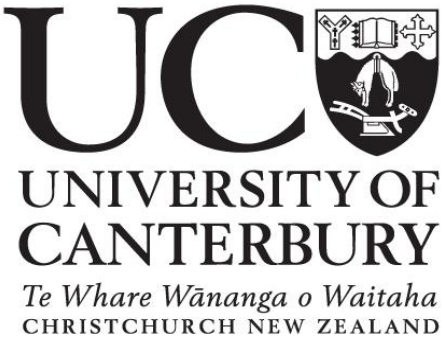

ANALYSIS, DEVELOPMENT AND MANAGEMENT OF GLUCOSE-INSULIN REGULATORY SYSTEM FOR OUT OF HOSPITAL CARDIAC ARREST (OHCA) PATIENTS, TREATED WITH HYPOTHERMIA

AZURAHISHAM SAH PRI

A thesis presented for the degree of
Doctor of Philosophy in
Mechanical Engineering
at the
University of Canterbury,
Christchurch, New Zealand.

November 2014

Acknowledgements

I would like to thank the following people and groups for their assistance, support and friendship during my doctoral study and make this research project possible.

I wish to express my gratitude to my principal supervisor, Distinguished Professor. Dr J. Geoffrey Chase for his advice, enthusiasm, encouragement and support during my study. I would also like to acknowledge the advice and guidance of my co-supervisors, Dr Thomas Desaive and Dr Chris Pretty.

I also wish to express my sincere appreciation to Jennifer Dickson, Liam Fisk and Aaron Le Compte for their for their informative discussions and continuous support in this research throughout the years. I also would like to convey many thanks to my colleagues, Matt, Azlan, Salwa, Musabir, Peng Guo, Shun, Alexander and Ina in the Centre for BioEngineering, for your friendship and making the work environment enjoyable and productive.

Finally, I wish to express my love and gratitude to my lovely wife, Nora Yusni Mohamed Yusop and children – Nurul Zahirah and Muaz, as well as my father and mother for their endless love, resolute support and encouragement in my life. My thanks are due to my siblings and family for their loving support. I would also like to extend my deepest gratitude to all my friends for their support and made my time here so enjoyable.

I am grateful for the financial support by the “Majlis Amanah Rakyat (MARA)” and Universiti Kuala Lumpur (UniKL) through the Academic Staff Training Scheme.

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Nomenclature

Acronyms and abbreviations

APACHE	Acute Physiological And Chronic Health Evaluation
ATP	Adenosine Triphosphate
BG	Blood Glucose
CDF	Cumulative Distribution Function
EGP	Endogenous Glucose Production
ICING	Intensive Control Insulin-Nutrition-Glucose
ICU	Intensive Care Unit
IQR	Interquartile Range
OHCA	Out of Hospital Cardiac Arrest
ROSC	Resumption of Spontaneous Circulation
SI	Insulin sensitivity parameter
SPRINT	Specialized Relative Insulin and Nutrition Tables
STAR	Stochastic TARgeted
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TGC	Tight Glycaemic Control
Uen	Endogenous insulin secretion

Mathematical variables

α_G	Michaelis-Menten constant for insulin binding saturation parameter [L/mU]
α_I	Michaelis-Menten constant for hepatic insulin clearance saturation parameter [L/mU]
c	Variance estimator modification constant
CNS	Central nervous system glucose uptake [mmol/min]
D(t)	Oral glucose input rate (enteral nutrition) [mmol/min]
d_1	Glucose transport rate from stomach to gut [1/min]
d_2	Glucose transport rate from gut to plasma [1/min]
EGP	Endogenous glucose production rate [mmol/min]
G	Blood glucose concentration [mmol/L]
I	Blood plasma insulin concentration [mU/L]
n_I	Trans-endothelial diffusion rate [1/min]
n_C	Interstitial insulin degradation rate [1/min]
n_K	Renal insulin clearance rate [1/min]
n_L	Hepatic insulin clearance rate [1/min]
x_L	Fractional first-pass hepatic insulin extraction
p_G	Non-insulin mediated glucose removal [1/min]
P_{max}	Maximum glucose flux from gut to plasma [mmol/min]
PN(t)	Intravenous glucose input rate (parenteral nutrition) [mmol/min]
u_{min}	Minimum pancreatic secretion rate [mU/min]
u_{max}	Maximum pancreatic secretion rate [mU/min]
$u_{ex}(t)$	Intravenous insulin input rate [mU/min]
V_G	Plasma glucose distribution volume [L]
V_I	Plasma and interstitial insulin distribution volume [L]

Academic Contribution

This doctoral thesis was completed by preparing a series of academic papers, with the main objective to develop safe and effective stochastic targeted model based glycaemic controller for highly intensive care Out of Hospital Cardiac Arrest (OHCA) patients using the existing ICING-2 model and STAR framework. The candidate's academic contributions are summarised as follows:

i) Perform evolution and variability analysis of OHCA patients based on metabolic, glycaemic and exogenous insulin and nutrition during hypothermia (cool period) and normothemia (warm period). The main findings from this study will be used to define control design specifications for the cohort.

ii) Develop new stochastic model, specifically for unique clinical and physiological case of the OHCA patients, treated with hypothermia based on clinically validated, model based insulin sensitivity during cool and warm period.

iii) Develop adaptive model based STAR-OHCA controller using cohort specific stochastic model with some modifications based on the constraints defined by control design specifications.

iv) Evaluate controller performance through virtual trial simulations.

The following publications were generated during this study.

1. Peer-Reviewed Journal Articles:

1.1 Sah Pri, A., J. G. Chase, C. G. Pretty, G. M. Shaw, J. C. Preiser, J. L. Vincent, M. Oddo, F. S. Taccone, S. Penning and T. Desaive (2014). "Evolution of insulin sensitivity and its variability in out of hospital cardiac arrest (OHCA) patients treated with hypothermia." Crit Care **18**(5): 586.

2. Papers Published in Refereed Conference Proceedings:

2.1 Sah Pri A, Chase J.G, Le Compte A.J, Shaw G.M, Preiser J.C, Taccone F, Penning S, Desaive T (2013). Insulin Sensitivity during Hypothermia in Critically Ill Patients. International Journal of Medical Sciences, vol 4 (2): 2013, 41-52

3. Papers Presented in Conference:

3.1 Insulin Sensitivity during Hypothermia in Critically Ill Patients (Paper no: 143)

This article was presented at the International Conference on Computational Bioengineering (ICCB), 11-13 September 2013 at Leuven, Belgium, and accepted for publication.

3.2 Insulin Sensitivity Variability during Hypothermia

This article has been accepted for oral presentation at the 19th (International Federation of Automatic Control) IFAC World Congress which will be held in Cape Town, South Africa, August 2014.

4. Paper Accepted for Poster Presentation in Conference:

4.1 Insulin Sensitivity in Out of Hospital Cardiac Arrest Patients Treated With Hypothermia

This article was accepted for poster presentation at the 26th Annual Congress of the European Society of Intensive Care Medicine (ESICM) which was held in Paris, France from 5-9 October 2013

5. Papers in Preparation

5.1 Stochastic Modelling of Insulin Sensitivity for Post-Cardiac Arrest Patients during hypothermia

5.2 Virtual trial simulation analysis of stochastic-based glycaemic control for OHCA patient, treated with hypothermia.

5.3 Blood glucose controller for OHCA patients, treated with hypothermia: Initial development and virtual trials

Abstract

Hyperglycaemia is prevalent in critical care and increases the risks of further complications and mortality. Glycaemic control has shown benefits in reducing mortality. However, due in parts to excessive metabolic variability, many studies have found it difficult to reproduce these results. Out-of-Hospital Cardiac Arrest (OHCA) patients have low survival rates and often experience hyperglycaemia. However, these patients belongs to one group who has shown benefit from accurate glycaemic control (AGC), but can be highly insulin resistant and variable, particularly on the first two days of stay.

Hypothermia is often used to treat post-cardiac arrest patients or out of hospital cardiac arrest (OHCA) and these same patients often simultaneously receive insulin. In general, it leads to a lowering of metabolic rate that induces changes in energy metabolism. However, its impact on metabolism and insulin resistance in critical illness is unknown, although one of the adverse events associated with hypothermic therapy is a decrease in insulin sensitivity and insulin secretion. However, this decrease may not be notable in the cohort that is already highly resistant and variable. Hence, understanding metabolic evolution and variability would enable safer and more accurate glycaemic control using insulin in this cohort.

OHCA patients were undergone preliminary analysis during cool and warm, which includes insulin sensitivity (SI), blood glucose (BG), and exogenous insulin and dextrose. Patients were analysed based on overall cohort, sub-cohorts, and 6 and 12 hour time block. Generally, the results show that OHCA patients had very low metabolic activity during cool period but significantly increased over time. In contrast, BG is higher during cool period and decreased over time. The analysis is equally important as the controller development since it provides scientific evidence and understanding of patients' physiology and metabolic evolution especially during cool and warm.

Model-based methods can deliver control that is patient-specific and adaptive to handle highly dynamic patients. A physiological ICING-2 model of the glucose-insulin regulatory system is presented in this thesis. This model has three compartments for glucose utilisation, effective interstitial insulin and its transport, and insulin kinetics in blood plasma, with

emphasis on clinical applicability. The predictive control for the model is driven by the patient-specific and time-varying insulin sensitivity parameter. A novel integral-based parameter identification enables fast and accurate real-time model adaptation to individual patients and patient condition.

Stochastic models and time-series methods for forecasting future insulin sensitivity are presented in this thesis. These methods can deliver probability intervals to support clinical control interventions. The risk of adverse glycaemic outcomes given observed variability from cohort-specific and patient-specific forecasting methods can be quantified to inform clinical staff. Hypoglycaemia can thus be further avoided with the probability interval guided intervention assessments.

Simulation studies of STAR-OHCA control trials on 'virtual patients' derived from retrospective clinical data provided a framework to optimise control protocol design in-silico. Comparisons with retrospective control showed substantial improvements in glycaemia within the target 4 - 7 mmol/L range by optimising the infusions of insulin. The simulation environment allowed experimentation with controller parameters to arrive at a protocol that operates within the constraints found earlier during patient analysis.

Overall, the research presented takes model-based OHCA glycaemic control from concept to proof-of-concept virtual trials. The thesis employs the full range of models, tools and methods to optimise the protocol design and problem solution.

Chapter 1: Introduction

Hyperglycemia, or elevated blood glucose level, is a common effect of uncontrolled diabetes and is prevalent in critical care patients (Capes et al., 2000, McCowen et al., 2001, Mizock, 2001, van den Berghe et al., 2001). During recent years, hyperglycemia was associated with adverse outcomes in various clinical settings (Rovlias and Kotsou, 2000, Umpierrez et al., 2002, Krinsley, 2003, Egi et al., 2010). For example, hyperglycemia predicted a higher risk after stroke and poor functional recovery in surviving patients. In patients with myocardial infarction (heart attack) and coronary artery disease, hyperglycemia was associated with an increase of further complications and mortality (Capes et al., 2000, van den Berghe et al., 2001).

This problem has attracted many researchers to conduct studies on hyperglycaemia in the critically ill, and specifically how to perform glycaemic control effectively and safely among those patients. Two landmark studies by Van den Berghe (van den Berghe et al., 2001, Van den Berghe et al., 2006a) and Krinsley (Krinsley, 2004) showed that tight glycaemic control can reduce patient mortality and led to several additional clinical and model-based studies (Chase et al., 2008b). However, while some were successful (van den Berghe et al., 2001, Krinsley, 2004, Chase et al., 2008b), others failed to repeat the results (Brunkhorst et al., 2008, Finfer et al., 2009, Preiser et al., 2009). As hyperglycaemia and its complications increase risk and costs, it has become a significant research area and was recently reviewed by Chase (Chase et al., 2006a, Chase et al., 2007a, Chase et al., 2011b).

1.1 Cardiac Arrest Patients

Cardiac arrest can be described as the cessation of normal circulation of the blood due to sudden loss of cardiac function, when the heart abruptly stops beating and pumping blood to the brain and other parts of the body (Jameson, 2005). Arrested blood circulation prevents delivery of oxygen to the body. Permanent brain damage and death is likely to occur unless the flow of blood to the brain is restored (Vespa et al., 2005). Ventricular fibrillation is the most common cause of cardiac arrest (Zipes and Wellens, 1998), which occurs due to heart

attack (myocardial infarction), respiratory arrest (loss of breathing function), choking, trauma, electrocution and drowning (Jameson, 2005).

A person whose heart has stopped will lose consciousness and stop normal breathing, and their pulse and blood pressure will be absent. Cardiac arrest leads to death within a few minutes and is obviously a serious emergency unless resuscitative efforts are begun immediately (Neumar et al., 2008). Early emergency treatment, such as cardiopulmonary resuscitation (CPR) and defibrillation (electrical impulses delivered to the chest to restore normal heart rhythm), are primary ways to reverse cardiac arrest and must be implemented within a few minutes to increase chances of survival.

1.2 Out of Hospital Cardiac Arrest (OHCA) Patients

Post-Cardiac Arrest or Out-of-Hospital Cardiac Arrest (OHCA) Syndrome is the medical emergency that occurs after the immediate resuscitation. It is characterized by resumption of spontaneous circulation (ROSC) after prolonged complete whole body ischemia, followed by resuscitation (Neumar et al., 2008). Once ROSC is achieved, the patient is technically alive. However, rates of early mortality in patients achieving ROSC after cardiac arrest vary dramatically among countries, regions and hospitals (Langhelle et al., 2003, Herlitz et al., 2006). The cause of these differences includes variability of patient populations, reporting methods, and, potentially, post-cardiac arrest care.

Approximately 166,200 out-of-hospital cardiac arrests occur annually in the US (Nolan et al., 2008). On average, approximately 6.4% of out-of-hospital cardiac arrest patients survive to hospital discharge. The in-hospital mortality rate of patients who achieve ROSC after cardiac arrest has not changed significantly over the past 50 years (Bloom et al., 2007, Ehlenbach et al., 2009, Tian et al., 2010). Thus, there may be room for improved treatment after ROSC to improve outcomes.

Hyperglycaemia is also common in OHCA patients and is associated with poor neurological outcome in survivors (Geocadin et al., 2008, Neumar et al., 2008). Post-cardiac arrest brain injury and myocardial dysfunction are common cause of morbidity and mortality which contribute to low survival rates after in- and out-of-hospital cardiac arrest (Stub et al., 2011) . However, there is growing evidence that appropriate post-cardiac arrest care, such as tight

glycaemic control and therapeutic hypothermia can improve mortality rate and functional outcome (Safar et al., 1996, Holzer and Behringer, 2005, Neumar et al., 2008). Hence, these findings open further research and development opportunities for improving the existing tight glycaemic control system to specifically benefit post-cardiac arrest patients in specific.

1.3 Aetiology of Hypothermia in OHCA Patients Care

Post-Cardiac Arrest or Out-of-Hospital Cardiac Arrest (OHCA) patients are one group who have shown benefit from Tight Glycaemic Control (TGC), but can be highly insulin resistant and variable, particularly on the first day of stay (Pretty et al., 2012) . Hypothermia or lowering body temperature below 35 degree Celsius is often used to treat out of hospital cardiac arrest (OHCA) (Graffagnino et al., 2012, Ornato et al., 2012, Reynolds and Lawner, 2012, Bucher et al., 2013, Dietrich et al., 2013, Scirica, 2013, Winters et al., 2013, Mearns, 2014, Picchi et al., 2014, Polderman et al., 2014) and these same patients often simultaneously receive insulin (Nolan et al., 2008) . Hypothermia leads to a further lowering of the metabolic rate and includes changes in energy metabolism and decreases in adenosine triphosphate (ATP) demand during cellular respiration process (Melhuish, 2009).

Symptoms of hypothermia may be vague of difficult to identify, with sympathetic nervous system excitation such as shivering, hypertension, tachycardia, tachypnea and vasoconstriction (Hanania and Zimmerman, 1999). Other symptoms, such as cold dieresis, mental confusion, and hepatic dysfunction, may also present (McCullough and Arora, 2004). Most hypothermia-related deaths are preventable but conversely statistical record in year 2001 have revealed that a total of 646 hypothermia-related deaths were reported in the United States, with an annual death rate of 0.2 per 100,000 population (Fallico et al., 2002). These statistics data suggest that hypothermia and its complications increase risk even though it is increasingly used for treating OHCA patients.

In the event of hypothermia, patients now frequently undergo intensive hypothermic therapy (Stub et al., 2011, Graffagnino et al., 2012, Ornato et al., 2012, Dietrich et al., 2013, Scirica, 2013) as the treatment offers beneficial effects physiologically and clinically (Dietrich et al., 2009, Marion and Bullock, 2009, Egi et al., 2010). One of the adverse events associated with hypothermic therapy is the decrease in insulin sensitivity and insulin secretion (Hayashi,

2009). The amount of insulin required to maintain glucose levels within normal range (80 to 110 mg/dL) is likely to increase during the induction of hypothermia, which can equally lead to increased risk of hyperglycaemia and hypoglycaemia. Therefore, these patients require additional care in metabolic management.

1.4 Hypothermia and Glucose-Insulin System Dynamics

The metabolic system is one of the important systems in human body. It processes the complex carbohydrate and sugar molecules from food and transforms them into glucose for storage and metabolism. The system comprises the stomach, pancreas, liver and cells where each organ has specific roles in digesting or storing glucose from food. Hormones, such as insulin and glucagon, assist the process by providing signals to the cells for releasing stored glucose or the liver for storing glucose from bloodstream.

After food is consumed, the body reduces complex carbohydrate and sugar molecules to the simple six-carbon sugar known as glucose. Glucose is the body's fuel, and upon the reduction by the body, it is either utilised or stored. Sensing glucose in the bloodstream leads the β-cells in the pancreas to produce insulin. The concentration of insulin acts as the body's signal to manage storage and transportation, and thus determines the utilisation or storage rate of glucose.

Insulin is a protein that consists of 51 amino acids in two closely connected chains. Insulin molecules and their connecting fragments are then packed together in small granules in the β-cells, which are secreted on demand through the islets of Langerhans in the pancreas. Along with β-cells, the 1 to 2 million islets of Langerhans contain α and δ cells, which secrete glucagon and somatostatin, respectively, and act as additional blood glucose regulatory hormones. The α, β and δ cells are approximately 25%, 60% and 10% of the total islets and are all very closely related (Guyton and Hall, 2000)

The level of insulin in the bloodstream is the signal that facilitates the proper metabolic response as shown in Figure 1.1 . A high insulin level promotes storage of glucose, and a low insulin and glucose level signals the need for the release of glucose fuels, currently in storage, back into the blood stream. A meal results in an increase of insulin concentration in the blood, due to the increased secretion of insulin by the β-cells, and signals the liver and

muscles to consume the extra fuel (glucose) available. The liver stores glucose as glycogen or fat, and the muscles utilise glucose primarily to repair damaged muscle cells, for energy storage as glycogen and lastly storage in fat cells.

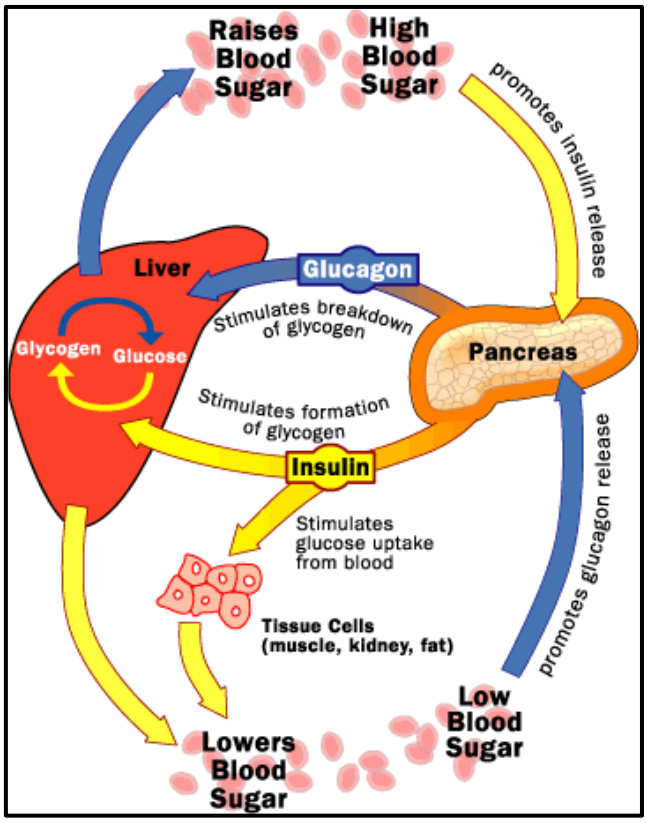

Figure 1.1: Model of Glucose-Insulin Regulatory System. The schematic shows the effect of high and low blood glucose levels in the body. Adapted from health.howstuffworks.com

Counter regulatory hormones, such as glucagon and adrenaline, signal the liver to release glucose. Too much glucose removal from the blood-stream can result in low blood glucose levels. When the glucose available is not sufficient enough to supply the brain's requirements, hypoglycaemic symptoms including hunger, anxiousness, restlessness, agitation, perspiration, tachycardia (racing pulse) and palpitation (irregular and/or forced heart-beats) occur. These symptoms are partly a result of the release of adrenaline by the body as a counter regulatory measure to restore normal blood glucose levels. When the amount of insulin released is suddenly reduced, the signal is not available to the body to indicate it should remove glucose from the blood stream. The blood glucose level therefore

rises until there is hyperglycaemia, requiring further insulin. It is thus a natural feedback system using glucose raising / glucagon and adrenaline, and lowering insulin hormones.

Insulin is an anabolic hormone and promotes growth, while lowering glucose levels (Vander, 2001). Insulin also increases the activity of other enzymes, primarily those involved in glycogen, lipid and protein synthesis, and inhibit the activity of those that catalyse glucose degradation. However, all these digestive and metabolic activities involving secretion of insulin, glycogen and other related hormones and enzymes are optimum only during normal body temperature between 36^{o}C and 37.5^{o}C (Lehninger, 1970, Wilson, 1988). At body temperature of higher or lower than normal range, the production of hormones and enzymes from the pancreas and other organs shows some decay and can eventually affect the metabolic rate and physiological condition of the body (Benz-Woerner et al., 2012).

To date, there is no scientific evidence explaining human glucose-insulin kinetics during hypothermia. However, by use of a newly developed technique, substrate profiles and their regulation by insulin were examined in hypothermic rats over 24h (Hoo-Paris et al., 1988, Cueni-Villoz et al., 2011), resulting in the following outcomes:

i) Plasma glucose concentrations increased during cooling and remained high thus reducing glucose utilization throughout the period of hypothermia (Escolar et al., 1990).
ii) Plasma insulin decreased dramatically during cooling and remained very low during the whole period of hypothermia, reflecting the suppression of endogenous insulin secretion seen in isolated islets at low temperatures (Escolar et al., 1987).
iii) Resistance to exogenous insulin is increased (Torlinska et al., 2002).

The role of pancreas in producing insulin and glycogen hormones is vital and its ability to perform at optimum level is important in regulating blood glucose level at normal glycaemic range. However, during hypothermia, the pancreas is unable to function normally, which can lead to increased or decreased blood glucose levels (Benz-Woerner et al., 2012). In general, hypothermia can be life threatening. However, it also benefits patients with recent heart attack.

1.5 The Problem Statement

To date, there are no clinically applied glucose-insulin regulatory models developed for specific patient cohorts with specific physiological conditions, such as post-cardiac arrest patients with hypothermia. The existing glucose-insulin regulatory models (Hann et al., 2005, Lin et al., 2011) are suitable when dealing with typical hyperglycaemia cases in critical care where all predictable symptoms have taken into account when developing the models, which are based on normal or elevated body temperature. However, when induced hypothermia is implemented during treatment, the condition is changed from this baseline and the existing models may not be able to respond optimally, leading to poor treatment. Thus, highly variable blood glucose levels which can adversely affect clinical outcomes and mortality.

Thus, there is a strong need for more rigorous analysis that reviews and improve existing model-based glycaemic control methods based on physiological response during hypothermia. This goal will lead to a review of the existing glycaemic model and the numerical parameters used, improve the insulin sensitivity prediction and blood glucose control methods, and improve the overall insulin-nutrition administration system. All of these will be specific to these hypothermia treated cohorts.

1.6 Significance of the Study

Rigorous studies in this area will end up developing a model-based glycaemic control approach that can deliver computerized glycaemic control adaptable to these specific critically ill patients. Additional features like cohort-specific stochastic modelling and adaptive control methods can further enhance model-based control with more accurate predictive performance and will be equally novel. The new glycaemic control should be able to overcome blood glucose variability problems, specific to post-cardiac arrest patients undergoing hypothermia, thus potentially improving care and reducing morbidity and mortality of ICU patients in this category.

1.7 Preface

This thesis is organized in two parts as shown in Figure 1.2. Part I is related to the patient analysis and clinical setting of this work. An existing metabolic system model is reviewed, considering the physiological conditions due to human body temperature change and available data sets are presented. Part II focuses on control system design and virtual trials simulation. Detailed overview of all chapters of this thesis is described as follows:

Chapter 2: Model Review and Development

This chapter reviews the physiology of the glucose-insulin regulatory system and describes the fundamental aspects of glycaemic control, which includes an overview of previous glycaemic models, metabolic system model (ICING model) used and the more recent ICING-2 model. This chapter is also reviewing the overall glycaemic control system model and its key components, including input, output, actuators, patient and controller in general. Then, the discussion is focused on glycaemic control and its development such as SPRINT and STAR controller. Finally, performance metrics, suitable for general TGC is also introduced.

Chapter 3: Patient Demography

This chapter summarizes the overall OHCA patient background with statistical analysis on the cohort by mortality, diabetes, sex and the return of spontaneous circulation (ROSC). This set of cohorts is used throughout the thesis.

Chapter 4: Insulin Sensitivity Level and Variability Analysis

This chapter explains the physiological and metabolic conditions of OHCA patients treated with hypothermia based on insulin sensitivity (SI) level and variability. Analysis and comparison is made between cool and warm conditions per-cohort and per-patient, which in turn characterize the overall evolution of SI for this cohort.

Chapter 5: Blood Glucose Level and Variability Analysis

This chapter explains the physiological and metabolic conditions of OHCA patients, treated with hypothermia based on blood glucose (BG) level and variability analysis. Analysis and comparison is made between cool and warm conditions per-cohort and per-patient, which in turn characterize the overall evolution of BG for this cohort. This topic overlaps Chapter 4, but also includes the impact of glycaemic control which differs between cohorts.

Chapter 6: Exogenous Insulin and Nutrition Analysis

This chapter describes a preliminary study of OHCA patients based on exogenous insulin and nutrition characteristics during hypothermia (cool period) and normothemia (warm period). It analyses the impact of exogenous insulin and nutrition modulation during TH on glycaemic outcome. Analysis and comparison is made between cool and warm conditions, which in turn characterize the overall insulin and nutrition administration for this cohort.

Chapter 7: Stochastic Modelling of Insulin Sensitivity Analysis

This chapter develops the method for insulin sensitivity variation forecasting for this specific cohort. Stochastic and time-series analysis techniques are used to generate likelihood bands for future blood glucose concentration. Observations of differences in stochastic behaviour between cool and warm, 12 and 6-hour time block, and patient characteristics such as diabetes, mortality, sex and ROSC may further develop protocols for different time blocks and groups.

Chapter 8: Summary of OHCA Patient Analysis

This chapter summarize the overall scenario and define glycaemic control problems based on analysis in chapter 4, 5, 6 and 7. It begins with describing overview of OHCA patient analysis and its relation with overall research work. Then, patient results from previous analysis were tabled based on overall cohort, 6 and 12-hour time block, and patient sub-cohorts. Patient conditions, problems and treatment observations are identified and discussed thoroughly.

Chapter 9: STAR Control Performance Analysis and Virtual Trials

This chapter presents a comparative study of STAR controller performance over Out-of-Hospital Cardiac Arrest (OHCA) patients based on general and OHCA-specific stochastic models. It analyses the improvement in glycaemic control that can be achieved by these stochastic models during treatment, including the evolution of blood glucose and its variability.

Chapter 10: Conclusions

Finally, this chapter summarize the overall research work and its important findings as well as proposing the possible future improvements and applications in relation to this studies.

Chapter 11: Future Work

Finally, this chapter summarize the overall research work and its important findings as well as proposing the possible future improvements and applications in relation to this studies.

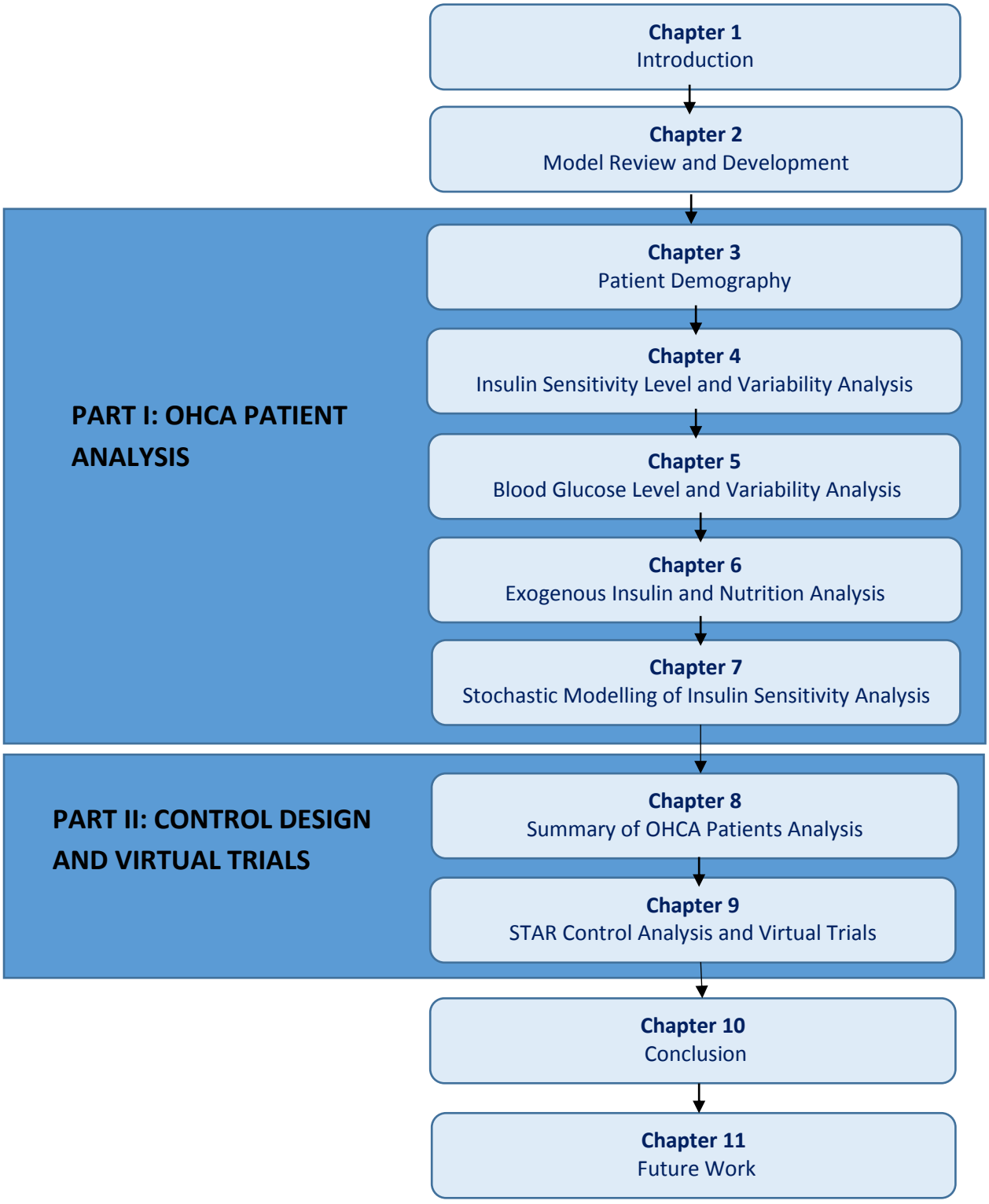

Figure 1.2: Thesis outline. Part I of this thesis introduces relevant background knowledge, analyse patients' data and determine control problem definitions. Part II presents the review of glycaemic control development and virtual trials.

Chapter 2: Model Review and Development

The dynamics of the human glucose-insulin regulatory system have been studied extensively. A number of researchers have developed models with distinct levels of complexity to suit different physiological conditions, clinical or research applications, and targeted clinical outcomes. For instance, many models have been designed to provide model-based measures to assess metabolic phenomena, with a particular focus on measuring insulin sensitivity (Bergman et al., 1979, Bergman et al., 1981, Bergman et al., 1985, Pacini and Bergman, 1986, Yang et al., 1987, Mari, 1998, Toffolo et al., 1999, Mari et al., 2001, Pacini and Mari, 2003, Toffolo et al., 2006). These investigations focused on understanding specific metabolic phenomena, rather than clinical intervention or control. They thus tended forward more minimal models of just glucose, insulin, and insulin sensitivity. Critically, a physiological model that captures the basic glucose-insulin dynamics and insulin sensitivity is also the starting basis for any glycaemic control problem.

Several researchers have constructed control system models due to a high demand for insulin infusion dose advice and control of blood sugar levels (Deutsch et al., 2004, Wong et al., 2008), model predictive control (MPC) (Hovorka et al., 2004) and automated or semi-automated glycaemic control (Parker et al., 1999, Parker et al., 2001, Hovorka et al., 2004, Lonergan et al., 2006b, Plank et al., 2006a, Chase et al., 2007b, Wong et al., 2008). These are all models for clinical intervention.

More advance biomedical control system models have additions that can capture, predict and control patient metabolic behaviour. Such a model offers a safe and fast means for protocol development without clinical testing and risk (Chase et al., 2010) . Equally, control system models must often work with the available clinical data in real-time, which demand a more robust modelling solution compared to models designed to model human physiology in research settings (Chase et al., 2006a).

This chapter examines several forms of existing metabolic control system models that have been used in adult intensive care. A glycaemic control system for OHCA patients, treated with hypothermia is developed from this foundation. Since the OHCA cohort patients are mainly adult, most of the model parameters during normal body temperature can be adapted. However, a clinically validated insulin sensitivity parameter (Chase et al., 2010) is identified in each period to understand the impact of hypothermia or metabolism.

2.1 Glucose-Insulin Models for Critical Care

Intensive care represents a highly controlled environment where most glucose-insulin system inputs and outputs can be accounted for and thus modelled. However, the stress of critical illness can significantly disturbs the glucose-insulin regulatory system from a healthy baseline (Capes et al., 2000, McCowen et al., 2001, Mizock, 2001, van den Berghe et al., 2001). This situation is exacerbated by the inconsistency and wide range of medications administered to the critically ill, many of which exhibit highly patient-specific effects on glucose metabolism (Pretty et al., 2011). Such detailed pharmacodynamics information may not be measurable in a typical clinical setting. Thus, any control system model must make a compromise between physiological validity, clinical applicability and mathematical identifiability.

A physiological model that captures glucose-insulin system dynamics and allows accurate blood glucose prediction is an acceptable basis for model-based glycaemic control. The vast majority of these models have their roots in basic compartment modelling with differential equations (Carson and Cobelli, 2001). These models and, in particular, those from which the model in this thesis is derived, have been extensively reviewed (Le Compte et al., 2009, Lin et al., 2011). This section provides a summary of the basic requirements for a compartment model that can be used in clinical real-time and introduces the ICING model used throughout the rest of this thesis.

A compartment model consists of five basic elements:

1. Compartments in which substances exist at varying concentrations or mass.
2. Kinetics describing the transport of substances between compartments such as mass or concentration.
3. Dynamics that describe the interaction of substances with each other or the environment.
4. Appearance of substances into the compartment system from the external environment.
5. Clearance of substances back to an external environment.

In addition to these five basic elements, a successful model for clinical control should also be physiologically valid, clinically applicable and mathematically identifiable (Chase et al., 2011a). These additional factors ensure that the model output provides useful information about patient physiology and status, and can be identified in clinical real-time using the limited measurement data available.

2.1.1 Critical care glucose–insulin model (ICU model)

The model from (Chase et al., 2007b) was developed and validated for glycaemic level management in the ICU. This model captures the fundamental dynamics seen in critically ill patients, yet has a relatively simple mathematical structure enabling rapid identification of patient-specific parameters (Hann et al., 2005). This model only blood glucose (BG) measurements, so it can be used at the bedside for clinical real-time identification and control. This structure has been widely used in clinical TGC studies and other analyses (Lin et al., 2008, Wong et al., 2008, Le Compte et al., 2009).

Equations (2.1) – (2.5) present this ICU model as used for glycaemic control in intensive care:

$$\dot{G} = -p_G.G(t) - S_I.G(t).\frac{Q(t)}{1+\alpha_G Q(t)} + \frac{P(t)+EGP_b - CNS}{V_G} \qquad (2.1)$$

$$\dot{I} = -\frac{nI}{\min(1+\alpha_I I,2)} + \frac{u(t)}{V_I} + 3e^{-(u(t)*k_I)} \tag{2.2}$$

$$\dot{Q} = -kQ + kI \tag{2.3}$$

$$\dot{P}_1 = -d_1 P_1 + P(t) \tag{2.4}$$

$$\dot{P}_2 = -\min\left(d_2 P_2, P_{\max}\right) + d_1 P_1 \tag{2.5}$$

where *G(t)* [mmol/L] denotes the total blood glucose, *I(t)* [mU/L] is the plasma insulin, *Q(t)* [mU/L] is the effect of previously infused insulin being utilized over time, with *k* [1/min] accounting for the effective life of insulin in the system. Endogenous glucose removal and insulin sensitivity are denoted p_G [1/min] and S_I [L/mU/min], respectively. V_I [L] is the insulin distribution volume and *n* [1/min] is the constant first order decay rate for insulin from plasma. Basal endogenous glucose production unsuppressed by glucose and insulin concentration is denoted by EGP_b [mmol/min] and V_G [L] represents the glucose distribution volume. *CNS* [mmol/min] represents non-insulin mediated glucose uptake by the central nervous system. Michaelis-Menten functions are used to model saturation, with α_I [L/mU] used for the saturation of plasma insulin disappearance, and α_G [L/mU] for the saturation of insulin-dependent glucose clearance. P_1 [mmol] represents the glucose in the stomach and P_2 [mmol] represents glucose in the gut. The rate of transfer between the stomach and gut is represented by d_1 [1/min], and the rate of transfer from the gut to the bloodstream is d_2 [1/min]. P_{max} represents the maximum disposal rate from the gut. Exogenous inputs are glucose appearance *P(t)* [mmol/min] and intravenous insulin u(t). A schematic of the model is shown in Figure 2.1.

This model was developed and validated in critical care glycaemic control studies (Wong et al., 2006b, Chase et al., 2007b). Insulin sensitivity S_I is identified hourly from patient data, producing a step-wise hourly varying profile that effectively describes the patients' physiological behaviour under various metabolic conditions (Hann et al., 2005). The validity and independence of this patient-specific parameter have been validated using data from clinically matched cohorts (Chase et al., 2010) and in gold-standard insulin sensitivity tests (McAuley et al., 2011).

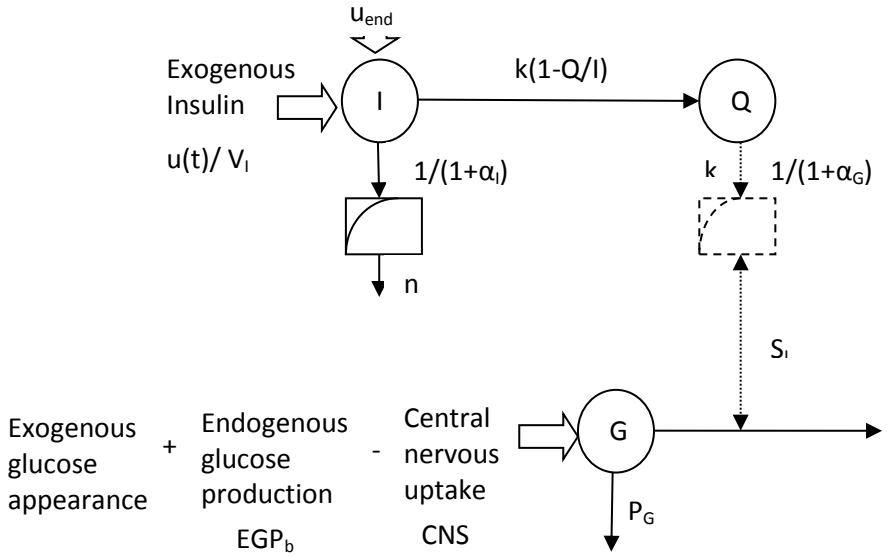

Figure 2.1: Critical care glucose-insulin model

2.1.2 Glucose–insulin model for insulin sensitivity test (S_I Test or DISST Model)

The second model from (Lotz et al., 2008) was developed for diagnosis of insulin resistance. The modelled insulin sensitivity has high correlation to the euglycaemic hyperinsulinemic clamp (EIC) and high repeatability (Lotz et al., 2006, Lotz et al., 2008). This model has more patient specific parameters, but is not suitable for real- time patient-specific parameter identification because it also requires non-real-time plasma insulin and C-peptide assays (Lotz et al., 2009). Hence, it is suitable for S_I screening and research tests. Recent work has sought to eliminate this issue in healthy subjects, but at a loss of a small amount of precision (Docherty et al., 2009).

Equations (2.6) – (2.8) presents this model:

$$\dot{G} = -p_G.G(t) - S_I.G(t).\frac{Q(t)}{1+\alpha_G Q(t)} + \frac{P(t)}{V_G} + EGP(t) \qquad (2.6)$$

$$\dot{Q} = \frac{n_I}{V_Q}(I(t) - Q(t)) - n_C Q(t) \qquad (2.7)$$

$$\dot{I} = -n_K I(t) - \frac{n_L I(t)}{1+\alpha_I I(t)} - \frac{n_I}{V_P}(I(t) - Q(t)) + \frac{u_{ex}(t)}{V_P} + (1 - X_L)\frac{u_{en}(t)}{V_P} \qquad (2.8)$$

The nomenclature for this model is largely the same as that for the ICU model in Section 2.1.1. This model has more parameters and more extensive insulin kinetics. The model also includes the endogenous glucose production rate EGP (mmol/L/min), as well as the endogenous insulin production u_{en} (mU/min). The endogenous insulin production can be calculated from C-peptide measurements using well validated insulin –C-peptide kinetics model (Van Cauter et al., 1992). Endogenous insulin goes through first pass hepatic extraction, where X_L is the fraction of extraction. This model also has more explicitly defined physiologically specific insulin transport parameters compared to the ICU model, where n_K is the kidney clearance rate of insulin from plasma [1/min], n_L is the liver clearance rate of insulin from plasma [1/min], n_I is the diffusion constant of insulin between compartments (L/min), and n_C is the cellular insulin clearance rate from interstitium [1/min]. Finally, it also uses different volumes for each compartment, where V_P (L) is the plasma and test exchanging tissues volume and V_Q (L) is the interstitial fluid volume.

In (Lotz et al., 2008, Lotz et al., 2009), measurements from insulin and C-peptide are used to identify n_L and X_L for each person. S_I and V_G are then calculated for each person using BG measurements. All other parameters are treated as population constants. The insulin sensitivity S_I identified using this model correlates highly ($r > 0.97$) to EIC results when both tests are modelled together (Lotz et al., 2006, Lotz et al., 2008). Therefore, this model is effective as a diagnostic tool for insulin resistance. However because plasma insulin and C-peptide measurements cannot be obtained in real time, this model cannot be readily adapted for TGC for ICU patients.

2.1.3 Intensive Control Insulin-Nutrition-Glucose model (ICING model)

The new and more physiologically comprehensive model ICING, addressing several implicit physiological aspects from prior models by (Chase et al., 2007b) and (Lotz et al., 2008) is presented in Equations (2.9) – (2.15):

$$\dot{G} = -p_G.G(t) - S_I.G(t).\frac{Q(t)}{1+\alpha_G Q(t)} + \frac{P(t) + EGP_b - CNS}{V_G} \quad (2.9)$$

$$\dot{I} = -n_K I(t) - \frac{n_L I(t)}{1+\alpha_I I(t)} - n_I(I(t) - Q(t)) + \frac{u_{ex}(t)}{V_I} + (1 - X_L)\frac{u_{en}(I)}{V_I} \quad (2.10)$$

$$\dot{Q} = n_I(I(t) - Q(t)) - n_C \frac{Q(t)}{1+\alpha_G Q(t)} \quad (2.11)$$

$$\dot{P_1} = -d_1 P_1 + D(t) \quad (2.12)$$

$$\dot{P_2} = -\min\left(d_2 P_2, P_{\max}\right) + d_1 P_1 \quad (2.13)$$

$$P(t) = \min\left(d_2 P_2, P_{\max}\right) + PN(t) \quad (2.14)$$

$$u_{en}(I) = k_1 e^{\frac{I(t)^{k2}}{k3}} \quad (2.15)$$

Where *G(t)* [mmol/L] denotes the absolute total blood glucose, *I(t)* [mU/L] is the plasma insulin, and *u(t)* [mU/min] represents exogenous insulin input. *Q(t)* [mU/L] is the effect of previously infused insulin being utilized over time, with n_I [1/min] accounting for the rate of transport between plasma and interstitial insulin compartments. Endogenous insulin production is model estimated with u_{en} [mU/min] based on clinical data and a validated insulin C-peptide kinetics model (Van Cauter et al., 1992), with first pass hepatic insulin clearance is represented by x_L. Patient endogenous glucose removal and insulin sensitivity are denoted p_G [1/min] and S_I [L/mU/min], respectively. The parameter V_I [L] is the insulin distribution volume and n_K [1/min] and n_L [1/min] the clearance rate of insulin from plasma via renal and hepatic routes respectively. Basal endogenous glucose production, unsuppressed by glucose and insulin concentration, is denoted by EGP_b [mmol/min], and V_G [L] represents the glucose distribution volume. Finally, *CNS* [mmol/min] represents non-insulin mediated glucose uptake by the central nervous system.

Michaelis-Menten functions are used to model effect saturation, with α_I [L/mU] used for the saturation of plasma insulin disappearance, and α_G [L/mU] for the saturation of insulin-dependent glucose clearance. P_1 [mmol] represents the glucose in the stomach and P_2 [mmol] represents glucose in the gut. The rate of transfer between the stomach and gut is represented

by d_1 [1/min], and the rate of transfer from the gut to the bloodstream is d_2 [1/min]. Amount of dextrose from enteral feeding is *D(t)* [mmol/min]. P_{max} represents the maximum disposal rate from the gut. Exogenous inputs are glucose appearance *P(t)* [mmol/min] from enteral food intake, flux out of the gut P_2 and intravenous insulin *u(t).* Any additional parenteral dextrose is represented by *PN(t).* Summary of parameter values and descriptions, and exogenous input variables for the ICING model are listed in Table 2.1 and 2.2 respectively. A schematic of the model is shown in Figure 2.2.

Table 2.1: Parameter values and descriptions for the ICING model

Parameter	Value	Unit	Description
p_G	0.006	1/min	Non-insulin mediated glucose removal
EGP	1.16	mmol/min	Endogenous glucose production rate
CNS	0.3	mmol/min	Central nervous system glucose uptake
V_G	13.3	L	Plasma glucose distribution volume
V_I	3.15	L	Plasma and interstitial insulin distribution volume
α_G	0.0154	L/mU	Insulin binding saturation parameter
α_I	0.0017	L/mU	Hepatic insulin clearance saturation parameter
n_I	0.003	1/min	Trans-endothelial diffusion rate
n_C	0.003	1/min	Interstitial insulin degradation rate
n_K	0.0542	1/min	Renal insulin clearance rate
n_L	0.1578	1/min	Hepatic insulin clearance rate
x_L	0.67		Fractional first-pass hepatic insulin extraction
d_1	0.0347	1/min	Glucose transport rate from stomach to gut
d_2	0.0069	1/min	Glucose transport rate from gut to plasma
P_{max}	6.11	mmol/min	Maximum glucose flux from gut to plasma
k_1	45.7	mU/min	Maximum endogenous insulin secretion rate
k_2	1.5		Insulin secretion suppression factor 1
k_3	1000		Insulin secretion suppression factor 2

Table 2.2: Exogenous input variables for the ICING model

Variable	Unit	Description
PN(t)	mmol/min	Intravenous glucose input rate (parenteral nutrition)
D(t)	mmol/min	Oral glucose input rate (enteral nutrition)
u_{ex}(t)	mU/min	Intravenous insulin input rate

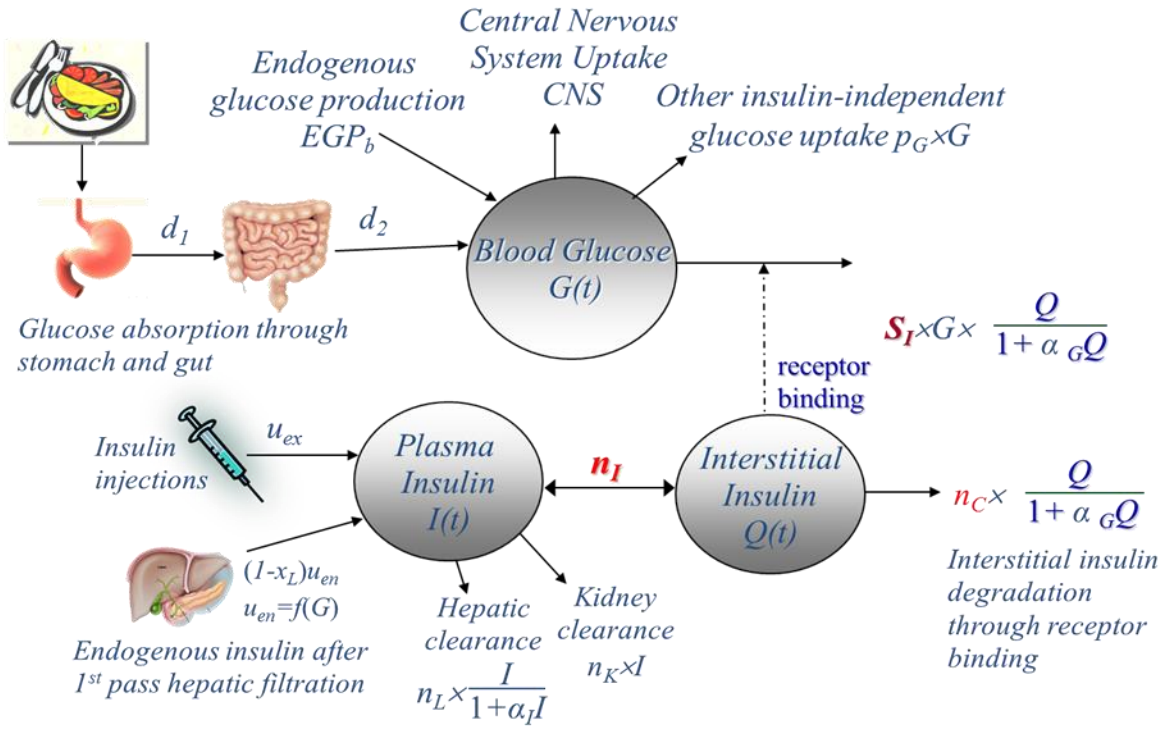

Figure 2.2: Intensive Control Insulin-Nutrition-Glucose (ICING) model overview

2.2 The Intensive Control Insulin-Nutrition-Glucose 2 model (ICING-2 model)

The ICING-2 model (Pretty, 2012) is the modified version of the ICING model (Lin et al., 2011) which proposed the following changes from its original:

i) New endogenous insulin secretion model as a function of blood glucose concentration.

ii) Improved insulin kinetics.

The model is presented in Equations (2.16) – (2.22) and the associated parameter values and descriptions are listed in Table 2.3, while Table 2.4 shows the exogenous input variables to the model. The model is defined:

$$\dot{G} = -p_G.G(t) - S_I.G(t).\frac{Q(t)}{1+\alpha_G Q(t)} + \frac{P(t)+EGP_b - CNS}{V_G} \qquad (2.16)$$

$$\dot{I} = -n_K I(t) - \frac{n_L I(t)}{1+\alpha_I I(t)} - n_I (I(t) - Q(t)) + \frac{u_{ex}(t)}{V_I} + (1 - X_L)\frac{u_{en}(G)}{V_I} \quad (2.17)$$

$$\dot{Q} = n_I (I(t) - Q(t)) - n_C \frac{Q(t)}{1+\alpha_G Q(t)} \quad (2.18)$$

$$\dot{P}_1 = -d_1 P_1 + D(t) \quad (2.19)$$

$$\dot{P}_2 = -\min\left(d_2 P_2, P_{\max}\right) + d_1 P_1 \quad (2.20)$$

$$P(t) = \min\left(d_2 P_2, P_{\max}\right) + PN(t) \quad (2.21)$$

$$u_{en}(G) = \min\left(\max(u_{\min}, k_1 G(t) + k_2), u_{\max}\right) \quad (2.22)$$

Table 2.3: Parameter values and descriptions for the ICING-2 model

Parameter	Value		Unit	Description
p_G	0.006		1/min	Non-insulin mediated glucose removal
EGP	1.16		mmol/min	Endogenous glucose production rate
CNS	0.3		mmol/min	Central nervous system glucose uptake
V_G	13.3		L	Plasma glucose distribution volume
V_I	4.0		L	Plasma and interstitial insulin distribution volume
α_G	0.0154		L/mU	Insulin binding saturation parameter
α_I	0.0017		L/mU	Hepatic insulin clearance saturation parameter
n_I	0.006		1/min	Trans-endothelial diffusion rate
n_C	0.006		1/min	Interstitial insulin degradation rate
n_K	0.0542		1/min	Renal insulin clearance rate
n_L	0.1578		1/min	Hepatic insulin clearance rate
x_L	0.67			Fractional first-pass hepatic insulin extraction
d_1	0.0347		1/min	Glucose transport rate from stomach to gut
d_2	0.0069		1/min	Glucose transport rate from gut to plasma
P_{max}	6.11		mmol/min	Maximum glucose flux from gut to plasma
u_{min}	16.7		mU/min	Minimum pancreatic secretion rate
u_{max}	266.7		mU/min	Maximum pancreatic secretion rate
k_1	ND	14.9	mU.L/mmol.min	Pancreatic insulin secretion glucose-sensitivity
	T2DM	4.9		
	T1DM	0.0		
k_2	ND	-49.9	mU/min	Pancreatic insulin secretion offset
	T2DM	-27.4		
	T1DM	16.7		

Table 2.4: Exogenous input variables to the ICING-2 model

Variable	Unit	Description
PN(t)	mmol/min	Intravenous glucose input rate (parenteral nutrition)
D(t)	mmol/min	Oral glucose input rate (enteral nutrition)
$u_{ex}(t)$	mU/min	Intravenous insulin input rate

2.3 Overview of Glycaemic System Model

The overview of Glycaemic System Model block diagram is shown in Figure 2.3. In general, this block diagram describes the overall glycaemic system model, and how they are related between each other. Besides, it also indicates the interaction between system model with actuators and patients. The Glycaemic System Model consists of inputs, outputs and control system as per explained below:

i) Inputs

There are two types of inputs which are internal and external. Internal inputs are any parameters generated from internal human body system for metabolic activities and will be used by the controller or metabolic system model (ICING) such as endogenous glucose production [EGP] and endogenous insulin production [U_{en}]. Unlike internal inputs, external inputs are any nutrients uptake by human from outside for metabolic activities such as nutrition [P] and exogenous insulin [U_{ex}]. At the moment, internal inputs are set based on population constant, whereas external inputs are determined by the controller.

ii) Control System

a) Metabolic system model

Model-based insulin sensitivity (S_I), generated from the ICING model will be able to describe metabolic system behaviour of OHCA patient. Thus, the analysis will provide scientific information about patient metabolic level and evolution over time, from cool to warm conditions. The understanding of S_I evolution is vital for design and implementation glycaemic control. In addition to that, model-based S_I can be exploited to create its stochastic model, which describes the metabolic variability conditions of the patient. Analysis of S_I

stochastic model is important for improving stochastic control, particularly in reducing metabolic and glycaemic variability.

b) Controller

Controller is a major part of the system where the decision is being made to determine how much insulin and nutrition should be given to the patients. It will developed based on various needs and problems, and use current BG, predicted BG, model-based S_I and current inputs to calculate the predicted insulin and nutrition. To date, there are various glycaemic controllers that are already developed such as SPRINT and STAR controllers. However, none of them cater for OHCA patients. Thus, rigorous analysis of OHCA patients conducted (Chapter 4-7) in this thesis will be used to develop new OHCA controller which consider the problems highlighted. In addition, the new model-based STAR_OHCA controller will be developed using single or multiple stochastic model OHCA.

iii) Output

The outcome of the system after undergo real or model process is called an output. In this system, blood glucose and plasma insulin have been chosen as output. However, BG is widely used as it become subject of reference whether the glycaemic control is successful or not.

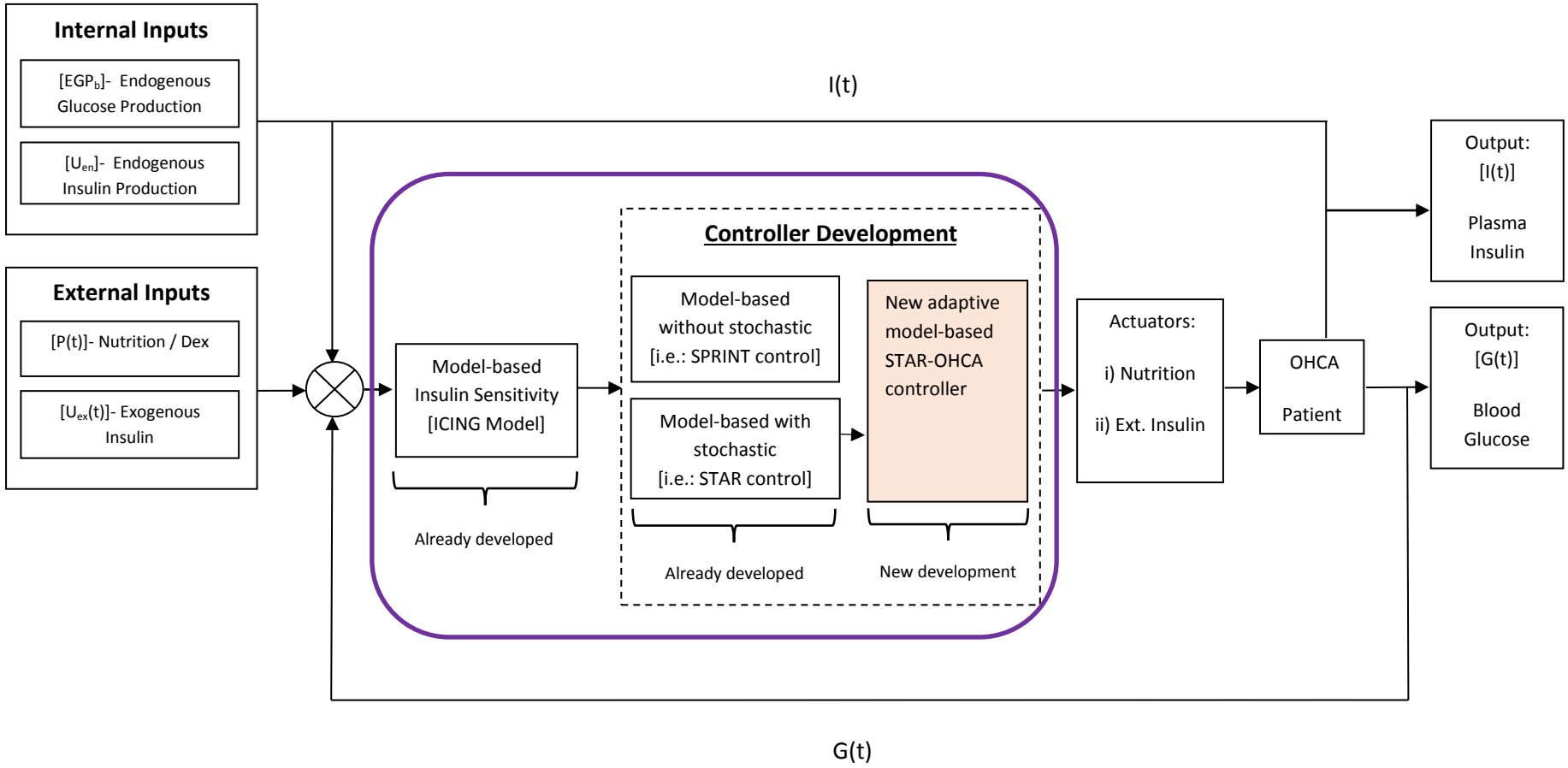

Fig 2.3: Overview of Tight Glycaemic Control block diagram

2.4 Glycaemic Controller Overview

2.4.1 The SPRINT Controller

Specialized Relative Insulin Nutrition Titration (SPRINT) is a model-derived protocol (Lonergan et al., 2006a, Wong et al., 2006b, Chase et al., 2007b, Chase et al., 2008b) that controls both insulin and (carbohydrate) nutrition inputs. It was implemented at the Christchurch Hospital Department of Intensive Care on August 2005 (Chase et al., 2008b) and has now been used on over 1,000 patients. In SPRINT, the interventions consider current and previous blood glucose measurements, current nutrition rate relative to a patient specific goal rate, and the prior hourly insulin dose to determine a new nutrition and insulin intervention for the coming 1-2 hour measurement interval defined in the protocol (Chase et al., 2008b)

The SPRINT protocol consists of two wheels dedicated to insulin bolus administration and enteral nutrition optimization, as shown in Figures 2.4 - 2.7. In SPRINT, blood glucose measurements are taken 1-2 hourly at bedside based on the protocol. The approach is patient-specific in nutrition rate and its titration of inputs in response to the patient-specific metabolic condition.

More specifically, SPRINT titrates its insulin and nutrition inputs to achieve a target range of 4-6 mmol/L based on the patient's current insulin sensitivity, which is effectively determined by the response to the insulin and nutrition interventions. More resistant patients receive more insulin and less nutrition (relative to their 100% goal feed rate). Stability and stopping criteria were also based on patient-specific insulin sensitivity. Hence, the protocol explicitly considers glycaemic response in the context of both insulin and carbohydrate intake and is thus not blind to carbohydrate intake, which is unique (Chase et al., 2011b). Virtually all other studies leave nutritional intake to local clinical standards and are thus blind to this critical parameter that directly affects glycaemic levels.

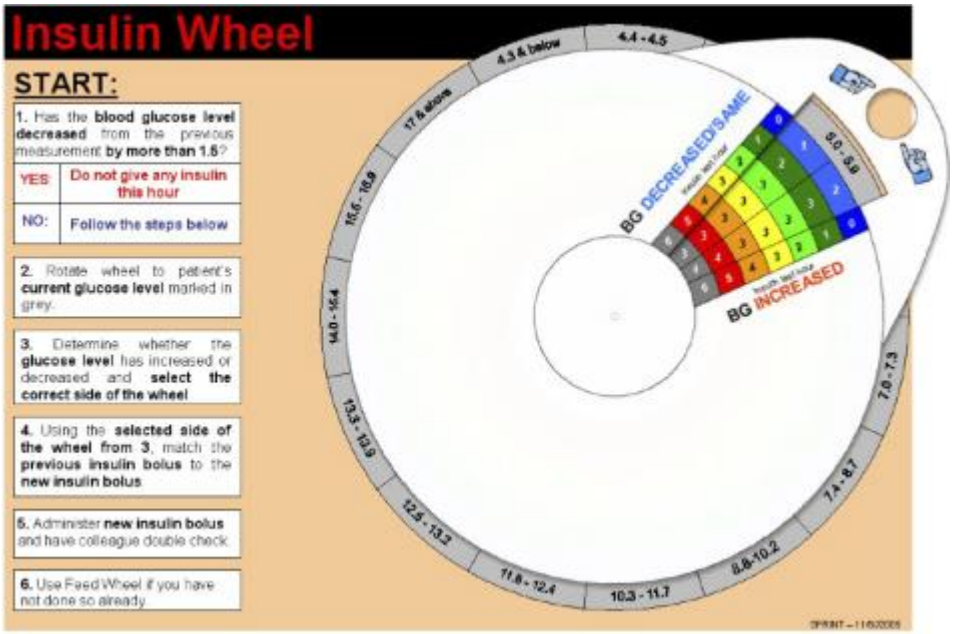

Fig 2.4: The SPRINT insulin wheel with dial (Lonergan et al., 2006a)

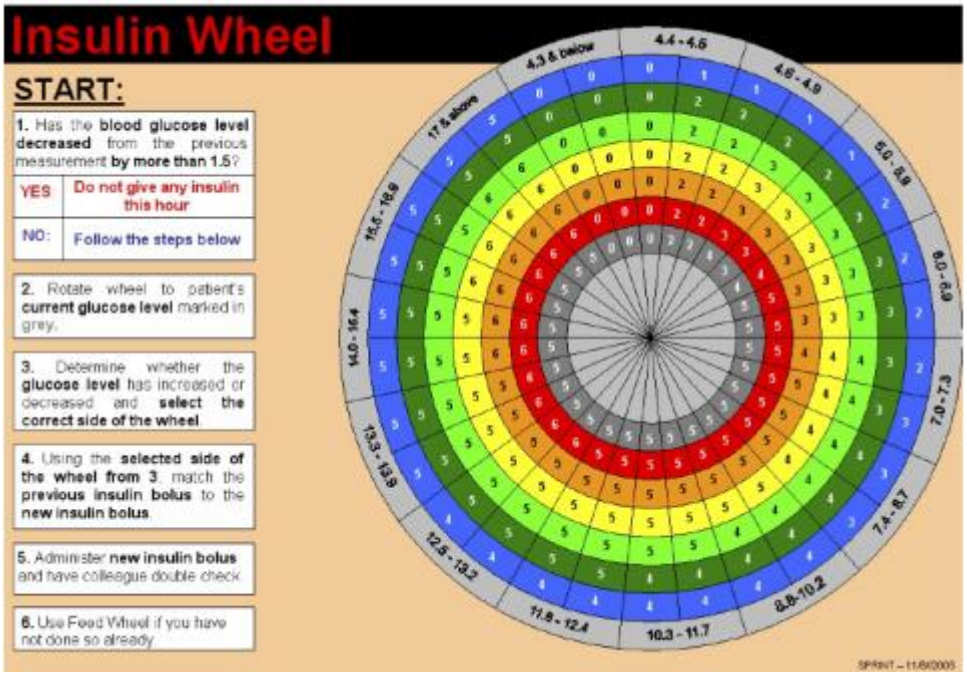

Fig 2.5: The SPRINT insulin wheel without dial (Lonergan et al., 2006a)

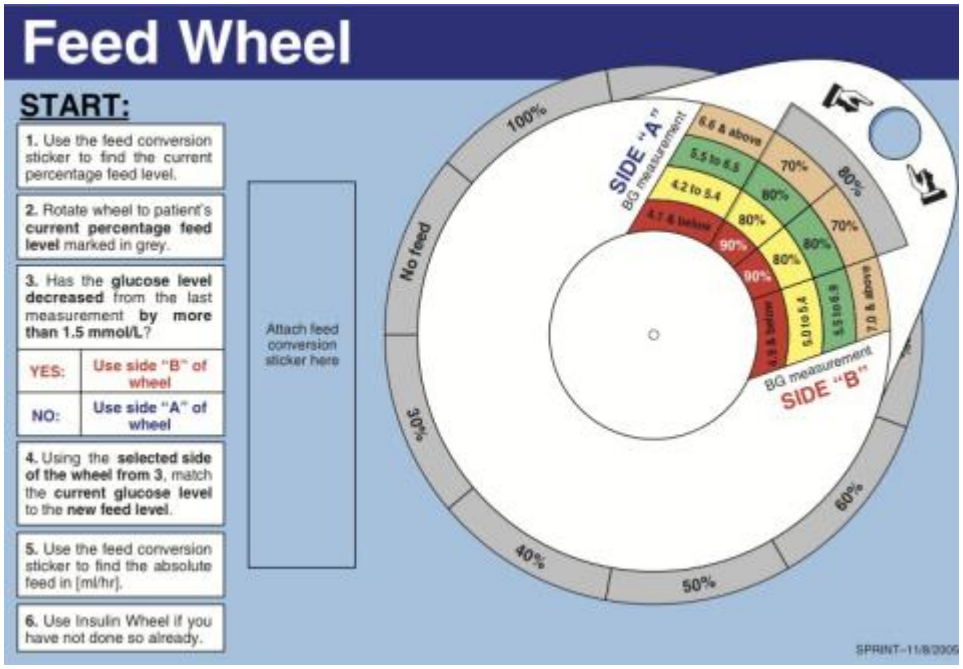

Fig 2.6: The SPRINT feed wheel with dial (Lonergan et al., 2006a)

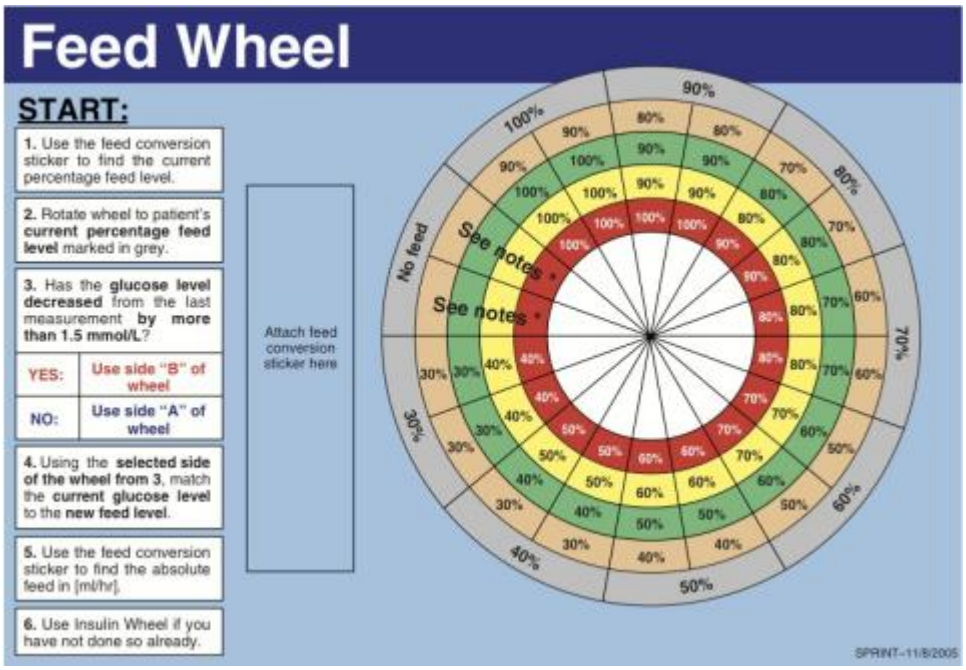

Fig 2.7: The SPRINT feed wheel without dial (Lonergan et al., 2006a)

A low carbohydrate enteral nutrition formula was also specified for all SPRINT patients, reducing the percentage of carbohydrate calories as a percentage of the total caloric intake. Minimum and maximum nutrition rates are 7.5 and 25 kcal/kg/day respectively, with 2.7 to 9 kcal/kg/day (35-40%) from carbohydrates, which matches ACCP guidelines at the maximum level (Cerra et al., 1997).

Finally, SPRINT uses insulin boluses, limited to 6U per hour to minimize insulin saturation (Prigeon et al., 1996, Natali et al., 2000, Chase et al., 2005). Boluses also avoid high rates of insulin infusion being left running when clinical staff are occupied, increasing potential safety, which is an important aspect in situations where high insulin infusion rates combined with infrequent measurement can lead to significantly increased hypoglycaemic events and variability resulting from acute changes in patient condition and metabolic response. This latter point is critical because, like hyperglycaemia, low BG or hypoglycaemia is also linked to increased mortality (Griesdale et al., 2009).

Overall, SPRINT is a unique TGC protocol among all those published. It was the only TGC protocol to reduce both mortality and hypoglycaemia, where many attempts fail at both (Van den Berghe et al., 2006b, Preiser and Devos, 2007, Brunkhorst et al., 2008, De La Rosa Gdel et al., 2008). Its uniqueness stems from its direct management of insulin and nutrition based on patient-specific, time varying insulin sensitivity. It thus manage inter- and intra-patient variability, and thus glycaemia and hypoglycaemia risk, better than others (Griesdale et al., 2009).

2.4.2 The STAR Controller

The Stochastic TARgeted (STAR) protocol is a unique, model-based TGC protocol (Chase et al., 2011b, Evans et al., 2011, Evans et al., 2012, Fisk et al., 2012) for insulin therapy that uses clinically validated metabolic and stochastic models (Lin et al., 2006, Lin et al., 2008) to optimize treatment in the context of possible future patient variation. Probabilistic forecasting enables more adaptive, optimized patient-specific care with clinically specified maximum risk(s) of hyper- and hypoglycaemia. This protocol implements insulin and nutrition interventions based on the current patient-specific insulin sensitivity ($S_I(t)$). Insulin sensitivity is identified hourly for each patient using recent BG measurements and a computerized metabolic system model. With this value, the predicted blood glucose response to a particular intervention can be calculated. The algorithm for STAR is illustrated in the Figure 2.10.

The stochastic forecasting is unique and enables a maximum likelihood approach to targeting a desired glycaemic range while enabling the clinical risk of hypo- or hyperglycaemia to be directly managed. It also enables patients with very different metabolic (intra- and inter-patient) variability to be directly managed and controlled within a single (STAR) model-based framework. Summary of protocol is shown at the Table 2.6.

The STAR protocol has the ability to specify risk of hypoglycemia below a clinically set threshold, and the ability to enable multiple hourly measurements based on clinically set glycemic thresholds. Within that framework, clinical or site-specific constraints may be added for how control is provided, which is via insulin and nutrition control. This approach can provide quality control performance that is tighter across patients and thus more patient-specific reduced light hypoglycaemia using a clinically specified maximum risk with stochastic forecasting of metabolic variation. However, there is no guarantee that all ICU patients would have similar metabolic variability (Le Compte et al., 2010, Penning et al., 2012).

Table 2.5: Summary of STAR protocol

Target Particular	STAR protocol
i) Blood Glucose Range	within 4 – 6.5 mmol/L as specified in 5-95th percentiles range.
ii) Clinical risk of hypo- or hyperglycemia	Maximum 5% risk of BG < 4.0
iii) Measurement interval	a) 1 - 3 hours when BG levels are within 4 – 7.5 mmol/L. b) Every hour when BG levels are outside range.
iv) Control intervention	Intervention of insulin and nutrition are based on the current patient-specific insulin sensitivity ($S_I(t)$) to maximize the likelihood of BG in a clinically specific range and maximum acceptable risk of hypoglycaemia.

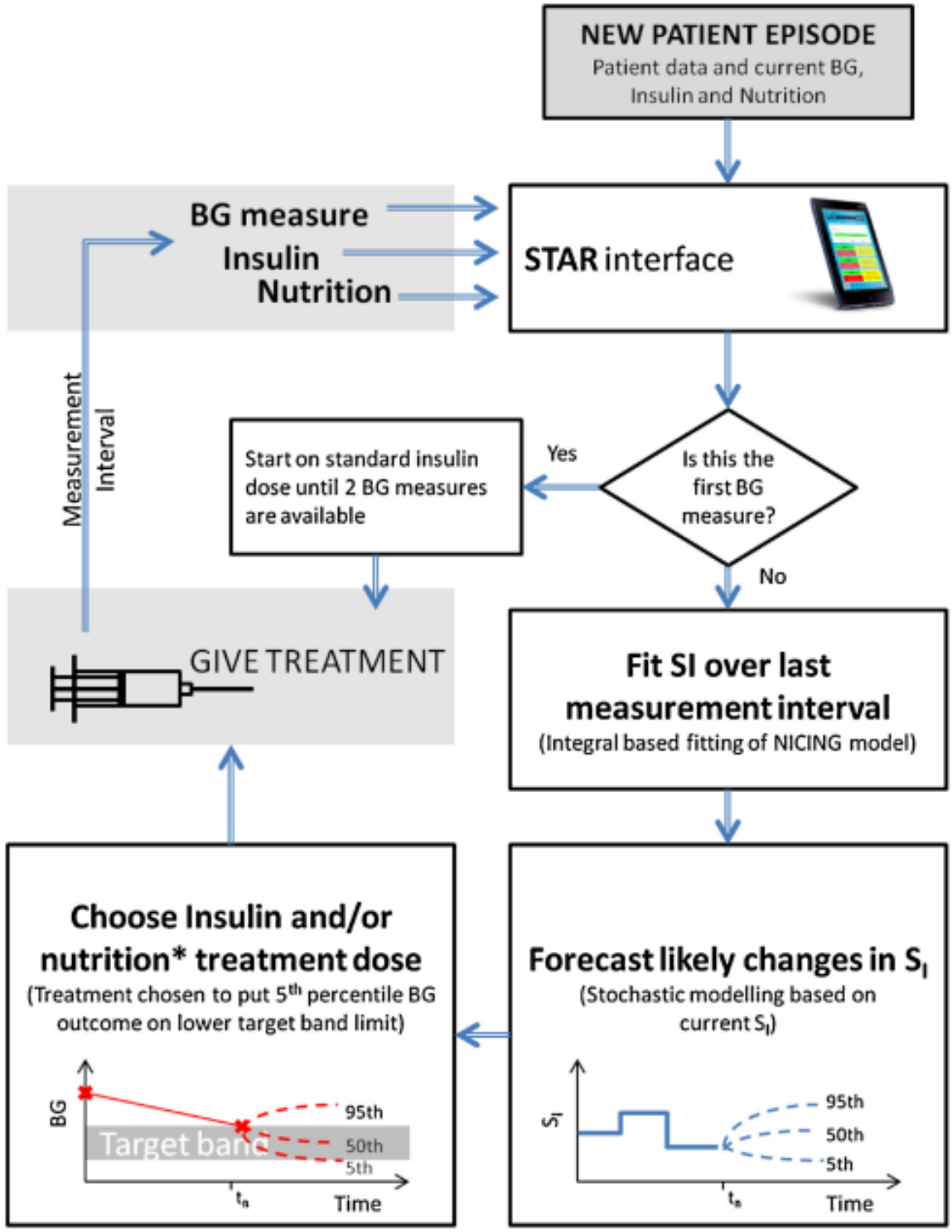

Fig 2.8: The STAR Algorithm (Dickson et al., 2013)

2.5 Summary

This chapter discusses the basis and background of the glucose-insulin system models dealing to the model used in this thesis, and reviews several other models that have been developed and used for glycaemic understanding, control and management. These models have been used clinically for various studies for understanding or intervention. The use for understanding versus intervention requires differences in model capability and complexity that may not translate directly from one use to another. However, not all of these models were physiologically complete and some failed to capture inter- and intra- patient variability. The ICING-2 model presented in this chapter provides an overall measure of a patient's insulin sensitivity, particularly to exogenous insulin and nutrition inputs that guide and determine the metabolic balance in ICU patients. It is also already proven to be suitable for clinical control, while accurately accounting for all relevant and observed physiological behaviour.

The overall glycaemic control system model and its key components, including input, output, actuators, patient and controller is also introduced to indicate the relation between glucose-insulin model and glycaemic control system model. The existing controllers such as SPRINT and STAR are explained since these controllers will be used during virtual trials. Control performance measures are defined to standardize the criteria assessment of the various controllers used in these studies.

Chapter 3: Patient Demography

This chapter presents the OHCA patient data used in this thesis. Patient data is analysed statistically to summarize the demography by whole cohort and by hospital. Additionally, the cohort is sub-divided and analysed by gender, diabetes status, mortality, and return of spontaneous circulation (ROSC). This data and analysis will be used in Chapter 4 – 7.

3.1 Introduction

A retrospective analysis of glycaemic control data from 180 OHCA patients (7812 hours) treated with hypothermia, shortly after admission to the Intensive Care Units (ICUs) of Erasme Hospital, Belgium and Lausanne Hospital, Switzerland. All patients were on local glycaemic protocols. Therapeutic Hypothermia (TH) was applied following a standardized written protocol.

All patients were treated with mild TH to 33 ± 1^{o}C for 24 hours, irrespective of age, initial arrest rhythm and other physiological conditions. TH was started immediately after admission and was induced with ice-cold packs and intravenous ice-cold fluids. Body temperature was maintained at hypothermia using a surface cooling device with a computerized adjustment of patient temperature target. During this time, some short-acting drugs, such as midazolam (0.1mg/kg.hr), fentanyl (1.5µg/kg/hr) and vecuronium (0.1mg/kg boluses), were used to administer sedation, analgesia and control shivering. Rewarming was achieved passively, and sedation-analgesia was stopped when patient temperature was greater than 35^{o}C.

Blood glucose (BG) and temperature readings were taken 1-2 hourly. Data were divided into three periods: 1) cool (T<=35^{o}C); 2) idle period of 2 hours as hypothermia was removed; and 3) warm (T>35^{o}C). A maximum of 24 and a minimum of 15 hours for the cool and warm periods were considered, ensuring a balance of contiguous data across the periods and transition. The idle period is not considered in the analysis.

3.2 OHCA Patient Demography by Cohort

Overall patient demography provides the cohort information such as level and range of inter-patient variations, or similarity in the different areas of data, as shown in Table 3.1. Additionally, per-hospital demographics as shown in Table 3.2 illustrate the variations between units due to differences in clinical practices and patient demography.

Table 3.1: Demographic data patients those who have met a minimum of 15 hours for both the cool and warm after periods. (All cohort)

Variables	Value	
	Cool	**Warm**
Total patients, number (n)	180	
Median age, years [IQR]	61 [51, 72]	
Female gender, number (%)	37 (20.6%)	
ICU mortality, number (%)	82 (45.6%)	
Diabetes, number (%)	23 (12.8%)	
ROSC < 15 min, number (%)	63 (35%)	
15 < ROSC < 30 min, number (%)	89 (49.4%)	
ROSC > 30 min, number (%)	28 (15.6%)	
Total treatment, hours (h)	3873	3939
Blood Glucose, median (mmol/L) [IQR]	7.6 [6.3, 9.7]	6.8 [5.9, 8.0]
Insulin Rate, median rate (U/hr) [IQR]	3.0 [1.3, 6.0]	2.5 [1.6, 5.0]
Glucose Rate, median rate (g/hr) [IQR]	2.7 [1.0, 5.3]	5.4 [2.7, 8.1]
Per-patient median BG, (mmol/L) [IQR]	7.5 [6.8, 8.6]	6.8 [6. 1, 7.5]
Per-patient median Insulin Rate, (U/hr) [IQR]	1.8 [1.0, 3.3]	1.6 [0.9, 3.7]
Per-patient median Glucose Rate, (g/hr) [IQR]	2.5 [0.8, 3.5]	3.2 [1.6, 5.3]

Data are presented as median [interquartile range] where appropriate.

Table 3.2: Patients' demographic data by hospital (Erasme, Lausanne)

Variables		Erasme Hospital		Lausanne Hospital		*p-value*
		Cool	Warm	Cool	Warm	
Total patients, (n)		122		98		
Median age, years [IQR]		61.5 [50 , 75]		60 [52 , 69]		
Female gender, (%)		18 (18.2%)		19 (23.5%)		0.3
ICU mortality, (%)		45 (45.5%)		37 (45.7%)		0.5
Diabetes, (%)		19 (19.2%)		4 (4.9%)		< 0.05
ROSC < 15 min, (%)		45 (45.5%)		18 (22.2%)		< 0.05
15 <ROSC< 30 min, (%)		44 (44.4%)		45 (55.6%)		0.2
ROSC > 30 min, (%)		10 (10.1%)		18 (22.2%)		< 0.05
Total treatment, hrs (h)		2714	2737	1927	1941	
External Inputs	Insulin *Insulin rate (U/hr) Median [IQR]*	2.5 [1.2,6.4]	1.7 [1.0,4.0]	3.3 [1.3,8.0]	3.9 [1.7,7.8]	
	Nutrition *Glucose rate (g/hr) Median [IQR]*	6.9 [4.2,9.4]	5.5 [2.8,8.2]	2.0 [0.8,4.1]	5.4 [2.7,8.1]	
Glycaemic Outputs	BG Level *Blood Glucose (mmol/L) Median [IQR]*	7.9 [6.4,10.4]	6.7 [5.7,7.9]	7.1 [6.3,8.6]	6.7 [6.0,7.7]	
	BG Variability *Hourly %ΔBG Median [IQR]*	-0.6 [-1.1,-0.2]	-0.2 [-0.6,0.3]	-1.1 [-1.9,-0.5]	-0.6 [-1.4,0.2]	

P-values are calculated using Fisher's Exact Probability Test 2x2. Data are presented as median [interquartile range] where appropriate.

In addition to the above, summary of blood glucose (BG) statistics of OHCA patients for the whole cohort is also presented in table 3.3, which describe the overall local protocol performance implemented at those hospitals. This summary provides a more detail analysis of BG in various conditions which gives general idea of the patients' characteristics per cohort that we are dealing with throughout the research studies.

Table 3.3: Summary BG statistics of OHCA patients (All cohort)

Summary of BG Statistics OHCA patients (All cohort)	**Value**		***p-value***
	Cool	**Warm**	
Whole cohort statistics:			
Total patients, number (n)	180	180	
Total treatment, hours (h)	3873	3939	
Blood Glucose, median (mmol/L) [IQR]-	7.6 [6.3, 9.7]	6.8 [5.9, 8.0]	
BG Mean (geometric) (mmol/L)	7.7	6.8	
BG Std.Dev (geometric) (mmol/L)	1.5	1.4	
% BG > 10.0 mmol/L	22.0	7.9	< 0.05
% BG within 8.0 – 10.0 mmol/L	21.5	17.4	0.3
% BG within 4.4 – 8.0 mmol/L	55.9	73.1	< 0.05
% BG within 4.4 – 7.0 mmol/L	38.3	53.3	< 0.05
% BG within 4.4 – 6.5 mmol/L	26.7	40.7	< 0.05
% BG < 4.4 mmol/L	1.4	2.4	0.8
% BG < 4.0 mmol/L	0.6	0.8	1.0
% BG < 2.22 mmol/L	0	0	1.0
Per-patient statistics with hourly resampled data			
Per-patient BG Median [IQR] (mmol/L) (resampled)	7.5 [6.4, 9.2]	6.7 [5.9 ,7.8]	
Per-patient % resampled BG > 10.0 mmol/L	18.4	5.8	< 0.05
Per-patient % resampled BG within 8.0 - 10.0 mmol/L	22.1	16.0	0.6
Per-patient % resampled BG within 4.4 - 8.0 mmol/L	59.2	77.1	< 0.05
Per-patient % BG resampled within 4.4 - 7.0 mmol/L	39.1	56.0	< 0.05
Per-patient % resampled BG within 4.4 - 6.5 mmol/L	26.8	40.6	< 0.05
Per-patient % resampled BG < 4.4 mmol/L	1.1	1.9	0.8
Per-patient % resampled BG < 4.0 mmol/L	0.4	0.7	1.0
Per-patient % resampled BG < 2.22 mmol/L	0	0	1.0
No of patients < 2.22 mmol/L (resampled)	0	0	1.0

P-values are calculated using Fisher's Exact Probability Test 2x2. Data are presented as median [interquartile range] where appropriate.

3.3 OHCA Patient Demography and Mortality

Table 3.4 presents OHCA patient demography by mortality comparing survivors and non-survivors data based on gender, diagnosed diabetes status and ROSC

Table 3.4: Demographic data patients based on mortality

Variables	**Survivors**		**Non-Survivors**		***p-values***
	Cool	Warm	Cool	Warm	
Total patients, (n)	98		82		
Median age, years [IQR]	61 [51, 72]		61 [50.5, 72]		
Female gender, (%)	17 (17.3%)		20 (24.4%)		0.2
Diabetes, (%)	13 (13.3%)		10 (12.2%)		0.6
ROSC < 15 min, (%)	47 (48.0%)		16 (19.5%)		< 0.05
15 < ROSC< 30 min, (%)	40 (40.8%)		49 (59.8%)		< 0.05
ROSC > 30 min, (%)	11 (11.2%)		17 (20.7%)		0.1
Total treatment, hours (h)	2123	2214	1750	1725	
Blood Glucose, median (mmol/L) [IQR]	7.5 [6.4, 9.4]	6.7 [5.8, 7.8]	7.7 [6.3, 10.2]	7.0 [6.0, 8.3]	
BG Mean (geometric) (mmol/L)	7.6	6.7	7.8	6.9	
BG Std.Dev (geometric) (mmol/L)	1.2	1.2	1.3	1.2	
% BG > 10.0 mmol/L	19.0	4.9	25.7	11.7	
% BG within 8.0 – 10.0 mmol/L	22.4	16.2	20.5	19.0	
% BG within 4.4 – 8.0 mmol/L	59.2	77.5	51.9	67.4	
% BG within 4.4 – 7.0 mmol/L	40.6	57.5	35.4	47.8	
% BG within 4.4 – 6.5 mmol/L	27.3	44.0	26.0	36.4	
% BG < 4.4 mmol/L	0.5	2.1	2.6	2.9	
% BG < 4.0 mmol/L	0.1	0.6	1.1	1.0	
% BG < 2.22 mmol/L	0	0	0	0	
Per-patient statistics with hourly resampled data					

Per-patient BG Median [IQR] (mmol/L) (resampled)	7.4 [6.4 – 8.9]	6.7 [5.8 – 7.7]	7.5 [6.3 – 9.6]	6.8 [6.0 – 8.1]	
Per-patient % resampled BG > 10.0 mmol/L	15.6	3.5	21.8	8.9	
Per-patient % resampled BG within 8.0 - 10.0 mmol/L	22.7	14.3	21.4	18.0	
Per-patient % resampled BG within 4.4 - 8.0 mmol/L	62.1	81.4	55.6	71.5	
Per-patient % BG resampled within 4.4 - 7.0 mmol/L	40.4	59.1	37.6	51.8	
Per-patient % resampled BG within 4.4 - 6.5 mmol/L	26.6	42.4	26.9	38.3	
Per-patient % resampled BG < 4.4 mmol/L	0.4	1.3	1.9	2.5	
Per-patient % resampled BG < 4.0 mmol/L	0.1	0.4	0.8	1.1	
Per-patient % resampled BG < 2.22 mmol/L	0.0	0.0	0.0	0.0	
No of patients < 2.22 mmol/L (resampled)	0	0	0	0	

P-values are calculated using Fisher's Exact Probability Test 2x2. Data are presented as median [interquartile range] where appropriate.

3.4 OHCA Patient Demography by Diagnosed Diabetes Status

The OHCA patient demography by diabetes (Table 3.5) compares the retrospective data between diabetes and non-diabetes patients based on gender, mortality and ROSC, and provides a more detail BG analysis which define patients' characteristics by these cohorts.

Table 3.5: Demographic data patients based on diagnosed diabetes status

Variables	**Diabetes**		**Non-Diabetes**		***p-value***
	Cool	Warm	Cool	Warm	
Total patients, (n)	23		157		
Median age, years [IQR]	61 [51, 73]		61 [51, 72]		
Female gender, (%)	3 (13.0%)		34 (21.7%)		0.4
ICU mortality, (%)	10 (43.5%)		72 (45.9%)		0.5
ROSC < 15 min, (%)	13 (56.5%)		50 (31.8%)		< 0.05
15< ROSC < 30 min, (%)	9 (39.1%)		80 (51.0%)		0.4
ROSC > 30 min, (%)	1 (4.3%)		27 (17.2%)		0.1
Total treatment, (h)	508	513	3365	3426	
Blood Glucose, median (mmol/L) [IQR]	8.5 [6.9, 10.9]	7.8 [6.2, 9.0]	7.4 [6.3, 9.5]	6.7 [5.8, 7.8]	
BG Mean (geometric) (mmol/L)	8.3	7.6	7.6	6.7	
BG Std.Dev (geometric) (mmol/L)	1.1	1.1	1.5	1.4	
% BG > 10.0 mmol/L	30.1	19.6	20.6	5.6	
% BG within 8.0 – 10.0 mmol/L	26.6	22.8	20.6	16.4	
% BG within 4.4 – 8.0 mmol/L	43.1	57.8	58.2	76.1	
% BG within 4.4 – 7.0 mmol/L	25.4	36.0	40.6	56.6	
% BG within 4.4 – 6.5 mmol/L	18.9	28.8	28.1	43.0	
% BG < 4.4 mmol/L	1.2	0.5	1.5	2.8	
% BG < 4.0 mmol/L	0.5	0.3	0.6	0.9	
% BG < 2.22 mmol/L	0	0	0	0	

Per-patient statistics with hourly resampled data					
Per-patient BG Median [IQR] (mmol/L) (resampled)	8.3 [6.9 –10.7]	7.7 [6.2-9.0]	7.4 [6.3-9.0]	6.7 [5.9-7.6]	
Per-patient % resampled BG > 10.0 mmol/L	28.9	18.5	16.8	3.9	
Per-patient % resampled BG within 8.0 - 10.0 mmol/L	25.3	22.8	21.7	14.9	
Per-patient % resampled BG within 4.4 - 8.0 mmol/L	45.7	59.0	61.2	79.8	
Per-patient % BG resampled within 4.4 - 7.0 mmol/L	27.4	39.0	40.9	58.4	
Per-patient % resampled BG within 4.4 - 6.5 mmol/L	20.2	30.6	27.7	42.1	
Per-patient % resampled BG < 4.4 mmol/L	0.9	0.6	1.1	2.0	
Per-patient % resampled BG < 4.0 mmol/L	0.4	0.2	0.4	0.7	
Per-patient % resampled BG < 2.22 mmol/L	0.0	0.0	0.0	0.0	
No of patients < 2.22 mmol/L (resampled)	0	0	0	0	

P-values are calculated using Fisher's Exact Probability Test 2x2. Data are presented as median [interquartile range] where appropriate.

3.5 OHCA Patient Demography by Gender

The OHCA patient demography by gender (Table 3.6) compares the retrospective data between male and female patients based on diabetes, mortality and ROSC, and provides a more detail BG analysis which define patients' characteristics by these cohorts.

Table 3.6: Demographic data patients based on gender

Variables	**Male**		**Female**		***p-value***
	Cool	Warm	Cool	Warm	
Total patients, (n)	143		37		
Median age, years [IQR]	61 [51, 72]		61 [51, 73]		
Diabetes, (%)	20 (14.0%)		3 (8.1%)		0.4
ICU mortality, (%)	62 (43.3%)		19 (51.3%)		0.5
ROSC < 15 min, (%)	53 (37.0%)		9 (24.3%)		0.2
15 < ROSC < 30 min, (%)	71 (49.7%)		15 (40.5%)		0.3
ROSC > 30 min, (%)	13 (9.1%)		6 (16.2%)		0.2
Total treatment, (h)	3094	3129	779	810	
Blood Glucose, median (mmol/L) [IQR]	7.6 [6.4, 9.6]	6.7 [5.9, 8.0]	7.4 [6.2, 10.1]	6.8 [5.8, 7.9]	
BG Mean (geometric) (mmol/L)	7.7	6.8	7.7	6.7	
BG Std.Dev (geometric) (mmol/L)	1.5	1.4	1.2	1.2	
% BG > 10.0 mmol/L	21.3	8.0	25.3	7.2	
% BG within 8.0 – 10.0 mmol/L	22.8	17.7	16.2	16.3	
% BG within 4.4 – 8.0 mmol/L	55.5	73.0	57.8	73.4	
% BG within 4.4 – 7.0 mmol/L	37.3	53.6	42.4	52.1	
% BG within 4.4 – 6.5 mmol/L	25.7	41.0	31.2	39.1	
% BG < 4.4 mmol/L	1.4	2.2	1.7	3.5	
% BG < 4.0 mmol/L	0.6	0.7	0.4	0.9	
% BG < 2.22 mmol/L	0	0	0	0	
Per-patient statistics with hourly resampled data					
Per-patient BG Median [IQR] (mmol/L) (resampled)	7.5 [6.4 – 9.1]	6.7 [5.9 – 7.8]	7.5 [6.4 – 9.6]	6.8 [5.9 – 7.7]	
Per-patient % resampled BG > 10.0 mmol/L	17.5	6.0	21.9	5.3	

Per-patient % resampled BG within 8.0 - 10.0 mmol/L	23.1	16.3	18.5	14,4	
Per-patient % resampled BG within 4.4 - 8.0 mmol/L	59.1	76.7	59.4	78.6	
Per-patient % BG resampled within 4.4 - 7.0 mmol/L	39.1	56.1	39.1	55.2	
Per-patient % resampled BG within 4.4 - 6.5 mmol/L	26.5	41.2	27.9	38.4	
Per-patient % resampled BG < 4.4 mmol/L	1.1	1.8	1.1	2.1	
Per-patient % resampled BG < 4.0 mmol/L	0.4	0.7	0.3	0.5	
Per-patient % resampled BG < 2.22 mmol/L	0.0	0.0	0.0	0.0	
No of patients < 2.22 mmol/L (resampled)	0	0	0	0	

P-values are calculated using Fisher's Exact Probability Test 2x2. Data are presented as median [interquartile range] where appropriate.

3.6 OHCA Patient Demography by ROSC

The OHCA patient demography by ROSC (Table 3.7) compares the retrospective data between ROSC<15 min, ROSC<30 min and ROSC>30 min patients based on gender, diabetes and mortality, and provides a more detail BG analysis which define patients' characteristics by these cohort categories.

Table 3.7: Demographic data patients based on return of spontaneous circulation (ROSC)

Variables	**ROSC < 15 min**		**15 < ROSC < 30 min**		**ROSC > 30 min**		***p-values***
	Cool	Warm	Cool	Warm	Cool	Warm	
Total patients (n)	63		89		28		
Median age [IQR]	61 [51, 73]		61 [51, 72]		61 [51, 72]		
Gender, female (%)	10 (15.9%)		18 (20.2%)		9 (32.1%)		0.2
Diabetes, (%)	13 (20.6%)		9 (10.1%)		1 (3.6%)		< 0.05
Mortality, (%)	16 (25.4%)		49 (55.1%)		17 (60.7%)		< 0.05
Total hours (h)	1407	1404	1872	1925	594	610	
BG median (mmol/L) [IQR]	7.8 [6.4, 9.6]	6.8 [5.8, 8.0]	7.4 [6.3, 9.7]	6.7 [6.0, 8.1]	7.4 [6.4,10.3]	6.7 [5.7, 7.8]	
BG Mean (geometric) (mmol/L)	7.8	6.9	7.7	6.7	7.6	6.7	
BG Std.Dev (geometric) (mmol/L)	1.4	1.2	1.5	1.4	1.2	1.2	
% BG > 10.0 mmol/L	20.0	8.0	22.5	8.3	26.4	6.0	
% BG within 8.0 – 10.0 mmol/L	26.2	18.0	19.3	17.9	15.7	14.2	
% BG within 4.4 – 8.0 mmol/L	53.7	72.4	57.4	72.7	57.3	77.0	
% BG within 4.4 – 7.0 mmol/L	36.8	51.2	38.8	54.3	40.6	56.6	
% BG within 4.4 – 6.5 mmol/L	26.7	40.3	27.2	40.2	25.4	43.7	
% BG < 4.4 mmol/L	0.6	2.9	2.1	1.8	1.3	3.5	
% BG < 4.0 mmol/L	0.3	0.9	0.8	0.5	0.8	1.3	
% BG < 2.22 mmol/L	0	0	0	0	0	0	
Per-patient statistics with hourly resampled data							
Per-patient BG Median [IQR] (mmol/L) (resampled)	7.6 [6.4 – 9.1]	6.9 [5.9 – 8.0]	7.4 [6.4 – 9.2]	6.7 [5.9 – 7.8]	7.3 [6.5 – 9.2]	6.7 [6.0 – 7.6]	
Per-patient % resampled BG > 10.0 mmol/L	17.1	6.8	18.8	5.9	20.3	3.6	

Per-patient % resampled BG within 8.0 - 10.0 mmol/L	25.0	18.3	21.2	15.2	18.2	13.0	
Per-patient % resampled BG within 4.4 - 8.0 mmol/L	57.7	73.2	59.6	78.3	61.4	81.8	
Per-patient % BG resampled within 4.4 - 7.0 mmol/L	38.6	50.0	38.7	59.5	41.8	58.0	
Per-patient % resampled BG within 4.4 - 6.5 mmol/L	27.1	37.8	26.9	42.8	25.6	40.1	
Per-patient % resampled BG < 4.4 mmol/L	0.6	2.7	1.5	1.2	0.8	1.9	
Per-patient % resampled BG < 4.0 mmol/L	0.2	1.1	0.5	0.4	0.5	0.6	
Per-patient % resampled BG < 2.22 mmol/L	0.0	0.0	0.0	0.0	0.0	0.0	
No of patients < 2.22 mmol/L (resampled)	0	0	0	0	0	0	

P-values are calculated using Fisher's Exact Probability Test 2x3. Data are presented as median [interquartile range] where appropriate.

3.7 Discussion

The overall patient demography presented in this chapter summarize the cohort information statistically based on retrospective data (Table 3.1). In general, majority of the patients in this cohort are male (79.4%), non-diabetic (87.2%) and ROSC below 30 minutes (84.4%). In terms of mortality, the percentage are not much significant between survive (54.4%) and non-survive (45.6%) patients. The overall summary of BG statistics (Table 3.1), summary by hospital (Table 3.2) and summary of BG statistics (Table 3.3) show that BG level is lower from cool to warm, where the percentage of BG within 4.4 – 8.0 mmol/L is increased from 56% to 73% , which observe the improvement made by local glycaemic protocol at the respective hospitals. Conversely, the percentage of BG below 4.4 mmol/L is also increased from 1.4% to 2.4% which indicate a major setback to the therapies conducted on this cohort even though the number of patients whose BG < 2.22 mmol/L is zero.

Apart from overall cohort demography, this chapter is also analysed the cohort background in more details based on the following categories;

i) Mortality

The purpose of analysing the cohort by mortality is to describe the patient demography and its glycaemic characteristics based on survive and non-survive and to observe any parameters and variables that might be significant between these two treatment outcomes. According to the table 3.4, it is obvious that variables such as gender and diabetes are similar between survive and non-survive. Percentage of BG in the analysis are similar and doesn't show any significant difference, even though the improvement shown by survived patients from cool to warm are much better than the non-survived patients. However, the ROSC shows some uniqueness in the results where the number of survived patients is higher (48%) compare to non-survive (19.5%) for ROSC lower than15 minutes. In contrast, the number of survived patients is lower (52%) compared to non-survive (80.5%) for ROSC greater than 15 minutes.

ii) Diabetes

Besides mortality, the cohort is analysed by diabetes which is aimed to describe the patient demography and its glycaemic characteristics based on healthy metabolic conditions and unhealthy metabolic conditions, and to observe any parameters and variables that might be significant to differentiate between these two physiological conditions. According to the table 3.5, it is obvious that variables such as gender, mortality and ROSCs are similar between diabetes and non-diabetes patients. However, the majority of percentages of BGs in the analysis are higher for diabetic patients despite improvement shown from cool to warm periods. Thus, none of these variables or parameters give significant results, suggesting that analysing or even developing control based on diabetes will not provide any significant impact on the treatment positive outcome. However, further research and analysis is required such as insulin sensitivity before making such conclusion

iii) Gender (Sex)

The patient demography is also being analysed by gender or sex based on male and female which is aimed to determine its glycaemic characteristics, and to observe any parameters and variables that might be significant to differentiate between these two physiological conditions. According to the table 3.6, it is obvious that variables such as diabetes, mortality and ROSCs are similar between male and female patients. In addition, percentages of BG in the analysis are similar and don't show any significant difference. Thus, none of these variables or parameters gives significant results, suggesting that analysing or even developing control based on gender will not provide any significant impact on the treatment positive outcome. However, further research and analysis is required such as insulin sensitivity before making such conclusion.

iv) Return of Spontaneous Circulation (ROSC)

Finally, the patient demography is being analysed by the return of spontaneous circulation (ROSC) which is aimed to determine its glycaemic characteristics and to observe any parameters and variables that might be significant to differentiate between these physiological conditions. According to the table 3.7, it is obvious that variables such as gender and diabetes are not much different between ROSCs. Percentages of BG in the

analysis are also similar and match with the improvement shown from cool to warm periods. However, it is evidence that the analysis based on mortality shows some uniqueness in the results where the number of non-survived patients is lower (25.4%) for ROSC lower than 15 minutes, compared to ROSC higher than 15 minutes but lower than 30 minutes (55.1%) as well as ROSC greater than 30 minutes (60.7%).

3.8 Summary

The results presented in these analyses indicate that all patients in this cohort had appropriate local protocol treatment at the respective hospitals and had shown some various physiological response individually which have resulted in the decreased of BG percentage above 8.0 mmol/L, the increased of BG percentage within 4.4 – 8.0 mmol/L and the increased in BG percentage below 4.4 mmol/L from cool to warm periods. While these trends for BG percentage above 8.0 mmol/L and BG percentage within 4.4 – 8.0 mmol/L looks improving, the increased of BG percentage below 4.4 mmol/L shows poor treatment conducted which shows that the glycaemic outcome for this cohort is vulnerable.

The analyses of cohort demography based on mortality, diabetes, sex and ROSC has revealed that the ROSC is most likely the variable or parameter that might be significant to differentiate between these mortality outcomes for OHCA patient, treated with hypothermia. However, further research and analysis is required such as insulin sensitivity and stochastic modelling before suggesting this parameter for control development.

Chapter 4: Insulin Sensitivity Level and Variability Analysis

This chapter describes a preliminary study of Out-of-Hospital Cardiac Arrest (OHCA) patients based on metabolic characteristics during hypothermia (cool period) and normothemia (warm period). It analyses the impact of therapeutic hypothermia (TH) on metabolism, including the evolution of insulin sensitivity (SI) and its variability. Patient data are analysed based for cohort and sub-cohort groups as defined in Chapter 3.

4.1 Introduction

Hypothermia is often used to treat OHCA patients (Andres, 2011, Brown and Bourdeaux, 2011, Karanjia and Geocadin, 2011, Kirkham, 2011, Kory et al., 2011, Stub et al., 2011, Graffagnino et al., 2012, Ornato et al., 2012, Reynolds and Lawner, 2012, Bucher et al., 2013, Dietrich et al., 2013, Scirica, 2013, Mangla et al., 2014, Mearns, 2014, Picchi et al., 2014, Polderman et al., 2014). In general, it leads to a lowering of metabolic rate that induces changes in energy metabolism. However, its impact on metabolism and insulin resistance in critical illness is unknown, although one of the adverse events associated with hypothermic therapy is a decrease in insulin sensitivity and insulin secretion (Hayashi, 2009). However, this decrease may not be notable in the cohort that is already highly resistant and variable (Pretty et al., 2012). Hence, understanding metabolic evolution and variability would enable safer and more accurate glycaemic control.

This study analyses the evolution of a clinically validated model-based insulin sensitivity (S_I) metric (Chase et al., 2010, McAuley et al., 2011) in OHCA patients to assess the impact of hypothermia. The analysis is performed at both a cohort and patient-specific level to better understand patient condition and physiology. The results should provide new insight to enable safer metabolic management.

4.2 Subjects and Methods

4.2.1 Patients and Data

This analysis was performed on a cohort of 180 OHCA patients (7812 hours) treated with hypothermia, shortly after admission in Intensive Care Units (ICUs) of Erasme Hospital, Belgium and Lausanne Hospital, Switzerland. These patients were on local AGC protocols. Data collections were carried out as per described in sub-chapter 3.1. Additional information for each patient such as mortality, diabetes history, gender and return of spontaneous circulation (ROSC) were recorded. These inputs will be taken into consideration for separate sub-analysis studies from full cohort. Details of the cohort demography, including sub-cohorts are presented in Table 3.1.

4.2.2 Analyses and Metrics

S_I level during the cool ($T<35^oC$) and warm ($T>37^oC$) periods were identified hourly using the ICING model (Lin et al., 2011) for each patient. S_I Variability was calculated as the hour-to-hour percentage change in S_I or $\%\Delta S_I$, defined:

$$\%\Delta S_I = \frac{\left(S_{I_{n+1}} - S_{I_n} \right)}{S_{I_n}} \, x \, 100 \qquad (4.1)$$

The use of percentage change, rather than absolute change, normalises the metric so patients with differing S_I levels can be compared fairly.

S_I level and variability were analysed during both cool and warm periods on overall cohort and per-patient bases as follows:

i) Overall cohort patient.
ii) Analysis of patient by 12-hour block.
iii) Analysis of patient by 6-hour block.

Cohort analysis assessed every hour of S_I level and variability for the entire cohort, and shows trend based on the overall group behaviour. In contrast, per-patient analysis examined the S_I level by median values within each timeframe. To quantify per-patient variability, the

interquartile range (IQR: 25^{th} -75^{th} percentile) of $\%\Delta S_I$ is calculated. This metric captures the width of the hour-to-hour variability distributions for each patient.

Table 4.1: Descriptions of 12-hour and 6-hour blocks for data analysis

Day	12-hour blocks			6-hour blocks		
	Block	Hours Range	Period	Block	Hours Range	Period
1	1	0 – 12 hours	Cool	1	0 – 6 hours	Cool
				2	6 – 12 hours	Cool
	2	12 – 24 hours	Cool	3	12 – 18 hours	Cool
				4	18 – 24 hours	Cool
2	3	24 – 36 hours	Warm	5	24 – 30 hours	Warm
				6	30 – 36 hours	Warm
	4	36 – 48 hours	Warm	7	36 – 42 hours	Warm
				8	42 – 48 hours	Warm

The S_I analysis of patients' uses 12-hour and 6-hour blocks is described in Table 4.1. It is aimed to capture S_I evolution over time with different resolution. For the cohort analysis, S_I and $\Delta\%S_I$ data from all patients was grouped into each appropriate time-block. Median values for each time-block were calculated for comparison to the previous block, thus capturing overall cohort changes over time in level and hour-to-hour variability. For the per-patient analysis, the median value of S_I and the interquartile range (IQR) of $\Delta\%S_I$ were calculated for each patient, for each time-block. The IQR captures the width of degree of variability for a given patient within each hour block. Thus, a reduction in the IQR of $\Delta\%S_I$ over time would indicate a reduction in hour-to-hour variability for a given patient.

S_I level and variability are non-Gaussian and thus were compared using non-parametric cumulative distribution functions (CDFs). All distributed data were compared using a Wilcoxon rank-sum test (Mann-Whitney U-test), except for S_I variability results. S_I variability was compared using the Kolmogorov-Smirnov (KS) test as it has greater power to detect differences in the shape of distributions when median values are similar. In all cases, $p < 0.05$ is considered statistically significant.

4.3 Results

4.3.1 Results by Overall Cohort

4.3.1.1 S_I Level Analysis

Figure 4.1 presents the cumulative distribution functions (CDFs) of hourly S_I level and its variability for both cool and warm after periods by cohort (left panel) and median hourly S_I per-patient (right panel) for all cohort patients. Table 4.2 summarizes S_I level results and analysis for overall OHCA cohort.

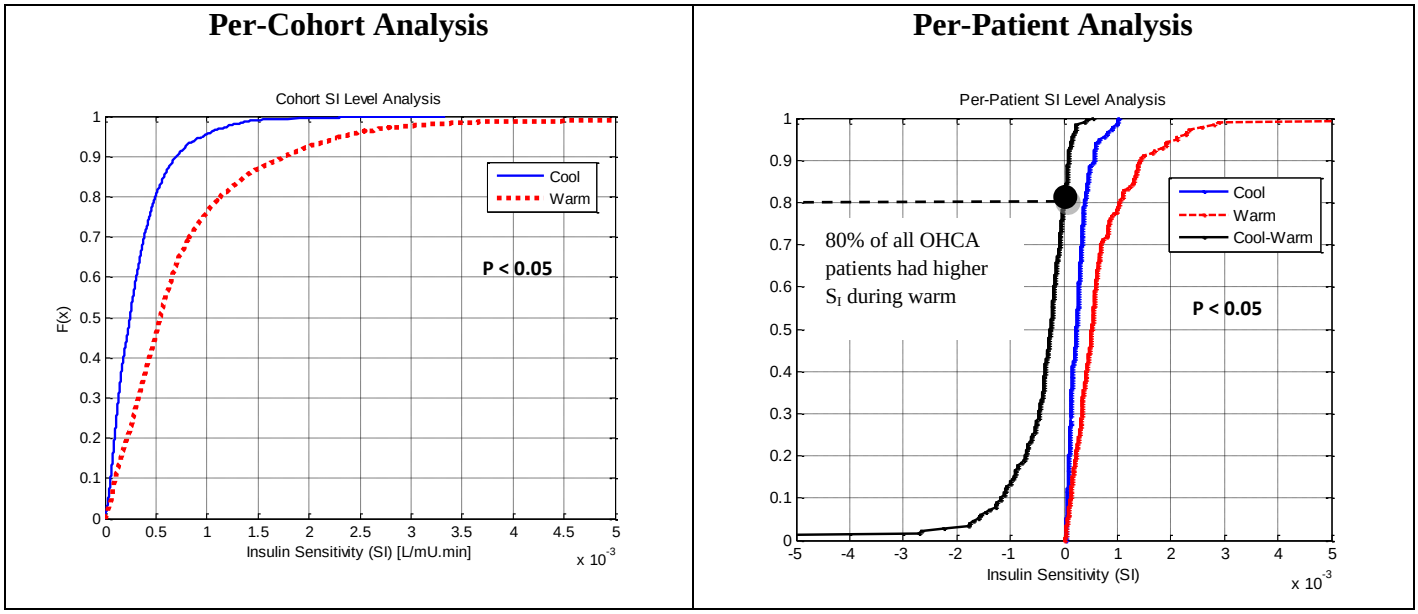

Fig. 4.1: Insulin sensitivity level and variability distribution by cohort (left) and per-patient median (right) during cool and warm after periods for all ICU patients

Table 4.2: Summary of S_I results for overall OHCA cohort.

Day	Period	Hours Range	Per-Cohort Median S_I [IQR] [L/mU/min]	Per-Patient Median S_I [IQR] [L/mU/min]
1	Cool	0 – 24 hours	2.4×10^{-4} [1.1, 4.4] $\times 10^{-4}$	2.4×10^{-4} [1.1, 3.5] $\times 10^{-4}$
2	Warm	24 – 48 hours	5.4×10^{-4} [2.8, 9.7] $\times 10^{-4}$	5.2×10^{-4} [2.8, 8.3] $\times 10^{-4}$
		p-value	$p < 0.05$	$p < 0.05$

The results show that insulin sensitivity levels are initially low during the cool period and significantly increase ($p<0.05$) over time for the first 2 days of ICU stay, with consistent trends between per-cohort and per-patient median values. However, there are around 20% (36 patients) of all patients that have contrasting results, where S_I level is higher during the cool period, counter to the overall trend.

Figure 4.2 presents the 12-hour block S_I level by cohort (left panel) and median S_I per-patient (right panel). Table 4.3 presents the summary of SI results based on 12-hour block and Table 4.4 presents the increase in median S_I between successive blocks.

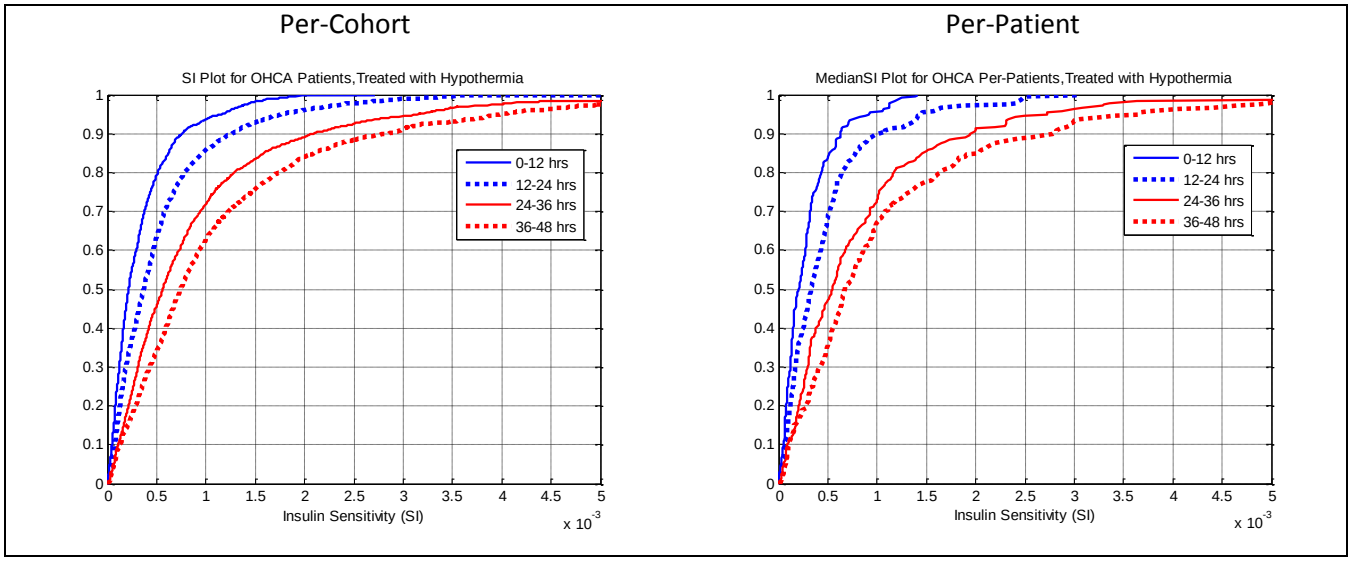

Fig. 4.2: S_I level distribution per-cohort (left) and per-patient median (right) for OHCA patients, treated with hypothermia using 12 hour blocks of data. Blue colour represent cool period and red colour represent warm period.

Table 4.3: Summary of S_I results for OHCA cohort based on 12-hours block.

Day	Block	Hours Range	Per-Cohort Median S_I [IQR] [L/mU/min]	Per-Patient Median S_I [IQR] [L/mU/min]
1	1	0 – 12 hours	2.0×10^{-4} $[1.0, 3.6] \times 10^{-4}$	1.9×10^{-4} $[1.0, 3.0] \times 10^{-4}$
	2	12 – 24 hours	3.0×10^{-4} $[1.3, 5.1] \times 10^{-4}$	2.7×10^{-4} $[1.2, 4.5] \times 10^{-4}$
2	3	24 – 36 hours	5.3×10^{-4} $[2.6, 9.8] \times 10^{-4}$	4.8×10^{-4} $[2.5, 8.3] \times 10^{-4}$
	4	36 – 48 hours	5.6×10^{-4} $[3.0, 9.5] \times 10^{-4}$	5.2×10^{-4} $[3.0, 8.5] \times 10^{-4}$

Table 4.4: Increasing cohort and per patient median S_I during cool and warm (12-hour blocks of data)

SI Level analysis [12-hr blocks]	**Cohort analysis**		**Per-patient analysis**	
	% Increase at median	*p-value*	% Increase at median	*p-value*
Block 1-2 (C) **(0 - 12 vs. 12 - 24 hr)**	50.0	<0.05	42.1	<0.05
Block 2-3 (C-W) **(12 - 24 vs. 24 - 36 hr)**	76.7	<0.05	77.8	<0.05
Block 3-4 (W) **(24 - 36 vs. 36 - 48 hr)**	5.7	0.1	8.3	0.4

P-values calculated using Wilcoxon rank-sum test

The results suggest that S_I increases for the cohort and per-patient are statistically significant for the first 36 hours ($p<0.05$) in both cases. Similarly, the percentage increase at median is also very high within these period. However, the percentage of SI increase is smaller after the subsequent hours.

Figure 4.3 presents the 6-hour block S_I level by cohort (left panel) and median S_I per-patient (right panel). Table 4.5 presents the summary of S_I results based on 6-hour block and Table 4.6 presents the increase in median S_I between successive blocks.

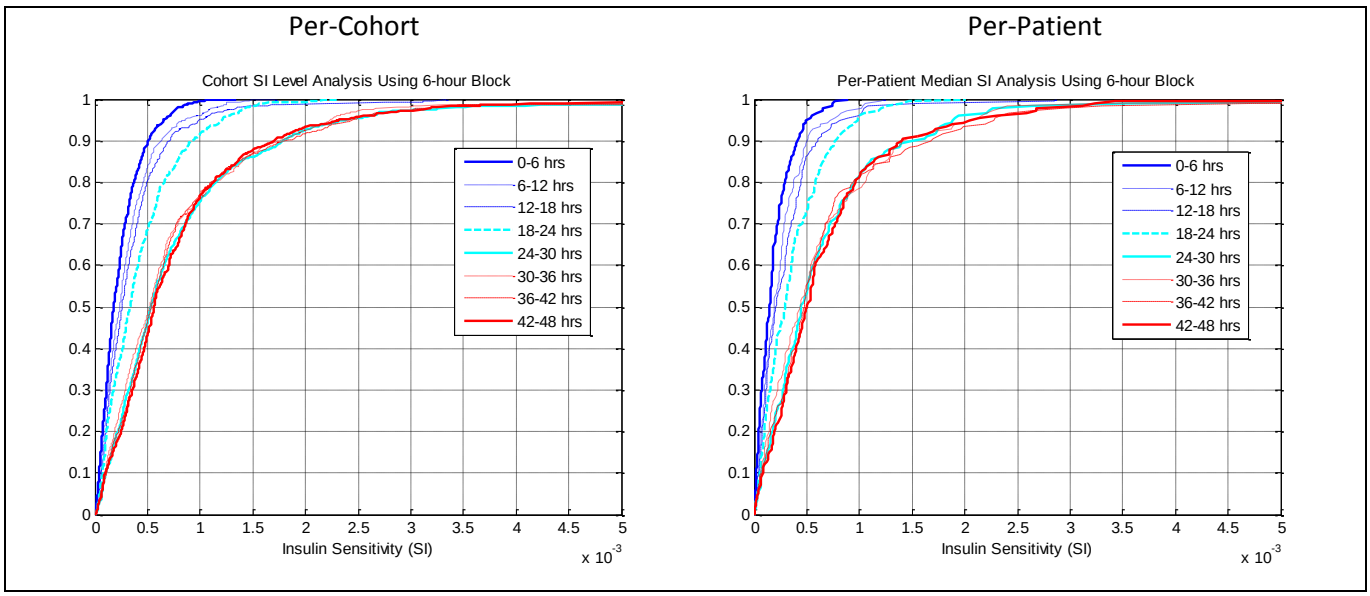

Fig. 4.3: S_I level distribution per-cohort (left) and per-patient median (right) for OHCA patients, treated with hypothermia using 6 hour blocks of data.

Table 4.5: Summary of S_I results for overall OHCA cohort based on 6-hour block.

Day	Block	Hours Range	Per-Cohort Median S_I [IQR] [L/mU/min]	Per-Patient Median S_I [IQR] [L/mU/min]
1	1	0 – 6 hours	1.8×10^{-4} $[0.9, 3.3] \times 10^{-4}$	1.5×10^{-4} $[0.6, 2.6] \times 10^{-4}$
	2	6 – 12 hours	2.3×10^{-4} $[1.0, 4.0] \times 10^{-4}$	1.9×10^{-4} $[0.9, 3.2] \times 10^{-4}$
	3	12 – 18 hours	2.6×10^{-4} $[1.2, 4.5] \times 10^{-4}$	2.1×10^{-4} $[1.0, 4.0] \times 10^{-4}$
	4	18 – 24 hours	3.4×10^{-4} $[1.4, 5.9] \times 10^{-4}$	3.0×10^{-4} $[1.2, 5.1] \times 10^{-4}$
2	5	24 – 30 hours	5.3×10^{-4} $[2.7, 9.8] \times 10^{-4}$	4.5×10^{-4} $[2.2, 8.3] \times 10^{-4}$
	6	30 – 36 hours	5.2×10^{-4} $[2.3, 9.7] \times 10^{-4}$	4.4×10^{-4} $[1.7, 8.7] \times 10^{-4}$
	7	36 – 42 hours	5.4×10^{-4} $[2.9, 9.3] \times 10^{-4}$	4.8×10^{-4} $[2.6, 7.7] \times 10^{-4}$
	8	42 – 48 hours	5.6×10^{-4} $[3.0, 9.6] \times 10^{-4}$	5.0×10^{-4} $[2.7, 8.5] \times 10^{-4}$

Table 4.6: Increasing cohort and per patient median S_I during cool and warm as per 6-hour blocks of data

SI Level analysis [6-hr blocks]	Cohort analysis		Per-patient analysis	
	% Increase at median	*p-value*	% Increase at median	*p-value*
Block 1-2 (C) **(0 - 6 vs. 6 - 12 hr)**	27.8	< 0.05	30.4	< 0.05
Block 2-3 (C) **(6 - 12 vs. 12 - 18 hr)**	13.0	< 0.05	8.8	< 0.05
Block 3-4 (C) **(12 - 18 vs. 18 - 24 hr)**	30.8	< 0.05	42.6	< 0.05
Block 4-5 (C-W) **(18 - 24 vs. 24 - 30 hr)**	55.9	< 0.05	52.1	< 0.05
Block 5-6 (W) **(24 - 30 vs. 30 - 36 hr)**	-1.9	0.2	-2.2	0.6
Block 6-7 (W) **(30 - 36 vs. 36 - 42 hr)**	3.8	0.2	9.3	0.3
Block 7-8 (W) **(36 - 42 vs. 42 - 48 hr)**	3.7	0.3	5.3	0.6

P-values calculated using Wilcoxon rank-sum test

The results suggest that S_I levels are initially low during the cool period and increase over time for the first 36-42 hours of ICU stay, matching the 12-hour block analyses. It is evident that the increase in S_I between each time block is significantly larger ($p < 0.05$) for the first 36 hours of treatment than after 36 hours which are not significantly different.

4.3.1.2 S_I Variability Analysis

Figure 4.4 presents the cumulative distribution functions (CDFs) of hourly S_I level and its variability for both cool and warm after periods by cohort (left panel) and median hourly S_I per-patient (right panel) for all cohort patients. Table 4.7 presents summary of S_I variability results for overall OHCA cohort.

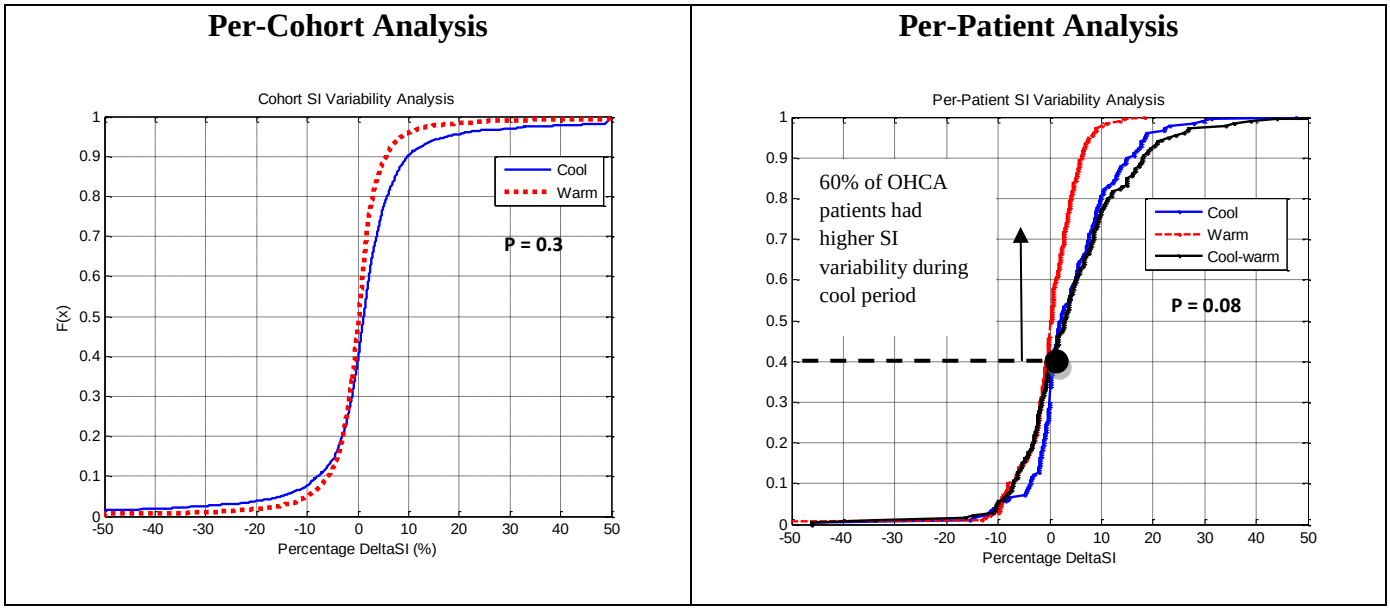

Fig. 4.4: Insulin sensitivity level and variability distribution by cohort (left) and per-patient median (right) during cool and warm after periods for all ICU patients

Table 4.7: Summary of S_I variability results for overall OHCA cohort.

Day	Period	Hours Range	Per-Cohort Median DeltaS_I [IQR] [%]	Per-Patient Median DeltaS_I [IQR] [%]
1	Cool	0 – 24 hours	1.1 [-1.8, 4.4]	2.3 [-0.8, 8.9]
2	Warm	24 – 48 hours	0.2 [-2.2, 2.2]	0.4 [-2.5, 3.4]
		p-value	0.3	0.08

The results in show that S_I is more variable during cool than warm and significantly decrease ($p<0.05$) over time for the first 2 days of ICU stay. However, there are around 40% (72 patients) of all patients that have contrasting results, where S_I variability is higher during the warm period, in contrast to the overall trend. The results also show that 60% of $\%\Delta S_I$ are positive bias both cool and warm periods, indicating more rising S_I as seen in Figure 4.4.

Figure 4.5 presents 12-hourly blocks of $\%\Delta S_I$ (left panel) and 50% range of S_I variability per-patient (right panel). Table 4.8 presents the summary of S_I variability results based on 12-hour block and Table 4.9 presents the reductions between successive blocks.

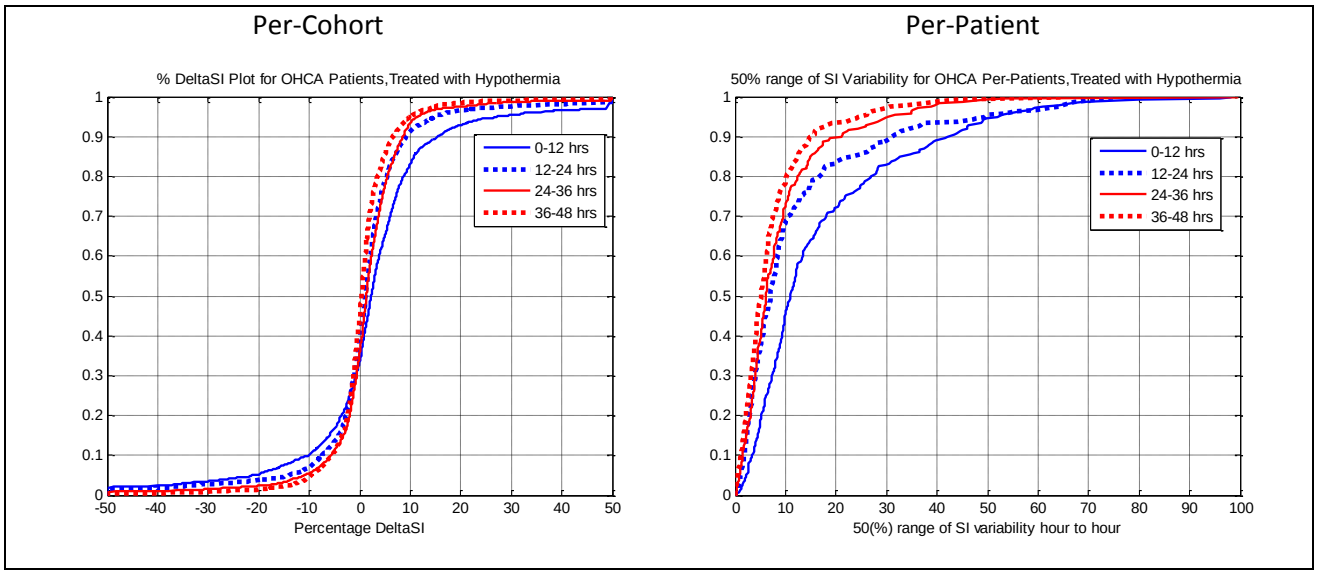

Fig. 4.5: S_I variability per-cohort (left) and 50% range of S_I variability per-patient (right) for OHCA patients, treated with hypothermia using 12 hour blocks. Blue and red represent cool and warm period respectively.

Table 4.8: Summary of S_I variability results for OHCA cohort based on 12-hours block.

Day	Block	Hours Range	Per-Cohort Median DeltaS_I [IQR] [%]	Per-Patient Median DeltaS_I [IQR] [%]
1	1	0 – 12 hours	1.1 [-2.2, 5.3]	9.0 [5.1, 17.0]
	2	12 – 24 hours	1.2 [-1.5, 3.7]	5.8 [2.8, 10.3]
2	3	24 – 36 hours	0.07 [-2.5, 2.0]	4.8 [2.8, 9.5]
	4	36 – 48 hours	0.3 [-1.7, 2.3]	4.8 [2.7, 9.2]

Table 4.9: Reductions in the IQR and median S_I per patient range of hour-to-hour percentage S_I change over time during cool and warm after as per 12-hour blocks of data

SI Variability analysis [12-hr blocks]	Cohort analysis		Per-patient analysis	
	% Reduction of IQR	*p-value*	% Decrease at median	*p-value*
Block 1-2 (C) **(0 - 12 vs. 12 - 24 hr)**	31.1	< 0.05	35.6	< 0.05
Block 2-3 (C-W) **(12 - 24 vs. 24 - 36 hr)**	12.4	0.9	17.2	0.2
Block 3-4 (W) **(24 - 36 vs. 36 - 48 hr)**	12.2	0.2	0.0	0.4

P-values are calculated using Kolmogorov-Smirnov test

The results and analyses from both per-cohort and per-patient suggest that insulin sensitivity is more variable during the cool period and significantly decreases over time for the first 12 hours of treatment. However, small decrease is observed between block 2 (12-24 hrs) and block 3 (24-36 hrs), but rise again for the next consequent block. The decrease between block 1-2 (cooling) and block 3-4 (warming) is statistically significant for both per-cohort and per-patient analyses, but the change is much less between block 2-3 (cooling-warming) and may not be significant.

Figure 4.6 presents 6-hourly blocks of $\%\Delta S_I$ (left panel) and 50% range of S_I variability per-patient (right panel). Table 4.10 presents the summary of S_I results based on 6-hour block and Table 4.11 presents the reductions between successive blocks.

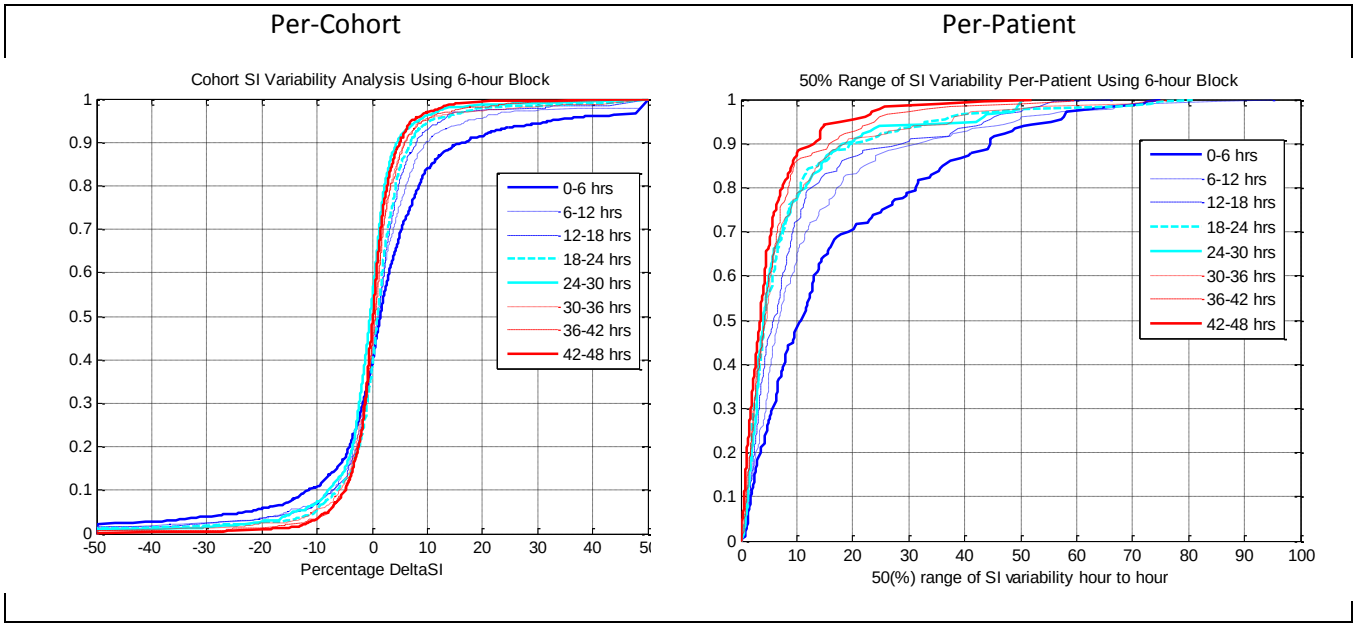

Fig. 4.6: Insulin sensitivity variability per-cohort (left) and 50% range of S_I variability CDF per-patient (right) for OHCA patients, treated with hypothermia using 6 hour blocks of data.

Cohort and per-patent variability decreases over time for the first 48 hours of ICU stay. However, it increases across the cool to warm transition, indicating some potential stress across the cool-warm transition with negative reductions. The decreasing trend returns for all subsequent blocks. The results suggest that $\%\Delta S_I$ decreases per-cohort and per-patient are statistically significant ($p<0.05$) for the first 36 hours in both cases.

Table 4.10: Summary of S_I variability results for overall OHCA cohort based on 6-hour block.

Day	Block	Hours Range	Per-Cohort Median DeltaS_I [IQR] [%]	Per-Patient Median DeltaS_I [IQR] [%]
1	1	0 – 6 hours	1.4 [-2.5, 6.2]	10.7 [4.7, 25.6]
	2	6 – 12 hours	0.9 [-2.0, 4.7]	6.8 [3.4, 14.4]
	3	12 – 18 hours	1.2 [-1.7, 3.9]	5.8 [2.9, 10.9]
	4	18 – 24 hours	1.1 [-1.4, 3.6]	4.3 [2.0, 8.6]
2	5	24 – 30 hours	-0.4 [-2.8, 1.7]	4.0 [2.4, 8.8]
	6	30 – 36 hours	0.5 [-2.3, 2.6]	4.5 [2.1, 9.0]
	7	36 – 42 hours	0.6 [-1.7, 2.5]	4.3 [2.1, 7.1]
	8	42 – 48 hours	0.2 [-1.7, 2.0]	4.2 [1.5, 6.3]

Table 4.11: Reductions in the interquartile range and median S_I per patient range of hour-to-hour percentage S_I change over time during cool and warm after as per 6-hour blocks of data

SI Variability analysis [6-hr blocks]	Cohort analysis		Per-patient analysis	
	% Reduction of IQR	*p-value*	% Decrease at median	*p-value*
Block 1-2 (C) **(0 - 6 vs. 6 - 12 hr)**	23.4	< 0.05	36.4	< 0.05
Block 2-3 (C) **(6 - 12 vs. 12 - 18 hr)**	15.8	< 0.05	14.7	< 0.05
Block 3-4 (C) **(12 - 18 vs. 18 - 24 hr)**	11.7	< 0.05	25.9	< 0.05
Block 4-5 (C-W) **(18 - 24 vs. 24 - 30 hr)**	9.4	0.6	9.3	0.8
Block 5-6 (W) **(24 - 30 vs. 30 - 36 hr)**	-8.5	0.5	-15.4	0.8
Block 6-7 (W) **(30 - 36 vs. 36 - 42 hr)**	13.7	0.4	4.4	0.6
Block 7-8 (W) **(36 - 42 vs. 42 - 48 hr)**	10.7	0.08	2.3	0.06

P-values calculated using Kolmogorov-Smirnov test

4.3.2 Results by Sub-Cohort

4.3.2.1 S_I Level Analysis

Table 4.12 presents the summary of S_I level results and analysis for OHCA Sub-Cohorts. The summary shows that S_I levels are low during the cool period and significantly increase ($p<0.05$) over time for the first 2 days of ICU stay, with consistent trends among all OHCA sub-cohorts. However, there are around 20% of each sub-cohort patients that have contrasting results against the overall trend.

Table 4.12: Summary of S_I level results and analysis for OHCA Sub-Cohorts

OHCA Sub-Cohort	No of Patients	Median S_I [IQR] at cool period [L/mU.min]	Median S_I [IQR] at warm period [L/mU.min]	% patients had higher S_I at warm period [Diff(Cool-warm)]	p-value
Overall OHCA cohort	180	2.5×10^{-4} $[1.1, 4.4] \times 10^{-4}$	5.4×10^{-4} $[2.8, 9.7] \times 10^{-4}$	80%	$p < 0.05$
Survived Patients	98	2.5×10^{-4} $[1.2, 4.5] \times 10^{-4}$	5.8×10^{-4} $[2.9, 10.6] \times 10^{-4}$	80%	$p < 0.05$
Non-Survived Patients	82	2.2×10^{-4} $[1.1, 4.2] \times 10^{-4}$	5.1×10^{-4} $[2.6, 8.4] \times 10^{-4}$	80%	$p < 0.05$
Diabetes Patients	23	2.3×10^{-4} $[1.1, 3.9] \times 10^{-4}$	4.1×10^{-4} $[2.5, 6.2] \times 10^{-4}$	80%	$p < 0.05$
Non-Diabetes Patients	157	2.4×10^{-4} $[1.1, 4.4] \times 10^{-4}$	5.7×10^{-4} $[2.8, 10.1] \times 10^{-4}$	80%	$p < 0.05$
Male Patients	143	2.5×10^{-4} $[1.2, 4.4] \times 10^{-4}$	5.6×10^{-4} $[2.9, 10.2] \times 10^{-4}$	80%	$p < 0.05$
Female Patients	37	2.0×10^{-4} $[0.9, 4.0] \times 10^{-4}$	4.8×10^{-4} $[2.5, 8.0] \times 10^{-4}$	80%	$p < 0.05$
ROSC < 15 mins	63	2.7×10^{-4} $[1.4, 4.5] \times 10^{-4}$	5.7×10^{-4} $[3.1, 9.7] \times 10^{-4}$	80%	$p < 0.05$
ROSC < 30 mins	89	2.3×10^{-4} $[1.0, 4.3] \times 10^{-4}$	5.3×10^{-4} $[2.8, 9.6] \times 10^{-4}$	80%	$p < 0.05$
ROSC > 30 mins	28	2.0×10^{-4} $[0.9, 3.9] \times 10^{-4}$	5.3×10^{-4} $[1.8, 9.8] \times 10^{-4}$	80%	$p < 0.05$

Table 4.13 presents the summary of increasing cohort and per patient median S_I during cool and warm as per 12-hour blocks of data for all OHCA sub-cohorts. The results suggest that S_I increases for the cohort and per-patient are statistically significant for the first 36 hours ($p<0.05$), with consistent trends among all OHCA sub-cohorts.

Table 4.13: Summary of increasing cohort and per patient median S_I during cool and warm as per 12-hour blocks of data for all OHCA sub-cohorts.

S_I Level analysis [12-hr blocks]	No of Patients	Block 1-2 (C) **(0 - 12 vs. 12 - 24 hr)**				Block 2-3 (C-W) **(12 - 24 vs. 24 - 36 hr)**				Block 3-4 (W) **(24 - 36 vs. 36 - 48 hr)**			
		Cohort analysis		Per-patient analysis		Cohort analysis		Per-patient analysis		Cohort analysis		Per-patient analysis	
		% Increase at median	*p-value*	% Increase at median	*p-value*	% Increase at median	*p-value*	% Increase at median	*p-value*	% Increase at median	*p-value*	% Increase at median	*p-value*
All OHCA patients	180	47.3	<0.01	45.6	<0.01	77.5	<0.01	77.8	<0.01	6.2	0.10	8.3	0.40
Survived Patients	98	52.6	<0.01	57.3	<0.01	66.3	<0.01	58.7	<0.01	9.1	0.12	15.1	0.50
Non-Survived Patients	82	42.7	<0.01	46.3	0.02	94.7	<0.01	96.5	<0.01	0.5	0.6	4.3	0.80
Diabetes Patients	23	40.2	<0.01	31.3	0.25	44.4	<0.01	22.2	<0.01	5.5	0.5	26.3	0.54
Non-Diabetes Patients	157	48.2	<0.01	48.9	<0.01	81.6	<0.01	84.3	<0.01	7.5	0.09	10.0	0.46
Male Patients	143	40.0	<0.01	44.3	<0.01	77.8	<0.01	66.6	<0.01	7.8	0.04	12.2	0.32
Female Patients	37	72.3	<0.01	77.3	<0.01	84.0	<0.01	94.8	<0.01	-3.8	0.9	-1.4	0.9
ROSC < 15 mins	63	55.5	<0.01	64.5	<0.01	60.0	<0.01	49.3	<0.01	0.6	0.4	0.4	0.9
ROSC < 30 mins	89	48.7	<0.01	38.5	0.03	77.7	<0.01	79.2	<0.01	10.1	0.2	11.7	0.3
ROSC > 30 mins	28	62.0	<0.01	60.5	0.11	88.8	<0.01	100.1	<0.01	19.5	0.4	11.7	0.9

P-values are calculated using Wilcoxon rank-sum test

4.3.2.2 S_I Variability Analysis

Table 4.14 presents the summary of S_I variability results and analysis for OHCA Sub-Cohorts. The results show that S_I is more variable during cool than warm and significantly decrease ($p<0.01$) over time for the first 2 days of ICU stay, with consistent trends among all OHCA sub-cohorts. However, there are around 30% - 40% patients for each sub-cohort that have contrasting results, where S_I variability is higher during the warm period, in contrast to the overall trend.

Table 4.14: Summary of S_I variability results and analysis for OHCA Sub-Cohorts

OHCA Sub-Cohorts	No of Patients	Median S_I variability [IQR] at cool period [$\%\Delta S_I$]	Median S_I variability [IQR] at warm period [$\%\Delta S_I$]	% patients had higher S_I variability during cool [Diff(Cool-warm)]	% patients had contrasting S_I variability against overall trend	p-value
Overall OHCA cohort	180	1.2 [-1.8, 4.4]	0.2 [-2.2, 2.2]	60%	40%	0.08
Survived Patients	98	1.0 [-1.8, 4.1]	0.3 [-2.0, 2.2]	60%	40%	0.1
Non-Survived Patients	82	1.4 [-1.9, 4.8]	0.07[-2.4, 2.1]	60%	40%	0.2
Diabetes Patients	23	1.0 [-1.3, 3.7]	0.04[-2.4, 2.2]	60%	40%	0.3
Non-Diabetes Patients	157	1.2 [-1.9, 4.6]	0.3 [-2.2, 2.2]	60%	40%	0.06
Male Patients	143	1.0 [-1.8, 4.4]	0.3 [-2.2, 2.3]	60%	40%	0.09
Female Patients	37	1.5 [-2.0, 4.5]	-0.3[-2.2,1.8]	70%	30%	0.5
ROSC < 15 mins	63	1.0 [-1.6, 3.6]	0.3[-2.2, 2.3]	60%	40%	0.2
ROSC < 30 mins	89	1.2 [-2.0, 5.0]	0.2[-1.9, 2.1]	60%	40%	0.3
ROSC > 30 mins	28	1.4 [-2.1, 4.7]	-0.1[-2.7,2.0]	70%	30%	0.5

Table 4.15 presents the summary of reductions in the IQR and median S_I per patient range of hour-to-hour percentage S_I change over time during cool and warm as per 12-hour blocks of data for all OHCA sub-cohorts. The results and analyses suggest that insulin sensitivity is more variable during the cool period and significantly decreases over time for the first 12 hours of treatment, with consistent trends among all OHCA sub-cohorts. However, the overall decrease at block 2-3 (cool-warm transition) and block 3-4 (warming) are not significant, even though some results are not consistent across each sub-cohort.

Similar S_I variability trends are observed between overall OHCA cohort and several sub-cohorts such as non-diabetes, male, female, survived, non-survived, ROSC<15 and ROSC<30. Other sub-cohorts such as diabetes and ROSC > 30 have shown different S_I variability trends compared to overall OHCA cohort. Thus, these results show that not all OHCA patients which are distinguished by sub-cohorts have the same way of S_I variability even though they have undergone the same treatment protocol from cool to warm period.

Table 4.15: Summary of reductions in the IQR and median S_I per patient range of hour-to-hour percentage S_I change over time during cool and warm as per 12-hour blocks of data for all OHCA sub-cohorts.

S_I variability analysis [12-hr blocks]	No of Patients	Block 1-2 (C) **(0 - 12 vs. 12 - 24 hr)**				Block 2-3 (C-W) **(12 - 24 vs. 24 - 36 hr)**				Block 3-4 (W) **(24 - 36 vs. 36 - 48 hr)**			
		Cohort analysis		Per-patient analysis		Cohort analysis		Per-patient analysis		Cohort analysis		Per-patient analysis	
		% Reduction of IQR	*p-value*	% Decrease at median	*p-value*	% Reduction of IQR	*p-value*	% Decrease at median	*p-value*	% Reduction of IQR	*p-value*	% Decrease at median	*p-value*
All OHCA patients	**180**	**31.3**	**0.3**	**36.2**	**0.02**	**12.4**	**0.9**	**17.3**	**0.2**	**12.2**	**0.15**	**-0.2**	**0.4**
Survived Patients	**98**	**32.1**	**0.4**	**33.6**	**0.01**	**3.4**	**0.01**	**11.2**	**0.5**	**19.8**	**0.03**	**2.7**	**0.4**
Non-Survived Patients	**82**	**30.0**	**0.04**	**35.7**	**0.01**	**20.8**	**0.01**	**30.6**	**0.2**	**4.0**	**0.07**	**-9.8**	**0.7**
Diabetes Patients	**23**	**35.7**	**0.3**	**60.8**	**0.07**	**-23.5**	**0.01**	**-84.1**	**0.2**	**23.0**	**0.40**	**21.1**	**0.3**
Non-Diabetes Patients	**157**	**30.0**	**0.3**	**32.0**	**0.03**	**17.2**	**<0.01**	**30.1**	**0.03**	**10.8**	**<0.01**	**9.0**	**0.7**
Male Patients	**143**	**30.0**	**0.04**	**35.0**	**0.04**	**10.0**	**<0.01**	**16.8**	**0.3**	**14.0**	**<0.01**	**-2.3**	**0.8**
Female Patients	**37**	**39.8**	**0.4**	**43.0**	**0.05**	**19.3**	**0.10**	**17.4**	**0.4**	**14.2**	**0.6**	**11.3**	**0.2**
ROSC < 15 mins	**63**	**34.4**	**0.7**	**43.0**	**0.05**	**-18.7**	**<0.01**	**-4.2**	**0.03**	**20.4**	**0.02**	**0.7**	**0.4**
ROSC < 30 mins	**89**	**31.0**	**0.03**	**23.6**	**0.04**	**25.1**	**<0.01**	**31.0**	**0.03**	**11.3**	**0.05**	**1.7**	**0.5**
ROSC > 30 mins	**28**	**35.1**	**0.9**	**47.0**	**0.02**	**25.3**	**<0.01**	**49.0**	**0.2**	**-8.3**	**0.11**	**-56.0**	**0.8**

P-values are calculated using Kolmogorov-Smirnov test

4.4 Discussion

4.4.1 Insulin sensitivity level

The insulin sensitivity level results for both per-cohort and per-patient analyses suggest that OHCA patients undergoing hypothermic treatment have significantly lower insulin sensitivity during the earlier cool period on day 1 than the later warm period on day 2. Both results follow the general trend for insulin sensitivity level for critically ill patients over time and are consistent with other ICU studies (Langouche et al., 2007, Pretty et al., 2012).

Further analysis shows that the increase in S_I level during the first 36 hours are large and statistically significant for this cohort. The rapid increases in S_I level for the first 36 hours is likely due to significant restart of human physiological systems and metabolic activities for these patients (Neumar et al., 2008). After 36 hours, the rapid S_I increase abates as the patients' metabolism improves and becomes more stable.

Several sub-cohorts have shown consistent S_I trend with overall OHCA patients, This suggest that analysing overall OHCA patients metabolic evolution is sufficient enough for developing control scheme.

4.4.2 Insulin sensitivity variability

Both per-cohort and per-patient analysis suggest that OHCA patients undergoing TH treatment have high initial variability that decreases over the first 36 hours. However, the cool to warm transition at 24 hours shows an increase in variability likely due to the change of physiological conditions as body temperature increase from cool to warm between 18 – 36 hours. The lower decrease in S_I variability after 36^{th} hours onwards suggests that the patients' metabolic condition has improved and become more stable.

Further analysis and comparison of S_I variability between general ICU patients (Pretty et al., 2012) and OHCA patients, treated with TH shows that the main difference between them is the S_I variability increase during the cool-warm transition period for the latter cohort. These S_I variability results do not follow the same trend with other general ICU studies by Pretty et

al. (Pretty et al., 2012), and it is a unique finding for this cohort that could significantly impact glycaemic control and safety from hypoglycaemia.

4.4.3 The Impact of S_I variability on glycaemic control

Clinically, these results have significant implications for managing glycaemia. Increased S_I variability leads to increased variability in BG level for a given insulin intervention (Chase et al., 2011b). With low and variable insulin sensitivity, glycaemic levels might appear to remain unchanged and difficult to control effectively with exogenous insulin. This situation may result in increased glycaemic variability as well as an increased risk of hyperglycaemia and hypoglycaemia during the first 36 hours of treatment due to greater hour-to-hour S_I variability with increased insulin resistance (Cueni-Villoz et al., 2011). Thus, since glycaemic variability and hypoglycaemia are independent risk factors for the critically ill, it is important to understand and manage these patient-specific dynamics, especially those unique to a cohort, when implementing glycaemic control. This outcome is particularly important when OHCA patients transition from cool to warm. These results may also generalise to other areas where glycaemic control is applied to hypothermic patients, such as in the operating theatre.

There are several ways that this low and variable insulin sensitivity could be managed during glycaemic control. Reducing exogenous insulin doses, coupled with modulation of the glucose content of nutrition would diminish the impact of sudden changes of insulin sensitivity on glycaemic outcome. Equally, increased blood glucose measurement frequency could improve control and reduce glycaemic variability. Accepting higher glycaemic targets during periods of increased variability would trade-off a reduced risk of hypoglycaemia against increased hyperglycaemia. Ultimately, the preferred method for any unit may be influenced by practical considerations, such as clinical workload.

4.5 Summary

This study analyses the metabolic evolution of OHCA patients treated with hypothermia. These analyses characterize the metabolic impact of hypothermic treatment on the level and variability of insulin sensitivity to inform control.

Two main conclusions are drawn as a result for these cohorts.

i) S_I level is much lower during hypothermia and consistently increases over time, both cool and warm periods.

ii) Insulin sensitivity is more variable during the cool period and shows contrasting behavior during cool-warm transition period between 18 – 30 hours, which indicates that there are major changes in physiology and metabolic conditions between cool and warm as influenced by human body temperature. Otherwise, it decreases over time.

Finally, this study shows the need for patient-specific glycemic management to ensure good control and safety during treatment. These results have significant potential clinical impact on the metabolic treatment of these patients, and changes in clinical therapy are required to safely treat patients as they transition from cool to warm.

Chapter 5: Blood Glucose Level and Variability Analysis

This chapter describes a preliminary study of Out-of-Hospital Cardiac Arrest (OHCA) patients based on glycaemic characteristics during hypothermia (cool period) and normothemia. It analyses the impact of therapeutic hypothermia (TH) on glycaemic outcome, including the evolution of blood glucose and its variability, in patients with coma after OHCA. Patients' data were analysed based on cohort as defined in Chapter 3, and results were summarized.

5.1 Introduction

One of the adverse events associated with hypothermic therapy is the decrease in insulin sensitivity and insulin secretion (Hayashi, 2009). The amount of insulin required to maintain glucose levels within normal range (4.4 to 6.1 mmol/L) is thus likely to increase during the induction of hypothermia due to both the initial insult and stress, and hypothermia itself. High insulin doses can lead to hypoglycaemia if patient condition improves and dosing is not adjusted accordingly. Thus, non-patient-specific approaches can result in highly variable BG, which can adversely affect clinical outcomes and mortality (Bagshaw et al., 2009).

This study analyses and compares blood glucose (BG) level and variability, and their evolution in OHCA patients undergoing hypothermic treatment. The results provide better understanding of the glycaemic condition of these patients which will help in improving glycaemic control protocol for use with TH.

5.2 Subjects and Methods

5.2.1 Patients and Data

This analysis was performed on a cohort of 180 OHCA patients (7812 hours) treated with hypothermia, shortly after admission in Intensive Care Units (ICUs) of Erasme Hospital, Belgium and Lausanne Hospital, Switzerland. These patients were on local AGC protocols. Data collections were carried out as per described in sub-chapter 3.1 Additional information

for each patient such as mortality, diabetes history, gender and return of spontaneous circulation (ROSC) were recorded. These inputs will be taken into consideration for separate sub-analysis studies from full cohort. Details of the cohort demography, including sub-cohorts are presented in Table 3.1.

5.2.2 Analyses and Metrics

BG level during the cool (T<35^{o}C) and warm (T>37^{o}C) periods were identified hourly. Variability of BG was calculated as the hour-to-hour percentage change in BG (%ΔBG), defined:

$$\%\Delta BG = \frac{(BG_{n+1} - BG_n)}{BG_n} x\ 100 \qquad (5.1)$$

The use of percentage change, rather than absolute change, normalises the metric so patients with differing BG levels can be compared fairly. BG level, variability and gradient were analysed during both cool and warm periods on overall cohort and per-patient bases as follows;

i) Overall cohort patient.
ii) Analysis of patient by 12-hour block.
iii) Analysis of patient by 6-hour block.

Cohort analysis assess every hours of BG level and variability for the entire cohort and shows trend based on the overall group behaviour, whereas per-patient analysis examined the BG level by median values within each timeframe. To quantify per-patient variability, the interquartile range (IQR) of %ΔBG is calculated and this metric captures the width of the hour-to-hour variability distributions for each patient.

The BG analysis of patients using 12-hour and 6-hour time blocks, which includes level and variability is described in Table 4.1. This method will examine group behaviour and assess its changes for every 12 and 6 hour blocks of the entire treatment from cool to warm periods. For cohort analysis, BG and Δ% BG data from all patients was grouped into each appropriate time-block. Median values for each time-block were calculated for comparison to the previous block, thus capturing overall cohort changes over time in level and hour-to-hour

variability. For per-patient analysis, the median value of S_I and the interquartile range (IQR) of Δ%BG were calculated for each patient, for each time-block. The IQR captures the width of degree of variability for a given patient within each hour block. Thus, a reduction in the IQR of Δ%BG over time would indicate a reduction in hour-to-hour variability for a given patient.

BG level and variability are non-Gaussian and thus were compared using non-parametric cumulative distribution functions (CDFs). All distributed data were compared using a Wilcoxon rank-sum test (Mann-Whitney U-test), except for BG variability results. BG variability was compared using the Kolmogorov-Smirnov test as it has greater power to detect differences in the shape of distributions when median values are similar. In all cases, $p < 0.05$ is considered statistically significant.

5.3 Results

5.3.1 Results for Complete Cohort

5.3.1.1 BG Level Analysis

Figure 5.1 presents the cumulative distribution functions (CDFs) of hourly BG level and its variability for both cool and warm periods by cohort (left panel) and per-patient median BG (right panel). Table 5.1 presents summary of BG results for overall OHCA cohort.

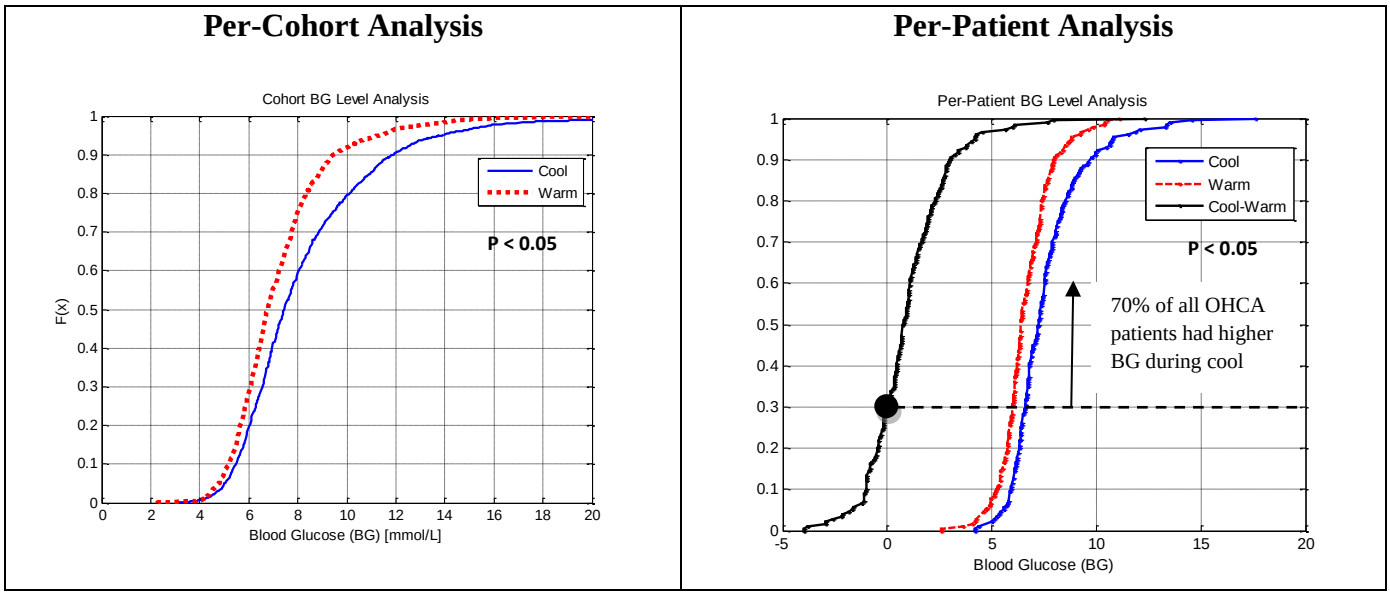

Fig. 5.1: Blood glucose level and variability distribution by cohort (left) and per-patient median (right) during cool and warm after periods for all OHCA patients

Table 5.1: Summary of BG results for overall OHCA cohort.

Day	Period	Hours Range	Per-Cohort Median BG [IQR [mmol/L]	Per-Patient Median BG [IQR] [mmol/L]
1	Cool	0 – 24 hours	9.7 [6.9, 13.1]	7.4 [6.5, 8.5]
2	Warm	24 – 48 hours	8.5 [6.1, 11.5]	6.5 [5.8, 7.4]
		p-value	$p < 0.05$	$p < 0.05$

The results show that blood glucose levels are initially high during the cool period and significantly decrease ($p<0.05$) over time for the first 2 days of ICU stay, with consistent trends between per-cohort and per-patient median values. However, there are around 30% (54 patients) of all patients that have contrasting results, where BG level is lower during the cool period, in contrast to the overall trend.

Figure 5.2 presents the 12-hour block BG level by cohort (left panel) and median BG per-patient (right panel). Table 5.2 presents the summary of BG results based on 12-hour block, and Table 5.3 presents the decrease in median BG between successive blocks.

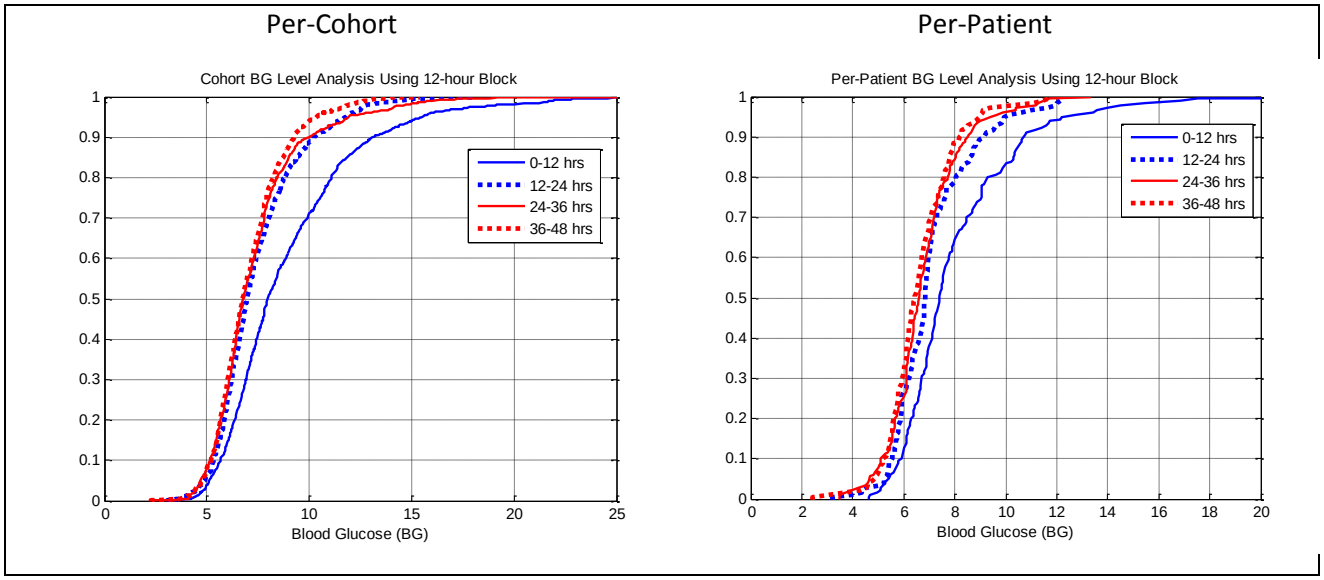

Fig. 5.2: BG level distribution per-cohort (left) and per-patient median (right) for OHCA patients, treated with hypothermia using 12 hour blocks of data. Blue colour represent cool period and red colour represent warm

Table 5.2: Summary of BG results for OHCA cohort based on 12-hours block.

Day	Block	Hours Range	Per-Cohort Median BG [IQR] [mmol/L]	Per-Patient Median BG [IQR] [mmol/L]
1	1	0 – 12 hours	9.7 [7.1, 13.2]	7.6 [6.5, 9.3]
	2	12 – 24 hours	8.5 [6.1, 10.2]	6.9 [5.9, 8.2]
2	3	24 – 36 hours	8.3 [6.1, 11.3]	6.7 [6.0, 7.8]
	4	36 – 48 hours	7.6 [5.8, 9.8]	6.4 [5.7, 7.6]

Table 5.3: Decreasing cohort and per patient median BG during cool and warm (12-hour blocks of data)

BG Level analysis [12-hr blocks]	**Cohort analysis**		**Per-patient analysis**	
	% Decrease at median	*p-value*	% Decrease at median	*p-value*
Block 1-2 (C) **(0 - 12 vs. 12 - 24 hr)**	12.4	<0.05	9.2	<0.05
Block 2-3 (C-W) **(12 - 24 vs. 24 - 36 hr)**	2.4	0.1	2.9	0.4
Block 3-4 (W) **(24 - 36 vs. 36 - 48 hr)**	8.4	0.1	4.5	0.2

P-values calculated using Wilcoxon rank-sum test

The results and analyses from both per-cohort and per-patient analyses suggest that BG levels were initially high during the cool period and decrease significantly over time for the first 12 hours in the ICU ($p < 0.05$). However, the subsequent blocks show smaller non-statistically significant BG decrease at median.

Figure 5.3 presents the 6-hour block BG level by cohort (left panel) and median BG per-patient (right panel). Table 5.4 presents the summary of BG results based on 6-hour block, and Table 5.5 presents the increase in median BG between successive blocks.

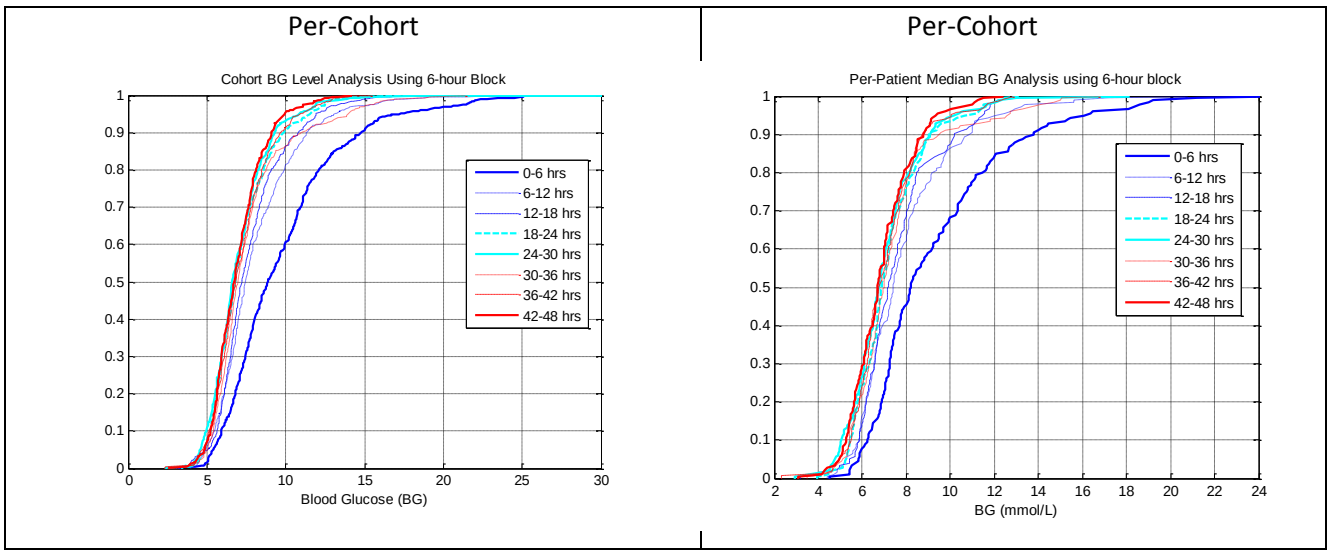

Fig. 5.3: BG level distribution per-cohort (left) and per-patient median (right) for OHCA patients, treated with hypothermia using 6 hour blocks of data.

Table 5.4: Summary of BG results for overall OHCA cohort based on 6-hour block.

Day	Block	Hours Range	Per-Cohort Median BG [IQR] [mmol/L]	Per-Patient Median BG [IQR] [mmol/L]
1	1	0 – 6 hours	9.9 [7.3, 13.4]	8.3 [7.1, 10.8]
	2	6 – 12 hours	8.3 [6.4, 10.9]	7.5 [6.5, 8.9]
	3	12 – 18 hours	7.9 [6.3, 9.9]	7.3 [6.3, 8.4]
	4	18 – 24 hours	7.7 [5.9, 9.5]	6.9 [5.9, 8.1]
2	5	24 – 30 hours	7.6 [5.8, 9.4]	6.8 [5.9, 8.0]
	6	30 – 36 hours	7.9 [6.1, 10.7]	7.0 [6.3, 8.0]
	7	36 – 42 hours	7.4 [5.9, 9.4]	6.9 [6.0, 7.9]
	8	42 – 48 hours	7.3 [5.7, 9.1]	6.8 [5.8, 7.8]

Table 5.5: Decreasing cohort and per patient median BG during cool and warm as per 6-hour blocks of data

BG Level analysis [6-hr blocks]	Cohort analysis		Per-patient analysis	
	% Decrease at median	*p-value*	% Decrease at median	*p-value*
Block 1-2 (C) **(0 - 6 vs. 6 - 12 hr)**	16.2	<0.05	9.6	<0.05
Block 2-3 (C) **(6 - 12 vs. 12 - 18 hr)**	4.8	0.06	2.7	0.1
Block 3-4 (C) **(12 - 18 vs. 18 - 24 hr)**	2.5	0.2	5.5	0.4
Block 4-5 (C-W) **(18 - 24 vs. 24 - 30 hr)**	1.3	0.8	1.4	0.4
Block 5-6 (W) **(24 - 30 vs. 30 - 36 hr)**	-3.9	0.06	-2.9	0.1
Block 6-7 (W) **(30 - 36 vs. 36 - 42 hr)**	6.3	0.05	1.4	0.2
Block 7-8 (W) **(36 - 42 vs. 42 - 48 hr)**	1.3	0.4	1.4	0.5

P-values calculated using Wilcoxon rank-sum test

The results suggest that BG levels are initially high during the cool period and decrease over time, matching the 12-hour block analyses. It is evident that the decrease in BG between each time block is significantly larger ($p < 0.05$) for the first 12 hours of treatment.

5.3.1.2 BG Variability Analysis

Figure 5.4 presents the cumulative distribution functions (CDFs) of BG variability for both cool and warm after periods by cohort (left panel) and median hourly BG per-patient (right panel) for all cohort patients. Table 5.6 presents the summary of BG variability results for overall OHCA cohort.

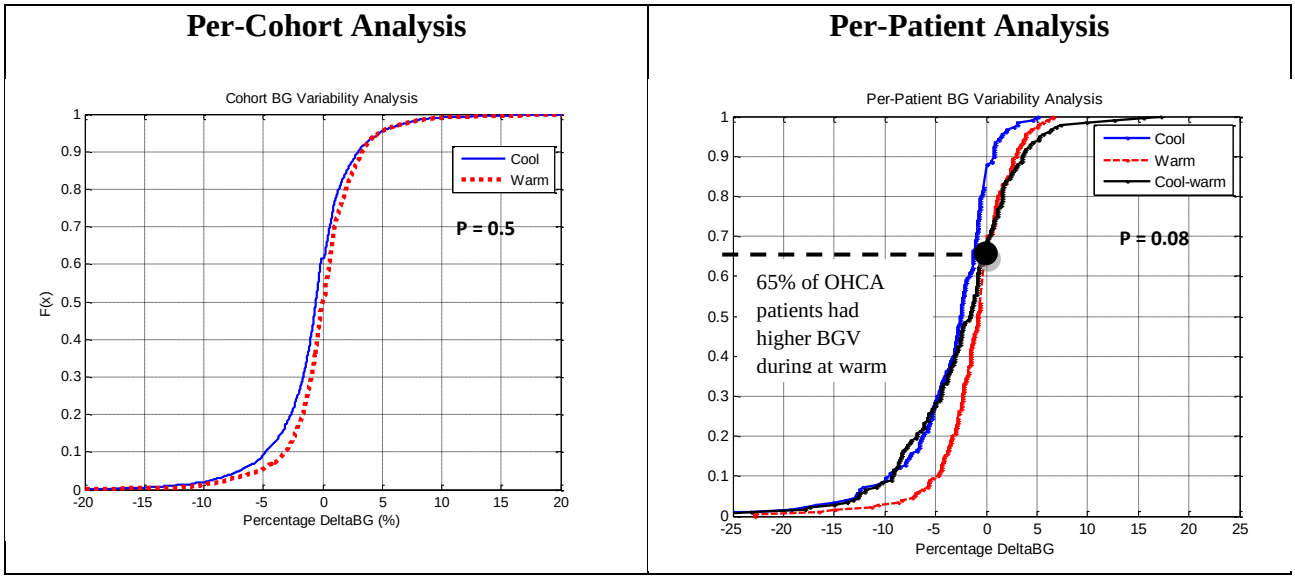

Fig. 5.4: Blood glucose level and variability distribution by cohort (left) and per-patient median (right) during cool and warm after periods for all ICU patients

Table 5.6: Summary of BG variability results for overall OHCA cohort.

Day	Period	Hours Range	Per-Cohort Median DeltaBG [IQR] [mmol/L]	Per-Patient Median DeltaBG [IQR] [mmol/L]
1	Cool	0 – 24 hours	-0.6 [-2.3, 1.0]	-2.8 [-5.6, -0.9]
2	Warm	24 – 48 hours	0.2 [-1.6, 1.9]	-1.5[-3.4, 1.0]
		p-value	0.5	0.08

The results show that BG variability trend is similar, both during cool and warm (p=0.5) over time for the first 2 days of ICU stay. Besides, there are around 65% (117 patients) of all patients that have higher BG variability during the warm period. The results also show that 85% of %ΔBG are negative bias at cool, compared to 65% at warm periods, indicating more rising BG as seen in Figure 5.4.

Figure 5.5 presents the cumulative distribution functions of the hour-to-hour percentage changes in BG (left panel) and distribution of 50% range of BG variability per-patient (right panel) using 12 hour blocks. Table 5.8 presents the summary of BG variability results based on 12-hour block, and Table 5.9 presents the percentage reduction in the interquartile range, percentage of BG variability decrease at median between successive blocks.

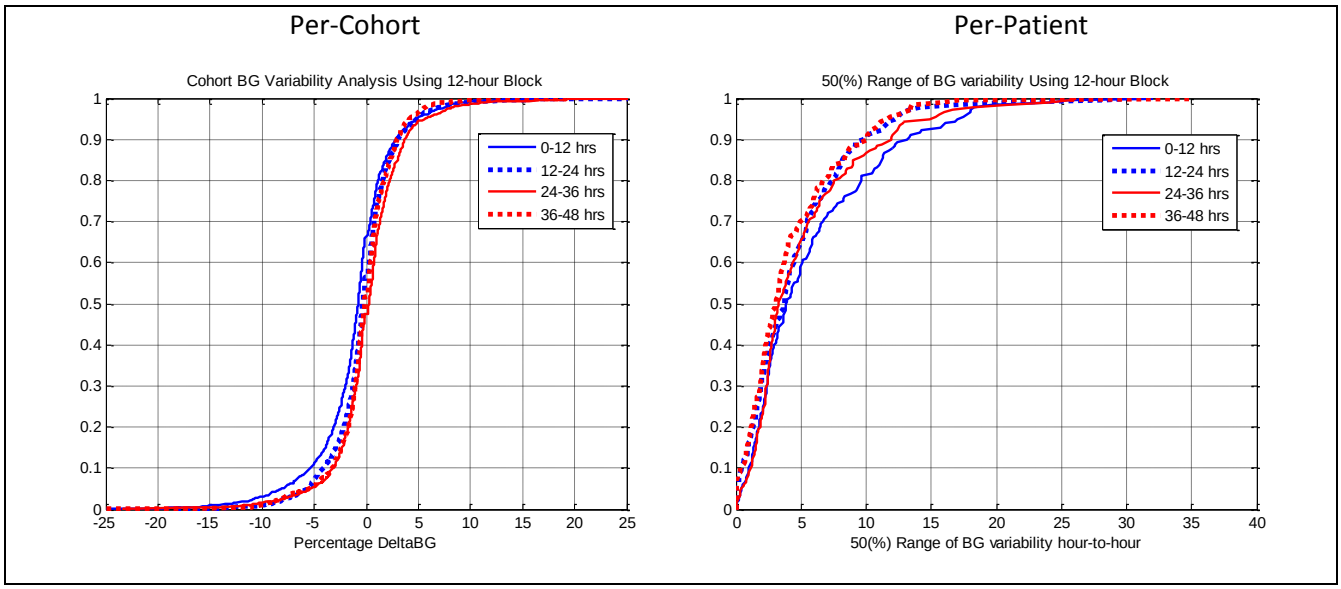

Fig. 5.5: BG variability per-cohort (left) and 50% range of BG variability per-patient (right) for OHCA patients, treated with hypothermia using 12 hour blocks of data. Blue and red lines represent cool warm period respectively.

Table 5.7: Summary of BG variability results for OHCA cohort based on 12-hours block.

Day	Block	Hours Range	Per-Cohort Median DeltaBG [IQR] [%]	Per-Patient Median DeltaBG [IQR] [%]
1	1	0 – 12 hours	-0.8 [-2.6, 0.8]	3.9 [2.1, 8.2]
	2	12 – 24 hours	-0.4 [-1.8, 1.1]	3.8 [1.8, 6.6]
2	3	24 – 36 hours	0.3 [-1.5, 2.0]	3.3 [2.2, 6.6]
	4	36 – 48 hours	-0.2 [-1.5, 1.4]	3.3 [1.8, 6.1]

The 12-hour block results and analyses from both per-cohort and per-patient suggest that blood glucose variability is initially high during the cool period and decreases over time. However, small decrease is observed insignificantly ($p > 0.05$) between these time blocks, which suggest that BG variability remains unchanged after 48 hours of treatment.

Table 5.8: Reductions in the IQR and median BG per patient range of hour-to-hour percentage BG change over time during cool and warm after as per 12-hour blocks of data

BG Variability analysis [12-hr blocks]	**Cohort analysis**		**Per-patient analysis**	
	% Reduction of IQR	*p-value*	% Decrease at median	*p-value*
Block 1-2 (C) **(0 - 12 vs. 12 - 24 hr)**	16.5	0.1	2.6	0.2
Block 2-3 (C-W) **(12 - 24 vs. 24 - 36 hr)**	-19.1	0.3	13.2	0.7
Block 3-4 (W) **(24 - 36 vs. 36 - 48 hr)**	17.6	0.2	0	0.2

P-values are calculated using Kolmogorov-Smirnov test

Figure 5.6 presents the cumulative distribution functions of the hour-to-hour percentage changes in BG (left panel) and distribution of 50% range of BG variability per-patient (right panel) using 6 hour blocks. Table 5.9 presents the summary of BG variability results based on 6-hour block, and Table 5.10 presents the percentage reduction in the interquartile range, percentage of BG variability decrease at median between successive blocks.

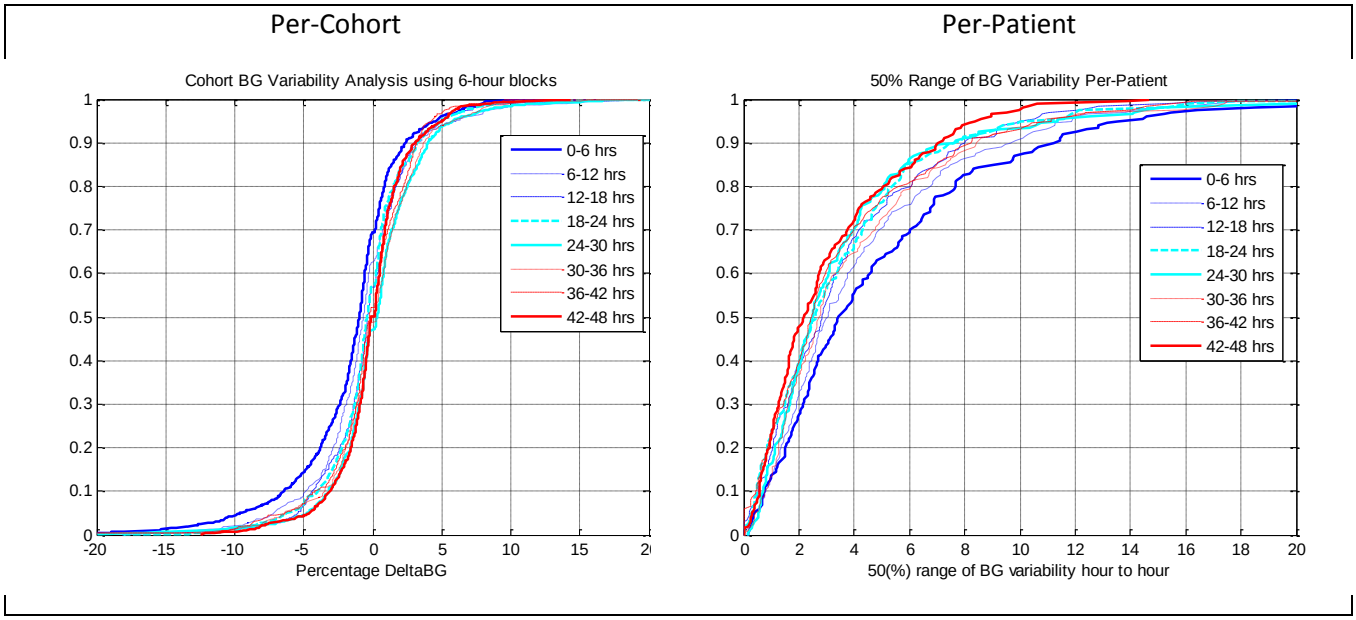

Fig. 5.6: Blood glucose variability per-cohort (left) and 50% range of BG variability CDF per-patient (right) for OHCA patients, treated with hypothermia using 6 hour blocks of data.

Table 5.9: Summary of BG variability results for overall OHCA cohort based on 6-hour block.

Day	Block	Hours Range	Per-Cohort Median DeltaBG [IQR] [%]	Per-Patient Median DeltaBG [IQR] [%]
1	1	0 – 6 hours	-0.9 [-2.9, 0.5]	3.4 [1.7, 6.6]
	2	6 – 12 hours	-0.6 [-2.3, 1.0]	2.9 [1.6, 5.3]
	3	12 – 18 hours	-0.3 [-1.5, 1.3]	2.8 [1.2, 4.8]
	4	18 – 24 hours	-0.4 [-1.8, 0.8]	2.5 [1.1, 4.7]
2	5	24 – 30 hours	0.4 [-1.3, 2.0]	2.4 [1.4, 4.2]
	6	30 – 36 hours	0.2 [-1.6, 1.9]	2.6 [1.4, 5.1]
	7	36 – 42 hours	-0.2 [-1.6, 1.6]	2.5 [1.2, 4.7]
	8	42 – 48 hours	-0.1 [-1.2, 1.1]	2.1 [1.0, 4.1]

Table 5.10: Reductions in the interquartile range and median BG per patient range of hour-to-hour percentage BG change over time during cool and warm after as per 6-hour blocks of data

BG Variability analysis [6-hr blocks]	Cohort analysis		Per-patient analysis	
	% Reduction of IQR	*p-value*	% Decrease at median	*p-value*
Block 1-2 (C) **(0 - 6 vs. 6 - 12 hr)**	2.4	0.07	14.7	0.2
Block 2-3 (C) **(6 - 12 vs. 12 - 18 hr)**	15.5	0.09	3.4	0.1
Block 3-4 (C) **(12 - 18 vs. 18 - 24 hr)**	5.5	0.2	10.7	0.5
Block 4-5 (C-W) **(18 - 24 vs. 24 - 30 hr)**	-22.6	0.06	4.0	0.9
Block 5-6 (W) **(24 - 30 vs. 30 - 36 hr)**	-5.1	0.5	-8.3	0.3
Block 6-7 (W) **(30 - 36 vs. 36 - 42 hr)**	9.0	0.06	3.8	0.6
Block 7-8 (W) **(36 - 42 vs. 42 - 48 hr)**	26.5	0.5	16.0	0.1

P-values calculated using Kolmogorov-Smirnov test

These results show that BG variability decreases over time from cool to warm, with consistent decrease for the first 24 hours of treatment. However, sudden BGV increases are shown between 24 – 36 hours, particularly during cool-warm transition period followed by a continuing decrease from 36 hours onwards. These small decreases are observed insignificantly ($p > 0.05$) between these time blocks, which match with previous results and analysis based on 12-hour blocks.

5.3.2 Results by Sub-Cohort

5.3.2.1 BG Level Analysis

Table 5.11 presents the summary of BG level results and analysis for OHCA Sub-Cohorts. The summary shows that BG levels are high during the cool period and significantly decrease ($p<0.05$) over time for the first 2 days of ICU stay. However, there are approximately around 30-35% of each sub-cohort patients that have contrasting results against the overall trend. Majority of the OHCA sub-cohorts have shown improvement from cool to warm ($p<0.05$), with consistent trends among all OHCA sub-cohorts except for the Diabetes group.

Table 5.11: Summary of BG level results and analysis for OHCA Sub-Cohorts

OHCA Sub-Cohort	No of Patients	No of Samples [Hour]	Median BG [IQR] at cool period [mmol/L]	Median BG [IQR] at warm period [mmol/L]	% patients had higher BG at cool period [Diff(Cool-warm)]	p-value
Overall OHCA cohort	180	7812	9.7 [6.9, 13.0]	8.5 [6.1, 11.5]	70%	< 0.05
Survived Patients	98	4337	9.1 [6.8, 11.7]	7.8 [5.8, 9.9]	70%	< 0.05
Non-Survived Patients	82	3475	9.2 [6.6, 12.2]	8.3 [6.0, 10.9]	70%	< 0.05
Diabetes Patients	**23**	**1021**	**8.8 [7.0, 11.5]**	**8.1 [6.2, 11.2]**	**70%**	**0.3**
Non-Diabetes Patients	157	6791	9.3 [6.7, 12.6]	8.1 [5.9, 10.6]	70%	< 0.05
Male Patients	143	6223	9.4 [6.8, 12.6]	8.4 [6.1, 11.3]	70%	< 0.05
Female Patients	37	1589	8.6 [6.3, 11.2]	7.3 [5.7, 9.1]	70%	< 0.05
ROSC < 15 mins	63	2811	8.7 [6.6, 11.3]	7.7 [5.8, 10.2]	65%	< 0.05
ROSC < 30 mins	89	3797	8.8 [6.4, 11.8]	8.1 [6.0, 10.6]	70%	< 0.05
ROSC > 30 mins	28	1204	8.5 [6.3, 11.8]	7.2 [5.7, 8.9]	65%	< 0.05

5.3.2.2 BG Variability Analysis

Table 5.12 presents the summary of BG variability results and analysis for OHCA Sub-Cohorts. The median BG variability results show that BG is more variable during cool than warm, and the results are consistent among the sub-cohorts. However, there are around 60% - 70% patients that have contrasting results, where BG variability is higher during the warm period, in contrast to the overall trend.

Table 5.12: Summary of BG variability results and analysis for OHCA Sub-Cohorts

OHCA Sub-Cohorts	No of Patients	No of Samples [Hour]	Median BG variability [IQR] at cool period [$\%\Delta S_i$]	Median BG variability [IQR] at warm period [$\%\Delta S_i$]	% patients had higher BGV during cool period [Diff(Cool-warm)]	p-value
Overall OHCA cohort	180	7812	-0.6 [-2.3,1.0]	0.2 [-1.6, 1.9]	30%	0.3
Survived Patients	98	4337	-0.5 [-1.9,0.9]	-0.1[-1.5, 1.7]	40%	0.3
Non-Survived Patients	82	3475	-0.7 [-2.6,1.0]	0.2 [-1.4, 1.7]	30%	0.3
Diabetes Patients	23	1021	-0.4 [-1.7,0.7]	-0.2 [-1.4,1.4]	40%	0.1
Non-Diabetes Patients	157	6791	-0.6 [-2.4,1.1]	0.2 [-1.6, 1.8]	30%	0.4
Male Patients	143	6223	-0.5 [-2.3,1.0]	-0.1 [-1.6,1.8]	30%	0.3
Female Patients	37	1589	-0.9 [-2.2,0.9]	0.2 [-1.3, 1.6]	30%	0.2
ROSC < 15 mins	63	2811	-0.5 [-1.8,0.8]	-0.2 [-1.4,1.6]	30%	0.1
ROSC < 30 mins	89	3797	-0.6 [-2.6,1.3]	-0.2 [-1.5,1.6]	35%	0.4
ROSC > 30 mins	28	1204	-0.9 [-2.6,0.7]	0.3 [1.7,1.9]	25%	0.3

5.4 Discussion

Hypothermia leads to lowering of human metabolic rate, including changes in energy metabolism (Melhuish, 2009). It also affects metabolism by reducing the production of hormones and enzymes from the pancreas and other organs, such as insulin, glucagon and adrenaline (Escolar et al., 1987, Escolar et al., 1990, Torlinska et al., 2002), which significantly alter metabolic balance and the stress response to insult. Hence, it is expected that during hypothermia, internal insulin production, its concentration and insulin sensitivity should be lower than normal and the stress response may be modulated to an unknown extent. Thus, it is hypothesized that BG may then be higher, as seen clinically in other studies for OHCA patients (Cueni-Villoz et al., 2011). Hence, glycaemic control would be more difficult given lower insulin sensitivity, requiring more insulin and potentially resulting in greater variability and hypoglycaemia. This outcome would typically be exacerbated by the stress of the initial insult.

5.4.1 Blood glucose level

BG level results for both per-cohort and per-patient analysis suggest that OHCA patients undergoing hypothermic treatment have higher BG levels at cool and decrease over time. This results determine general trends for blood glucose levels and are consistent with other BG level ICU studies (Neumar et al., 2008). These results are also supported by (Cueni-Villoz et al., 2011), who have recently showed that mild TH or cool period was associated with higher BG levels, increased BG variability, and greater insulin requirements compared to the post-rewarming normothermic phase. These researchers were also found that mean BG level was higher during hypothermia, but not associated with hospital mortality.

Further studies from both 12-hour and 6-hour blocks analysis show that the decrease in BG level during the first 12 hours is large and statistically significant ($p<0.05$) for this cohort. The rapid decreases in BG level are likely due to restart of human physiological systems and metabolic activities for these patients (Pretty et al., 2012). After 12 hours, BG level shows smaller decrease with no significant different except for block 5-6 (warm) which is between (24-30 hrs) and (30-36 hrs). BG is increased by knowing its negative values and are likely due to poor neurological outcome (Daviaud et al., 2014). Hence, this results gives

an idea of glycemic variability and evolution for this cohort which looks more dynamics and responsive during these periods.

Analysis of OHCA sub-cohorts for BG level show that most of the sub-cohorts are recovering well based on percentage of BG decrease over time from overall summary. It is evidence that diabetic sub-cohort has shown some BG decrease from cool to warm, but with slow progress (p=0.3).In fact, this sub-cohort patients experience longer BG level increase during transition and warm periods. These findings will lead to a more special control requirement for treating OHCA patients with special conditions such as diabetic.

5.4.2 Blood glucose variability

In general, per-cohort and per-patient results suggest that there are no significant BG variability differences between cool and warm periods, although variability during the cool period is slightly higher than the warm period. Both results determine general trends for blood glucose variability and are consistent with similar studies by (Cueni-Villoz et al., 2011), who have recently showed that mild TH or cool period was associated with increased BG variability.

Further studies from both 12-hour and 6-hour blocks analysis show that majority of increased BG variability events occur during transition (cool-warm) and warm periods. The BGV increase indicates some potential stress across the cool-warm transition with negative reductions. These results are likely influenced by local treatment protocol and change of physiological conditions due to body temperature increase from cool to warm between 24 – 36 hours. Recent studies by (Daviaud et al., 2014) concerning BG variability found that for low level of BG, high variations were more frequently observed in patients with a poor outcome. Hence, these findings reveal that some sub-cohorts might experience longer poor outcome that the others and occurs anytime during treatment (Kauffmann et al., 2011, Meynaar et al., 2012) . In fact, high BG variations found during low BG level seems to be true since BG level decrease over time from cool to warm.

Analysis of OHCA sub-cohorts for BG level show that most of the sub-cohorts are recovering well based on percentage of BG decrease over time from overall summary as well as both 12 -hour and 6-hour blocks analysis except for diabetic sub-cohort. It is evidence that diabetic

sub-cohort has shown some BG decrease from cool to warm, but with slow progress (p=0.3).In fact, this sub-cohort patients experience longer BG level increase during transition and warm periods. These findings will lead to a more special control requirement for treating OHCA patients with special conditions such as diabetic.

5.4.3 Implications for glycaemic control

The demographic patient data by cohort in chapter 3 summarizes the glycaemic management inputs and outputs for OHCA patients, treated with hypothermia. In general, patients were given the substantial amount of insulin during both periods, but less amount of nutrition at cool. As a result, BG levels are recorded high during cool and more likely within the 4 – 7 mmol/L glycaemic range at warm.

It is recognized that these variations in insulin and nutrition delivery will result in different glycaemic outcomes. These results show that the glycaemic control protocols to treat hypothermic OHCA patients had different performance. They also indicate the need for patient-specific approaches to balance insulin and nutrition in a patient-specific manner (Fisk et al., 2012). The evolution and metabolic dynamics among these patients is also similar during hypothermia and the first 24 hours of normothermia.

Clinically, these results have significant potential implications for managing glycaemia while treating OHCA patients especially during hypothermia, followed by the first 24 hours of rewarming. It is important to understand these dynamics, especially those unique to a cohort, when implementing glycaemic control, since glycaemic variability and hypoglycaemia are independent risk factors for the critically ill (Egi et al., 2006, Bagshaw et al., 2009, Krinsley, 2009). More specifically, these results suggest that any insulin therapy should not over use insulin as per Pretty et.al (Pretty et al., 2012), while treating this cohort patients. Due to high level of insulin resistance and the saturation of insulin action (Natali et al., 2000), modulating carbohydrate and nutrition inputs might also be explicitly considered (Chase et al., 2008b). In particular, early or, excessive nutritional regimes might be avoided in consideration of better managing the metabolic dynamics observed in this study.

5.5 Summary

This study analyses the glycaemic outcomes of OHCA patients treated with hypothermia. It analyses blood glucose (BG) level, its variability and evolution of post-cardiac arrest patients who were undergoing hypothermic treatment. It is the first study to fully quantify or characterize BG evolution in this cohort including level and variability of both cohort and per-patient level.

OHCA Patients treated with hypothermia saw consistently decreasing BG over time, but evidenced greater variability, counter to normal trends where both metrics tend to go down over the first 48 hours (Pretty et al., 2012). This trend can result in more insulin demand during hyperglycemia and a greater risk of hypoglycemia as variability rises, all of which indicates the need for patient-specific approaches in each phase.

These results present the first analysis of the hourly evolution of BG level and variability on a cohort and per-patient basis. They should lead to better understanding of patient physiological conditions based on different perspective such as glycemic outcomes, as well as providing the data to implement safer and more accurate glycemic control in this cohort. Finally, the outcome of this studies strongly suggest the need to consider both control of BG level and minimization of BG variability to improve post-resuscitation care of OHCA patients treated with hypothermia.

Chapter 6: Exogenous Insulin and Nutrition Analysis

This chapter describes a preliminary study of Out-of-Hospital Cardiac Arrest (OHCA) patients based on exogenous insulin and nutrition characteristics during hypothermia (cool period) and normothemia (warm period). It analyses the impact of exogenous insulin and nutrition modulation during therapeutic hypothermia (TH) on glycaemic outcome. Patient data was analysed based on the cohorts, defined in Chapter 3.

6.1 Introduction

Exogenous insulin and nutrition administration play influential role in ICU patient treatment progress. The amount of insulin and nutrition is determined based on per-patient physiology and metabolic conditions, which were analysed in chapter 4 and 5 previously. Additional considerations such as secretion of endogenous insulin and other hormones by pancreas will eventually affect the decision as the trend is non-linear (Mitsis et al., 2009) .

This study analyses exogenous insulin and nutrition administration of out of hospital cardiac (OHCA) arrest patients from who were undergoing hypothermic treatment. The results should provide better understanding of the input elements of these patients for metabolic management and their relation with metabolic and glycaemic evolution in the cohort.

6.2 Subjects and Methods

6.2.1 Patients and Data

This analysis was performed on a same ICU cohort of 180 OHCA patients (7812 hours) treated with hypothermia from Erasme Hospital, Belgium and Lausanne Hospital, Switzerland as per explained in Section 3.1. A summary of the full cohort and sub-cohorts is presented in the Table 4.1.

6.2.2 Analyses and Metrics

External insulin and nutrition during the cool ($T<35^{o}C$) and warm ($T>37^{o}C$) periods were identified from patient data and analysed as follows:

i) Overall cohort patient.

ii) Analysis of patient by 12-hour block.

iii) Analysis of patient by 6-hour block.

Cohort analysis assessed external insulin and nutrition infusions hourly for the entire cohort, and shows trends based on the overall group behaviour. Per-patient analysis examined both inputs by median values per-patient within each timeframe.

External insulin and nutrition analysis of patients using 12-hour and 6-hour blocks is described in the Table 4.1. This method will examine group behaviour and assess its changes for every 12 and 6 hour blocks of the entire treatment from cool to warm periods. For cohort analysis, external insulin and nutrition data from all patients was grouped into each appropriate time-block. Median values for each time-block were calculated for comparison to the previous block, thus capturing overall cohort changes over time. For per-patient analysis, the median insulin and nutrition inputs were calculated for each patient, for each time-block, compared to the previous block.

External insulin and nutrition data are non-Gaussian and were thus compared using non-parametric cumulative distribution functions (CDFs) and non-parametric statistics. All distributed data were compared using a Wilcoxon rank-sum test (Mann-Whitney U-test) comparing median values. In all cases, $p < 0.05$ is considered statistically significant.

6.3 Results on Exogenous Insulin

6.3.1 Results for complete cohort

Figure 6.1 presents the cumulative distribution functions (CDFs) of hourly external insulin infusion for both cool and warm periods by cohort (left panel) and median hourly per-patient (right panel) for all ICU patients. Table 6.1 summarizes exogenous insulin results and analysis for overall OHCA cohort.

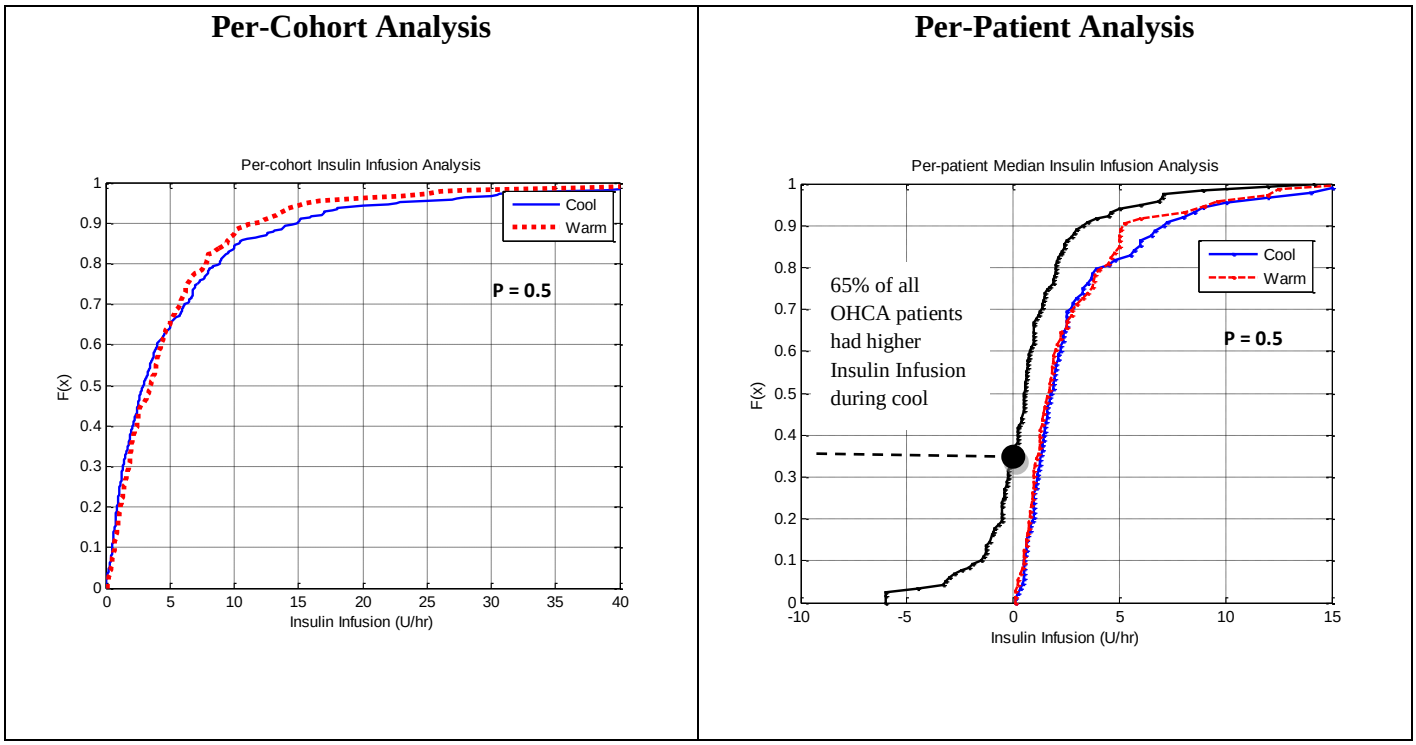

Fig. 6.1: Exogenous insulin distribution by cohort (left) and per-patient median (right) during cool and warm after periods for all ICU patients

Table 6.1: Summary of Exogenous Insulin results for overall OHCA cohort.

Day	Period	Hours Range	Per-Cohort Median Ex. Insulin [IQR] [U/hr]	Per-Patient Median Ex. Insulin [IQR] [U/hr]
1	Cool	0 – 24 hours	2.95	1.80
2	Warm	24 – 48 hours	2.51	1.65
		p-value	0.5	0.5

The results in the Table 6.1 show that exogenous insulin levels are initially higher during the cool period and lower during the warm period, but the difference are not significant ($p > 0.05$). However, there are around 35% (63 patients) of all patients that have contrasting results, where insulin is higher during the warm period, in contrast to the overall trend.

Figure 6.2 presents the 12-hour block exogenous insulin by cohort (left panel) and median per-patient (right panel). Table 6.2 presents the summary of insulin infusion results based on 12-hour blocks and Table 6.3 presents the decrease in median per-patient insulin infusion between successive blocks.

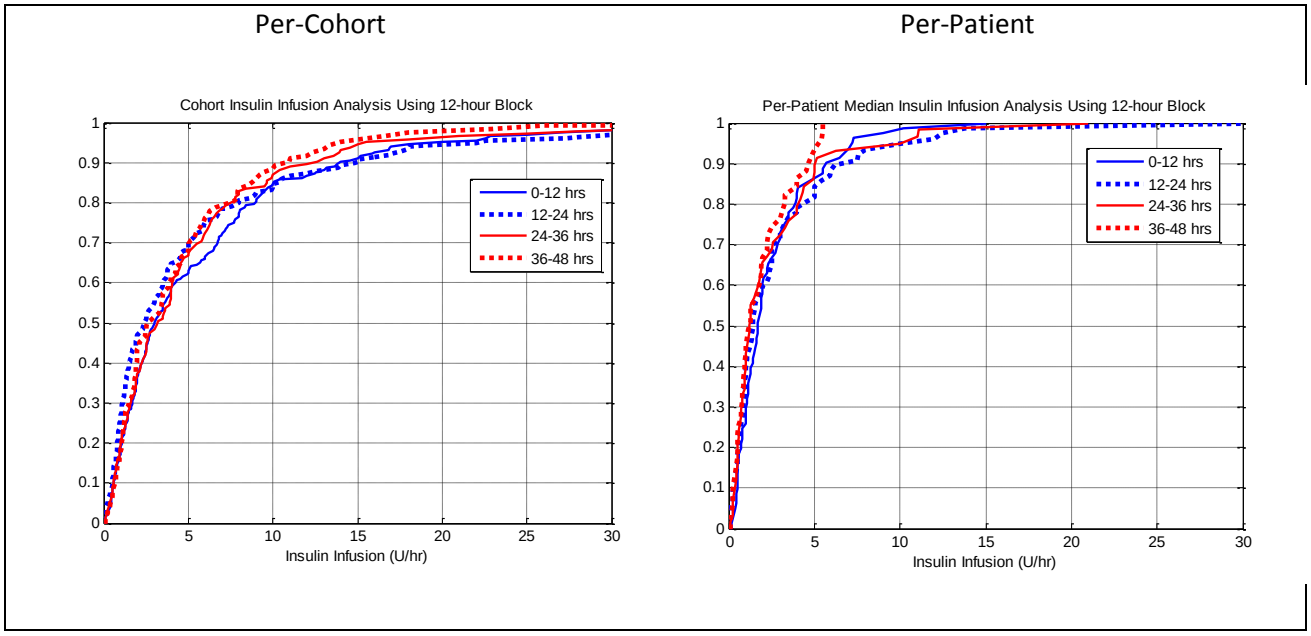

Fig. 6.2: Exogenous Insulin distribution per-cohort (left) and per-patient median (right) for OHCA patients, treated with hypothermia using 12 hour blocks of data. Blue colour represent cool period and red colour represent warm

Table 6.2: Summary of exogenous insulin results for OHCA cohort based on 12-hours block.

Day	Block	Hours Range	Per-Cohort Median Ex. Insulin [IQR] [U/hr]	Per-Patient Median Ex. Insulin [IQR] [U/hr]
1	1	0 – 12 hours	3.02	1.70
	2	12 – 24 hours	2.45	1.40
2	3	24 – 36 hours	3.20	1.20
	4	36 – 48 hours	2.70	1.19

The results and analyses from the Table 6.3 for both per-cohort and per-patient suggest that Ex. insulin infusion are initially high during the cool period and decreases over time for the first 2 days in the ICU. However, the decrease is not significant during these period, which suggest that the amount of exogenous insulin given to OHCA patients is not much difference between cool and warm.

Table 6.3: Decreasing cohort and per patient median insulin infusion during cool and warm (12-hour blocks of data)

Ex. Insulin analysis [12-hr blocks]	**Cohort analysis**		**Per-patient analysis**	
	% Decrease at median	*p-value*	% Decrease at median	*p-value*
Block 1-2 (C) **(0 - 12 vs. 12 - 24 hr)**	18.6	0.07	17.9	0.5
Block 2-3 (C-W) **(12 - 24 vs. 24 - 36 hr)**	-30.4	0.2	14.3	0.7
Block 3-4 (W) **(24 - 36 vs. 36 - 48 hr)**	15.9	0.6	0.3	0.7

P-values calculated using Wilcoxon rank-sum test

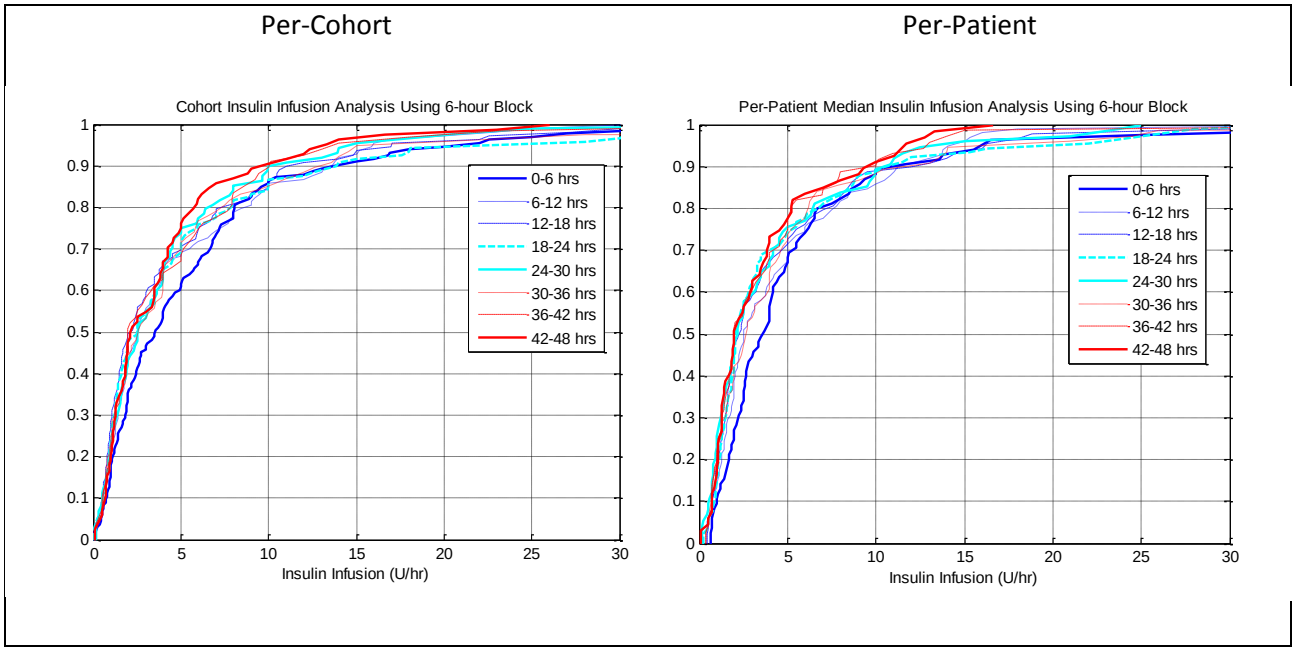

Fig. 6.3: Exogenous Insulin distribution per-cohort (left) and per-patient median (right) for OHCA patients, treated with hypothermia using 6 hour blocks of data.

Table 6.4: Summary of Exogenous Insulin results for overall OHCA cohort based on 6-hour block.

Day	Block	Hours Range	Per-Cohort Median Ex. Insulin [IQR] [U/hr]	Per-Patient Median Ex. Insulin [IQR] [U/hr]
1	1	0 – 6 hours	3.56	3.70
	2	6 – 12 hours	2.50	2.52
	3	12 – 18 hours	2.25	2.31
	4	18 – 24 hours	2.50	2.37
2	5	24 – 30 hours	2.55	2.46
	6	30 – 36 hours	2.62	2.70
	7	36 – 42 hours	2.00	2.00
	8	42 – 48 hours	2.00	2.00

Table 6.5: Decreasing cohort and per patient median Exogenous Insulin during cool and warm as per 6-hour blocks of data

Ex. Insulin analysis [6-hr blocks]	Cohort analysis		Per-patient analysis	
	% Decrease at median	*p-value*	% Decrease at median	*p-value*
Block 1-2 (C) **(0 - 6 vs. 6 - 12 hr)**	29.8	0.2	31.2	0.2
Block 2-3 (C) **(6 - 12 vs. 12 - 18 hr)**	10.0	0.4	8.5	0.4
Block 3-4 (C) **(12 - 18 vs. 18 - 24 hr)**	-11.1	0.6	-2.6	0.9
Block 4-5 (C-W) **(18 - 24 vs. 24 - 30 hr)**	-2.0	0.9	-3.8	0.6
Block 5-6 (W) **(24 - 30 vs. 30 - 36 hr)**	-2.7	0.9	-9.8	0.5
Block 6-7 (W) **(30 - 36 vs. 36 - 42 hr)**	23.7	0.8	25.9	0.5
Block 7-8 (W) **(36 - 42 vs. 42 - 48 hr)**	0.0	0.8	0.0	0.9

P-values calculated using Wilcoxon rank-sum test

Figure 6.3 presents the 6-hour block exogenous insulin by cohort (left panel) and median per-patient (right panel). Table 6.4 presents the summary of insulin results based on 6-hour block and Table 6.5 presents the decrease in median insulin between successive blocks. The results and evolution of exogenous insulin, both per-cohort and per-patient reveal that even though insulin infusions are initially high during the cool period and decrease over time, there is an increased of amount of insulin given between block 4 (18-24 hours) and block 6 (30-36 hours) before it returns to decreasing over time in subsequent blocks. This increase occurs during the transition from cool to warm and suggest that there is a unique evolution which demand for more exogenous insulin infusion during these time periods. Further analysis and comparison with other parameters, such as blood glucose and insulin sensitivity will be explained in Chapter 8.

6.3.2 Results for sub-cohorts

Table 6.6 presents the summary of Ex. Insulin results and analysis for OHCA Sub-Cohorts. The summary shows that all OHCA sub-cohorts are consistent with the overall OHCA cohort. In general, analyzing the overall OHCA patients is sufficient even though the cohort consists of various different backgrounds. Importantly, the clinical outcome of ROSC sub-cohort showed no difference in exogenous insulin delivered.

Table 6.6: Summary of Ex. Insulin results and analysis for OHCA Sub-Cohorts

OHCA Sub-Cohort	No of Patients	Median Ex. Insulin [IQR] at cool period [U/hr]	Median Ex. Insulin [IQR] at warm period [U/hr]	% patients had higher Ex. Insulin at cool period [Diff(Cool-warm)]	p-value
Overall OHCA cohort	180	1.8 [1.0, 3.3]	1.6 [0.9, 3.7]	65%	0.5
Survived Patients	98	1.7 [1.0, 3.0]	1.4 [0.7, 3.1]	65%	0.3
Non-Survived Patients	82	2.0 [1.0, 3.4]	1.4 [0.8, 2.9]	65%	0.3
Diabetes Patients	23	1.9 [1.1, 3.2]	1.7 [0.9, 2.9]	40%	0.7
Non-Diabetes Patients	157	1.7 [1.0, 3.0]	1.5 [0.8, 3.5]	70%	0.4
Male Patients	143	1.9 [1.1, 3.3]	1.7 [0.9, 3.7]	60%	0.5
Female Patients	37	1.6 [1.0, 2.7]	1.0 [0.6, 1.9]	70%	0.1
ROSC < 15 mins	63	1.4 [0.9, 2.5]	1.0 [0.6, 2.6]	70%	0.4
15 < ROSC < 30 mins	89	2.0 [1.0, 3.9]	1.4 [0.8, 3.3]	70%	0.4
ROSC > 30 mins	28	2.5 [1.1, 5.0]	1.5 [0.8, 4.1]	70%	0.3

6.4 Results on Nutrition/ Dextrose Administration

6.4.1 Results for complete cohort

Figure 6.4 presents the cumulative distribution functions (CDFs) of hourly nutrition/ dextrose modulation for both cool and warm periods by cohort (left panel) and median hourly per-patient (right panel) for all ICU patients. Table 6.7 presents summary of nutrition results for overall OHCA cohort. These results show that the OHCA patients were given lower amounts of nutrition/dextrose during the cool period (at initial), and significantly ($p < 0.05$) increased over time during the first 2 days of treatment. However, there are around 35% (63 patients) of all patients that have contrasting results, where nutrition is higher during the cool period.

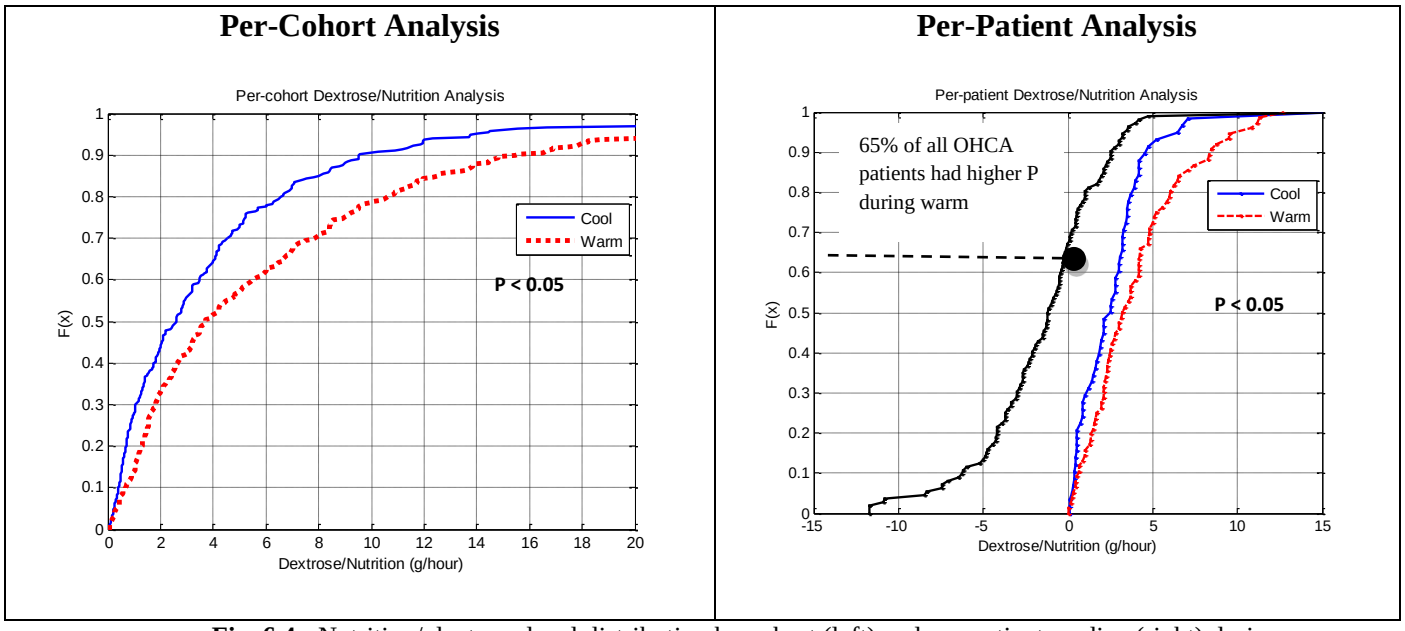

Fig. 6.4: Nutrition/ dextrose level distribution by cohort (left) and per-patient median (right) during cool and warm periods for all ICU patients

Table 6.7: Summary of nutrition results for overall OHCA cohort.

Day	Period	Hours Range	Per-Cohort Median Nutrition [IQR] [g/hour]	Per-Patient Median Nutrition [IQR] [g/hour]
1	Cool	0 – 24 hours	2.58	2.50
2	Warm	24 – 48 hours	3.72	3.23
		p-value	< 0.05	< 0.05

Figure 6.5 presents the 12-hour block nutrition/dextrose by cohort (left panel) and median per-patient (right panel). Table 6.8 presents the summary of nutrition/dextrose results based on 12-hours block and table 6.9 presents the decrease in median nutrition/dextrose between successive blocks. The results and analyses show that nutrition/dextrose during the cool period (initially), and increased over time during the first 2 days of treatment. However, the increase is significant comparing the cool period to the warm period (Table 6.4).

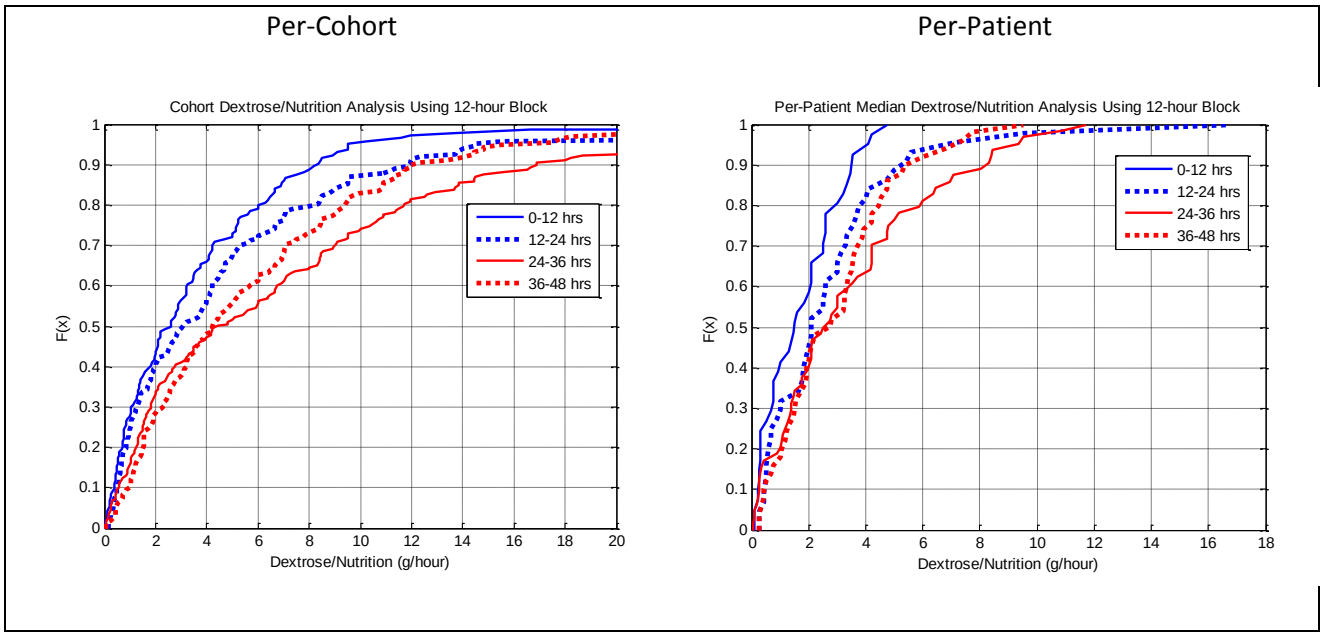

Fig. 6.5: Nutrition/ dextrose distribution per-cohort (left) and per-patient median (right) for OHCA patients, treated with hypothermia using 12 hour blocks of data. Blue colour represent cool period and red colour represent warm

Table 6.8: Summary of nutrition results and analysis for overall OHCA cohort based on 12-hours block.

Day	Block	Hours Range	Per-Cohort Median Nutrition [IQR] [g/hour]	Per-Patient Median Nutrition [IQR] [g/hour]
1	1	0 – 12 hours	2.60	1.48
	2	12 – 24 hours	3.10	2.10
2	3	24 – 36 hours	4.63	2.50
	4	36 – 48 hours	4.22	2.74

Table 6.9: Decreasing cohort and per patient median nutrition during cool and warm (12-hour blocks of data)

Nutrition analysis [12-hr blocks]	**Cohort analysis**		**Per-patient analysis**	
	% Decrease at median	*p-value*	% Decrease at median	*p-value*
Block 1-2 (C) **(0 - 12 vs. 12 - 24 hr)**	-19.4	< 0.05	-41.5	< 0.05
Block 2-3 (C-W) **(12 - 24 vs. 24 - 36 hr)**	-49.7	< 0.05	-19.1	< 0.05
Block 3-4 (W) **(24 - 36 vs. 36 - 48 hr)**	8.8	0.6	-9.6	0.8

P-values calculated using Wilcoxon rank-sum test

Figure 6.6 presents the 6-hour block nutrition/dextrose by cohort (left panel) and median per-patient (right panel). Table 6.10 presents the summary of nutrition/dextrose results based on 6-hour block and Table 6.11 presents the decrease in median nutrition/dextrose between successive blocks. The results reveal that even though nutrition/dextrose is initially low during the cool period and increases over time, right after the transition from cool to warm and specifically between block 5 (24-30 hours) and block 6 (30-36 hours), it decreases. Thus, the highest amount of nutrition/ dextrose given occurs during the warm period, right after transition from cool to warm and suggests that there is a unique evolution that demands more nutrient/dextrose during these time periods compared to a largely decreasing insulin trend in.

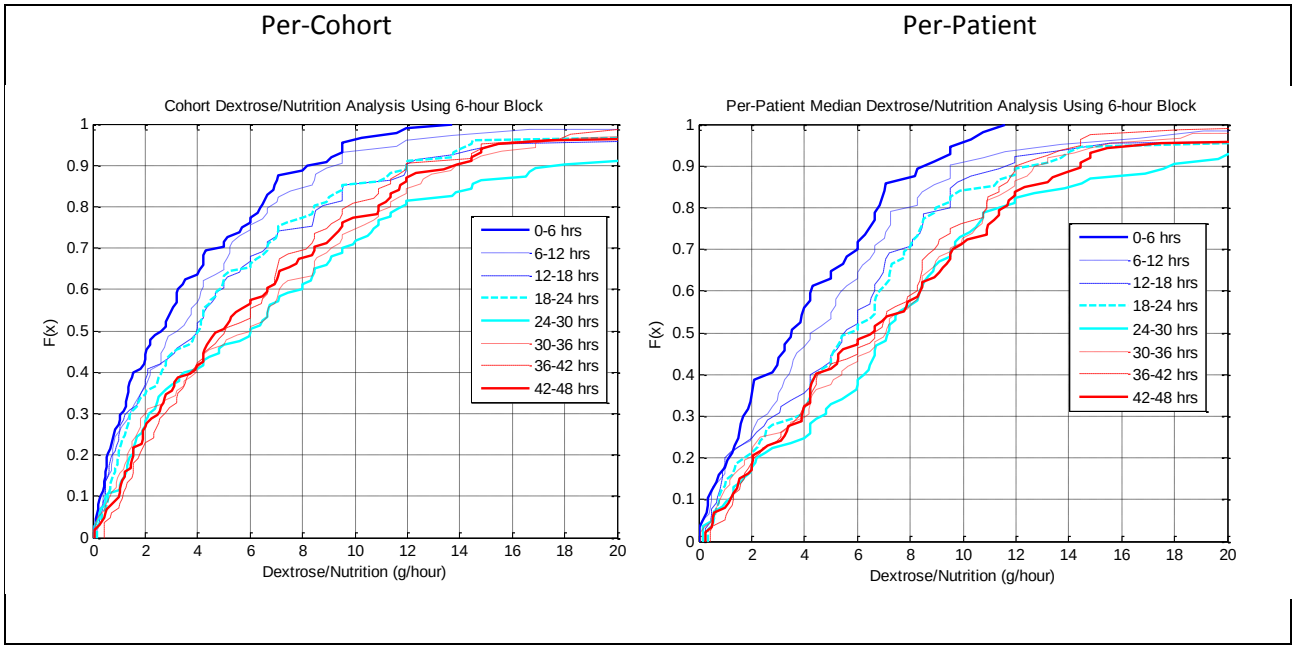

Fig. 6.6: Nutrition/ dextrose distribution per-cohort (left) and per-patient median (right) for OHCA patients, treated with hypothermia using 6 hour blocks of data.

Table 6.10: Summary of nutrition/dextrose results and analysis for overall OHCA cohort based on 6-hours block.

Day	Block	Hours Range	Per-Cohort Median Nutrition [IQR] [U/hr]	Per-Patient Median Nutrition [IQR] [U/hr]
1	1	0 – 6 hours	2.70	3.53
	2	6 – 12 hours	3.34	4.43
	3	12 – 18 hours	4.00	5.60
	4	18 – 24 hours	4.06	6.00
2	5	24 – 30 hours	6.00	7.23
	6	30 – 36 hours	6.00	7.09
	7	36 – 42 hours	5.09	6.80
	8	42 – 48 hours	5.00	6.66

Table 6.11: Decreasing cohort and per patient median nutrition/dextrose during cool and warm as per 6-hour blocks of data

Nutrition analysis [6-hr blocks]	Cohort analysis		Per-patient analysis	
	% Decrease at median	*p-value*	% Decrease at median	*p-value*
Block 1-2 (C) **(0 - 6 vs. 6 - 12 hr)**	-24.0	< 0.05	-25.3	< 0.05
Block 2-3 (C) **(6 - 12 vs. 12 - 18 hr)**	-19.3	< 0.05	-26.4	< 0.05
Block 3-4 (C) **(12 - 18 vs. 18 - 24 hr)**	-1.9	< 0.05	-7.3	< 0.05
Block 4-5 (C-W) **(18 - 24 vs. 24 - 30 hr)**	-47.9	< 0.05	-20.5	< 0.05
Block 5-6 (W) **(24 - 30 vs. 30 - 36 hr)**	0.1	0.5	2.0	0.5
Block 6-7 (W) **(30 - 36 vs. 36 - 42 hr)**	15.2	0.8	4.2	0.9
Block 7-8 (W) **(36 - 42 vs. 42 - 48 hr)**	1.8	0.9	1.9	0.7

P-values calculated using Wilcoxon rank-sum test

6.4.2 Results for sub-cohorts

Table 6.13 presents the summary of nutrition/dextrose results and analysis for OHCA Sub-Cohorts. The summary shows that results and analysis among all OHCA sub-cohorts are consistent with overall OHCA cohort. Most of the sub-cohorts had significant increase in nutrition intake from cool to warm, except sub-cohorts where 15 < ROSC < 30 mins, and ROSC > 30 mins.

Table 6.12: Summary of nutrition/dextrose results for OHCA Sub-Cohorts

OHCA Sub-Cohort	No of Patients	Median Nutrition [IQR] in cool period [g/hour]	Median Nutrition [IQR] in warm period [g/hour]	% patients had higher Nutrition in cool period [Diff(Cool-warm)]	p-value
Overall OHCA cohort	180	2.5 [0.8, 3.5]	3.2 [1.6, 5.3]	30%	< 0.05
Survived Patients	98	2.6 [0.9, 3.9]	3.2 [1.6, 5.0]	30%	< 0.05
Non-Survived Patients	82	2.1 [0.9, 3.4]	3.0 [2.0, 4.8]	30%	< 0.05
Diabetes Patients	23	2.1 [1.0, 4.2]	4.2 [2.0, 6.2]	15%	< 0.05
Non-Diabetes Patients	157	2.1 [0.8, 3.5]	3.0 [1.6, 5.1]	35%	< 0.05
Male Patients	143	2.5 [1.0, 3.5]	3.1 [1.5, 5.1]	35%	< 0.05
Female Patients	37	2.1 [0.7, 3.2]	3.7 [2.0, 5.7]	25%	< 0.05
ROSC < 15 mins	63	2.5 [0.9, 4.1]	4.2 [2.2, 5.9]	30%	< 0.05
15 < ROSC < 30 mins	89	2.5 [1.1, 3.3]	2.7 [1.4, 4.8]	30%	0.2
ROSC > 30 mins	28	2.1 [1.3, 3.5]	2.2 [0.5, 4.1]	40%	0.7

6.5 Discussion

6.5.1 Exogenous Insulin and Nutrition Modulation during cool and warm

This studies show that upon admission into ICU, OHCA patients treated with hypothermia received more exogenous insulin during the cool period and that these infusions decrease over time as does hyperglycaemia, as seen in Chapter 5. However, similar cohort were given small amount of nutrition / bolus at initial treatment and increased significantly over time during hypothermia.

During the warm period, it is obvious that the OHCA patients had received more exogenous insulin and nutrient for the first 12 hours of warm period before decreasing the amount at the consequent blocks. The increased amount of insulin and nutrient given between block 5 (24 – 30 hours) and block 6 (30 – 36 hours) is likely due to slight increase in BG level and variability during these periods which lead to physiological stress. These results are consistent with BG level results as shown in Chapter 5.

6.5.2 The effect of Insulin and Nutrition Control Approach

Previous studies have proved that modulating nutritional rates in addition to insulin can achieve very tight control, more successfully than using insulin alone (Chase et al., 2006a). For example, van den Berghe et al (van den Berghe et al., 2001) used an average of ~3U/hr during trials. Additionally, modulating nutrition also provides a potentially safer method for highly critical ill patients (Van den Berghe et al., 2006a). More specifically, as patient condition evolves, feed reductions allow less insulin to be used for the same or greater glycaemic reduction, avoiding saturation and/or sudden changes in glycaemic level due to excessive insulin.

In this study, dynamic increases and reductions in enteral glucose administration rates were used to assist glycaemic control during cool and warm periods. In fact, the high blood glucose level at the beginning of cool period would demand more insulin infusion required at initial before decreases over time, thus implies a reasonable decay of glucose appearance in the bloodstream. In contrast, the nutritional feed increase from the beginning until cool-warm transition period would indicate the patients' metabolic/ energy demand, following the

increase in body temperature from cool to warm. However, as glucose drops are relatively slow, but sudden low glycaemic levels can be raised relatively rapidly by increasing the feed rate, special care in nutritional feed is required since the patient is still experiencing hyperglycaemia and had low metabolic activities during cool period, but needs some glucose to rewarm his/ her body.

Overall, this approach of modulating nutrition in addition to exogenous insulin is a significant method from other approaches in this field, which use insulin alone. It is supported by recent studies that low-calorie (or low dextrose) nutritional inputs reduce hyperglycaemia (Ahrens et al., 2005, Dickerson, 2005, McCowen et al., 2000, Patino et al., 1999) and above ~30% of standard goal feed rates do not increase infectious complications (Krishnan et al., 2003, Rubinson et al., 2004). However, it should be noted that insulin plays multiple roles that are both metabolic and non-metabolic. As a result, an insulin plus nutrition approach as presented here may have a lesser effect on mortality in a longer randomized trial due to using reduced levels of insulin (van den Berghe et al., 2001, Van den Berghe et al., 2006a).

6.6 Summary

This study analyses the impact of exogenous insulin and nutrition modulation during therapeutic hypothermia (TH) on glycaemia outcome. There are three (3) main results from this analysis.

1. Glycemic control during hypothermia and rewarming has achieved by modulating dextrose more than exogenous insulin, thus matches results seen in SPRINT control (Chase et al., 2008b) .

2. Some patient sub-cohorts saw major increases in nutrition from cool to warm such as diabetes and ROSC < 15 min. Since the significant increase in nutrition occurs while insulin modulation is steadily consistent. This shows that patients with diabetes or ROSC < 15 sub-cohorts are likely to experience major stress hyperglycemia than other sub-cohorts, thus need further research.

3. In view of control implications, both exogenous insulin and nutrition show major increase at transition (18 – 30 hours) while nutrition delayed or maintain doses for another 6 hours after transition, thus falls steadily by blocks.

Chapter 7: Stochastic Insulin Sensitivity Modelling Analysis

This chapter presents the adaptation of a stochastic model for S_I prediction from adult critical care to the unique clinical and physiological case of the OHCA patients, treated with hypothermia. Clinically validated, model-based insulin sensitivity (S_I) (Chase et al., 2010, Evans et al., 2011) is used to provide a more accurate measure of patient metabolic state and its stochastic modelling during cool and warm periods. Modifications to the initial kernel density estimation model are made to explore and optimise the relationship between model accuracy in predicting ranges of S_I variability and the underlying clinical data and dataset. Patient data was analysed for the cohort and sub-cohorts defined in Chapter 3, and results were summarized.

7.1 Introduction

Model-based glycaemic control methods using both insulin and/or nutrition modulation have been employed successfully in the control of hyperglycaemia, as reviewed by Chase et al. (Chase et al., 2006b). These methods allow the derivation of patient metabolic state, S_I in this case, by using serial blood glucose (BG) measurements, and records of nutrition and insulin administration (Chase et al., 2007b). Once the current S_I has been identified, prediction of future S_I would allow predictions of outcome BG concentration for an intended insulin and nutrition intervention.

Variations in the S_I parameter reflect the metabolic response to stress (McCowen et al., 2001) and drug therapy (Pretty et al., 2011). Thus, tracking and forecasting this parameter is important to provide safe glycaemic control in highly dynamic Out-of-Hospital Cardiac Arrest (OHCA) patients, treated with hypothermia. Since stochastic modelling has shown its ability to quantify the probability of a future S_I (Lin et al., 2008), the resulting distribution of BG concentrations that would result from a given intervention can be determined (Lin et al., 2008, Le Compte et al., 2010, Evans et al., 2011, Fisk et al., 2012). This information can be used to guide both insulin and/or nutrition interventions, which is the key to avoid unintended hypoglycaemia, improve overall glycaemic control, and identify periods of potential high glucose variability that may be indicative of unusual clinical events (Thomas et al., 2014).

7.2 Subjects and Methods

7.2.1 Patients and Data

This analysis was performed on a same ICU cohort of 180 OHCA patients (7812 hours) treated with hypothermia from Erasme Hospital, Belgium and Lausanne Hospital, Switzerland as per explained in Section 3.1. A summary of the full cohort and sub-cohorts is presented in the Table 4.1.

7.2.2 Analyses and Metrics

Stochastic model of insulin sensitivity will be analysed as follows:

i) Overall cohort patient.

ii) Analysis of patient by 12-hour block.

iii) Analysis of patient by 6-hour block.

Overall cohort analysis assessed the stochastic model behaviour of insulin sensitivity during both cool and warm, which includes percentage of S_I and BG within prediction interval and analysis of modifying kernel density estimation.

The stochastic model of S_I using 12-hour and 6-hour blocks is described in the Table 4.1. This method will examine stochastic model group behaviour and assess its changes for every 12 and 6 hour blocks of the entire treatment from cool to warm periods. The analysis includes percentage of S_I and BG within prediction interval and analysis of modifying kernel density estimation.

7.2.3 The Stochastic Model

A 2-D kernel density estimation method is used to construct the stochastic model that describes the hourly transition of S_I. The kernel density method combines probability distribution functions for each point of data to generate an overall density function for the dataset. This method has the advantage of producing a smooth, physiologically likely, continuous function across the parameter range to provide continuity when interpolating S_I forecasts to account for each particular patient state. It also automatically accounts for any possible multimodality where the density of data may show several distinct peaks corresponding to patterns of changes in S_I. The overall result is a bivariate probability density function for the potential parameter values.

The goal of this statistical model is to quantify the range of S_I one or more hours ahead in time ($S_{I,n+1}$) based on available data ($S_{I,n}$, $S_{I,n-1}$, $S_{I,n-2}$, . . ., $S_{I,0}$) to guide real-time clinical control (Evans et al., 2011, Lin et al., 2011, Thomas et al., 2014). Thus, it is important that the model is also cohort-specific as possible for greatest accuracy.

A 2-D kernel density method is chosen because the distribution of $S_{I,n+1}$ varies with $S_{I,n}$, and cannot be simply described with a single standard statistical distribution (Lin et al., 2008). Thus, variations in S_I can be treated as a Markov process. A Markov process has the property that the conditional probability density function of future states of the process, given the current state, depends only upon the current state. Therefore, using the Markov property of the stochastic behaviour of S_I, the conditional probability density of $S_{I,n+1}$ taking on a value y can be calculated by knowing $S_{I,n} = x$. Model equations and its derivations were defined in (Lin et al., 2006, Lin et al., 2008).

$$P\left(S_{I,n+1} = y \middle| S_{I,n} = x\right) = \frac{P(S_{I,n} = x, S_{I,n+1}y)}{P(S_{I,n} = x)} \tag{7.1}$$

Considering the fitted S_I in a 2-D space. ($S_{I,n}\, S_{I,n+1}$), the joint probability density function across the x–y ($S_{I,n} - S_{I,n+1}$) plane is defined by the fitted values shown by the dots, whose coordinates are denoted by x_i and y_i :

$$\mathrm{P(x,y)} = \frac{1}{n}\sum_{i=1}^{n}\frac{\varphi\,(x;\ xi,\ \sigma_{xi}^2)}{P_{xi}}\,\frac{\varphi(y;yi,\sigma_{yi}^2\ )}{P_{yi}} \tag{7.2}$$

where:

$$P_{xi} = \int_{S_{I,lower}}^{S_{I,upper}} \varphi(x;xi,\sigma_{xi}^2)\,dx \tag{7.3}$$

$$P_{yi} = \int_{S_{I,lower}}^{S_{I,upper}} \varphi(y;yi,\sigma_{yi}^2)\,dy \tag{7.4}$$

Effectively, the joint 2-D probability density function is the normalized summation of normal probability density functions $\varphi(x;xi\,,\sigma_{xi}^2)$ centered at each individual data point. It thus turns discrete data into a smooth analytically defined function.

In Equations (7.2)–(7.4), the variance σ at each data point is a function of the local data density in a centred and orthonormalised space of x and y. Putting Equations (7.3) and (7.4) into Equation (7.2) normalises each $\varphi(x;xi\,,\sigma_{xi}^2)$ and $\varphi(x;xi\,,\sigma_{xi}^2)$ in the positive domain, effectively putting boundaries along $x = S_{I,lower}$ and $y = S_{I,upper}$, and enforcing the physiological validity of the S_I values.

In Equation (7.1), the right hand side denominator can be calculated by integrating Equation (7.2) with respect to y. Hence, Equation (7.1) can be calculated:

$$\mathrm{P}(S_{I,n+1} = \mathrm{y} \mid S_{I,n} = \mathrm{x}) = \sum_{i=1}^{n}\omega_i(x)\frac{\varphi(y;yi,\sigma_{yi}^2)}{P_{yi}} \tag{7.5}$$

where:

$$\omega_i(x) = \frac{\varphi\,(x;\ xi,\ \sigma_{xi}^2)\Big/P_{xi}}{\sum_{j=1}^{n} \varphi\,(x;\ xj,\ \sigma_{xj}^2)\Big/P_{xj}} \tag{7.6}$$

Thus, knowing $S_{I,\,n} = x$ at hour n, the probability of $S_{I,\,n+1} = y$ at hour $(n+1)$ can be calculated using Equations (7.5) and (7.6) across the x–y plane. Where there is a higher density of data, more certainty can be drawn on the "true" behavioural pattern.

In conclusion, Equations (7.5) and (7.6) define the 2-dimensional kernel density estimation in conditional S_I variability. Note that S_{In+1} variability is "conditional" because it depends on the prior state S_{In}. More specifically, knowing S_I at any hour n, $S_{In} = x$, the probability of S_I at hour $n + 1$, S_{In+1} = y, can be calculated from Equation (7.5).

In summary, the 2-dimensional kernel density estimation method creates a smooth, continuous model surface that reflects the sample data pattern. Note that the example shown is the "conditional" 2-dimensional kernel density estimate function as defined in Equation (7.5). Every slice of the surface in panel C along the y axis is the probability distribution in y (S_{In+1}) given x (S_{In}), and therefore its area under the curve along the y axis sums to 1.0. In comparison, the kernel density estimation joint probability function defined in Equation (7.2) has the volume under the 3-D surface equal to 1.0. The final 3-D S_I stochastic model is thus developed and shown in Figure 7.2 for the data set used for this study.

Based on results from in-sample tests, where the stochastic model is generated from the entire retrospective dataset and tested on the same data, and out-of-sample tests, where different subsets of data are used for model generation and testing, the kernel density estimator was modified by multiplying the variance estimators by a constant c (i.e., $c\sigma_x$ and $c\sigma_y$) to explore the model probability bound determination for this data. This adjustment to the variance estimator effectively adjusts the kernel bandwidth and the degree of smoothing over the data.

7.3 Stochastic Analysis by Overall Cohort

7.3.1 Hourly Insulin Sensitivity Variation in OHCA Patients

Figure 7.1 presents the distribution of hourly variation in S_I for the 180 OHCA patients during cool (4987 hours) and warm (5001 hours) periods. Approximately 85% of the values during cool period, and 70% during warm period are below 1.0 x 10^{-3} L/(mU.min). The results show that the hourly variation of S_I is wider during cool period, but there are higher S_I values in the warm period.

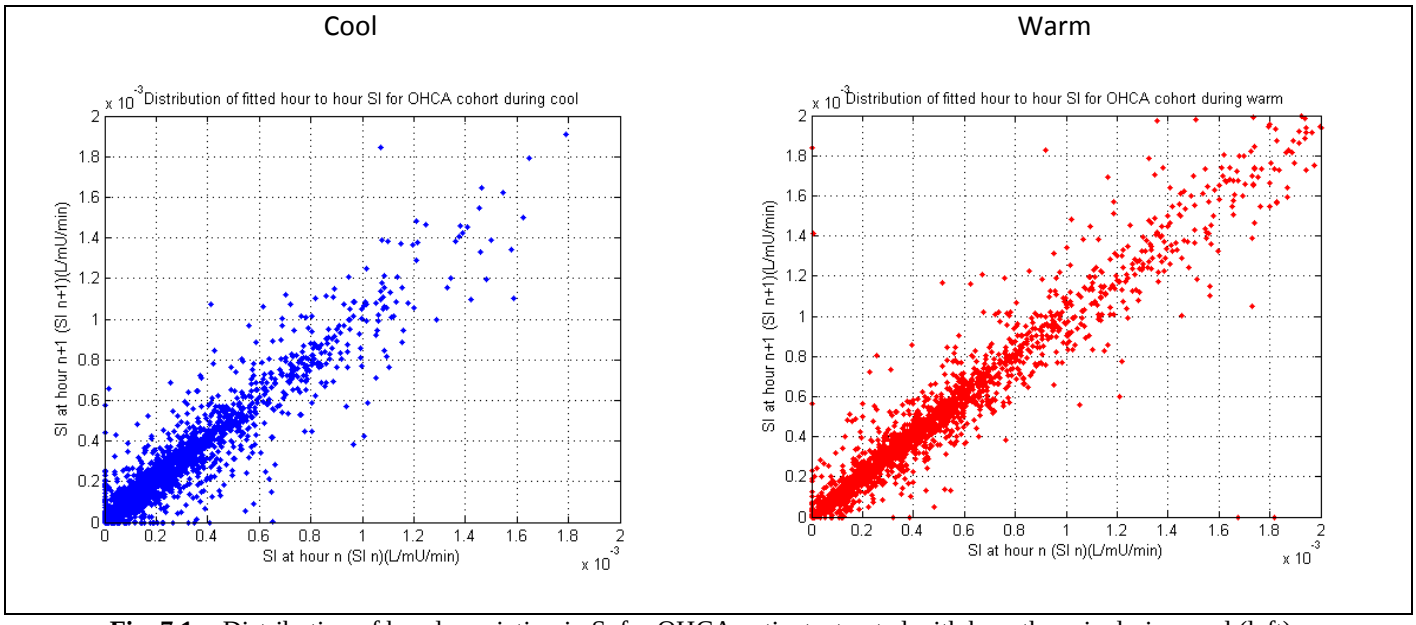

Fig. 7.1: Distribution of hourly variation in S_I for OHCA patients, treated with hypothermia during cool (left) and warm (right) periods as presented in 2-D kernel density method.

7.3.2 Conditional Probability Density Function

Figure 7.2 presents the conditional probability density plot for the stochastic model described in Section 7.2.3. These 3-D plots indicate the overall cohort variations in S_I at the x-y plane and the conditional probability density of $S_{I,n+1}$ at the z-plane. The results show that the conditional probability density $p[S_{I(n+1)}|S_{I(n)}]$ at the value $S_I < 1.0 \times 10^{-3}$ during the cool period is wider than during the warm period.

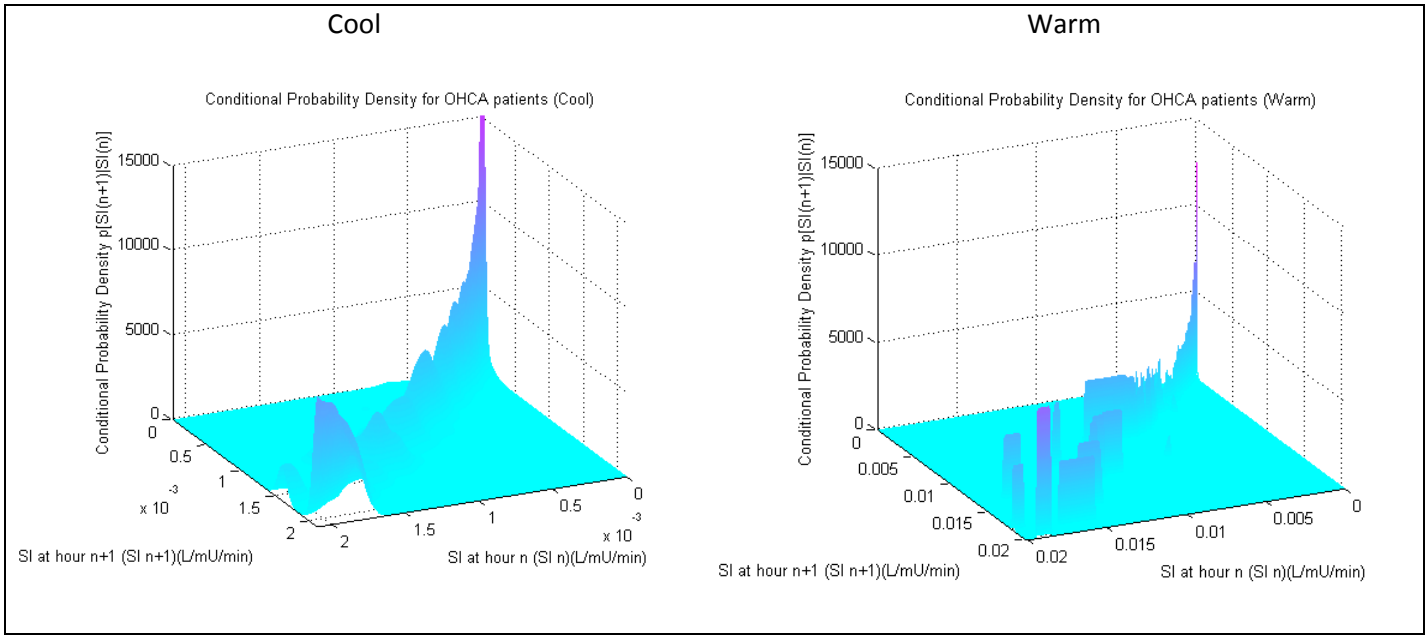

Fig. 7.2: Conditional probability density function S_I, n+1 knowing SI, n for OHCA patients, treated with hypothermia during cool (left) and warm (right) periods. The structure of the plot is unimodal in the region S_I, n $< 1.0 \times 10^{-3}$ and S_I, n+1 $< 1.0 \times 10^{-3}$, corresponding to the region of dataset density.

Figure 7.3 presents the 5th, 25th, 50th, 75th, and 95th percentile probability bounds calculated for both cool and warm periods by integrating the conditional probability density function in Figure 7.2, including the distributing points. In return, the forecasted BG values are calculated based on an equal-tailed 0.9 probability interval of S_I (i.e. $BG_{n+1} = [f(S_{I95}), f(S_{I5})]$) (Lin et al., 2006).

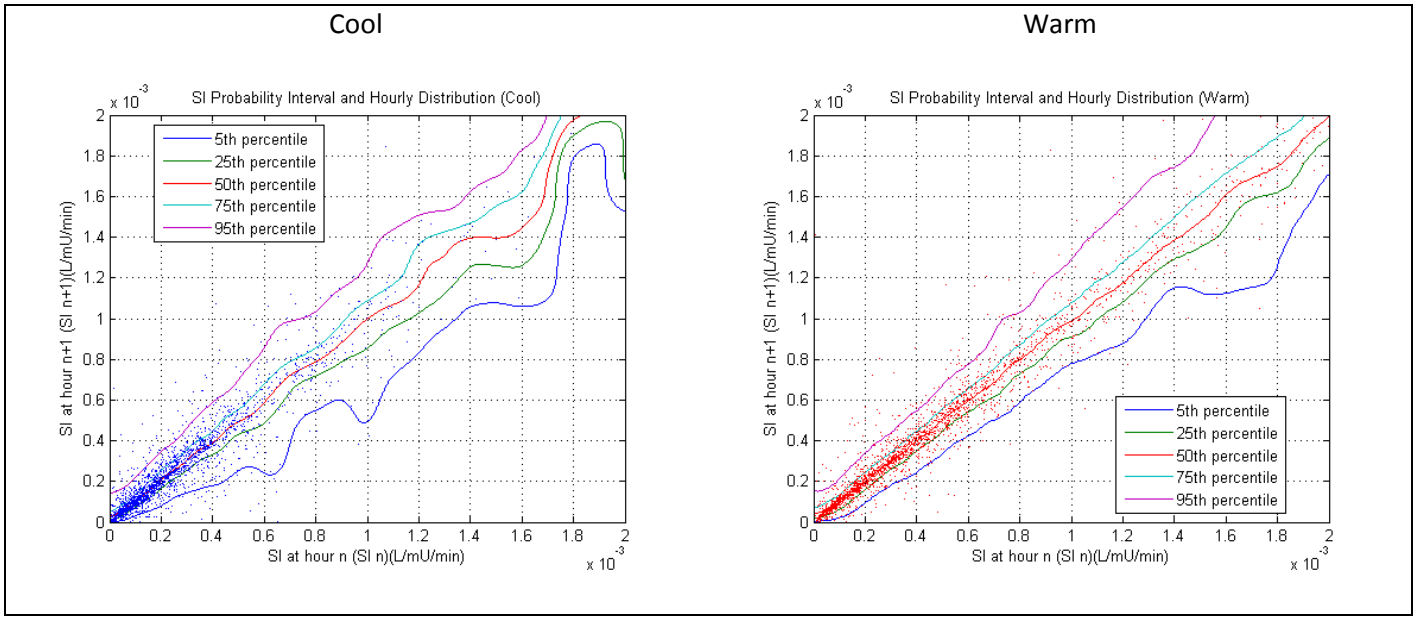

Fig. 7.3: Probability interval and distribution of hourly variation in S_I for OHCA patients, treated with hypothermia during cool (left) and warm (right) periods.

7.3.3 Stochastic Model Prediction Width

Table 7.1 shows the in-sample results of stochastic model prediction widths for both cool (n_{cool} = 4622 predictions) and warm (n_{warm} = 4832 predictions) periods at c=1. The number of predictions is less than the total hours of S_I as the patient data records are not always evenly divisible by 1h, and predictions can only be computed after the second hour of patient data.

Table 7.1: Sample results for stochastic model prediction widths at c= 1

Variable	Prediction width / Range	Value	
		Cool	Warm
% SI within prediction interval	[25th – 75th]	60.7 %	62.8 %
	[5th – 95th]	90.2 %	92.1 %
% BG within prediction interval	[25th – 75th]	59.4 %	62.1 %
	[5th – 95th]	92.6 %	92.8 %
BG prediction interval width	[25th – 75th]	2.8 mmol/L	1.9 mmol/L
	[5th – 95th]	8.0 mmol/L	5.4 mmol/L
Median absolute percent BG point prediction error		5.5 %	5.0 %
Median absolute BG point prediction error		0.4 mmol/L	0.35 mmol/L

Data are presented as cohort median (n_{cool} = 4622 predictions and n_{warm} = 4832 predictions)

For the cool period, S_I predictions (60.7%) were within the (25th–75th) probability intervals, corresponding to 59.4% of BG predictions. Similarly, 90.2% of S_I predictions were within the (5th–95th) probability intervals, corresponding to 92.6% of BG predictions. Thus, the proportion of fitted S_I and predicted BG values that fell within the (25th–75th) probability intervals were measurably higher than the expected 50%, but approximately closer to 90% for the (5th–95th) probability intervals. The overall median absolute prediction error comparing predicted BG based on the 50th percentile of predicted S_I to the interpolated value from retrospective data is 5.5%, corresponding to an average BG error of 0.4 mmol/L. The width of the (25th–75th) BG probability interval is 2.8 mmol/L. Similarly, the (5th–95th) BG probability interval width is 8.0 mmol/L.

For the warm period, the median absolute percentage BG point prediction error comparing predicted BG based on the 50th percentile of predicted S_I to the interpolated value from retrospective data is 5.0%, corresponding to an average BG error of 0.35 mmol/L. The width of the (25th–75th) BG probability interval is 1.9 mmol/L and the (5th–95th) BG probability interval width is 5.4 mmol/L. S_I predictions of 62.8% were within the (25th–75th) probability intervals, corresponding to 62.1% of BG predictions. Similarly, 92.1% of S_I predictions were within the (5th–95th) probability intervals, corresponding to 92.8% of BG predictions. Thus, the proportion of fitted S_I and predicted BG values that fell within the (25th–75th) were measurably higher than expected 50% but closer to the expected 90% within (5th–95th) probability intervals.

7.3.4 Cross-Validation Comparison Studies

Table 7.2 and 7.3 shows the results of the cross validation comparison study for 180 patients' cohort during cool and warm respectively. Generally, these results are consistent between groups, suggesting that the overall model contains sufficient data to account for the range of dynamics observed in this cohort.

Table 7.2: Cross-validation comparison study for 180 patient cohort (Cool period)

Group [Cool]	Groups used to create model	% SI within interval		% BG within interval		BG interval width (mmol/L)		BG point prediction error (%)	BG point prediction error (mmol/L)
		[25th -75th]	[5th- 95th]	[25th-75th]	[5th- 95th]	[25th-75th]	[5th- 95th]		
1	[-,2,3,4,5]	60.1	90.5	48.4	87.6	2.5	7.4	15.0	1.1
2	[1,-,3,4,5]	61.2	90.0	49.5	89.7	2.5	7.6	9.5	0.65
3	[1,2,-,4,5]	61.9	90.8	57.8	94.1	2.8	8.0	4.0	0.3
4	[1,2,3,-,5]	61.9	90.8	59.6	95.6	2.9	8.5	4.0	0.3
5	[1,2,3,4,-]	62.6	90.7	58.8	94.5	3.1	8.7	3.5	0.3
Overall	**[1,2,3,4,5]**	**60.7**	**90.2**	**59.4**	**92.6**	**2.8**	**8.0**	**5.5**	**0.4**

Table 7.3: Cross-validation comparison study for 180 patient cohort (Warm period)

Group [Warm]	Groups used to create model	% SI within interval		% BG within interval		BG interval width (mmol/L)		BG point prediction error (%)	BG point prediction error (mmol/L)
		[25th-75th]	[5th- 95th]	[25th-75th]	[5th- 95th]	[25th-75th]	[5th- 95th]		
1	[-,2,3,4,5]	64.1	92.3	62.5	93.1	1.7	5.2	12.5	1.0
2	[1,-,3,4,5]	64.0	92.6	62.7	92.9	1.7	4.6	7.0	0.5
3	[1,2,-,4,5]	61.7	91.8	61.7	92.9	1.9	5.7	4.5	0.3
4	[1,2,3,-,5]	63.1	92.7	61.9	92.9	1.9	5.5	4.5	0.3
5	[1,2,3,4,-]	63.8	92.8	64.0	93.4	2.0	5.7	4.0	0.3
Overall	**[1,2,3,4,5]**	**62.8**	**92.1**	**62.1**	**92.8**	**1.9**	**5.4**	**5.0**	**0.35**

7.3.5 Probability Bound-Determination

Table 7.4 shows the effect of modifying the kernel density estimation for several values of c, ranging from 0.1 to 3.0 for the stochastic model derived from OHCA retrospective data. For this cohort, the increase of c values higher than 1.0, yield better coverage widths that contain numbers closer to the approximately expected proportion of original sample data values. Thus for cool period, the value c=1.0 enables S_I probability values to provide equivalent BG optimal coverage in the (25th–75th) intervals with 60.7% and 59.4% and in the (5th–95th) intervals with 90.2% and 92.6% respectively. Similarly, for warm period, the value c=3.0 will ensure S_I probability values to provide equivalent BG optimal coverage in the (25th–75th) intervals with 64.9% and 59.8% and in the (5th–95th) intervals with 91.5% and 91.1% respectively.

Table 7.4: Comparison of probability bounds for modifications of kernel density estimator ($\sigma`_x = c\sigma_x$ AND $\sigma`_y = c\sigma_y$) during both cool and warm periods.

C	**Cool Period**				**Warm Period**			
	% of S_I within probability bounds		% of BG within prediction bounds		% of S_I within probability bounds		% of BG within prediction bounds	
	[25th-75th]	[5th-95th]	[25th-75th]	[5th-95th]	[25th-75th]	[5th-95th]	[25th-75th]	[5th-95th]
0.1	49.3	87.8	49.4	89.3	45.5	83.7	40.7	80.5
0.2	50.2	88.4	50.3	87.7	48.2	84.4	42.4	80.8
0.3	51.1	88.5	51.2	90.3	50.4	85.2	44.0	80.8
0.5	53.5	88.6	53.4	91.1	52.2	85.9	47.7	81.1
1.0	**60.7**	**90.2**	**59.4**	**92.6**	55.8	87.1	49.1	82.8
1.5	66.2	91.3	65.3	94.5	58.0	88.9	51.2	84.5
2.0	69.6	92.1	70.1	96.4	60.4	90.1	53.2	87.1
2.5	72.2	92.7	74.3	97.5	62.8	91.2	57.3	89.3
3.0	74.0	93.4	77.6	98.3	**64.9**	**91.5**	**59.8**	**91.1**
Ideal	**50%**	**90%**	**50%**	**90%**	**50%**	**90%**	**50%**	**90%**

Results in Table 7.4 at c=1.0 during cool period and c=3.0 during warm period are further reflected in Figure 7.4 which shows the probability-bound determination for raw S_I data and its corresponding BG forecasted values based on an equal-tailed 0.90 S_I probability interval.

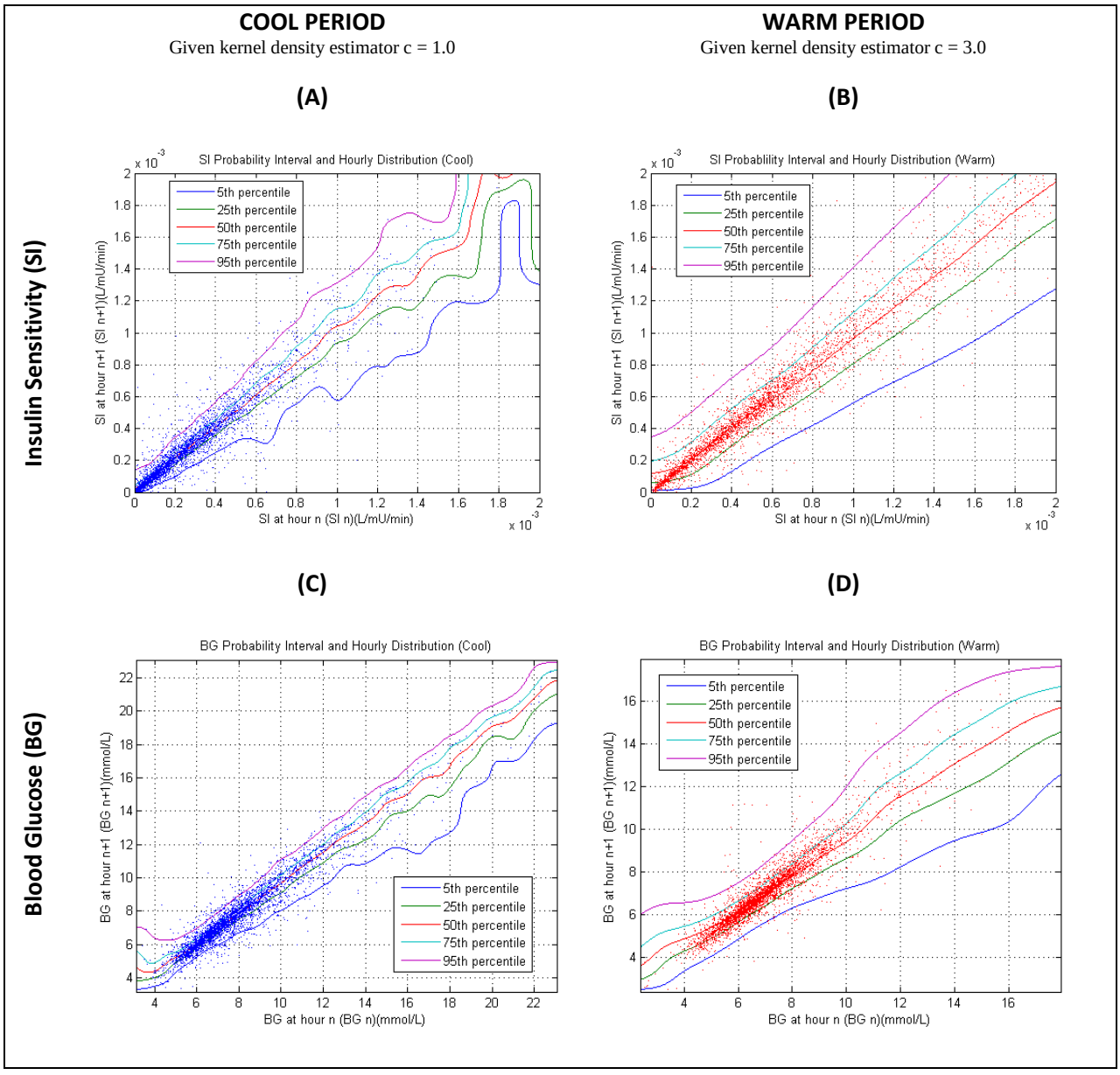

Fig. 7.4: Probability-bound determination for raw S_I data and corresponding BG forecasted values based on an equal-tailed 0.90 probability interval of S_I between 5^{th} -95^{th} at local variance estimator, both cool (c=1.0) and warm (c=3.0) period. The solid lines represent the 5%, 25%, 50%, 75% and 95% probability bounds.

The difference of optimal c values between cool and warm suggests that the variation and stochastic modelling for both periods are different, leading to different control requirements to ensure safe glycaemic control in the highly dynamic conditions. In particular, c=1.0 could be suitable during cool period since the S_I data is more dense at lower percentiles, but at high

variation. However, at warm conditions, the stochastic model shows higher probability distribution coverage of S_I variations, which usually occur when S_I data distribution is wider, less variable and closer to ideal percentage within bounds. Thus, c=3.0 would be a better level of stochastic control for this cohort during warm period.

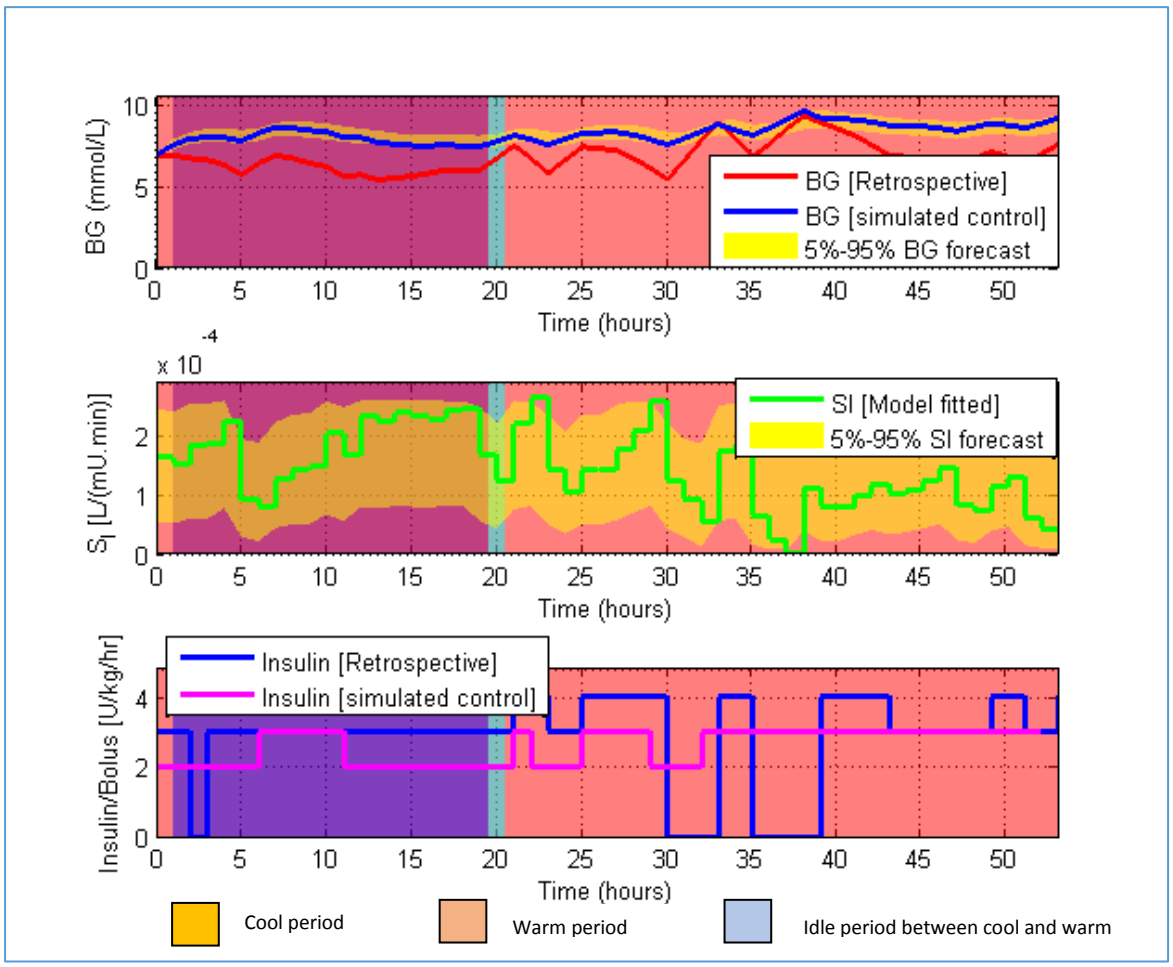

Fig. 7.5: Simulated trial using model-based control with stochastic model forecasts. The top plot shows the comparison between blood glucose concentration under simulated control (blue line) and retrospective control (red line). The middle plot shows model-fitted S_I (green line) and the bottom plot shows administration of insulin during simulated control (pink line) compared to retrospective control (blue line). The yellow shaded areas in the top and middle plots show the 5^{th}-95^{th} percentile of forecasted BG and S_I respectively.

Figure 7.5 shows a simulated trial results for individual OHCA patient, demonstrating the combination of Intensive Control Insulin-Nutrition Glucose (ICING) system model and the stochastic model, specifically the model forecasts for the 5^{th} and 95^{th} percentiles of future S_I. These values are substituted into equation (2.32), and systems of equations are solved over the forecast interval to generate the series of future BG based on variability in S_I. The result of forecasted BG is compared to the interpolated value from retrospective or clinical data to determine model forecast performance.

7.4 Stochastic Analysis by 12-hours Block

7.4.1 Stochastic Model Prediction Width

Table 7.5 shows the in-sample results of stochastic model prediction widths based on 12 block hours analysis at c=1.

Table 7.5: Stochastic model prediction widths at c= 1 based on 12-block analysis

Variable	Prediction width / Range	Cool		Warm	
		Block 1 [0-12 hrs]	Block 2 [12-24 hrs]	Block 3 [24-36 hrs]	Block 4 [36-48 hrs]
% SI within prediction interval	[25^{th} – 75^{th}]	58.7	55.1	52.7	50.7
	[5^{th} – 95^{th}]	90.4	88.1	87.7	86.7
% BG within prediction interval	[25^{th} – 75^{th}]	51.5	50.7	48.1	46.6
	[5^{th} – 95^{th}]	91.2	88.2	85.1	84.7
BG prediction interval width (mmol/L)	[25^{th} – 75^{th}]	3.5	2.1	2.0	1.8
	[5^{th} – 95^{th}]	9.8	5.9	5.7	4.9
Median absolute percent BG point prediction error (%)		4.5	6.5	4.5	6.0
Median absolute BG point prediction error (mmol/L)		0.35	0.4	0.3	0.4

Generally, S_I and BG prediction interval coverage meets the prediction expectation despite exceeding its ideal values of 50% and 90% for both (25^{th} – 75^{th}) and (5^{th}-95^{th}) interval width respectively. To improve the percentage optimization of prediction internal coverage, it is suggested that the stochastic model uses smaller values of local variance estimator for each time block. BG probability interval width for both (25^{th} – 75^{th}) and (5^{th}-95^{th}) is wider at block 1, and subsequently decreased for the remaining blocks. The median 1-h absolute BG prediction error, comparing predicted BG based on the median of predicted S_I to the interpolated value from retrospective data is ranged between 4.5 – 6.5 %, corresponding to an average BG errors of 0.3 – 0.4 mmol/L. Thus, the proportion of fitted S_I and predicted BG values that fell within the (25^{th} – 75^{th}) and (5^{th} – 95^{th}) probability intervals for 12-hour block analysis were measured higher than the expected 50% and 90%.

7.4.2 Probability Bound-Determination

Table 7.6 shows the effect of modifying the kernel density estimation for several values of c, ranging from 0.1 to 3.0 based on 12-hour block analysis. For this cohort, the increase of c values higher than 1.0, yield better coverage widths to the approximately expected proportion of original sample with highly variable data values. In contrast, lower values of c provides better coverage widths for original sample with less variable data values, especially at higher values of S_I where data are less dense. Besides, the modification of the kernel bandwidth will also affect the subsequent degree of smoothing, where the probability distribution becomes less smooth due to smaller c ($c < 1.0$).

To improve the percentage optimization of prediction internal coverage, this analysis suggested that the stochastic model uses bigger values of local variance estimator ($c > 1.0$), for each time block. The results has shown that for block 1, c=1.0 and followed by block 2 (c=1.5), and block 3 and 4 (c=2.0 and 2.5). The trend shows the value of estimator, c is increasing as S_I increases from cool to warm. The difference of optimal c values between 12-hour blocks suggests that the variation and stochastic modelling for each time block is different, leading to different control requirements to ensure safe glycaemic control in the highly dynamic conditions.

Table 7.6: Comparison of probability bounds for modifications of kernel density estimator ($\sigma`_x = c\sigma_x$ AND $\sigma`_y = c\sigma_y$) based on 12-hour block analysis

c	Cool Period				Warm Period			
	% of S_I within probability bounds at Block 1 [0 – 12] hours		% of S_I within probability bounds at Block 2 [12 – 24] hours		% of S_I within probability bounds at Block 3 [24 – 36] hours		% of S_I within probability bounds at Block 4 [36 – 48] hours	
	[25^{th}-75^{th}]	[5^{th}-95^{th}]	[25^{th}-75^{th}]	[5^{th}-95^{th}]	[25^{th}-75^{th}]	[5^{th}-95^{th}]	[25^{th}-75^{th}]	[5^{th}-95^{th}]
0.1	51.6	88.9	47.5	85.8	45.4	83.8	44.4	81.9
0.2	51.4	89.3	47.7	86.2	47.1	84.1	45.3	83.2
0.3	51.7	89.5	49.1	86.8	49.9	84.4	47.0	84.6
0.5	53.1	89.7	52.1	87.3	51.1	86.2	48.6	85.3
1.0	**58.7**	**90.4**	55.1	88.1	52.7	87.7	50.7	86.7
1.5	62.7	91.0	**58.4**	**90.0**	54.9	89.2	51.5	87.4
2.0	65.6	91.5	62.7	90.5	**56.0**	**90.4**	53.1	89.0
2.5	67.3	92.3	64.3	91.4	59.2	92.2	**54.7**	**90.4**
3.0	68.0	92.8	66.2	91.9	63.1	93.3	57.5	92.7
Ideal	**50%**	**90%**	**50%**	**90%**	**50%**	**90%**	**50%**	**90%**

7.5 Stochastic Analysis by 6-hour Block

7.5.1 Stochastic Model Prediction Width

In addition to 12-hour block analysis, further stochastic analysis by 6-hour block is carried out in similar method to analyse S_I variation and forecasting evolution for this cohort in more details. Table 7.7 presents the in-sample results of stochastic model prediction widths based on 6 hour block analysis at c=1.

Table 7.7: Stochastic model prediction widths at c= 1 based on 6-hour block analysis

Variable	Prediction width / Range	Cool				Warm			
		Block 1 [0-6 hrs]	Block 2 [6-12 hrs]	Block 3 [12-18 hrs]	Block 4 [18-24 hrs]	Block 5 [24-30 hrs]	Block 6 [30-36 hrs]	Block 7 [36-42 hrs]	Block 8 [42-48 hrs]
% SI within prediction interval	[25th – 75th]	58.7	57.2	56.9	55.5	51.9	52.1	52.6	52.6
	[5th – 95th]	90.4	89.5	89.0	87.3	87.2	88.2	88.3	87.7
% BG within prediction interval	[25th – 75th]	52.4	51.5	50.3	49.2	47.2	46.8	47.1	47.3
	[5th – 95th]	91.1	89.0	88.2	86.5	84.7	83.2	83.5	83.3
BG prediction interval width	[25th – 75th]	4.2	2.7	2.2	2.1	2.0	1.9	1.9	1.7
	[5th – 95th]	10.9	7.3	6.1	5.9	5.2	6.4	5.4	4.5
Median absolute percent BG point prediction error		2.5	6.5	4.5	7.0	4.0	5.5	4.5	5.5
Median absolute BG point prediction error (mmol/L)		0.2	0.4	0.3	0.45	0.25	0.4	0.35	0.35

The results show that S_I and BG prediction interval coverage meets the prediction expectation despite exceeding its ideal values of 50% and 90% for both (25^{th} – 75^{th}) and (5^{th}-95^{th}) interval width respectively. BG probability interval width for both (25^{th} – 75^{th}) and (5^{th}-95^{th}) is wider at block 1, and subsequently decreased for the remaining blocks, except block 6. This is due to higher BG variation as a results of TGC for this cohort.

The median 1-h absolute BG prediction error, comparing predicted BG based on the median of predicted S_I to the interpolated value from retrospective data is ranged between 2.5 – 7.0 %, corresponding to an average BG errors of 0.2 – 0.5 mmol/L. It is also observed that the proportion of fitted S_I and predicted BG values that fell within the (25^{th} – 75^{th}) and (5^{th} – 95^{th}) probability intervals for 6-hour block analysis were measured higher than the expected 50%

and 90%. Thus, majority of the 6-hour block stochastic model analysis results match with the 12-hour block stochastic model analysis which suggest that further stochastic control will be sufficient with 12-hour block stochastic models.

7.5.2 Probability Bound-Determination

Table 7.8 shows the effect of modifying the kernel density estimation for several values of c, ranging from 0.1 to 3.0 based on 6 hour block analysis. For this cohort, the results has shown that for block 1, c=1.0 and followed by block 2 to block 3 (c=1.5), and block 4 to block 5 (c=2.0). The trend shows that the value of estimator, c is increasing as S_I increases from cool to warm, and match with 12-hour block stochastic model analysis as shown in the Table 7.6.

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Table 7.8: Comparison of probability bounds for modifications of kernel density estimator ($\sigma`_x = c\sigma_x$ AND $\sigma`_y = c\sigma_y$) based on 6-hour block analysis

C	Cool Period								Warm Period							
	% of S_I within probability bounds at Block 1 [0 – 6] hours		% of S_I within probability bounds at Block 2 [6– 12] hours		% of S_I within probability bounds at Block 3 [12 – 18] hours		% of S_I within probability bounds at Block 4 [18 – 24] hours		% of S_I within probability bounds at Block 5 [24 –] hours		% of S_I within probability bounds at Block 6 [36 – 48] hours		% of S_I within probability bounds at Block 7 [36 – 48] hours		% of S_I within probability bounds at Block 8 [36 – 48] hours	
	[25^{th}-75^{th}]	[5^{th}-95^{th}]	[25^{th}-75^{th}]	[5^{th}-95^{th}]	[25^{th}-75^{th}]	[5^{th}-95^{th}]	[25^{th}-75^{th}]	[5^{th}-95^{th}]	[25^{th}-75^{th}]	[5^{th}-95^{th}]	[25^{th}-75^{th}]	[5^{th}-95^{th}]	[25^{th}-75^{th}]	[5^{th}-95^{th}]	[25^{th}-75^{th}]	[5^{th}-95^{th}]
0.1	51.6	88.9	52.7	85.3	53.5	85.8	51.7	86.0	44.9	84.2	45.0	85.3	45.5	85.5	46.2	85.6
0.2	51.4	89.3	53.5	86.2	54.3	86.6	52.1	86.2	45.3	84.5	45.4	85.8	46.2	85.8	46.7	85.9
0.3	51.7	89.5	54.0	86.9	54.7	86.9	53.5	86.6	46.3	85.8	46.7	86.6	47.4	86.6	48.0	86.7
0.5	53.1	89.7	55.6	88.8	55.1	87.8	54.3	87.4	48.4	86.5	48.6	87.0	49.2	87.1	49.3	87.3
1.0	**58.7**	**90.4**	57.2	89.5	56.9	89.0	55.5	87.3	51.9	87.2	52.1	88.2	52.6	88.3	52.6	87.7
1.5	62.7	91.0	**58.9**	**90.7**	**58.0**	**90.6**	57.2	88.2	54.9	87.8	55.2	88.6	55.5	88.8	55.7	88.3
2.0	65.6	91.5	61.0	93.5	60.2	92.1	**59.2**	**90.7**	**55.6**	**90.3**	56.1	89.3	56.2	89.5	57.2	88.9
2.5	67.3	92.3	63.4	94.2	62.7	92.5	60.8	92.4	56.2	91.9	**55.8**	**90.9**	**57.3**	**90.1**	58.5	89.5
3.0	68.0	92.8	65.7	94.9	63.9	92.6	62.1	92.9	56.7	92.8	57.5	91.2	57.9	91.3	**59.0**	**90.7**
Ideal	**50%**	**90%**	**50%**	**90%**	**50%**	**90%**	**50%**	**90%**	**50%**	**90%**	**50%**	**90%**	**50%**	**90%**	**50%**	**90%**

7.6 Stochastic Analysis by Sub-Cohort

7.6.1 Stochastic Model Prediction Width

Tables 7.9 and 7.10 show summary of cross-validation comparison study for OHCA sub-cohorts at both cool and warm respectively with c=1. Looking at these tables, it must be noted that S_I and BG results for all sub-cohorts are not much different compared to the overall OHCA cohort, even though the percentage of S_I and BG values within interval during warm are slightly higher than cool for each respective sub-cohorts. This outcome suggests that stochastic models derived from the overall cohort are different between cool and warm, but applicable for sub-cohorts, regardless of patient background and any other status.

Predicting BG values based on an equal-tailed 0.90 S_I probability interval is a more practical forecasting approach (Lin et al., 2008, Evans et al., 2011, Fisk et al., 2012) . Ideally, the probability-bound determination for raw S_I data and its corresponding BG forecasted values based on an equal-tailed 0.90 S_I probability interval must be about the same. In general, the sub-cohort analysis shows that the S_I percentage coverage in the (25th–75th) and the (5th–95th) intervals and BG percentage coverage in the (25th–75th) and the (5th–95th) intervals are not much different within a tolerance of ± 3.0%.

However, there are two sub-cohorts that show differences greater than ± 3.0% which are Diabetes and ROSC > 30 mins. For example, the S_I and BG percentage coverage in the (5th–95th) interval for diabetic sub-cohort during cool period is 87.8 % and 95.1 % respectively and the difference is 7.3%. Since the error and bounds are larger for diabetes and ROSC > 30 mins, predicting BG values based on an equal-tailed 0.90 S_I probability interval is most likely inaccurate for both cool and warm periods in these cases. Thus, if making a stochastic model for these sub-cohorts, values of c >1.0 would be required.

Table 7.9: Cross-validation comparison study for OHCA sub-cohorts (Cool period) at c=1.

OHCA Sub-Cohort	No of Patient	% SI within interval		% BG within interval		BG interval width (mmol/L)		BG point prediction error (%)	BG point prediction error (mmol/L)
		[25th -75th]	[5th- 95th]	[25th-75th]	[5th- 95th]	[25th-75th]	[5th- 95th]		
Overall OHCA cohort	180	60.7	90.2	59.4	92.6	2.8	8.0	5.5	0.4
Survived Patients	98	64.6	91.5	64.4	93.8	2.5	7.5	4.0	0.3
Non-Survived Patients	82	60.0	89.7	61.5	94.2	3.1	8.9	7.0	0.5
Diabetes Patients	23	68.6	83.4	65.0	87.2	3.8	8.7	12.5	1.2
Non-Diabetes Patients	157	60.9	90.0	58.4	92.5	2.6	7.7	6.5	0.45
Male Patients	143	61.8	90.8	59.8	92.8	2.7	8.0	5.0	0.35
Female Patients	37	64.8	89.6	61.7	94.7	3.1	8.4	7.0	0.45
ROSC < 15 mins	63	69.3	92.7	66.4	93.7	2.7	7.9	2.5	0.2
ROSC < 30 mins	89	61.1	90.5	63.3	94.4	2.8	7.7	8.0	0.55
ROSC > 30 mins	28	63.5	87.8	66.8	95.1	2.6	11.2	15.5	1.5

Table 7.10: Cross-validation comparison study for OHCA sub-cohorts (Warm period) at c=1.

OHCA Sub-Cohort	No of Patient	% SI within interval		% BG within interval		BG interval width (mmol/L)		BG point prediction error (%)	BG point prediction error (mmol/L)
		[25th -75th]	[5th- 95th]	[25th-75th]	[5th- 95th]	[25th-75th]	[5th- 95th]		
Overall OHCA cohort	180	62.8	92.1	62.1	92.8	1.9	5.4	5.1	0.35
Survived Patients	98	66.3	93.1	63.2	93.0	1.8	4.6	5.2	0.35
Non-Survived Patients	82	63.0	92.6	56.1	93.9	2.0	6.4	4.5	0.35
Diabetes Patients	23	68.1	94.9	63.8	96.3	2.8	7.9	8.0	0.5
Non-Diabetes Patients	157	63.4	92.4	61.7	92.7	1.7	4.7	5.5	0.4
Male Patients	143	63.2	92.2	61.8	92.9	1.9	5.3	5.0	0.35
Female Patients	37	61.4	95.5	61.6	95.3	1.7	5.5	5.5	0.35
ROSC < 15 mins	63	65.6	92.5	63.8	93.5	2.1	5.7	4.0	0.3
ROSC < 30 mins	89	69.6	95.0	65.4	93.8	1.8	5.4	5.5	0.4
ROSC > 30 mins	28	61.4	95.3	56.8	93.9	1.5	4.5	7.0	0.5

7.6.2 Probability Bound-Determination

Table 7.11 shows the summary analysis of the effect of modifying kernel density estimation, c ranging from 0.1 to 4.0 for OHCA sub-cohorts. In general, the increased values of c yield wider coverage width whereas the decreased value of c yields narrow coverage width.

Table 7.11: Cross-validation comparison study for 180 patient cohort (Warm period)

OHCA Sub-Cohort	No of Patient	c, Kernel Density Estimator [Range: 0.1 – 4.0]	
		Cool Period	Warm Period
Overall OHCA cohort	180	1.0	3.0
Survived Patients	98	1.0	2.0
Non-Survived Patients	82	1.5	3.5
Diabetes Patients	**23**	**1.5**	**4.0**
Non-Diabetes Patients	157	1.0	3.0
Male Patients	143	1.0	3.0
Female Patients	37	1.0	3.0
ROSC < 15 mins	63	1.0	2.0
ROSC < 30 mins	89	1.0	2.5
ROSC > 30 mins	**28**	**1.5**	**4.5**

Looking at the above table, it must be noted that kernel density estimator for all sub-cohorts are not much different compared to the overall OHCA cohort for both cool and warm. However, there are two sub-cohorts that show unique kernel density estimator results which are diabetes (1.5, 4.0) and ROSC > 30 mins (1.5, 4.5). These results shown in the bracket are out of range compared to overall OHCA cohort and other sub-cohorts. Since kernel density estimator difference is highest for both diabetes and ROSC > 30 mins, the system need more powerful controller and may require further specific module in order to process the data and match with the variation difficulties from these two sub-cohorts.

7.7 Discussion

The stochastic model presented in this paper is constructed by the distribution of insulin sensitivity variation using a 2-D kernel density method. This model has been employed previously on a cohort of adult intensive care (Lin et al., 2008) and neonatal intensive care patients (Le Compte et al., 2010). The percentage S_I within prediction interval results by Lin et al. of 54.0% within the (25th–75th) probability bound shows that normal adult ICU patients with normal body temperature produce far closer to the ideal 50%, followed by neonates' results by Le Compte et al. which record 62.6% at the same interval. However, the stochastic model results of 60.7% at cool and 62.8% at warm on the same probability bound for the OHCA patients, treated with hypothermia as shown in Table 7.1 appear to be unique and surprisingly more similar to neonates (Le Compte et al., 2010) . Additionally, the model-based S_I parameter used in this study is also model-specific, and thus may also account for different physiological effects in cardiac arrest patients compared to normal adult ICU patients both during cool and the first 24 hours of warm period after induced hypothermia.

The kernel density estimator (c) method employed in this stochastic model provides a layer of safety as wider probability bounds would be more likely to capture dynamics and any changes not observed in the cohort. The choice of kernel density estimator depends on the S_I data variations, and its corresponding BG forecasted values based on an equal-tailed 0.90 S_I probability interval between 5^{th} – 95^{th} at local variance estimator. Lower values of c means the distribution of S_I is narrower, and vice versa. The correct choice of c will ensure the prediction accuracy is maintained at 90% of total distribution.

As the (5^{th} - 95^{th}) band is what has been used for control previously (Le Compte et al., 2010), these cohort shows that they are closer to ideal 90%. However, wider coverage bands may also have impact on glycaemic control performance. As the wider probability band might be useful to avoid potential hypoglycaemia, it may also force a controller to maintain a mildly hyperglycaemic state. This is very true for OHCA patients, treated with hypothermia as the overall BG interval width of the (5th–95th) percentile probability band for c = 1.0 were 8.0 mmol/L and 5.4 mmol/L during cool and warm respectively, which is relatively very wide and would likely to have a significant impact on performance for a controller targeting a typical range between 4–7 mmol/L or 3 mmol/L BG interval width.

The cross validation comparison study for the 180 patient cohort showed consistent results, suggesting that the cohort dataset is large enough to reasonably reflect the vast majority of target patients presented. However, the contrasting trend has shown for patients group during warm period, where the percentage of S_I within this interval is higher than the percentage of forecasted BG. In fact, this trend matches results for adult intensive care (Lin et al., 2008) and neonatal intensive care patients (Le Compte et al., 2010). Thus, this is also appear to be another unique findings for this cohort suggesting different control scheme should be defined for cool and warm periods.

Modifying local data density variance estimator c to the value greater than 1.0 will result in more accurately distributions that better reflect the observed data prediction coverage (Le Compte et al., 2010). However, 60% of S_I and BG distributions for the OHCA patients' cohort are within the (25th–75th) prediction interval and around 5% -12% are out of bound for both cool and warm periods. Thus, a more robust modelling is required for highly variable patient. Hence, value of c = 1.0 and 3.0 provides the best tradeoff of bias and variance during cool and warm periods respectively. These chosen probability bound values have shown smooth probability bounds containing an appropriate proportion of prediction to obtain the desired prediction and glycaemia control performance at different physiology conditions.

7.8 Summary

Overall, this stochastic method and analysis in this study provides predictions based on a cohort dataset. The prediction bounds for more dynamic patients are difficult to decide since the S_I variability distribution for this cohort is unique, particularly during cool period. This observation is far differing than for the less dynamic patients who are typically more conservative. Thus, the probability bounds are optimized in a cohort sense, but not necessarily applicable on a per-patient basis.

Chapter 8: Summary of OHCA Patient Analysis

This chapter presents the analysis summary of OHCA patients based on metabolic, glycaemic, and exogenous insulin and nutrition characteristics and evolution during hypothermia (cool period) and normothemia (warm period). Patients were analysed based on overall cohort, sub-cohorts, and 6 and 12 hour time block. Results from each patient characteristics were combined and summarized. Finally, the summary of main findings from this study determines control design consideration for this cohort.

8.1 Overview of OHCA Patient Analysis

The overview of OHCA patient analysis is shown in Figure 8.1. In general, OHCA patients were undergone preliminary analysis during cool and warm before proceeding with new glycaemic controller design and development. The analysis is equally important as the controller development since it provides scientific evidence and understanding of patients' physiology and metabolic evolution especially during cool and warm. Besides, this analysis will embark further discussion and predictions on why these unique phenomena occur at specific time range. Hence, the outcome will benefit glycaemic controller development with proposed clinical settings.

The analyses are divided into 3 main parts:

i) Input

Exogenous insulin and nutrition are regarded as 'inputs' in the system since OHCA patient will receive these materials during treatment. Thus, the analysis of inputs will give an idea of how determine the best insulin and nutrition modulation strategy to deal with highly resistive and variable patient, particularly at critical situation and time. This idea in turn will be adopted and implemented in control design.

ii) System

Model-based insulin sensitivity (S_I), generated from the ICING model will be able to describe metabolic system behaviour of OHCA patient. Thus, the analysis will provide scientific information about patient metabolic level and evolution over time, from cool to warm conditions. The understanding of S_I evolution is vital for design and implementation glycaemic control. In addition to that, model-based S_I can be exploited to create its stochastic model, which describes the metabolic variability conditions of the patient. Analysis of S_I stochastic model is important for improving stochastic control, particularly in reducing metabolic and glycaemic variability.

iii) Output

Blood glycose (BG) is regarded as 'output' in the system since this metric will be measured and monitored during treatment. Thus, the analysis of glycaemic output will give an idea of how OHCA patient physiological and metabolic conditions response to insulin and nutrition administration as well as other inputs. This idea in turn will be adopted and implemented in control design.

These parameters will undergo the same analysis method and format since it is easier to gather results, analyse and summarize, which lead to better interpretation of unique phenomena at certain conditions and time. The overall analysis will allow interpretation and comparison of OHCA patients during cool and warm, while the time-block analysis will allow the same interpretation at specific time range. Thus, this will provide better reference and guidance in the effort to develop and implement safer metabolic management.

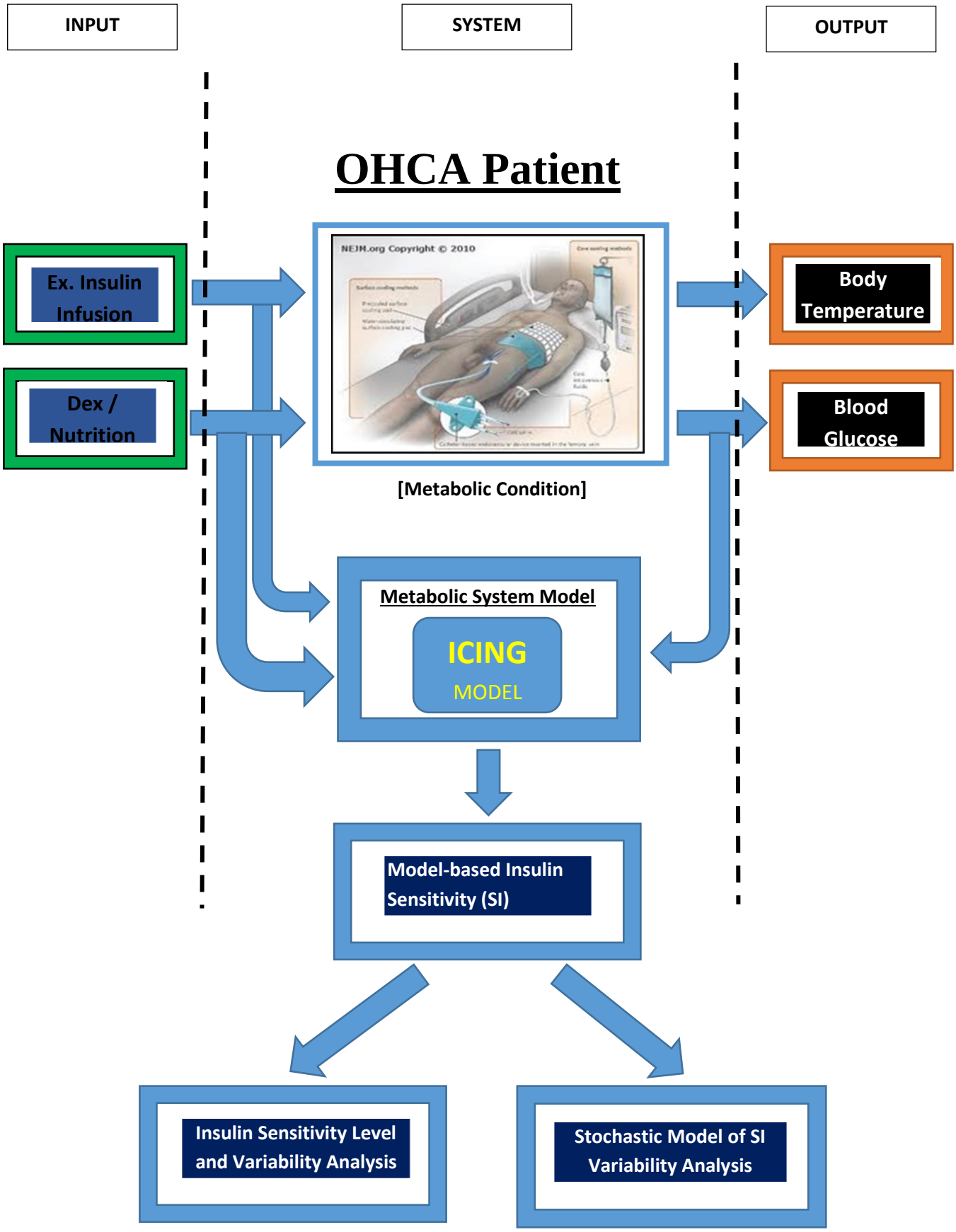

Fig. 8.1: Overview of OHCA patient analysis

8.2 Analysis Summary by Overall Cohort

8.2.1 Statistical Analysis Summary

A statistical analysis which summarize OHCA patient assessment results per-cohort based on metabolic, glycaemic, and exogenous insulin and nutrition characteristics and evolution during hypothermia (cool period) and normothemia (warm period) is presented in the Table 8.1. Stochastic model of S_I during cool and warm will use Kernel Density Estimator, c in this analysis.

Patient conditions and problem identifications is added in the list to explain about physiology and metabolic conditions during cool and warm. Any problems identified or unique phenomena observed from the analysis shall be included. Treatment observation will describe about how treatment was done based on insulin and nutrition analysis.

Referring to the Table 8.1, it shows that OHCA patient had very low metabolic activity during cool period but significantly increased over time. This shows that generally OHCA patients have improved physiologically and metabolically during treatment in ICU. Additionally, these patient would have higher metabolic variability during cool and decreases at warm. However, the metabolic variability decrease is not significant, implying that not much different in this aspect between cool and warm for the first 48 hours of treatment. Hence, implementing conventional glycaemic control on these patients is difficult, suggesting that model-based patient specific approach should be the way during this duration.

The physiology and metabolic conditions during cool and warm is also influencing the glycaemic outcome of the patient. The summary results in the Table 8.1 show that BG during cool is significantly higher than warm. This shows that these patients were undergo glycaemic control successfully during treatment in ICU, resulted in BG level decrease from cool to warm. However, glycaemic variability decrease is not significant, implying that not much different between cool and warm for the first 48 hours of treatment. Thus, this shows that implementing glycaemic control can only improve BG level, but difficult to reduce BG variability using these method due to high metabolic variability.

Insulin and nutrition administration presents how the treatment was done on OHCA patients. In this summary, it shows that more exogenous insulin is given during cool than warm. This trend match with the fact that BG is higher during cool period and decreases over time. However, the feeding decrease is not significant, implying that not much different or less modulation of insulin during cool and warm for the first 48 hours of treatment.

Unlike insulin, less nutrition is given during cool and significantly increases over time. This is because when the patient was initially admitted and hypotenized, blood glucose level is very high and demand more insulin to decrease. However, metabolic activity is low but highly variable. As metabolic activity increased and glycaemic level decreased, it is predicted that the body needs more energy. The situation is exaberated by the temperature rise from cool to warm. Hence, nutrition modulation plays significant role during treatment which support patients glucose needs while insulin amount is maintained to support metabolic activities.

With these insulin and nutrition modulation strategy, it resulted in improving glycaemic level but difficult to reduce BG variability using this method due to high metabolic variability. However, these findings is important to enable current glycaemic control method for OHCA patients is studied carefully, understand its background and problems and finally model the suitable controller to overcome the problems.

Table 8.1: Summary of S_I results for overall OHCA cohort.

Variable	Metrics	Period (2 days in ICU)		p-value
		Cool	Warm	
Insulin Sensitivity (S_I) [L/mU/min]1.0	Median S_I [IQR] [L/mU/min]	2.4×10^{-4} $[1.1, 3.5] \times 10^{-4}$	5.2×10^{-4} $[2.8, 8.3] \times 10^{-4}$	$p < 0.05$
	Median $\%\Delta S_I$ [IQR][%]	2.3 [-0.8, 8.9]	0.4 [-2.5, 3.4]	0.08
Blood Glucose (BG) [mmol/L]	Median BG [IQR] [L/mU/min]	7.4 [6.5, 8.5]	6.5 [5.8, 7.4]	$p < 0.05$
	Median $\%\Delta$BG [IQR][%]	-2.8 [-5.6, -0.9]	-1.5 [-3.4, 1.0]	0.08
Insulin Infusion (U) [U/hour]	Median U [IQR] [U/hour]	1.80 [1.0, 3.3]	1.65 [0.9, 3.7]	0.5
Dex / Nutrition (P) [g/hour]	Median P [IQR] [g/hour]	2.50 [0.8, 3.5]	3.23 [1.6, 5.3]	$p < 0.05$
Stochastic Model of S_I	Kernel Density Estimator, c	1.0	3.0	
Patient conditions and problem identifications		Lower metabolic activities due to low body temperature. $T < 35^o$ ---------- Low S_I but highly S_I resistance and variable. ---------- Higher BG level and variability.	Metabolic activities increased at optimum working temperature. $36.5^o < T < 37.5^o$ ---------- S_I increases, lower S_I resistance and less variable. ---------- BG level decreases and variability reduced but not significant.	
Treatment observations		Patients were given higher doses of exogenous insulin. ---------- Received average amount of nutrition.	Patients were given slightly lower doses of exogenous insulin ---------- Received significant increase amount of nutrition.	

8.2.2 Analysis Summary by 6-hour and 12-hour blocks

Table 8.2 and Table 8.3 illustrate statistical analyses which summarize OHCA patients' metabolic, glycaemic, and exogenous insulin and nutrition characteristics and evolution based on 12-hour and 6-hour blocks respectively.

Analysis summary by 12-hour blocks shows that OHCA patients had low metabolic activity during block 1 (0 -12 hours) but significantly increased over time. However, these patients would have higher metabolic variability during cool and significantly decreases for the first 24 hours of treatment. After 24 hours, the metabolic variability decrease is not significant. This results match with overall analysis summary (Table 8.1) and analysis by 6-hour block (Table 8.3), which indicate that implementing glycaemic control is difficult with different characteristics and evolution for each time block, suggesting that developing control based on per time block should be another alternative apart from per cohort.

The summary results in the Table 8.2 and Table 8.3 show that these patients were undergo glycaemic control successfully during treatment in ICU, resulted in BG level decrease significantly from block 1 (0 -12 hours) over time. However, glycaemic variability decrease is not significant, implying that not much different between these time blocks for the first 48 hours of treatment. This results match with overall analysis summary (Table 8.1) and analysis by 6-hour block (Table 8.3), which indicate that that implementing glycaemic control can only improve BG level, but difficult to reduce BG variability due to variations of metabolic variability between each time blocks.

Insulin and nutrition administration presents how the treatment was done on OHCA patients per each time block. In this summary, it shows that more exogenous insulin is given during block 1 (0 -12 hours) but decreased over time insignificantly. In contrast, less nutrition is given during when the patient is initially admitted to ICU, and significantly increases over time. This results match with overall analysis summary and analysis by 6-hour block. With these insulin and nutrition modulation strategy, it resulted in improving glycaemic level but difficult to reduce BG variability due to high metabolic variability. However, this finding is important to study current glycaemic control method for OHCA patients based on per time block.

Table 8.2: Summary of results for overall OHCA cohort based on 12-hour block analysis

Variable	Metrics	Cool Period [0-24 hours]		Warm Period [24-48 hours]	
		Block 1 [0-12] hours	Block 2 [12-24] hours	Block 3 [24-36] hours	Block 4 [36-48] hours
Insulin Sensitivity (S_I) [L/mU/min]	Median S_I [IQR] [L/mU/min]	1.9×10^{-4} $[1.0, 3.0] \times 10^{-4}$	2.7×10^{-4} $[1.2, 4.5] \times 10^{-4}$	4.8×10^{-4} $[2.5, 8.3] \times 10^{-4}$	5.2×10^{-4} $[3.0, 8.5] \times 10^{-4}$
	Median $\%\Delta S_I$ [IQR][%]	9.0 [5.1, 17.0]	5.8 [2.8, 10.3]	4.8 [2.8, 9.5]	4.8 [2.7, 9.2]
Blood Glucose (BG)[mmol/L]	Median BG [IQR] [L/mU/min]	7.6 [6.5, 9.3]	6.9 [5.9, 8.2]	6.7 [6.0, 7.8]	6.4 [5.7, 7.6]
	Median $\%\Delta$BG [%][IQR]	3.9 [2.1, 8.2]	3.8 [1.8, 6.6]	3.3 [2.2, 6.6]	3.3 [1.8, 6.1]
Insulin Infusion (U) [U/hour]	Median U [IQR] [U/hour]	2.7	2.4	2.2	2.2
Dex / Nutrition (P) [g/hour]	Median P [IQR] [g/hour]	2.5	4.1	4.5	3.8
Stochastic Model of S_I	Kernel Density Estimator, c	1.0	0.5	0.3	0.3
Patient conditions and problem identifications		Maintenance phase --- Low SI, but highly resistance and variable --- High BG and variability	Rewarming phase --- Low S_I, but start rising, and variable --- Reduced BG and variability	Rewarming phase --- S_I start rising, and variable --- Reduced BG and variability	Maintenance phase --- S_I rising, and variable --- Reduced BG and variability
Treatment observations		High insulin, low nutrition	Average insulin and nutrition	High insulin and nutrition	Average insulin and nutrition

Table 8.3: Summary of results for overall OHCA cohort based on 6-hour block analysis

Variable	Metrics	Cool Period [0-24 hours]				Warm Period [24-48 hours]			
		Block 1 [0-6] hours	Block 2 [6-12] hours	Block 3 [12-18] hours	Block 4 [18-24] hours	Block 5 [24-30] hours	Block 6 [30-36] hours	Block 7 [36-42] hours	Block 8 [42-48] hours
Insulin Sensitivity (S_I) [L/mU/min]	Median S_I [IQR] [L/mU/min]	1.5×10^{-4} [0.6, 2.6] $\times 10^{-4}$	1.9×10^{-4} [0.9, 3.2] $\times 10^{-4}$	2.1×10^{-4} [1.0, 4.0] $\times 10^{-4}$	3.0×10^{-4} [1.2, 5.1] $\times 10^{-4}$	4.5×10^{-4} [2.2, 8.3] $\times 10^{-4}$	4.4×10^{-4} [1.7, 8.7] $\times 10^{-4}$	4.8×10^{-4} [2.6, 7.7] $\times 10^{-4}$	5.0×10^{-4} [2.7, 8.5] $\times 10^{-4}$
	Median $\%\Delta S_I$ [IQR][%]	10.7 [4.7, 25.6]	6.8 [3.4, 14.4]	5.8 [2.9, 10.9]	4.3 [2.0, 8.6]	4.0 [2.4, 8.8]	4.5 [2.1, 9.0]	4.3 [2.1, 7.1]	4.2 [1.5, 6.3]
Blood Glucose (BG)[mmol/L]	Median BG[IQR] [L/mU/min]	8.3 [7.1, 10.8]	7.5 [6.5, 8.9]	7.3 [6.3, 8.4]	6.9 [5.9, 8.1]	6.8 [5.9, 8.0]	7.0 [6.3, 8.0]	6.9 [6.0, 7.9]	6.8 [5.8, 7.8]
	Median $\%\Delta$BG [IQR][%]	3.4 [1.7, 6.6]	2.9 [1.6, 5.3]	2.8 [1.2, 4.8]	2.5 [1.1, 4.7]	2.4 [1.4, 4.2]	2.6 [1.4, 5.1]	2.5 [1.2, 4.7]	2.1 [1.0, 4.1]
Insulin Infusion (U) [U/hour]	Median U [IQR] [U/hour]	3.70	2.52	2.31	2.07	2.16	2.70	2.00	2.00
Dex / Nutrition (P) [g/hour]	Median P [IQR] [g/hour]	3.53	4.43	5.60	6.00	7.23	7.09	6.80	6.66
Stochastic Model of S_I	Kernel Density Estimator, c	1.0	0.5	0.5	0.5	0.5	0.3	0.3	0.3
Patient conditions and problem identifications		Maintenance phase --- Low SI, but highly resistance and variable --- High BG and variability		Rewarming phase --- Low S_I, but start rising, and variable --- Reduced BG and variability		Rewarming phase --- S_I start rising, and variable --- Reduced BG and variability		Maintenance phase --- S_I rising, and variable --- Reduced BG and variability	
Treatment observations		High insulin, low nutrition		Average insulin and nutrition		High insulin and nutrition		Average insulin and nutrition	

8.3 Analysis by Sub-Cohort

Table 8.4 presents statistical analyses which summarize OHCA patients' metabolic, glycaemic, and exogenous insulin and nutrition characteristics and evolution by sub-cohorts.

Generally, majority of results from sub-cohorts match with overall OHCA patients which suggest that analysis of overall OHCA patients is sufficient to represent each sub-cohort. However, it is observed that diabetes sub-cohort has shown difficulties to decrease BG level even though the treatment received are the same as the other sub-cohorts.

Table 8.4: Analysis summary for OHCA patients by sub-cohort

Analysis Summary by Sub- Cohort	No	Insulin Sensitivity (S_I) [L/mU/min]			SI Variability (%ΔS_I) [%]			Blood Glucose (BG)[mmol/L]			BG Variability (%ΔBG) [%]			Insulin Infusion (U) [U/hour]			Dex / Nutrition (P) [g/hour]		
		Cool	Warm	p-value	Cool	Warm	p-value	Cool	Warm	p-value	Cool	Warm	p-value	Cool	Warm	p-value	Cool	Warm	p-value
All OHCA patients	180	2.5 x10^{-4}	5.4 x10^{-4}	< 0.05	1.2	0.2	0.08	9.7	8.5	< 0.05	-0.6	0.2	0.3	1.8	1.6	0.5	2.5	3.2	< 0.05
Survived Patients	98	2.5 x10^{-4}	5.8 x10^{-4}	< 0.05	1.0	0.3	0.1	9.1	7.8	< 0.05	-0.5	-0.1	0.3	1.7	1.4	0.3	2.6	3.2	< 0.05
Non-Survived Patients	82	2.2 x10^{-4}	5.1 x10^{-4}	< 0.05	1.4	0.07	0.2	9.2	8.3	< 0.05	-0.7	0.2	0.3	2.0	1.4	0.3	2.1	3.0	< 0.05
Diabetes Patients	23	2.3 x10^{-4}	4.1 x10^{-4}	< 0.05	1.0	0.04	0.3	**8.8**	**8.1**	**0.3**	-0.4	-0.2	0.1	1.9	1.7	0.7	2.1	4.2	< 0.05
Non-Diabetes Patients	157	2.4 x10^{-4}	5.7 x10^{-4}	< 0.05	1.2	0.3	0.06	9.3	8.1	< 0.05	-0.6	0.2	0.4	1.7	1.5	0.4	2.1	3.0	< 0.05
Male Patients	143	2.5 x10^{-4}	5.6 x10^{-4}	< 0.05	1.0	0.3	0.09	9.4	8.4	< 0.05	-0.5	-0.1	0.3	1.9	1.7	0.5	2.5	3.1	< 0.05
Female Patients	37	2.0 x10^{-4}	4.8 x10^{-4}	< 0.05	1.5	-0.3	0.5	8.6	7.3	< 0.05	-0.9	0.2	0.2	1.6	1.0	0.1	2.1	3.7	< 0.05
ROSC < 15 mins	63	2.7 x10^{-4}	5.7 x10^{-4}	< 0.05	1.0	0.3	0.2	8.7	7.7	< 0.05	-0.5	-0.2	0.1	1.4	1.0	0.4	2.5	4.2	< 0.05
ROSC < 30 mins	89	2.3 x10^{-4}	5.3 x10^{-4}	< 0.05	1.2	0.2	0.3	8.8	8.1	< 0.05	-0.6	-0.2	0.4	2.0	1.4	0.4	**2.5**	**2.7**	**0.2**
ROSC > 30 mins	28	2.0 x10^{-4}	5.3 x10^{-4}	< 0.05	1.4	-0.1	0.5	8.5	7.2	< 0.05	-0.9	0.3	0.3	2.5	1.5	0.3	**2.1**	**2.2**	**0.7**

* Results comparison based on per-cohort

8.4 Control Design Considerations

Hyperglycaemia or high blood sugar (glucose) is prevalent in critical care (Capes et al., 2000, McCowen et al., 2001, Mizock, 2001, van den Berghe et al., 2001) which increases the risks of further complications and mortality (Capes et al., 2000, van den Berghe et al., 2001, Krinsley, 2003) . An analysis summary of OHCA patient, treated with hypothermia shown in this chapter suggests that the main intention of glycaemic control on these cohort during cool and warm is solely to maintain blood glucose level within normal range (4.4 to 6.1 mmol/L) (Plank et al., 2006b), even though the metabolic and physiological conditions are still unstable. This is obvious since consistent insulin dosage is given to the patients throughout the first 2 days of treatment, while modulating nutrient ensures patients glucose needs to support metabolic activities. As a results, majority of blood glucose levels (Table 8.3) are recorded at moderate level (6.1 to 8.0 mmol/L), except for block 1 (0-6 hours).

The success in maintaining blood glucose level within 6.1 to 8.0 mmol/L at this stage is important since the patients had highly insulin resistant and variable during the first 2 days of cool and warm. The difficulties in dealing with these metabolic and physiological backgrounds paid off by maintaining blood glucose at these levels before further decrease to within normal range. Hence, exogenous insulin and nutrition administration approach for this cohort is the key for successful glycemic control. However, the ability of insulin and nutrition modulation method to reduce BG level for this cohort does not reflect the mortality statistics as shown in the Table 3.4. There are about 45.6% OHCA patient who were not survived after undergo the same therapies as mention above. This fact is supported by a study of survival rates from OHCA found that 14.6% of those who had received resuscitation by ambulance staff survived as far as admission to hospital. Of these, 54% died during admission, half of these within the first 24 hours, while 46% survived until discharge from hospital. Of those who were discharged from hospital, 70% were still alive 4 years (Cobbe et al., 1996). This shows that mortality rate is still high even though glycaemia control is implemented and successfully maintaining blood glucose level within 6.1 to 8.0 mmol/L at this stage. The question is, besides hyperglycemia what else causing a cardiac arrest patient to increase its mortality rate?

Referring to the summary results in the Table 8.1-8.3, it shows that glycaemic variability (%ΔBG) decrease is not significant, implying that there is not much different in glycaemic variability between cool or warm for the first 48 hours of treatment ($p > 0.05$). Since there are about 45.6% OHCA patient who were not survived after undergo the same therapies, the inability of glycemic control to reduce glycemic variability significantly from cool to warm might be the possible cause of cardiac arrest patient's high mortality rate. This fact is consistent with similar studies by Krinsley (Krinsley, 2009), who have showed that increased glycaemic variability is associated with mortality in critically ill patients. Additionally, the event of hypoglycaemia (BG < 2.22 mmol/L) is potentially increased during rewarming (Lee et al., 2013), which is also contributed to higher risk of death (Finfer et al., 2012).

Thus, even though the glycaemic control scheme implemented on these cohort has shown successful in maintaining blood glucose level within 6.1 to 8.0 mmol/L throughout the treatment from cool to warm, but the fact that only 54.4% survive from this method has ruined its reputation. This method is unable to decrease glycemic variability significantly as mentioned above. Hence, different glycemic control approach and settings should be proposed in order to overcome the problems posed by this cohort.

In order to develop suitable glycaemic controller for OHCA patients, treated with hypothermia, the design should consider several problems identified from the above analysis:

i) Very low metabolic activities, but high glycaemic level at initial (cool period), which demand too much insulin given during cool period

It is not surprised that an OHCA patient, treated with hypothermia will have a very high blood glucose level at the initial of cool period. Hyperglycaemia is dangerous and demand more insulin externally. However, an overdose insulin infusion might increase metabolic variability, which will influence higher glycaemic variability, which may cause hypoglycaemia and associated with mortality. Thus, controller design should consider higher BG target (Moghissi et al., 2009), and gradually BG decrease from cool to warm rather than drastic change. This consideration will affect insulin and nutrition administration to ensure safe and reliable glycaemic control.

ii) **High glycaemic variability due to metabolic variability, which may cause hypoglycaemia episode and associated with mortality.**

The event of hypothermia and the first 24 hours of rewarming is critical for an OHCA patient since metabolic conditions is unstable and highly variable especially at transition period between cool and warm. This may cause hypoglycemia, which is associated with mortality (Egi et al., 2006, Bagshaw et al., 2009, Krinsley, 2009). It was notable that modulating both insulin and nutrition inputs may achieve good control with lesser insulin and reduces hypoglycemic risk. Thus, controllers with the ability to adapt patient-specific metabolic conditions and forecast possible future parameter values such as blood glucose should be able to provide better modulation of insulin and nutrition inputs.

However, the unique metabolic evolution and variability found in OHCA cohort during the cool-warm transition period between 18 – 30 hours (Sah Pri et al., 2014) suggested that either higher BG targets (Moghissi et al., 2009) , and/or adding nutritional intake (Suhaimi et al., 2010) must be considered, in addition to patient-specific adaptive glycaemia control.

8.5 Control Performance Measures

Understanding the difficulties and defining desired controller performance is the first step to controller design. A variety of performance metrics have been used in different critical care glycaemic studies, with their differences often confounding direct comparisons between studies. These metrics can be summarised as five basic goals:

i) Mean blood glucose level

Mean blood glucose level is calculated over all measurements (Krinsley, 2004) or over limited measurements, such as first morning measurement (van den Berghe et al., 2001, Van den Berghe et al., 2003). The average is the simplest performance measure and the one used in both landmark clinical studies. However, it provides no further information on glucose excursions or tightness of control. In addition, an average value should utilise all blood glucose measurements and not just a morning average (van den Berghe et al., 2001), which can hide variability and poor control.

ii) Distribution of blood glucose level:

Most studies report an average glycaemic level and standard deviation, assuming blood glucose measurements are normally distributed. As a negative blood glucose concentration is physically impossible, a log-normal distribution provides a more accurate representation of the underlying spread of measurements. Finally, empirical cumulative distribution functions provide a framework to display all measurements and allow interpretation of results for any desired glycaemic band.

iii) Time in a glycaemic band:

Time in a glycaemic band is calculated as the time or percentage of measurements in a specific band, such as 4–6.1 mmol/L (Wong et al., 2006a, Wong et al., 2006b) or 4.5–6.1 mmol/L (Plank et al., 2006b). Maximising this metric is essentially equivalent to minimising the Hyperglycaemic Index (HGI) or area under the blood glucose level curve (Van den Berghe, 2004, Vogelzang et al., 2004). This metric provides a surrogate measure of the average value, as well as an indication of the tightness of the glycaemic control result. Using

multiple overlapping or contiguous bands provides a good definition of the total glucose distribution under control.

iv) Glucose variability:

Glucose variability measured as the standard deviation or 90% interval over the data. This metric has only been employed recently (McDonnell et al., 2005) and measures the tightness of blood glucose control around the average or target value. However, it provides no indication of the absolute glycaemic levels obtained and some methods assume normal or other statistical distributions that may not match the data. Hence, confidence intervals determined from the data may prove more useful.

v) Hypoglycaemic episodes:

Hypoglycaemic episodes measured as the number or percentage of measurements that are below a defined hypoglycaemic threshold. The typical definition is 2.2 mmol/L, although some studies use higher thresholds (Lonergan et al., 2006b, Plank et al., 2006b). Variability also captures some of this information when associated with the average or median glucose values. More importantly, this measure is a critical indicator of the safety of the control methods used.

Finally, clinical end-points such as mortality are a patient-specific outcome and tied to the control of glucose on a per-patient basis. Whole cohort results allow analysis of the full glycaemic control data set to assess outcomes such as hypoglycaemia, which has a typically low incidence rate but great clinical implications. Thus, each categorisation method provides a different insight into the data, and both are required to clearly describe the performance of a particular protocol (Goldberg et al., 2006).

Chapter 9: STAR Control Performance Analysis and Virtual Trials

This chapter presents a comparative study of STAR controller performance over Out-of-Hospital Cardiac Arrest (OHCA) patients based on general and OHCA-specific stochastic models. It analyses the improvement in glycaemic control that can be achieved by these stochastic models during treatment, including the evolution of blood glucose and its variability.

9.1 Introduction

Cardiac arrest patients in particular have benefited from TGC (van den Berghe et al., 2001), but can be highly insulin resistant and variable, especially during the first 24 hours of stay (Pretty et al., 2012). Hypothermia or lowering body temperature below 35 degree Celsius is increasingly used to treat out of hospital cardiac arrest (OHCA) (Hayashi, 2009, Turk, 2010) and these patients often simultaneously receive insulin. During hypothermia, physiological and metabolic conditions can be highly variable, unstable and beyond patient-specific prediction. The result leads to ad-hoc treatment protocols based primarily on local clinical experience.

The development and implementation of glycaemic control for the OHCA cohort is not straightforward, as the cohort is known to be highly resistant and metabolically variable, particularly during hypothermia and the first 24 hours after rewarming (Sah Pri et al., 2014) . However, the OHCA patient analysis summary from Chapter 8 should lead to better understanding of patient physiological conditions and its evolution from various perspectives, such as metabolic and glycaemic outcomes. Thus, input from that analysis could prove very important to develop safer and more accurate glycaemic control in this cohort.

Several design parameters must be considered in designing this glycaemic control algorithm. Virtual trial offers the opportunity to explore control strategies in simulation before pilot clinical trials (Lonergan et al., 2006a, Chase et al., 2007b) . In particular, the proposed control algorithm needs to reduce elevated blood glucose levels in a controlled, predictable manner

while directly accounting for external nutrition. The controller must also account for inter and intra- patient variability and varying physiological condition. Hence, it must be adaptive and/or able to identify changes in patient dynamics, particularly with respect to insulin sensitivity. The protocol should also require relatively infrequent (1-3 hours) sensor measurements to minimise labour and comply with existing protocols to ensure the method developed could be readily implemented in a clinical environment (Chase et al., 2008a, Mackenzie et al., 2005).

STAR (Stochastic TARgeting) is a stochastic targeted, model based glycaemic control framework (Evans et al., 2012, Evans et al., 2011, Fisk et al., 2012, Le Compte et al., 2009, Le Compte et al., 2012) that uses a time varying insulin sensitivity (S_I [L/mU/min]) (Chase et al., 2010) to provide an adaptive patient-specific response that accounts for both inter-patient variability and future intra-patient variability over time. This insulin sensitivity characterizes a patient's current metabolic state, and likely future changes in that state are forecast using population based stochastic modelling (Lin et al., 2008). This approach creates a range of possible future insulin sensitivity outcomes based on a patient's current insulin sensitivity. It enables a treatment to be selected that best overlaps the range of possible BG outcomes with a clinically defined target band, and a prescribed, typically 5^{th} percentile, level of hypoglycaemic risk. Detailed descriptions of stochastic model methods and the STAR protocol can be found in Section 2.5.2.

The performance and safety of STAR is highly dependent on the effectiveness of the stochastic modelling. Poor stochastic forecasting results in poor glycaemic control (Dickson et al., 2013). High variability in insulin sensitivity over time and between patients has been shown to limit possible performance of glycaemic control in simulation (Chase et al., 2011b, Dickson et al., 2012). Conservatively, high variability results in overly conservative stochastic models for some critical care patients. The resulting stochastic forecasting bands are wide, which may not be representative of the overall OHCA cohort, resulting in lower doses of insulin and higher BG levels. To enable better and equally safe control for this cohort of patients, the stochastic model used needs to be improved.

More specifically, the current STAR controller employs a stochastic model derived from adult ICU clinical data from patients treated using the SPRINT protocol. It include all diagnoses and all days of stay (Lin et al., 2008, Fisk et al., 2012). Thus, a new stochastic model will be developed, specifically for the OHCA cohort, and cool-warm periods. The analysis includes blood glucose (BG) level and variability, and control performance in treating OHCA patients.

9.2 Subjects and Methods

9.2.1 Patients and Data

This analysis was performed on a cohort of 180 OHCA patients (7812 hours) treated with hypothermia, shortly after admission in the Intensive Care Units (ICUs) of Erasme Hospital, Belgium and Lausanne Hospital, Switzerland. Patients were on local AGC protocols. BG and temperature readings were taken 1-2 hourly. Data were divided into three periods: 1) cool ($T<35^{o}C$); 2) an idle period of 2 hours as hypothermia was removed; and 3) warm ($T>37^{o}C$). A maximum of 24 and a minimum of 15 contiguous hours for each period were considered, ensuring a balance of contiguous data between periods. A summary of the full cohort with sub-analysis studies are presented in Chapter 3.

9.2.2 Controller Development and Implementation

The model-based insulin sensitivity parameter S_I, drives the dynamics of the blood glucose model and has been shown to be independent of the exogenous insulin and nutrition administration inputs from which it is identified (Chase et al., 2010). As a results, once a patient-specific profile of time-varying insulin sensitivity is identified from clinical data, it can be used to simulate and predict blood glucose concentration based on different insulin and nutrition control schemes. Such analyses have been used extensively in protocol design for adult critical care using the model (Chase et al., 2007b, Lonergan et al., 2006b) and others (Wilinska et al., 2008).

The clinical implementation procedure for a virtual trial of a model-based controller is shown in Figure 10.1. A BG measurement and subsequent controller intervention represents one cycle of the loop. The virtual trial procedure replaces the ‘Patient’ with a forward solution of

the model using an insulin sensitivity profile previously generated from retrospective clinical data. Sensor noise and other variations can be included as required (Lonergan et al., 2006b, Chase et al., 2007b) .

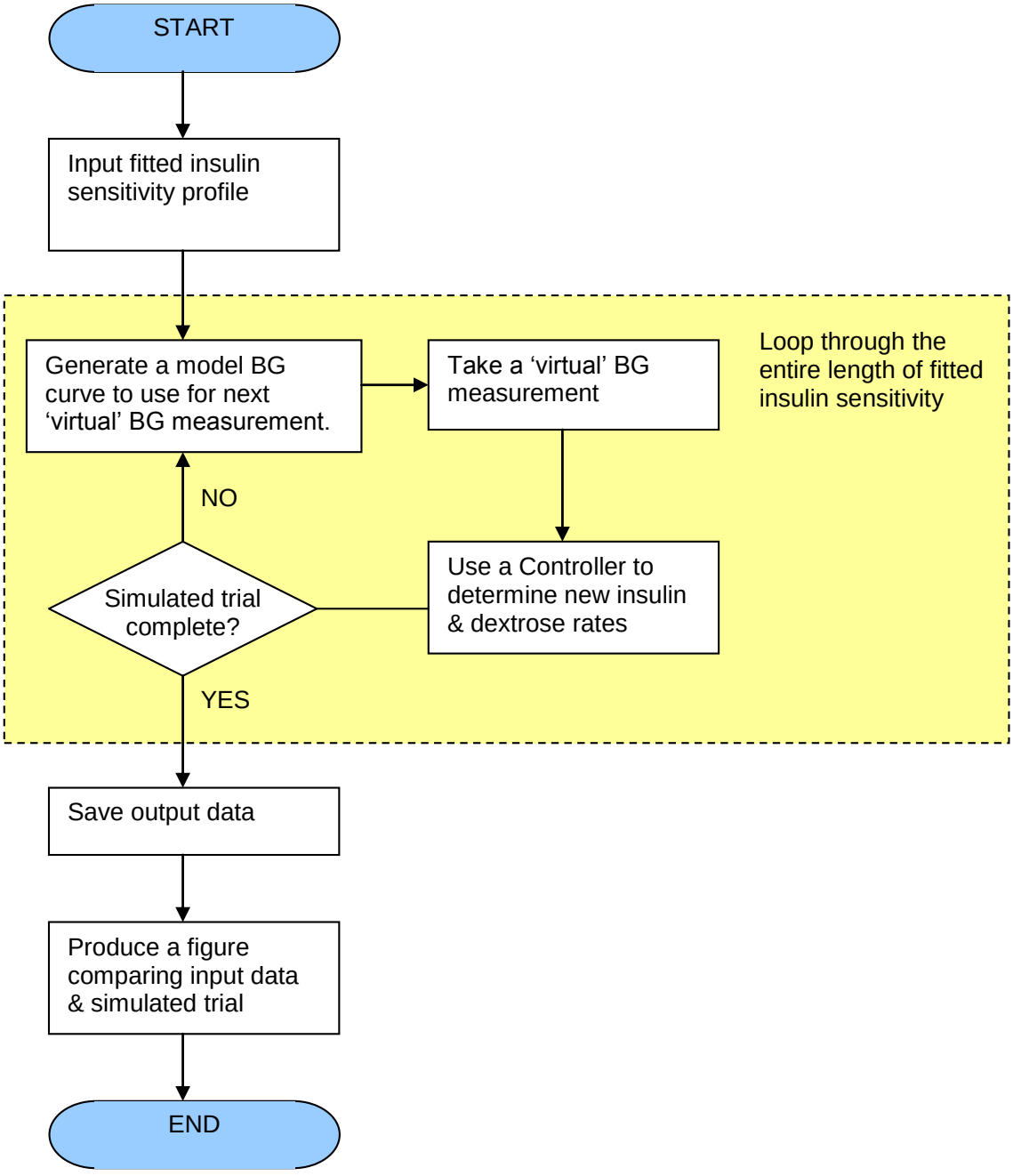

Fig. 9.1: Virtual trial procedure

To create a virtual trial patient, their blood glucose history, along with the administered insulin and nutrition history, are used to fit the patient-specific insulin sensitivity profile. This

S_I profile is then used by the controller to solve Equations 2.16 - 2.22 (Chapter 2) to predict blood glucose concentration based on controller specified insulin and nutrition rates. Several combinations of infusion rates can be simulated to select the dosage that will most likely meet target BG concentration or other criteria. Thus, the model-based controller adapts to the current metabolic state of the cardiac arrest patients in real-time.

In this research, virtual trials were carried out over all OHCA cohort by using a clinically validated model (Chase et al., 2007b, Chase et al., 2008b, Le Compte et al., 2009) . Insulin sensitivity (SI) generated from each patient is used as the critical marker of a patient's metabolic state, and is assumed independent of the insulin and nutrition inputs. There are strong reasons why virtual trials simulation is used extensively throughout these studies:

i) Virtual trials enable the rapid testing of new TGC intervention protocols, as well as analysis with respect to glycaemic control protocol performance, safety from hypoglycaemic, clinical burden, and the ability to handle dynamic changes in patient metabolic state (Lin et al., 2006, Chase et al., 2008b).
ii) Virtual patients trial methods presented are validated in their ability to accurately simulate in advance the clinical results of an independent TGC protocol, and directly enabling rapid design and optimization of safe and effective TGC protocols (Chase et al., 2010).

The STAR controller has already fulfilled the control requirements defined in Chapter 8 and has already shown its capability to perform tight glycaemic control over general ICU patients (Fisk et al., 2012). The controller is patient-specific, effectively manages BG level within 4 – 7 mmol/L and has an element of prediction. The stochastic features in the controller provide the ability to adapt to future patient-specific variations. The algorithm for STAR controller is shown in the Figure 2.10.

The new stochastic model for a specific STAR-OHCA controller is developed using this retrospective OHCA cohort data. The model is generated from changes in insulin sensitivity over this cohort. Hence, it is more specialized for OHCA patients, compared to the current stochastic model used by STAR. The stochastic model for this controller uses the best kernel density estimation values [c] during cool (c=1) and warm (c = 3), as determined in Chapter 7.

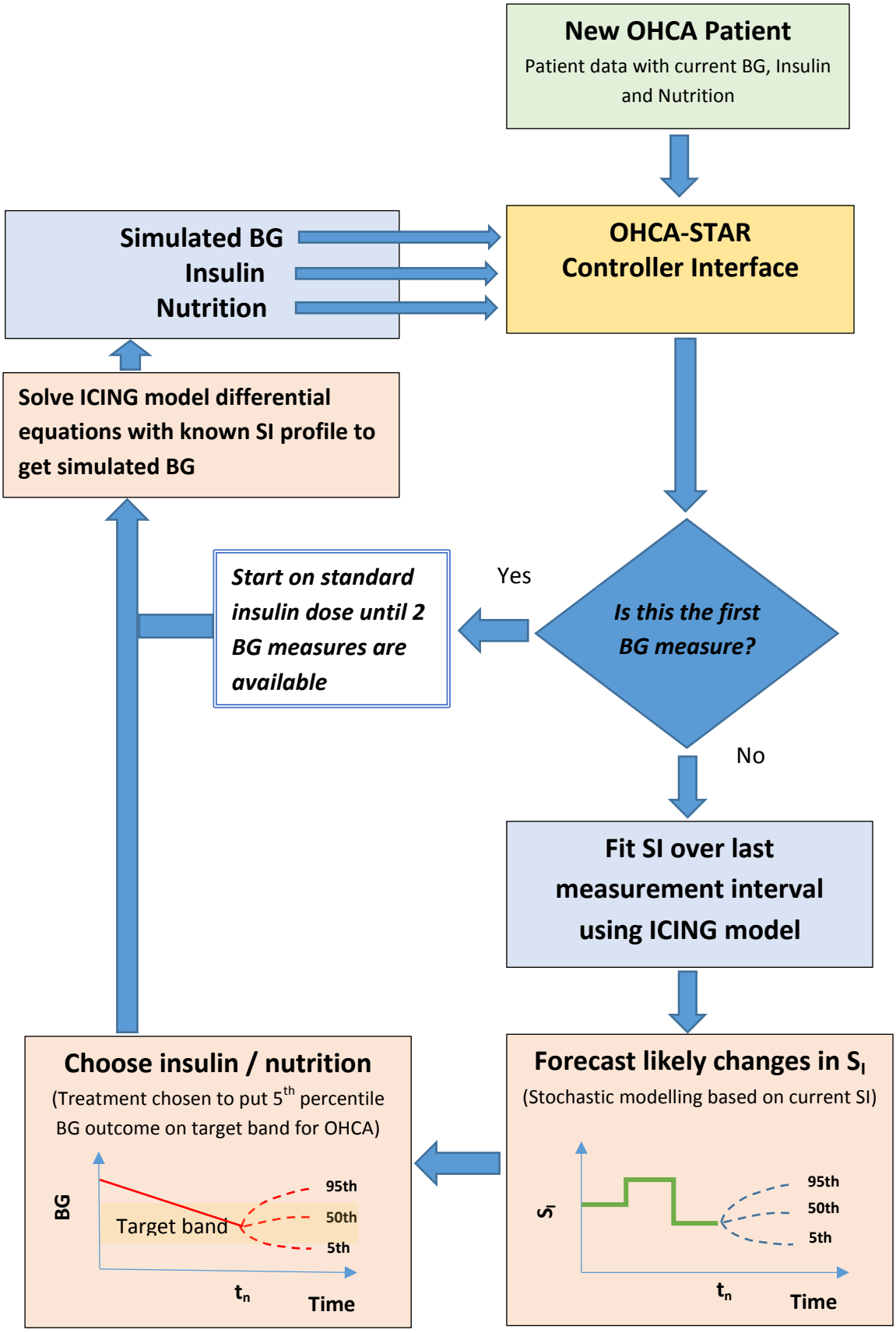

Fig 9.2: The STAR-OHCA Controller Algorithm

The model-based STAR-OHCA controller is implemented using the same clinically validated metabolic system model and stochastic models. The algorithm for STAR-OHCA controller is shown in the Figure 9.2. Controller assessment was carried for the following cases:

i) STAR controller with insulin input only, maintain original dextrose. The controller is denoted as **STAR 1** throughout the assessment.
ii) STAR controller with modulating insulin and nutrition/ dextrose over 30% goal feed if such patients exist, else insulin input only. The controller is denoted as **STAR 2** throughout the assessment.
iii) STAR-OHCA controller with insulin input only, maintain original dextrose. The controller is denoted as **STAR-OHCA 1** controller throughout the assessment.
iv) STAR-OHCA controller with modulating insulin and nutrition/ dextrose over 30% goal feed if such patients exist, else insulin input only. The controller is denoted as **STAR-OHCA 2** controller throughout the assessment.

Results and performance are compared with the retrospective clinical data.

9.2.3 Analyses and Metrics

Control performance outcomes are compared and analysed statistically by percentage time in the 4-8 mmol/L band and percentage BG > 10 mmol/L. Safety is evaluated in the percentage BG < 4.0 mmol/L and number of patients with severe hypoglycaemia (BG < 2.22 mmol/L). As the STAR framework is the same in all cases, controller effort is not assessed. These data are non-Gaussian and were thus compared using non-parametric cumulative distribution functions (CDFs) and non-parametric statistics. All distributed data were compared using a Wilcoxon rank-sum test (Mann-Whitney U-test) comparing median values. In all cases, $p < 0.05$ is considered statistically significant.

9.3 Virtual Trial Analysis and Discussion

9.3.1 Comparative Analysis with the Retrospective Data

Figure 9.3 shows the cumulative distribution functions (CDFs) of hourly BG level for the retrospective data, and the STAR and STAR-OHCA controller combination for the cool (left panel) and warm (right panel) periods. Table 9.1 summarizes the BG level results. Table 9.2 presents a comparative analysis of these controllers. The results show that four controllers had significantly lower BG in the warm period ($p < 0.05$) than the retrospective data. The cool periods were similar.

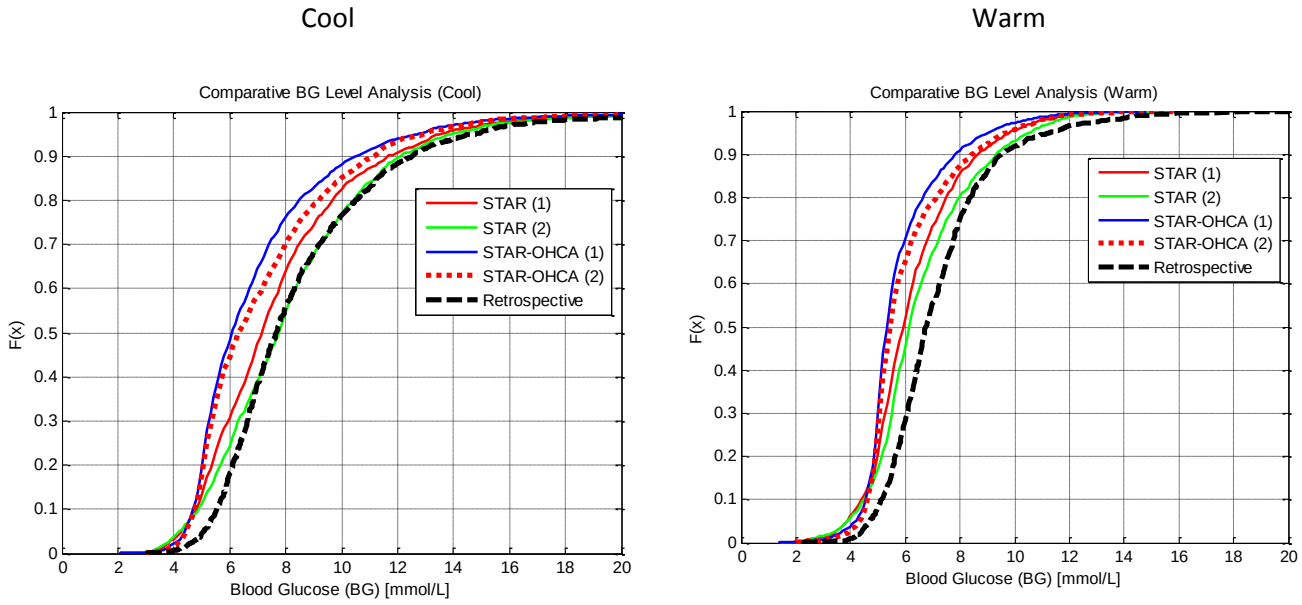

Fig. 9.3: Cumulative distribution functions (CDFs) of hourly BG level for the retrospective data and the STAR and STAR-OHCA controller combination, both cool (left panel) and warm (right panel) periods.

Table 9.1: Summary of BG level results for retrospective data, and STAR and STAR-OHCA controller combination

Controllers	Median BG [IQR] at cool period [mmol/L]	Median BG [IQR] at warm period [mmol/L]	% patients had higher BG at cool [Diff(Cool-warm)]	p-value
STAR Controller 1	7.2 [5.9, 8.5]	5.9 [5.1, 6.9]	75%	< 0.05
STAR Controller 2	7.5 [6.1, 9.1]	6.1 [5.2, 7.5]	70%	< 0.05
STAR-OHCA Controller 1	6.7 [5.7, 8.1]	5.6 [5.0, 6.7]	70%	< 0.05
STAR-OHCA Controller 2	7.1 [5.7, 8.6]	5.9 [5.1, 7.0]	70%	< 0.05
Retrospective Data	7.4 [6.5, 8.5]	6.5 [5.8, 7.4]	70 %	< 0.05

P-values calculated using Wilcoxon rank-sum test

Table 9.2: BG level comparative analysis of stochastic based controllers with the retrospective data.

BG Level Analysis [Controllers]	**Cool Period**		**Warm Period**	
	% Decrease at median	*p-value*	% Decrease at median	*p-value*
Retrospective vs STAR Controller 1	6.5	0.22	13.0	< 0.05
Retrospective vs STAR Controller 2	1.7	0.12	9.3	0.05
Retrospective vs STAR-OHCA Controller 1	32.1	0.18	25.2	< 0.05
Retrospective vs STAR-OHCA Controller 2	19.8	0.08	23.2	< 0.05

P-values calculated using Wilcoxon rank-sum test

Figure 9.4 shows the cumulative distribution functions (CDFs) of hourly BG variability for the retrospective data and stochastic based controllers. Table 9.3 summarizes the results. Table 9.4 presents the BG variability comparative analysis. While BG variability is slightly higher for the stochastic based controllers, the changes are not statistically or clinically significant. This variability is likely a result of lowering BG levels further in the warm period than the retrospective control was able to accomplish.

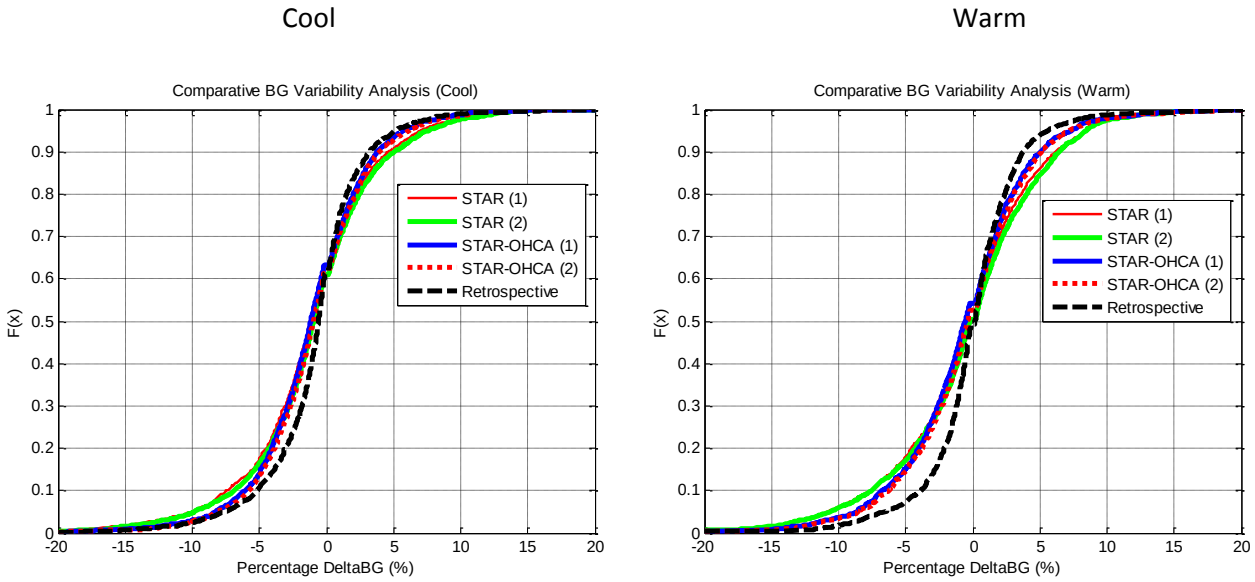

Fig. 9.4: Cumulative distribution functions (CDFs) of hourly BG variability for retrospective data and stochastic based controllers, both cool (left panel) and warm (right panel) periods.

Table 9.3: Summary of BG variability results for retrospective data and stochastic based patient-specific controllers

Controllers	Median BG variability [IQR] at cool period [%ΔBG]	Median BG variability [IQR] at warm period [%ΔBG]	% patients had higher BGV during cool period [Diff(Cool-warm)]	p-value
STAR Controller 1 [With insulin only]	-3.9 [-7.5, -1.7]	-1.9 [-5.3, 1.5]	35	0.24
STAR Controller 2 [With insulin and dextrose]	-3.9 [-6.6, -1.5]	-1.7 [-3.1, 1.5]	30	0.15
STAR-OHCA Controller 1 [With insulin only]	-2.9 [-5.4, -1.7]	-1.8 [-3.4, 1.1]	30	0.21
STAR-OHCA Controller 2 [With insulin and dextrose]	-2.9 [-5.2, -1.6]	-1.8 [-2.9, 1.1]	30	0.11
Retrospective Data	-2.8 [-5.7, -0.9]	-1.5 [-3.3, 1.0]	30	0.30

P-values calculated using Wilcoxon rank-sum test

Table 9.4: BG variability comparative analysis of patient-specific controllers with the retrospective data.

BG Variability Analysis [Controllers]	**Cool Period**		**Warm Period**	
	% Reduction of IQR	*p-value*	% Reduction of IQR	*p-value*
Retrospective vs STAR Controller 1	-36.8	0.34	-43.9	0.51
Retrospective vs STAR Controller 2	-35.8	0.28	-46.1	0.4
Retrospective vs STAR-OHCA Controller 1	-25.7	0.22	-37.6	0.06
Retrospective vs STAR-OHCA Controller 2	-30.1	0.15	-36.2	0.12

P-values calculated using Wilcoxon rank-sum test

9.3.2 Control Performance Analysis

Table 9.5 and Table 9.6 presents the summary of STAR, STAR-OHCA and retrospective controller performance analysis during cool and warm respectively. This summary compares the performance of STAR and STAR-OHCA controller with retrospective or clinical data.

During the cool period, stochastic-based controllers have shown better performance in managing glycaemia than retrospective control. These stochastic-based controllers delivered a higher percentage of BG within desired glycemic bands and a lower percentage of BG within the hyperglycemic band. In contrast, the retrospective control had performed much better in ensuring safety and minimizing hypoglycemic events among the cardiac arrest patients than other stochastic-based controllers. This outcome is illustrated by lower percentages of BG < 4 mmol/L.

During warm period, all controllers have shown some improvement compared to the cool period. However, the trend remain the same where STAR controllers have shown better performance in managing glycaemia than the retrospective data. This time, they have delivered higher percentage of BG within desired glycemic band and lower percentage of BG within the hyperglycemic band as compared to the non-stochastic-based controllers.

In terms of glycemic safety, all controllers have shown some increase in percentage of BG < 4 mmol/L during the warm period compared to the cool period. The increase have also increased the number of hypoglycemic events among the OHCA patients for model-based controllers, except for retrospective data. Stochastic-based controllers have shown poor performance in ensuring safety during warm where percentage of BG < 4 mmol/L has increased to 5% and around 4 patients experienced hypoglycemic episode during treatment. This has revealed that for OHCA cohort, glycemic variability is increased during rewarming or at transition period between cool and warm which is also matched with metabolic evolution studies (Sah Pri et al., 2014).

Table 9.5: Summary of STAR, STAR-OHCA and retrospective controller performance analysis during cool period

Summary of STAR, STAR-OHCA and retrospective controller performance analysis during warm period	Retrospective Data	STAR Controller 1	STAR Controller 2	STAR-OHCA Controller 1	STAR-OHCA Controller 2
Whole cohort statistics:					
Total patients, number (n)	180	180	180	180	180
Total treatment, hours (h)	3693	3693	3693	3693	3693
BG Median [IQR], (mmol/L)	7.6 [6.3, 9.7]	7.1 [5.6,8.9]	7.7 [6.0 , 9.7]	6.1 [5.2, 7.8]	6.3 [5.2, 8.5]
Hyperglycaemic bands:					
% BG > 10.0 mmol/L	22.8	17.2	22.8	12.0	15.0
% BG within 8.0 – 10.0 mmol/L	20.8	18.8	22.7	12.0	15.4
Desired glycaemic bands:					
% BG within 4.0 – 8.0 mmol/L	55.8	61.0	51.6	74.3	68.2
% BG within 4.0 – 7.0 mmol/L	37.5	44.3	36.4	61.8	56.7
Safety glycaemic bands:					
% BG < 4.4 mmol/L	1.4	5.5	5.7	4.0	3.6
% BG < 4.0 mmol/L	0.6	3.1	2.9	1.8	1.4
% BG < 2.22 mmol/L	0.0	0.04	0.0	0.03	0.0
No of patients < 2.22 mmol/L	0	1	0	1	0
Interventions:					
Median insulin rate [IQR] (U/hr)	2.0	3.5	4.0	4.5	6.0
Median glucose rate [IQR] (g/hr)	4.0	3.9	4.2	2.2	3.3
Med. glucose rate [IQR] (% goal)	61.2	60.0	64.2	34.2	50.0

Table 9.6: Summary of STAR, STAR-OHCA and retrospective controller performance analysis during warm period

Whole cohort statistics:					
Total patients, number (n)	180	180	180	180	180
Total treatment, hours (h)	3760	3760	3760	3760	3760
BG Median [IQR], (mmol/L)	6.8 [5.9, 8.0]	6.0 [5.2, 7.1]	6.2 [5.4, 7.5]	5.4 [5.0, 6.3]	5.5 [5.0, 6.6]
Hyperglycaemic bands:					
% BG > 10.0 mmol/L	8.1	4.4	7.0	2.7	4.4
% BG within 8.0 – 10.0 mmol/L	17.1	10.6	13.2	6.5	8.7
Desired glycaemic bands:					
% BG within 4.0 – 8.0 mmol/L	74.0	80.0	74.9	87.5	84.6
% BG within 4.0 – 7.0 mmol/L	53.5	67.3	61.5	79.7	76.1
Safety glycaemic bands:					
% BG < 4.4 mmol/L	2.4	8.7	8.0	6.2	4.7
% BG < 4.0 mmol/L	0.8	5.0	4.9	3.3	2.3
% BG < 2.22 mmol/L	0.0	0.5	0.3	0.3	0.2
No of patients < 2.22 mmol/L	0	4	4	4	3
Interventions:					
Median insulin rate [IQR] (U/hr)	1.0	1.5	2.0	2.0	2.0
Median glucose rate [IQR] (g/hr)	6.4	4.6	6.1	5.2	6.5
Med. glucose rate [IQR] (% goal)	97.4	70.6	93.2	80.0	99.4

9.3.3 Dealing with Hypoglycaemic Episodes

Figure 9.5 and 9.6 present patient plots who had experienced hypoglycemia after simulation with STAR1-OHCA and STAR2-OHCA controller respectively, during warm period.

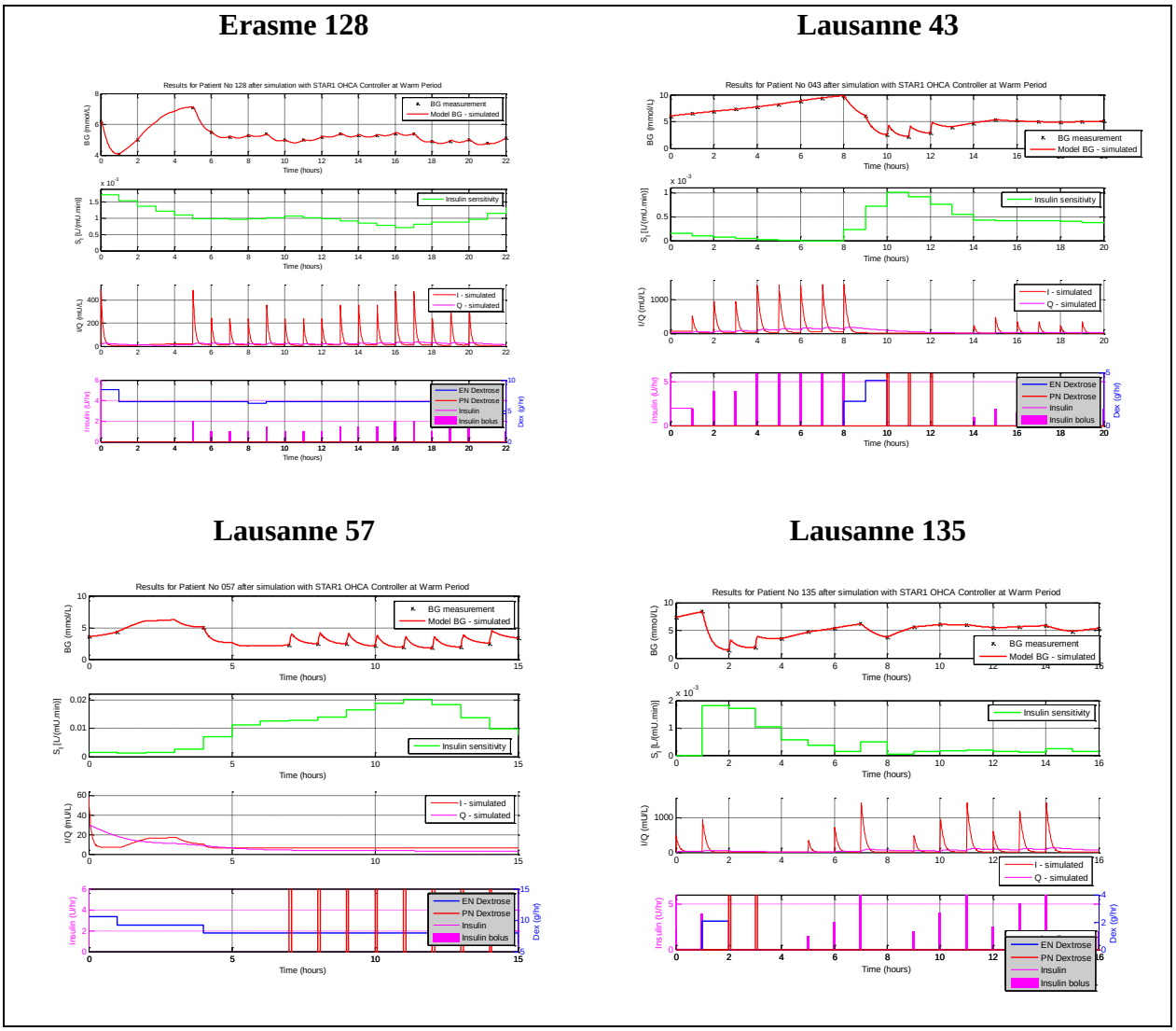

Fig. 9.5: BG control during virtual trial for OHCA patients. These patients had experienced hypoglycemia after simulation with STAR1-OHCA controller during warm period.

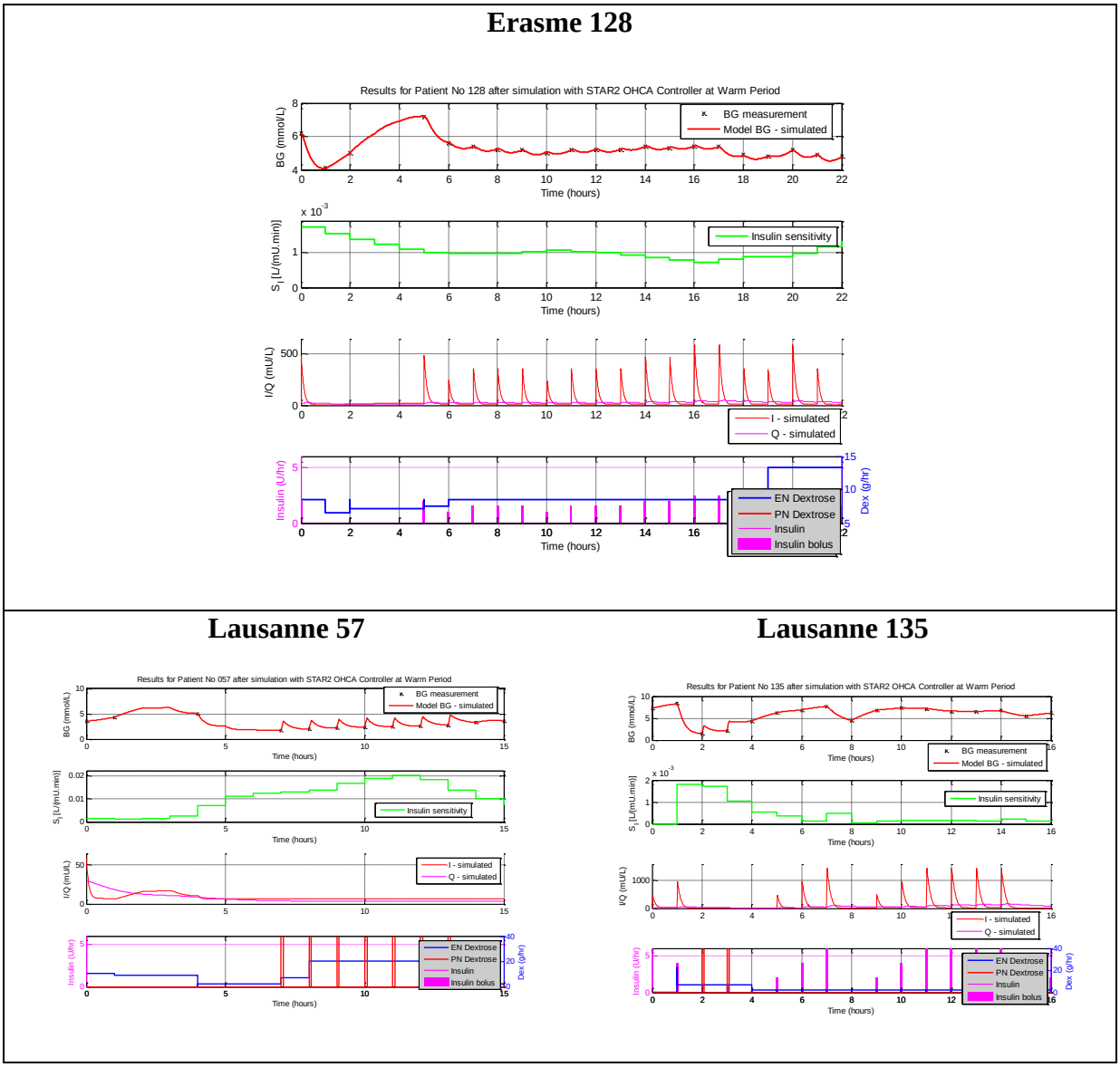

Fig. 9.6: BG control during virtual trial for OHCA patients. These patients had experienced hypoglycemia after simulation with STAR2-OHCA controller during warm period.

In general, these results have suggested that hypoglycemia have occurred for the first 12 hours of warm period. This indicates that the sudden drop of insulin sensitivity (SI) before or in the first few hours of warm period, followed by continued rise which cause hypoglycemia. This result match with the metabolic evolution and variability uniqueness of the OHCA cohort, particularly at transition period between cool and warm (Sah Pri et al., 2014). Thus, it is suggested that these controller should consider adding nutritional intake (Suhaimi et al., 2010) and limit the insulin infusion during this period, in addition to patient-specific adaptive glycaemia control. In specific, for the first 12 hours of rewarming, set the controller to limit maximum insulin dose at 2U or 3U, while adding more dextrose to 20% or 40%.

9.4 Summary

Knowing that this cohort has high metabolic variation, the additional element of stochastic provides better control. With its capability to predict future BG ranges based on current BG level and insulin sensitivity, it allows the controller to select the best possible intervention for performance and safety. Thus, results from virtual trials have shown that a STAR controller, with cohort-specific stochastic models can significantly improve performance.

The performance of STAR-OHCA controller during cool and warm, with both insulin and nutrition inputs is slightly better than the controller with insulin only. By adding nutrition / dextrose input, it will elevate higher BG level, which resulted in more BG percentage within hyperglycaemic band. Even though the percentage of BG within the desired bands would be slightly less, but this approach will improve safety and minimize hypoglycaemic episodes.

STAR-OHCA controller with modulating insulin and nutrition/ dextrose over 30% goal feed appears to be the best controller for OHCA patients based on virtual trial simulation. The controller has performed well in glycaemic management, while minimizing the number of patients who have BG < 2.22 mmol/L to 3 patients only. These patients represent 1.7% of OHCA cohort, which is relatively very low for the controller, compared to any published protocol, which normally average of 8-15% hypoglycaemic episodes.

Chapter 10: Conclusion

The work in this thesis presents the development of a complete system for model-based glycaemic control in cardiac arrest patients. It covers the analysis of cohort data to proof-of-concept virtual trials. A valid physiological system model (ICING-2 model) was employed to determine patient-specific metabolic state. Prediction and control were assisted by a stochastic model of insulin sensitivity variation as part of a STAR framework approach. A clinical simulation framework built around trials on 'virtual patients' provided an environment to optimise protocol development. The finalized system is thus ready for clinical validation and eventual use.

10.1 Introduction

Out-of-Hospital Cardiac Arrest (OHCA) patients often experience hyperglycaemia (Neumar et al., 2008, Taylor et al., 1994). These patients belong to one group who can be highly insulin resistant and variable, particularly on the first two days of stay (Pretty et al., 2012), as well as those who may particularly benefit from glycaemic control (van den Berghe et al., 2001). Therapeutic hypothermia (TH) is often used with OHCA patients to protect against brain injury (Eisenburger et al., 2001, Lee and Asare, 2010), which leads to a lowering of metabolic rate, reduce plasma insulin, induce insulin resistance and alter blood glucose homeostasis (Cueni-Villoz et al., 2011). One of the adverse events associated with hypothermic therapy is a decrease in insulin sensitivity and endogenous insulin secretion (Hayashi, 2009). Recent studies in adults have shown that a 17% - 45% reduction in mortality can be gained if tight glucose regulation is achieved to average levels from 6.0 mmol/L - 7.75 mmol/L (Chase et al., 2008b, Krinsley, 2004, van den Berghe et al., 2001) . However, such a level of tight control is difficult to achieve for the cardiac arrest patients who are already highly insulin resistant and variable (Pretty et al., 2012). The goals for this research is to develop effective and safe tight glycaemic control for OHCA patient, treated with hypothermia.

10.2 OHCA Patient Analysis

The OHCA patient analysis in this research studied the physiology and patient background per-cohort and per-patient, which involve inputs (external insulin and nutrition), output (blood glucose) and metabolic behaviour (insulin sensitivity) during the cool and warm periods. A validated ICING-2 model of the glucose regulatory system from adult critical care was employed for the case of OHCA patients treated with hypothermia, to create virtual patients and analyse metabolic response. Model performance and its accuracy was within variations that would also account for dynamic patient evolution. The model thus provided a first in-silico result for capturing the metabolic dynamics of OHCA patients treated with hypothermia. Its validity and accuracy are equally important, as the results would be used to lead to good glycaemic control for this specific cohort.

Analyses of metabolic evolution assessed the metabolic impact of cardiac arrest and subsequent hypothermic treatment. In particular, the level and variability of insulin sensitivity ($S_{I)}$ over time are presented for the first time and display unique characteristics, specific to this cohort. Generally, S_I level is much lower during hypothermia and consistently increases over time, during both the cool and warm periods. Insulin sensitivity is more variable during the cool period and shows contrasting behavior during the cool-warm transition period between 18 – 30 hours, which indicates that there are major changes in physiology and metabolic conditions at the transition between cool and warm. This is a unique outcome never observed in other critically ill cohorts (Sah Pri et al., 2014).

Analyses of glycemic evolution and outcomes of OHCA patients treated with hypothermia saw consistently decreasing BG over time, but evidenced greater variability, counter to typical trends in the critically ill, where both metrics tend to go down over the first 48 hours (Pretty et al., 2012). This trend can result in more insulin demand during hyperglycemia and a greater risk of hypoglycemia as variability rises, all of which indicates the need for patient-specific approaches in each phase. Thus, the outcome of this studies strongly suggest the need to consider both control of BG level and minimization of BG variability to improve post-resuscitation care of OHCA patients treated with hypothermia.

The impact of exogenous insulin and nutrition modulation during therapeutic hypothermia (TH) on glycaemia outcome has also been studied in this research apart from insulin sensitivity and glycemic analysis. Glycemic control during hypothermia and rewarming has achieved by modulating dextrose more than exogenous insulin. In view of control implications, both exogenous insulin and nutrition show major increases at the transition (18 – 30 hours), while nutrition is delayed or maintained for another 6 hours after transition, and afterward falls steadily by blocks. These trends lead to more difficult control and increased risk in these periods.

A stochastic model to provide insulin sensitivity predictions was developed from a set of insulin sensitivity data for the OHCA cohort. The model provided conservative prediction estimators that resulted in greater coverage than expected from the probability bounds. Modifying the data density estimator by introducing a constant scaling factor showed appropriate coverage was obtained at approximately 10-50% of the original value. Desired prediction performance can be obtained by choosing suitable value of scaling factor for the probability bound. Importantly, cool and warm periods showed very different stochastic behaviour, further reinforcing the need for cohort specific models in this case.

Finally, these studies all show the need for patient-specific glycemic management to ensure good control and safety during treatment. These results could have significant potential clinical impact on the metabolic treatment of these patients. As a result, changes in clinical therapy are suggested to safely treat these patients, particularly as they transition from cool to warm.

10.3 Control Design Requirements and Specifications

The OHCA patient analysis was summarized, where results and analysis from the inputs (external insulin and nutrition), output (blood glucose) and metabolic behaviour (insulin sensitivity) were gathered to observe the overall situation from cool to warm as well as based on time block, 12-hour / 6-hour blocks. This information was used to come up with control design requirement and specifications.

The main objective of glycaemic control design requirements and specifications is to minimize glycaemic variability and hypoglycaemia, while maintaining BG level at desired target levels. This new control definitions and clinical settings have led to a new glycaemic controller development specifically for OHCA patients, treated with hypothermia. The development of a stochastic-based STAR-OHCA controller inherits some methods from the STAR framework used previously, but with modifications to the stochastic models, based on this retrospective OHCA data. The overall approach is thus a new control method for this specific and unique cohort.

10.4 Virtual Trials Validation

Results from virtual trials simulation have shown that stochastic based control such as STAR and STAR-OHCA can provide better glycemic management performance for OHCA patients, in both the cool and warm periods, compared to retrospective data. In contrast, stochastic-based controllers may be less able to ensure safety and minimizing hypoglycemic events during the cool-warm transition period. However, limiting insulin dosing at this time solves this issue.

All controllers are also struggled to minimize hypoglycemic events. These last results show that the performance of stochastic based control have limits, but can provide safe and effective control of this highly unique metabolic situation.

Chapter 11: Future Work

The patient analysis, models development and control methods presented in this thesis provide a framework for glucose control in OHCA patients, treated with hypothermia. These developments open the doors for wider use of tight glucose control as a treatment in highly critical care such as cardiac arrest patients with physiological conditions in cool and warm, as well as in further research opportunities.

11.1 Reviewing Endogenous Insulin Secretion (U_{en}) Parameters for the ICING-2 Model during Cool and Warm

The endogenous insulin secretion model based as a function of BG (Equation 2.45) in the ICING-2 model was successfully developed by Pretty (Chase et al., 2007b). Its upper and lower bounds on pre-hepatic insulin secretion rates of U_{min} (1000 mU/hr) and U_{max} (16000 mU/hr) were defined by (Chase et al., 2010) and (Chase et al., 2008a). The parameter k1 and k2 of this model were determined based on distribution of c-peptide and BG samples obtained from clinical trials studying sepsis in Christchurch Hospital ICU. However, these clinical trials did not consider change of human body temperature will affect the accuracy of U_{en} as well as the ICING-2 model in calculating model-based insulin sensitivity. In particular, there was no separation of samples taken between cool and warm body temperature during the trials.

Thus, it is recommended that a comprehensive study on endogenous insulin secretion should be conducted to validate the endogenous insulin secretion model based as a function of BG (Equation 2.45) in the ICING-2 model particularly during cool and warm. It would be best if these samples are obtained from cardiac arrest patient treated with hypothermia. The outcome results should lead to the ICING-2 model parameter review.

11.2 Clinical Trials for Performance Validation

Controller performance is assessed based on virtual trials. The selection STAR-OHCA controller for tight glycaemic control refers to virtual trial results. However, these results were not validated clinically. Thus, there is a need for validating its control performance against real patients by conducting clinical trials against OHCA patients. While do trial, additional data from patient could be recorded such as blood pressure, and heart bit, as well as sample c-peptide for endogenous insulin secretion analysis during cool and warm.

Additionally, these clinical trials can also validate the accuracy of the ICING-2 model in generating model-based insulin sensitivity during cool and warm. The model performance can be compared between virtual trial and clinical trial results. Thus, the outcome should be able to determine model errors and explore ways of improving these errors separately between cool and warm.

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11.3 Investigation of Stochastic Control based on Sub-Cohort Models

The stochastic models presented in this thesis are created using 180 OHCA patients' intensive care data, which include overall cohort and sub-cohorts. Further observations of metabolic behaviour between patients sub-cohort were analysed in the sub-chapter 4.3.2 and the results showed unique insulin sensitivity variation across each sub-cohort. A summary of sub-cohort results based 6 hour block analysis can also be referred to Appendix 1 and 2. These studies have helped better understanding of metabolic dynamics for each sub-cohort. Thus, advance study on stochastic model and control between sub-cohorts should create the opportunity to improve the stochastic based controller problems in reducing BG variability and minimizing hypoglycaemic event. It is recommended that virtual and clinical trials should be conducted based on sub-cohorts stochastic model in search for better tight glycaemic control (TGC). In addition to that, the outcome of this study should lead to identifying better potential illness biomarker for future OHCA treatment and control such as ROSCs and diabetes.

11.4 Further Improvement of STAR-OHCA Controller

The outcome of research studies have shown that the performance of stochastic based control such as STAR and STAR-OHCA have a limit. Even though these controllers were the best for effective TGC, but it is too risky to implement on highly variable patients, in particular during transition period at warm (Sah Pri et al., 2014). In order to improve the controller, it is suggested that:

i) Combine patient-specific stochastic-based control with targeted control approach, particularly in setting the upper and lower glycaemic limit.

   It is noted that for STAR controller, upper and lower limits are set by the stochastic model whereas for Targeted controller (Chase et al., 2005, Magee, 2007), both limits are set by the end user. With these features, STAR controller is more patient-specific and suitable for optimization control. Targeted controller is suitable for robust control since the controller is good in enforcing BG values within the desired target range. Thus, by combining both features, the controller can behave as patient-specific stochastic-based with targeted glycaemic range control.

ii) Applying separate stochastic model method (Thomas et al., 2014), particularly at the transition period (rewarming phase) during warm conditions.

   The 12-hour block approach can be applied during warm period, where a stochastic model can be developed solely for the first 12 hours of warm period, followed by another stochastic model for the subsequent hours after rewarming.

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Appendix 1

Summary of increasing cohort and per patient median S_I during cool and warm as per 6-hour blocks for all OHCA sub-cohorts

S_I Level analysis [6-hr blocks]	No of Patients	Block 1-2 (C) **(0 - 6 vs. 6 - 12 hr)**				Block 2-3 (C) **(6 - 12 vs. 12 - 18 hr)**				Block 3-4 (C) **(12 - 18 vs. 18 - 24 hr)**				Block 4-5 (C-W) **(18 - 24 vs. 24 - 30 hr)**				Block 5-6 (W) **(24 - 30 vs. 30 - 36 hr)**				Block 6-7 (W) **(30 - 36 vs. 36 - 42 hr)**				Block 7-8 (W) **(36 - 42 vs. 42 - 48 hr)**			
		Cohort analysis		Per-patient analysis		Cohort analysis		Per-patient analysis		Cohort analysis		Per-patient analysis		Cohort analysis		Per-patient analysis		Cohort analysis		Per-patient analysis		Cohort analysis		Per-patient analysis		Cohort analysis		Per-patient analysis	
		% Increase at median	*p-value*	% Increase at median	*p-value*	% Increase at median	*p-value*	% Increase at median	*p-value*	% Increase at median	*p-value*	% Increase at median	*p-value*	% Increase at median	*p-value*	% Increase at median	*p-value*	% Increase at median	*p-value*	% Increase at median	*p-value*	% Increase at median	*p-value*	% Increase at median	*p-value*	% Increase at median	*p-value*	% Increase at median	*p-value*
All OHCA patients	**180**	**30.6**	**<0.01**	**30.4**	**<0.01**	**8.9**	**0.1**	**8.8**	**0.2**	**31.3**	**<0.01**	**42.6**	**0.01**	**57.4**	**<0.01**	**52.1**	**<0.01**	**-1.5**	**0.16**	**-2.2**	**0.6**	**2.8**	**0.22**	**9.3**	**0.4**	**5.0**	**0.3**	**5.3**	**0.6**
Survived Patients	**98**	**33.0**	**<0.01**	**26.4**	**0.05**	**15.5**	**0.01**	**26.6**	**0.3**	**28.1**	**<0.01**	**31.1**	**0.03**	**51.2**	**<0.01**	**46.5**	**<0.01**	**-1.8**	**0.4**	**0.2**	**0.8**	**7.4**	**0.5**	**4.2**	**0.6**	**0.6**	**0.3**	**9.1**	**0.6**
Non-Survived Patients	**82**	**31.3**	**<0.01**	**18.6**	**0.05**	**8.2**	**0.3**	**18.0**	**0.4**	**26.7**	**<0.01**	**31.0**	**0.02**	**76.3**	**<0.01**	**64.3**	**<0.01**	**-2.7**	**0.2**	**4.1**	**0.5**	**-3.4**	**0.4**	**0.5**	**0.4**	**10.6**	**0.6**	**4.6**	**0.9**
Diabetes Patients	**23**	**28.2**	**0.04**	**45.3**	**0.02**	**4.4**	**0.3**	**4.0**	**0.8**	**53.0**	**0.05**	**50.7**	**0.3**	**29.0**	**<0.01**	**22.2**	**<0.01**	**-25.3**	**0.1**	**-6.0**	**0.7**	**17.2**	**0.3**	**22.4**	**0.6**	**10.0**	**0.3**	**8.6**	**0.8**
Non-Diabetes Patients	**157**	**31.2**	**<0.01**	**30.3**	**0.02**	**10.3**	**0.02**	**7.0**	**0.2**	**27.3**	**<0.01**	**44.1**	**0.03**	**64.7**	**<0.01**	**63.9**	**<0.01**	**-0.4**	**0.4**	**-4.2**	**0.7**	**5.3**	**0.3**	**9.6**	**0.5**	**2.6**	**0.4**	**8.4**	**0.7**
Male Patients	**143**	**36.6**	**<0.01**	**45.6**	**<0.01**	**6.3**	**0.1**	**-0.5**	**0.4**	**25.2**	**<0.01**	**32.0**	**0.05**	**61.5**	**<0.01**	**55.8**	**<0.01**	**-3.2**	**0.2**	**-4.0**	**0.6**	**7.0**	**0.2**	**8.3**	**0.4**	**3.2**	**0.1**	**11.3**	**0.5**
Female Patients	**37**	**1.0**	**0.6**	**7.6**	**0.5**	**46.0**	**0.03**	**13.6**	**0.4**	**47.0**	**<0.01**	**79.0**	**0.1**	**45.0**	**<0.01**	**55.6**	**0.07**	**3.6**	**0.8**	**-0.4**	**0.9**	**-1.3**	**0.7**	**10.3**	**0.8**	**-9.6**	**0.4**	**-5.5**	**0.9**
ROSC < 15 mins	**63**	**36.0**	**<0.01**	**52.0**	**0.06**	**10.7**	**0.02**	**18.6**	**0.2**	**43.8**	**<0.01**	**26.9**	**0.08**	**43.6**	**<0.01**	**40.1**	**<0.01**	**-5.9**	**0.06**	**-6.0**	**0.6**	**-1.7**	**0.8**	**-0.4**	**0.9**	**4.0**	**0.3**	**12.8**	**0.5**
ROSC < 30 mins	**89**	**30.0**	**<0.01**	**28.2**	**0.02**	**9.7**	**0.2**	**24.4**	**0.5**	**13.0**	**0.1**	**17.0**	**0.1**	**72.0**	**<0.01**	**78.5**	**<0.01**	**0.9**	**1.0**	**3.7**	**0/9**	**4.4**	**0.2**	**16.8**	**0.3**	**7.2**	**0.4**	**-0.1**	**0.9**
ROSC > 30 mins	**28**	**4.2**	**0.6**	**25.0**	**0.2**	**14.8**	**0.3**	**30.0**	**0.6**	**22.4**	**0.1**	**-14.0**	**0.3**	**57.5**	**<0.01**	**39.0**	**<0.01**	**-6.6**	**0.4**	**24.0**	**0.7**	**26.0**	**0.2**	**-39.0**	**0.6**	**3.0**	**0.7**	**-2.5**	**1.0**

P-values are calculated using Wilcoxon rank-sum test

Appendix 2

Summary of reductions in the interquartile range and median S_I per patient range of hour-to-hour percentage S_I change over time during cool and warm after as per 6-hour blocks of data for all OHCA sub-cohorts

S_I variability analysis [6-hr blocks]	No of Patients	Block 1-2 (C) **(0 - 6 vs. 6 - 12 hr)**				Block 2-3 (C) **(6 - 12 vs. 12 - 18 hr)**				Block 3-4 (C) **(12 - 18 vs. 18 - 24 hr)**				Block 4-5 (C-W) **(18 - 24 vs. 24 - 30 hr)**				Block 5-6 (W) **(24 - 30 vs. 30 - 36 hr)**				Block 6-7 (W) **(30 - 36 vs. 36 - 42 hr)**				Block 7-8 (W) **(36 - 42 vs. 42 - 48 hr)**			
		Cohort analysis		Per-patient analysis		Cohort analysis		Per-patient analysis		Cohort analysis		Per-patient analysis		Cohort analysis		Per-patient analysis		Cohort analysis		Per-patient analysis		Cohort analysis		Per-patient analysis		Cohort analysis		Per-patient analysis	
		% Reduction of IQR	*p-value*	% Decrease at median	*p-value*	% Reduction of IQR	*p-value*	% Decrease at median	*p-value*	% Reduction of IQR	*p-value*	% Decrease at median	*p-value*	% Reduction of IQR	*p-value*	% Decrease at median	*p-value*	% Reduction of IQR	*p-value*	% Decrease at median	*p-value*	% Reduction of IQR	*p-value*	% Decrease at median	*p-value*	% Reduction of IQR	*p-value*	% Decrease at median	*p-value*
All OHCA patients	**180**	**23.4**	**0.02**	**36.3**	**<0.01**	**15.8**	**0.9**	**13.5**	**0.1**	**11.7**	**0.63**	**26.8**	**0.03**	**9.4**	**0.6**	**7.8**	**0.8**	**-8.5**	**0.5**	**-13.5**	**0.8**	**13.7**	**0.4**	**4.1**	**0.7**	**10.7**	**0.04**	**19.1**	**0.03**
Survived Patients	**98**	**21.6**	**0.05**	**26.5**	**0.03**	**13.3**	**0.03**	**14.5**	**0.3**	**22.4**	**0.15**	**28.0**	**0.05**	**9.4**	**<0.01**	**8.9**	**0.06**	**-6.4**	**<0.01**	**-12.8**	**0.08**	**15.1**	**0.6**	**16.4**	**0.43**	**17.2**	**0.9**	**9.4**	**0.2**
Non-Survived Patients	**82**	**28.0**	**0.9**	**45.2**	**0.06**	**21.5**	**0.01**	**16.4**	**0.2**	**13.6**	**0.4**	**21.6**	**0.2**	**25.0**	**<0.01**	**24.2**	**0.03**	**-15.7**	**<0.01**	**-17.8**	**0.09**	**15.5**	**0.6**	**10.1**	**0.7**	**2.8**	**0.02**	**24.6**	**0.06**
Diabetes Patients	**23**	**8.0**	**0.5**	**-11.4**	**0.7**	**35.0**	**0.5**	**35.7**	**0.4**	**8.0**	**0.04**	**35.6**	**0.2**	**-28.3**	**0.1**	**-125.0**	**0.08**	**-13.5**	**0.3**	**22.2**	**0.5**	**0.7**	**0.9**	**20.7**	**0.5**	**44.6**	**0.3**	**38.1**	**0.05**
Non-Diabetes Patients	**157**	**25.0**	**0.02**	**42.6**	**<0.01**	**14.5**	**0.7**	**8.8**	**0.1**	**9.6**	**0.9**	**28.0**	**0.06**	**14.3**	**<0.01**	**9.9**	**0.03**	**-7.0**	**<0.01**	**-7.4**	**0.08**	**13.4**	**0.5**	**-2.6**	**0.8**	**5.5**	**0.07**	**16.3**	**0.1**
Male Patients	**143**	**21.3**	**0.04**	**40.0**	**<0.01**	**14.2**	**0.7**	**17.0**	**0.08**	**15.3**	**0.6**	**24.0**	**0.04**	**4.7**	**<0.01**	**3.6**	**0.06**	**-8.8**	**<0.01**	**-20.0**	**0.8**	**14.7**	**0.6**	**4.0**	**0.9**	**8.5**	**0.08**	**21.7**	**0.03**
Female Patients	**37**	**28.7**	**0.5**	**15.2**	**0.8**	**27.5**	**0.6**	**15.0**	**0.7**	**-1.3**	**0.9**	**22.4**	**0.4**	**19.0**	**<0.01**	**20.0**	**0.03**	**-7.0**	**0.5**	**10.5**	**0.7**	**14.0**	**0.5**	**20.7**	**0.3**	**14.1**	**0.2**	**5.5**	**0.8**
ROSC < 15 mins	**63**	**17.4**	**0.7**	**33.8**	**0.04**	**16.0**	**0.8**	**18.2**	**0.6**	**26.3**	**0.8**	**27.8**	**0.1**	**-48.1**	**<0.01**	**-20.8**	**0.05**	**13.5**	**0.2**	**5.7**	**0.2**	**-4.7**	**0.6**	**-11.9**	**0.7**	**30.0**	**0.6**	**26.4**	**0.08**
ROSC < 30 mins	**89**	**7.0**	**<0.01**	**29.2**	**0.02**	**23.5**	**0.9**	**15.0**	**0.1**	**16.0**	**0.4**	**28.6**	**0.1**	**24.1**	**<0.01**	**10.6**	**0.02**	**-20.8**	**<0.01**	**-20.0**	**0.07**	**20.0**	**0.7**	**15.4**	**0.6**	**10.0**	**0.01**	**15.9**	**0.2**
ROSC > 30 mins	**28**	**56.4**	**0.5**	**45.0**	**0.04**	**5.5**	**0.5**	**43.7**	**0.4**	**-17.5**	**0.6**	**14.1**	**0.5**	**40.2**	**<0.01**	**24.6**	**0.04**	**-30.7**	**<0.01**	**-18.5**	**0.07**	**14.3**	**0.7**	**16.3**	**0.6**	**-34.4**	**0.08**	**-7.2**	**0.8**

P-values are calculated using Kolmogorov-Smirnov test