springer.

Koo, Vincent, Beattie, Irene, & Young, Michael. (2010). Improved cost-effectiveness and efficiency with a slower shockwave delivery rate. *British Journal of Urology International, 105*(5), 692-696.

Krambeck, Amy E, Gettman, Matthew T, Rohlinger, Audrey L, Lohse, Christine M, Patterson, David E, & Segura, Joseph W. (2006). Diabetes mellitus and hypertension associated with shock wave lithotripsy of renal and proximal ureteral stones at 19 years of followup. *The Journal of Urology, 175*(5), 1742-1747.

Krestin, GP, Fischbach, R, Vorreuther, R, & Von Schulthess, GK. (1993). Alterations in renal morphology and function after ESWL therapy: evaluation with dynamic contrast-enhanced MRI. *European Radiology, 3*(3), 227-233.

Lalak, NJ, Moussa, SA, Smith, G, & Tolley, DA. (2002). The Dornier Compact Delta lithotripter: the first 150 ureteral calculi. *Journal of Endourology, 16*(9), 645-648.

Lambert, Erica H, Walsh, Rhonda, Moreno, Melissa W, & Gupta, Mantu. (2010). Effect of escalating versus fixed voltage treatment on stone comminution and renal injury during extracorporeal shock wave lithotripsy: a prospective randomized trial. *The Journal of Urology, 183*(2), 580-584.

Laugani, G, Grunberger, I, & Godec, C. (1991). Clinical experience with the Diasonics Thersonic lithotripter: impact of repeat treatment on results and complications. *Journal of Endourol, 5*(S), 52.

Lazo, P, Vlatko, I, Florina, PP, Nikola, A, & Dobrila, TL. (2012). Morphometrical evaluation of some anatomical features in pig kidneys: are they different from human kidneys. *Macedonian Veterinary Review, 35*(1), 35-42.

Li, Guangyan, Williams Jr, James C, Pishchalnikov, Yuri A, Liu, Ziyue, & McAteer, James A. (2012). Size and location of defects at the coupling interface affect lithotripter performance. *British Journal of Urology International, 110*(11c), E871-E877.

Li, Kaiwen, Lin, Tianxin, Zhang, Caixia, Fan, Xinxiang, Xu, Kewei, Bi, Liangkuan, . . . Dong, Wen. (2013). Optimal Frequency of Shock Wave Lithotripsy in Urolithiasis Treatment: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *The Journal of Urology*.

Lingeman, James, & Bhojani, Naeem. (2013). ESWL Principles *Surgical Management of Urolithiasis* (pp. 151-158): Springer.

Lingeman, James E. (2013). Shock Wave Lithotripsy: Opinion–the Ideal Machine *Clinical Management of Urolithiasis* (pp. 77-81): Springer.

Lingeman, James E, Kim, Samuel C, Kuo, Ramsay L, McAteer, James A, & Evan, Andrew P. (2003). Shockwave lithotripsy: anecdotes and insights. *Journal of Endourology, 17*(9), 687-693.

Lingeman, James E, McAteer, James A, Gnessin, Ehud, & Evan, Andrew P. (2009). Shock wave lithotripsy: advances in technology and technique. *Nature Reviews Urology, 6*(12), 660-670.

Lingeman, James E, Woods, John R, & Toth, Phillip D. (1990). Blood pressure changes following extracorporeal shock wave lithotripsy and other forms of treatment for nephrolithiasis. *JAMA: The Journal of the American Medical Association, 263*(13), 1789-1794.

Lingerman, JL, Newman, D, & Mertz, JH. (1986). Extracorporeal shock wave lithotripsy: the Methodist Hospital of Indianna. *Journal of Urology, 135*, 1134-1137.

Lipkin, Michael, & Shah, Ojas. (2006). The use of alpha-blockers for the treatment of nephrolithiasis. *Reviews in urology, 8*(Suppl 4), S35.

Lipsky, Michael J, Shapiro, Edan Y, Cha, Doh Yoon, & Gupta, Mantu. (2013). Modified-PCNL Without Modified Instruments: A Description of Technique. *Journal of Endourology, 27*(6), 684-687.

Liston, TG, Montgomery, BS, Bultitude, MI, & Tiptaft, RC. (1992). Extracorporeal shock wave lithotripsy with the Storz Modulith SL20: the first 500 patients. *British Journal of Urology, 69*, 465-469.

Littleton, Ray, Melser, M, & Kupin, W. (1988). Acute renal failure following bilateral extracorporeal shock wave lithotripsy in the absence of obstruction. *Journal of Endourology, 2*(3), 241-246.

Logarakis, Nick F, Jewett, Michael, Luymes, J, & Honey, R. (2000). Variation in clinical outcome following shock wave lithotripsy. *The Journal of Urology, 163*(3), 721-725.

Lokhandwalla, Murtuza, & Sturtevant, Bradford. (2000). Fracture mechanics model of stone comminution in ESWL and implications for tissue damage. *Physics in Medicine and Biology, 45*(7), 1923.

Lopez, Alexandra, Chen, Qian, Deiling, Brittany L, Iames, Edward S, & Young, Lindon. (2013). The Effects of Modulating Endothelial Nitric Oxide Synthese (eNOS) Activity and Coupling in Extracorporeal Shock Wave Lithotripsy (ESWL).

Loske, Achim M. (2010). The role of energy density and acoustic cavitation in shock wave lithotripsy. *Ultrasonics, 50*(2), 300-305.

Lotan, Yair, & Pearle, Margaret S. (2007). Economics of Stone Management. *Urologic Clinics of North America, 34*(3), 443-453. doi: http://dx.doi.org/10.1016/j.ucl.2007.04.008

Lucas, Stephen D, Zheng, Gang, & Gravenstein, Dietrich. (2014). Extracorporeal Shock Wave Therapy and Percutaneous Nephrolithotripsy *Anesthesia for Urologic Surgery* (pp. 75-91): Springer.

Lukeš, Petr, Šunka, Pavel, Hoffer, Petr, Stelmashuk, Vitaliy, Beneš, Jiří, Poučková, Pavla, . . . Zeman, Jan. (2012). Generation of Focused Shock Waves in Water for Biomedical Applications *Plasma for Bio-Decontamination, Medicine and Food Security* (pp. 403-416): Springer.

Madbouly, Khaled, El-Tiraifi, Abdel Moneim, Seida, Mohamed, El-Faqih, Salah R, Atassi, Ramiz, & Talic, Riyadh F. (2005). Slow versus fast shock wave lithotripsy rate for urolithiasis: a prospective randomized study. *The Journal of Urology, 173*(1), 127-130.

Madbouly, Khaled, Sheir, Khaled Z, Elsobky, Emad, Eraky, Ibrahim, & Kenawy, Mahmoud. (2002). Risk factors for the formation of a steinstrasse after extracorporeal shock wave lithotripsy: a statistical model. *The Journal of Urology, 167*(3), 1239-1242.

Madore, Odette. (1993). *The Health Care Syestem in Canada: Effectiveness and Effeciency*. Toronto.

Maloney, Michaella E, Marguet, Charles G, Zhou, Yufeng, Kang, David E, Sung, Jeffery C, Springhart, W Patrick, . . . Preminger, Glenn M. (2006). Progressive increase of lithotripter output produces better in-vivo stone comminution. *Journal of Endourology, 20*(9), 603-606.

Marckmann, Peter, Osther, Palle, Pedersen, Agnes N, & Jespersen, Bente. (2015). High-Protein Diets and Renal Health. *Journal of Renal Nutrition, 25*(1), 1-5.

Martini, Gianmaria, Berta, Paolo, Mullahy, John, & Vittadini, Giorgio. (2014). The effectiveness– efficiency trade-off in health care: The case of hospitals in Lombardy, Italy. *Regional Science and Urban Economics*.

Mathers, J, Harding, L, Smeulders, N, Davies, R, & Hume-Smith, H. (2014). Re "Cardiac dysrhythmias induced by extracorporeal shock wave lithotripsy in children". *Journal of Pediatric Urology, 10*(6), 1288.

Matin, Surena F, Yost, Agnes, & Streem, Stevan B. (2001). Extracorporeal shock-wave lithotripsy: a comparative study of electrohydraulic and electromagnetic units. *The Journal of Urology, 166*(6), 2053-2056.

Matlaga, Brian R, Coe, Fredric L, Evan, Andrew P, & Lingeman, James E. (2007). The role of Randall's plaques in the pathogenesis of calcium stones. *The Journal of Urology, 177*(1), 31-38.

Mays, N, Challah, S, & Patel, S. (1988). Clinical comparrison of extracorporeal shock wave lithotripsy and percutaneous nephrolithotomy in treating renal calculi. *British Medical Journal, 297*, 253-258.

McAteer, James A, & Evan, Andrew P. (2008). *The acute and long-term adverse effects of shock wave lithotripsy.* Paper presented at the Seminars in nephrology.

McAteer, James A., Evan, Andrew P., Williams, James C., & Lingeman, James E. (2009). Treatment protocols to reduce renal injury during shock wave lithotripsy. *Current Opinion in Urology, 19*(2), 192-195.

McCauley, Lipika R, Dyer, Anthony J, Stern, Karen, Hicks, Thomas, & Nguyen, Mike M. (2012). Factors influencing fluid intake behavior among kidney stone formers. *The Journal of Urology, 187*(4), 1282-1286.

McConnell, JD. (2001). The development of urology in the 21st century. *BJU international, 88*(s2), 2-6.

Meschi, Tiziana, Nouvenne, Antonio, & Borghi, Loris. (2011). Lifestyle recommendations to reduce the risk of kidney stones. *Urologic Clinics of North America, 38*(3), 313-320.

Micali, S, Grande, M, Sighinolfi, MC, Carne, C De, Stefani, S De, & Bianchi, G. (2006). Medical therapy of urolithiasis. *Journal of Endourology, 20*(11), 841-847.

Miernik, Arkadiusz, Wilhelm, Konrad, Ardelt, Peter Uwe, Adams, Fabian, Kuehhas, Franklin Emmanuel, & Schoenthaler, Martin. (2012). Standardized flexible ureteroscopic technique to improve stone-free rates. *Urology, 80*(6), 1198-1202.

Miller, HC, Collins, LA, Turbow, AM, Turbow, BA, Beall, ME, Berger, RM, . . . JB, Karol. (1989). Initial EDAP LT-01 lithotripsy group experience in the United States. *Journal of Urology, 142*(6), 1412-1414.

Mobley, TB, Myers, DA, Grine, WB, Jenkins, JM, & Jordan, WR. (1993). Low energy lithotripsy with the Lithostar: treatment results with 19,962 renal and ureteral calculi. *Journal of Urology, 149*(6), 1419-1424.

Moe, Orson W, Pearle, Margaret S, & Sakhaee, Khashayar. (2010). Pharmacotherapy of urolithiasis: evidence from clinical trials. *Kidney International, 79*(4), 385-392.

Molimard, Benoit, Al-Qahtani, Saeed, Lakmichi, Amine, Sejiny, Majed, Gil-Diez de Medina, Sixtina, Carpentier, Xavier, & Traxer, Olivier. (2010). Flexible Ureterorenoscopy With Holmium Laser in Horseshoe Kidneys. *Urology, 76*(6), 1334-1337. doi: http://dx.doi.org/10.1016/j.urology.2010.02.072

Monga, Manoj. (2011). The effect of fat and nonfat components of the skin-to-stone distance on shockwave lithotripsy outcome. *International Brazilian Journal of Urology, 37*(1), 116-116.

Morton, A. Ross, & Iliescu, Eduard A. (2004). Kidney Stones. In Martini Editor-in-Chief: Luciano (Ed.), *Encyclopedia of Endocrine Diseases* (pp. 140-145). New York: Elsevier.

Mustafa, Mahmoud. (2012). Is the gravity effect of radiographic anatomic features enough to justify stone clearance or fragments retention following extracorporeal shock wave lithotripsy (SWL). *Urological Research, 40*(4), 339-344.

Mykulak, DJ, Grunberger, I, & Macchia, RJ. (1992). Initial experience with therasonic lithotriptor. *Urology, 39*(4), 346-351.

Nash, William A, & Potter, Merle C. (1998). *Schaum's Outline of Strength of Materials*: McGraw-Hill Companies.

Neisius, Andreas, Wöllner, Jens, Thomas, Christian, Roos, Frederik C, Brenner, Walburgis, Hampel, Christian, . . . Gillitzer, Rolf. (2013). Treatment efficacy and outcomes using a third generation shockwave lithotripter. *British Journal of Urology International, 112*(7), 972-981.

Neri, Eugenio, Capannini, Gianni, Diciolla, Francesco, Carone, Enrico, Tripodi, Alberto, Tucci, Enrico, & Sassi, Carlo. (2000). Localized dissection and delayed rupture of the abdominal aorta after extracorporeal shock wave lithotripsy. *Journal of Vascular Surgery, 31*(5), 1052-1055.

Neucks, Joshua S, Pishchalnikov, Yuri A, Zancanaro, Anthony J, VonDerHaar, Jonathan N, Williams Jr, James C, & McAteer, James A. (2008). Improved acoustic coupling for shock wave lithotripsy. *Urological Research, 36*(1), 61-66.

Ng, Chi-Fai, Lo, Anthony K. Y., Lee, Kim W. M., Wong, K. T., Chung, Wai-yee, & Gohel, Danny. (2012). A Prospective, Randomized Study of the Clinical Effects of Shock Wave Delivery for Unilateral Kidney Stones: 60 Versus 120 Shocks per Minute. *The Journal of Urology, 188*(3), 837-842. doi: http://dx.doi.org/10.1016/j.juro.2012.05.009

Ng, Chi-Fai, Lu, Ye, Yuen, John, & Gohel, Danny. (2014). The Effects of Different Treatment Protocols on the Degree of Renal Injury in Patients with Renal Stones Receiving Shockwave Lithotripsy. *The Journal of Urology, 191*(4), e208.

Nguyen, Daniel P, Hnilicka, Stefanie, Kiss, Bernhard, Seiler, Roland, Thalmann, George N, & Roth, Beat. (2015). Optimization of extracorporeal shock wave lithotripsy delivery rates achieves excellent outcomes in ureteral stones. Results of a prospective, randomized trial. *The Journal of Urology*.

Niazi, Sarfaraz K. (2014). *Handbook of bioequivalence testing*: CRC Press.

Ogden, J. A., Toth-Kischkat, A., & Schultheiss, R. (2001). Principles of shock wave therapy. *Clinical Orthopaedic and Related Research*(387), 8-17.

Okhunov, Zhamshid, Friedlander, Justin I, George, Arvin K, Duty, Brian D, Moreira, Daniel M, Srinivasan, Arun K, . . . Okeke, Zeph. (2013). STONE nephrolithometry: novel surgical classification system for kidney calculi. *Urology, 81*(6), 1154-1160.

Olivi, B, Védrine, N, Costilles, T, Boiteux, JP, & Guy, L. (2011). [Extra corporeal shock wave lithotripsy in patients with body mass index over 35 Kg/m2]. *Progres en urologie: journal de l'Association francaise d'urologie et de la Societe francaise d'urologie, 21*(4), 254-259.

Osman, Mahmoud M, Alfano, Yvonne, Kamp, Stefan, Haecker, Axel, Alken, Peter, Michel, Maurice Stephan, & Knoll, Thomas. (2005). 5-year-follow-up of patients with clinically insignificant residual fragments after extracorporeal shockwave lithotripsy. *European Urology, 47*(6), 860-864.

Osman, Yasser, Harraz, Ahmed M, El-Nahas, Ahmed R, Awad, Bassam, El-Tabey, Naser, Shebel, Haytham, . . . El-Kenawy, Mahmoud. (2013). Clinically insignificant residual fragments: an acceptable term in the computed tomography era? *Urology, 81*(4), 723-726.

Ötünçtemur, Alper, Çakır, Süleyman Sami, Dursun, Murat, Polat, Emre Can, Somay, Adnan, Özbay, Nurver, . . . Özbek, Emin. (2012). Scientific Program for 30th World Congress of Endourology & SWL. *Journal of Endourology, 26*(S1), P1-A572.

Pace, Kenneth T., Ghiculete, Daniela, Harju, Melanie, & Honey, R. John D'A. (2005). Shock wave lithotripsy at 60 or 120 shocks per minute: A randomised double-blind trial. *The Journal of Urology, 174*(2), 595-599. doi: http://dx.doi.org/10.1097/01.ju.0000165156.90011.95

Pak, Charles Y. C. (1998). Chapter 25 - Kidney Stones: Pathogenesis, Diagnosis, and Therapy. In V. Avioli Louis & M. Krane Stephen (Eds.), *Metabolic Bone Disease and Clinically Related Disorders (Third Edition)* (pp. 739-758). San Diego: Academic Press.

Palfrey, EL, Bultitude, MI, & Challah, S. (1986). Report on the first 1000 patients treated at St Thomas Hospital by extracorporeal shock wave lithotripsy. *British Journal of Urology, 58*, 573-577.

Pareek, Gyan, Armenakas, Noel A, Panagopoulos, Georgia, Bruno, John J, & Fracchia, John A. (2005). Extracorporeal shock wave lithotripsy success based on body mass index and Hounsfield units. *Urology, 65*(1), 33-36.

Parks, Jennifer A, & Wike, Victoria S. (2010). *Bioethics in a changing world*: Prentice Hall Upper Saddle River, NJ.

Parmar, Malvinder S. (2004). Kidney stones. *British Medical Journal, 328*(7453), 1420.

Patel, M. S., Blacklock, N. J., & Rao, P. N. (1987). Economic evaluation of six scenarios for the treatment of stones in the kidney and ureter by surgery or extra-corporeal shock wave lithotripsy. *Health Policy, 8*(2), 207-225. doi: http://dx.doi.org/10.1016/0168-8510(87)90063-7

Paterson, Ryan F, Lifshitz, David A, Lingeman, James E, Evan, Andrew P, Connors, Bret A, Fineberg, Naomi S, . . . Mcateer, James (2002). Stone fragmentation during shock wave lithotripsy is improved by slowing the shock wave rate: studies with a new animal model. *The Journal of Urology, 168*(5), 2211-2215.

Paul, Arun Kumar. (2006). *Clinical Anaesthesia*: Jaypee Brothers Publishers.

Pearle, Margaret S. (2012). Shock-wave lithotripsy for renal calculi. *New England Journal of Medicine, 367*(1), 50-57.

Pearle, Margaret S, Lingeman, James E, Leveillee, Raymond, Kuo, Ramsay, Preminger, Glenn M, Nadler, Robert B, . . . Dushinski, John. (2005). Prospective, randomized trial comparing shock wave lithotripsy and ureteroscopy for lower pole caliceal calculi 1 cm or less. *The Journal of Urology, 173*(6).

Pearle, Margaret S, Nadler, Robert, Bercowsky, Eduardo, Chen, Cathy, Dunn, Matt, Figenshau, R Sherburne, . . . Nakada, Stephen Y. (2001). Prospective randomized trial comparing shock wave lithotripsy and ureteroscopy for management of distal ureteral calculi. *The Journal of Urology, 166*(4), 1255-1260.

Percutaneous trocar (needle) nephrostomy in hydronephrosis. *Journal of the American Medical Association, 157*(11), 891-894.

Pickens, Ryan B, & Miller, Nicole L. (2013). Complications of Ureteroscopy 11. *Surgical Management of Urolithiasis: Percutaneous, Shockwave and Ureteroscopy*, 137.

Pishchalnikov, Yuri A, McAteer, James A. , Williams, James C. Jr., Pishchalnikova, Irina V. , & Vonderhaar, Jason (2006). Why stones break better at slow shock wave rate than at fast rate: in vitro study with a research electrohydraulic lithotripter. *Journal of Endourology, 20*(8), 537-541.

Pishchalnikov, Yuri A, Neucks, Joshua S, VonDerHaar, R Jason, Pishchalnikova, Irina V, Williams Jr, James C, & McAteer, James A. (2006). Air pockets trapped during routine coupling in dry head lithotripsy can significantly decrease the delivery of shock wave energy. *The Journal of Urology, 176*(6), 2706-2710.

Pishchalnikov, Yuri A, Sapozhnikov, Oleg A, Bailey, Michael R, Williams Jr, James C, Cleveland, Robin O, Colonius, Tim, . . . McAteer, James A. (2003). Cavitation bubble cluster activity in the breakage of kidney stones by lithotripter shockwaves. *Journal of Endourology, 17*(7), 435-446.

Polat, Fazlı, Yeşil, Süleyman, Ak, Esat, Farahvash, Amirali, Karaoğlan, Üstünol, Biri, Hasan, & Bozkırlı, İbrahim. (2012). Safety of ESWL in elderly: Evaluation of independent predictors and comorbidity on stone-free rate and complications. *Geriatrics & Gerontology International, 12*(3), 413-417.

Politis, G, & Griffith, GP. (1987). ESWL: stone-free efficacy based upon stone size and location *World Journal of Urology, 5*(4), 255-258.

Preminger, G, Badlani, G, Kavoussi, L, & Smith, A (Eds.). (2011). *Smith's Textbook of Endourology* (3rd ed.). London: Wiley-Blackwell.

Psihramis, KE, Jewett, MA, Bombardier, C, Caron, D, & Ryan, M. (1992). Lithostar extracorporeal shock wave lithotripsy: the first 1,000 patients. Toronto Lithotripsy Associates. *Journal of Urology, 147*(4), 1006-1009.

Punch, Keith F. (2013). *Introduction to social research: Quantitative and qualitative approaches*: Sage.

Rabinovich, Yakov I., Esayanur, Madhavan, Daosukho, Saijit, Byer, Karen J., El-Shall, Hassan E., & Khan, Saeed R. (2006). Adhesion force between calcium oxalate monohydrate crystal and kidney epithelial cells and possible relevance for kidney stone formation. *Journal of Colloid and Interface Science, 300*(1), 131-140. doi: http://dx.doi.org/10.1016/j.jcis.2006.03.070

Rajamahanty, Srinivas, & Grasso, Michael. (2008). Flexible ureteroscopy update: indications, instrumentation and technical advances. *Indian journal of urology: IJU: Journal of the Urological Society of India, 24*(4), 532.

Ramsey, Sara, Robertson, Alan, Ablett, Mark J, Meddings, Robert N, Hollins, Graham W, & Little, Brian. (2010). Evidence-based drainage of infected hydronephrosis secondary to ureteric calculi. *Journal of Endourology, 24*(2), 185-189.

Rassweiler, J, Gumpinger, R, Buh, P, Kohl, H, Mayer, A., & Eisenberger, F (1989). Wolf Piezolith 2200 versus the Modified Dornier HM3. *European Urology, 16*, 1-6.

Rassweiler, J, Köhrmann, U, Heine, G, Back, W, Wess, O, & Alken, P. (1990). Modulith SL 10/20-- experimental introduction and first clinical experience with a new interdisciplinary lithotriptor. *European Urology, 18*(4), 237.

Rassweiler, Jens J, Knoll, Thomas, Köhrmann, Kai-Uwe, McAteer, James A, Lingeman, James E, Cleveland, Robin O, . . . Chaussy, Christian. (2011). Shock wave technology and application: an update. *European Urology, 59*(5), 784-796.

Rebuck, David A, Macejko, Amanda, Bhalani, Vishal, Ramos, Patrick, & Nadler, Robert B. (2011). The natural history of renal stone fragments following ureteroscopy. *Urology, 77*(3), 564-568.

131

Resorlu, Berkan, Unsal, Ali, Tepeler, Abdulkadir, Atis, Gokhan, Tokatli, Zafer, Oztuna, Derya, . . . Saglam, Remzi. (2012). Comparison of retrograde intrarenal surgery and mini-percutaneous nephrolithotomy in children with moderate-size kidney stones: results of multi-institutional analysis. *Urology, 80*(3), 519-523.

Reynard, John, Brewster, Simon, & Biers, Suzanne. (2013). *Oxford handbook of urology*: Oxford University Press.

Riehle, RA Jr, Fair, WR, & Vaughan, ED Jr. (1986). Extracorporeal shock wave lithotripsy for upper urinary tract calculi. One year's experience at a single center. *JAMA: The Journal of the American Medical Association, 255*, 2043-2048.

Rigatti, P, Francesca, F, & Montorsi, F. (1989). Extracorporeal lithotripsy and combined surgical procedures in the treatment of renoureteral stone disease: our experience with 2955 patients. *World Journal of Surgery, 13*, 765-774.

Rodgers, Allen L., & Lewandowski, Sonja. (2002). Effects of 5 Different Diets On Urinary Risk Factors For Calcium Oxalate Kidney Stone Formation: Evidence of Different Renal Handling Mechanisms in Different Race Groups. *The Journal of Urology, 168*(3), 931-936. doi: http://dx.doi.org/10.1016/S0022-5347(05)64545-4

Romero, Victoriano, Akpinar, Haluk, & Assimos, Dean G. (2010). Kidney stones: a global picture of prevalence, incidence, and associated risk factors. *Reviews in Urology, 12*(2-3), e86.

Rule, Andrew D, Krambeck, Amy E, & Lieske, John C. (2011). Chronic kidney disease in kidney stone formers. *Clinical Journal of the American Society of Nephrology, 6*(8), 2069-2075.

Ryan, PC, Jones, BJ, Kay, EW, Nowlan, P, Kiely, EA, Gaffney, EF, & Butler, MR. (1991). Acute and chronic bioeffects of single and multiple doses of piezoelectric shockwaves (EDAP LT. 01). *The Journal of Urology, 145*(2), 399-404.

Sakhaee, Khashayar, Adams-Huet, Beverley, Moe, Orson W, & Pak, Charles YC. (2002). Pathophysiologic basis for normouricosuric uric acid nephrolithiasis. *Kidney International, 62*(3), 971-979.

Sakhaee, Khashayar, Maalouf, Naim M, & Sinnott, Bridget. (2012a). Kidney stones 2012: pathogenesis, diagnosis, and management. *Journal of Clinical Endocrinology & Metabolism, 97*(6), 1847-1860.

Sakhaee, Khashayar, Maalouf, Naim M, & Sinnott, Bridget. (2012b). Kidney stones 2012: pathogenesis, diagnosis, and management. *The Journal of Clinical Endocrinology & Metabolism, 97*(6), 1847-1860.

Salem, Hosni Khairy, Fathy, Hesham, ElFayoumy, Hanny, Aly, Hussein, Ghonium, Ahmed, Mohsen, Mostafa A, & Hegazy, Abd El Rahim. (2014). Slow vs Rapid Delivery Rate Shock Wave Lithotripsy for Pediatric Renal Urolithiasis: A Prospective Randomized Study. *The Journal of Urology, 191*(5), 1370-1374.

Sandison, AT, & Tapp, Edmund. (1998). Disease in ancient Egypt. *ROM I: Mummification for the common people," in Mummies, Disease and Ancient Cultures. 2nd ed. Aidan Cockburn, Eve Cockburn, and Theodore A. Reyman, eds*, 38-58.

Sapozhnikov, Oleg A, Maxwell, Adam D, MacConaghy, Brian, & Bailey, Michael R. (2007a). A mechanistic analysis of stone fracture in lithotripsy. *The Journal of the Acoustical Society of America, 121*(2), 1190-1202.

Sapozhnikov, Oleg A, Maxwell, Adam D, MacConaghy, Brian, & Bailey, Michael R. (2007b). A mechanistic analysis of stone fracture in lithotripsy. *The Journal of the Acoustical Society of America, 121*, 1190.

Sarica, Kemal, Erturhan, Sakip, Yurtseven, Cihanser, & Yagci, Faruk. (2006). Effect of potassium citrate therapy on stone recurrence and regrowth after extracorporeal shockwave lithotripsy in children. *Journal of Endourology, 20*(11), 875-879.

Sassi, Franco. (2006). Calculating QALYs, comparing QALY and DALY calculations. *Health Policy and Planning, 21*(5), 402-408.

Sato, Yoshikazu, Tanda, Hitoshi, Kato, Shuji, Ohnishi, Shigeki, Nakajima, Hisao, Nanbu, Akihito, . . . Hanzawa, Tatsuo. (2008). Shock wave lithotripsy for renal stones is not associated with hypertension and diabetes mellitus. *Urology, 71*(4), 586-591.

Scales, Charles D, Smith, Alexandria C, Hanley, Janet M, Saigal, Christopher S, & Project, Urologic Diseases in America. (2012). Prevalence of kidney stones in the United States. *European Urology, 62*(1), 160-165.

Scales Jr, Charles D, Curtis, Lesley H, Norris, Regina D, Springhart, W Patrick, Sur, Roger L, Schulman, Kevin A, & Preminger, Glenn M. (2007). Changing gender prevalence of stone disease. *The Journal of Urology, 177*(3), 979-982.

Semins, Michelle J., & Matlaga, Brian R. (2013). Kidney Stones and Pregnancy. *Advances in Chronic Kidney Disease, 20*(3), 260-264. doi: http://dx.doi.org/10.1053/j.ackd.2013.01.009

Semins, Michelle Jo, Trock, Bruce J., & Matlaga, Brian R. (2008). The Effect of Shock Wave Rate on the Outcome of Shock Wave Lithotripsy: A Meta-Analysis. *The Journal of urology, 179*(1), 194-197. doi: http://dx.doi.org/10.1016/j.juro.2007.08.173

Shafquat, Azam. (2012). Cardiac Rhythm Management Devices *Urolithiasis* (pp. 563-565): Springer.

Shah, J, & Whitfield, HN. (2002). Urolithiasis through the ages. *British Journal of Urology International, 89*(8), 801-810.

Sheng, Xiaoxia, Ward, Michael D, & Wesson, Jeffrey A. (2003). Adhesion between molecules and calcium oxalate crystals: critical interactions in kidney stone formation. *Journal of the American Chemical Society, 125*(10), 2854-2855.

Shung, K Kirk, Smith, Michael, & Tsui, Benjamin MW. (2012). *Principles of Medical Imaging*: Academic Press.

Simon, D. (1995). Experience with 500 extracorporeal shockwave lithotripsy patients using a low-cost unit: the "Econolith". *Journal of Endourology, 9*(3), 215-218.

Simpson, John Andrew, & Weiner, Edmund SC. (1989). *The Oxford English Dictionary* (Vol. 2): Clarendon Press Oxford.

Singh, Kamal Jeet, & Kaur, Jaspreet. (2011). Comparison of three different endoscopic techniques in management of bladder calculi. *Indian journal of urology: IJU: Journal of the Urological Society of India, 27*(1), 10.

Skinner, Thomas AA, & Norman, Richard W. (2012). Variables influencing the likelihood of cardiac dysrhythmias during extracorporeal shock wave lithotripsy. *Canadian Urological Association Journal, 6*(2), 107.

Smith, Arthur D. (2007). *Smith's textbook of endourology*: PMPH-USA.

Smith, Joseph A. (1992). *High tech urology: Technologic innovations and their clinical applications*: WB Saunders Company.

Sorensen, Carsten, Chandhoke, Paramjit, Moore, Michael, Wolf, Connie, & Sarram, Ali. (2002). Comparison of intravenous sedation versus general anesthesia on the efficacy of the Doli 50 lithotriptor. *The Journal of Urology, 168*(1), 35-37.

Sorensen, Mathew D., Kahn, Arnold J., Reiner, Alex P., Tseng, Timothy Y., Shikany, James M., Wallace, Robert B., . . . Stoller, Marshall L. (2012). Impact of Nutritional Factors on Incident Kidney Stone Formation: A Report From the WHI OS. *The Journal of Urology, 187*(5), 1645-1650. doi: http://dx.doi.org/10.1016/j.juro.2011.12.077

Soygür, Tarkan, Akbay, Aysegül, & Küpeli, Sadettin. (2002). Effect of potassium citrate therapy on stone recurrence and residual fragments after shockwave lithotripsy in lower caliceal calcium oxalate urolithiasis: a randomized controlled trial. *Journal of Endourology, 16*(3), 149-152.

Srisubat, Attasit, Potisat, Somkiat, Lojanapiwat, Bannakij, Setthawong, Vasun, & Laopaiboon, Malinee. (2009). Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones. *Cochrane Database Syst Rev, 4*.

Steinholt, Johan Markus. (2013). Testing Effective Kidney Stone Fragmentation.

Streem, SB, Yost, A, & Mascha, E. (1996). Clinical implications of clinically insignificant store fragments after extracorporeal shock wave lithotripsy. *Journal of Urology, 155*(4), 1186-1190.

Swanson, SK, Larson, TR Begun, FP, Lamm, DL, Fuchs, EF, Hyman, J, & JL, Huffman. (1992). Clinical trials of the Northgate SD-3 dual-purpose lithotriptor for renal calculi. *Journal of Urology, 148*(3 Pt 2), 1047-1051.

Tailly, Geert G. (2013). Extracorporeal shock wave lithotripsy today. *Indian Journal of Urology : IJU : Journal of the Urological Society of India, 29*(3), 200-207. doi: 10.4103/0970-1591.117283

Takahara, Kiyoshi, Ibuki, Naokazu, Inamoto, Teruo, Nomi, Hayahito, Ubai, Takanobu, & Azuma, Haruhito. (2012). Predictors of success for stone fragmentation and stone-free rate after extracorporeal shockwave lithotripsy in the treatment of upper urinary tract stones. *Urology Journal, 9*(3), 549-552.

Talati, J, Shah, T, & Memon, A. (1991). Extracorporeal shock wave lithotripsy for urinary tract stones using MPL 9000 spark gap technology and ultrasound monitoring. *Journal of Urology, 146*, 290-293.

Tamošaitytė, Sandra, Hendrixson, Vaiva, Želvys, Arūnas, Tyla, Ramūnas, Kučinskienė, Zita A, Jankevičius, Feliksas, . . . Šablinskas, Valdas. (2013). Combined studies of chemical composition of urine sediments and kidney stones by means of infrared microspectroscopy. *Journal of Biomedical Optics, 18*(2), 027011-027011.

Tan, EC, Tung, KH, & Foo, KT. (1990). Piezoelectric extracorporeal shock wave lithotripsy by EDAP
    LTO1 : The Singapore experience. *Journal of Lithotripsy and Stone Disease, 2*, 19-23.

Taylor, Eric N, Stampfer, Meir J, & Curhan, Gary C. (2005). Obesity, weight gain, and the risk of
    kidney stones. *JAMA: The Journal of the American Medical Association, 293*(4), 455-462.

Taylor, Eric N., & Curhan, Gary C. (2008). Chapter 35 - Evaluation and Management of Kidney Stone
    Disease. In S. Wilcox Christopher, Md, PhD, Frcp & M. D. PhD Frcp Facp Facpa2 - Christopher
    S. Wilcox (Eds.), *Therapy in Nephrology & Hypertension (Third Edition)* (pp. 429-436).
    Philadelphia: W.B. Saunders.

Teichman, Joel MH. (2004). Acute renal colic from ureteral calculus. *New England Journal of
    Medicine, 350*(7), 684-693.

The Open University. (1996). Sound – a wave phenomenon Retrieved 19th April, 2015, from
    http://www.met.reading.ac.uk/pplato2/h-flap/phys5_7.html

Tipu, Salman Ahmed, & Jamalullah, Muhammad. (2011). Treatment of Vesicle Calculi – comparison
    of ESWL and cystolithopaxy. *ISRA Medical Journal*, 16.

Tiselius, Hans-Göran, & Chaussy, Christian G. (2012). Aspects on how extracorporeal shockwave
    lithotripsy should be carried out in order to be maximally effective. *Urological Research,
    40*(5), 433-446. doi: 10.1007/s00240-012-0485-z

Toronto Western Hospital. (2008). Characterisitcs of Ultrasound Retrieved 5th April, 2014, from
    http://www.usra.ca/characteristics.php

Tortora, Gerard J, & Derrickson, Bryan H. (2008). *Principles of anatomy and physiology*: John Wiley
    & Sons.

Tsang, CF, Fu, KF, Wong, EMH, Ho, KL, & Yiu, MK. (2013). *Predictive factors for extracorporeal
    shockwave lithotripsy success in ureteric stones, does skin-stone distance and Hounsfield Unit
    matter?* Paper presented at the BJU international.

137

Turk, C, Knoll, T, & Petrik, A. (2014). EAU Guidelines on Urolithiasis. 2014.

Türk, C, Knoll, T, Petrik, A, Sarica, K, Straub, M, & Seitz, C. (2011). Guidelines on urolithiasis. *European Association of Urology*.

Turney, Benjamin W, Reynard, John M, Noble, Jeremy G, & Keoghane, Stephen R. (2012). Trends in urological stone disease. *British Journal of Urology International, 109*(7), 1082-1087.

Tuteja, A. K., Pulliam, J. P., Lehman, T. H., & Elzinga, L. W. (1997). Anuric renal failure from massive bilateral renal hematoma following extracorporeal shock wave lithotripsy. *Urology, 50*(4), 606-608. doi: 10.1016/s0090-4295(97)00313-0

Urology, European Association of. (2012). EAU Clinical Guidelines Retrieved 1.8.12, 2012, from http://www.uroweb.org/guidelines/

Vallancien G, Aviles J, Munoz, R , Veillon, B , Charton, M, & Brisset, JM (1988). Piezoelectric extracorporeal lithotripsy by ultrashort waves with the EDAP LT 01 device. *Journal of Urology, 139*(4), 689-694.

Vallancien, G, Munoz, R, Borghi, M, Veillon, B, Brisset, JM, & Daudon, M. (1989). Relationship between the frequency of piezoelectric shock waves and the quality of renal stone fragmentation. In vitro study and clinical implications. *European Urology, 16*(1), 41.

Wang, Hsin-Hsiao Scott, Huang, Lin, Routh, Jonathan C., & Nelson, Caleb P. (2012). Shock Wave Lithotripsy vs Ureteroscopy: Variation in Surgical Management of Kidney Stones at Freestanding Children's Hospitals. *The Journal of Urology, 187*(4), 1402-1407. doi: http://dx.doi.org/10.1016/j.juro.2011.12.010

Wang, Y, Chen, X, Song, Y, Caballero, B, & Cheskin, LJ. (2007). Association between obesity and kidney disease: a systematic review and meta-analysis. *Kidney International, 73*(1), 19-33.

Whitson, Jared M, Stackhouse, G Bennett, & Stoller, Marshall L. (2010). Hyperoxaluria after modern bariatric surgery: case series and literature review. *International Urology and Nephrology, 42*(2), 369-374.

Wiesenthal, Joshua D, Ghiculete, Daniela, Honey, R John D'A, & Pace, Kenneth T. (2010). Evaluating the importance of mean stone density and skin-to-stone distance in predicting successful shock wave lithotripsy of renal and ureteric calculi. *Urological Research, 38*(4), 307-313.

Wiesenthal, Joshua D, Ghiculete, Daniela, Honey, R John D'A, & Pace, Kenneth T. (2011a). A comparison of treatment modalities for renal calculi between 100 and 300 mm2: are shockwave lithotripsy, ureteroscopy, and percutaneous nephrolithotomy equivalent? *Journal of Endourology, 25*(3), 481-485.

Wiesenthal, Joshua D, Ghiculete, Daniela, Ray, A Andrew, Honey, R John D'A, & Pace, Kenneth T. (2011b). A clinical nomogram to predict the successful shock wave lithotripsy of renal and ureteral calculi. *The Journal of Urology, 186*(2), 556-562.

Wilbert, DM, Reichenberger, H, Hutschenreiter, G, Riedmiller, H, Alken, P, & Hohenfellner, R. (1987). Second generation shock wave lithotripsy: experience with the lithostar *World Journal of Urology, 4*, 225-228.

Willis, Lynn R, Evan, Andrew P, Connors, Bret A, Handa, Rajash K, Blomgren, Philip M, & Lingeman, James E. (2006). Prevention of lithotripsy-induced renal injury by pretreating kidneys with low-energy shock waves. *Journal of the American Society of Nephrology, 17*(3), 663-673.

Worster, A, & Richards, C. (2005). Fluids and diuretics for acute ureteric colic. *Cochrane Database Syst Rev, 3*.

Ye, Zhangqun, Yang, Huan, Li, Hong, Zhang, Xiaochun, Deng, Yaoliang, Zeng, Guohua, . . . Mi, Qiwu. (2011). A multicentre, prospective, randomized trial: co. parative efficacy of tamsulosin and

nifedipine in medical expulsive therapy for distal ureteric stones with renal colic. *British Journal of Urology International 108*(2), 276-279.

Yilmaz, Erdal, Batislam, Ertan, Basar, Murad, Tuglu, Devrim, Mert, Cagatay, & Basar, Halil. (2005). Optimal frequency in extracorporeal shock wave lithotripsy: prospective randomized study. *Urology, 66*(6), 1160-1164.

Zagsebski, Linda. (1996). *Essentials of Ultrasound Physics*: Mosby

Zanetti, Gianpaolo, Ostini, Fabio, Montanari, Emanuele, Russo, Riccarda, Elena, Andrea, Trinchieri, Alberto, & Pisani, Enrico. (1999). Cardiac dysrhythmias induced by extracorporeal shockwave lithotripsy. *Journal of Endourology, 13*(6), 409-412.

Zhang, Xiao, Yu, Jianjun, & Yang, Ranxing. (2013). Minimally Invasive Management with Holmium Laser in Total Urinary Tract Calculi. *Photomedicine and Laser surgery, 31*(5), 230-235.

Zhong, P., Xi, X., Zhu, S., Cocks, F. H., & Preminger, G. M. (1999). Recent developments in SWL physics research. [Research Support, U.S. Gov't, P.H.S.]. *Journal of Endourology, 13*(9), 611-617.

Zhong, Pei, Zhou, Yufeng, Zhu, Songlin, Cocks, Franklin, & Preminger, Glenn. (2003). Innovations in shock wave lithotripsy technology. *The Journal of the Acoustical Society of America, 114*, 2455.

Zhou, Yufeng, Cocks, Franklin H, Preminger, Glenn M, & Zhong, Pei. (2004a). The effect of treatment strategy on stone comminution efficiency in shock wave lithotripsy. *The Journal of Urology, 172*(1), 349-354.

Zhou, Yufeng, Cocks, Franklin H, Preminger, Glenn M, & Zhong, Pei. (2004b). Innovations in shock wave lithotripsy technology: updates in experimental studies. *The Journal of Urology, 172*(5), 1892-1898.

Zhu, Songlin, Cocks, Franklin H, Preminger, Glenn M, & Zhong, Pei. (2002). The role of stress waves and cavitation in stone comminution in shock wave lithotripsy. *Ultrasound in medicine & biology, 28*(5), 661-671.

Appendix A

Literature Search Strategy

Search terms (wildcard characters such as * also used)	**Kidney OR renal OR calyx OR ureter** **Extracorporeal OR shockwave OR shock wave OR ESWL OR ESWT** **The related articles function was also used to broaden the search and additional studies were manually searched in the reference lists of retrieved articles.**
Databases searched	CINAHL, ProQuest, PubMed, and Science Direct
Part of journals searched	Keywords in abstract and title, subject heading where possible
Years of search	1980-2015
Language	English
Types of studies to be included	Randomised controlled trials, observational series, experimental studies, case studies, meeting abstracts, and reviews
Inclusion criteria	Studies that included different success rates related to changing either the rate, power, or using a power ramping technique.

	Population generalizable to New Zealand
Exclusion	Studies that evaluated differences in outcomes by non-surgical factors, including:
	Anaesthesia type
	Imaging type (ultrasound or fluoroscopy)
	Studies that evaluated differences in outcome by patient factors, including:
	Age
	Gender
	Race/ethnicity