Continuous Glucose Monitoring for Optimising Glycaemic Performance in Individuals without Diabetes

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“Only those who risk going too far can possibly find out how far one can go”

T.S. Eliot

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Nomenclature

Acronyms and abbreviations

ADA – American Diabetes Association
APACHE – Acute Physiological and Chronic Health Evaluation
BG – Blood Glucose
BPM – Beats per Minute
BSA – Body Surface Area
CDF - Cumulative Distribution Function
CGM – Continuous Glucose Monitoring
CHO – Carbohydrate
CT – Computer Tomography
EGP – Endogenous Glucose Production
EX – Exhaustion
FB – Fluid Balance
FBG – Fasting Blood Glucose
FIS – Fasting Insulin Secretion
FPI – Fasting Plasma Insulin
GC – Glycaemic Control
GLUT4 – Glucose Transporter Type 4
HR – Heart Rate
ICING - Intensive Control Insulin-Nutrition-Glucose
ICU – Intensive Care Unit
IQR – Interquartile Range
MARD – Mean Absolute Relative Difference
MC – Monte Carlo
OGTT – Oral Glucose Tolerance Test
PPG – Postprandial Glucose
PPGR – Postprandial Glucose Response
PSS – Poor Sensor Signal
RS – Replace Sensor
Sensor failure modes
    AF – Adhesive failure
    BL - Bleeding
    BP – Bent Pins
    CF – Crimped Filaments
    IC – Inconclusive
SG – Sensor Glucose
SI – Insulin Sensitivity
SIRS – Systemic Inflammatory Response Syndrome
STAR – Stochastic TARgeted
RCT – Randomised Control Trial
T1DM – individuals with type 1 diabetes
T2DM – individuals with type 2 diabetes
USDA - United States Department of Agriculture
VO2max – Maximal Oxygen Uptake

Abstract

Continuous glucose monitoring (CGM) devices are becoming ubiquitous in the of care individuals with type 1 and type 2 diabetes. However, to a lesser extent, these devices could have further benefit in optimising blood glucose (BG) levels and related aspects in individuals without diabetes in physiologically stressful situations. This research centres on the metabolic effects of systemic inflammation and the use of these emerging glucose sensors to detect metabolic changes for use in computer aided monitoring and decision support. Specifically, this work investigates the use of CGM sensors in critically ill patients and endurance athletes to improve performance of glycaemic control and optimise nutrition delivery.

Critically ill patients often experience high levels of insulin resistance and stress-induced hyperglycaemia, which can negatively impact outcomes. Studies have shown glycaemic control (GC) can reduce intensive care unit (ICU) patient mortality. However, there is a significant difficulty in creating protocols that produce GC without excessive hypoglycaemia. Thus, continuous glucose monitors with their 2-5 minute measurement provide the opportunity to better monitor BG levels and thus aviod hypoglycaemia.

Recently, a CGM device specifically designed for the ICU became available, The Sentrino (Medtronic, MiniMed, Northridge, California). Hence, a large scale study was designed for implementation in Christchurch Hospital mixed medical ICU to gather further information about the feasibility of CGM in ICU. First, the performance of the Sentrino CGM system in a mixed medical ICU environment was analysed. CGM and BG data were gathered from 13 patients recruited to Phase 1 of the trial. The Sentrino device achieved a mean absolute relative difference (MARD) of 14.7%. Overall, the Sentrino performance was acceptable, but required calibration measurements every 4 hours on average.

Hence, questions still remain if this CGM system can reduce the time and workload cost of glycaemic control.

Phase IIA was an observational study of the performance and integration of hyper- and hypo-glycaemic guardrail alarms with an existing, proven GC protocol. This study analysed sensor glucose (SG) and BG data, and alarm data from 8 patients recruited to this phase of the trial. Overall, sensor and alarm performance was good, only 32/93 total alarms required calibration due to a significant difference between SG and BG. However, there was a high rate of false positive alarms, 27/29 hypoglycaemic alarms were false positives.

An analysis was undertaken to better understand the impact of sepsis, oedema, and some medications on CGM results, as well as to assess the nurse compliance and feedback to gain insight of the clinical impact of using CGM to guide GC. This analysis used data from 21 patients in Phase I and Phase IIA. Approximately 50% of all enrolled subjects were severely oedematous and/or septic by design. For any CGM to be successful in reducing nurse workload and increasing patient safety, the following recommendations are made:

- Avoid severely oedematous patients where fluid is likely to leak from ruptured skin
- Waterproof CGM sensors
- Reconsider insertion technique to lessen the risk of capillary damage
- Wireless transmission between sensor and monitor unit for ease of patient mobility

Before CGM can be used to guide glycaemic control protocols, the impact of suboptimal accuracy resulting from CGM error must first be characterised. The impact of CGM sensor error on the Stochastic TARgeted (STAR) GC protocol was then investigated using the simple CGM error model

generated from the Sentrino data. Currently, the sensor technology trialled here is not accurate enough and if it was used to guide glycaemic control there would be a large increase in hypoglycaemic events with a median time below 4.4 mmol/L of 2.25%. In addition, the STAR protocol achieves very good and safe control already. Hence, improving the "safety" of the protocol is difficult with only 1.35% time below 4.4 mmol/L. Potentially, a less successful glycaemic control protocol would display the greater benefit of the Sentrino guardrails and CGM in general.

The glucose metabolism of athletes is not fully defined in current literature and nor are the effects of exercise on the overall glucose metabolism of athletes. There are only a few studies that investigate how metabolic parameters, such as endogenous glucose production change with exercise, and none that attempt to quantify endogenous insulin secretion or sensitivity during exercise. Additionally, an individual's tolerance of carbohydrate is highly variable and is related to a number of factors including age and genetics. CGM devices have the potential to personalise nutrition based on glucose response. Such research using continuous glucose monitors has not been undertaken in athletic subjects before.

In a study of 10 sub-elite athletes, it was found hyperglycaemia persists >60 mins post exercise after race simulation exercise test. Plasma insulin and insulin secretion both peaked 60 mins post intense exercise to median cohort values of 256 pmol/L and 1150 pmol/min, respectively. These median peak values of plasma insulin and insulin secretion were approximately 5 and 9 times higher than the median fasting levels in this cohort, respectively. In general, this response is greater and more prolonged than reported in previous studies. The most likely reason for this outcome is subjects received two glucose boluses, one during and immediately one post exercise, as per recommended nutritional guidelines for competition while in other studies athletes remained fasted.

From the same 10 athletes, a simple 1-dimensional model of endogenous insulin secretion was created, with an $R^2 = 0.53$ and a glucose coefficient (a_1) of 2559 mU.l/mmol.hr. The proposed model of endogenous insulin secretion, based on physiological measurements, provides a simple estimate of insulin secretion with comparable physiological parameters to existing literature.

The successful Intensive Control Insulin-Nutrition-Glucose model was adapted to allow insulin sensitivity to be identified during and after exercise in a well-trained cohort. The model appeared to be best able to identify insulin sensitivity during steady state periods of exercise as insulin sensitivity (SI) trends in these periods match known physiology. However, when boluses were delivered non-physiological jumps in SI occur as the model does not capture the highly patient-specific transient effects of glucose boluses, and non-constant rates of endogenous glucose production and/or non-insulin mediated glucose uptake.

The performance of CGM during exercise was investigated by comparing reference measurements to CGM data collected form the 10 subjects during the exercise test. During steady state exercise, all sensors performed better than results reported for diabetes cohorts with median MARD of 9.7%, 9.6% and 11.1% for each sensor analysed. Sensors agreed very well with each other with zero-lag cross-correlation coefficients between 0.88 and 0.97 for the different sensor pairings. Overall, these results demonstrate the good accuracy and performance of CGM devices in active athletes while exercising, confirming the applicability of these monitors for use in this new domain.

When the sensor glucose profiles of 10 athletes over a 6 day monitoring period 4/10 athletes studied spent more than 70% of the total monitoring time above 6 mmol/L even with the 2 hour period after meals removed. Only one participant spent substantial time below 4 mmol/L and this was largely due

to a significantly lower overall calorie intake compared to recommendations. This study provides a unique insight in to the day to day glucose levels of athletes that could only be achieved through the use of CGM devices highlighting the need for further investigation on the recommend diets of athletes to better determine the causes and impact of the hyperglycaemia seen on health and performance.

Overall this research delineates the potential and pitfalls of using CGM to optimise blood glucose levels in ICU and athletes. In particular, it highlights areas that need to be improved before they can be relied upon to guide GC protocols in ICU. In addition, the ability to examine blood glucose trends over a longer period highlighted several aspects of the athlete metabolism that are contradictory to current literature. The results presented are promising for these devices in both fields. However, improvement in CGM sensor technology and further research is needed before CGM can be used to optimise glycaemic performance in ICU patients and athletes.

Le résumé

Les dispositifs de monitoring continu de la glycémie (CGM) deviennent omniprésents chez les personnes atteintes du diabète de type 1 et de type 2. Cependant, ces dispositifs pourraient être avantageusement utiliser pour optimiser les niveaux de glucose dans le sang (BG) chez des individus sans diabète et dans des situations physiologiquement stressantes. Cette recherche porte sur les effets métaboliques de l'inflammation systémique et l'utilisation de ces capteurs de glucose émergents pour détecter les changements métaboliques pour une utilisation dans la surveillance assistée par ordinateur et l'aide à la décision. Plus précisément, ce travail étudie l'utilisation des capteurs CGM chez les patients critiques et les athlètes afin d'améliorer les performances du contrôle glycémique et d'optimiser l'apport nutritionnel.

Les patients critiques présentent souvent des niveaux élevés de résistance à l'insuline et d'hyperglycémie induite par le stress, ce qui peut avoir un impact négatif sur les résultats cliniques. Des études ont montré que le contrôle glycémique (GC) peut réduire la mortalité des patients des soins intensifs (ICU). Cependant, il existe une difficulté importante dans la création de protocoles qui produisent un GC sans hypoglycémie excessive. Ainsi, les dispositifs de monitoring continu du glucose avec leur mesure toutes les 2-5 minutes offrent la possibilité de mieux surveiller les niveaux de BG et donc d'éviter l'hypoglycémie.

Récemment, un dispositif CGM spécialement conçu pour les soins intensifs , le Sentrino (Medtronic, MiniMed, Northridge, Californie), est devenu disponible. Une étude à grande échelle a été développée à dans une unité médicale mixte de soins intensifs de l'hôpital de Christchurch pour recueillir de plus amples informations sur la faisabilité de l’utilisation de CGM aux soins intensifs. Tout d'abord, nous avons analysé les performances du système Sentrino CGM aux soins intensifs. Les données de CGM et

de BG ont été recueillies auprès de 13 patients recrutés lors de la phase 1 de l'essai. Le dispositif Sentrino a obtenu une moyenne absolue des différences relatives (MARD) de 14,7%. Dans l'ensemble, la performance du Sentrino était acceptable, mais il exigeait des mesures d'étalonnage toutes les 4 heures en moyenne. Par conséquent, des questions demeurent pour savoir si ce système CGM peut réduire le temps et le coût de la charge de travail du contrôle glycémique.

La phase IIA était une étude observationnelle de la performance et de l'intégration des alarmes hyper-hypo-glycémiques avec un protocole existant et vérifié de GC. Cette étude a analysé les données des capteurs de glucose (SG) et du BG, et les données d'alarme de 8 patients recrutés pour cette cette phase de l'essai. Dans l'ensemble, les performances des capteurs et des alarmes étaient bonnes, seules 32/93 alarmes ont nécessité un étalonnage en raison d'une différence significative entre SG et BG. Cependant, il y avait un taux élevé de faux positifs avec 27/29 alarmes hypoglycémiques qui étaient des faux positifs.

Une analyse a été entreprise afin de mieux comprendre l'impact du sepsis, de l'œdème et de certains médicaments sur les résultats des CGM, ainsi que pour évaluer la compliance des infirmières pour mieux comprendre l'impact clinique de l'utilisation des CGM pour guider le GC. Cette analyse a utilisé les données de 21 patients des Phase I et Phase IIA. Environ 50% de tous les sujets étaient sévèrement œdémateux et / ou septiques. Pour que les CGM puissent permettre de réduire la charge de travail des infirmières et augmenter la sécurité des patients, les recommandations suivantes sont faites:

- Évitez les patients sévèrement œdémateux où du fluide risque de fuir en cas de rupture de la peau
- Capteurs CGM étanches
- Reconsidérer la technique d'insertion pour diminuer le risque de dommages capillaires

- Transmission sans fil entre capteur et unité de surveillance pour faciliter la mobilité des patients

Avant que les CGM puissent être utilisés pour guider les protocoles de contrôle glycémique, l'impact de la précision sous-optimale résultant de l'erreur des CGM doit tout d'abord être caractérisé. L'impact de l'erreur du capteur CGM sur le protocole de Stochastic TARgeted (STAR) GC a ensuite été étudié en utilisant le modèle d'erreur simple généré à partir des données Sentrino. Actuellement, la technologie des capteurs testés ici n'est pas suffisamment précise et si elle était utilisée pour guider le contrôle glycémique, il y aurait une forte augmentation des hypoglycémies avec un temps médian inférieur à 4,4 mmol/L de 2,25%. De plus, le protocole STAR permet déjà un contrôle très efficace et sûr. Par conséquent, l'amélioration de la «sécurité» du protocole est difficile avec seulement 1,35% de temps en dessous de 4,4 mmol/L. Potentiellement, un protocole de contrôle glycémique moins efficace afficherait un plus grand bénéfice de l’utilisation du Sentrino et des CGM en général.

Le métabolisme du glucose des athlètes ainsi que les effets de l'exercice sur ce dernier ne sont pas parfaitement caractérisés dans la littérature. Il existe seulement quelques études qui étudient comment les paramètres métaboliques, tels que la production endogène de glucose changent avec l'exercice, et aucune n’essaye de quantifier la sécrétion endogène d’insuline ou la sensibilité à l’insuline pendant l'exercice. En outre, la tolérance d'un individu à l'égard des glucides est très variable et est liée à un certain nombre de facteurs, tels que l'âge et la génétique. Les dispositifs de CGM offrent la possibilité de personnaliser la nutrition en se basant sur la réponse glycémique. Une telle recherche utilisant des dispositifs de monitoring continus du glucosechez les athlètes n'a jamais été entreprise auparavant.

Dans une étude sur 10 athlètes, il a été constaté que l'hyperglycémie persiste> 60 minutes après l'exercice après le test de simulation de course. L'insuline plasmatique et la sécrétion d'insuline ont tous deux atteint un maximum 60 minutes après un exercice intensif, avec des valeurs médianes de cohorte de 256 pmol/L et 1150 pmol/min, respectivement. Ces valeurs médianes du pic de l'insuline plasmatique et de la sécrétion d'insuline étaient respectivement environ 5 et 9 fois plus élevées que les niveaux médians à jeun dans cette cohorte. En général, cette réponse est plus grande et plus longue que celle rapportée dans des études antérieures. La raison la plus probable de ce résultat est que les sujets ont reçu deux bolus, un pendant et un immédiatement après l'exercice, selon les directives nutritionnelles recommandées pour la compétition tandis que dans d'autres études les athlètes sont restés à jeun.

A partir de ces mêmes 10 athlètes, nous avons créé un modèle simple unidimensionnel de la sécrétion d'insuline endogène, avec un R2 = 0,53 et un coefficient de glucose (a1) de 2559 mU.l/mmol.hr. Le modèle proposé de sécrétion d'insuline endogène, basé sur des mesures physiologiques, fournit une estimation simple de la sécrétion d'insuline avec des paramètres physiologiques comparables à la littérature existante.

Le modèle de contrôle intensif d'insuline-nutrition-glucose a été adapté pour permettre l'identification de la sensibilité à l'insuline pendant et après l'effort. Le modèle semblait être le plus apte à identifier la sensibilité à l'insuline pendant les périodes d'exercice à l'état d'équilibre, car les tendances de la sensibilité à l'insuline (SI) pendant ces périodes correspondent à une physiologie connue. Cependant, lorsque des bolus ont été administrés, des sauts de SI non physiologiques apparaissent car le modèle ne capture pas les effets transitoires hautement patient-spécifiques des bolus de glucose et des taux non constants de production de glucose endogène et/ou d'absorption de glucose non insulinodéprimée.

La performance des CGM pendant l'exercice a été étudiée en comparant les mesures de référence aux données de CGM recueillies sur 10 sujets pendant le test d'exercice. Au cours de l'exercice en régime permanent, tous les capteurs ont obtenu de meilleurs résultats que ceux rapportés pour les cohortes de diabètes avec une DMAR médiane de 9,7%, 9,6% et 11,1% pour chaque capteur analysé. Globalement, ces résultats démontrent la bonne précision et la performance des dispositifs CGM chez les athlètes actifs pendant l'exercice, ce qui confirme l'applicabilité de ces moniteurs pour l'utilisation dans ce nouveau domaine.

Les profils de glucose des capteurs des 10 athlètes sur une période de surveillance de 6 jours montrent que 4/10 athlètes étudiés ont passé plus de 70% du temps de surveillance totale au-dessus de 6 mmol/L même en enlevant la période de 2 heures après les repas. Un seul participant a passé beaucoup de temps en dessous de 4 mmol/L, ce qui s'explique en grande partie par un apport calorique global nettement inférieur aux recommandations. Cette étude fournit un aperçu unique sur l'évolution quotidienne des niveaux de glucose des athlètes qui ne pouvait être obtenue sans l'utilisation de dispositifs CGM. Elle souligne également la nécessité d'une analyse plus approfondie des régimes recommandé aux athlètes pour mieux déterminer les causes et l'impact de l'hyperglycémie sur leur santé et leur rendement.

En conclusion, cette recherche étudie les avantages et les inconvénients de l'utilisation de CGM pour optimiser la glycémie chez les patients critiques et chez les athlètes. En particulier, elle met en évidence les domaines qui doivent être améliorés avant que les CGM ne puissent être utilisés pour guider les protocoles de GC auxsoins intensifs. De plus, la capacité d'examiner les tendances de la glycémie sur une période plus longue met en évidence plusieurs aspects du métabolisme des athlètes qui sont en contradiction avec la littérature actuelle. Les résultats présentés dans ce travail sont prometteurs dans ces deux cohortes de patients extrêmes. Toutefois, l'amélioration de la technologie

des capteurs CGM et de nouvelles recherches sont nécessaires avant que les CGM ne puissent être utilisés pour optimiser la performance glycémique chez les patients critiques et les athlètes.

Chapter 1. Introduction

Continuous glucose monitoring (CGM) devices are becoming ubiquitous in the care of type 1 and type 2 diabetes (T1DM and T2DM) (Breton et al., 2008, Klonoff, 2005a, Klonoff, 2005b). However, to a lesser extent, these devices could have further benefit in optimising blood glucose (BG) levels and related aspects in individuals without diabetes in physiologically stressful situations. This research centres on the metabolic effects of systemic inflammation and the use of these emerging glucose sensors to detect these changes for use in computer aided monitoring and decision support. It thus seeks to broaden approaches to metabolic care and management through the model-based analysis of this metabolic impact. Specifically, this work investigates the use of CGM sensors in critically ill patients and endurance athletes to improve performance of glycaemic control and optimise nutrition delivery.

Critically ill patients can behave similarly to individuals with diabetes resulting in high blood glucose levels, hyperglycaemia, and insulin resistance due the bodies stress response to trauma or illness (Capes et al., 2000, Finney et al., 2003, Krinsley, 2003, McCowen et al., 2001, Mizock, 2001, Umpierrez et al., 2002, Van den Berghe et al., 2001). This metabolic response can negatively impact outcomes and increase the length of patient stay in the intensive care unit (ICU) (Capes et al., 2000, Finney et al., 2003, Krinsley, 2003, Bistrian, 2001, Van den Berghe et al., 2001). Studies have shown that controlling blood glucose levels to a more normal range can reduce ICU patient mortality (Van den Berghe et al., 2001, Van den Berghe et al., 2006, Krinsley, 2004, Chase et al., 2008b). However, there is difficulty in creating protocols that produce good control of glucose levels without excessive low blood glucose, hypoglycaemia, and a significant increase in nursing workload. Thus, continuous glucose monitors with their 2-5 minute measurement provide the opportunity to better monitor BG levels so hypoglycaemia can be avoided.

Typically in critical care situations, BG is measured 1-4 hourly and more frequently only if the levels are hypoglycaemic or nearly so. More frequent measurement is uncommon due to the clinical effort required in a very busy clinical environment (Mackenzie et al., 2005, Chase et al., 2008a, Carayon et al., 2005). The result can be extremely variable glycaemic control, especially with longer measurement intervals (Chase et al., 2011, Lonergan et al., 2006b). Thus, CGM may allow BG levels to be managed more successfully, while minimizing glycaemic variability and reducing nurse work load (Krinsley, 2008, Egi et al., 2006, Signal et al., 2010).

There have been relatively few successful investigations of CGM devices in critical care (Goldberg et al., 2004, Holzinger et al., 2010, Signal et al., 2013). In particular, one set of glycaemic control (GC) trials using CGM technology was not particularly successful due, in part, to significant sensor noise and error (Chee et al., 2003a, Chee et al., 2003b). Another more recent observational study highlighted the potential of CGM in ICU patients, but concluded that further understanding of factors that alter CGM performance is required before glycaemic control can be realized (Signal et al., 2013). Hence, they have not been successfully applied in critical care outside of use in monitoring glucose levels and to reduce hypoglycaemia in adults and neonates (Harris et al., 2010, Holzinger et al., 2010). There are a number of reasons for this that are addressed in this work. More specifically, they are not part of standard care and not use outside of research at this time.

Critical illness, some forms of diabetes, and athletic activity all share a common factor of systemic inflammation due to their condition or induced by strenuous effort. Hyperglycaemia is an inflammatory marker (Collier et al., 2008) and blood glucose variability is a known risk factor in T2DM (Monnier et al., 2006, Brownlee et al., 2006). The immune system also fails to function optimally in the presence of high blood glucose levels (Sanchez et al., 1973, Marik et al., 2004, Jeandidier et al., 2006, Turina et al., 2005, Kijak et al., 1964). For example, a single 100g dose of glucose and resulting

hyperglycaemia can significantly impair the immune system for more than 5 hours (Sanchez et al., 1973, Kijak et al., 1964). Normoglycaemia is, thus, important for general health and well-being, and thus potentially equally or more important to a competitive athlete. Hence, well controlled glucose level through correct nutritional inputs during training, racing and recovery could play a critical role in athletic results.

Studies comparing the metabolic and hormonal response to exercise between trained and untrained normal glucose tolerant individuals have found glucose, glycerol and free fatty acid concentrations are higher but lactate, pyruvate and alanine were lower in trained individuals, compared to untrained individuals (Kjaer et al., 1986, Bloom et al., 1976). Cortisol levels were also higher in trained individuals (Bloom et al., 1976). In addition, insulin secretion is diminished in well-trained individuals due to increased insulin sensitivity (Lohmann et al., 1978). Together, these results suggest there is significant adaptation to the metabolism of well-trained individuals. However, only a few studies investigate how metabolic parameters such as endogenous glucose production (EGP) or endogenous insulin secretion, change with exercise (Rossi et al., 2010, Levitan et al., 2004, American Diabetes, 2010, Kretowski et al., 2015, Gallwitz, 2009, Jee et al., 2005). Further, none attempt to quantify insulin sensitivity, the metabolic exchange between insulin and glucose uptake for storage or energy, during exercise.

CGM can thus potentially be employed to enable optimal nutrition delivery using a similar model-based approach as has been successfully used in critically ill patients and individuals with diabetes (Lin et al., 2011, Wong et al., 2008a, Chase et al., 2006, Bergman et al., 1981, Hovorka et al., 2008, Mari et al., 1997, Wong et al., 2008b, Bergman et al., 1979, Cobelli et al., 1984). CGM also has the potential to aid an athlete's decision making on when and what to consume during different stages of training, racing and recovery, by providing information on BG levels in a minimally-invasive manner. Using this data, this work extends proven metabolic modelling (Lin et al., 2011) and CGM research in critical

illness (Signal et al., 2013) into the sporting domain to see if model-based inulin sensitivity can capture effort and recovery in endurance athletics. Such research, particularly using continuous glucose monitors, has not been undertaken in athletic subjects before. However, the ability to have real time knowledge of blood variables, such as blood glucose, is noted as the "future' of sports technology (Gizmag Team, 2007, Metz, 2014).

This research has a twofold pathway. The first investigates, develops, and validates methods and algorithms to combine CGM data with validated models of patient physiology in intensive care to provide tighter, safer glycaemic control with reduced clinical effort. The second pathway reworks these existing metabolic models to create a more general metabolic modelling system and approach, and, in doing so, to more specifically produce 'athlete like' insulin sensitivity models. These models could then be used to investigate, simulate and validate optimal nutrition delivery based on CGM data for athletes during training, recovery and racing.

Main Hypothesis: Systemic inflammation in extreme cases (effort and illness) causes metabolic impact and this impact can be captured and modulated via metabolic models coupled with high-resolution BG data. The goal is to determine if that the benefits of a fundamental model of metabolic dynamics can be translated from the ICU to the playing field.

1.1 Preface

This thesis is presented in two parts: Part I investigates the use of CGM in critically ill adults, in the ICU and, Part II investigates the use of CGM in competitive athletes. The chapters in this thesis are arranged as follows:

Part I – CGM in ICU

Chapter 2 provides an in-depth background on stress-induced hyperglycaemia in intensive care patients and an overview over this is currently managed, before the way CGM can potentially optimise blood glucose is control methods in ICU is discussed.

Chapter 3 presents the result of Phase I of the Sentrino trial, a trial designed to test the latest CGM device designed for the ICU environment. Phase I investigated the performance of the device in an observational trial of 13 patients in Christchurch ICU.

Chapter 4 presents the results of Phase IIA of the Sentrino trial. Phase IIA investigated the performance of hyper- and hypo- glycaemic alarms in 8 patients in Christchurch ICU.

Chapter 5 discusses the factors that influence the success of CGM in the ICU and important issues that must be addressed before CGM can be relied upon in this setting.

Chapter 6 creates and validates a model of CGM dynamics so that the feasibility of using CGM to drive glycaemic control protocols can be tested in-silico.

Chapter 7 presents virtual simulations using the CGM model developed in Chapter 6 to drive the existing STAR glycaemic control protocol and discusses the achievability of using the current sensor technology as the sole input for glycaemic control protocols.

Chapter 8 summaries the research on CGM in ICU patient, presented in Chapters 2 – 7.

Part II – Glucose metabolism and CGM in Athletes

Chapter 9 provides a detailed background of the current literature about the glucose metabolism during exercise, before the prospective benefits of CGM in athletes are considered.

Chapter 10 investigates the extended period of hyperglycaemic and hyperinsulinemia seen post exercise when nutritional guidelines are followed during an exercise test in 10 trained subjects.

Chapter 11 presents a model of endogenous insulin secretion during and immediately post exercise for well trained subjects. *Material in Chapter 11 has been presented as: Thomas, F, Pretty, CG, Stewart, K, Shaw, GM, Desaive, T and Chase, JG (2016). "A Model of Endogenous Insulin Secretion during Exercise," 16th Annual Diabetes Technology Meeting (DTM), Bethesda, MD, USA, November 10-12, 1-page. (Bronze Award)*

Chapter 12 attempts to create a model of insulin sensitivity for athletes during and immediately after exercise based on the successful Intensive Control Insulin-Nutrition-Glucose model designed for glycaemic control in the ICU.

Chapter 13 presents the results of a study investigating the accuracy and performance of CGM devices, designed for individuals with Type 1 and Type 2 diabetes, in 10 well trained subjects to justify their use in this cohort. *Material in Chapter 13 has been published in: Thomas, F., Pretty, C.G., Signal, M.,*

Shaw, G. and Chase, J.G., 2017. Accuracy and performance of continuous glucose monitors in athletes. Biomedical Signal Processing and Control, 32, pp.124-129.

Chapter 14 presents the results from 6 days of CGM in 10 subelite athletes and investigates the potential of using CGM to improve athletes' dietary habits. *Material in Chapter 14 has been published in: Thomas, F., Pretty, C.G., Desaive, T. and Chase, J.G., 2016. Blood Glucose Levels of Subelite Athletes During 6 Days of Free Living. Journal of Diabetes Science and Technology, p.1932296816648344.*

Chapter 15 summarises the research on the glucose metabolism during exercise and CGM in athletes presented in Chapters 9 – 14.

Chapter 16 contains discussion of future work, for CGM in the ICU, metabolic modelling and CGM in athletes

Part I – CGM in ICU

Chapter 2. Background CGM in the Intensive Care Unit

This chapter provides background on the possible causes and effects of hyperglycaemia in critically ill patients. The importance of glycaemic control (GC) to regulate this hyperglycaemia is explained and the risks associated with GC are also considered. Finally, the potential application of CGM devices for GC in the intensive care unit (ICU) is reviewed. In particular, their potential to enhance the safety and efficacy of GC protocols, thus assessing their ability to mitigate key risks of GC, and enhance its performance.

2.1 Hyperglycaemia and glycaemic control in critically ill patients

Critically ill patients often experience high levels of insulin resistance (Capes et al., 2000, Finney et al., 2003, Krinsley, 2003, McCowen et al., 2001, Mizock, 2001, Umpierrez et al., 2002, Van den Berghe et al., 2001) leading to stress-induced hyperglycaemia, which negatively impacts outcomes (Capes et al., 2000, Finney et al., 2003, Krinsley, 2003, Bistrian, 2001, Van den Berghe et al., 2001). Stress-induced hyperglycaemia is prevalent in critical care, and can occur in patients with no history of diabetes (Capes et al., 2000, Van den Berghe et al., 2001, Mizock, 2001, McCowen et al., 2001). Hyperglycaemia worsens outcomes in these patients, leading specifically to further risk of complications, including sepsis (Bistrian, 2001), myocardial infarction (Capes et al., 2000), polyneuropathy, and multiple organ failure (Van den Berghe et al., 2001).

The principal cause of stress-induced hyperglycaemia is heightened levels of counter-regulatory hormones, released in response to critical illness (McCowen et al., 2001). Critically ill patients can experience a significant increase in several hormones including glucagon, growth hormone, catecholamines and glucocorticoids in response to physiological stress (Turina et al., 2005). These

hormones increase glucose production by stimulating the metabolic pathways for gluconeogenesis, glycogenolysis and lipolysis. Gluconeogenesis is the creation of glucose from lactic acid and certain amino acids, glycogenolysis is the breakdown of glycogen stored in the liver into glucose, and lipolysis is the breakdown of lipids into smaller molecules, including glycerol, which is then converted into glucose by the liver. This dysregulation of endogenous glucose production causes blood glucose levels to rise. In particular, the hormonal action raises glucose levels by blocking normal regulatory behaviours that reduce glucose production when glucose levels are elevated. Finally, these hormones also increase insulin resistance by reducing the ability of cells to absorb glucose through insulin mediated pathways, as well as by inhibiting insulin secretion despite high glucose levels, resulting in further amplified BG concentration (Chase et al., 2011, Gearhart et al., 2006).

In addition, some medications and therapies commonly used in the ICU can increase the severity of hyperglycaemia. Glucocorticoid steroids, the catecholamines epinephrine and norepinephrine, and β-blockers have all been shown to reduce insulin sensitivity (SI) and increase EGP, thus can increase BG levels in critically ill patients (Pretty et al., 2011, Binnert et al., 2004, Perry et al., 2003, Larsson et al., 1996, Nicod et al., 2003, Pagano et al., 1983). Other sources that increase BG levels in these patients with reduced SI include excess calories from parenteral and enteral nutrition, as well as dextrose infusions used for fluid resuscitation and drug delivery (Mizock, 2001, Nylen et al., 2004). Finally, the pro-inflammatory immune response heightens glucose levels similarly to catecholamines (Weekers et al., 2003, Marik et al., 2004). Hence, the overall system can act strongly, via several pathways, with positive feedback loops, to rapidly elevate glucose levels.

Untreated hyperglycaemia, over a long time period such as 10 – 20 years, can lead to costly complications such as retinopathy, cataracts, ulcers, skin infections, heart disease, peripheral vascular disease, cerebrovascular disease and neuropathy (Bistrian, 2001, Capes et al., 2000, Van den Berghe et al., 2001, Barrett-Connor et al., 1988, Alberti et al., 1998, Livingstone et al., 2003, Ben-Mahmud et al., 2006). The immune system also fails to function optimally in the presence of high blood glucose levels (Marik et al., 2004, Jeandidier et al., 2006, Turina et al., 2005, Weekers et al., 2003). In particular, at a blood glucose level of 8 mmol/L, the immune response is only 50% or less effective than at normal levels, and at 10 mmol/L the immune response is essentially completely ineffective (Weekers et al., 2003). An ineffective immune response for an ICU patient can have significant consequences, as they are unable resist common bacterial or viral infections. In addition, a less effective response to infection may prolong illness and the hyperglycaemic, pro-inflammatory, immune response. Hence, controlling blood glucose to within a normoglycaemic range, preferably less than 8mmol/L, has the potential to speed recovery and decrease negative outcomes associated with hyperglycaemia.

The first randomised control trial (RCT) to demonstrate that GC can improve patient outcomes was Van den Bergh et al. (2001). This RCT showed tight blood glucose control to less than 6.1 mmol/L reduced mortality in cardiac surgical ICU patients by 18-45%. Krinsley (2004) then reported in a retrospective study a 17–29% total reduction in mortality over a wider, more critically ill, ICU population with a higher glucose limit of 7.75 mmol/L. In 2006 Van den Bergh et al. (2006) again reported positive results with reduced morbidity and mortality in patients who stayed in the ICU > 3 days. A further retrospective study modulated insulin and nutrition to reduce both mortality and hypoglycaemia (Chase et al., 2008b). However, repeating these positive results indicating GC reduced mortality and improved other outcomes has been difficult (Griesdale et al., 2009).

Other large scale studies have shown conflicting results and a concerning increase in hypoglycaemia in glycaemic control cohorts (Brunkhorst et al., 2008, Finfer et al., 2009, Preiser et al., 2009, Treggiari et al., 2008, De La Rosa et al., 2008, Finfer et al., 2008, Griesdale et al., 2009). These results are a side effect of poor glycaemic control protocols and a lack of understanding of the blood glucose dynamics. Patients can be highly variable and unless this variability is understood there is a risk of causing hypoglycaemic events and large fluctuations in glucose when treating patients with insulin.

Hypoglycaemic and glycaemic variability have been independently linked to mortality in critically ill patients. In particular, Bagshaw et al (2009) showed variability and hypoglycaemia with in the first 24 hours of ICU stay are each associated with increased mortality and two other studies have reiterated this finding (Egi et al., 2006, Krinsley, 2008) . Thus, much controversy still surrounds GC and its application in the ICU, even though the need to safely lower and reduce the variability of blood glucose levels is well-known and widely accepted.

The biggest challenge surrounding the application of GC in the ICU is achieving a generalizable protocol that can reduce hyperglycaemia and avoid hypoglycaemia, while requiring minimal nurse effort. An ideal protocol is difficult to achieve due to significant inter-patient variability in illness and response to insulin treatment (Chase et al., 2011, Lin et al., 2008, Suhaimi et al., 2010, Pretty et al., 2012) , as well as significant intra-patient variability as patient condition evolves over time (Pretty et al., 2012, Lin et al., 2006, Lin et al., 2008) . If this variability is not accounted for, especially with protocols that utilize large insulin doses, high glycaemia variability and/or excessive hypoglycaemia is likely to occur making it difficult to show the direct benefits of GC (Chase et al., 2011, Meijering et al., 2006).

Regular, intermittent BG measurements are used to diagnose hyperglycaemia in the ICU. However, diagnostic criteria and levels can vary between intensive care units. Typically, 1-2 consecutive BG measurements above a threshold of 8 – 10mmol/L is considered hyperglycaemia (Singer et al., 2009, Umpierrez et al., 2012).

ICU glycaemic control protocols typically rely on intravenous insulin and require blood glucose measurements every 1-4 hours (Evans et al., 2012, Lonergan et al., 2006a, Plank et al., 2006, Blaha et al., 2009, Stewart et al., 2016), resulting in approximately 12-16 blood draws a day per patient. More frequent measurement, is uncommon due to the clinical effort required (Mackenzie et al., 2005, Chase et al., 2008a, Carayon et al., 2005), particularly because these blood draws represent a significant part of nurse workload (Carayon et al., 2005, Holzinger et al., 2005). However, longer measurement intervals coupled with suboptimal insulin doing protocols can also lead to increased glycaemic variability (Lonergan et al., 2006b). Hence, more frequent measurement could aid control quality and safety, given a safe, effective insulin protocol, if it didn't significantly increase nursing burden.

2.2 The continuous glucose monitoring system and use in the critically ill

Continuous glucose monitoring (CGM) devices were first developed in the 1980's to help individuals with type 1 diabetes manage their glucose levels. The first CGM device available was the Minimed Continuous Glucose Monitoring System (CGMS system gold, Medtronic, MiniMed, Northridge, California), which was approved for commercial use by the Food and Drug Administration in 1999 (Rebrin et al., 1999). There are now a range of different systems available to individuals with type 1 and type 2 diabetes individuals (T1DM and T2DM), including the wireless real time Guardian device shown in Figure 2.1.

Figure 2.1 *Guardian Real-Time CGM System, Medtronic, MiniMed, Northridge, California*

Most CGM devices consist of a small pager-like monitoring device that receives information from a sensor inserted into the subcutaneous layer, just beneath the skin (Rebrin et al., 1999). For the device in Figure 2.1, the platinum sensor produces a small electrical current as glucose in the interstial fluid is oxidised. The sensor is coated with a flux limiting glucose-oxidase membrane, which limits the flow of glucose in interstitial fluid to the electrode and thus provides a stable calibration between current and local glucose concertation. The monitor samples the electrical current every minute and a 1 - 5 minute average glucose estimate is stored in the monitor (~288 measurements per day). Some devices are known to have a fixed 10 minute time delay for every sample to account for the transport of glucose from the blood to the interstitial fluid, and thus enable direct comparison to blood - based measurements (Rossetti et al., 2010). This overall method of operation is typical of most CGM devices (Medtronic MiniMed, 2006, Medtronic MiniMed, 2010, Medtronic Inc, 2004).

These sensors require calibration by the user. This calibration is achieved by taking a blood glucose measurement with a point of care device, usually a glucometer, and entering it in to the CGM device. The device then knows what current correlates to what blood glucose level. These devices are recommended to be calibrated 2-4 times per day for best performance, depending on the specific device, and calibration is typically required at least every 12 hours for the device to continue recording sensor glucose (SG) values.

Thus, CGM devices, with their 1-5 minute measurement interval (Girardin et al., 2009), may allow BG levels to be managed more successfully, while minimizing glycaemic variability (Krinsley, 2008, Egi et al., 2006) and reducing nurse work load (Signal et al., 2010, Holzinger et al., 2010). However, CGM devices have shown suboptimal accuracy resulting from error or delay in calibration measurement, sensor drift and delayed glucose diffusion (Facchinetti et al., 2014, Reifman et al., 2007, Kuure-Kinsey et al., 2006, Zimmermann et al., 2012). There have been relatively few successful investigations of CGM in critical care use (Goldberg et al., 2004, Holzinger et al., 2010). In particular, one set of GC trials using CGM technology was not particularly successful due, in part, to significant sensor noise (Chee et al., 2003a, Chee et al., 2003b). Hence, they have not been successfully applied as a standard of care in critical care, outside of use in specific studies monitoring glucose levels and to reduce hypoglycaemia in adults and neonates (Harris et al., 2010, Holzinger et al., 2010).

However, several more recent in-silico studies (Signal et al., 2010, Mombaerts et al., 2015) and a recent pilot observational trial (Signal et al., 2013) have shown CGM devices, when coupled with a well-designed GC protocol, offer several potential benefits over the standard practice of intermittent, 1-4 hourly, BG monitoring. These studies show CGM devices have the ability to reduce hypoglycaemia, maintain BG control and reduce nurse workload. However, these studies and several others have also raised several

potential issues relating to using CGM in the ICU, especially the reduced accuracy achieved compared to that seen in T1DM and T2DM (Vlkova et al., 2009, Brunner et al., 2011, Rabiee et al., 2009, Signal et al., 2013), which would impact the GC protocol using these measurements.

All of the devices studied in ICU settings so far have been off-the-shelf CGM devices designed and intended for use by T1DM and T2DM to aid in BG management. The fact they are not designed specifically for the ICU environment makes them vulnerable to interference from certain medications, treatments and therapies, all which can vary significantly between critical care centres.

The previously mentioned pilot observational study highlighted the potential of CGM in ICU patients, but concluded that further understanding of factors that alter CGM performance is required before glycaemic control in the ICU could be realized (Signal et al., 2013). In particular, it highlighted a number of issues that could affect sensor performance in this cohort including, serve oedema, sepsis, and certain drugs or therapies. Several other studies also highlighted how patient condition may affect sensor performance in the ICU including the effect of sepsis and septic shock (Lorencio et al., 2012, Holzinger et al., 2010, Holzinger et al., 2009).

In addition, certain medications/therapies commonly used in the ICU, such as paracetamol, can influence CGM device performance (Moser et al., 2010). Contrary to expectations, commonly used vasoactive medications, such as dopamine, norepinephrine, ketanserin, enoximone, and nitro-glycerine, are reported to have little or no effect on the accuracy of at least one type of glucose sensor (Holzinger et al., 2009). Muscle trauma or surgery has potential to impact sensor performance. Klueh et al. (Klueh et

al., 2010, Klueh et al., 2014) demonstrated how cytokine expression is related to sensor function with increased inflammation and decreased sensor function in mice deficient in interleukin-1-receptor-anagonist cytokine. Muscle trauma, which is common cause of admission in the ICU, is known to alter cytokine expression (Jackson et al., 2011). Hence, there are several further potential factors inhibiting typical CGM sensor performance in ICU that do not exist in T1DM and T2DM.

Finally, the severity of illness encountered and therefore the level of dysregulation of BG is a further challenge for these devices. However, a real-time device specifically designed for the ICU recently became available, The Sentrino (Medtronic, MiniMed, Northridge, California), and has displayed promising results in initial trials with in the cardiac ICU (Kosiborod et al., 2013) . Hence, a large scale study was designed for implementation in Christchurch Hospital ICU. The following chapters investigate using the Sentrino CGM devices in adult ICU, with the over goal of improving BG control and increasing patient safety, while reducing nurse workload.

Chapter 3. The Sentrino Trials – Phase I

A recent observational study highlighted the potential of CGM in ICU patients, but also concluded that further understanding of factors that alter CGM performance is required before glycaemic control in the ICU could be realized (Signal et al., 2013). Therefore, a larger scale study was designed to investigate the performance of the latest available CGM device specifically designed for the ICU environment, the Sentrino (Medtronic, MiniMed, Northridge, California). The trial was designed and undertaken in 2 phases that were run partially in parallel. The aim of this study was to investigate the performance of these new devices first observationally to ensure the safety and efficacy of their performance (Phase I), then a further observational study the performance and integration of hyper- and hypo- glycaemic alarms (Phase IIA). Finally, the design and implementation of a protocol using CGM values to guide glycaemic control (GC) (Phase IIB). This chapter discusses the results of Phase I of the Sentrino Trials focusing on the overall device performance and impact of sensor site on results.

3.1 Introduction

Several in-silico studies (Signal et al., 2010, Mombaerts et al., 2015) and a recent pilot observational trial (Signal et al., 2013) have shown that CGM devices, when coupled with a well-designed GC protocol, offer several potential benefits over the standard practice of intermittent BG monitoring to guide GC. These studies show that CGM devices have the ability to reduce hypoglycaemia, maintain BG control and reduce nurse workload. However, these studies and several others have also raised several potential issues relating to using CGM in the ICU, especially the reduced accuracy compared to that seen in individuals with diabetes (Vlkova et al., 2009, Brunner et al., 2011, Rabiee et al., 2009, Signal et al., 2013).

All of the devices studied so far in ICU settings have been off-the-shelf CGM devices designed and intended for use by T1DM and T2DM to aid BG management. The fact they are not designed specifically for the ICU environment make them vulnerable to interference from certain medications, treatments, and therapies, all which vary between critical care centres. Additionally, the servery of illness encountered, and therefore the level of dysregulation of BG, is a further challenge for these devices. However, a real-time device specifically designed for use in the ICU recently became available, the Sentrino (Medtronic, MiniMed, Northridge, California). This device has displayed promising results in initial trials in the cardiac ICU (Kosiborod et al., 2013) . Hence, a large scale study was designed for implementation in Christchurch Hospital ICU. The first step in this study (Phase I) was to validate the performance of these devices in a mixed-medical ICU and confirm the optimal sensor location.

3.2 Subjects and Methods

3.2.1 Subjects

This study uses data from an observation pilot study of CGM in patients admitted to the Christchurch Hospital ICU during 2014. CGM and BG data were gathered from 13 patients who were recruited to this phase of the trial. All patients were recruited by a physician in the ICU, and informed written consent was obtained from the next of kin if the patient was unable to consent, and follow up consent was obtained from the patient at a later date if applicable.

Inclusion criteria for this study were two consecutive BG measurements greater than 8 mmol/L, indicating the need for insulin therapy using the local standard of care, the Stochastic TARgeted (STAR) GC protocol (Evans et al., 2012), expected length of stay of at least 3 days, over 18 years of age, and with

a platelet count > 30,000/mL. Patients were excluded from the trial if they were not expected to survive, receiving Hydroxyurea, pregnant, and/or lacked clinical equipoise. This study and use of data was approved by the Upper South A Regional Ethics Committee, New Zealand. Table 3.1 shows the patient demographics.

Table 3.1 Patient Demographics data presented as median [interquartile range (IQR)] where appropriate.

Patients	13
Ages (years)	59 [57 – 62]
Sex (M/F)	8/5
APACHE II	17 [16 – 22]
APACHE III	67 [50 – 87]
SAPS II	42 [35 – 51]
ICU admission (days)	21 [11 – 25]
Outcome (Lived/Died)	9/4
Diabetes (None/T1/T2)	10/0/3

3.2.2 Continuous glucose monitoring

Each participant in this phase of the study was monitored concurrently for a period of up to 3 days with 2 independent CGM devices, the Sentrino (Medtronic, MiniMed, Northridge, California) CGM system. This device is specifically designed for ICU conditions and consists of the set up shown in Figure 3.1. The CGM system comes in three parts, a disposable dual filament sensor, a cable to transit the sensor signal and a touch screen monitor. The underside of the sensor can be seen in Figure 3.2. The sensor in inserted manually using two hollow needles that encase the sensor filaments and then retract once the insertion is complete.

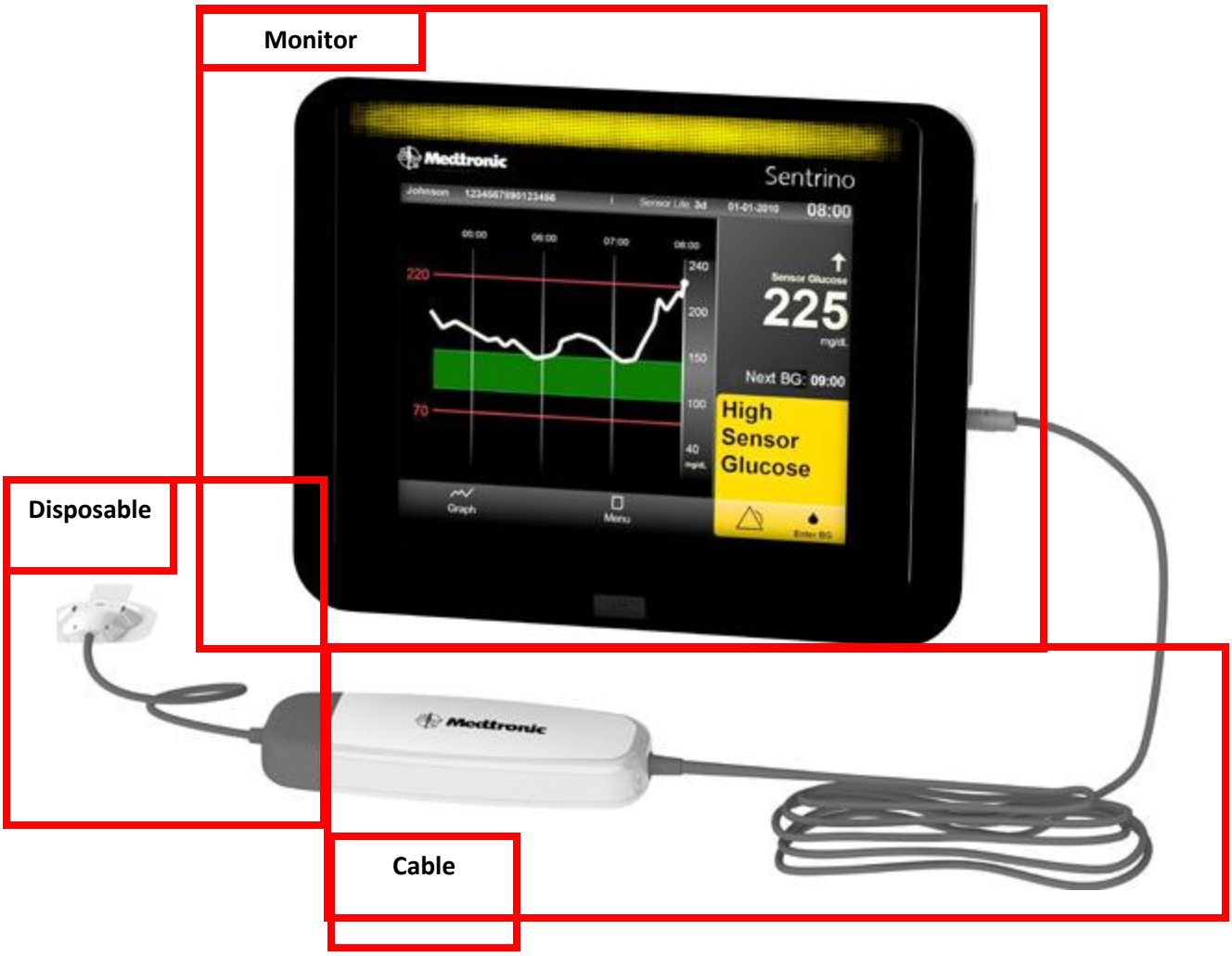


Figure 3.1 *The Sentrino CGM system featuring a disposable sensor, transmitting cable and touch screen monitor*

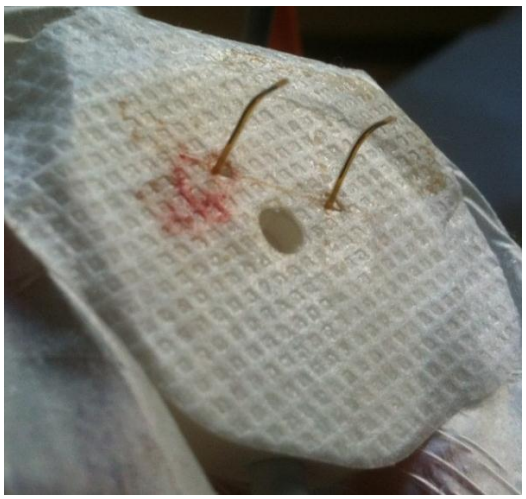


Figure 3.2 *The underside of the Sentrino sensor. The two filaments are inserted in to the subcutaneous layer with the help of two hollow retractable needless that encase the filaments.*

For each patient, 1 sensor was inserted in the abdomen and 1 sensor was inserted in the thigh to allow the effect of sensor site to be investigated. However, it should be noted that in later trials two sensors were inserted in the abdomen in 3 patients instead of a thigh sensor, allowed under the existing ethics, to further investigate the effect of sensor site.

Calibration BG measurements were obtained by specifically trained ICU nurses at least 3 times per day, as recommended by the device manufacturer (Medtronic, MiniMed, Northridge, California) using a Roche Accu-chek Inform II (F. Hoffmann-La Roche Ltd, Basle, Switzerland) hospital grade glucose meter and arterial blood as is standard practice in the Christchurch ICU. Roche devices are reported of have a mean error (bias) of -0.2 (0.3) mmol/L when compared to blood gas analyser results (Thomas et al., 2014b). Devices were not be blinded to nursing staff, but were strictly not to be used for GC. BG measurements for STAR were taken separately every 1-3 hours.

3.2.3 Intermittent BG monitoring

In addition to BG measurements used for calibration of SG data, each patient had intermittent BG monitoring every few hours. The STAR protocol requires, on average, 12-14 BG measurements per day to guide insulin/nutrition therapy (Fisk et al., 2012, Stewart et al., 2016). In this study, BG measurements were determined using Roche Accu-chek Inform II (F. Hoffmann-La Roche Ltd, Basle, Switzerland) hospital grade glucose meter which is the standard of care in the Christchurch ICU, with blood typically obtained from an arterial line.

3.2.4 Analysis

To assess the accuracy of the Sentrino CGM, the mean absolute relative difference (MARD) was calculated between reference BG measurements collected for use with STAR and the sensor glucose (SG) values:

$$MARD = mean\left(abs\left(\frac{SG-BG}{BG}\right)\right) * 100 \quad \text{Eq. 3.1}$$

MARD was considered for each device and also between the two sensor sites, of a single patient. Bland-Altman plots (Bland et al., 1986) were produced for the device as a whole to consider how SG errors were associated with blood glucose level. A MARD was only calculated if subjects had at least 5 independent reference measurements to compare with SG data. MARD is a commonly used reference metric for CGM devices to it was selected in this case to allow easy comparison to other studies. Additionally Clarke Error Grid analysis was undertaken to determine the clinical impact of any errors.

To assess the agreement of the CGM devices, zero-lag cross-correlation was applied. Zero-lag cross-correlation is the dot product applied to two signals with no time shift, and yields a value between -1 to +1 assessing measure-to-measure agreement as shown in Equation 3.2:

$$\cos\theta = \left(\frac{A.B}{||A||||B||}\right) \quad \text{Eq. 3.2}$$

Where A = [a_1, a_2 …. a_n] represents the n x 1 vector of measurements from one CGM signal and B = [b_1, b_2 …. b_n] the n x 1 vector of measurements from the other. The resultant angle ,θ, shows the trend similarity between two vectors and its cosine has values in the range -1 and +1 demonstrating opposing to complete agreement. Thus, it uses the inner product definition to define how much of vector A is projected on to vector B, where 1 indicates equal vectors. The resulting value is referred to as the zero lag correlation co-efficient. All signals were first mean-centred. Cross correlation allows the trending and agreement of the sensor pairs to be analysed in a scale invariant manner and thus, it was selected for this analysis.

The number of poor sensor signal (PSS) and replace sensor (RS) alarms delivered by the devices were also counted for each patient. PSS alarms can occur when the sensor is not performing as expected. This behaviour may be due to a variety of reasons, including a BG calibration value very different from that expected by sensor algorithm, an unexpectedly low sensor signal and/or dislodgement of the sensor filaments. A RS alarm will occur after 4 hours without a valid signal. This alarm thus indicates the sensor no longer continues to function and requires replacing.

3.3 Results

The overall results from the analysis of BG data show that intermittent BG measurements were taken frequently with the median time between consecutive measurements of 1.8 hours (~13 measures/day). The STAR protocol achieved good control in these subjects resulting in a median [interquartile range (IQR)] BG of 7.2 [6.3 – 8.9] mmol/L. However, this result is a little higher than the median BG normally seen in cohorts controlled by STAR (Evans et al., 2012) indicating more serve hyperglycaemia in this cohort, especially in one particularly difficult to control, spinal injury patient (Figure 3.4, B). These results are shown in Table 3.2. Plots of all CGM data from the Sentrino Phase 1 trial can be found in Appendix A.

CGM data shown in Table 3.3 highlights that most patients had at least 2 days of monitoring. While calibrations were only requested every 8 hours, there is a much higher frequency of calibration with the median [IQR] time between calibrations across both devices being 4.2 [1.3 – 6.9] hours. The median [IQR] SG results are very similar to the BG results with 6.9 [5.9 – 8.0] and 7.3 [6.4 – 8.2] mmol/L for abdomen and thigh devices, respectively.

The MARD for the abdomen device was 16.6%, while for the thigh device it was only 11%. However, there were more abdomen SG data sets assessed (N = 16 vs. N = 10). Trend results, Table 3.4, using the cross correlation show decidedly average correlation between the SG pairs. There appears to be only a slightly better correlation of two abdomen signals compared to an abdomen signal and a thigh signal with median [IQR] correlation coefficients of 0.47 [0.46 – 0.52] and 0.45 [0.22 – 0.65], respectively. Although the data is limited. The median [IQR] number of episodes of poor sensor signal was 1 [0 – 1] for both device locations. However, the abdomen sensors have a greater range (0 – 4) compared to the thigh sensor (0 – 2). The number of replace sensor events was the same for both device locations.

The Bland-Altman plots in Figure 3.3 show how SG error changes with glucose level. There does not seem to be any strong association between glucose level and SG error in any data set. The thigh data once again shows better performance with much tighter 95% range than the abdomen data. Although there are less measurements above 10 mmol/L in the thigh data cohort. The overall mean error of the Sentrino device is only -0.1 mmol/L but the 95% range values are at -3.4 and 4.4 mmol/L, suggesting error can be relatively large for this device. However, once the outliers highlighted in Figure 4.4 are removed these bounds tighten to -2.58 and 2.18 mmol/L respectively. Removing these outliers also improve the overall

performance of the device with a MARD of 11.6% and median [IQR] SG value reduces to 6.9 [6.0 – 7.8] mmol/L which is more typical of the control achieved by STAR (results not shown).

Clarke Error Grid Analysis of abdomen data, Figure 3.5 (left), showed 96.8% of all measurements fell in zones A and B, with 70.4% in zone A and 26.5% in zone B, which would not lead to inappropriate treatment in cohorts for with this error grid was designed (Clarke et al., 2005). Only 0.8% or 2 points fell within region D and none within region E. Thigh data, Figure 3.5 (right), showed even better results with 100% of measurements in zone A and B, with 80.1% in zone A.

Table 3.2 BG and SG data results. Results are shown as median [IQR] (range) where appropriate.

Blood Glucose Results	*Roche Accu-chek Inform II*
Number of Patients	13
Time between BG (hrs)	1.8 [1.1 – 3.1]
Median [IQR] BG (mmol/L)	7.2 [6.3 – 8.9]

Table 3.3 SG data results. Results are shown as median [IQR] (range) where appropriate.

CGM Results	*Sentrino – Abdomen*	*Sentrino – Thigh*	*Sentrino - Overall*
Number of SG data sets	16	10	26
Duration of CGM (hrs)	56.8 [45.1 – 71.1]	45.6 [43.5 – 70.9]	52.4 [43.9 – 70.9]
Time between calibration BG (hrs)	4.6 [1.2 – 6.9]	3.6 [1.3 – 6.8]	4.2 [1.3 – 6.9]
Median [IQR] SG (mmol/L)	6.9 [5.9 – 8.0]	7.3 [6.4 – 8.5]	7.1 [6.1 – 8.2]
MARD (%)	16.6	11.1	14.7
Poor Sensor Signal (no. episodes)	1 [0 – 1] (0 – 4)	1 [0 – 1] (0 – 2)	1 [0 – 1] (0 – 4)
Replace Sensor (no. occurrences)	0 [0 – 1] (0 – 1)	0 [0 – 1] (0 – 1)	0 [0 – 1] (0 – 1)

Table 3.4 SG correlations results. Results are shown as median [IQR] (range) where appropriate. Ab = abdomen, Th = thigh

CGM Correlation	*Ab vs. Th*	*Ab vs. Ab*
Number of pairs	10	3
Correlation Coefficient	0.45 [0.22 – 0.65]	0.47 [0.46 – 0.52]

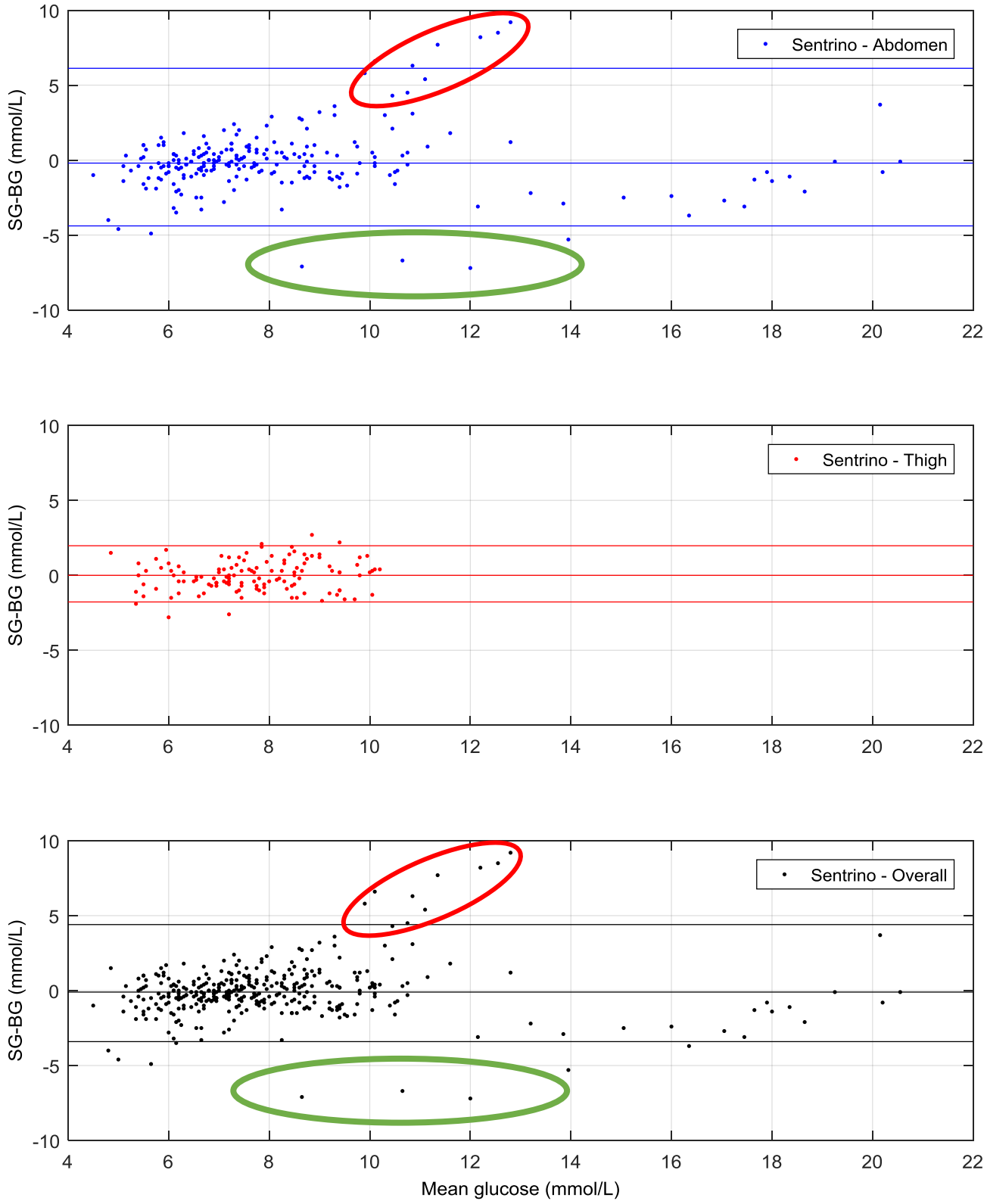


Figure 3.3 *Bland Altman plot for all patients for the different device locations and overall results. Red and Green ovals correspond to the SG traces in Figure 3.4, horizontal lines represent mean and 95% range.*

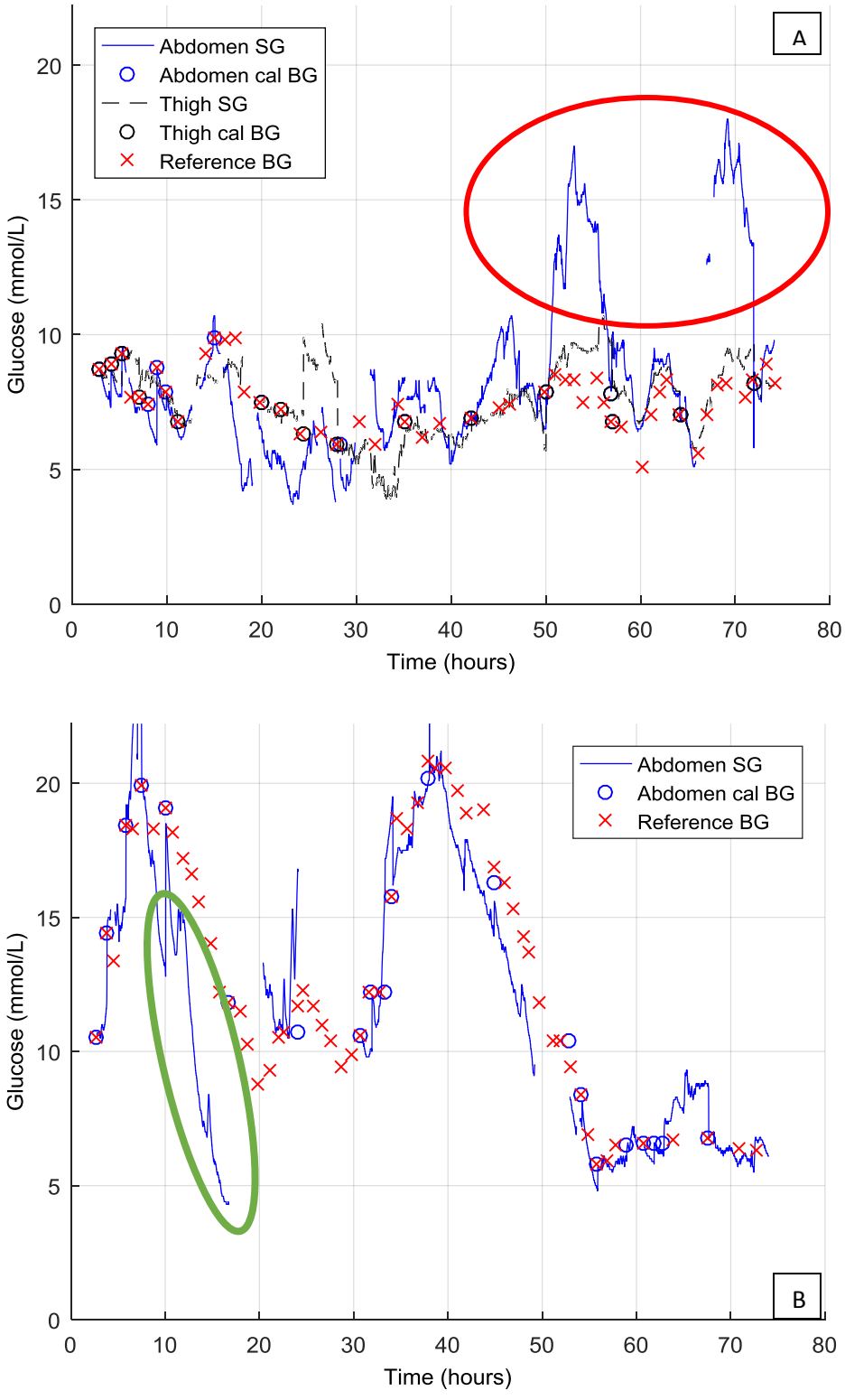


Figure 3.4 *SG plots of the two patients responsible for the majority of the outliers seen in the Bland-Altman plots due to sensor failures leading to uncharacteristic sensor behaviour. A) Patient 1 abdomen sensor b) Patient 5 abdomen sensor*

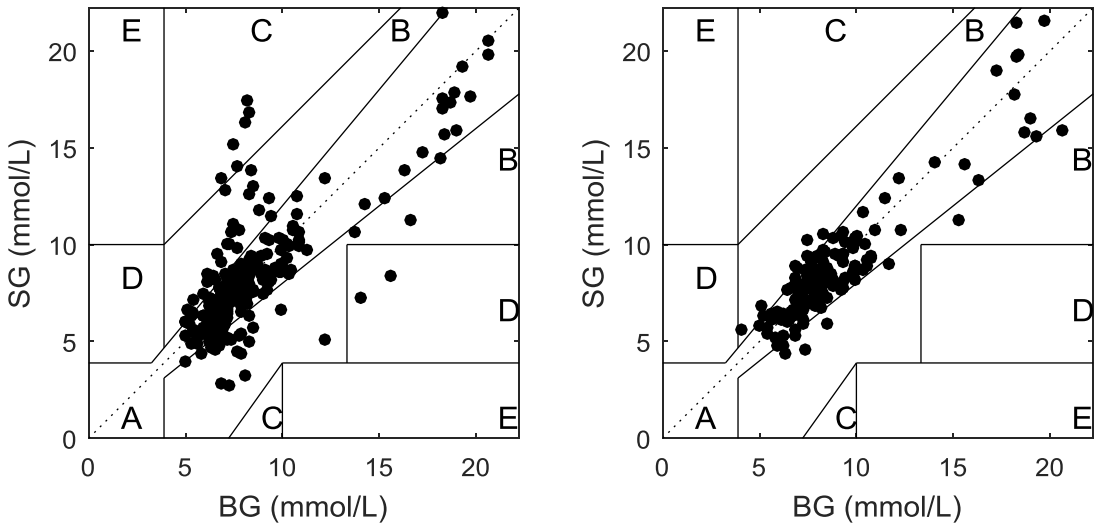


Figure 3.5 *The Clarke error grid analysis for the abdomen SG (left) and thigh SG (right) compared to reference BG measurements*

3.4 Discussion

The results in Table 3.2 show that glycaemia was monitored closely during the study, by intermittent BG measurements and CGM, with both methods producing similar overall glycaemic results. In terms of CGM accuracy, the overall error from both abdomen and thigh data is 14.7%. This is result is similar to accuracy seen in previous CGM studies with off-the-shelf CGM devices designed for T1DM and T2DM (Vlkova et al., 2009, Brunner et al., 2011, Rabiee et al., 2009, Signal et al., 2013) and slightly higher than the 12.2% reported in an initial Sentrino study of cardiac ICU patients (Kosiborod et al., 2013). However, Kosiborod et al. (2013) only used the thigh location for sensor insertion. Therefore, the thigh MARD of 11% is comparable if not slightly better than Kosiborod et al.'s results. Additionally, the Clarke Error Grid analysis shows the clinical impact of this error was likely to be minor.

The MARD for the abdomen SG data is approximately 4% higher than that for the thigh SG data and a higher range of poor sensor signal was seen in abdomen devices. Figure 3.3 shows a much wider 95% range for the abdomen SG compare to reference BG data than the thigh data. These results indicate that sensor location does affect sensor performance and following the manufacturers' recommendation of insertion in the thigh is important. However, once the outliers highlighted in Figure 3.4 are removed, this difference reduces significantly. These large excursions in sensor signal are uncharacteristic of a working sensor and are due to sensor failure causing the sensor to act erroneously. In this study, there are a lower number of thigh SG signals than abdomen. However, in Chapter 4 results from an additional 8 thigh SG data sets are analysed as part of Phase IIA of the Sentrino trial.

In this study, a much higher rate of calibration is seen compared to what was required by the device manufacturer. This increase is predominately due to the initial start-up protocol requiring 3 blood glucose measurements within three hours during initialisation. However, a number of incidences of poor sensor signal would also increase the number of calibrations because a calibration is recommended by the manufacturer to correct a PSS alarm. Additionally, the Sentrino was programed to alarm 75 mins prior to the calibration being required to allow the nurse to align a STAR measurement with the calibration of the devices, but this may have resulted in more calibrations being received especially for patients requiring hourly BG. The rate of calibration, approximately every 4 hrs, is still much lower than the average STAR measurement time of 1.8 hrs. However, if such frequent calibration is required it does call into question the ability of CGM to cure the time cost of GC and increased calibration may have resulted in better than expected accuracy.

3.5 Summary

The aim of this chapter was to analyse the performance of the Sentrino CGM system in a mixed medical ICU environment and confirm the optimal sensor location. Overall, the Sentrino device achieved a MARD of 14.7%. This result demonstrated slightly reduced performance from what was reported in an initial trial in a cardiac ICU of 12.2% MARD. However, when considering device location, thigh SG achieved a MARD of 11.0% while abdomen SG achieved a MARD of 16.6%. This result indicates that following the manufacturers' recommendation of thigh insertion, which is different to the location used for devices designed for T1DM and T2DM, is important to ensure sensor performance. The number of calibrations undertaken was double that recommended by the protocol and may have improved overall accuracy. This is likely due to the Sentrino initialisation requiring 3 additional measurements within 2 hours and relatively short 2-3 day monitoring periods. However, a high rate of poor sensor signal, median of 1 episode per patient, also leads to more calibrations being undertaken to attempt to correct this reduced signal. Overall the Sentrino performance was acceptable, but with such a high number of additional calibration measurements required, questions still remain if this CGM system can reduce the time cost of glycaemic control.

Chapter 4. The Sentrino Trial Phase IIA

As noted in Chapter 3, a larger scale study was designed to investigate the performance of the latest available CGM device specifically designed for the ICU environment, the Sentrino (Medtronic, MiniMed, Northridge, California). The trial was designed and undertaken in 2 phases run partially in parallel. This chapter details the results of Phase IIA, run concurrently with Phase I as a further observational study in to the performance and integration of hyper- and hypo-glycaemic alarms.

4.1 Introduction

CGM does not just offer reduced nurse workload by reducing the number of manual BG measurements required. CGM also offers trend information and potentially early warning of hyper- and hypo-glycaemic events compared to intermittent monitoring (Signal et al., 2010), which can miss them entirely (Harris et al., 2010). To optimise the information provided by CGM hyper- and hypo- glycaemic alarms can be added in the settings of the Sentrino device. These alarms sound if the CGM value becomes lower or higher than a user defined threshold. The aim of this chapter was to investigate the performance of these alarms and how they can best be integrated in to current clinical practices, to ensure reduced nurse workload and increased patient safety.

4.2 Subjects and Methods

4.2.1 Subjects

This study uses data from an observational pilot study of CGM in patients admitted to the Christchurch Hospital ICU during 2014. This analysis uses CGM and BG data from 8 patients who were recruited to this

phase of the trial, Phase II. These patients are independent of the patients examined in the Chapter 3. All patients were recruited by a physician in the ICU and informed written consent was obtained from the next of kin if the patient was unable to consent and follow up consent was obtained from the patient at a later date if applicable. This study and use of data was approved by the Upper South A Regional Ethics Committee, New Zealand. Table 4.1 shows the patient demographics.

Inclusion criteria were two consecutive BG measurements greater than 8 mmol/L, indicating the need for insulin therapy using the STAR protocol (Evans et al., 2012) , expected admission of at least 3 days, over 18 years of age, and with a platelet count > 30,000/mL. Patients were excluded from the trial if they were not expected to survive, receiving Hydroxyurea, pregnant, and/or lacked clinical equipoise.

Table 4.1 Patient Demographics presented as median [IQR] where appropriate

Patients	8
Ages (years)	66 [54 – 71]
Sex (M/F)	5/3
APACHE II	23 [16 – 29]
APACHE III	72 [62 – 111]
SAPS II	45 [35 – 63]
ICU admission (days)	10 [7 – 14]
Outcome (Lived/Died)	5/3
Diabetes (None/T1/T2)	5/0/3

Each participant in this phase of the study was monitored concurrently using 1 CGM device for a period up to 3 days using the Sentrino (Medtronic, MiniMed, Northridge, California) CGM system. This device is specifically designed for ICU conditions and is presented in detail in Chapter 3. The subcutaneous sensor

was inserted into the thigh of each patient based on manufacturer recommendations (Medtronic, MiniMed, Northridge, California).

Calibration BG measurements were obtained by specifically trained ICU nurses at least 3 times per day as recommended by the device manufacturer (Medtronic, MiniMed, Northridge, California) using a Roche Accu-chek Inform II (F. Hoffmann-La Roche Ltd, Basle, Switzerland) hospital grade glucose meters, and arterial blood samples, as is standard practice in the Christchurch ICU. Roche devices are reported of have a mean error (bias) of -0.2 (0.3) mmol/L when compared to blood gas analyser results (Thomas et al., 2014b). CGM Devices were strictly not to be used for glycaemic control

4.2.2 Guardrails

An upper guardrail of 10 mmol/L and lower guardrail of 4.2 mmol/L were added in the device settings. If SG was predicted to be approaching either of these values a "predicting low sensor glucose" or "predicting high sensor glucose" alert, which are predefined on the device, would appear on the screen of the monitor. This specific alert required no action from the nurse. However, when the SG value crossed either of the thresholds the alert on the screen would change to the device defined "Low sensor glucose" or "High sensor glucose" and an alarm would sound. The Nurse was now instructed to pause the alarm silencing it for one hour and immediately take a Roche BG measurement and compare it to the SG:

- If SG <= the lower guardrail and the absolute difference between BG and SG is greater than 0.5mmol/L the Sentrino must be calibrated using that BG value

- If SG >= the upper guardrail and the absolute difference between BG and SG is greater than 2mmol/L the Sentrino must be calibrated using that BG value

If left unattended, and the SG remained above or below the threshold the alarm would continue to sound every 15 minutes. In addition to BG measurements used for calibration of SG data, each patient had intermittent BG monitoring every few hours for GC with STAR. The STAR protocol requires, on average, 12 – 14 BG measurements per day to guide insulin/nutrition therapy (Fisk et al., 2012). In this study, BG measurements were made using Roche Accu-chek Inform II (F. Hoffmann-La Roche Ltd, Basle, Switzerland) and arterial blood samples, which is the standard of care in the unit.

4.2.3 Analysis

To assess the accuracy of the Sentrino CGM, MARD was calculated between reference BG measurements collected for use with STAR and the CGM signal. The MARD was calculated for each sensor and reference measurement pairing, as detailed in Chapter 3. MARD was only calculated if subjects had at least 5 independent reference measurements to compare with SG data.

Alarm performance was investigated by considering the number of episodes of SG >10 mmol/L or SG < 4.2 mmol/L, and the overall numbers of warning alerts and alarms. An episode was considered to begin when SG crossed either threshold and ended when SG rose above or fell below the same threshold. These episodes were counted independently to the number of alarms and warning alarms as once a threshold is crossed the alarm will sound every 15 minutes if left unattended. Once attended to, the alarm will sound again in 1 hour if SG is still outside of the threshold bounds. Warning alerts also can occur without the

bounds being crossed. Therefore, the number of episodes of hyper- or hypo-glycaemia, above and below the thresholds, is different to the number of warning alerts or alarms.

The number of calibrations required due to a difference of more than 0.5 mmol/L or 2.0 mmol/L depending on the alarm threshold were also calculated. The number of calibrations received and time taken to measure BG was considered to investigate nurse compliance. Finally, the number of false positive and false negative alarms was considered. A false positive alarm was defined as when an SG alarm occurred, for a threshold crossing, but the measured BG was still below or above the relevant threshold and thus still with in the 4.2 mmol/L – 10.0 mmol/L band as defined. A false negative alarm was defined as when any measured BG was above or below either threshold, but an SG was not and therefore an alarm did not occur.

4.3 Results

The overall results from the analysis of BG data show that intermittent BG measurements were taken frequently with the median time between consecutive measurements of 1.8 hours (~13 measures/day). The STAR protocol achieved good control in these subjects resulting in a median [IQR] BG of 7.2 [6.3 – 8.9] mmol/L. These results are shown in the upper section of Table 4.2.

CGM data shown in the lower section of Table 4.2 highlights that most patients had at least 2 days of monitoring. The CGM performance is similar if not slightly improved from that reported in Chapter 3 with a MARD of 9.7%. The median [IQR] SG results are very similar to the BG results with 7.1 [6.1 – 8.3] and 7.2 [6.3 – 8.9] mmol/L, respectively.

Table 4.2 BG and SG data results. Results are shown as median [IQR] where appropriate.

Blood Glucose Results	
Number of Patients	8
Time between BG (hours)	1.8 [1.0 – 3.0]
Median [IQR] BG (mmol/L)	7.2 [6.2 – 8.9]
CGM Results	
Number of SG data sets	8
Duration of CGM (hours)	61.1 [36.1 – 68.5]
Time between calibration BG (hours)	6.4 [1.3 – 7.0]
Median [IQR] SG (mmol/L)	7.1 [6.1 – 8.3]
MARD (%)	9.7%

Table 4.3 summarises the warning alert and alarm performance across the 8 patients. There were only 11 hyperglycaemic (SG > 10 mmol/L) and 6 hypoglycaemic (SG < 4.2 mmol/L) episodes, displaying the good control achieved by the STAR protocol, especially considering the high rate of false positives seen (SG exceed the threshold but BG does not). Out of the 29 hypoglycaemic alarms 27 were false positives, indicating the BG had not been below 4.2 mmol/L. Figure 4.2 demonstrates how sensor artefacts, either drop outs or spikes in sensor glucose, generated false positive hypoglycaemic alarms.

Table 4.3 Hyperglycaemic and hypoglycaemic alarm performance results. Results are show as median [IQR} where appropriate

	Hypoglycaemic SG<4.2 mmol/L	**Hyperglycaemic SG>10 mmol/L**	**Total**
No. episodes	6	11	17
No. warning alerts	11	17	28
No. alarms	29	64	93
Time taken to measure BG (mins)	4.0 [-21.3 – +19.0]	-1.5 [-17.5 – +18.5]	-1.0 [-18.5 – +19.0]
No. calibrations required	25	7	32
No. calibrations required received	23	3	26
No. calibrations received not required	2	10	12
No. false positive alarms	27	29	56
No. false negatives	0	1	1

The median [IQR] time to measure BG once an alarm had sounded was -1.0 [-18.5 – 19.0] minutes. While the median suggests good compliance the large interquartile range with nurses using measurements from ~20 minutes prior to the alarm or not measuring for ~20 minutes post alarm indicates otherwise. The high rate of false positives may have contributed to this lack of compliance with 29 false positive hyperglycaemic alarms and 27 false positive hypoglycaemic alarms. However, there was only one false negative alarm during the entire monitoring period. Figure 4.1 highlights an example of good nurse compliance with repeated true alarms compared to poor nurse compliance due to repeated false positive alarms. Only 32/93 total alarms required calibration and 26/32 of these calibrations were undertaken and entered in to the device. There were 12 additional calibrations made after alarms that were not required.

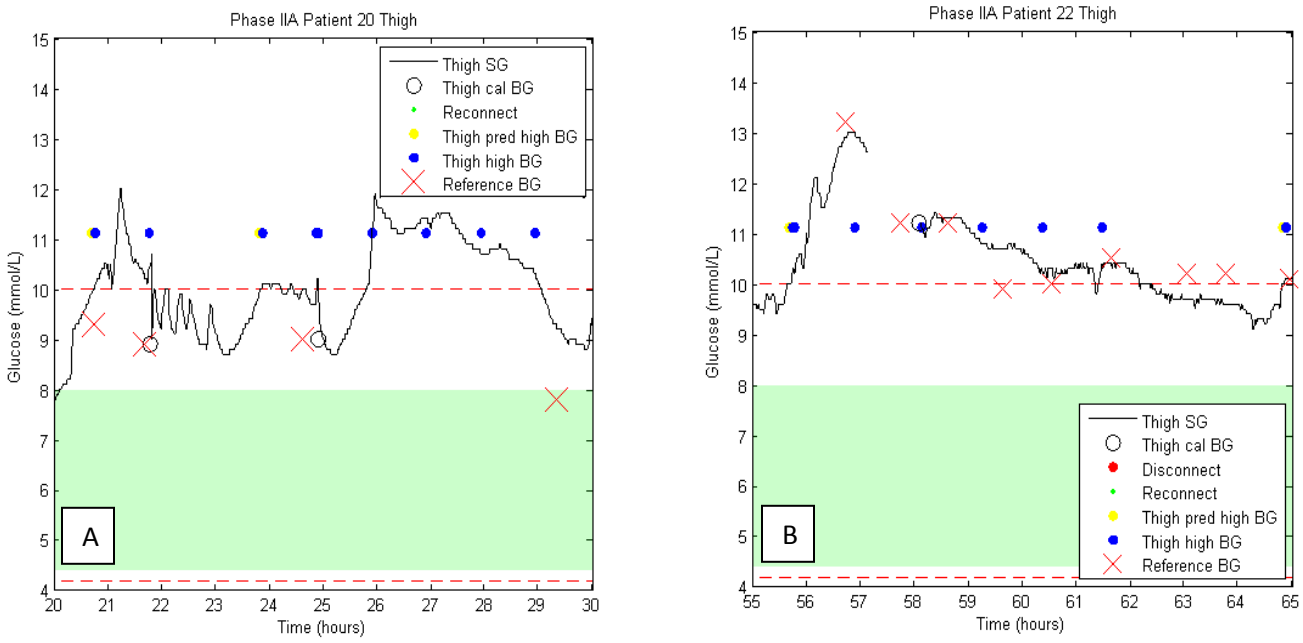


Figure 4.1 *Examples of repeated alarms A) displays an example of repeated false positive alarms resulting in poor compliance B) displays repeated true alarms resulting in good nurse compliance*

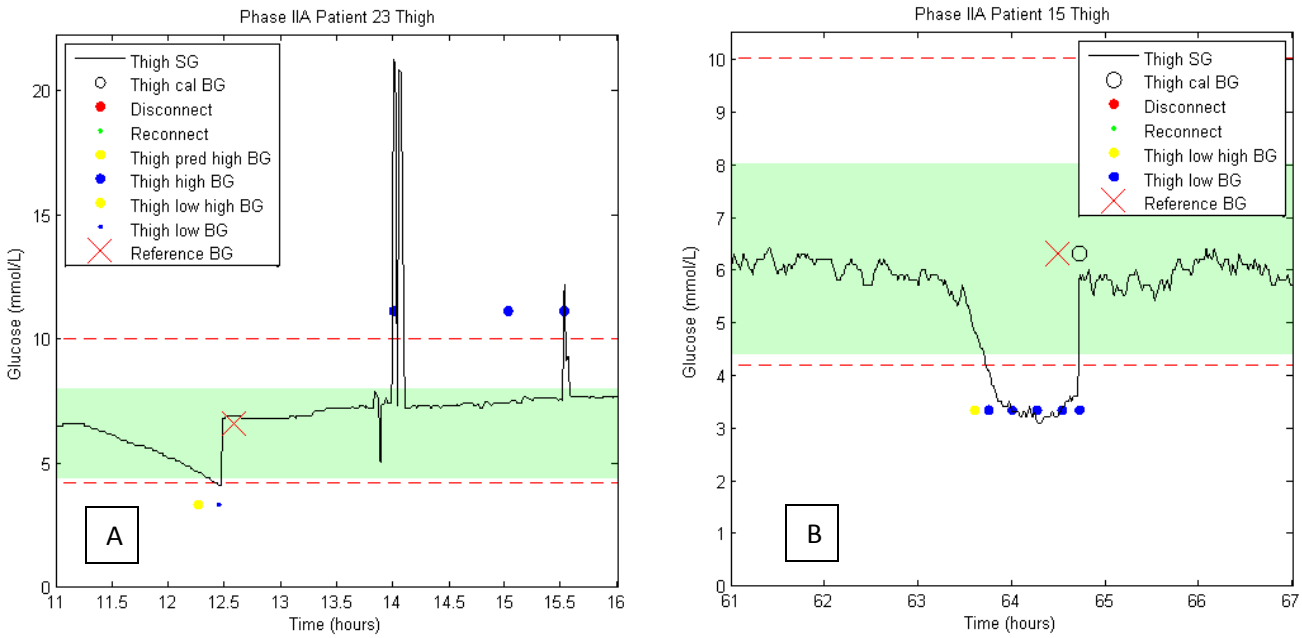


Figure 4.2 *Examples of sensor artefacts resulting in false positive alarms*

4.4 Discussion

Overall sensor and alarm performance was good. Only 32/93 alarms required calibration with the majority of those calibrations required for the lower bound, 25/32, where the safety tolerance for the difference between sensor glucose was only 0.5 mmol/L in this hypoglycaemic range versus 2 mmol/L for the hyperglycaemic upper bound. There was only one instance of a false negative alarm, where BG was above 10 mmol/L but SG was not, displaying a high level of safety.

However, there was a high rate of false positive alarms. Many of these false positives were caused by sensor artefacts, unexplained spikes or dips in sensor glucose, as shown in Figure 4.2, or sensor drift as shown in Figure 4.1A. While false positives are safer for managing patient blood glucose than false

negatives, they can lead to alarm fatigue and non-compliance. This issue is demonstrated in Figure 4.1A. where SG has drifted above the threshold for the hyperglycaemic alarm, but, measured BG is below the threshold. To prevent the alarm from continuing to sound the nurse has calibrated the Sentrino even though SG – BG < 2 mmol/L and by the protocol calibration is not required. These calibrations have not prevented SG drifting again above the threshold so the next 5 alarms have seen no action taken. This patient has diabetes so nurses have the option to adjust the target band to 4.4 – 9.0 mmol/L or 6.0 – 9.0 mmol/L. In this case the target range has been adjusted. Therefore, even though the patients BG is above 8.0 mmol/L the nurses still can select the longest measurement interval of 3 hourly BG measurement intervals. Hence, to measure BG every hour with a repeated false alarm generates extra nurse work load, which has resulted in non-compliance.

This compliance issue is contrasted by the good compliance seen in Figure 4.1B. This patient had very high blood glucose and there are many more examples of true hyperglycaemic alarms (39 in total). However, there has been a BG measurement taken with each alarm. This patient does not have diabetes and the target range has remained 4.4 – 8.0 mmol/L. Therefore, once a patients BG is above 8.0 mmol/L the STAR protocol will request hourly measurements so to measure with each hourly alarm when a patient is truly hyperglycaemic the work load is not increased due to additional alarms. It is also interesting to note that none of these 39 alarms required calibration showing good agreement between SG and BG even at high glucose levels.

One mild hypoglycaemic event (BG = 3.9 mmol/L) was captured by the Sentrino guardrails that would have otherwise been missed by STAR alone. This result highlights the ability improve safety with hypoglycaemic guardrails. However, hypoglycaemic events are rare with the STAR protocol with clinical

results from 286 patients resulting in only 1.35% of BG < 4.4 mmol/L (Stewart et al., 2016). Hence, the high rate of false alarms may generate more nurse workload and alarm fatigue that is not offset enough by the improved safety.

There were numerous episodes of hyperglycaemia that were captured first by the Sentrino guardrails and only later by the STAR measurements, if at all. This result highlights the potential ability of the Sentrino's ability to improve performance if nurses are altered to hyperglycaemia earlier. However, it is not possible to deduce what percentage improved performance could be achieved from this study as CGM was strictly not used for glycaemic control.

The guardrails of 4.2 mmol/L and 10 mmol/L demonstrate the potential of guardrails to improve safety and performance while still reducing nurse workload. However, it is not clear if the values of the guardrails are optimal. These Guardrails were selected based on clinician and manufacturer recommendations. To improve performance it may be better to lower the upper guardrail to 8.0 mmol/L so the nurse is alerted as soon as the sensor glucose has left the desired target band. To improve safety it may be better to increase the lower guardrail to 4.4 or even 5.0 mmol/L so the nurse is aware that the patient has left or is about to leave the target band. However, both of these changes are likely to increase workload with a greater number of alarms, both false and true. The optimal guardrail setting is investigated further in virtual trials in Chapter 7.

4.5 Summary

This chapter details the results of Phase IIA of the Sentrino trial which was an observational study of the performance and integration of hyper- and hypo-glycaemic guardrail alarms with an existing, proven GC protocol. This study analysed SG and BG data, and alarm data from 8 patients who were recruited to this phase of the trial. An upper guardrail of 10.0 mmol/L and lower guardrail of 4.2 mmol/L were added in the device settings. When the SG value crossed either threshold an alarm would sound. BG measurement was then taken and compared it to the SG, where it would be used for recalibration if the SG-BG error exceeded a predefined value.

Overall sensor and alarm performance was good, only 32/93 alarms required calibration with the majority of those calibrations required for the lower bound, 25/32, where the tolerance for the difference between sensor glucose was only 0.5 mmol/L compared to 2.0 mmol/L for the upper bound. However, there was a high rate of false positive alarms. Many of these false positives were caused by sensor artefacts, unexplained spikes or dips in sensor glucose or sensor drift. While false positives are safer for managing patient blood glucose than false negatives, of which there was only one, they did lead to nursing non-compliance in some cases. In summary, alarms performed well for the most part, but to ensure better integration with current practices and nurse compliance, the protocol regarding false positives needs to be optimised.

Chapter 5. Factors affecting CGM performance in the ICU

Chapters 3-4 have detailed the specific aims and results of the first two phases of the Sentrino Trial. This chapter uses the data and observations of both phases of this trial to highlight the key factors affecting the performance of CGM in the ICU. In particular, the effect of sepsis, oedema and some medications on the performance of CGM are investigated in this chapter. Other practical observations such as nurse feedback and compliance, are also considered.

5.1 Introduction

A recent observational study highlighted the potential of CGM in ICU patients, but concluded that further understanding of factors altering CGM performance is required before CGM guided glycaemic control in the ICU could be safely and effectively realised (Signal et al., 2013). This study highlighted a number of potential issues that could affect sensor performance, including serve oedema, sepsis, certain drugs or therapies.

Serval other studies have also highlighted how patient condition may affect sensor performance in the ICU, including the effect of sepsis and septic shock (Lorencio et al., 2012). In addition, certain medications/therapies commonly used in the ICU, such as paracetamol, can influence CGM device performance (Moser et al., 2010). Vasoactive medications, such as dopamine, norepinephrine, ketanserin, enoximone and nitro-glycerine, are reported to have little or no effect on the accuracy of one type of glucose sensor despite expectations to the contrary (Holzinger et al., 2009).

Muscle trauma or surgery may also impact sensor performance. Klueh et al. (Klueh et al., 2010, Klueh et al., 2014) demonstrated how cytokine expression is related to sensor function with increased inflammation and decreased sensor function in mice deficient in interleukin-1-receptor-antagonist cytokine. Muscle trauma, which is one common cause of admission in the ICU, is known to alter cytokine expression (Jackson et al., 2011). Hence, it is another factor to consider.

Given all these issues, this studied aimed for ~50% of the recruited patients to have sepsis and/or severe oedema, and the remaining ~50% to be non-septic/non-inflammatory ICU patients and act as a control. As a result, a detailed history of the cause of admission, drugs administered and therapies used during the monitoring period was kept to investigate the influence of these factors. A nurse survey was undertaken to gather feedback on the practicality of the device in an ICU setting. Nurse compliance was also analysed. The overall goal was to understand the variability induced by these factors and their potential clinical impact in using CGM for guided GC.

5.2 Subjects and Methods

5.2.1 Subjects

This study uses data from an observation pilot study of CGM in patients admitted to the Christchurch Hospital ICU. This analysis uses CGM and BG data from 21 patients who were recruited to Phase I and Phase IIA of the Sentrino trial as detailed in Chapters 3-4. All patients were recruited by an ICU physician and informed written consent was obtained from the next of kin if the patient was unable to consent and follow up consent was obtained from the patient at a later date if applicable.

Inclusion criteria were two consecutive intermittent BG measurements greater than 8mmol/L, indicating the need for insulin therapy using the STAR protocol (Evans et al., 2012, Stewart et al., 2016), expected admission of at least 3 days, over 18 years of age, and with a platelet count > 30,000/mL. Patients were excluded from the trial if they were not expected to survive, receiving Hydroxyurea, pregnant, and/or lacked clinical equipoise. This study and use of data was approved by the Upper South A Regional Ethics Committee, New Zealand. Table 5.1 summarises the patient demographics.

Table 5.1 Patient demographics displayed as median [IQR] where appropriate

Patients	21
Ages (years)	60 [55 – 68]
Sex (M/F)	11/9
APACHE II	20 [16 – 25]
APACHE III	72 [52 – 96]
SAPS II	43 [34 – 59]
ICU admission (days)	14 [8 – 25]
Outcome (Lived/Died)	14/7
Diabetes (None/T1/T2)	15/0/6

All patients were monitored for up to 3 days using the Sentrino monitoring system (Medtronic, MiniMed, Northridge, California) as detailed in Chapter 3. Patients had either one abdomen and one thigh sensor, two abdomen sensors or one thigh sensor inserted by a trained clinician, depending on which trial phase they were enrolled in.

Calibration BG measurements were obtained by specifically trained ICU nurses at least 3 times per day as recommended by the device manufacturer (Medtronic, MiniMed, Northridge, California). Calibration measures used a Roche Accu-chek Inform II (F. Hoffmann-La Roche Ltd, Basle, Switzerland) hospital grade

glucose meter and arterial blood which is standard practice in the Christchurch ICU. CGM devices were strictly not to be used for glycaemic control.

In addition to BG measurements used for calibration of SG data, each patient had intermittent BG monitoring every few hours. The STAR protocol requires, on average, 12-14 BG measurements per day to guide insulin/nutrition therapy (Fisk et al., 2012, Stewart et al., 2016). In this study, BG measurements were determined using Roche Accu-chek Inform II (F. Hoffmann-La Roche Ltd, Basle, Switzerland) hospital grade glucose meter which is the standard of care in the Christchurch ICU, with blood typically obtained from an arterial line.

5.2.2 Analysis

The MARD was calculated for each sensor and reference measurement pairing, as detailed in Chapter 3. MARD was only calculated if subjects had at least 5 independent reference measurements to compare with SG data. MARD results were then compared to oedema level and septic status, as well as any specific drug therapies.

The level of patient oedema was judged based on the calculated cumulative fluid balance (FB) and an oedema score given by the clinician on sensor insertion. The daily fluid balance tallies all the fluids given minus the amount of fluid excreted by a patient. This balance obviously does not include fluid loss through sweat and other unmeasurable means. However, cumulative FB provides an estimate of how much fluid a patient is retaining and is well-accepted clinically (Boyd et al., 2011). An oedema score is based on 1 - 4 standard scale based on a clinician's interpretation of the response of the patient's skin to pressure

(O'Sullivan, 2007). For this analysis a patient was considered severely oedematous if their cumulative FB increased by more than 5L during the course of monitoring, or if they were given an oedema score of 3 or higher at sensor insertion.

A patient was considered septic if they has a systemic inflammatory response syndrome score (SIRS) > 2 (Kaukonen et al., 2015) and were receiving antibiotics. These two factors are the best indicators available for sepsis. Timely treatment of sepsis is critical, clinicians often will not wait for cultures to confirm the septic state of a patient, and will begin a course of antibiotics immediately. Hence, these criteria are a defacto standard diagnosis (Brun-Buisson et al., 1995, Kaukonen et al., 2015).

When the CGM reading becomes unreliable the Sentrino device will display a poor sensor signal alarm and stop showing glucose values. In some instances this poor sensor signal can be corrected with calibration but it can also lead to sensor failure. The number of occurrences of poor sensor signal was considered as another measure of sensor performance. The number of poor sensor signal events was considered over the duration of poor sensor signal as the duration is dependent on if the sensor was calibrated to attempt to correct the signal or if the sensor was replaced immediately which would have been affected by the availability of a trained clinician to replace the sensor, among other factors. Therefore, one sensor could have multiple instances of poor sensor signal if the reading was corrected by a calibration and then proceeded to fail again during the monitoring period.

The main known causes of all sensor failures were examined, and are detailed in Table 5.2. This summary allows known sensor failure causes to be excluded and inconclusive (IC) sensor failures to be examined

with respect to oedema and septic state. Other metrics relating to these methods of failure were also investigated, such as if the patient was receiving anti-coagulants or the number and duration of sensor cable disconnects.

Nurse compliance was investigated by considering the time between calibrations requested by the Sentrino device and the calibrations being entered. The number of misentered calibrations was also considered based on comparison to the Accuchek meter stored value. Nurse survey results based on questions asking for a 1 -5 ranking, where 1 - Strongly disagree and 5 - Strongly agree, are summarised and presented as median [IQR], and the survey is shown in Figure 5.1.

Continuous Glucose Monitoring in the ICU - The Sentrino Trial

Nurse survey

This is survey for the ICU nurses involved in the Sentrino® Continuous Glucose Management (CGM) System trial. The survey is anonymous and participation is not mandatory, however, the results of this survey may influence future use of these devices in the Christchurch ICU so it is recommended that everyone involved in the study participates in the survey. Thank you for taking the time to complete this survey and we appreciate any feedback.

Rank: 1 - Strongly disagree → 3 - Neutral → 5 - Strongly agree

	Please circle
1. The device was easy to set up and/or use:	1 2 3 4 5
2. I was overall satisfied with the Sentrino CGM System	1 2 3 4 5
3. Sentrino CGM System adds clinical value into my ICU practices	1 2 3 4 5
4. I was confident using Sentrino in my routine ICU practices	1 2 3 4 5
5. I recommend the future routine use of this device in the ICU:	1 2 3 4 5
6. I felt the use of this device could reduce the number of BG measurements I had to do for STAR:	1 2 3 4 5

Please feel free to write any thoughts or comments relating to the future use of this device in the ICU. For example, how you think it could be integrated into standard clinical care.

Comments:_____

_____

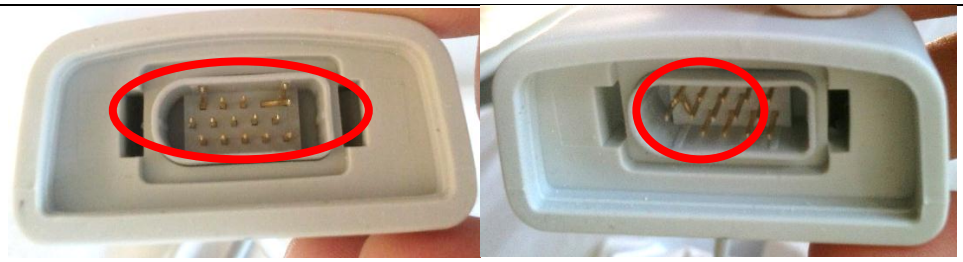
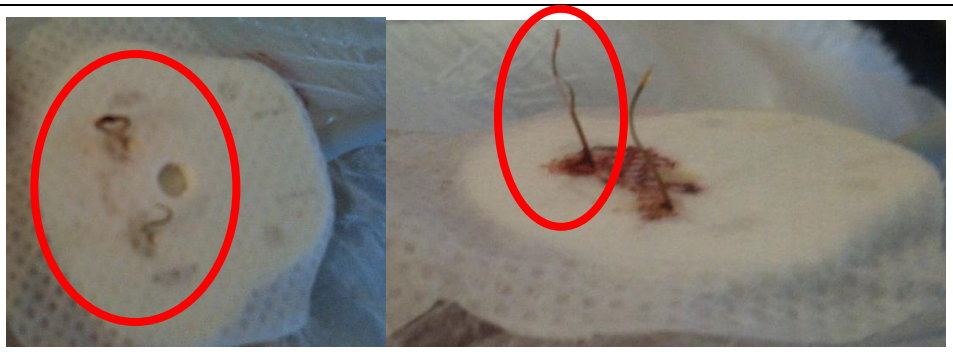
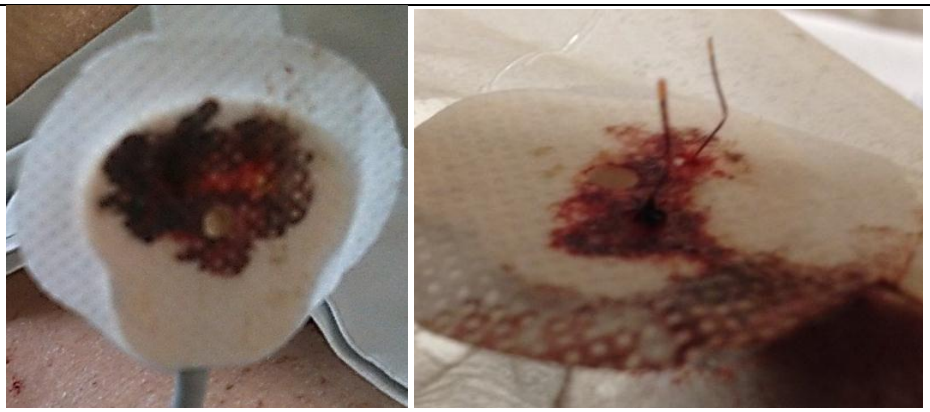
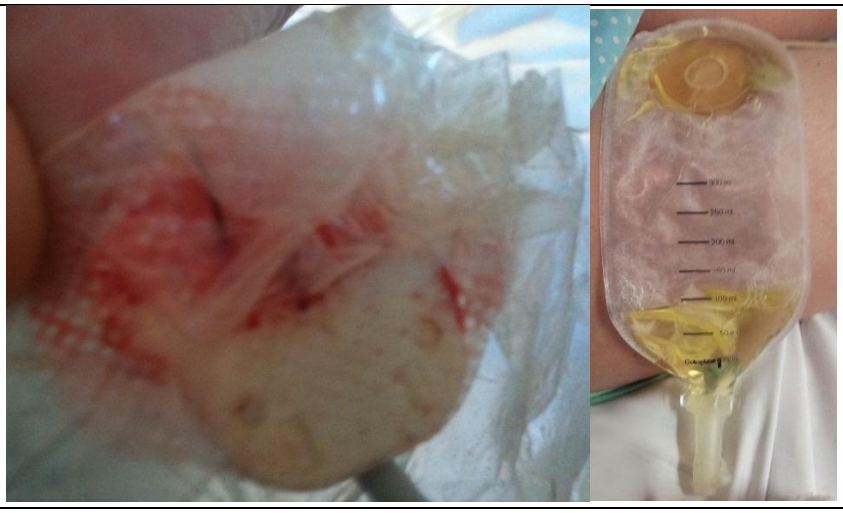
_____

_____

_____

Figure 5.1 *The nurse survey form that was handed out to those nurses who participated in the Sentrino study*

Table 5.2 Examples of the four main sensor failure methods noted during the trial

Failure Mode	Example	Cause
Bent Pins (BP)		Disconnects/ reconnects (excerbated by patient movement)
Crimped Filaments (CF)		Large shear forces between loose subcutaneous fat and sensor site (excerbated by patient movement)
Bleeding (BLD)		Hitting a capillary on insertion (excerbated by anti-coagulants)
Adhesive Failure (AF)		Oedema – adhedsive dressing sweated off or fluid leaking from sensor filament holes resulting in sensor dislodgement

5.3 Results

5.3.1 Effect of Oedema, Sepsis, Medications, and Therapies

A large proportion of this cohort had some level of oedema with 15/21 patients having a cumulative FB > 5L on the day of sensor insertion as shown in Table 5.3. A total of 11/21 patients were judged severely oedematous during the trial with an increase in cumulative FB > 5L between day 1 and the end of the trial or an oedema score of >= 3 on sensor insertion. Two sensor failures were unquestionably the result of oedema as the adhesive dressing applied failed to remain in place on these patients and fluid leaking from the sensor filament holes resulted in the sensor being dislodged. These failures are shown in Table 5.2.

However, comparing the MARD results from those severely oedematous patients compared to those not severely oedematous shows no significant difference, with a median [IQR] of 10.9 [8.0 – 15.8] % and 10.6 [9.6 – 13.7] %, as shown in Table 5.4. The number of poor sensor signal events did increase in the severely oedematous patients with 15 occurrences compared to 10 in those without severe oedema.

A total of 12/21 patients had a SIRS score > 2 and were receiving antibiotics, indicating sepsis. Once again, MARD results indicate no difference between septic patients and non-septic achieving a median [IQR] of 10.7 [8.1 – 13.6] % and 10.7 [9.5 – 13.5] %, respectively. However, the number of poor sensor signal occurrences was higher in the septic cohort with 17 occurrences compared to 8.

Table 5.3 Summary of each patients MARD results and the factors which may have affected sensor performance or caused sensor failure (if applicable).Where FB = Fluid Balance, Ab = abdomen, Th = Thigh, BP = Bent Pins, AF = adhesive failure, CF = crimped filaments, BLD = Bleeding, IC = Inconclusive – see table 5.2 for further explanation of these failure methods

Study No.	Phase No.	Length of monitoring (hrs)			MARD			Oedema Score	Cumulative FB (mL)	Cumulative FB (mL)	Sepsis	Anticoagulants	Operative or Trauma	Acetaminophen	Vasopressors	No. of Disconnects / Duration of disconnects (mins)		Sensor Failure Method	
		Ab		*Th*	*Ab*		*Th*	*Insertion*	*Day 1*	*End of trial*		*Y/N*	*Y/N*	*Y/N*	*Y/N*	*Ab*	*Th*	*Ab*	*Th*
1	I	71.2		71	39.8		14	1	15118	21030	N	N	N	Y	N	16/27	14/20	BP	
2	I	57.6		22	13.4		10	-	9503	11616	N	Y	N	Y	Y	2/1	2/0	BP	BP
3	I	70.7		45	9.4		12	-	10651	13435	Y	Y	Y	Y	N	4/121	9/121		BP
4	I	70.9		71	20.8		6.8	-	3224	8248	Y	Y	Y	Y	N	6/5	3/2	IC	
5	I	71.3		44	16.4		-	1	-1130	2648	Y	Y	Y	Y	Y	11/118	-	IC	
6	I	70.9		71	13.2		11	3	7222	958	Y	Y	N	Y	N	10/171	6/36		
7	I	46.2		46	-		-	1	14174	10759	N	Y	Y	Y	Y	11/21	6/24		
9	I	43.5		44	-		-	2	9880	15610	N	Y	N	N	N	02/23	3/556		BLD
13	IIa			68			12	2	8701	5289	N	Y	N	N	Y		2/0		
15	IIa			65			11	1	11165	5657	Y	Y	Y	Y	N		2/59		
17	IIa			12			-	3	25457	28382	Y	Y	Y	N	Y		2/9		AF
19	IIa			71			7.7	2	9506	7833	Y	Y	Y	Y	Y		0/0		
20	IIa			46			22	2	7611	7148	N	Y	N	N	Y		0/0		
21	IIa			26			8.1	3	18597	20869	Y	Y	Y	N	Y		0/0		AF
22	IIa			69			5.7	2	2151	7917	Y	Y	Y	N	Y		2/108		
23	IIa			58			8	3	1259	-10502	N	Y	N	N	Y		3/3		
24	I	2.9		6.7	-		-	1	2889	3192	N	Y	N	Y	Y	0/0	2/0	CF	CF
25	I	48.9		49	10.2		7.4	1	7646	8525	N	N	N	Y	N	0/0	0/0		
27	I	55.9	56		15	6.9		1	N	27938	N	Y	N	N	Y	04/25	3/19	IC	
28	I	71.3	71		8.7	11		1	N	11005	Y	Y	N	N	N	3/4	5/2		
30	I	43.8	44		-	-		1	N	11866	N	Y	N	N	N	0/0	0/0		

Table 5.4 Summary of overall sensor performance as comparing septic or oedematous cohorts and not septic or oedematous cohorts.

	Septic	Not Septic	Severely Oedematous	Not Severely Oedematous
No. Patients (No. Sensors) [No. MARD]	12 (18) [15]	9 (16) [9]	11 (15) [14]	10 (19) [10]
Median [IQR] MARD	10.7 [8.1 – 13.6]	10.7 [9.5 – 13.5]	10.9 [8.0 – 15.8]	10.6 [9.6 – 13.7]
No. Inconclusive Sensor Failures (No. Adhesive failures)	2 (2)	1 (0)	1 (2)*	2 (0)
No. Poor Sensor Signal Occurrences	17	8	15	10

**Adhesive failures were directly caused by oedematous patients as leaking fluid prevented dressings from sticking*

5.3.2 Nurse Compliance and Feedback

Overall, nurse compliance was good, with a median [IQR] delay between a calibration being required and a calibration being received only 2 [1 – 31] minutes, as seen in Table 5.5. However, approximately 20% of all calibrations, 81/410, were entered incorrectly as determined by comparing the entered value to the stored measured value of the Roche glucometer. The median absolute difference between the measured value and the entered value was 0.3mmol/L with an interquartile range of 0.5 – 1.0mmol/L.

Approximately 30 surveys were handed out to nurses who used the Sentrino CGM system and 22 anonymous responses were returned. Nurse feedback suggests feelings were neutral about the Sentrino CGM system with the approximately 30% of responses being a 3 or 4 for all but one question, as shown in Table 5.6. The most common concern or complaint was the number of disconnects between the sensor and sensor cable, with some patients, such as Patient 1, having a total of 30 disconnects during a monitoring period of 71.2 hours (Table 5.3).

Table 5.5 Summary of total calibrations made and the rate of misentry and delay between a calibration being required and entered

No. Calibrations	410
No. Misentered Calibrations	81
Absolute Misentry Amount median [IQR]	0.5 [0.3 – 1.0]
Calibration Delay (min) median [IQR]	2 [1 – 31]

Table 5.6 Summarised results of a survey undertaken by the ICU nurses involved with the Sentrino study.

Questions (given a score 1 - Strongly disagree → 3 - Neutral → 5 - Strongly agree)	**Response (%)**				
	1	**2**	**3**	**4**	**5**
The device was easy to set up and/or use:	10	5	35	30	20
I was overall satisfied with the Sentrino CGM System:	14	10	38	33	5
Sentrino CGM System adds clinical value into my ICU practices:	14	19	29	33	5
I was confident using Sentrino in my routine ICU practices:	5	19	24	38	14
I recommend the future routine use of this device in the ICU:	10	19	33	33	5

Positive feedback for the Sentrino:	**Major Concerns/Criticism:**
1. Anything that reduces time consuming STAR measurements is welcome 2. Good tool aside from these issues (see concerns 1 and 6) 3. Would have liked to have used it more than once	1. Sensor often disconnecting during turns (requiring recalibration) 2. Not always reading accurately and/or sensors diverging therefore reservations using Sentrino to change or commence new treatments 3. Great difficulty when patient needs to be mobilized, CT scan etc 4. Cable connection gets very hot and is difficult to position away from patient 5. Skin probe causes oozing in oedematous patients 6. Used up too much bed space which is at a premium with busy patients

5.4 Discussion

5.4.1 Effect of Oedema, Sepsis, Medications and Therapies

The level of oedema does not appear to correlate with sensor performance as judged by MARD analysis. However, meaningful MARD results were not calculated in two severely oedematous patients as sensor failure occurred before enough data (> 5 reference BG measurements) could be collected. These two sensor failures were conclusively caused by oedema, as the sensors were dislodged from their site of insertion due to fluid leaking from this area. The picture in the last row of Table 5.2 shows 100mL of fluid that was collected overnight from the insertion site after the sensor had been dislodged. It is evident that in cases of severe oedema, such as highlighted here, current CGM devices cannot provide cannot provide consistent performance. This issue is exacerbated by the Sentrino sensors not being waterproof. Hence, even if the sensors remained in place the leaking fluid could damage the sensors, which may have been the case in the inconclusive failure for the oedematous cohort noted in Table 5.4.

Sepsis also does not appear to correlate with MARD results. However, the number of poor sensor signal episodes is much higher in the septic cohort. It is difficult to separate out the effect of sepsis as many septic patients were also oedematous and receiving anticoagulants.

The effect of anticoagulants is important as often blood was noticed on the sensor probes upon removal. In the example shown in Table 5.2, the extent of the bleeding caused sensor failure. Blood clotting around the sensor filaments reduces the area for the glucose-oxidase reaction to occur and could therefore induce a weakened signal. However, all but 2/21 patients were receiving anticoagulant medication.

Hence, it impossible to quantify the direct impact of this medication on sensor performance separate from other factors.

In addition, there is a small chance that a capillary is hit on insertion. The anticoagulants then result in the bleeding from this event being more pronounced. The best way avoid this interference from blood clotting around the filaments and fouling the sensor may be an improved sensor design or insertion technique, as it would be impractical to avoid all ICU patients receiving anticoagulant medication.

Other medications, such as vasopressors, showed no effect on the performance of sensor signal matching already published results (Holzinger et al., 2009). Contrary to literature results linking sensor function to cytokine expression (Klueh et al., 2014, Klueh et al., 2010), which is known to be altered by muscle trauma (Jackson et al., 2011), patients who underwent surgical procedures or had wounds did not show any difference in sensor performance in this study. Acetaminophen also showed no effect on performance. It is also possible that any potential influence these factors have was masked by the other issues mentioned, which had a far greater influence on sensor performance.

5.4.2 Nurse Compliance and Feedback

Overall nurse compliance was good, although approximately 20% of calibration measurements were entered incorrectly. It is likely that given time this number would decrease, as the mistakes in entering calibration values occur more often when nurses are unfamiliar with the technology. Additionally, the entry interface could be designed to minimise errors (Ward et al., 2012). The Sentrino was also only

observational, so its lack of influence in care may have reduced the care taken to enter the correct value as the CGM value.

The nursing feedback received was broadly neutral. Nurses were neither pleased nor displeased with the Sentrino. This is a positive outcome, as it indicates the nurses saw potential for the use of CGM in ICU even with the extra work load studies, such as this one, generate for nurses and the issues encountered during the trial. The high number of disconnects, especially in the first few patients (Table 5.3), attracted the most criticism from the nurses. Most of these disconnects happened during turning which is undertaken every 2-4hrs in the Christchurch ICU as part of routine practice, and highlight the difficulty with any extra line attached to a patient.

Repeated disconnects increase nurse workload. Not only must they reconnect the device, which if done incorrectly can lead to bent pins and sensor failure (Table 5.2), but the nurse must also follow on screen prompts to confirm if the sensor is a new sensor or old sensor. If this process is done incorrectly the sensor will go through the initialising sequence again requesting repeated calibrations. In addition, if the sensor is disconnected for > 30mins this reinitialising process must occur, regardless. Hence, patient mobility is increasingly difficult especially if the patient requires further testing outside the ICU, such as a Computer Tomography (CT) scan. Furthermore, early ICU patient mobility has been shown to improve patient outcomes (Adler et al., 2012) and is a clear focus in the Christchurch ICU. Therefore anything this that restricts this is discouraged, and CGM issues exacerbated by lack of mobility, such as oedema, can become an even larger problem to their use.

5.4.3 Practical recommendations for CGM in ICU

The Sentrino study has highlighted several practical issues regarding the use of CGM in the ICU. For CGM to be successful in reducing nurse workload and increasing patient safety, the following recommendations are made:

- Avoid severely oedematous patients where fluid is likely to leak from ruptured skin
- Waterproof CGM sensors
- Reconsider insertion technique to lessen the risk of capillary damage
- Wireless transmission between sensor and monitor unit for ease of patient mobility and minimisation of sensor disconnects

Overall, the Sentrino and CGM has shown potential to reduce nurse workload for the glucose measurement and increase patient safety. However, until the above complications are addressed they are unlikely to be commonplace within the ICU.

5.5 Summary

The overall goal of this analysis was to better understand the impact of sepsis, oedema and some medications on CGM results and take note of nurse compliance and feedback to gain insight in to the potential clinical impact of using CGM to guide GC. This analysis used data from 21 patients enrolled in two different phases of the Sentrino trial. Approximately 50% of all enrolled subjects were severely oedematous and/or septic by design.

Results indicate that while oedema and sepsis do not affect the sensor performance as judged by MARD they can lead to increased number of sensor failures and poor sensor signals. The medication that affected

sensor performance the most was likely to be anticoagulants leading to excessive bleeding if sensor insertion ruptured a capillary, as it generated at least one conclusive sensor failure. However, as all but 2 patients were receiving anticoagulant medication it was impossible to quantify the direct impact of this medication on MARD. Nurse compliance was good and feedback was mainly neutral. The high number of disconnects of sensor cable and monitor was a key concern for nurses.

For CGM to be successful in reducing nurse workload and increasing patient safety the following recommendations are made:

- Avoid severely oedematous patients where fluid is likely to leak from ruptured skin
- Waterproof CGM sensors
- Reconsider insertion technique to lessen the risk of capillary damage
- Wireless transmission between sensor and monitor unit for ease of patient mobility

In summary, the Sentrino CGM system has shown potential to be of assistance in the ICU environments. However, these issues must be addressed before being used for CGM guided glycaemic control in this cohort.

Chapter 6. Sensor Modelling

Before CGM can be used to guide glycaemic control protocols the impact of suboptimal accuracy resulting from error or delay in calibration measurement, sensor drift, and delayed glucose diffusion must first be characterised. Characterising this error allows models to be formed so in-silico simulations can test the performance and safety of CGM driven glycaemic control protocols and examine best and worst scenarios. In this chapter a CGM model is formed based on the clinical data collected in Phase I and IIA of the Sentrino trial. This data will then be used in the Chapter 7, to investigate the impact in silico of using Sentrino measurements to guide glycaemic control.

6.1 Introduction

Two in-silico studies (Signal et al., 2010, Mombaerts et al., 2015) and a recent pilot observational trial (Signal et al., 2013) have shown that CGM devices, when coupled with a well-designed GC protocol, offer several potential benefits over the standard practice of intermittent BG monitoring. These studies have shown that CGM devices have the ability to reduce hypoglycaemia, maintain BG control, and reduce nurse workload.

Typical glycaemic control protocols require BG measurements every 1-4 hours (Evans et al., 2012, Lonergan et al., 2006a, Plank et al., 2006, Blaha et al., 2009, Stewart et al., 2016), typically resulting in approximately 12-16 blood draws a day per patient. This frequency can represent a measurable part of total nurse workload (Carayon et al., 2005, Holzinger et al., 2005). CGM devices have the potential to drastically reduce the number of BG measurements per day, positively impacting workload, while improving patient safety and increasing time in the desired BG target band.

However, CGM devices tend to have suboptimal accuracy resulting from error or delay in calibration measurement, sensor drift and delayed glucose diffusion (Zimmermann et al., 2012, Facchinetti et al., 2014, Reifman et al., 2007, Kuure-Kinsey et al., 2006). Thus, before CGM can become ubiquitous in the care of critically ill patients these errors on BG control must first be quantified and understood. Subsequently, their interaction with GC protocols and resulting impact on performance and safety can be assessed.

Despite significant outpatient use and promise for CGM (Breton et al., 2008, Klonoff, 2005a, Klonoff, 2005b) the literature contains very few reports of error models derived from clinical SG data. Without a good model of CGM dynamics the feasibility of CGM combined with GC cannot be assessed in-silico. Two studies have provided sufficient details of CGM device error characteristics to allow models to be created or reproduced for use in-silico (Breton et al., 2008, Goldberg et al., 2004). However, these models are now ten years old and significant advances in sensor technology mean the level of error produced by these models no longer characterises the dynamics of more recent CGM devices. Therefore, this chapter presents and validates a simple CGM error model based on the latest available CGM devices.

6.2 Subjects and Methods

6.2.1 Patients

This study uses data from an observational pilot study of CGM in patients admitted to the Christchurch Hospital ICU during 2014-15. This analysis uses CGM and BG data from 21 patients who were recruited to Phase I and Phase IIA of the Sentrino trial, as detailed in Chapters 3-5. All patients were recruited by a physician in the ICU and informed written consent obtained. If the patient was unable to consent next of

kin were approached for consent and follow up consent was obtained from the patient at a later date if applicable. Inclusion criteria were:

1) Two consecutive BG measurements greater than 8 mmol/L, indicating the need for insulin therapy using the STAR protocol (Evans et al., 2012)
2) Expected admission of at least 3 days
3) Over 18 years of age
4) A platelet count > 30,000/mL.

Patients were excluded if they were not expected to survive, receiving hydroxyurea, pregnant, and/or lacked clinical equipoise. This study and use of data was approved by the Upper South A Regional Ethics Committee, New Zealand (URA/12/02/004). Table 6.1 shows the patient demographics.

Table 6.1 Patient demographics displayed as median [IQR] where appropriate. APACHE II = Acute Physiology and Chronic Health Evaluation II

Patients	21
Ages (years)	60 [55 – 68]
Sex (M/F)	11/9
APACHE II score	20 [16 – 25]
Outcome (Lived/Died)	14/7

All patients were monitored for a period of up to 3 days using the Sentrino monitoring system (Medtronic, MiniMed, Northridge, California), as detailed in Chapter 3. Patients had either one abdomen and one thigh sensor, two abdomen sensors or one thigh sensor inserted by a trained clinician, depending on which trial phase they were enrolled in. Calibration BG measurements were obtained by specifically trained ICU nurses at least 3 times per day as recommended by the device manufacturer (Medtronic, MiniMed, Northridge, California) using the Roche Accu-chek Inform II (F. Hoffmann-La Roche Ltd, Basle, Switzerland) hospital grade glucose meters as is standard practice in the Christchurch ICU, with blood typically obtained

from an arterial line. CGM devices were strictly not used for determining treatment for GC during this study.

In addition to BG measurements used for calibration of SG data, each patient had intermittent BG monitoring every few hours. The STAR protocol requires, on average, 12-14 BG measurements per day to guide insulin/nutrition therapy (Fisk et al., 2012). These additional reference measurements can be used to assess CGM accuracy.

Each SG signal was treated separately for modelling purposes. Three patients were excluded from the analysis, Patients 17, 21 and 24. As noted in Chapter 5, these patients had early sensor failure and were deemed clinically unsuitable for replacement sensors. Hence, not enough data was collected from these patients to be relevant to the model. Additionally, any data characteristic of a failed sensor or uncharacteristic of a sensor signal was removed, shown in Figures 6.1 – 6.6. This removal resulted in 28 separate SG signals for analysis. Table 6.2 summarises the data used for modelling and validation.

Table 6.2 Data used for modelling and validation

No. SG signals	28
No. SG hours	1689
No. Calibration measurements	380
No. Reference measurements	669

6.2.2 The Model

The error in a CGM signal can be broken down into separate parts specifically, the true BG signal noise and drift:

$$CGM = BG_{real} + noise + drift \quad \text{Eq. 6.1}$$

Where *noise* is the random error centred about zero and *drift* is a linear bias between calibration measurements. Noise and drift were modelled based on clinical Sentrino data to create a model of CGM behaviour to be added to reference blood glucose values in order to simulate the effects of CGM error on GC results.

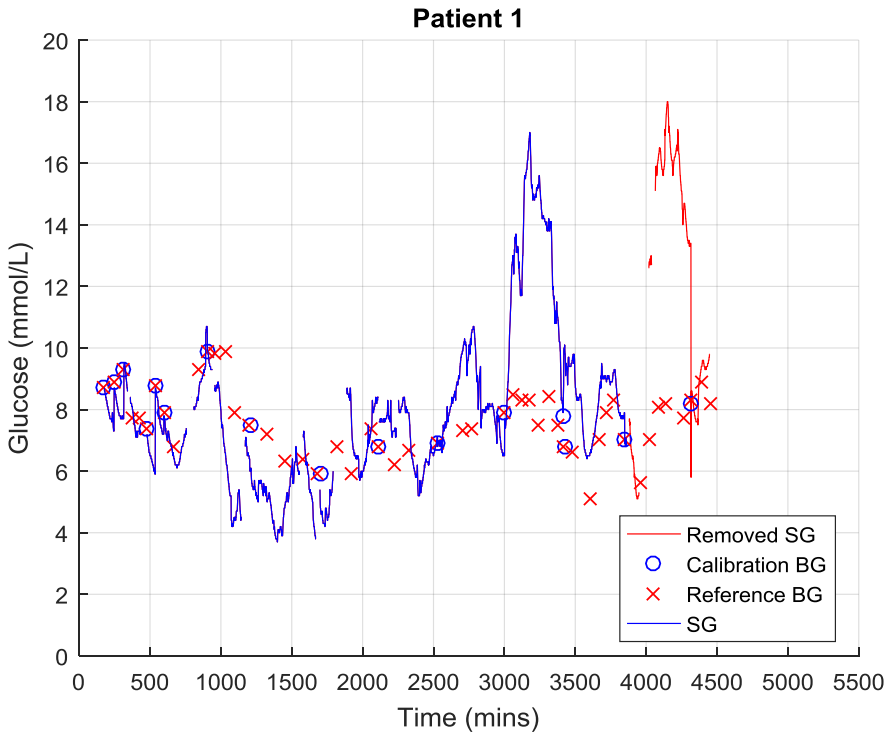


Figure 6.1 *The sensor glucose that was removed from Patient 1's sensor glucose signal is shown in red. This data was removed as the sensor plug pins had become bent at ~4000 mins resulting in poor sensor signal alerts until the sensor was removed at ~4500 mins.*

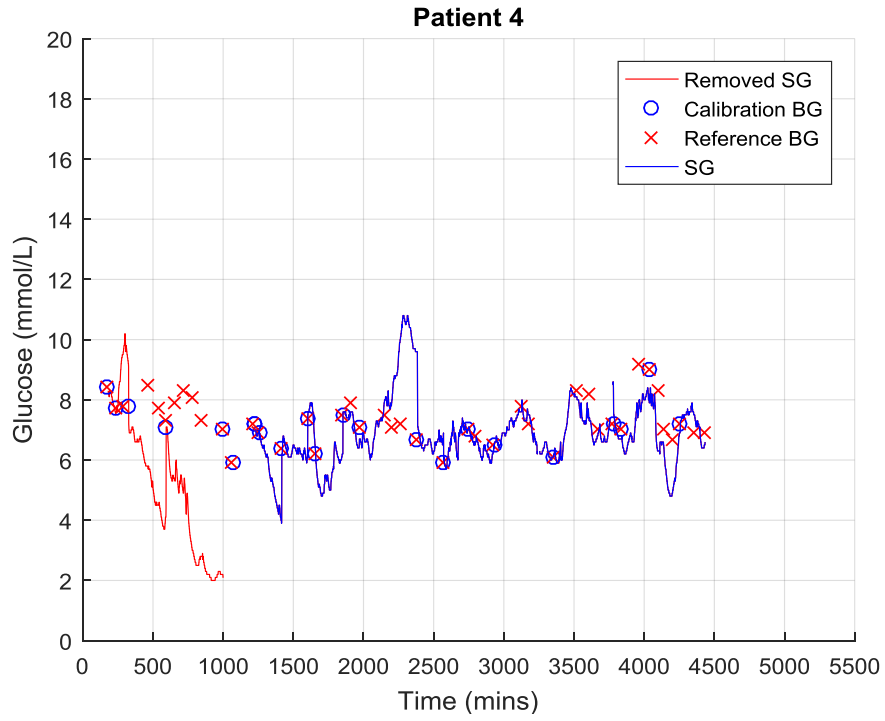


Figure 6.2 *The sensor glucose that was removed from Patient 4's sensor glucose signal is shown in red. This data was removed as after the initial calibration sequence the sensor has failed immediately.*

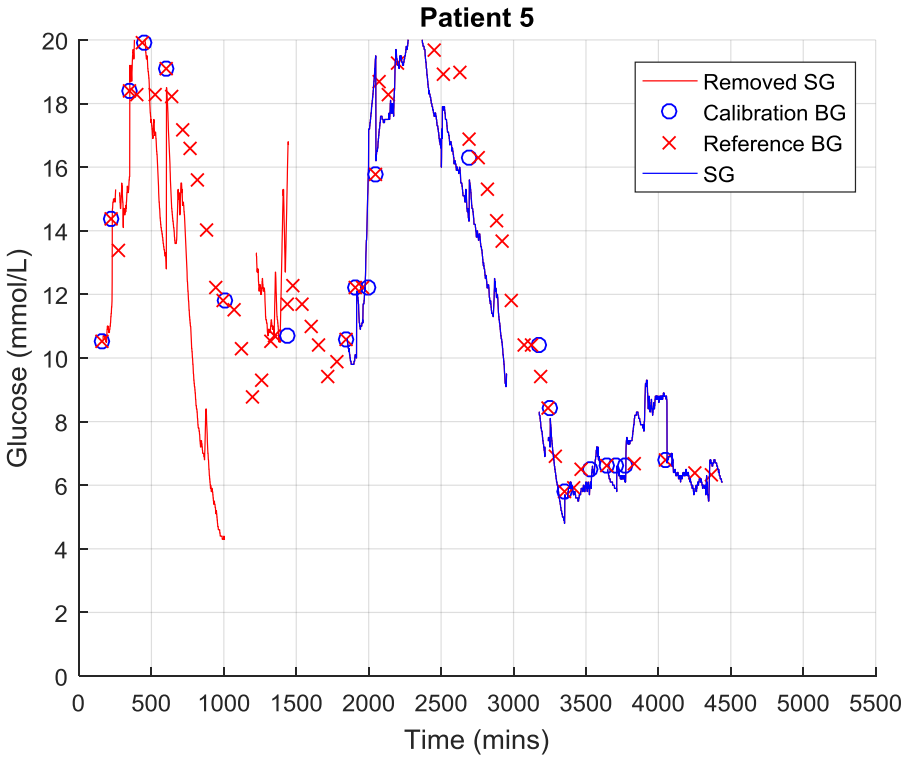


Figure 6.3 *The sensor glucose that was removed from Patient 5's sensor glucose signal is shown in red. The sensor has failed very early on and been replaced at ~1600 minutes.*

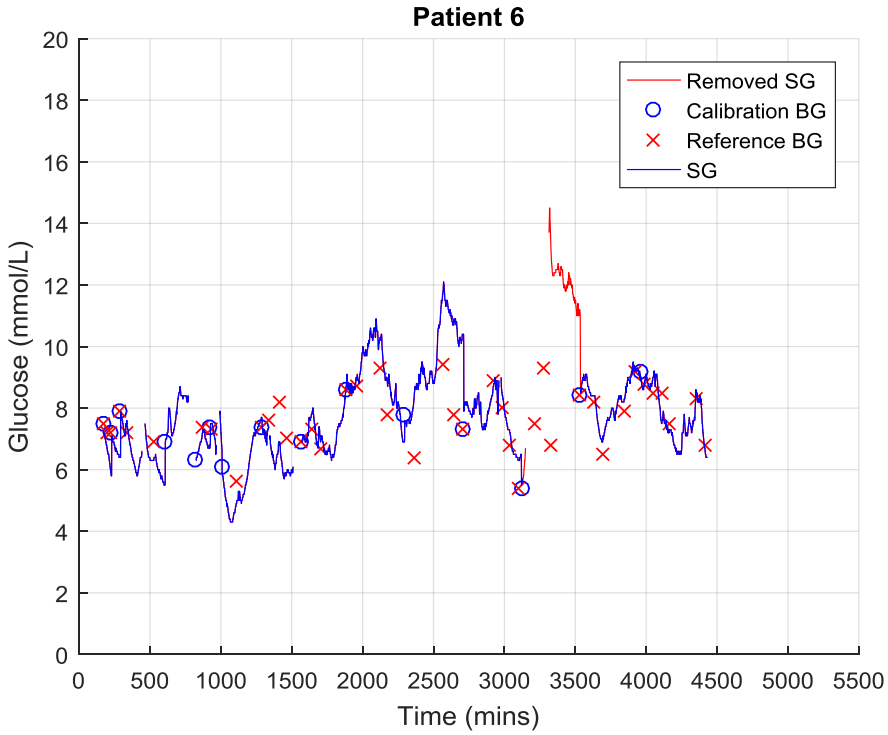


Figure 6.4 *The sensor glucose that was removed from Patient 6's sensor glucose signal is shown in red. The sensor has become disconnected from the monitor resulting in an erroneous spike when reconnected.*

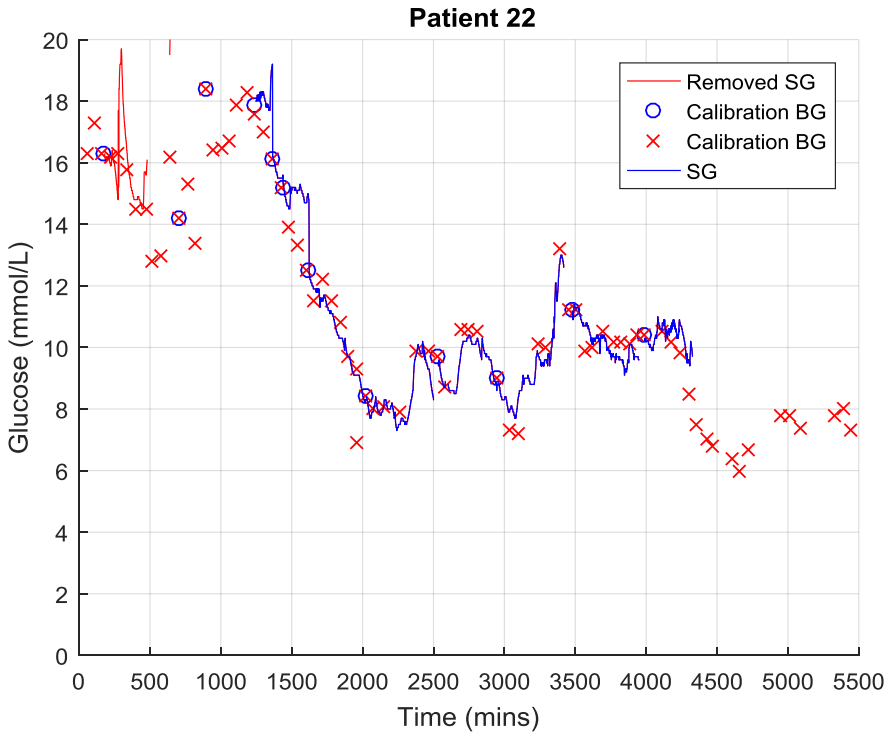


Figure 6.5 *The sensor glucose that was removed from Patient 22's sensor glucose signal is shown in red. Sensor has failed upon insertion and has then been replaced at ~1200 minutes*

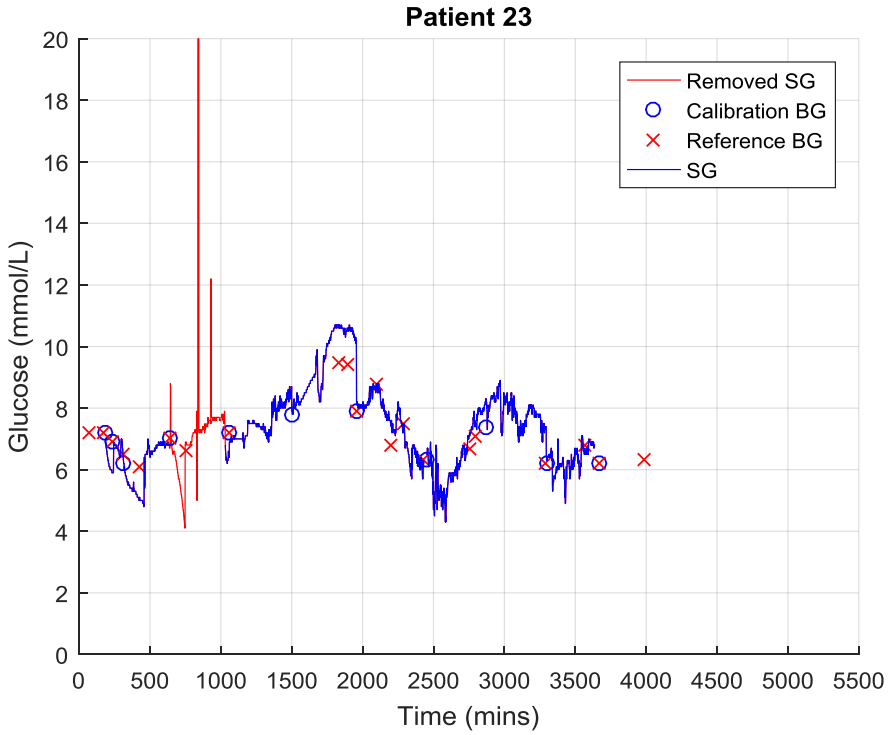


Figure 6.6 *The sensor glucose that was removed from Patient 23's sensor glucose signal is shown in red. These large spikes in sensor glucose were not seen in any other patient and are likely caused by damaged pin ports on the sensor - monitor connection. A hardware fault rather than a characteristic of the sensor.*

6.2.2.1 Drift

A constant rate drift with a linear bias, was assumed for the drift model. Drift was defined as the rate of increase in discrepancy between CGM signal and reference BG measurements between calibration BG measurements. Simply, drift is the rate of change of CGM bias relative to BG measurements. The drift profile between any two calibration BG measurements was then defined by *delta,* the accumulated drift magnitude. The magnitude of accumulated drift between any two calibration BGs was found by measuring the size of the bias (CGM value – Calibration BG) at the second calibration BG as shown in Figure 6.7. Once *delta* is identified for each calibration measurement it can be removed from the SG for further analysis. This calculation resulted in a new drift-corrected CGM profile as shown in Figure 6.7.

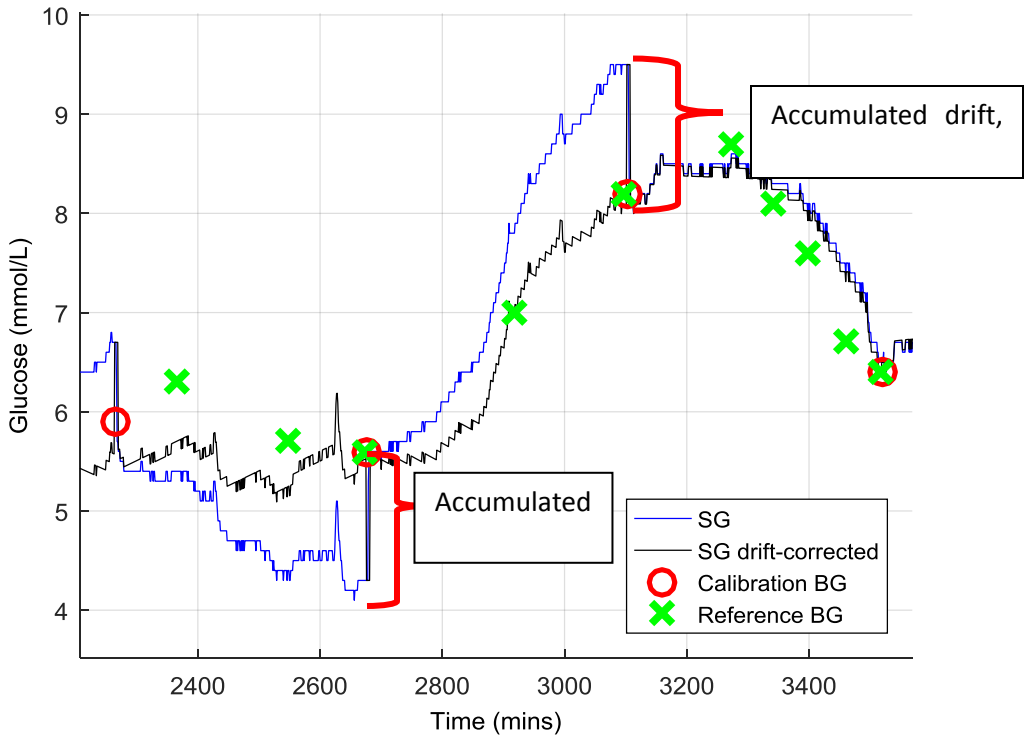


Figure 6.7 *Example of accumulated drift in a SG signal and a SG signal once drift is removed*

The section between each calibration measurement was considered independently in further analysis because calibration should correct for any drift. Autocorrelation of the delta data shows no tendency for a sensor to repeatedly drift in the same direction, as shown in Figure 6.8. Autocorrelation is the normalised dot product of the signal after it has been shifted in time by some amount. The resultant angle ,θ, shows the trend similarity between two vectors and its cosine has values from -1 and +1 demonstrating opposing to complete agreement. A lag window of up to 10 minutes was considered. Therefore, the similarity of the signal to itself was compared every minute from 10 minutes before to 10 minutes after the current time. The *delta* data was first mean shifted before autocorrelation was applied to remove bias.

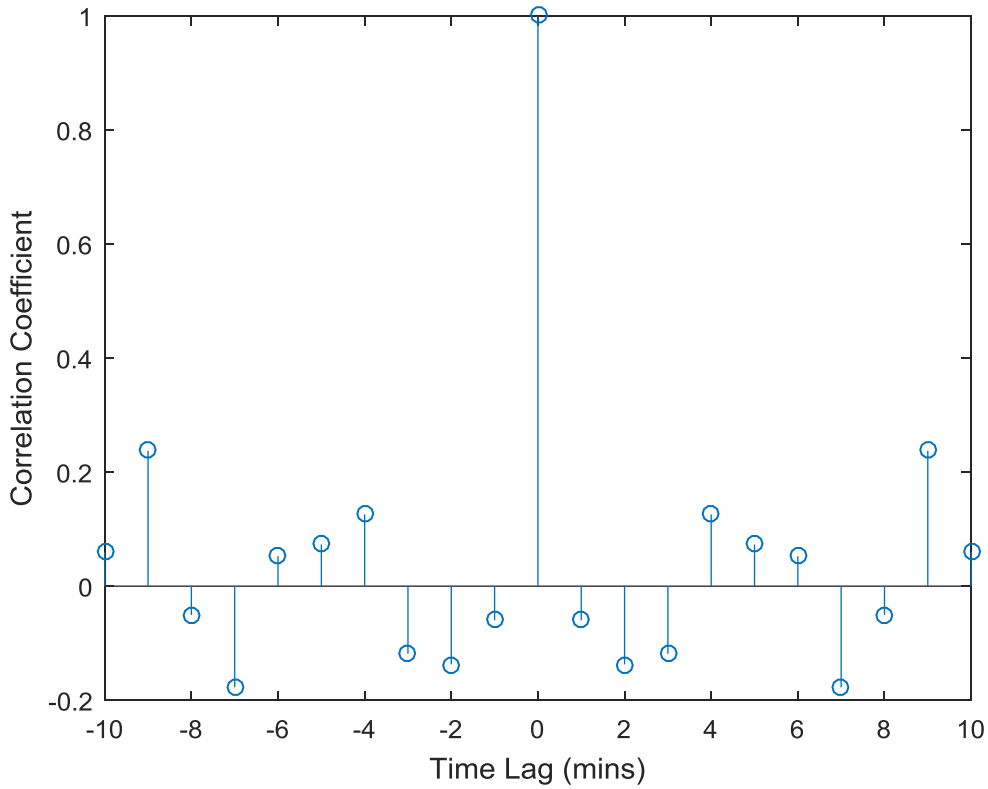


Figure 6.8 *The autocorrelation of the delta drift data over a lag window of +10 and -10 minutes, for all data points. There is no correlation evident with in this window.*

An empirical model of drift was implemented from the cumulative distribution function (CDF) of the *delta* data across the entire cohort using inverse transform sampling, as shown in Figure 6.9. This method is implemented by interpolating the CDF to 100,000 points to ensure a smooth curve. A uniform random number generator then selects a value in the range 0 – 1 which was then used to obtain the corresponding interpolated CDF delta value. The process can be repeated resulting in a dataset that has the same distribution as per the empirical data.

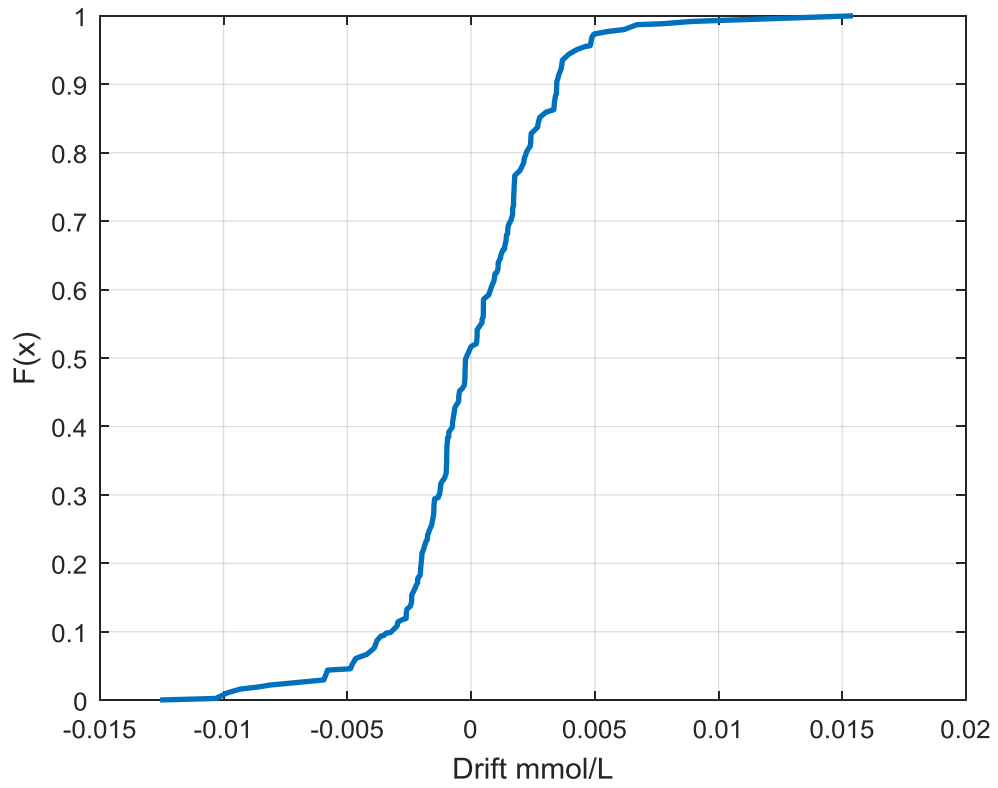


Figure 6.9 *The cumulative distribution function of the delta drift data*

6.2.2.2 Noise

Sensor noise contributes the remaining zero mean, random error to the modelled CGM signal of Equation 1. Noise was split into two components, low and high frequency noise. Low frequency noise is considered "the long duration" sensor noise, or, in this case, the difference between reference BG and the SG once drift is removed. High frequency noise is the "minute to minute" noise that gives the SG signal a jagged appearance.

The low frequency noise was considered to be the difference between the each independent reference BG and the drift-corrected SG signal. Low frequency noise accounts for the error that occurs intermittently over longer time periods, which could be induced by events such as turning or other accidental pressure applications on the sensor site (Helton et al., 2011a, Helton et al., 2011b). As was done for the drift data, an empirical model was generated from a CDF of low frequency noise by inverse sampling.

Unlike low frequency sensor noise, high frequency sensor noise occurs minute-to-minute and results in the 'jagged' appearance of the CGM signal. High frequency noise represents electrical noise, random variation induced by the imperfect reading and transmission of the sensor signal. High frequency noise is very small in magnitude thus does not affect the identification of low frequency noise. A simple model was created using the CGM data by calculating the size of the changes in glucose from sample to sample (every minute). The sample-to-sample change was then halved to obtain an amplitude because noise is assumed to be zero mean so sample-to-sample changes would double the amplitude found over many measurements. Thus, it yields an independent, random added noise with sample-to-sample changes similar to those observed in the empirical data.

6.2.3 Modelling Sensor Glucose

To ensure the CGM model produced similar dynamics to the CGM sensors, the 28 data sets containing true reference and calibration BGs provided the framework to generate modelled SG signals. The reference and calibration BGs were linearly interpolated to give a 'true BG signal'. CGM drift, and noise are added to this ‘true BG signal’, as shown in subplot A of Figure 6.10.

A drift profile was then created using the empirical drift model to randomly generate a drift *delta* value for each 8 hour calibration interval, as shown in subplot B of Figure 6.10. A low frequency noise profile created by sampling every 160 minutes from the low frequency error model. Samples were taken at 160 min intervals as opposed to at the time of reference BG measurements because some data sets contained infrequent reference BG measurements and the mean reference measurement interval across the available dataset was 160 minutes. Consecutive samples were linearly interpolated and a median filter was used to smooth the error signal, as shown in subplot C of Figure 6.10, where the median filtering removes the uncharacteristic sharp edges introduced by the linear interpolation between the error points. Finally, a high frequency noise profile was generated every minute by randomly sampling from the empirical high frequency model, as shown in subplot D of Figure 6.10. The summed result of each component yields a simulated true BG with CGM error, as shown in Figure 6.10 subplot E.

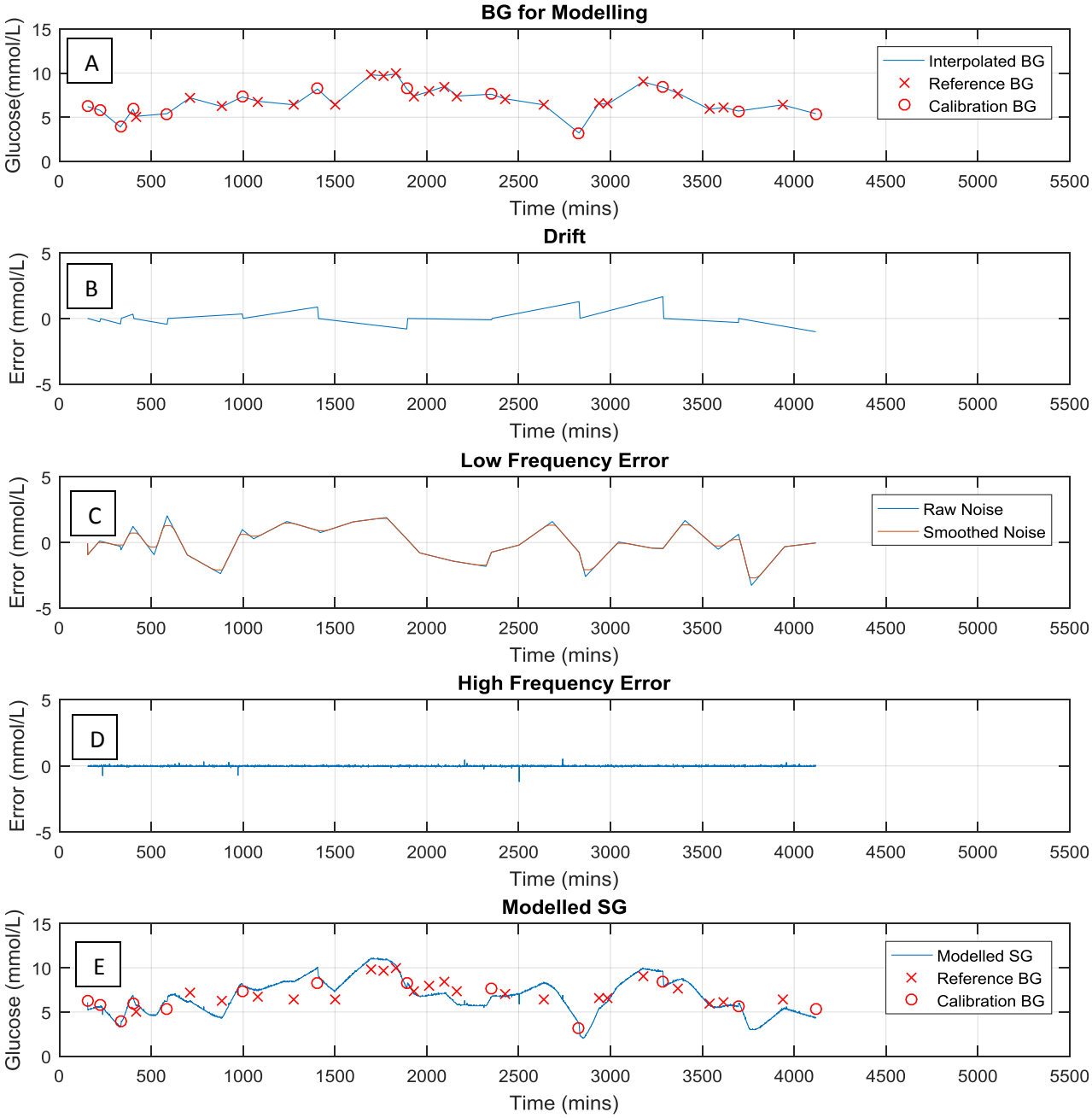


Figure 6.10 *Example of the process undertaken to model a SG signal. First the BG measurements are interpolated, A. Then drift, low frequency and high frequency error are found by sampling from their empirical distributions, B, D and C respectively. Finally, the error is added to the interpolated BG to prove the simulated signal, E.*

6.4 CGM Sensor Model Validation

The CGM model is a created using random process. Therefore, it cannot be deterministically compared to actual measured CGM data and no two uses of the model for the same true BG data yield the same result. Thus, to validate the modelled signals, autocorrelation was used to assess the similarity of the simulated CGM signals to the original CGM data. All signals were first mean shifted to remove bias before autocorrelation was applied to remove bias. If the resulting autocorrelation coefficients of the simulated SG and real SG are similar then the model can be considered to provide a realistic approximation of the sensor dynamics.

Fifty SG signals were simulated for each patient and the autocorrelation coefficient was calculated for the real and each simulated signal over a +10 mins to -10 mins window. The median and range of correlation coefficients of the modelled SG was then compared to the correlation coefficient of the measured SG. The closer the agreement between the correlation coefficients of the simulated signals, and the correlation coefficient of the real CGM signal the better the model.

6.5 Results and Discussion

Visually and qualitatively, the CGM model generates similar signals to the empirical data. An example signal is shown in Figure 6.11 with real SG and 3 simulated signals. In particular, it is difficult to distinguish the real CGM signal from the modelled signals.

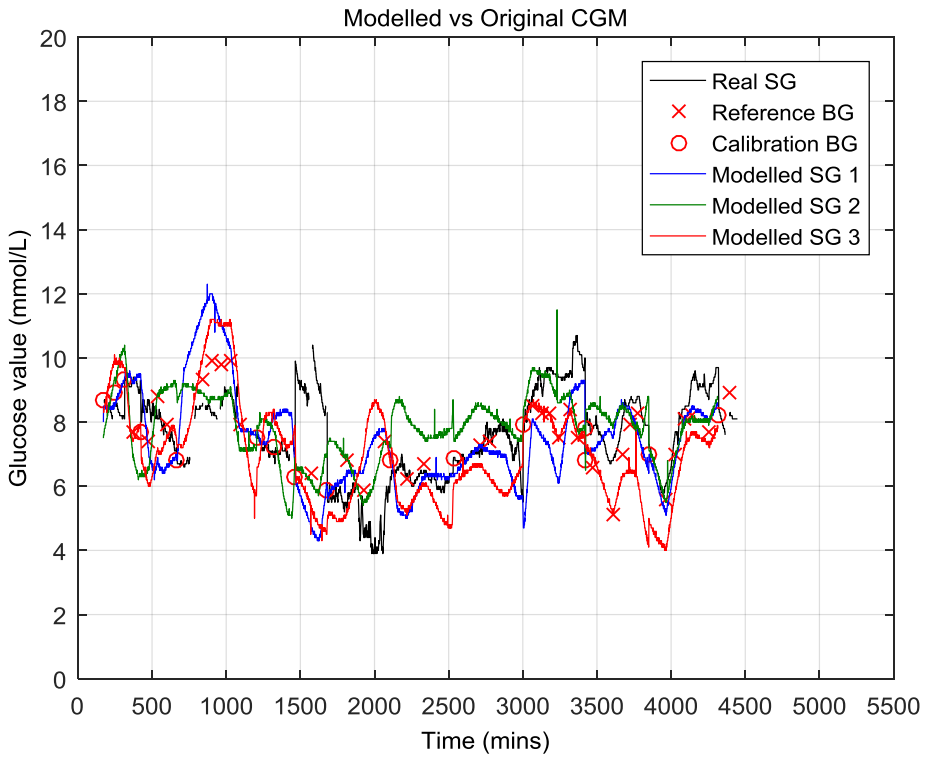


Figure 6.11 *Comparing the original SG signal to that of three different modelled signals using the CGM modelled generated from empirical data*

Figure 6.12 displays the median and range of autocorrelation values for each time lag for each patient's modelled SG signals. The modelled SG show very similar autocorrelation trends to those displayed by the measured data. Measured SG is less tightly correlated than the median modelled SG in the majority of cases. However, only 3/28 measured SG values (A, B and C in Figure 6.11) do not sit within the range of modelled SG across all of the 20 minute windows and the median difference between the modelled and measured SG correlation values was 0.007 with a range of 0 – 0.13, the biggest differences occurring at the +10 or -10 minute time shift, where correlation might generally be expected to be weaker.

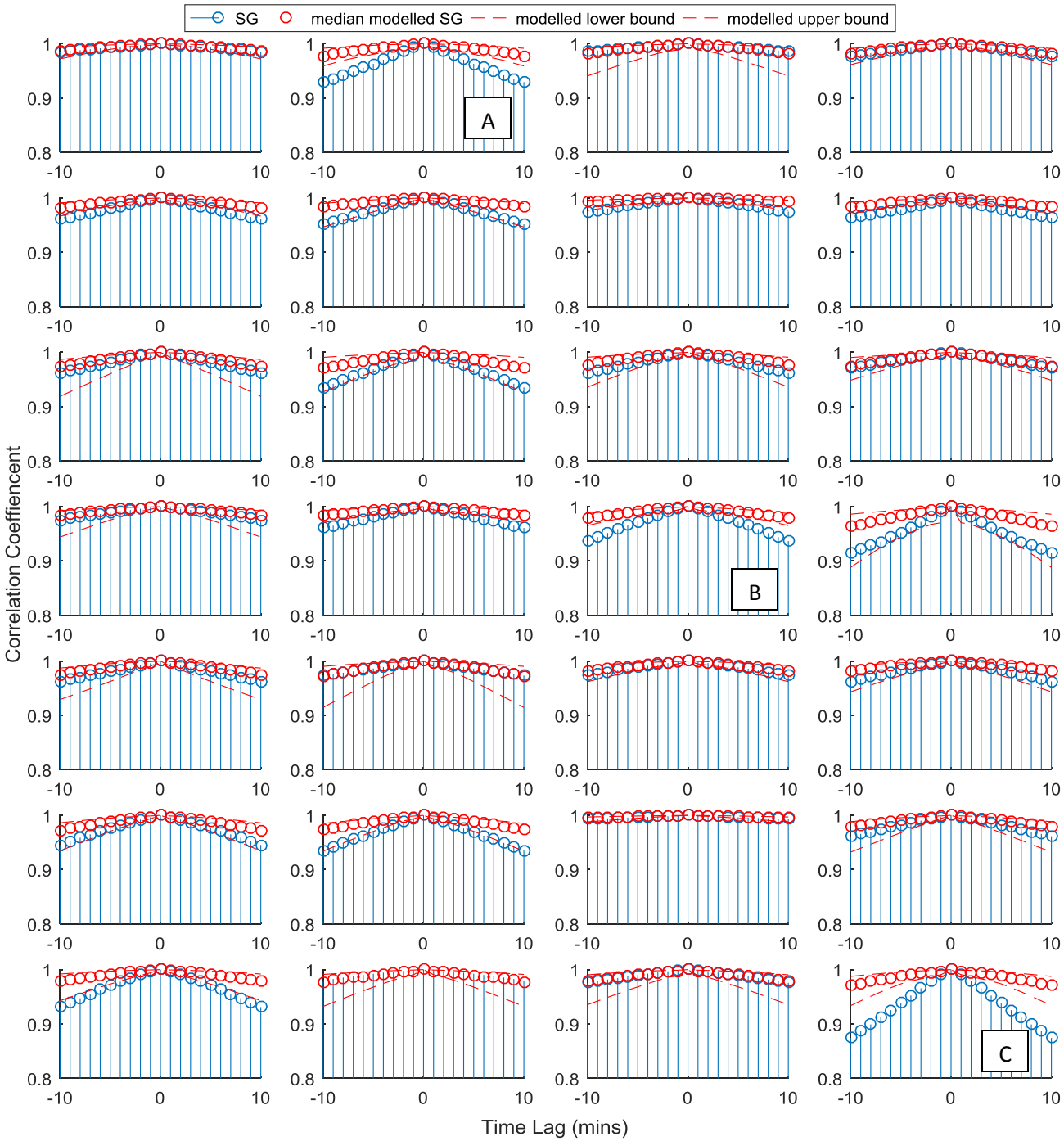


Figure 6.12 *Comparing the autocorrelation coefficients for the real SG to the median and range correlation coefficients of the modelled SG. A, B, and C are where the measured SG autocorrelation does not fall within the range of modelled SG autocorrelation.*

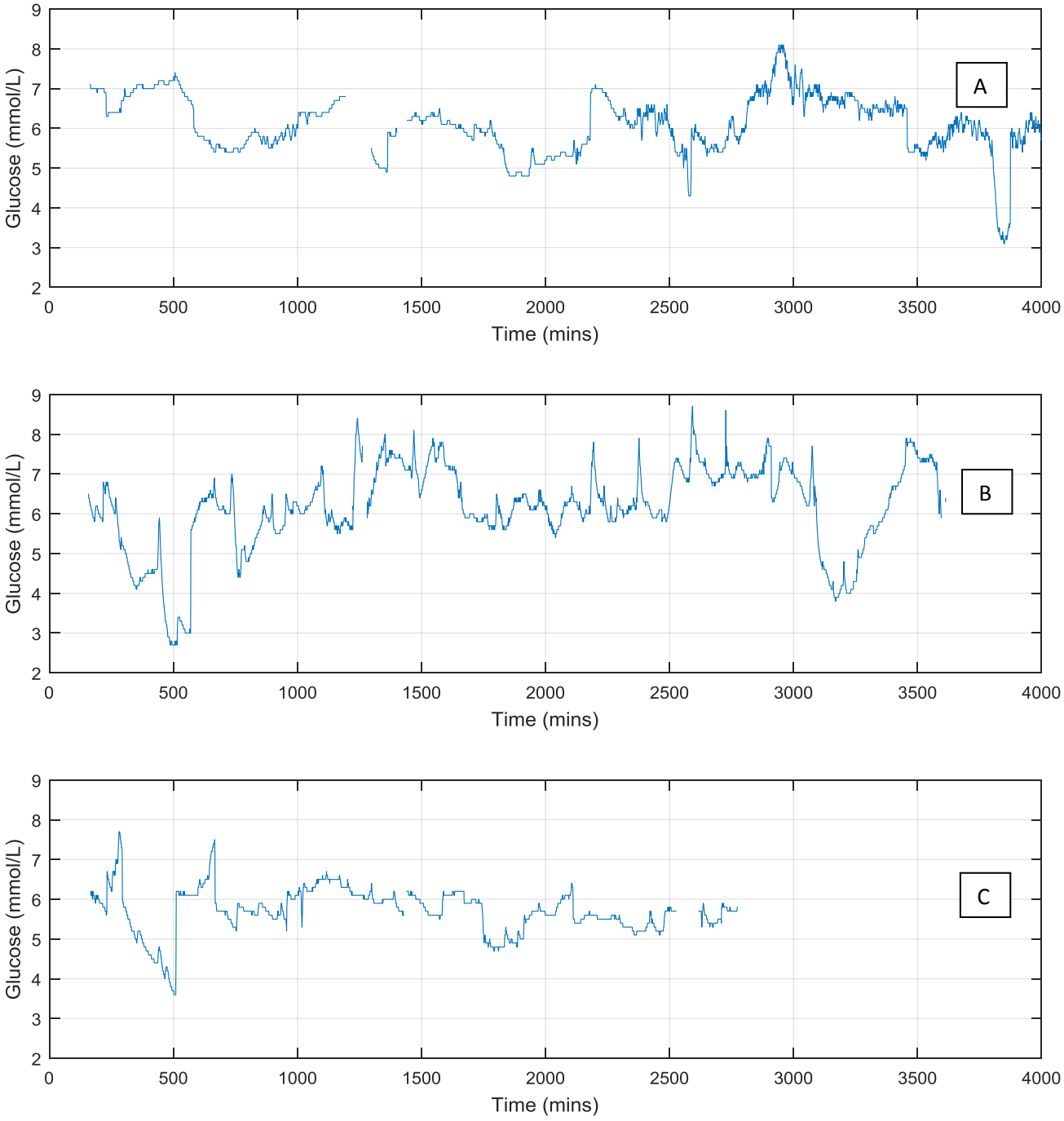


Figure 6.13 *The sensor glucose for the three instances where the autocorrelation range of the modelled SG does not include the autocorrelation of the measured SG for all time lags. A, B and C correspond to the A, B and C of Figure 6.11.*

The SG of the three instances (A, B and C in Figure 6.11) where the measured SG autocorrelation does not fall within the range of modelled SG autocorrelation for all time lags are shown in Figure 6.13. It is evident the lack of agreement is most likely due to individual cases where the sensor did not behave as expected and the behaviour cannot be easily explained by the noise and error types defined. Subplot A corresponds to the A in Figure 6.12 and the high frequency noise has increased noticeably about halfway through the signal which is not seen in any of the other 28 SG signals. Subplot B corresponds to the SG of Figure 6.13.B. The sensor glucose has many small unusual spikes uncharacteristic of the other sensors. Subplot C corresponds to Figure 6.13.C where there is a large drop out at 300 minutes in SG compared to an otherwise stable signal with some strange spikes.

Additionally, over all patients sensor glucose is very tightly correlated in both measured and modelled SG. This result is logical as the rate of which blood glucose can change is physiologically limited and under normal conditions blood glucose will be related over a short time period, such as 10 minutes. However, if the time lag is extended to ±20 or ±30 minutes the correlation coefficients of both the modelled SG and measured SG reduce, as expected.

6.5.1 Limitations

This analysis is limited by only have 28 data sets to generate the model from. A larger cohort would provide more data to generate the empirical models from. However, the consistency of the autocorrelation coefficients of the simulated signals to the real SG value indicates there is enough data to provide an acceptable model.

Another limitation is the limited choice of noise/error types. However, the 3 choices cover most variations observed clinically without adding extra complexity and unnecessary dynamics. Finally, this model is limited by the fact it is data driven, not a dynamic, deterministic model. The benefits of this method are that it simplifies the process of calculating exact dynamic and electronic, physiological and other noise causes/sources.

6.6 Summary

The CGM error model generated using the Sentrino data provides a realistic SG signal. Only 3 of 28 measured SG values do not sit with in the range of modelled SG across the entire 20 minute window considered. The median absolute difference between modelled and measured SG autocorrelation values was 0.007 with a range of 0 – 0.13. Hence, the model is judged to be suitable for use in simulation to provide better insight into using CGM to guide GC will effect control and its safety and performance. The overall modelling process is data drive and readily generalised to any other CGM.

Chapter 7. Virtual Trials with Continuous Glucose Monitoring Data

This chapter investigates the impact of CGM sensor errors on GC results using the simple CGM error model developed in Chapter 6. Virtual trials are used to test the impact of CGM guided GC using the STAR protocol. Virtual trials allow the safety and performance of CGM guided GC to be tested and a protocol to be optimally designed before attempting real world clinical trials. These virtual trials were necessary to assess impact of Phase IIB of the Sentrino trial, using CGM to guide STAR, to ensure patient safety before the interventional clinical trial was undertaken.

7.1 Introduction

Continuous glucose monitoring (CGM) devices, with their 1-5 minute measurement interval, have recently been used to monitor critical care patients' BG in a more continuous, less invasive manner than intermittent bedside BG measurements alone (Pretty et al., 2010, Signal et al., 2010, Beardsall et al., 2005, Harris et al., 2010, Holzinger et al., 2010, Brunner et al., 2011). Typical GC protocols for intensive care require BG measurements every 1-4 hours (Evans et al., 2012, Lonergan et al., 2006a, Plank et al., 2006, Blaha et al., 2009, Stewart et al., 2016), resulting in approximately 12-16 blood draws a day per patient. Thus, GC related activity represents a significant component of nurse workload (Carayon et al., 2005, Holzinger et al., 2005). CGM devices have the potential to drastically reduce the number of BG measurements per day, and thus the workload associated with GC protocols, while ensuring patient safety and increased time in the desired BG target band.

However, CGM devices can display suboptimal accuracy resulting from error or delay in calibration measurement, sensor drift and delayed glucose diffusion (Castle et al., 2010, Facchinetti et al., 2014,

Zimmermann et al., 2012, Reifman et al., 2007, Kuure-Kinsey et al., 2006). Thus, before CGM can become ubiquitous in the care of critically ill patients these errors and the effects of these errors on BG control must first be quantified and understood. In particular, quantifying their impact on GC will enable better GC protocol design that best utilizes the advantages of these devices, while minimizing the impact of their disadvantages.

This chapter uses the simple CGM error model presented in Chapter 6 to investigate the impact of the CGM error on the results of the STAR protocol (Stochastic TARgeted) (Evans et al., 2012), which has been standard care in Christchurch ICU since. Alarms and guardrail threshold settings are investigated to ensure patient safety, especially in the hypoglycaemic region, while avoiding nurse alarm fatigue. The overall goal is to delineate the impact of the advantages and disadvantages offered by CGM devices on GC and this specific protocol.

7.2 Subjects and Methods

7.2.1 Subjects

Virtual trials were performed using retrospective data from 286 patients treated by the STAR glycaemic control protocol at Christchurch Hospital ICU between 2011 and 2013. All patients were treated with the tablet-based STAR protocol for > 10 hours. Cohort demographics are presented in Table 7.1.

Table 7.1 Cohort demographics of the patients used for virtual trials. Data are presented as median [interquartile range] where appropriate.

Number	286
Age (years)	64.0 [54.0 - 72.0]
Gender (M/F)	189/97
APACHE II score	21.0 [16.0 - 27.0]
Hospital mortality (L/D)	192/94

7.2.2 Virtual Trials

The effect of CGM error on GC was tested using a virtual trial approach (Chase et al., 2010). This approach uses virtual patients, each comprising an insulin sensitivity (SI) profile identified from the clinical data of a real patient using a pharmacokinetic-pharmacodynamic (PK-PD) model of the glucose-insulin system (Lin et al., 2011). The SI profile can then be used with the PK-PD model to simulate the glycaemic outcome of different insulin and nutrition interventions.

To test different combinations of guardrails in Monte Carlo (MC) simulations a smaller sub cohort was randomly chosen from the original cohort to reduce computational time. Table 7.2 shows the measures used to characterise the cohorts are very similar and p-values calculated using the non-parametric Wilcoxon rank sum test show that the randomly selected test cohort and the original cohort are not significantly different.

Table 7.2 Summary data used to characterise the original and test cohort. Data are presented as median [interquartile range] where appropriate.

	Test Cohort	**Entire Cohort**	**P-value**
Number	20	286	
Median time analysed [IQR] (Days):	2.17 [1.53 - 5.97]	2.21 [1.17 - 3.89]	0.40
Median [IQR] Measures/day (Per-Patient):	12.94 [10.32 - 14.61]	12.80 [11.34 - 15.10]	0.29
BG median (mmol/L):	6.48 [6.35 - 6.59]	6.50 [6.14 - 6.90]	0.37
BG mean (mmol/L):	6.59 [6.46 - 6.87]	6.66 [6.36 - 7.21]	0.46
BG SD (mmol/L):	1.27 [0.92 - 1.88]	1.17 [0.85 - 1.65]	0.55

Guardrails, as outlined in Chapter 7, are upper and lower limits of SG. When the SG value crosses either the upper or lower limit the Sentrino will alarm, alerting the nurse that the SG has left the desired range. Their goal is to minimise the impact of CGM drift and also increase patient safety by alerting staff to

potential hypo- or hyper- glycaemic events. In this virtual simulation, if the hypo or hyper alarm was triggered a BG measurement was taken to verify the event or correct the sensor.

To use CGM values to drive STAR, a minutely CGM signal was created using the method and sensor model detailed in Chapter 6 and virtual patient data to represent patient specific response. When STAR required a BG input during the virtual trials the CGM value at that time point was taken and used to determine insulin and nutrition values. If a guardrail was crossed at any time a BG value was virtually measured and compared to the modelled sensor glucose value. If the absolute difference of SG and BG was greater than the allowed tolerance the CGM was recalibrated using this BG measure, and the BG measurement was used for control. This recalibration was performed by resetting the drift to zero. If the absolute difference of SG and BG was less than the allowed tolerance then the SG measurement was still used for control. In each case these added measurements count towards assessed control.

To test the best possible guardrail and tolerance combination lower guardrails of 4.0, 4.5 and 5.0 mmol/L were selected. The absolute difference between the sensor glucose and the measured blood glucose when a lower alarm occurred was allowed to be 0.5 mmol/L or 1.0 mmol/L. The hyperglycaemic alarms trialled were at 8.0, 9.0 and 10.0 mmol/L with a tolerance of either 1.0 mmol/L or 2.0 mmol/L. The smaller tolerance on the hypoglycaemic alarms was selected due to safety being the most important clinical factor when considering glycaemic control.

7.2.2 Analysis

MC methods were employed to reduce the impact of randomly sampled outliers on results. A 50-run MC simulation was completed for each virtual patient. Blood glucose values were generated using the clinically validated Intensive Control Insulin-Nutrition-Glucose (ICING) model of the glucose-insulin system (Lin et al., 2011) was used. Sensor drift and noise was added to the measurements using the CGM model. These BG measurements were then given to the STAR protocol generate insulin and nutrition interventions. This situation simulates what it would be like if CGM devices were being used to guide the protocol in clinic.

The metric to assess performance was selected to be %time in the desired 4.4 – 8mmol/L band. To assess safety the percentage of time spent hypoglycaemic, %time below 4.4mmol/L and the percentage of severe hypoglycaemia - %time below 2.2mmol/L was considered. The total number of blood draws and number of alarms were used to assess the resulting workload of using CGM devices, with and without guardrails, to guide the STAR protocol. MC results were compared the clinical results of the 286 STAR patients.

7.3 Results and Discussion

Simulating STAR driven by sensor glucose measurements without guardrails on the test cohort resulted in a median [IQR] time in the 4.4 – 8.0 mmol/L band of 74.1 [73.4 75.2] %. The median [IQR] percentage of time below 4.4 mmol/L was 3.1 [2.7 3.4] % and time below 2.22 mmol/L was 0.0 [0.0 0.1]. The total number of blood draws was 291 [291 291] compared to 970 measurements required by STAR, a reduction of 70%.

Table 7.3 summarises the performance, safety and workload metrics across all 36 different combinations of guardrails and allowable SG error. It is evident that to improve safety most effectively, guardrails of 4.0 – 8.0 mmol/L should be in place as the median [IQR] percentage of time below 4.4 mmol/L is reduced to 2.5 [2.1 3.2] %. However, this slight increase in safety translates to a large increase in workload compared to not using guardrails with 863[850 872] blood draws required and 572[559 581] alarms and only slightly less blood draws than required by STAR.

The most effective way to improve performance with the least measurements are guardrails of 5.0 – 10.0 mmol/L. The median [IQR] time in the 4.4 – 8.0 mmol/L band is 77.1[76.3 77.9] % with 693[679 707] blood draws and 403[388 416] alarms. However, safety decreases with an increase in time below 4.4 mmol/L and time below 2.22 mmol/L.

The lowest workload is achieved with guardrails of 4.0 – 10.0 mmol/L. The median [IQR] number of blood draws is 532[519 542] with 241[228 251] alarms. However, performance and safety are no better than when guardrails are not applied, but the number of blood draws required is nearly double.

The tolerance value, the absolute difference between the SG and the measured BG when an alarm occurs, does not appear to have much impact on safety, workload, or performance with the tolerance values selected. Safety appears slightly better with the hyperglycaemia alarm tolerance of 1.0 mmol/L and counter intuitively workload appears marginally less. There is no distinguishable difference between the hypoglycaemic alarm tolerance of 0.5 mmol/L or 1.0 mmol/L. Hence, the tolerance of 0.5 mmol/L for hypoglycaemic alarms and 1.0 mmol/L for hyperglycaemic alarms was selected as the best solution.

Safety is one of the most clinically important factors when considering glycaemic control protocols. Hence, the guardrails that produced the lowest amount of hypoglycaemia were selected to be simulated with the entire cohort data. In addition, the improvements seen in performance for this case were not substantial and still required a higher workload than desired. Table 7.4 shows the comparison between STAR, STAR CGM without guardrails, and STAR CGM with guardrails at 4.0 – 8.0 mmol/L.

When guardrails are used there are only 1474 less blood draws on average than clinical STAR resulting in 5 less blood draws per patient on average, saving approximately 10 minutes per patient or 49 hours total. While, there are 8124 less blood draws on average without guardrails resulting in 28 less blood draws per patient, saving approximately 56 minutes per patient or 270 hours total. Guardrails make very small improvements in safety compared to STAR CGM with the median interquartile range for the number of serve hypoglycaemia events being 10 [8 11] and 10 [9 12], respectively. However there is a median of 993 hypoglycaemic alarms and 5672 hyperglycaemic alarms, and 3 and 20 alarms per patient, respectively.

In theory, guardrails are introduced to improve safety and performance by alerting the nurse to when the patient has or is about to leave the desired target band of 4.4 – 8.0 mmol/L. For this idea to work in practice, the sensors need to be accurate enough to avoid too many instances where drift results in false alarms. Some further discussion and examples of this behaviour can be seen in Chapter 4, in particular Figure 4.2. Currently, with the limitations discussed in Chapter 5 the Sentrino sensors are not accurate enough to display the benefit of guardrails with blood draws being required to correct the Sentrino signal on nearly every alarm. Additionally, the STAR protocol achieves very good and safe control already. Hence, improving the “safety” of the protocol is difficult with only 1.35% time below 4.4mmol/L. Perhaps, with a less successful glycaemic control protocol, the benefit of the Sentrino guardrails would be more evident.

STAR achieves better control when BG measurements are used for control rather than SG measurements, as the protocol depends on the current and previously entered glucose values to identify SI. If there is large error in one or both of these entered values then the SI level identified will not be correct leading to a reduction in model-based control quality. In particular, the SI level identified is used with a stochastic model to forward predict what BG is likely to be in 1, 2 or 3 hours time and the nutrition and insulin required to achieve this outcome. Therefore, if SI is incorrectly identified due to erroneous SG measurements the nutrition and insulin recommended by STAR is also likely to be incorrect resulting in the patient becoming either hypo- or hyper- glycaemic depending on the direction the sensor is drifting.

Future work in this area could include the addition of adaptive guardrails that can adjust targets and tolerances based on how the sensor is performing and observed patient variability. However, the sensor performance would need to improve for these additions to be effective and prevent alarm fatigue. Also to implement adaptive alarms there would need to additional functionality in the CGM device, something that is not currently available with the Sentrino or other similar devices. Another future study, using the drift model from Chapter 6 and this virtual trial method, investigating the level of drift acceptable performance could be useful. This way, device manufacturers would have a better idea of what performance is needed before a device, such as this, will be successful in a clinical setting.

Table 7.3 Summary of safety, performance and workload metrics for each differ combination of guardrail and sensor error allowed. Data are presented as median [interquartile range] where appropriate.

	Lower Guardrail			4		4.5		5	
			abs(SG - BG)	0.5	1	0.5	1	0.5	1
Safety - % BG < 4.4 mmol/L (% BG < 2.2 mmol/L)	Upper Guardrail	8	1	2.6[2.2 3.1] (0.0[0.0 0.1])	2.5[2.1 3.2] (0.0[0.0 0.1])	2.8[2.3 3.1] (0.0[0.0 0.1])	2.6[2.3 3.0] (0.0[0.0 0.1])	3.0[2.6 3.2] (0.0[0.0 0.1])	2.6[2.2 2.9] (0.0[0.0 0.1])
			2	3.2[2.7 3.4] (0.0[0.0 0.1])	2.7[2.4 3.3] (0.0[0.0 0.1])	3.2[2.8 3.5] (0.1[0.0 0.1]	3.2[2.8 3.4] (0.0[0.0 0.1)]	3.2[2.8 3.4] (0.0[0.0 0.1])	3.0[2.4 3.5] (0.0[0.0 0.1])
		9	1	3.1[2.8 3.6] (0.1[0.0 0.2])	3.1[2.7 3.5] (0.0[0.0 0.1])	3.3[2.8 3.7] (0.1[0.0 0.1])	3.2[2.9 3.6] (0.0[0.0 0.1])	3.5[3.1 4.1] (0.1[0.0 0.2])	3.2[2.8 3.5] (0.1[0.0 0.2])
			2	3.3[2.8 3.7] (0.1[0.0 0.2])	3.2[2.7 3.7] (0.1[0.0 0.1])	3.3[3.0 3.7] (0.1[0.0 0.2])	3.3[3.0 3.8] (0.0[0.0 0.2])	3.7[3.2 4.1] (0.1[0.0 0.2])	3.3[2.9 3.8] (0.0[0.0 0.2])
		10	1	3.5[3.0 3.9] (0.1[0.0 0.2])	3.6[3.2 4.0] (0.1[0.0 0.2])	3.7[3.3 4.0] (0.1[0.0 0.2])	3.7[3.2 4.4] (0.1[0.0 0.2])	4.0[3.6 4.4] (0.1[0.0 0.2])	3.8[3.5 4.5] (0.2[0.0 0.2])
			2	3.8[3.5 4.0] (0.1[0.0 0.1])	3.4[2.8 3.9] (0.1[0.0 0.2])	3.6[3.4 4.3] (0.1[0.0 0.2])	3.4[3.0 3.9] (0.1[0.0 0.2])	4.0[3.4 4.5] (0.1[0.0 0.2])	3.7[3.1 4.1] (0.1[0.0 0.2])
Performance - % BG 4.4 – 8.0 mmol/L	Upper Guardrail	8	1	74.1[73.5 74.9]	74.2[73.1 75.0]	75.2[74.3 75.7]	75.5[74.7 76.1]	76.5[75.9 77.3]	76.3[75.9 77.2]
			2	75.1[74.3 75.9]	75.5[74.6 76.5]	76.5[75.9 77.4]	76.1[75.3 77.0]	77.8[77.0 78.5]	77.4[76.4 78.4]
		9	1	74.6[73.3 75.5]	74.2[73.3 74.8]	75.9[75.1 76.7]	75.1[74.4 76.2]	76.9[76.0 77.4]	76.7[76.0 77.3]
			2	75.0[74.2 75.9]	74.9[73.9 75.9]	76.3[75.7 76.9]	76.1[74.9 77.1]	77.6[76.8 78.1]	77.1[76.6 77.7]
		10	1	74.7[73.9 75.4]	74.6[73.5 75.7]	76.1[75.3 76.8]	75.8[75.2 76.8]	77.1[76.3 77.9]	76.8[76.2 77.2]
			2	74.7[74.2 75.6]	75.2[74.3 76.0]	74.9[74.0 75.6]	76.4[75.4 77.4]	77.0[76.2 78.0]	77.0[76.0 78.1]
Workload - No. blood draws (No. Alarms)	Upper Guardrail	8	1	859[842 869] (568[551 578])	863[850 872] (572[559 581])	898[891 912] (607[600 621])	912[901 929] (621[610 638])	983[963 1003] (692[672 712])	985[971 1002] (694[680 711])
			2	900[885 915] (609[594 624])	907[892 921] (616[601 630])	952[937 970] (661(646 679)]	961[947 975] (670[656 684])	1027[1008 1050] (736[717 760])	1050[1023 1067] (759[732 776])
		9	1	651[639 660] (360[348 369])	654[644 667] (363[353 376])	706[693 716] (415[402 425])	714[698 732] (423[407 441])	791[782 802] (500[491 511])	802[795 822] (511[504 531])
			2	686[673 698] (395[382 407])	689[671 705] (398[380 414])	742[728 759] (451[437 468])	752[729 766] (461[438 475])	817[800 842] (526[509 551])	841[832 859] (551[541 568])
		10	1	532[519 542] (241[228 251])	538[528 551] (248[237 260])	593[587 604] (302[296 313])	610[601 617] (319[310 326])	693[679 707] (403[388 416])	707[698 717] (416[407 426])
			2	554[542 562] (263[251 271])	553[544 561] (262[253 270])	552[544 562] (261[253 271])	629[613 640] (339[322 349])	710[696 724] (419[405 433])	719[704 726] (428(413 435])

Table 7.4 Summary of performance, safety and workload of STAR CGM compared to Clinical STAR data. Data are presented as median [interquartile range] where appropriate.

	STAR CGM Guardrails	STAR CGM	Clinical STAR
No. Patients	286	286	286
No. Hours	21770 [21761 21776]	21765 [21756 21775]	21769
No. STAR Measurements	13758 [13721 13804]	14622 [14574 14687]	11552
No. Blood Draws	10078 [10033 10137]	3428	11552
Median BG	7.35 [7.34 7.36]	7.20 [7.19 7.21]	6.61
% BG 4.4 – 8.0 mmol/L	70.9 [70.4 71.0]	72.2 [71.9 72.4]	83.3
% BG < 4.4 mmol/L	2.25 [2.19 2.33]	2.62 [2.53 2.71]	1.35
% BG < 2.2 mmol/L	0.09 [0.07 0.10]	0.09 [0.08 0.10]	0.005
No. Episodes BG < 2.22 mmol/L	10 [8 11]	10 [9 12]	4
% BG > 10 mmol/L	4.56 [4.51 4.62]	4.44 [4.38 4.49]	4.10
No. Hypo Alarms	993 [975 1017]	0	0
No. Hyper Alarms	5672 [5614 5703]	0	0

7.4 Summary

This chapter investigates the impact of CGM sensor error on the STAR glycaemic control protocol using the simple CGM sensor error model created in Chapter 6. Alarms and guardrail threshold settings were also investigated to insure patient safety, especially in the hypoglycaemic region, while avoiding nurse alarm fatigue. The effect of CGM error on glycaemic control was tested using a clinically validated virtual trial approach using retrospective data from 286 patients treated by the STAR glycaemic control protocol at Christchurch Hospital ICU between 2011 and 2013.

Multiple Monte Carlo simulations on a sub cohort displayed the trade-off between safety, performance and workload. A hypoglycaemic alarm threshold of 4.0 mmol/L and a hyperglycaemic alarm threshold of 8.0 mmol/L best balanced the trade-off between performance and workload, while maintaining high safety. The most clinically important feature of any glycaemic control protocol. In full cohort simulations,

there were only 1474 less blood draws on average than clinical STAR resulting in 5 less blood draws per patient on average. While, there are 8124 less blood draws on average without guardrails resulting in 28 less blood draws per patient. Guardrails, thus, make very small improvements in safety compared to STAR CGM without guardrails with the median interquartile range for the number of serve hypoglycaemia events being 10 [8 11] and 10 [9 12], respectively.

Guardrails are introduced to improve safety and performance by alerting the nurse to when the patient has or is about to leave the desired target band. However, to be effective the sensors need to be accurate enough to avoid too many false alarms. Currently, the sensor technology trialled here, with the issues outlined in Chapter 5, is not accurate enough to display the benefit of guardrails and if it was used to guide glycaemic control there would be a large increase in hypoglycaemic events. Additionally, the STAR protocol achieves very good and safe control already hence improving the "safety" of the protocol is difficult with only 1.35% time below 4.4 mmol/L. Potentially, a less successful glycaemic control protocol would display the greater benefit of the Sentrino guardrails.

Due to the concerns surrounding the performance of the sensor the interventional phase of the Sentrino trial, Phase IIB, was not implemented. For an interventional trial like Phase IIB to commence, the sensor technology would need to be improved following the recommendations presented in Chapters 2 – 7. Specifically, in this chapter the quality of measurement has been shown to be more important than the frequency of measurement for glycaemic control performance and safety.

Chapter 8. Summary of CGM in ICU

The potential benefits and pitfalls of CGM in the intensive care unit have been identified in an observational pilot trial using off-the-shelf CGM devices designed for use individuals with Type 1 and Type 2 diabetes (Signal et al., 2013). Recently, a CGM device specifically designed for the ICU became available, The Sentrino (Medtronic, MiniMed, Northridge, California), and has displayed promising results in initial trials in the cardiac ICU (Kosiborod et al., 2013) . Hence, a larger scale study was designed for implementation in Christchurch Hospital mixed medical ICU to gather further information about the feasibility of CGM in ICU. The first half of this thesis investigates using the Sentrino CGM devices in adult ICU, with the overall goal of improving BG control and increasing patient safety, while reducing nurse workload. In short, can greater data of potentially lesser quality outweigh much lesser amounts of higher quality data? An assumption that some in the field believe to be true (Krinsley et al., 2008).

The Sentrino trial was designed and undertaken in 2 phases run partially in parallel. The aim of this study was to investigate the performance of these new devices first observationally to ensure the safety and efficacy of their performance (Phase I). A further observational study assessed the performance and integration of hyper- and hypo- glycaemic alarms (Phase IIA). Finally, the design of a protocol using CGM measures to guide glycaemic control and investigation of the feasibility of implementing this protocol (Phase IIB).

First, the performance of the Sentrino CGM system in a mixed medical ICU environment was analysed and the optimal sensor location confirmed. CGM and BG data were gathered from 13 patients recruited to Phase 1 of the trial. Each participant in this study phase was monitored for a period of up to 3 consecutive

days with 2 independent Sentrino devices. For the majority of patients, 1 sensor was inserted in the abdomen and 1 sensor was inserted in the thigh. Overall, the Sentrino device achieved a MARD of 14.7%. This result demonstrated slightly reduced performance from what was reported in an initial trial in a cardiac ICU where a MARD of 12.2% was seen. However, when considering device location, thigh SG achieved a MARD of 11.0% while abdomen SG achieved a MARD of 16.6%. This result indicates that following the manufactures recommendation of thigh insertion, which is different to the location used for devices designed for ambulatory individuals with diabetes, is important to ensure sensor performance. The number of calibrations undertaken was double that recommended by the protocol and may have improved overall accuracy. Overall, the Sentrino performance was acceptable, but with such a high number of additional calibration measurements required, questions still remain if this CGM system can reduce the time and workload cost of glycaemic control.

Phase IIA was an observational study of the performance and integration of hyper- and hypo- glycaemic guardrail alarms with an existing, proven GC protocol. This study analysed SG and BG data, and alarm data from 8 patients recruited to this phase of the trial. An upper guardrail of 10.0 mmol/L and lower guardrail of 4.2 mmol/L were added in the device settings. When the SG value crossed either threshold an alarm would sound. BG measurement was then taken and compared to the SG value, where it would be used for recalibration if the SG-BG error exceeded a predefined threshold.

Overall, sensor and alarm performance was good. However, there was a high rate of false positive alarms. Many of these false positives were caused by sensor artefacts, unexplained spikes or dips in sensor glucose or sensor drift. While false positives are safer for managing patient blood glucose than false negatives, of which there was only one, they did lead to nursing non-compliance in some cases. In summary, alarms

performed well for the most part, but to ensure better integration with current practices and nurse compliance, the protocol regarding false positives needs to be optimised.

The next analysis was undertaken to better understand the impact of sepsis, oedema and some medications on CGM results, as well as to assess the nurse compliance and feedback to gain insight in to the potential clinical impact of using CGM to guide GC. This analysis used data from 21 patients in Phase I and Phase IIA. Approximately 50% of all enrolled subjects were severely oedematous and/or septic by design, and thus represent a worst case, but typical cohort for a mixed medical ICU.

For CGM to be successful in reducing nurse workload and increasing patient safety the following recommendations are made:

- Avoid severely oedematous patients where fluid is likely to leak from ruptured skin
- Waterproof CGM sensors
- Reconsider insertion technique to lessen the risk of capillary damage
- Wireless transmission between sensor and monitor unit for ease of patient mobility

Before CGM can be used to guide glycaemic control protocols the impact of suboptimal accuracy resulting from error or delay in calibration measurement, sensor drift, and delayed glucose diffusion must first be characterised. Characterising this error allows models to be formed so in-silico simulations can test the performance and safety of CGM driven glycaemic control protocols and examine best and worst scenarios. Hence, a CGM model was formed based on the clinical data collected in Phase I and IIA of the Sentrino trial.

The CGM error model generated using the Sentrino data provides a realistic SG signal. Only 3 of 28 sets of SG do not sit within the range of modelled autocorrelation results across the entire 20 minute window considered. The median absolute difference between modelled and measured SG autocorrelation values was 0.007 with a range of 0 – 0.13. Hence, the model is judged to be suitable for use in simulation to provide better insight into using CGM to guide GC will effect control and its safety and performance. The overall modelling process is data driven and readily generalised to any other CGM.

Finally, the impact of CGM sensor error on the STAR glycaemic control protocol was investigated using the simple CGM error model generated. Alarms and guardrail threshold settings were also investigated to insure patient safety, especially in the hypoglycaemic region, while avoiding nurse alarm fatigue. The effect of CGM error on glycaemic control was tested with a virtual trial approach using retrospective data from 286 patients treated by the STAR glycaemic control protocol at Christchurch Hospital ICU between 2011 and 2013.

Guardrails are introduced to improve safety and performance by alerting the nurse to when the patient has or is about to leave the desired target band. However, to be effective the sensors need to be accurate enough to avoid too many instances of drop outs or drift resulting in false alarms. Currently, the sensor technology trialled here is not accurate enough to display the benefit of guardrails and if it was used to guide glycaemic control there would be a large increase in hypoglycaemic events. Additionally, the STAR protocol achieves very good and safe control already hence improving the “safety” of the protocol is difficult with only 1.35% time below 4.4 mmol/L. Potentially, a less successful glycaemic control protocol would display the greater benefit of the Sentrino guardrails.

Due to the concerns surrounding the performance of the sensor Phase IIB of the Sentrino was not implemented. For an interventional trial like Phase IIB to commence, the sensor technology would need to be improved following the recommendations listed here. Overall, the work presented in Chapters 2 – 7 contributes valuable information and insight to the use of CGM device in the intensive care unit. This work provides clear guidelines for how CGM devices can be optimised for this environment considering both the engineering and clinical perspective. The results presented provide a significant advancement to the body of knowledge surrounding the use of these devices in ICU and should be of significant use to researchers and device manufactures alike.

Part II – Glucose Metabolism and CGM in Athletes

Chapter 9. Background Glucose Metabolism and CGM in Athletes

This chapter provides background on the effects of exercise on the glucose metabolism during exercise and the effects of exercise on the overall glucose metabolism of athletes. An interesting comparison between the metabolism of intensive care patients and athletes is also made. Finally, the potential application of CGM devices to aid in improving athlete nutrition is reviewed. In particular, their potential to improve race performance and recovery.

9.1 The Athlete Glucose Metabolism

Exercise is well known and accepted to improve insulin sensitivity via acute and long-term training effects (Borghouts et al., 2000). However, the intensity of exercise defines the main source of energy, lipids or carbohydrates, during this exercise period and the metabolic response of the glucose metabolism (Marliss et al., 2002). Thus, the effects may vary not only between athletes, but by relative intensity and its impact on metabolism.

During moderate exercise an increase in glucose utilisation is apparent (Goodyear et al., 1998, Marliss et al., 2002, Richter, 1996). This increased utilisation may in part be due to increased insulin sensitivity, as exercise increases the delivery of insulin to muscle by increasing peripheral blood flow allowing better use of plasma insulin (Marliss et al., 2002, Goodyear et al., 1998, Richter, 1996). However, an increase of non-insulin mediated glucose uptake is likely to be the dominant factor based on published literature, because, despite falling plasma insulin and similar insulin secretion levels, glucose utilisation increases (Marliss et al., 2002, Douen et al., 1989, Coderre et al., 1995, Richter, 1996).

This increase in glucose utilisation is attributed to exercise allowing glucose uptake to occur through non-insulin mediated GLUT4 transporters that are translocated to the cell wall without the need for the insulin signalling cascade (Goodyear et al., 1998, Marliss et al., 2002). Thus, while an increase in catecholamine production, which is known to inhibit glucose utilisation (Marliss et al., 2002), is likely to be present, the dominant effects of increased GLUT4 transport and delivery of insulin to muscles allows blood glucose utilization and production to remain stable.

However, during intense exercise (VO2max > 80%) blood glucose and insulin secretion rise. This response is generated by the marked catecholamine response to intense exercise (Marliss et al., 2002, Calles et al., 1983, Kjaer et al., 1986). In general, this catecholamine response leads to increased hepatic glucose production and restriction of peripheral glucose utilisation resulting in hyperglycaemia and hyperinsulinemia at the end of an intense exercise session (Marliss et al., 2002, Kjaer et al., 1986, Calles et al., 1983). This response is similar to the stress-induced hyperglycaemia seen in ICU patients, the common factor being systemic inflammation due to their illness or induced by strenuous effort and its impact on insulin sensitivity, glucose uptake and hepatic glucose production (Collier et al., 2008).

Studies comparing the metabolic and hormonal response to exercise between trained and untrained normal glucose tolerant individuals have found that glucose, glycerol, and free fatty acid concentrations are higher, but lactate, pyruvate, and alanine were lower in trained individuals, than in untrained individuals (Kjaer et al., 1986, Bloom et al., 1976). Cortisol, another stress hormone with hyperglycaemic effects, levels were also found to be higher in trained individuals (Bloom et al., 1976). Additionally, insulin secretion is known to be diminished in well trained individuals due to increased sensitivity and non-insulin mediated uptake (Lohmann et al., 1978). These results suggest there is significant adaptation of the

metabolism in well-trained individuals. However, there are only a few studies that investigate how metabolic parameters, such as endogenous glucose production change with exercise (Jeukendrup et al., 1999, McConell et al., 2000), and none that attempt to quantify endogenous insulin secretion or sensitivity during exercise.

9.2 Continuous Glucose Monitoring in Athletes

Carbohydrates and lipids are the main fuel sources utilised during exercise. The more intense and longer duration the exercise the greater the dependence on carbohydrates. Lipids require more energy to be broken down for fuel. Hence, the body will rely more and more on carbohydrates as the intensity of exercise increases (respiratory exchange ratio > 0.75), primarily from muscle glycogen stores.

When exercise is prolonged (>60mins) muscle glycogen stores become depleted. Therefore, the body becomes more reliant on plasma glucose, liver glycogenolysis and gluconeogenesis for energy. After approximately 90 minutes of fasted exercise, blood glucose will begin to fall because glycogen stores are depleted and liver gluconeogenesis cannot fully compensate for energy expenditure (Felig et al., 1982).

Plasma glucose levels are known to remain stable during moderate exercise < 60min (Romijn et al., 1993), but as intensity and duration increase it is likely this balance is difficult to maintain, especially in ultra-distance events when gastrointestinal problems, reducing calorie intake, are common (Jeukendrup, 2004, Rehrer et al., 1992, Glace et al., 2002, Pfeiffer et al., 2012). Athletes are advised to consume 30-60g of carbohydrate/h during endurance exercise lasting > 1hr (American Dietetic et al., 2009, Jeukendrup, 2004) to ensure optimal performance and maintain blood glucose levels. In one study (Fallon et al., 1998),

blood glucose was measured four times during an ultra-distance race (100km race, average finishing time 10hr 39min) and found to remain relatively constant at each time point even though carbohydrate intake varied between 21.8 – 66.0 g/h. However, it is difficult to extrapolate between these time points to have any real understanding of blood glucose trends, and thus metabolic changes, during long distance events.

An individual's tolerance of carbohydrate is highly variable and is related to a number of factors including age and genetics (Zeevi et al., 2015, Vrolix et al., 2010). CGM devices have the potential to personalise nutrition based on post prandial glucose response (Zeevi et al., 2015). In addition, many athletes do not meet sports nutritional recommendations for carbohydrate intake, especially those in the sub elite category (Masson et al., 2016). CGM could provide a greater insight in to what impact this failure to meet recommended guidelines has on plasma glucose levels, before, during and after an event.

Such research using continuous glucose monitors has not been undertaken in athletic subjects before. However, real time knowledge of blood variables, such as glucose, is noted as the "future" of sports technology (Gizmag Team, 2007, Metz, 2014). It is important to assess if knowledge of real-time blood glucose can provide a deeper insight in to athletic performance or if it will just be a gimmick provided by sports device manufacturers to increase the popularity of their device. The following chapters investigate what, if any, benefit continuous glucose monitoring can provide to competitive athletes.

Chapter 10. Hyperglycaemia and Hyperinsulinemia Post Exercise

Chapter 10 investigates the glycaemic response during and after strenuous exercise. Strenuous exercise leads to a marked catecholamine response and rise in blood glucose, similar to that seen in stress-induced hyperglycaemia in ICU patients. While this effect is noted in existing literature, the effect has not been examined thoroughly and not in a manner that is typical of an endurance event. This chapter characterises the hyperglycaemia and hyperinsulinemia seen post exercise to better understand athlete metabolism, enabling a more realistic model to be developed.

10.1 Introduction

To ensure optimal recovery of glycogen stores, it is recommended and common practice to consume 1.0 - 1.5 gcarbohydrate/kg within 30 mins after intense exercise (American Dietetic et al., 2009). This recommendation stems from the 1988 study by Ivy et al. (1988) that compared the level of glycogen restoration when 2g carbohydrate/kg was delivered immediately after exercise or delayed for two hours. The results of this study displayed a marked increase in muscle glycogen synthesis when carbohydrate was ingested immediately after exercise.

However, this study and others also noted a persistent elevation of insulin-antagonistic hormones and free fatty acids post intense exercise (Conlee et al., 1978, Danforth, 1965, Galbo et al., 1979, Ivy et al., 1988, Marliss et al., 2002). This behaviour results in hyperglycaemia, hyperinsulinemia, and effective whole body insulin resistance, at the end of an intense exercise session. Marlis and Vranic (2002) reported that marked catecholamine responses to intense exercise are the main cause of the increase in hepatic glucose production and restraint of glucose utilization.

Hyperglycaemia is an inflammatory marker (Collier et al., 2008) and blood glucose variability is a known risk factor in type 2 diabetes (Monnier et al., 2006, Brownlee et al., 2006). The immune system also fails to function optimally in the presence of high blood glucose levels (Sanchez et al., 1973, Marik et al., 2004, Jeandidier et al., 2006, Turina et al., 2005, Kijak et al., 1964). A single 100g dose of glucose can significantly impair the immune system for more than 5 hours (Sanchez et al., 1973, Kijak et al., 1964). Furthermore, according to some surveys common minor illnesses, such as sore throats and flu-like symptoms are more common in athletes and may last longer (Gleeson, 2006). This compromised immune response has been linked to depression of immune system function, which is most pronounced after prolonged moderate to high intensity training or competition performed without food intake (Gleeson, 2006). Hence, as normoglycaemia is important for general health and well-being, it is thus equally or more important to a competitive athlete.

This chapter examines the immediate effect of post intense effort glucose ingestion in a fashion more comparable to an actual athletic event to consider the duration and effect of post exercise hyperglycaemia and hyperinsulinemia induced by following current recommended nutritional guidelines for during and after exercise.

10.2 Methods

10.2.1 Subjects

Ten fit, healthy, sub-elite athletes (resting heart rate (HR) < 60 beats per minute (BPM)) were recruited under informed written consent for a study investigating optimal athlete nutrition (henceforth referred to as athletes). Table 10.1 summarizes the cohort demographics. Seven out of the ten participants cycled

regularly and all subjects trained >6 hours per week in a range of endurance based sports, predominantly running and cycling. The research procedures and use of data were approved by the University of Canterbury Ethics Committee.

Table 10.1 *Cohort demographics of the participants. Data are presented as median [interquartile range] where appropriate*

Number	10
Age (yr)	28 [23 37]
Gender (M/F)	7/3
BMI (kg/m^2)	22 [21 24]
Resting HR (bpm)	55 [53 56]
VO2max (mL/kg/min)	46 [39 59]
Trained Cyclist (Y/N)	7/3

10.2.2 Experimental protocol

Fasting exercise tests were carried out, as shown in Figure 10.1. Subjects were required not to exercise the day before the test. On the day of testing, the exercise protocol began at 8am after overnight fasting, and is defined:

- **0 - 60 min**: Cycling on a stationary trainer (Cyclus 2, RBM elektronik-automation GmbH, Lepzig, Germany) in the submaximal endurance HR zone <70%VO2max with a resistance set to 2 W/kg for female and untrained cyclists or 2.5 W/kg for trained males.
- **30 min**: Consume a 0.5 g/kg of body weight (30-45 g) glucose drink as per recommended practice of 30-60 g/h during endurance exercise lasting > 1hr (American Dietetic et al., 2009). This drink was consumed after blood samples for 30 min were taken.
- **60 min→ exhaustion (EX) (~90 min):** Steadily increase effort until volitional exhaustion by increasing required power by 20W every 5 minutes mimicking the later stages of an endurance event where the effort required is likely to increase until the finish

- **EX:** Consume a 1 g/kg of body weight (60-90 g) glucose drink as per recommended practice to consume 1-1.5 g/kg of glucose for recovery of muscle glycogen post strenuous exercise lasting > 1hr (American Dietetic et al., 2009). This drink was consumed after blood samples for EX were taken.

Blood Samples assayed for plasma insulin and C-peptide were taken at:

- 0, 30, 45, EX, EX + 15 min, EX + 30 min (5/10 subjects), EX + 60 min

Reference BG measurements were taken:

- **0 - 60 min**: Every 10 min
- **60 min – EX + 30 min (~120 min):** Every 5 min to better capture the changes in blood glucose after the during an intense work period and after the large glucose bolus
- **Exhaustion + 30 min (~120 min) – exhaustion + 60 min (~150 min):** Every 10 min

Other measurements:

- Body weight, BMI, Body composition Analyser (InBody230, InBody Bldg, Seoul, Korea)
- Indirect calorimetry (MetaLyzer 3B - R2, CORTEX Biophysik GmbH, Lepzig, Germany)
- Lactate (Lactate Pro, Arkray Inc, Kyoto Miyuki Bldg. 10F, 689 Takanna-cho, Nakagyo-ku, Kyoto 604-8153, Japan)

Reference and calibration BG measurements were taken using capillary finger stick measurements and the Abbott Optimum Xceed (Abbott Diabetes Care, Alameda, CA) glucometer. The Abbott device has reported error of 5-10% (Abbott Diabetes Care, 2010, Thomas et al., 2014a, Signal, 2013). Insulin and C-peptide concentrations were determined using immunometric assays (Elecsys 2010, Roche

Diagnostics, Germany). Only 5/10 subjects Ath06-Ath10 had a blood sample at exhaustion+30 minute due to an amendment in the protocol to allow the additional measurement.

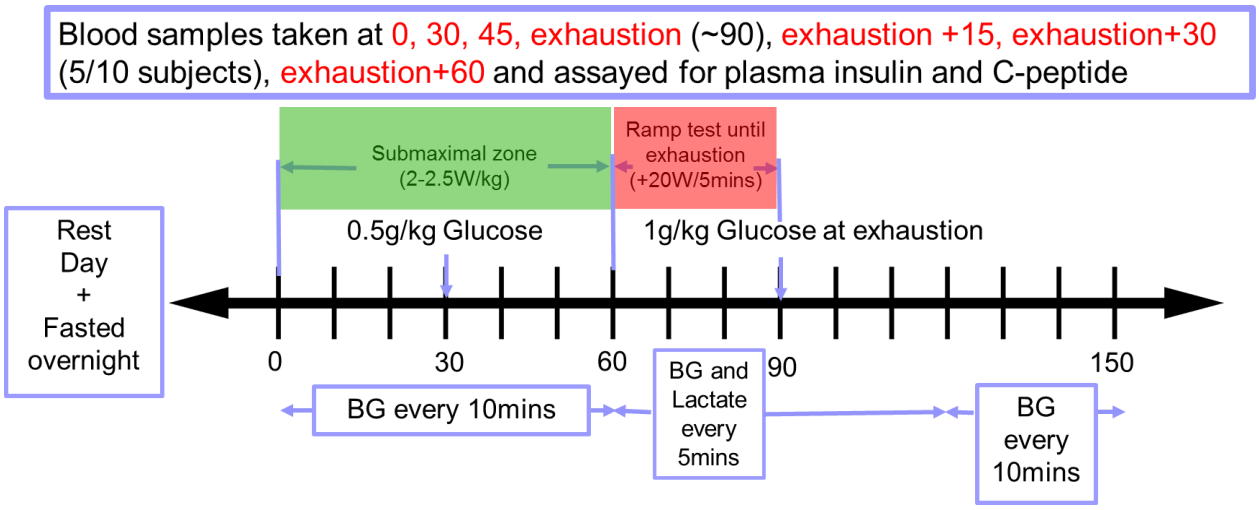


Figure 10.1 *Schematic displaying experimental procedure*

10.2.3 Analysis

Pancreatic insulin secretion can be determined from a series of plasma C-peptide measurements. C-peptide is produced by the pancreatic β-cells as a by-product of splitting insulin from its precursor, proinsulin, and is secreted in equimolar ratio with insulin (Rubenstein et al., 1969). Unlike insulin, C-peptide is cleared almost entirely by the kidneys, making it a much more reliable marker of endogenous secretion than plasma insulin concentrations. Therefore, models describing C-peptide kinetics and insulin kinetics can be used to determine and capture pre-hepatic insulin secretion (Polonsky et al., 1986, Van Cauter et al., 1992). The pharmacokinetic model and population kinetic parameters reported by Van Cauter et al. (1992) were used to deconvolve insulin secretion rates from measured C-peptide data. Age-based kinetic parameters were used for each subject.

To report the overall impact on blood glucose, median and IQR are reported for BG, C-peptide, insulin secretion, and plasma insulin for each measured blood parameter at key points during the test. The individual values of each athlete for these parameter are also reported.

10.4 Results

Figure 10.2a, Figure 10.2b, and Table 10.2 show that during the first 30 minutes of cycling at submaximal levels (65-70% VO2max) blood glucose utilization and production remain in equilibrium as blood glucose remains constant with median [IQR] 5.5 [5.2 6.1] mmol/L at 0 minutes to 5.7 [5.3 6.3] mmol/L at 30 minutes. However, there is a decrease in plasma insulin from median [IQR] 52 [38 63] pmol/L to 30.5 [20 40] pmol/L during this initial phase of exercise. This decrease is important as it sensitizes the liver to glucagon to enhance hepatic gluconeogenesis (Marliss et al., 2002). Once the glucose bolus at 30 minutes is delivered there appears to be an increase in non-insulin mediated glucose uptake for 8/10 athletes, as seen in Figure 10.3a and 10.3b, because only Ath09 and Ath10 display any increase in insulin secretion and rise in blood glucose in response to this oral glucose does during this time.

From 30 minutes until exhaustion, blood glucose levels rise, 5.7 [5.3 6.3] mmol/L to 8.0 [7.1 10.1] mmol/L, as a result of the first glucose bolus at 30min and increased hepatic glucose production due to the ramp test from 60min until exhaustion (>80%VO2max). However, plasma insulin and C-peptide do not begin to rise until exhaustion is reached with concentrations similar to basal levels measured at exhaustion of 46.5 [37 55] pmol/L and 635 [363 698] pmol/L, respectively. Insulin secretion rate is higher than basal levels when exhaustion is reached 600 [323 824] pmol/min compared to 133 [91.4 155] pmol/min.

After exhaustion, hyperglycaemia and hyperinsulinemia persists for >60min in 9/10 subjects with glucose concentrations of 9.6 [7.6 10.5] mmol/L at EX + 60min. Plasma insulin peaks for the same 9/10 subjects at EX + 60min with a median cohort value of 256 pmol/L, which is approximately 5 times greater than basal levels. C-peptide levels also peak at EX + 60min, 2010 [1700 2500] pmol/L. The median cohort value of insulin secretion, 1150 pmol/min, is approximately 8 times greater than fasting levels 133 pmol/min, at EX + 60min.

In Figure 10.3b panel B, it can be seen that 7/10 subjects reach their maximum insulin secretion at EX + 60min. Of the remaining 3 subjects, two, Ath07 and Ath10, whose insulin levels peak 30 minutes post exhaustion, continue to secrete elevated levels of insulin after their 30 minute peak. Only 1/10 subjects, Ath08, returns to a basal level of insulin secretion within 60 minutes post exercise.

Table 10.2 Summary of blood glucose, plasma insulin, C-peptide, and insulin secretion across the cohort at four key points during the exercise test. Results are presented as median [IQR].

Median [IQR]	0 min	30 min	EX (75-105 min)	EX + 60 min
Blood Glucose (mmol/L)	5.5 [5.2 6.1]	5.7 [5.3 6.3]	8.0 [7.1 10.1]	9.6 [7.6 10.5]
Plasma Insulin (pmol/L)	52 [38 63]	30.5 [20 40]	46.5 [37 55]	256 [193 586]
C-peptide (pmol/L)	562 [345 601]	405 [298 517]	635 [363 698]	2010 [1700 2500]
Insulin Secretion (pmol/min)	133 [91.4 155]	179 [93.9 323]	600 [323 824]	1150 [817 1482]

10.5 Discussion

During the initial 60 minutes of submaximal exercise (65-70%VO2max) an increase in non-insulin mediated glucose uptake is apparent after the initial oral glucose bolus. This response is attributed to the observed increased uptake of glucose without an increase in insulin secretion in 8/10 Athletes. This result may in part be due to increased insulin sensitivity, as exercise increases insulin delivery to muscle by

increasing peripheral blood flow allowing better utilization of plasma insulin (Marliss et al., 2002, Goodyear et al., 1998, Richter, 1996). However, an increase of non-insulin mediated glucose uptake is likely to be the dominant factor, based on published literature, because despite falling plasma insulin and similar insulin secretion levels, glucose utilization increases (Marliss et al., 2002, Douen et al., 1989, Coderre et al., 1995, Richter, 1996).

This increase in glucose utilization is further attributed to exercise allowing glucose uptake to occur through non-insulin mediated GLUT4 transporters (Goodyear et al., 1998). Exercise has been shown to cause GLUT4 to migrate to the cell-wall without the need for the insulin signalling cascade (Goodyear et al., 1998, Marliss et al., 2002). Thus, while an increase in catecholamine production, which is known to inhibit glucose utilization (Marliss et al., 2002), is likely to be present, the dominant effects of increased GLUT4 transport and delivery of insulin to muscles allows blood glucose utilization and production to remain stable.

After 60 minutes of moderate exercise, the subjects commenced intense exercise (>80%VO2max) in the form of a ramp test (+20W every 5 min) until exhaustion. During this period of intense exercise blood glucose and insulin secretion begin to rise. This response is generated by the marked catecholamine response to intense exercise (Marliss et al., 2002, Marliss et al., 1992, Dimsdale et al., 1984, Purdon et al., 1993, Zouhal et al., 2008, Kjaer et al., 1986). In general, this catecholamine response leads to increased hepatic glucose production and restriction of glucose utilization resulting in hyperglycaemia and hyperinsulinemia at the end of an intense exercise session (Marliss et al., 2002, Marliss et al., 1992, Purdon et al., 1993, Kjaer et al., 1986), as uniformly observed in this study.

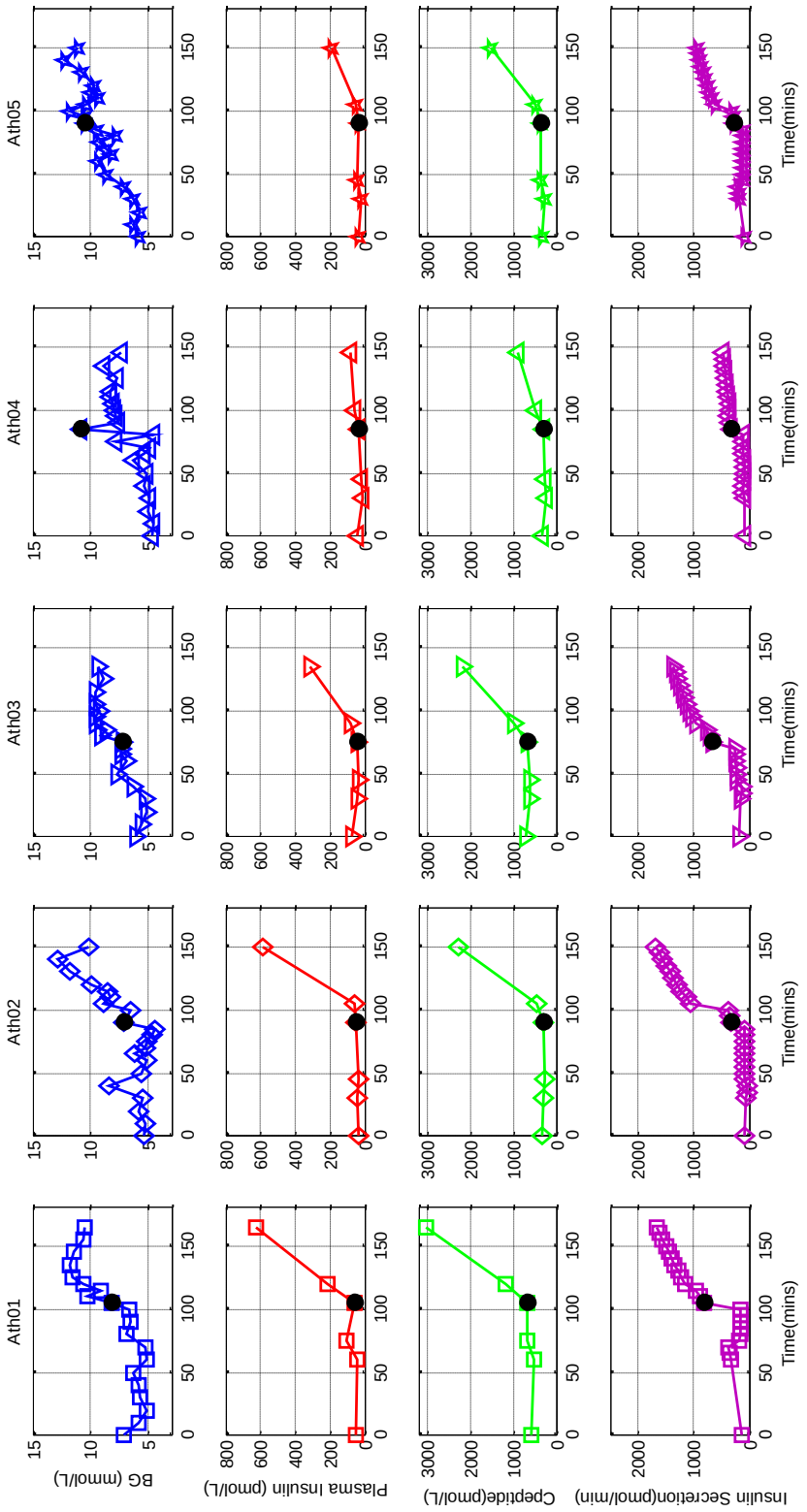


Figure 10.2a *Individual glucose, plasma insulin, C-peptide, and insulin secretion responses for athletes Ath01-Ath05. The black dots represent the point of exhaustion for each participant.*

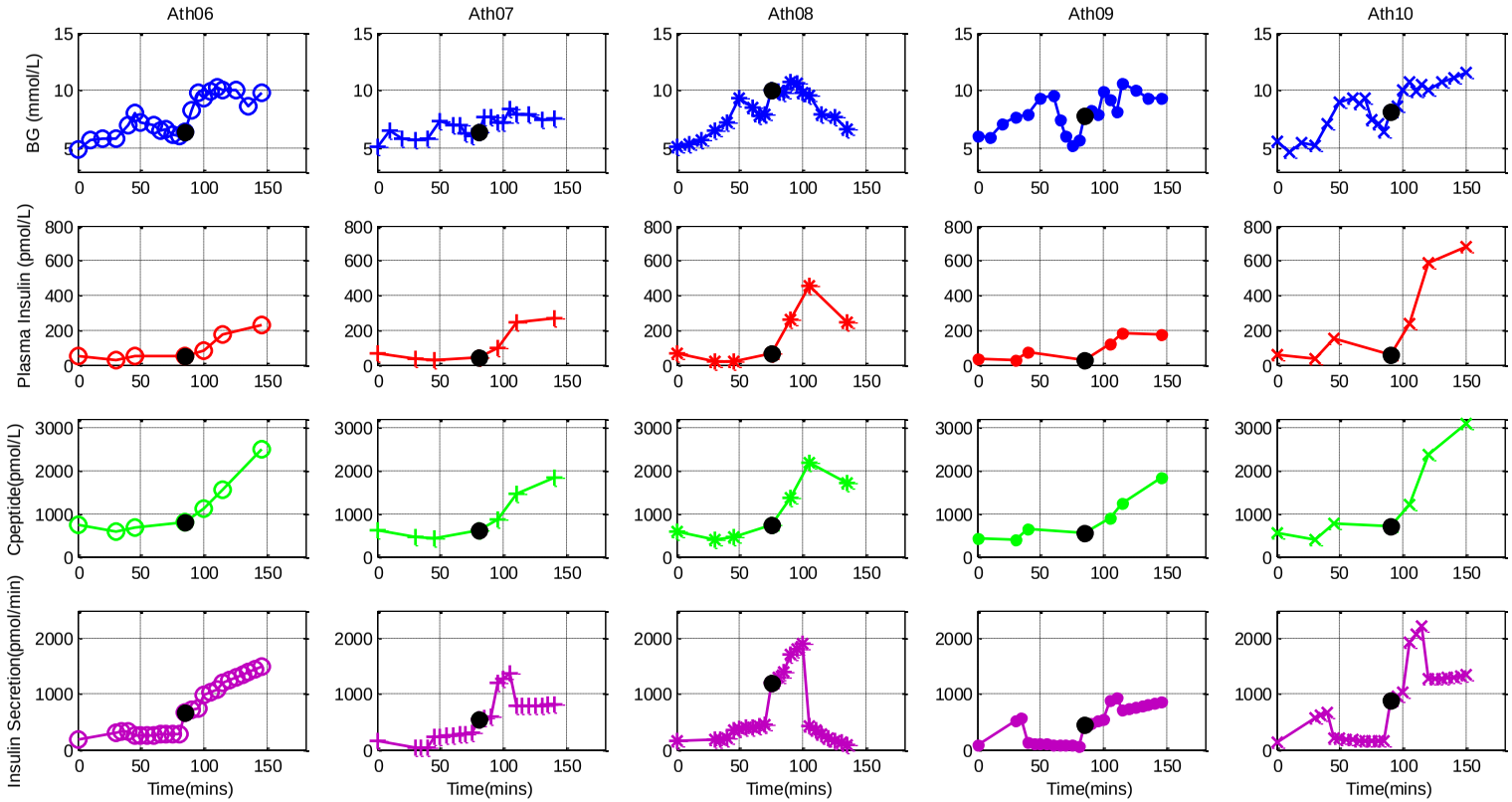


Figure 10.2b *Individual glucose, plasma insulin, C-peptide, and insulin secretion responses for athletes Ath06-Ath10. The black dots represent the point of exhaustion for each participant*

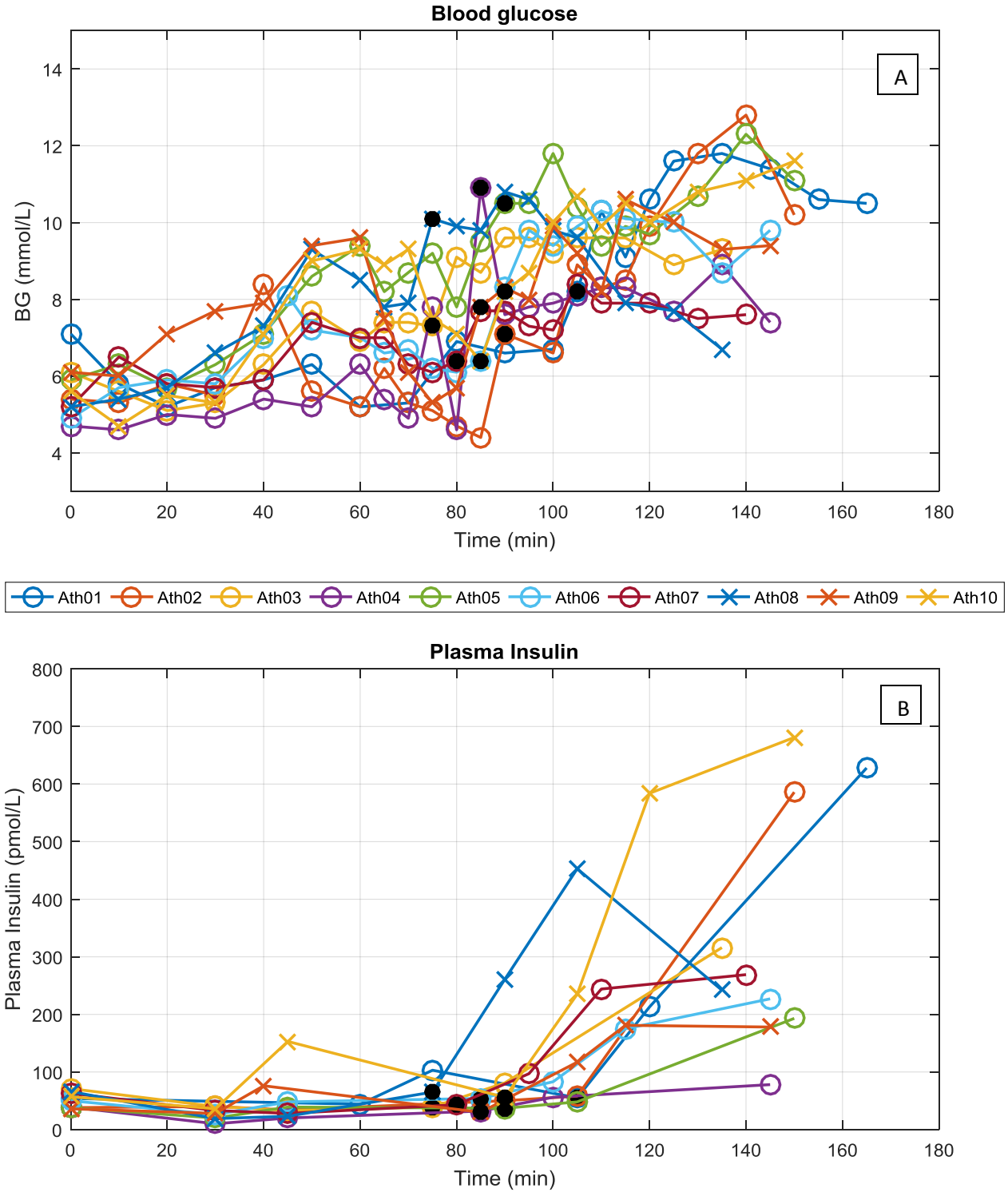


Figure 10.3a *Measured variables blood glucose (A) and plasma insulin (B) during the exercise test. The black dots represent the point of exhaustion for each participant*

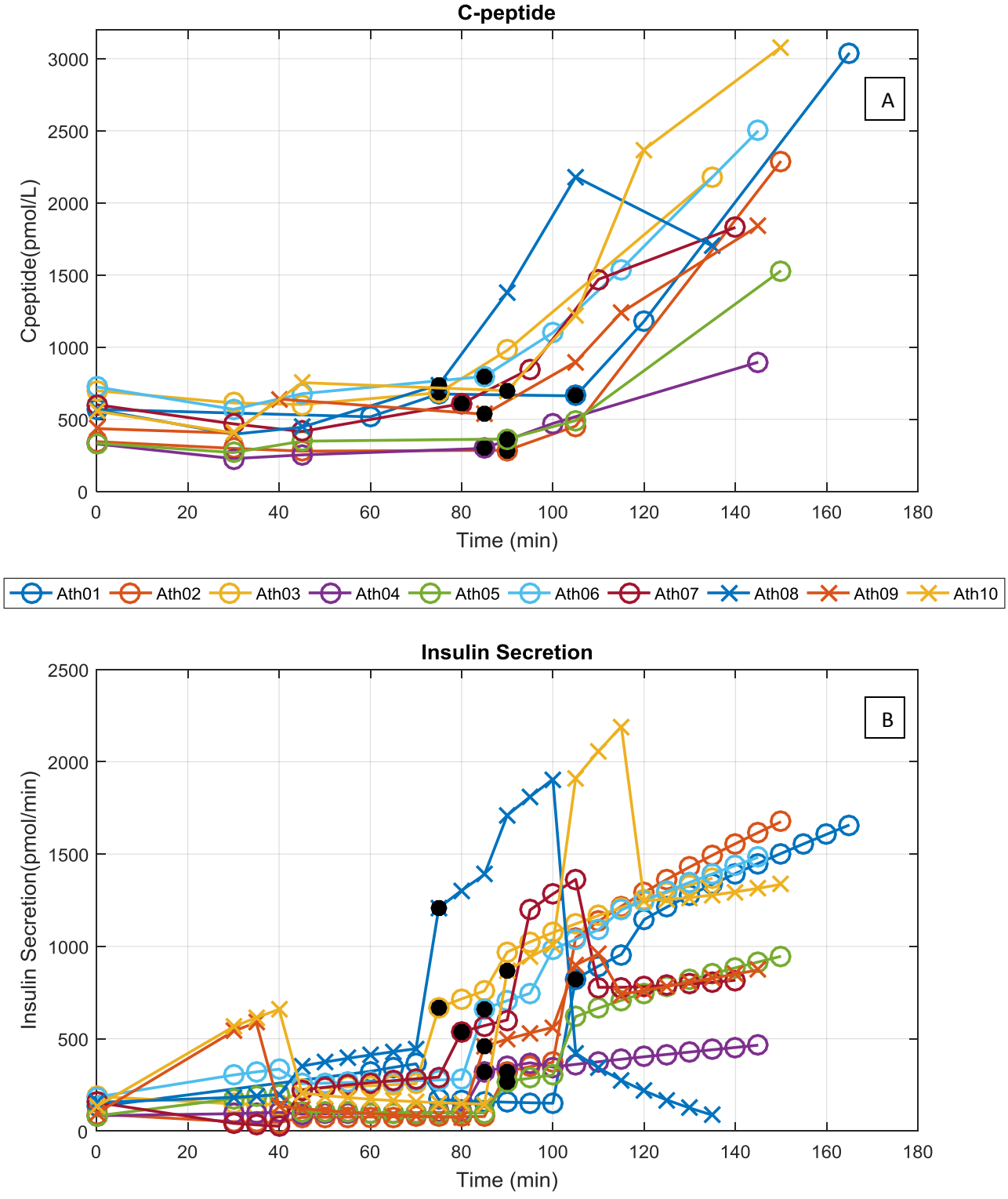


Figure 10.3b *Measured variables C-peptide (A) and insulin secretion (B) during the exercise test. The black dots represent the point of exhaustion for each participant*

However, rapid waning of catecholamine response is typically observed after short duration intense exercise (Marliss et al., 2002, Ivy et al., 1988, Marliss et al., 1992, Dimsdale et al., 1984, Purdon et al., 1993, Kjaer et al., 1986). This rapid reduction leads to blood glucose and plasma insulin to return to fasted levels within 60min post exercise if post exercise carbohydrate is not received (Marliss et al., 2002, Ivy et al., 1988, Marliss et al., 1992, Purdon et al., 1993, Kjaer et al., 1986). In studies where exercise is prolonged and carbohydrate > 1g/kg is ingested immediately post exercise blood glucose and plasma levels remain elevated 60min post exercise. However, the maximum value of blood glucose is achieved within 30mins post exercise and mean maximum plasma insulin achieved is 160 - 270pmol/L (Blom et al., 1987, Burke et al., 1993, Ivy et al., 1988) . In this study the duration and amount of hyperglycaemia and hyperinsulinemia seen is extended and increased, peaking at EX + 60min for the majority of athletes, with a maximum mean cohort plasma insulin value of 340pmol/L.

There are several potential reasons for this increased and extended period of hyperglycaemia. The combination of prolonged and intense exercise caused a larger catecholamine response. The aforementioned studies, where carbohydrates were administered post exercise were similar or longer in duration to the protocol described here, but perhaps did not require as intense a final effort. Another possible cause is the relative fitness levels of the subjects. It has been shown that compared to untrained individuals, trained subjects have a higher catecholamine response leading to a greater rise in blood glucose and insulin post exercise (Koivisto et al., 1982, Zouhal et al., 2008, Kjaer et al., 1986, Bloom et al., 1976). So there is likely to be some difference between subjects who are trained to different levels of fitness. However, the mean VO2max of athletes in this study is actually lower than that of the comparative studies, indicating a potentially lesser, rather than greater, response might be expected.

The most interesting reason to consider is that the athletes were not fasted at the end of the exercise. They had received a glucose bolus at 30mins into the exercise protocol as per recommended practice of 30-60g/h during endurance exercise lasting > 1hr (American Dietetic et al., 2009). It is likely that during competition and training, athletes will not be fasted and will be following the nutritional guidelines as above. The majority of studies on the glycemic response post exercise have been carried out in the fasted state, which does not represent how an athlete would train and compete in real life. It is also interesting to note that while the rate of carbohydrate oxidation is ~1g/min during exercise (Jeukendrup, 2004) at high intensity exercise (>80% VO2max) reduced blood flow to the gut may result in decreased absorption of glucose and water (Brouns et al., 1993). Thus, slowing the rate of appearance of the glucose challenge and potentially prolonging the period of hyperglycemia, as it is unlikely that this effect wanes immediately once exercise ceases.

Hyperglycaemia acts to induce a pro-inflammatory state, which includes both cellular inflammation and oxidative stress (Collier et al., 2008). A 75g glucose load given orally can result in significant oxidative stress and inflammatory changes at the cellular and molecular level (Collier et al., 2008, Mohanty et al., 2000). The immune system also fails to function optimally in the presence of high blood glucose levels (Marik et al., 2004, Jeandidier et al., 2006, Turina et al., 2005, Kijak et al., 1964, Sanchez et al., 1973). Hence, maintaining constant, normal, blood glucose levels is important for general health and well-being. Based on the results of this study, athletes following the recommended practice of consuming 1.0-1.5g carbohydrate/kg within 30 mins of an intense training session or competition are likely to be regularly inducing a prolonged period of hyperglycaemia and hyperinsulinemia to an extent that has not been reported before in studies examining athletes in the fasted state only.

This outcome potentially puts their bodies under significant inflammatory and oxidative stress while also weakening their immune systems. Furthermore, there is evidence to show athletes experience an immune system function depression, which is most pronounced after prolonged moderate to high intensity training or competition (Gleeson, 2006). The cause of this immune system depression is not fully understood (Gleeson, 2006) but the hyperglycaemic and hyperinsulinemia state induced could be additionally detrimental.

10.5.1 Limitations

This study is limited by the lack of catecholamine analysis to assess or segregate inflammation induced effects from other metabolic impacts. Therefore, in particular, we are unable to confirm the hypothesis that the catecholamine response is prolonged after intense, long duration exercise. However, Marlis and Vranic (2002) have conclusively shown the catecholamine response is responsible for hyperglycaemia and hyperinsulinemia after 15 minutes of intense exercise, which supports our hypothesis and is worthy of further investigation.

Another limitation is not having muscle glycogen measurements. Therefore, the amount of muscle glycogen storage obtained post-test is unknown. It is unlikely this rate differs much to those found in already published results studying carbohydrate load directly after exercise (American Dietetic et al., 2009). However, this study cannot develop conclusive statements, it does provide the foundation to justify and design specific further investigations.

10.6 Summary

To ensure optimal recovery of glycogen stores it is common practice to consume 1.0-1.5g carbohydrate/kg within 30 mins after intense exercise (American Dietetic et al., 2009). However, this practice does not ensure optimal blood glucose and plasma insulin levels. Hyperglycaemia persists >60 mins post exercise. Plasma insulin and insulin secretion both peak 60 mins post intense exercise to median [IQR] cohort values of 256 [193 586] pmol/L and 1150 [817 1482] pmol/min respectively.

In general, this response greater and more prolonged than reported in previous metabolic studies. The most likely reason for this is the subjects received two glucose boluses, one during and immediately one post exercise, as per recommended nutritional guidelines. Therefore, the main outcome of this chapter is to highlight the glycaemic dysregulation seen post exercise and potential for a re-examination of the post exercise feeding protocol used by many athletes to achieve both optimal glycogen recovery and optimal blood glucose levels.

Chapter 11. Insulin Secretion During and After Exercise

This chapter investigates a mathematical model to represent an important aspect of athlete metabolism, pancreatic insulin secretion. The endogenous insulin secretion model is of particular importance as, unlike critical care patients, athletes are not receiving exogenous insulin. Thus, any model of endogenous insulin secretion determines the identified values of insulin sensitivity (SI). Hence, understanding secretion in exercise and immediately after could shed significant insight on the metabolic changes induced by exercise.

11.1 Introduction

Endogenous insulin secretion models have a significant role in model-based glycaemic management. Endogenous insulin secretion can have a significant impact on identified parameters such as SI, especially in the absence of exogenous insulin or with low doses. Hence, reducing error in the insulin secretion model can reduce variability in identified SI and thus increase the accuracy and utility of the parameter for glycaemic control.

The models of endogenous insulin secretion already established in the literature are almost exclusively based on sedentary, healthy, and individuals with diabetes (Camastra et al., 2005, Ferrannini et al., 2005, Mari et al., 2002b). These models primarily focus on the endogenous response to glycaemic change resulting from meals. Therefore, these models may not be appropriate for during, and immediately after exercise.

Intense exercise causes a marked catecholamine response (Marliss et al., 2002, Calles et al., 1983, Kjaer et al., 1986). In general, this catecholamine response leads to increased hepatic glucose production and restriction of glucose utilization, resulting in hyperglycaemia and hyperinsulinemia at the end of an intense exercise session (Marliss et al., 2002, Kjaer et al., 1986, Calles et al., 1983). This response is similar to the stress-induced hyperglycaemia seen in ICU patients, the common factor being systemic inflammation due to their illness or induced by strenuous effort (Collier et al., 2008).

Studies comparing the metabolic and hormonal response to exercise between trained and untrained, normal glucose tolerance individuals have found that in trained individual's, glucose, glycerol, and free fatty acid concentrations are higher, but lactate, pyruvate, and alanine were lower than untrained individuals (Kjaer et al., 1986, Bloom et al., 1976). Cortisol levels were also found to be higher in trained individuals (Bloom et al., 1976). Additionally, insulin secretion is known to be diminished in well trained individuals as an adaptation to physical training (Lohmann et al., 1978). These results suggest there are significant differences of metabolism in well-trained individuals compared to sedentary, healthy subjects.

A thorough search of the literature has not located any studies in which endogenous secretion was determined for trained subjects during exercise. The significant metabolic impact of exercise on the metabolism indicates a potential gap in knowledge. Therefore this chapter develops an endogenous insulin secretion model for trained individuals during exercise and immediately after.

11.2 Subjects and Methods

11.2.1 Subjects and Exercise Test Protocol

Table 11.1 summarises the cohort demographics. Data from the ten fit, healthy, sub-elite athletes described in Chapter 10 was used for this analysis. Fasting exercise tests were carried out as shown in Figure 11.1. Subjects were required not to exercise the day before the test. On the day of testing, the exercise protocol typically began at 8am after an overnight fast and followed the protocol that is described in detail in Chapter 10. The research procedures and use of data were approved by the University of Canterbury Ethics Committee.

BG measurements were taken using capillary finger stick measurements and the Abbott Optimum Xceed (Abbott Diabetes Care, Alameda, CA) glucometer. The Abbott device has reported error of 5-10% (Abbott Diabetes Care, 2010, Brunner et al., 2011, Thomas et al., 2014a, Signal, 2013). Insulin and C-peptide concentrations were determined using immunometric assays (Elecsys 2010, Roche Diagnostics, Germany). Only 5/10 subjects Ath06-Ath10 had a blood sample at exhaustion + 30 minute due to an amendment in the protocol to allow the additional measurement.

Table 11.1 Cohort demographics of the participants. Data are presented as median [interquartile range] where appropriate

Number	10
Age (yr)	28 [23 37]
Gender (M/F)	7/3
BMI (kg/m2)	22 [21 24]
Resting HR (bpm)	55 [53 56]
VO2max (mL/kg/min)	46 [39 59]
Trained Cyclist (Y/N)	7/3
Length of CGM data (hr)	140 [105 141]

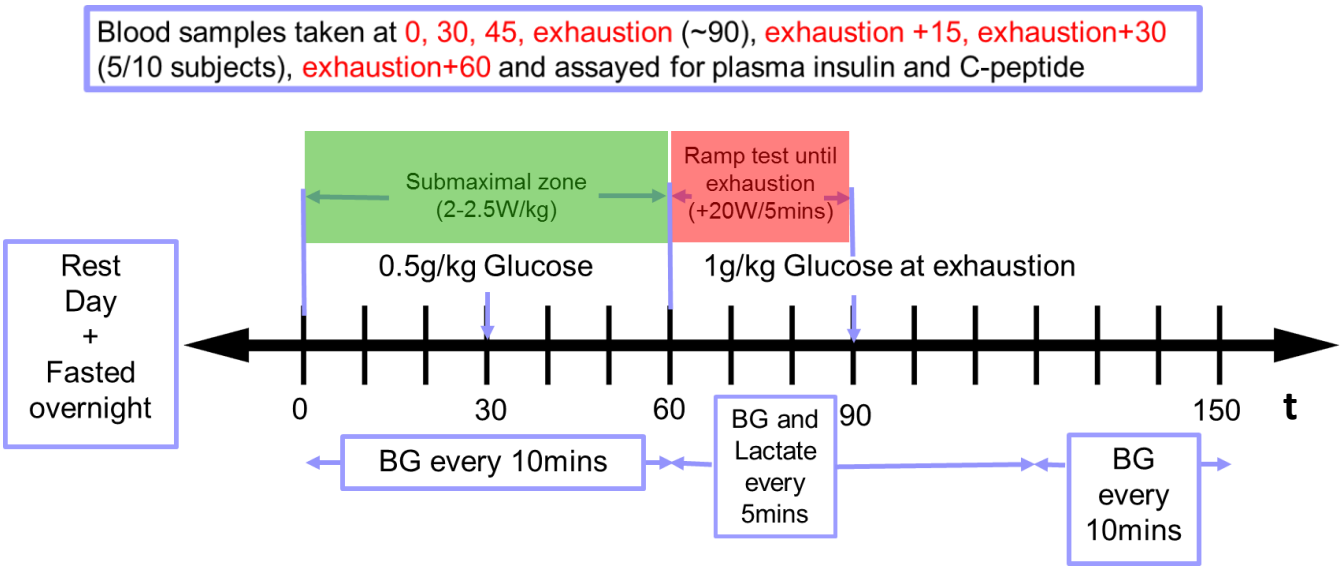


Figure 11.1 *Schematic of exercise trial protocol*

11.3 Analysis

11.3.1 Insulin Secretion

Pancreatic insulin secretion can be determined from a series of plasma C-peptide measurements. C-peptide is produced by the pancreatic β-cells as a by-product of splitting insulin from its precursor, proinsulin, and is secreted in equimolar ratio with insulin (Rubenstein et al., 1969). Unlike insulin, C-peptide is cleared almost entirely by the kidneys, making it a much more reliable marker of endogenous secretion than plasma insulin concentrations, which have multiple clearance routes to consider. Therefore, models independently linking C-peptide kinetics and insulin kinetics can be used to determine and capture pre-hepatic insulin secretion (Polonsky et al., 1986, Van Cauter et al., 1992). The pharmacokinetic model and population kinetic parameters reported by Van Cauter et al. (1992) were used to deconvolve insulin secretion rates from measured C-peptide data. Age-based kinetic parameters were used for each subject.

11.3.2 Secretion Rate Bounds

It is physiologically likely that there is an upper limit and lower limit on pancreatic secretion rate as described by Pretty (2012). The upper and lower bounds of insulin secretion rates of 16000 mU/hr and 1000 mU/hr were selected as in Pretty (2012). These limits were selected based on results of measured insulin secretion in healthy controls (Ferrannini et al., 2005, Kjems et al., 2003). Due to a lack of data specifically from athletic or active cohorts these limits were deemed to be the suitable for this analysis, and are wide enough to include a range of potential results.

11.3.3 Model Fitting

As in previous studies (Camastra et al., 2005, Ferrannini et al., 2005, Mari et al., 2002b), models were fitted to the data, defined:

$$f(x) = \sum_j a_j x_j + \mathrm{c} \qquad \text{Eq. 11.1}$$

Where $f(x)$ is estimated endogenous insulin production, x_j denotes the independent variables (BG, dBG/dt, plasma insulin) and *c* is a constant bias.

Model fitting was performed by minimising the sum of the geometric means of the squared deviations in each dimension. This method allows for uncertainty in both the dependent and independent variables, while maintaining scale invariance (Tofallis, 2002, Draper et al., 1997). Goodness of fit was assessed using the coefficient of determination, R2, calculated for the constrained model.

11.4 Results and Discussion

Endogenous secretion was constrained between upper and lower bounds of 16000 mU/hr and 1000 mU/hr. The model parameters were identified across all values, and then separately to the measurements collected during exercise and after exercise. The resulting model coefficients (a_j) and goodness of fit values are shown in Table 11.2.

A simple 1-dimensional model, shown in Figure 11.2, using all the measured values demonstrates the best fit with $R^2 = 0.53$. There was no benefit from additional complexity as shown in the goodness of fit values of Table 11.2. In addition, creating separate models for during and after exercise periods provided no benefit, most likely as there was then not enough values to generate an accurate model.

Table 11.2 Coefficients for endogenous insulin secretion models fitted with 1, 2 and 3 independent variables (dimensions) for all values measured, the values measured during exercise and the after exercise.

	Model	**Coefficients**				**Goodness of fit (R^2)**
		Constant c (mU/hr)	**BG a_1 (mU.l/mmol.hr)**	**dBG/dt a_2 (mU.l/mmol)**	**Plasma Insulin a_3 (l/hr)**	
All values	*1 dim.*	*-14140*	*2559*			*0.54*
	2 dim.	-15973	2977	-728		0.33
	3 dim.	-24954	4734	-1161	-185	-0.13
During exercise	1 dim.	-5325	1153			-0.50
	2 dim.	-11717	2429	-745		-1.19
	3 dim.	-9859	2369	-639	-225	-0.92
After exercise	1 dim.	-18667	3049			0.04
	2 dim.	-27076	4142	-845		-0.71
	3 dim.	-45933	7107	-1474	-219	-1.64

The insulin secretion model depicted in Figure 11.2 is defined:

$$Uen = 2559 \times BG - 14140 \qquad \text{Eq. 11.2}$$

The equation is constrained to [1000 – 16000] mU/hr

There are numerous data points below the minimum secretion level of 1000 mU/hr. Both the inter- and intra- patient variability, and the number of points below the lower bound are likely a result of using population kinetic parameters for the C-peptide model. The study by Van Cauter et al. (1992) shows considerable variation between patients. Coefficients of variation for the kinetic parameters of normal subjects were reported in the range 16-36% and the linear regression of long half-life against age had a correlation coefficient, r=0.28. Thus, there was significant variation of individual subject kinetic parameters around the best-fit population values, which can lead to errors in the calculated secretion rates. This variation is not uncommon when modelling insulin secretion in this way and similar variability was seen in an intensive care unit patient cohort (Pretty, 2012). Despite the variability in the resulting model, it is now successfully used for model based control in the intensive care unit (Pretty, 2012, Stewart et al., 2016).

Additionally, these parameters are calculated for “normal” subjects, as is the lower bound. It is reported in literature that athletes have a much lower plasma insulin concentrations when a glucose bolus and infusion are given when compared to healthy controls (Lohmann et al., 1978). This lack of secretion is not attributed to a diminished secretion capacity, as with individuals with diabetes, but because they are more efficient in insulin-mediated glucose disposal expressing a metabolic adaption to training. It is thus likely the lower bounds for insulin secretion do not represent an athletic cohort accurately, even though insulin secretion rates have not been deconvoled from c-peptides in this cohort before. Hence, using a healthy

sedentary population bound until more data is collected in this cohort is the most valid option especially as fitting with lower bounds does not improve the goodness of fit reported.

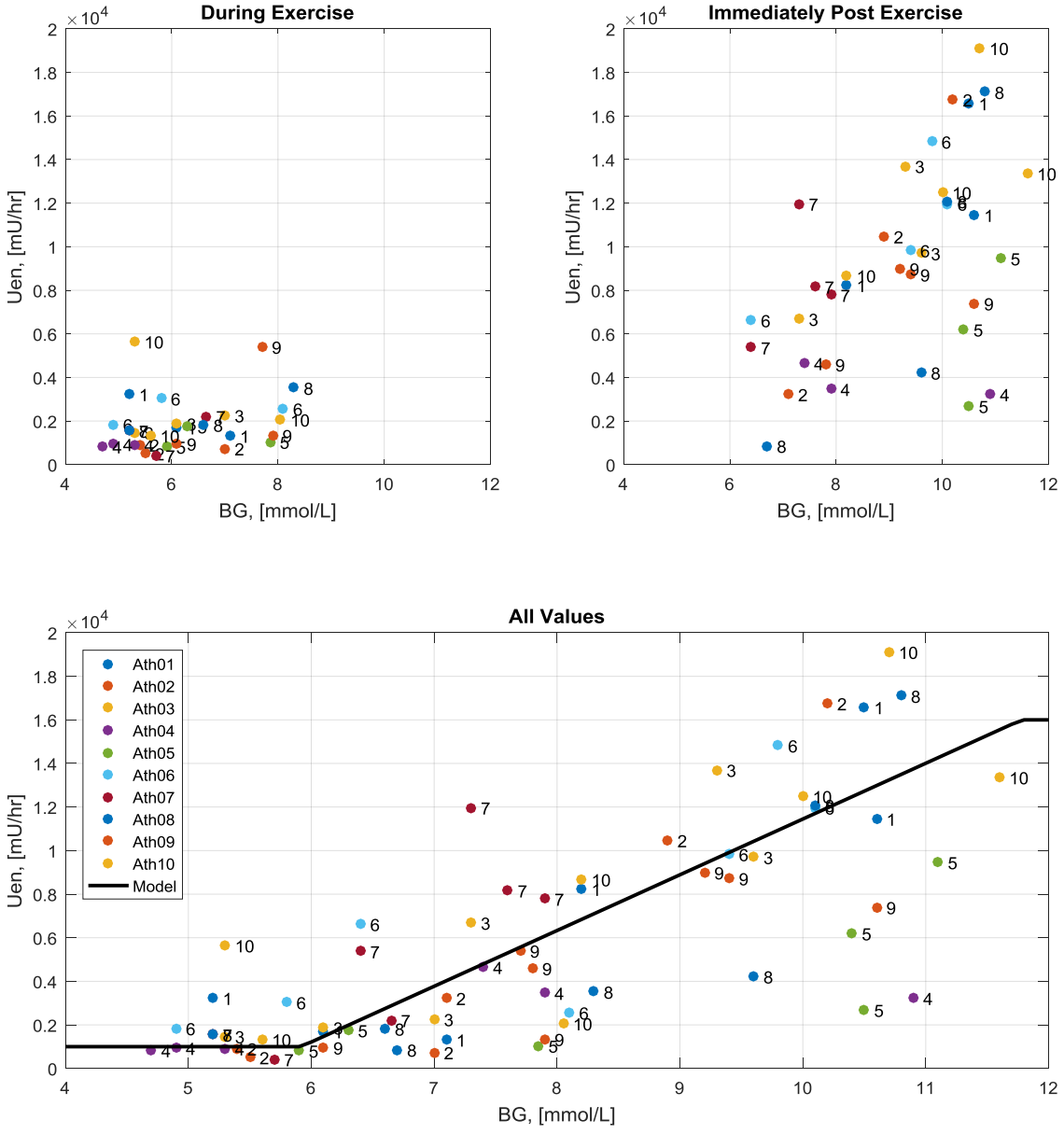


Figure 11.2 *Pre-hepatic insulin secretion data from the 10 athletes and the one dimensional model fit (R^2 = 0.53)*

To validate the secretion model, comparisons were made to published data. There no data available in the literature concerning insulin secretion rates in athletes. Most studies tend to focus on sedentary,

healthy subjects and those with diabetes. Table 11.3 presents the results of a number of published studies in which insulin secretion profiles have been related to blood glucose levels. All these studies used the method and kinetic parameters of Van Cauter et al. (1992) to calculate insulin secretion rates from measured plasma C-peptide concentrations. Reported results for the glucose coefficient (a_1) are at the upper end of the reported range of 2646 – 485 mU.L/mmol.hr for healthy subjects. Some of the reason for this large variation in coefficients may be due to model variables not being completely independent. Therefore, if models are built with a different number of parameters then the coefficients will be affected.

11.4.1 Limitations

One of the major limitations of this study is that there is no other published data from athletic subjects or any subjects during exercise and immediately after exercise. This lack of data restricts the upper and lower limits of the model to match that of "healthy" or "normal glucose tolerance" individuals. It also prevents a more thorough validation of the model, as the resulting glucose coefficient (a_1) can once again only be compared to control subjects. However, this study provides a good first initial investigation in to the effects of training and exercise on insulin secretion which later studies can build on.

The second major limitation of the study is that insulin secretion rates calculated in this study rely on the population kinetic parameters reported by Van Cauter et al. (1992) for sedentary, healthy subjects. Use of these values assumes that renal uptake of C-peptide in athletic subjects during exercise is not significantly different to sedentary, healthy subjects. There is no existing literature reporting renal C-peptide metabolism in athletic subjects. Hence, they are the best available transport parameters for this analysis.

Table 11.3 Glucose coefficient data from the literature. Results have been converted to the units of measurement used in this study where necessary. Assumptions used for these conversions were: w = 80 kg; BSA = 1.8 m^2; Bold face indicates those subject most similar to this athletic cohort.

Study	Cohort	Glucose coefficient, a_1, [mU.L/mmol.hr]
Ferrannini et al. (2005)	**Lean normal glucose tolerance**	**2646**
	Obese normal glucose tolerance	19332
	Impaired glucose tolerance	1155
	T2DM	294
Mari et al. (2002a)	**Control**	**2664**
	T2DM	1113
Mari et al. (2002b)	**Healthy 24 hr meal test (5-7 mmol/L)**	**2196**
	Healthy 2 hr protocol (5-7 mmol/L)	**2592**
	Healthy OGTT (5-7mmol/L)	**2754**
Camastra et al. (2005)	**Healthy controls**	**1290**
	20 Obese Non-Diabetic	1860
Kjems et al. (2003)	**Healthy saline infusion**	**480**
	T2DM saline infusion	160
	Healthy GLP-1 max. infusion	**5360**
	T2DM GLP-1 max. infusion rate	1040
Jones et al. (1997)	**Non-diabetic insulin sensitive**	**485**
	Non-diabetic insulin resistant	664
Byrne et al. (1995)	No MODY1 mutation baseline	761
	No MODY1 mutation glucose-primed	1400
Chang et al. (2003)	T2DM with NN2211 (GLP-1 derivative)	1008
	T2DM with Placebo	432
	Controls	**1152**

11.5 Summary

A simple 1-dimensional model demonstrates the best model of endogenous insulin secretion with an R2 = 0.53 and a glucose coefficient (a1) of 2559 mU.l/mmol.hr. The proposed model of endogenous insulin secretion, based on physiological measurements, provides a simple estimate of insulin secretion with comparable physiological parameters to existing literature. Overall, the endogenous insulin secretion model provides a valuable addition to glucose-insulin modelling, specifically for athletic individuals during exercise and immediately after**.**

Chapter 12. Insulin Sensitivity During and After Exercise

The Intensive Control Insulin-Nutrition-Glucose (ICING) model has been successful in accurately identifying SI for glycaemic control. However, this model and its model parameters are formulated for intensive care patients, rather than healthy subjects. Therefore, this chapter aims to adapt this model to allow insulin sensitivity to be identified during and after exercise in a well-trained, athletic cohort.

Exercise is well known to increase insulin sensitivity by both long and short term effects. This chapter is the first attempt to formally quantify this value during exercise and immediately after exercise. An improved understanding insulin sensitivity levels during and after exercise has the potential to optimise and individualise nutrition for athletes and provide an indication of recovery from an intense bout of exercise.

12.1 Introduction

Models of glucose-insulin dynamics have been developed with varying degrees of complexity for a range of purposes, primarily to identify SI in individuals with type 1 or type 2 diabetes and intensive care patients (Bergman et al., 1981, Hovorka et al., 2008, Mari et al., 1997, Wong et al., 2008b, Bergman et al., 1979, Cobelli et al., 1984). This identified insulin sensitivity can then be used to create targeted treatment strategies for individuals in these cohorts. In some cases, normally in the Intensive Care Unit (ICU), SI is used to predict nutritional and insulin inputs to optimise BG levels in patients with stress-induced hyperglycaemia (Stewart et al., 2015, Evans et al., 2012, Lonergan et al., 2006a).

The ICING model was based on the minimal model (Bergman et al., 1981) and developed to be used with a GC protocol in the intensive care unit (Lin et al., 2011). The ICING model is uniquely identifiable (Docherty et al., 2012) and has been a major factor in the success of the STAR GC protocol (Evans et al., 2012) in the Christchurch Hospital ICU (Stewart et al., 2016). The model has been revised and optimised several times since it was first published to ensure the most up to date, physiologically representative, model as possible (Pretty, 2012, Fisk et al., 2012, Stewart et al., 2015).

Exercise is well known and accepted to improve insulin sensitivity by both short term acute effects and long term training effects (Borghouts et al., 2000). Moderate exercise increases non-insulin mediated glucose uptake during exercise and for up to 2 hours post exercise. A single bout of exercise can increase also insulin sensitivity for up to 16 hours post exercise (Borghouts et al., 2000). Finally, as a result, insulin secretion is known to be diminished in well trained individuals due to increased sensitivity (Lohmann et al., 1978).

However, during intense exercise blood glucose and insulin secretion rise, due to the marked catecholamine response to intense exercise (Marliss et al., 2002, Calles et al., 1983, Kjaer et al., 1986). This behaviour is similar to stress-induced hyperglycaemia seen in ICU patients (Collier et al., 2008). The catecholamine response leads to increased hepatic glucose production and restriction of peripheral glucose utilisation, resulting in hyperglycaemia and hyperinsulinemia at the end of an intense bout of exercise. This change can last for over 60 minutes, as discussed in Chapter 10. This overall physiological response indicates a significant potential reduction in insulin sensitivity during and immediately after intense exercise.

Better understanding variations in insulin sensitivity during and after exercise has the potential to optimise and individualise nutrition plans for athletes, and could provide an indication of recovery from an intense bout of exercise. To the author's knowledge, a model of insulin sensitivity for an athletic cohort has not been reported in the literature. This chapter aims to create a physiological model of insulin sensitivity based on the successful ICING model and fit insulin sensitivity during and immediately after exercise using only BG measurements and nutritional inputs.

12.2 Methods

12.2.1 Subjects

Table 12.1 summarises the cohort demographics. Data from the 10 fit, healthy, sub-elite athletes described in Chapter 10 was used for this analysis. Fasting exercise tests were carried out as shown in Figure 12.1. Subjects were required not to exercise the day before the test. On the day of testing, the exercise protocol typically began at 8am after an overnight fast and followed the protocol and followed the protocol that is described in detail in Chapter 10. The research procedures and use of data were approved by the University of Canterbury Ethics Committee.

Table 12.1 Cohort demographics of the participants. Data are presented as median [interquartile range] where appropriate

Number	10
Age (yr)	28 [23 37]
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VO2max (mL/kg/min)	46 [39 59]
Trained Cyclist (Y/N)	7/3
Length of CGM data (hr)	140 [105 141]

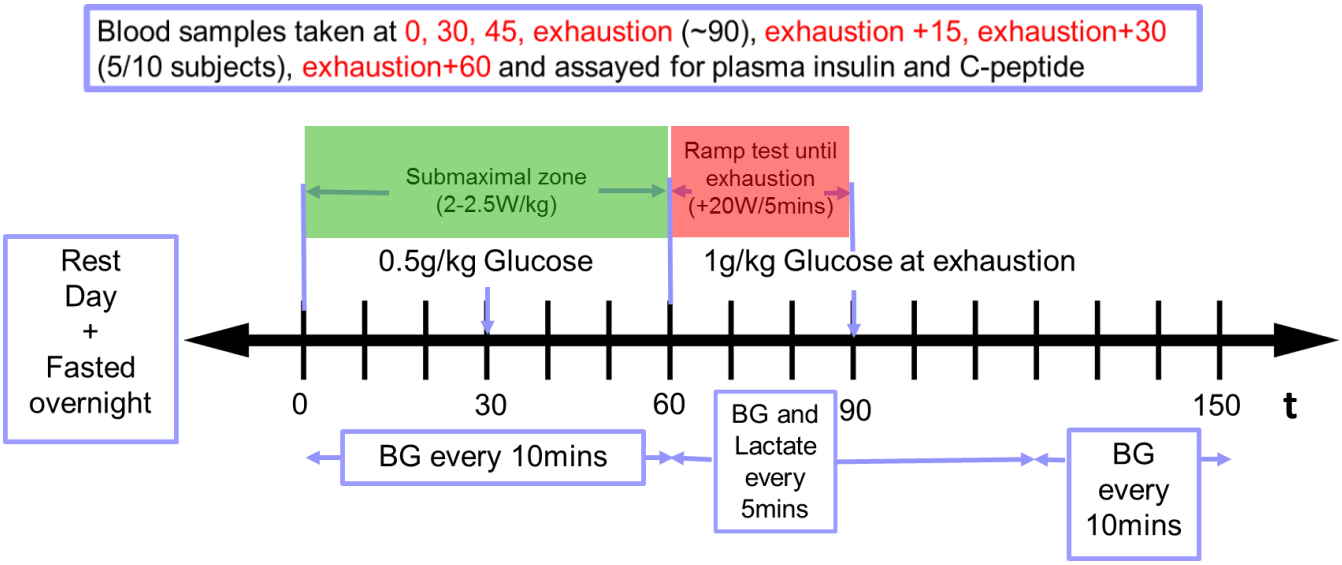

Figure 12.1 *Schematic of exercise trial protocol*

BG measurements were taken using capillary finger stick measurements and the Abbott Optimum Xceed (Abbott Diabetes Care, Alameda, CA) glucometer. The Abbott device has reported error of 5-10% (Abbott Diabetes Care, 2010, Brunner et al., 2011, Thomas et al., 2014a, Signal, 2013). Insulin and C-peptide concentrations were determined using immunometric assays (Elecsys 2010, Roche Diagnostics, Germany). Only 5/10 subjects Ath06-Ath10 had a blood sample at exhaustion + 30 minute due to an amendment in the protocol to allow the additional measurement.

12.2.2 Model

The ICING model (Lin et al., 2011) was simplified and adapted to describe athlete glucose insulin metabolic system dynamics. This modified model is defined:

$$\dot{P1} = -d1 * P1 + P(t) \quad \text{Eq. 12.1}$$

$$\dot{P2} = -d2 * P2 + d1 * P1 \quad \text{Eq. 12.2}$$

$$P(t) = \min([d2 * P2 * HE, P_{max}]) \quad \text{Eq. 12.3}$$

$$\dot{Q} = \left(I - Q\right) * n_L - Q * n_c \quad \text{Eq. 12.3}$$

$$\dot{G} = SI * \frac{Q}{1+\alpha_g} * \mathrm{G} - p_g * G + \frac{EGP}{V_g} + \frac{P(t)}{V_g} \quad \text{Eq. 12.4}$$

The model parameters are described in Table 12.2 and the key variables are listed in Table 12.3.

First pass hepatic extraction (HE) was added to the model because in health individuals 5 -10% of a glucose load is extracted on first pass of the liver and does not reach the blood stream (Radziuk et al., 1978). During exercise there is potential for this value to be even higher as glycogen stores are being rapidly diminished. However, there have been no published studies looking at hepatic extraction during exercise. Stomach and gut clearance parameter values, *d1* and *d2*, are taken from Dalla Man et al. (2006) in a study of health individuals during an oral glucose tolerance test (OGTT). Non-insulin mediated glucose uptake (p_g) was identified in Bergman et al. (1981) for 5 lean subjects with good glucose tolerance. The value used for endogenous glucose production (EGP) was taken from a study that investigated the glucose metabolism in the leg of healthy individuals while cycling at three different workloads (Wahren et al., 1971). This study used arterial-femoral venous difference to calculate the EGP. They did not find EGP to be constant. However, EGP is held constant for simplicity, as in the ICING model, as there is currently no non-invasive means to effectively monitor or measure it. More modern tracer studies of EGP while exercising also provide a range of 0.00 – 3.23 mmol/min depending on the amount of glucose ingested (Jeukendrup et al., 1999, McConell et al., 2000). All other parameters in Table 12.2 have remained the same from the ICING model due to a lack of other data in the literature for healthy individuals.

In this study, the model was simplified, as plasma insulin was measured during the exercise test and did not need to be explicitly modelled. Therefore, instead of calculating plasma insulin from an endogenous insulin model, the measured insulin was entered directly into this model. If the plasma insulin is not available the endogenous insulin model presented in Chapter 11 could be used as per the most current variant of the ICING model (Stewart et al., 2015) to calculate the plasma and interstitial insulin concentrations.

Table 12.2 Parameter values and description for the Athlete ICING model.

Variable	Description	Athlete Value	Reference
p_g	Non- insulin mediated glucose uptake	0.0464 min^{-1}	(Bergman et al., 1981)
d_1	Stomach clearance	0.222 min^{-1}	(Dalla Man et al., 2006)
d_2	Gut clearance	0.013 min^{-1}	(Dalla Man et al., 2006)
EGP	Endogenous glucose production	3.00 mmol/min	(Wahren et al., 1971)
HE	First pass hepatic extraction	0.90	(Radziuk et al., 1978) (Radziuk et al., 2001)
P_{max}	Maximal gut clearance	6.11 mmol/L	(Noah et al., 2000)
V_G	Glucose volume of distribution	13.3 L	(Lin et al., 2011)
α_G	Saturation of insulin mediated glucose uptake	0.01538 $L.mU^{-1}$	(Doran, 2004)
n_L	Hepatic clearance	0.1578 min^{-1}	(Lotz et al., 2008)
n_C	Interstitial clearance	0.006 min^{-1}	(Pretty et al., 2014)

Table 12.3 Key time dependent variables for the Athlete ICING model.

Variable	Unit	Description
Q(t)	mU/L	Interstitial insulin concentration
P(t)	mmol/min	Glucose appearance in plasma from oral glucose intake
I(t)	mU/L	Measured plasma insulin concentration
G(t)	mmol/L	Measured blood glucose concentration
$S_i(t)$	L/mU/min	Insulin sensitivity

12.3.3 Analysis

SI was identified using the integral based fitting method (Hann et al., 2005). This method holds SI constant over a fitting period, but allows it to change each fitting interval. For each subject, SI was identified over 3 different time intervals to try to best capture the changes in insulin sensitivity during exercise and assess any cohort trends, specifically:

- Every plasma insulin measurement - 0 – 30, 30 – 45, 45 – EX, EX – EX + 15, EX + 15 – EX + 60 min
- Moderate exercise, intense exercise and post exercise - 0 – 60, 60 – EX, EX +60 min
- Across the entire period - 0 – EX + 60 min

12.4 Results and Discussion

Figure 12.2 shows SI identified over every plasma insulin measurement interval. It is evident from this figure that the boluses at 30 min and exhaustion have a large impact on the model. SI jumps significantly with the boluses, especially the first bolus. Within the model, this jump occurs because a substantial amount of glucose has been delivered in a short time frame and blood glucose has remain relatively constant for most subjects. Thus, the gut model dynamics do not capture this bolus intake and its appearance well, and since EGP and p_g are fixed the model cannot adapt to the observed glucose data well. In reality, SI is unlikely to jump in this manner, because other factors, such as EGP and/or p_g, will be altered instead. However, the model cannot capture this behaviour when only fitting one variable, and thus SI must rise to match this data. The effect is not so pronounced at the end of intense exercise, as intense exercise causes blood glucose to rise due to increases hepatic glucose production, masking some of these issues.

Figure 12.3 and Table 12.2 show SI identified during moderate exercise, intense exercise and immediately after exercise. If the 30 minutes after each bolus is ignored, as in Table 12.2, to remove the initial transient effects of the bolus it is evident that SI is highest during moderate exercise with a median interquartile range of 0.0000 [-0.0003 0.0027]. SI then drops substantially during intense exercise to a median interquartile range of -0.0042 [-0.0118 -0.0008] and then recovers somewhat 30 minutes post exercise, but is still diminished compared to the first 30 min with a median interquartile range of -0.0012 [-0.0035 -0.0009].

These changes in insulin sensitivity support what is reported in literature and reported in Chapter 7. Moderate exercise increases insulin sensitivity through an exercise induced increase in glucose utilisation exercise allowing glucose uptake to occur through non-insulin mediated GLUT4 transporters (Goodyear et al., 1998) by relocating them closer to the blood stream (Goodyear et al., 1998, Marliss et al., 2002). However, during intense exercise the increase in non-insulin mediated uptake is countered by a marked catecholamine response to intense exercise (Marliss et al., 2002, Marliss et al., 1992, Dimsdale et al., 1984, Purdon et al., 1993, Zouhal et al., 2008, Kjaer et al., 1986). In general, this catecholamine response leads to increased hepatic glucose production and restriction of glucose utilization resulting in hyperglycaemia and hyperinsulinemia at the end of an intense exercise session (Marliss et al., 2002, Marliss et al., 1992, Purdon et al., 1993, Kjaer et al., 1986). This response is comparable to the stress induced hyperglycaemia seen in the intensive care unit. It is thus logical that this response would generate a reduction in insulin sensitivity, as shown in Figure 12.3.

The fact that SI is still reduced 30 minutes post exercise is not necessarily in line with current literature as the a rapid waning of catecholamine response is typically observed after short duration intense exercise

(Marliss et al., 2002, Ivy et al., 1988, Marliss et al., 1992, Dimsdale et al., 1984, Purdon et al., 1993, Kjaer et al., 1986). Thus, blood glucose and plasma insulin are expected to return to fasted levels within 60min post exercise, if post exercise carbohydrate is not received (Marliss et al., 2002, Ivy et al., 1988, Marliss et al., 1992, Purdon et al., 1993, Kjaer et al., 1986). However, as reported in Chapter 10, this outcome did not occur during this study. Hyperinsulinemia and hyperglycaemia remained for at least 60 min post exercise. Therefore, it is possible that insulin sensitivity also does not return to the same or a similar level as initially observed, which is shown in column four of Table 12.2.

Figure 12.4 shows SI identified across the entire exercise test and post exercise period, approximately 140 minutes. Ath04 has a much higher overall SI then any of the other subjects. This interesting result relates to the findings of Chapter 14, when the subject's blood glucose was monitored over a 6 day period, it was evident that Ath04 achieved the most stable blood glucose trace (Figure 14.3). Over 99% of the monitoring time, when meals are accounted for, blood glucose was between 4.0 – 6.0 mmol/L for Ath04. However, this correlation between long term blood glucose trends and the SI identified across the entire test period does not hold. Ath01 and Ath10 both spent 86.6% of the 6 day monitoring period in the 4.0 – 6.0 mmol/L band, but have the lowest SI, while Ath09 only spent 9.7% and has a mid-range SI value.

Another interesting point to note is that SI is often identified as negative. In a purely physiological sense, negative SI does not make sense. Negative or zero SI indicates that the body is producing glucose faster than dissipating it. This result indicates that model is not capturing the true dynamics due to the oversimplification of holding EGP and/or p_g constant. To model both moderate and intense exercise, a model would need to be able to account for both non-constant non-insulin mediated uptake and endogenous glucose production. This goal could be potentially be achieved by making p_g, and EGP

dependent on heart rate or some other suitable marker of effort. However, this choice would add additional complexity, would likely be subject and/or day specific, and would thus be difficult to generalise. Before a model of SI can be used to accurately identify SI in an athletic cohort during exercise accuracy further studies in to EGP and p_g during both moderate and intense exercises are necessary.

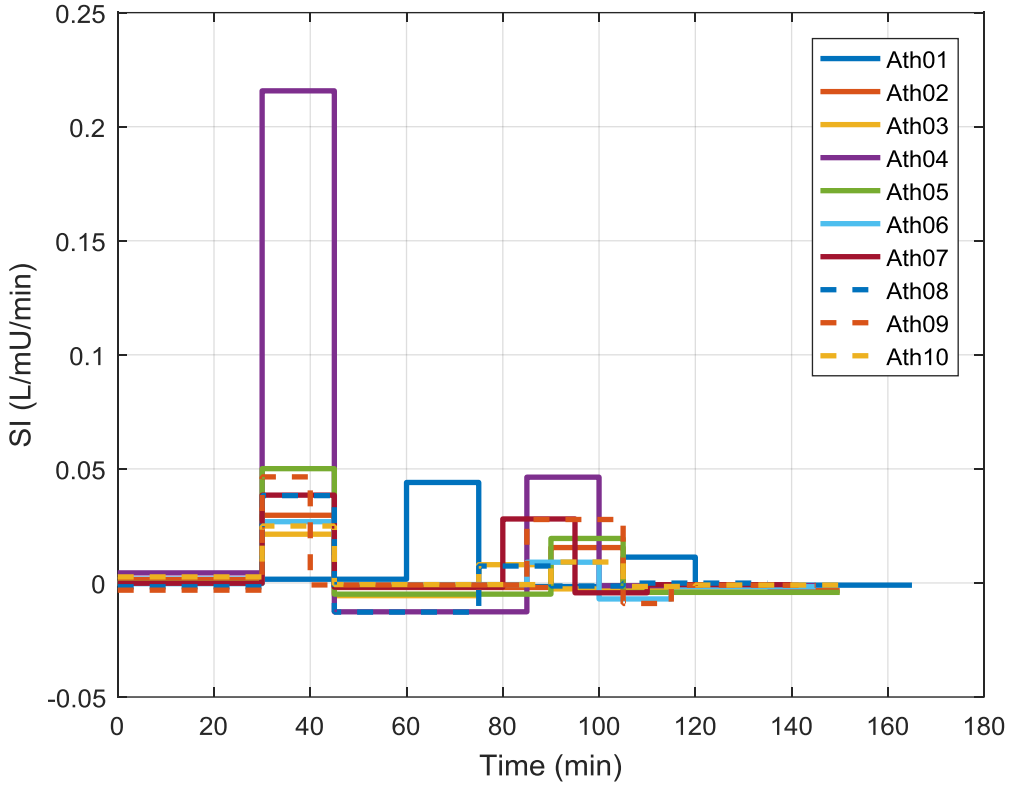

Figure 12.2 *SI identified over every plasma insulin measurement interval (0 – 30, 30 – 45, 45 – EX, EX – EX + 15, EX + 15 – EX + 60 min). N.B. Ath01 had a slightly different protocol that Ath02 – 10 resulting in the first glucose bolus being delivered at 60 min*

This model and assumptions appears to be able to best physiologically represent SI during periods of steady state, away from bolus periods. This outcome is evident from the fact the cohort follows the expected trends for SI during moderate exercise, intense exercise, and post exercise when the bolus periods are not considered, as shown in Table 12.3. The model is currently unable to deal with the rapid

and transient effects of boluses, especially as the gut model parameters, *d1* and *d2*, may not be suitable during exercise.

The ICING model has similar issues when exogenous insulin is not delivered to patients and must thus rely on estimates of endogenous secretion. Exogenous insulin delivery saturates the endogenous insulin secretion model and overwhelms the effects of the gut model, lessening the dependence of these assumed dynamics on the modelling process. Additionally, ICU patients do not receive bolus meals, but constant infusions, so the gut model is much more useful in steady state. Improving the gut model would be a first step to allowing the model to better cope with the dynamics induced when glucose is consumed.

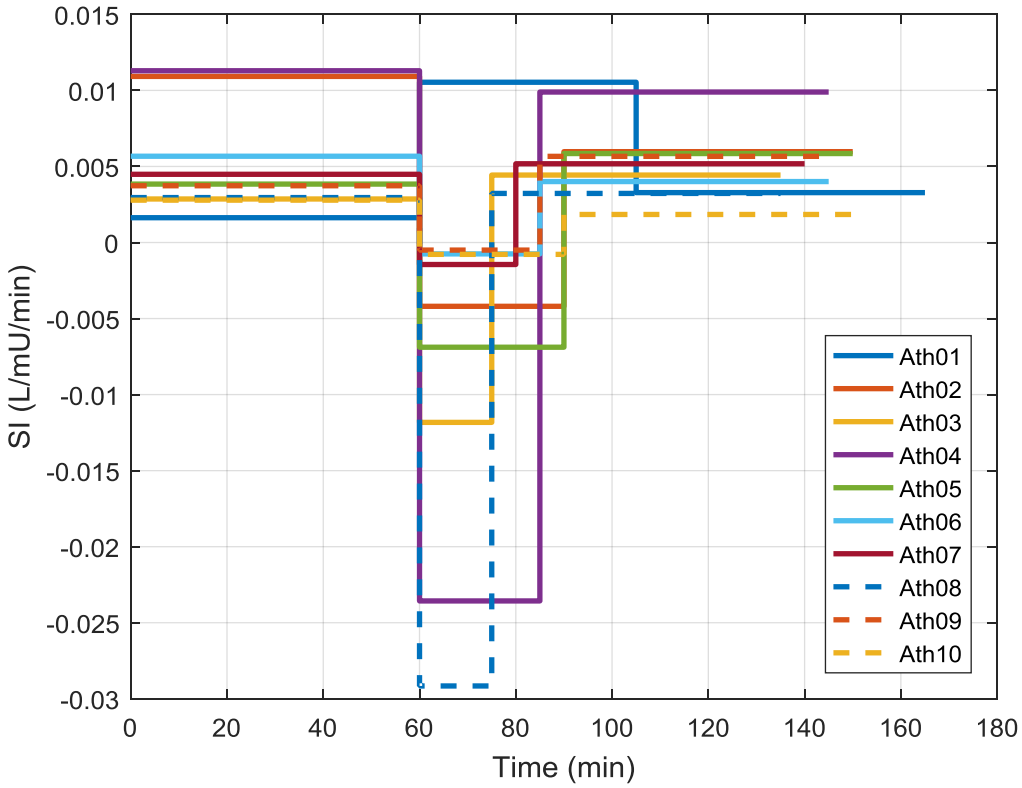

Figure 12.3 *SI identified during moderate exercise, intense exercise and post exercise (0 – 60, 60 – EX, EX +60 min) N.B. Ath01 had a slightly different protocol that Ath02 – 10 resulting in the first glucose bolus being delivered at 60 min.*

Table 12.3 SI values during moderate exercise, intense exercise and post exercise removing 30 minutes after every glucose bolus to reduce impact of the gut model, values are presented as median [interquartile range (IQR)] where appropriate.

	SI moderate exercise (0 – 30 min)	SI intense exercise (60 min – EX)	SI post exercise (EX + 30 – EX + 60 min)
ATH01	0.0028	-0.0043	-0.0011
ATH02	0.0014	-0.0042	-0.0046
ATH03	0.0001	-0.0118	-0.0035
ATH04	0.0044	-0.0236	-0.0013
ATH05	-0.0002	-0.0069	-0.0062
ATH06	-0.0003	-0.0007	-0.0016
ATH07	-0.0001	-0.0014	-0.0008
ATH08	-0.0017	-0.0292	-0.0001
ATH09	-0.0032	-0.0005	-0.001
ATH10	0.0027	-0.0008	-0.0009
Median [IQR]	0.0000 [-0.0003 0.0027]	-0.0042 [-0.0118 -0.0008]	-0.0012 [-0.0035 -0.0009]

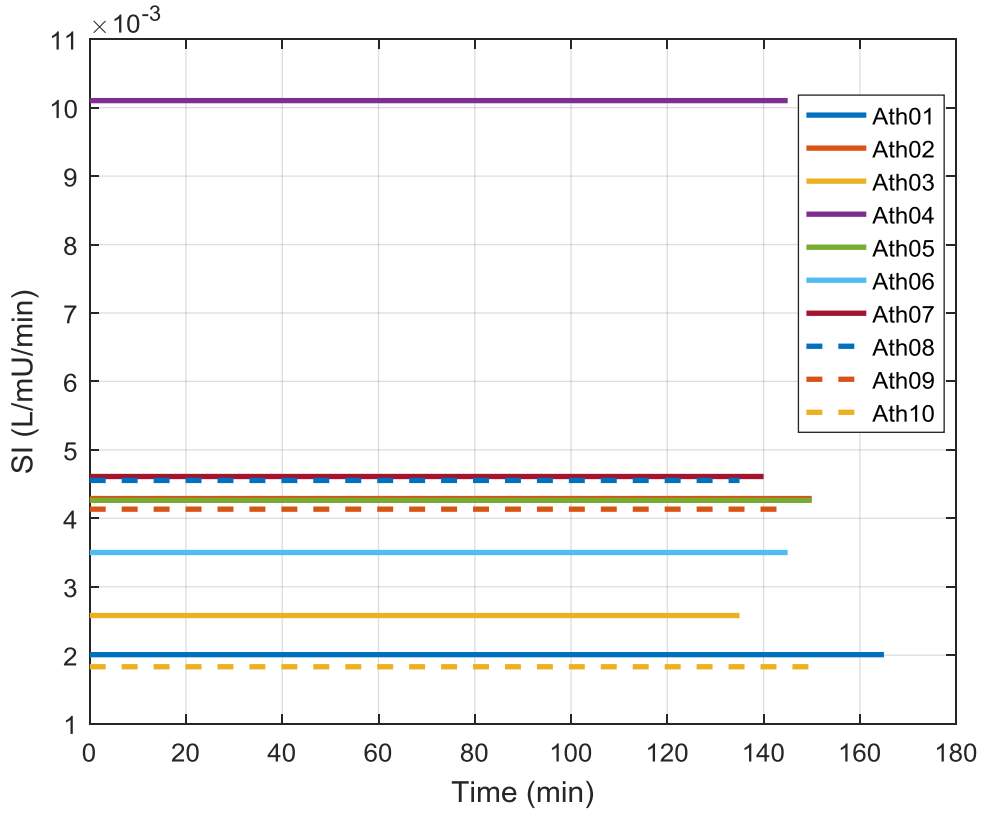

Figure 12.4 *SI identified across the entire period (0 – EX + 60 min)*

12.5 Summary

This chapter aimed to adapt the successful ICING model to allow insulin sensitivity to be identified during and after exercise in a well-trained cohort. Exercise is well known to improve insulin sensitivity by both long and short term effects, but this chapter is the first attempt to formally quantify during exercise and immediately after exercise.

The ICING model was simplified to remove the unnecessary plasma insulin compartment as plasma insulin was measured regularly during exercise. All other parameters were adjusted to be values from athletic or lean, healthy cohorts where possible. SI was identified using the integral fitting method over various different intervals to investigate how to best capture the changes in insulin sensitivity during exercise and assess any cohort trends. The model appears to be best able to identify insulin sensitivity during steady state periods of exercise, as SI trends in these periods match known physiology. When boluses are delivered non-physiological jumps in SI take place as the model cannot cope with the transient effects of glucose boluses and non-constant endogenous glucose production or non-insulin mediated glucose uptake.

Identified SI was often negative, indicating the model was not able to accurately capture the BG dynamics with current parameter values and assumptions. While an improved understanding of insulin sensitivity levels during and after exercise has the potential, further research is needed to understand how to model the ingestion of glucose, endogenous glucose production and non-insulin mediated glucose uptake in a way that does not over-complicate the model, while remaining physiologically realistic.

This chapter provides a unique insight in to the day to day glucose levels of athletes that could only be achieved through the use of CGM devices highlighting the need for further investigation on the recommend diets of athletes to better determine the causes and impact of the hyperglycaemia seen on health and performance.

Chapter 13. Accuracy and Performance of CGM in Athletes

CGM devices have the potential to provide important feedback to athletes to aid in the optimisation of blood glucose levels during training, racing and recovery. However, these devices are designed for use in T1DM and T2DM, who typically experience different glycaemic ranges, and have not been tested in this cohort before. Therefore, their performance in athlete subjects during intense physical exercise is unknown. This chapter investigates the accuracy and performance of the retrospective Ipro2 and Guardian Real-time CGM devices (Medtronic Minimed, Northridge, CA, USA), while subjects are exercising in a manner representative of an endurance event or sport.

13.1 Introduction

CGM devices, with their 1-5 minute measurement interval, allow BG dynamics to be captured more frequently and less invasively than traditional measures of BG. CGM devices typically consist of a small pager-like monitoring device that receives a signal from a sensor inserted into the subcutaneous layer. The sensor creates a signal using the glucose oxidase reaction and produces a current proportional to the glucose concentration in the surrounding interstitial fluid. Calibration algorithms convert the signal into a BG value by comparing it to calibration BG measurements, which are entered into the monitor by the user every 6-8hrs.

These devices are primarily designed for use in individuals with type 1 and type 2 diabetes to aid BG regulation and are well studied in this cohort (Gandhi et al., 2011, Hoeks et al., 2011). However, because of the increased measurement frequency and reduced invasiveness they have recently been applied to other cohorts, such as intensive care patients, to manage stress-induced hyperglycaemia, and neonates, to prevent hypoglycaemia, with varying success (Chee et al., 2003a, Holzinger et al., 2010, Brunner et al., 2011, Thomas et al., 2015, Signal et al., 2013, Signal et al., 2010, Beardsall et al.,

2005, Harris et al., 2010). Another cohort where CGM may be beneficial is athletes. This cohort is yet to be thoroughly investigated, but optimisation of an athlete's BG has the potential to increase race performance, speed recovery, and aid training (Jeukendrup, 2004, Achten et al., 2004, Koopman et al., 2004, Brown, 2002, Halson et al., 2004)

In particular, there is ongoing research to improve carbohydrate delivery and oxidation, resulting in less accumulation of carbohydrate in the gastrointestinal tract to decrease gastrointestinal problems during prolonged exercise (Jeukendrup, 2004). CGM data could aid optimal carbohydrate delivery by allowing an athlete to know the best time and the amount of carbohydrate to consume. Additionally, optimal timing and rate of carbohydrate delivery has the potential to increase glycogen storage, speeding athlete recovery and providing additional energy for racing and training (Ivy et al., 1988, Conlee et al., 1978).

However, before these benefits can be realised, the accuracy and performance of CGM devices in active, trained athletes must be evaluated, which has not been done before. This evaluation is especially important as in populations with type 1 diabetes CGM has shown suboptimal accuracy during exercise (Kumareswaran et al., 2013) while other studies have shown improved accuracy (Yardley et al., 2013). Hence, the aim of this chapter is to characterise the accuracy and performance of CGM in athletes while exercising in a manner representative of an endurance event or sport.

13.2 Subjects and Methods

13.2.1 Subjects and Experiments

Table 13.1 summarises the cohort demographics. Data from the ten fit, healthy, sub-elite athletes described in Chapter 10 was used for this analysis. The research procedures and use of data were approved by the University of Canterbury Ethics Committee. This is the same cohort that has been used in Chapters 10 – 12.

Table 13.1 Cohort demographics of the participants. Data are presented as median [interquartile range] where appropriate

Number	10
Age (yr)	28 [23 37]
Gender (M/F)	7/3
BMI (kg/m2)	22 [21 24]
Resting HR (bpm)	55 [53 56]
VO2max (mL/kg/min)	46 [39 59]
Trained Cyclist (Y/N)	7/3
Length of CGM data (hr)	140 [105 141]

Two Ipro2 and one Guardian Real-time CGM devices (Medtronic Minimed, Northridge, CA, USA) (Medtronic MiniMed, 2006, MiniMed, 2010) were inserted into the abdomen of each athlete at least 24 hours prior to the first 'fasted exercise test'. The CGM device remained in each subject for 4-6 days. For all athletes, the Ipro2 CGM devices were both inserted in to the left side of the abdomen and the Guardian in the right side as shown in Figure 13.1. These devices are referred to as sensor 1 (SG1), the lower left abdomen sensor, sensor 2 (SG2), the upper left abdomen sensor and real-time sensor, the right abdomen sensor (SGrealtime).

During the 6 days of CGM:

- Blood glucose was measured 4 times per day prior to meals and sleeping. These measurements were used to calibrate the device (calibration BG)
- All meals and snacks were recorded and carbohydrate intake calculated
- Any additional exercise was also recorded and energy expenditure estimated

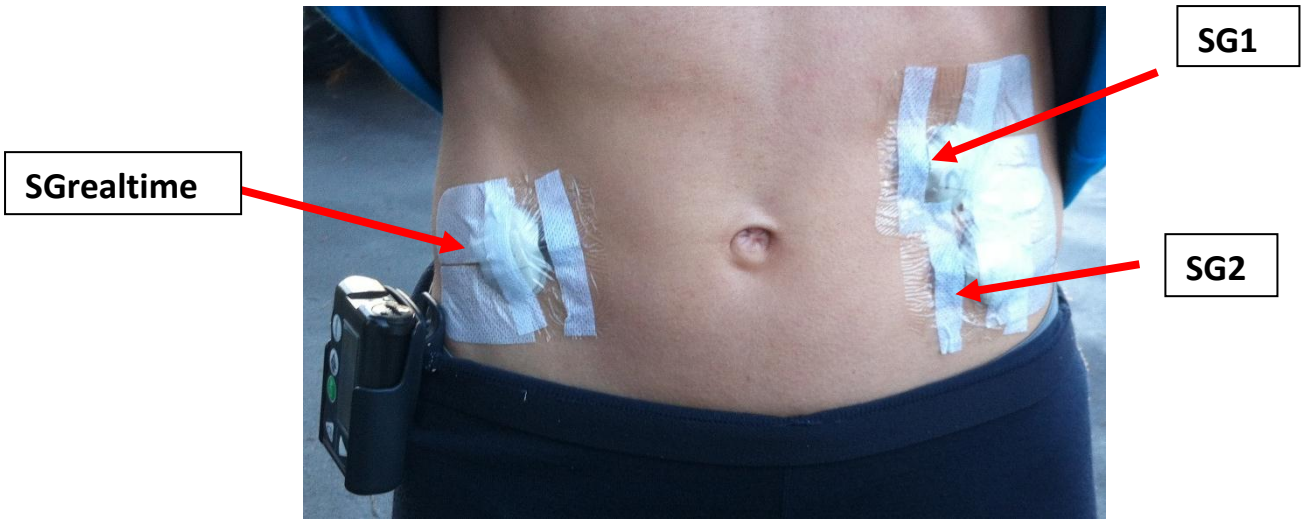

Figure 13.1 *Photo showing the locations of each CGM devices*

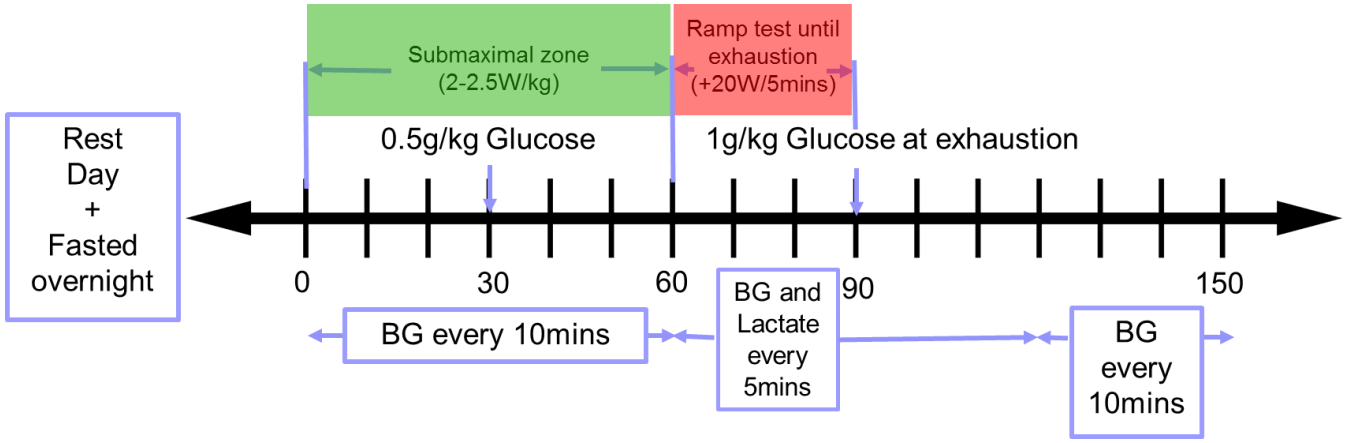

Figure 13.2 *Schematic of exercise trial protocol*

Fasting exercise tests were carried out as shown in Figure 13.2. Subjects were required not to exercise the day before the test. On the day of testing, the exercise protocol typically began at 8am and is defined:

- **0 – 60 min**: Cycling on a stationary trainer (Cyclus 2, RBM elektronik-automation GmbH, Lepzig, Germany) after overnight fast. Cycling was carried out in the submaximal endurance HR zone <70% VO2max resulting in a resistance set to 2 W/kg for female and untrained cyclists or 2.5 W/kg, replicating the earlier stages of an endurance event where the athlete is likely to remain in the submaximal zone conserving energy and glucose stores.

- **30 min**: Consume a 0.5 g/kg of body weight (30-45g) glucose drink as per recommended practice of 30-60g/h during endurance exercise lasting > 1 hr (American Dietetic et al., 2009)
- **60 min – Exhaustion (~90 min):** Steadily increase effort until volitional exhaustion by increasing required power by 20W every 5 minutes mimicking the later stages of an endurance event where the effort required is likely to increase until the finish
- **Exhaustion**: Consume a 1 g/kg of body weight (60-90g) glucose drink as per recommended practice to consume 1-1.5 g/kg of glucose for recovery of muscle glycogen post strenuous exercise lasting > 1 hr (American Dietetic et al., 2009)

Reference BG measurements:

- **0 – 60 min**: Every 10 min
- **60 – exhaustion+ 30 min (~120 min):** Every 5 min to better capture the changes in blood glucose after the during an intense work period and after the large glucose bolus
- **Exhaustion + 30 min (~120 min) – exhaustion + 60 min (~150 min)** : Every 10 min

Reference measurements were not used for CGM calibration.

Other measurements:

- Body weight, BMI, Body composition Analyser (InBody230, InBody Bldg, Seoul, Korea)
- Indirect calorimetry (MetaLyzer 3B - R2, CORTEX Biophysik GmbH, Lepzig, Germany)

Reference and calibration BG measurements were taken using capillary finger stick measurements and the Abbott Optimum Xceed (Abbott Diabetes Care, Alameda, CA) glucometer. The Abbott device has reported error of 5-10% (Abbott Diabetes Care, 2010, Brunner et al., 2011, Thomas et al., 2014a, Signal, 2013).

13.2.2 Analysis

To assess the accuracy of the CGM during exercise the mean absolute relative difference (MARD) was calculated between reference BG measurements collected during the fasting tests and the CGM trace:

$$MARD = mean(abs\left(\frac{CGM-BG}{BG}\right)) * 100 \quad \text{Eq. 13.1}$$

MARDs were assessed during three different phases during the trial, 0 – 30 min, 30 min – exhaustion and exhaustion – exhaustion + 60 min. MARD was also calculated over the entire test. This consideration of different phases allowed an assessment of accuracy when glucose levels were rapidly changing, after each glucose bolus, and when they are relatively stable, during exercise.

To assess the agreement of the CGM devices during the exercise test, zero-lag cross-correlation was applied. Zero-lag cross-correction is the dot product applied to two equal length signals with no time shift, and yields a metric of "measure to measure" agreement:

$$\cos\theta = \left(\frac{A.B}{||A||||B||}\right) \quad \text{Eq. 13.2}$$

Where A = [a1, a2 …. an] represents the n x 1 vector of measurements from one CGM signal and B = [b1, b2 …. bn] the n x 1 vector of measurements from the other.

The resultant angle,θ, shows the trend similarity between two vectors and its cosine has values from -1 and +1 demonstrating opposing to complete agreement. Thus, it uses the inner product definition to define how much of vector A is projected on to vector B, where 1 indicates equal vectors. This resultant value is referred to as the zero lag correlation co-efficient. All signals were first mean-centred to remove bias.

13.3 Results and Discussion

Figure 13.3 provides an example of the good sensor agreement seen over the 6 days of monitoring. Both sensor current and sensor glucose visually agree well across the entire 6 days of monitoring. The results in Figure 13.4, Table 13.2 and Table 13.3 clearly show Ipro2 CGM devices, SG1 and SG2, are accurate during intense exercise. The MARD values in Table 13.2 and Table 13.3 are equivalent if not better than the performance reported for CGM in diabetic subjects (Keenan et al., 2012, Kovatchev et al., 2008, Bailey et al., 2014, Matuleviciene et al., 2014, Calhoun et al., 2013) .

Bailey et al. (2014) reported an overall MARD of 13.6% from a study using the same sensors in 90 type 1 diabetic subjects. Overall, the Ipro2 devices match this performance and performed better than expected during 0 – 30 min of steady state exercise with median MARD of 9.7% and 9.6% for SG1 and SG2, respectively. Even during times of rapid glucose change after the glucose boluses were given and changes in exercise intensity (Figure 13.4) the Ipro2 CGM devices proved accurate resulting in an overall median [IQR] MARD of 11.2 [10.8 13.2] % and 13.6 [11.9 14.7] %.

However, the Guardian real-time performance was mixed. The literature reports an overall MARD of 15-17.8% for Guardian CGM in diabetic individuals (Kovatchev et al., 2008, Matuleviciene et al., 2014, Calhoun et al., 2013). During the first 30min of exercise the Guardian out-performed the expected result with a median [IQR] MARD of 11.1 [7.2 16.0] %. However, across the entire test, the Guardian devices only achieved a median [IQR] MARD of 20.3 [16.1 23.8] %. This result indicates the Guardian struggled to track the fast changing glucose dynamics once the glucose boluses were taken and exercise intensity changed, and which might not necessarily be seen in the individuals with diabetes that they are designed for.

The Guardian device is calibrated in real-time and provides a real-time approximation of blood glucose concentration on a monitor that communicates wirelessly with the sensor. This real-time approximation means that the device can only use the previous and current calibration measurements to calibrate the current signal from the interstitial fluid. In comparison, the Ipro2 devices (SG1 ad SG2) store all current data on the sensor, which is then downloaded at the end of monitoring and calibrated retrospectively. Thus, both future and past measurements can be used for calibrating the iPro2 signal. However, to generate a real-time control algorithm for athlete nutrition a real-time device like the Guardian would be necessary. However, these issues might be offset if glucose ingestion, such as from an energy drink, was known, and this information could be available to the device.

The more accurate results obtained during steady state exercise compared to published results in diabetes cohorts are likely due to interstitial fluid not being actively pumped like blood. Interstitial fluid relies on muscle movement to circulate and mix. Thus, it can be expected that during exercise more accurate results are seen as the rigorous movement and increased overall blood flow allows rapid mixing and equilibrium between the blood and interstitial fluid. In addition, more accurate reference BG measurements due to high skin temperatures and increased circulation, might be expected, Haupt et al. (2005) and King, et al. (1995) suggest lower skin temperatures lead to BG meters producing lower than expected values. This conclusion is supported by the results of Yardley et al (2013) who found increased CGM performance during exercise in a population with type 1 diabetes.

However, as evident with the real-time calibrated device, rapid mixing between the interstitium and blood is not enough to ensure ideal performance when large disturbances, such as glucose boluses, are added to the system. This increased error is likely due to the gradient of BG change being higher, so the delay in transport to interstitial fluid and sensor results in a larger discrepancy in measured

values compared to a blood-based reference (Boyne et al., 2003). The cessation of exercise prior to the ingestion of the bolus may slow the mixing of the interstitial fluid and blood also increasing the error.

Table 13.2 MARD results for each athlete and sensor combination for the entire duration of the test. The gaps in column three represent where sensor failures prevented the collection of CGM data.

Subject	SG1 MARD (%)	SG2 MARD (%)	SGrealtime MARD (%)
ATH01	11.2	13.4	19.0
ATH02	15.2	14.9	15.9
ATH03	9.0	8.9	24.9
ATH04	12.3		16.3
ATH05	13.8	11.9	10.7
ATH06	12.7	13.8	23.9
ATH07	11.1	32.3	23.8
ATH08	10.6	14.2	20.5
ATH09	10.9	11.9	20.3
ATH10	20.0		28.9
Median[IQR]	11.2 [10.8 13.2]	13.6 [11.9 14.7]	20.3 [16.1 23.8]

Table 13.3 MARD presented as median [IQR] of the cohort for each stage during the exercise test.

	0 – 30min	30min – Exhaust	Exhaust – Exhaust+60min
SG1	9.7 [6.0 17.8]	11.3 [8.9 13.8]	11.4 [8.5 15.7]
SG2	9.6 [7.3 17.5]	12.5 [10.1 17.4]	17.0 [12.1 20.3]
SGrealtime	11.1 [7.2 16.0]	19.9 [16.9 23.5]	21.1 [18.2 27.0]

Table 13.4 Correlation coefficient for each sensor combination using the CGM data generated during the exercise test.

Correlation Coefficient	SG1 vs. SG2	SG1 vs. SGrealtime	SG2 vs. SGrealtime
ATH01	0.99	0.90	0.89
ATH02	0.98	0.97	0.98
ATH03	0.96	0.92	0.81
ATH04		0.80	
ATH05	0.98	0.89	0.95
ATH06	1.00	0.81	0.79
ATH07	0.92	0.96	0.84
ATH08	0.74	0.32	0.87
ATH09	0.95	0.81	0.89
ATH10		0.96	
Median[IQR]	0.97 [0.94 0.99]	0.90 [0.81 0.95]	0.88 [0.83 0.91]

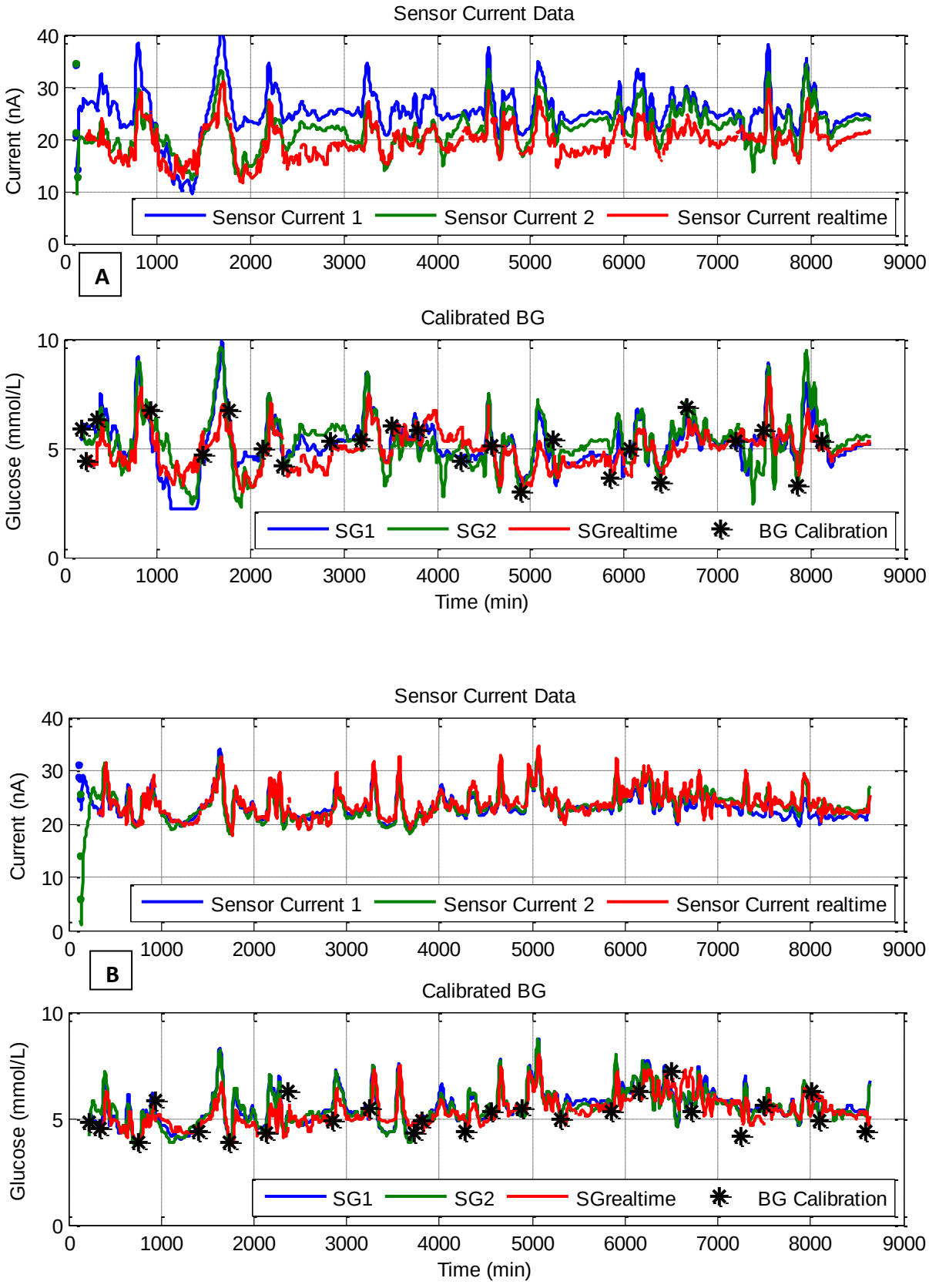

Figure 13.3 *Examples of current and sensor glucose data captured over the 6 days of monitoring. Subject ATH03 is presented in A and ATH06 in B.*

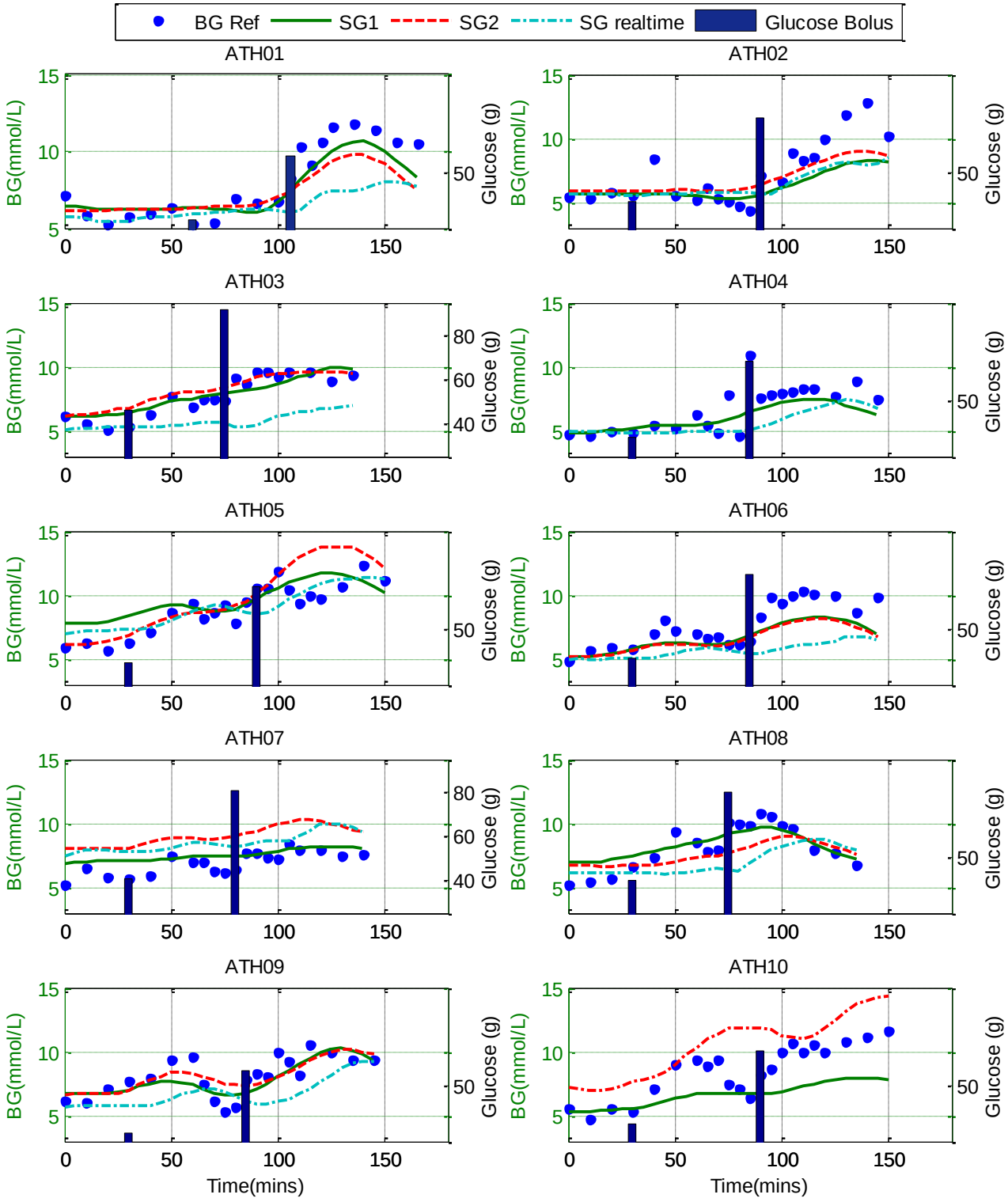

Figure 13.4 *Blood glucose reference values. CGM values and glucose bolus data for each athlete. Ath01-Ath10 in descending order as reading from right to left.*

The zero-lag correlation between all three sensors is very good, as seen in Table 13.4. SG1 and SG2 have a median [IQR] correlation coefficient of 0.97 [0.94 0.99]. It is expected that these signals would correlate the best as they are the same device inserted in the same side of the abdomen. Both SG1 and SG2 also correlate very well with the SGrealtime, with median correlation coefficients of 0.90 and 0.88, respectively. This good correlation between all three signals suggests the error between glucose concentrations measured by CGM and from blood is not random, but likely due to effects such as transport delays and local glucose uptake. As the interstitial fluid is the medium from which glucose enters muscle cells, this CGM value might be more useful than BG in determining glucose availability for athletes.

13.3.1 Limitations

This study is a proof of concept demonstration and thus the relatively small data set is a limitation. These tests were trialled in 10 athletes and results are likely to vary between individuals. However, there is a clear difference in signal quality between retrospective and real-time devices, as well as between periods of steady state exercise and periods of glucose disturbance. A larger trial in a bigger cohort is recommended to confirm these findings, as well as incorporating further investigation in to the optimisation of an athletes BG using CGM technology.

Ideally, a retrospective device, such as the Ipro2, should be used for these further investigation, especially if rapid changes in BG are likely, as they demonstrated improved performance compared to the real-time device. However, to be able to optimise an athletes BG in real-time, a real-time CGM is necessary. In this case, this potential error must be considered if devising nutritional strategies based on real-time CGM values, or the technology should be optimised for better performance in this regard.

13.4 Summary

Optimisation of an endurance athlete's BG via intra-event nutrition has the potential to increase race performance, speed recovery, and aid training. During steady state exercise, all sensors performed better than results reported for diabetes cohorts, with median MARD of 9.7%, 9.6% and 11.1% for SG1, SG2 and SGrealtime, respectively. However, there is increased error after an oral glucose bolus likely due to the gradient of BG change being higher, so the delay in transport to interstitial fluid and sensor results in a larger discrepancy to measured blood based reference values.

CGM devices agree very well with each other during rigorous exercise with median zero-lag cross-correlation coefficients between 0.88 and 0.97 for the different sensor pairings. The good correlation between all three signals suggests the error between glucose measured by CGM and from blood is not random. The error is likely due to transport/uptake effects differing between the blood and interstitial fluid from which the CGM measures glucose.

The interstitial fluid is the medium from which glucose enters muscle cells. Therefore, it is possible this CGM value might be more useful than BG in determining glucose availability for athletes. Overall these results demonstrate the good accuracy and performance of CGM devices in active athletes while exercising, confirming the applicability of these monitors to this new domain.

Chapter 14. Blood Glucose Levels of Sub-Elite Athletes during 6-days of Free Living

This chapter examines blood glucose levels of sub-elite athletes over a 6 day monitoring period using continuous glucose monitor devices. Blood glucose levels during exercise have been examined previously and the increased overall insulin sensitivity of athletes noted. However, CGM devices provide an opportunity to examine what effect this increased insulin sensitivity has over a much longer time period. In addition, it is well documented that athletes, especially those in the sub-elite category, do not meet nutritional recommendations for their level of energy expenditure. Therefore, CGM devices have the potential to highlight the effect of not meeting these recommendations on blood glucose levels and the subsequent potential impact on recovery. Data from CGM would present significant new insight into managing recovery, a key element in overall athlete management, along with the capability of CGM devices to enable this assessment.

14.1 Introduction

The World Health Organisation (WHO) defines normal glycaemia as fasting glucose less than 6.1mmol/L and recommends glucose <7.8 mmol/L 2 hours after a 75g oral glucose tolerance test (OGTT) test (World Health Organisation, 2006). The American Diabetes Association (ADA) considers those with a fasting glucose of 5.6 – 6.9 mmol/L and blood glucose (BG) > 7.8 - 11.0 mmol/L after an OGTT at increased risk of diabetes (American Diabetes, 2010). However, as the WHO guidelines explain, there is no definitive cut off for “normoglycaemia” (World Health Organisation, 2006), and dysglycaemia thus exists on a continuous analogue scale.

CGM devices allow BG dynamics to be captured far more frequently and less invasively than traditional BG measures. These devices are primarily designed for use in individuals with type 1 and type 2 diabetes to aid BG regulation and are well studied in this cohort (Gandhi et al., 2011, Hoeks et al., 2011). However, because of the increased measurement frequency and reduced invasiveness they have recently been applied to other cohorts, such as intensive care patients and neonates, with varying success (Chee et al., 2003a, Holzinger et al., 2010, Bloom et al., 1976, Thomas et al., 2015, Signal et al., 2013, Signal et al., 2010, Dimsdale et al., 1984, Koivisto et al., 1982). These cohorts all suffer a combination of inflammation and dysglycaemia. Thus, another perhaps overlooked, cohort where the more intensive metabolic monitoring provided by CGM may be beneficial is athletes.

Physical training is known to improve insulin sensitivity, both immediately post exercise and through multiple long term adaptations in glucose transport and metabolism (Borghouts et al., 2000) and athletes are traditionally encouraged to consume a diet rich in carbohydrates to ensure adequate glycogen stores and improve performance (IOC, 2010, 2000, Jacobs et al., 1999).. However in contrast, strenuous exercise is known to increase circulating concentrations of pro-inflammatory catecholamines, such as adrenalin and noradrenaline, to near pathological levels (Bloom et al., 1976, Rehrer et al., 1992). This combination of high carb input and circulating hormones can result in hyperglycaemia and hyperinsulinemia post intense exercise (Bloom et al., 1976, Ivy et al., 1988, Marliss et al., 2002) and discussed in Chapter 10.

This chapter aims to use the CGM blood glucose profiles and dietary habits of sub-elite athletes to investigate if this cohort is achieving optimal blood glucose levels during normal free living and training. In particular, it asks what impact their increased insulin sensitivity, heightened energy expenditure, and increased exposure to stress hormones have on their blood glucose levels. The CGM data provides a

unique insight in to the day to day blood glucose levels of athletes that could not be achieved without the application of this technology.

14.2 Subjects and Methods

14.2.1 Subjects

Table 14.1 summarises the cohort demographics. Data from the ten fit, healthy, sub-elite athletes described in Chapter 10 was used for this analysis. The research procedures and use of data were approved by the University of Canterbury Ethics Committee.

Two Ipro2 and one Guardian Real-time CGM devices (Medtronic Minimed, Northridge, CA, USA) were inserted into the abdomen of each athlete. These devices are referred to as sensor 1 (SG1), the lower left abdomen sensor, sensor 2 (SG2), the upper left abdomen sensor, and the real-time sensor in the right abdomen sensor (SGrealtime). Figure 14.1 shows these locations which are typical for these devices (Medtronic MiniMed, 2010, Medtronic MiniMed, 2006). The Guardian Real-time data was not used in this analysis as it is less accurate than the Ipro2 data, as seen in Chapter 13. Chapter 13 also details the protocol followed by each athlete during the 6 days of monitoring,

Calibration BG measurements were taken using capillary finger stick measurements and the Abbott Optimum Xceed (Abbott Diabetes Care, Alameda, CA) glucometer. The Abbott device has reported error of 5-10% (Abbott Diabetes Care, 2010, Brunner et al., 2011, Thomas et al., 2014a, Signal, 2013). An impedance based body composition analysis was undertaken by 8 of the 10 participants prior to the fasting test using a Body composition Analyser (InBody230, InBody Bldg, Seoul, Korea).

Table 14.1 Cohort demographics of the participants. Data are presented as median [interquartile range] where appropriate

Number	10
Age (yr)	28 [23 37]
Gender (M/F)	7/3
BMI (kg/m^2)	22 [21 24]
Resting HR (bpm)	55 [53 56]
VO2max (mL/kg/min)	46 [39 59]

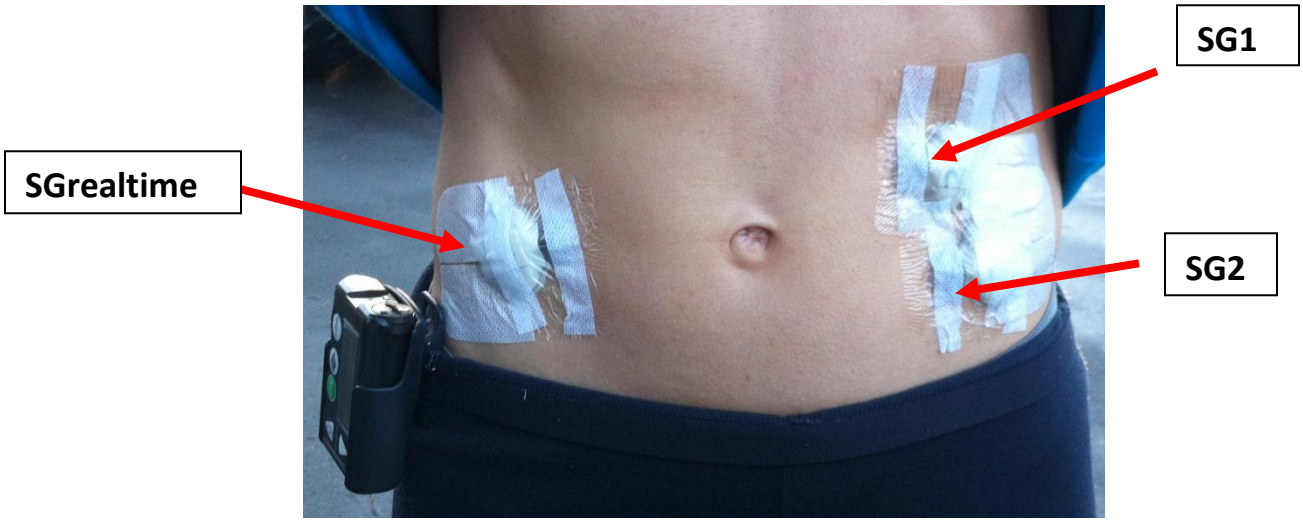

Figure 14.1 *Photo showing the locations of each CGM devices*

14.2.2 Analysis

Sensor glucose (SG) data from measured CGM traces of the two Ipro2 devices was analysed. These devices have been shown to have very good accuracy and sensor agreement in active individuals (Bailey et al., 2014, Thomas et al., 2015), as discussed in Chapter 13. The two signals were averaged at each time step for the time period they were worn to provide a single, reliable trace of BG. For Ath04, Ath09, and Ath10 only one CGM trace was available due to sensor failure.

For each athlete, the cumulative distribution (CDF) of BG data was analysed for the entire 5-6 days of monitoring, and re-analysed with the 2 hour period following any meal or snack removed. Time in band was calculated as the percentage of SG with in the 4.0 - 6.0 mmol/L during the two different monitoring periods. Although a consensus has yet to be reached on what constitutes normal glucose levels, intensive insulin therapy studies show achieving higher time in this band results in improved patient outcomes (Krinsley, 2004, Chase et al., 2008b, Van den Berghe et al., 2001) and it lies below typical thresholds for diabetes diagnosis (World Health Organisation, 2006, American Diabetes, 2010). Many studies have also demonstrated the linearly increasing risks associated with hyperglycaemia, regardless of diabetes status, with lower limits between 4.0 – 6.0 mmol/L (Brunner et al., 2006, Jee et al., 2005, Kijak et al., 1964, Levitan et al., 2004, Nishida et al., 2006, World Health Organisation, 2006, Tirosh et al., 2005).

The average carbohydrate, sugar, and fibre intake (g/day) while using CGM were calculated from nutrition diaries kept by each subject. First, daily caloric intake was calculated using basal metabolic rate (BMR) as estimated by the body composition analysis. For 2/10 athletes, Ath02 and Ath03, body composition analysis results were not available. Therefore, BMR was estimated using the standard equations (Harris et al., 1918) that take in to account height, weight and age. This BMR was then multiplied by an activity factor (Black, 2000) considering the amount of exercise undertaken by the athlete during the monitoring period. This process and relating caloric requirements are shown in Table 14.2.

US dietary guidelines (USDA, 2015b) recommend 45-65% of total calorie intake be from carbohydrates and the recommended amount of added sugars is also related to calorie level in these guidelines. Added sugar content of food consumed during the monitoring period was obtained from the United States

Department of Agriculture (USDA) database (USDA, 2015a). If the added sugar content was not available from the database it was assumed to be zero, providing an overall conservative estimate.

Table 14.2 The process of calculating the caloric requirements based on BMR and activity level and the average calorie intake achieved by each subject. * Values were calculated using standard equations rather than a body composition analysis.

Subject	BMR (kcal)	Average Exercise (min/day)	Activity Factor	Calories Required (kcal/d)	Average Calorie Intake per Day (kcal/d)
ATH01	1342	84	1.9	2550	2147
ATH02	1868*	41	1.7	3176	3864
ATH03	1927*	68	1.9	3661	1877
ATH04	1770	93	2.1	3717	3555
ATH05	1680	158	2.3	3864	2568
ATH06	1694	28	1.5	2541	2654
ATH07	1780	20	1.5	2670	2838
ATH08	1895	24	1.5	2843	4144
ATH09	1379	102	2.1	2896	2726
ATH10	1400	42	1.7	2380	2363

Fasting blood glucose (FBG) was calculated as the median value of the calibration measurements taken prior to breakfast over the 5 – 6 days of CGM monitoring. Fasting plasma insulin (FPI) was determined by the first plasma insulin measurement taken prior to starting the fasted exercise test on Day 2 (the fasting exercise test protocol is detailed fully in Chapter 10). Fasting insulin secretion (FIS) was calculated from the initial C-peptide measurement taken prior to starting the fasted exercise test using the method of Van Cauter et al. (1992) assuming steady-state, as subjects were fasted.

Postprandial glucose response (PPGR) was calculated as the incremental area under the BG curve after a meal (Wolever et al., 1986). Only the area above the starting glucose value was considered. PPGR was only considered for meals that had greater than 30g of carbohydrate, and where there was no meal of

greater than 15g carbohydrate in the 2 hours prior to or after this meal. If meals were consumed within 15 minutes then carbohydrate content was combined and the 2 hour area under the curve considered from the start of the second meal. Postprandial glucose (PPG) was the glucose value recorded two hours after a meal under the same conditions as above.

14.3 Results

Individual SG profiles are shown in Figures 14.2 and 14.3. These profiles highlight the very unique response of each individual to exercise and carbohydrates. Ath02 and Ath04 both show very little variation in SG but Ath02 SG, is centred on a higher glucose value resulting in more time out of the 4.0 – 6.0 mmol/L. Other subjects such as Ath03 and Ath09 show a large variation in SG, once again centred on different glucose levels, resulting in Ath03 displaying the most hypoglycaemia and Ath09 displaying the most hyperglycaemia.

In Figure 14.4 it is further evident several participants spend a significant amount of time outside the normoglycemic 4.0 - 6.0 mmol/L range. Once meals are removed, in the bottom plot, there is a distinct separation between 4/10 of the subjects (Ath05, 07, 08, 09) who have less than 30% time in the 4.0 - 6.0mmol/L range. In contrast, the remaining 6/10 participants achieve over 85% time in the desired 4.0 - 6.0mmol/L range, which is clear when comparing the distributions.

All but 4 participants consumed on average an amount of carbohydrate that was between 45 – 65% of their recommended daily calorie intake. Ath03, Ath05 and Ath09 did not reach the minimum recommended amount of carbohydrate. Ath08 consumed more than 65% of their recommended intake

as carbohydrate. All participants achieved their recommended fibre intake of >25g. Some participants, such as Ath07 and Ath08, have a very low fibre to sugar ratio and nearly double the recommended intake of added sugars (Figure 14.5). Ath03 consumed on average ~150g of carbohydrate less than the lower recommended limit, 1770 kcal less than required (Table 2) and was the only participant to demonstrate a significant amount time below 4.0mmol/L.

Table 14.3 shows Ath05, Ath07 and Ath09 have elevated fasting glucose within the pre-diabetes range 5.6 - 6.9 mmol/L suggested by the ADA. However, none of the subjects met the pre-diabetes criteria of PPG > 7.8 mmol/L. Although this PPG criteria is based on the BG 2 hours after a 75g glucose tolerance test, rather than after an uncontrolled meal. The mean PPGR ranges from 0.2 – 2.0 mmol/L.hr displaying a wide range intra- and inter- carbohydrate sensitivity. High PPGR did not necessarily correlate with time out side of the 4.0 – 6.0 mmol/L band.

14.4 Discussion

Physical training is known to improve insulin sensitivity, both immediately post exercise (up to 2 hrs) and through multiple adaptations in glucose transport and metabolism (Borghouts et al., 2000). Therefore, it could be expected high BG would not be frequently seen in athletes and low BG would be of greater concern due to increased energy expenditure. However, this hypothesis does not appear to be the case in the data collected.

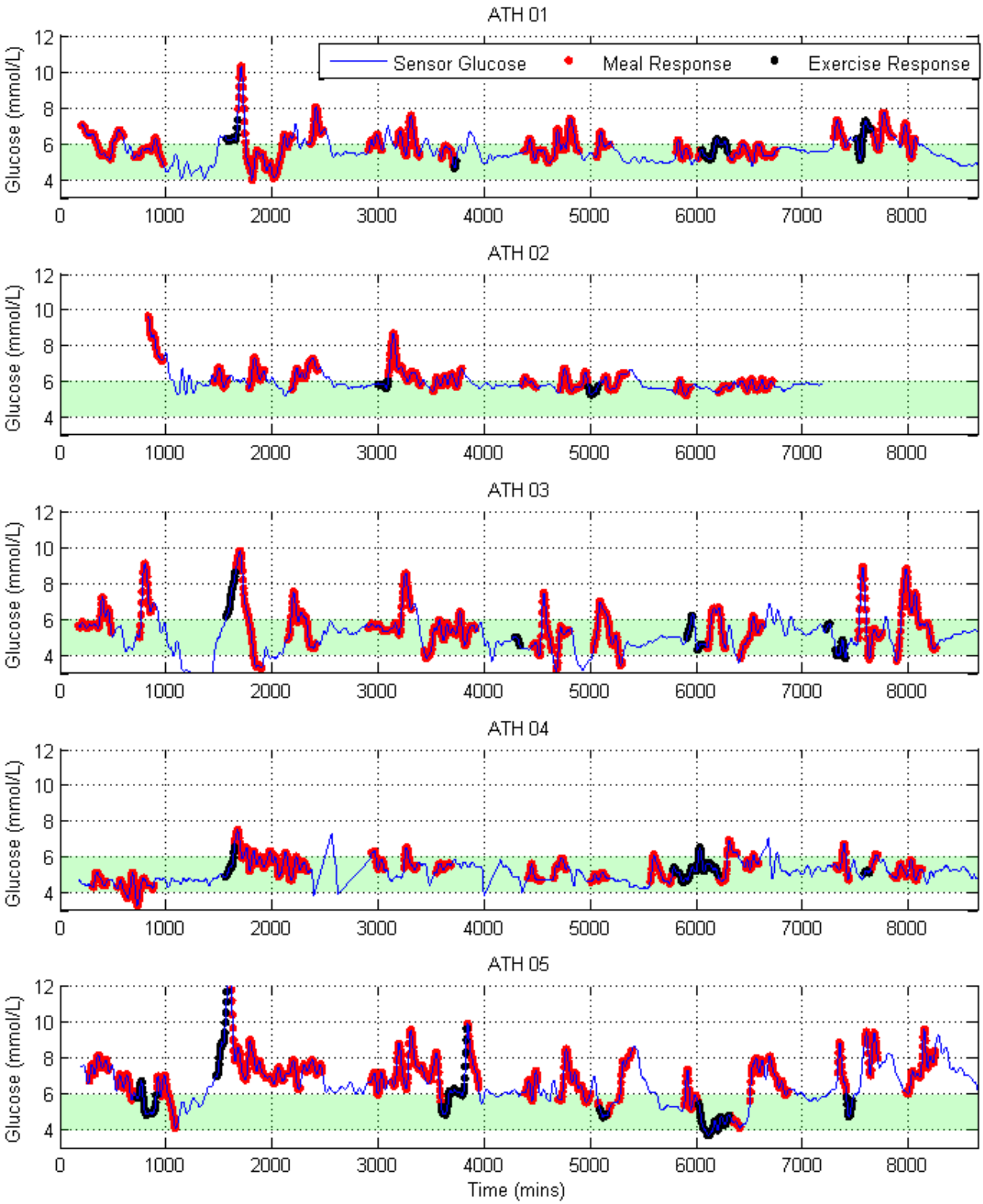

Figure 14.2 *CGM profiles for the first 5 subjects. The 2 hour postprandial meal response is highlighted in red and periods of exercise are highlighted in black.*

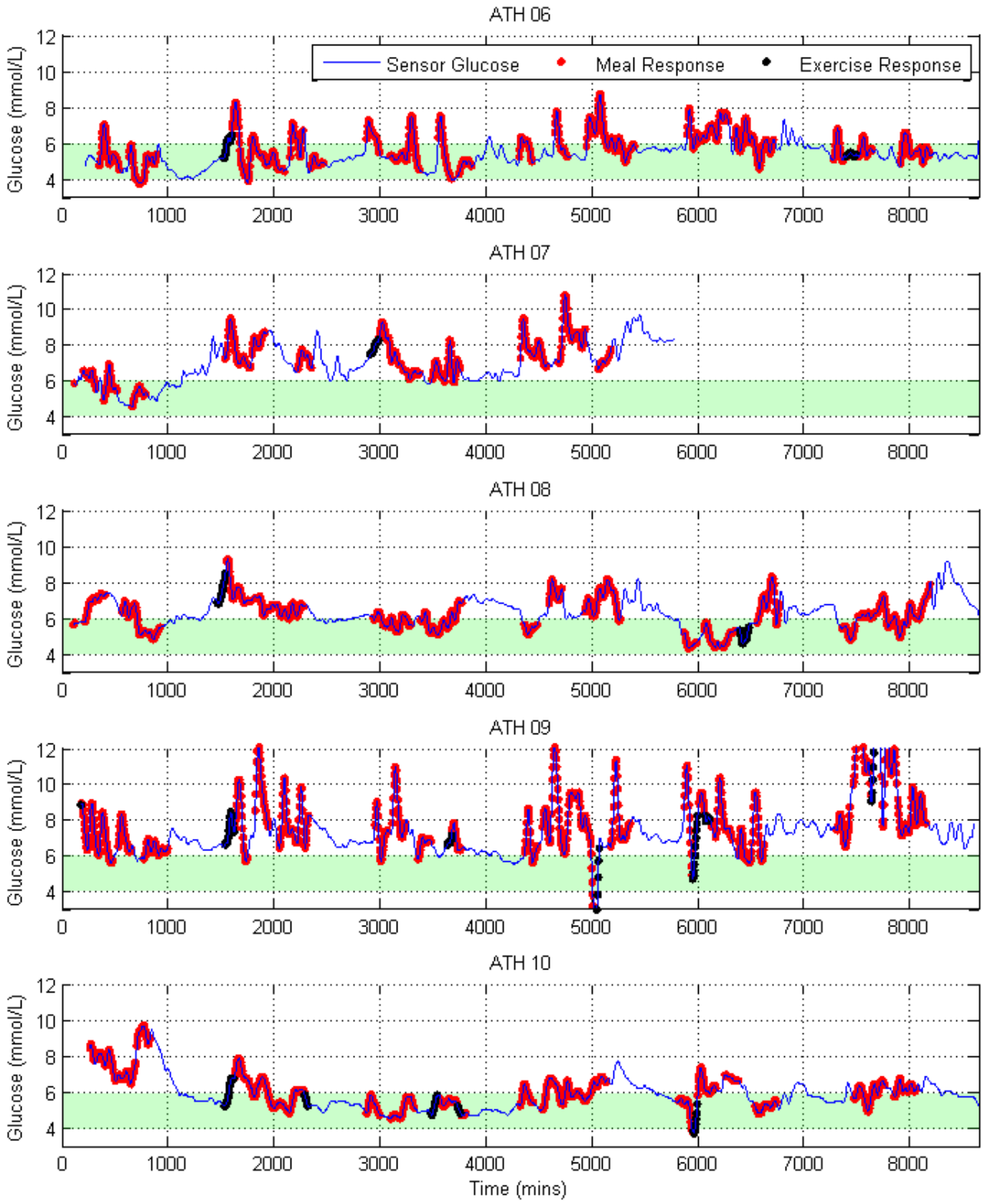

Figure 14.3 *CGM profiles for the last 5 subjects. The 2 hour postprandial meal response is highlighted in red and periods of exercise are highlighted in black.*

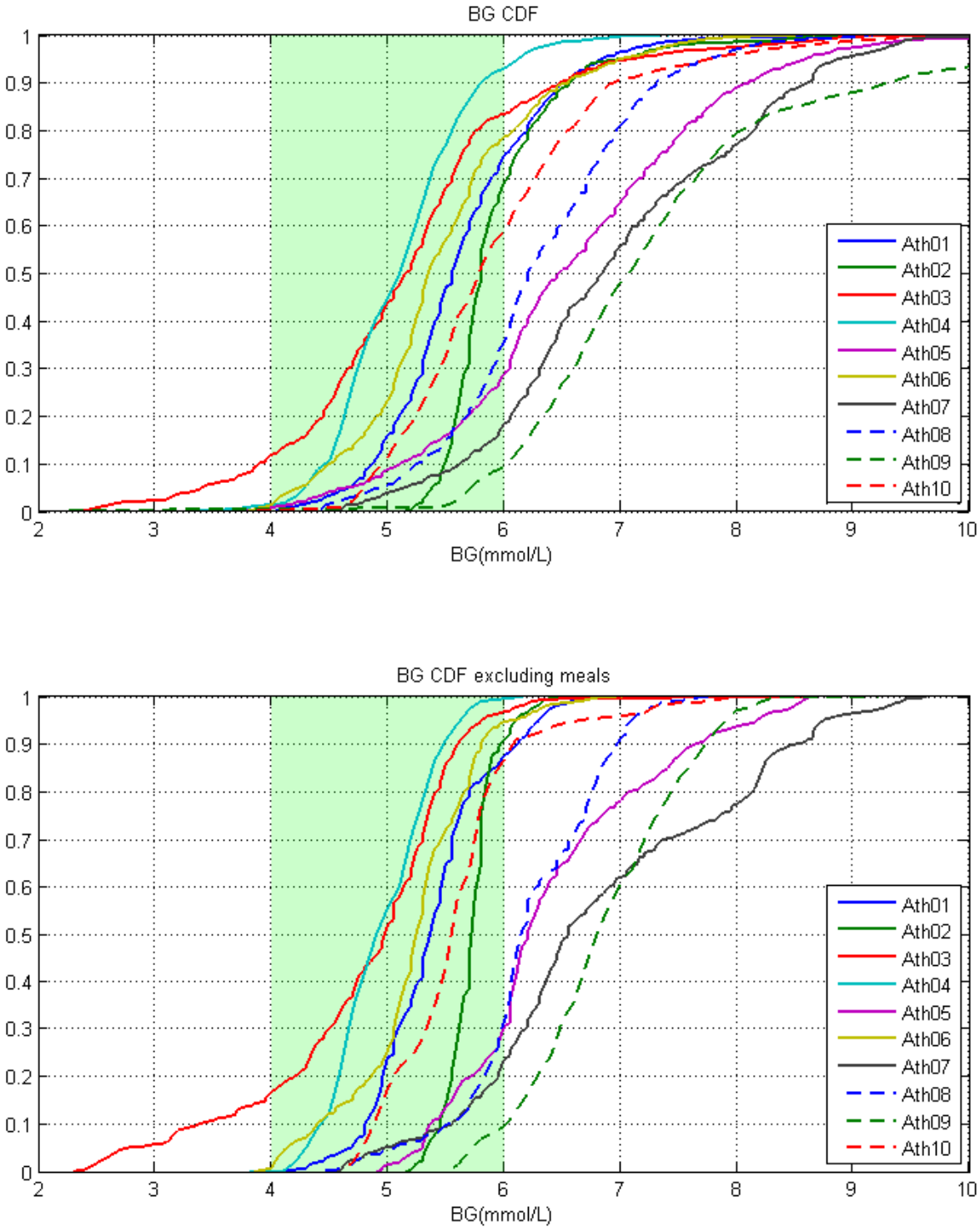

Figure 14.4 *Cumulative distribution plots of measured CGM values. The Top plot is the CDF of the entire averaged CGM signal. The bottom plot is the CGM signal with 2 hours from the beginning of each meal and snack removed. The green band represents the normal range.*

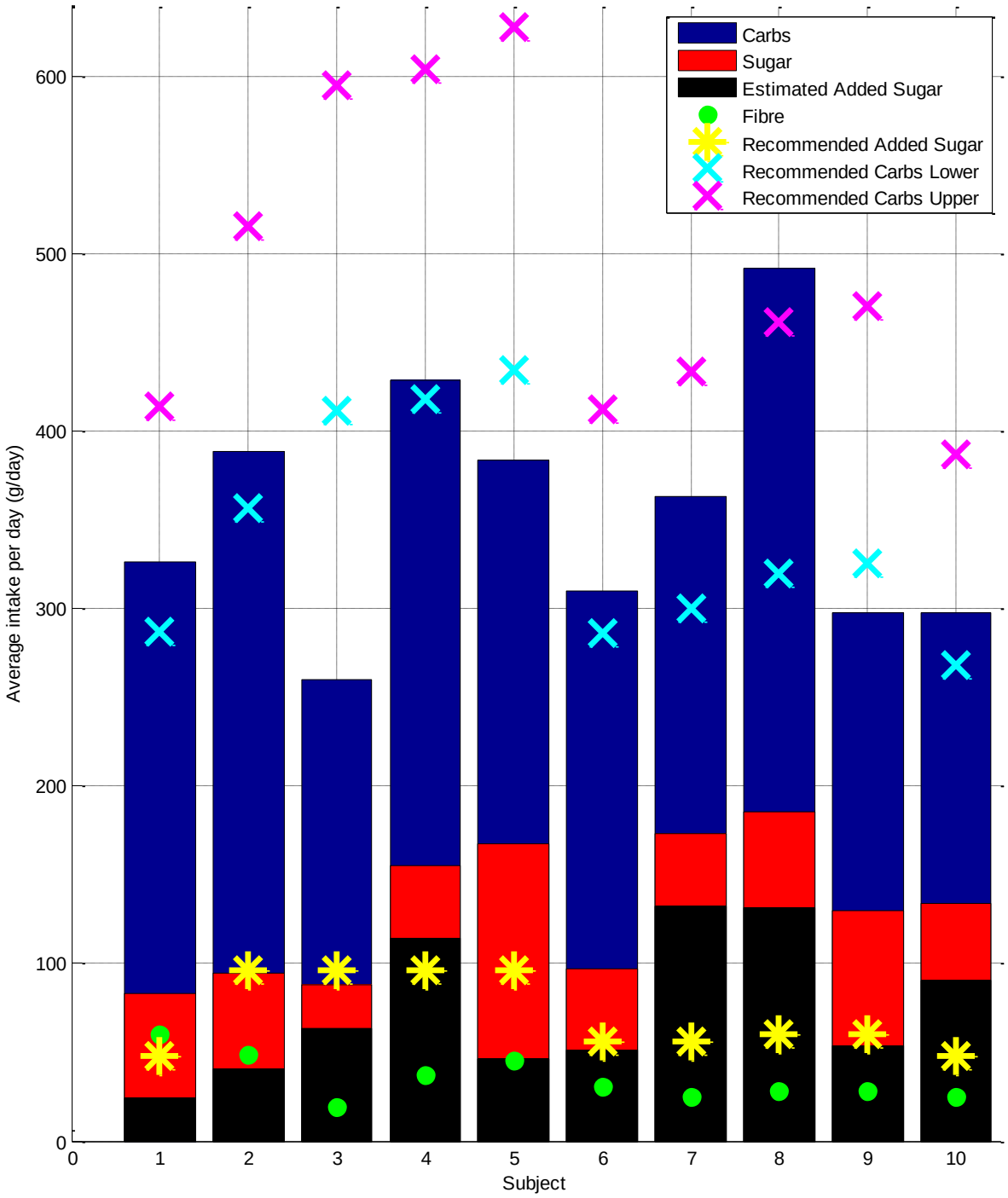

Figure 14.5 *Bar plot showing the average intake per day of carbohydrate, sugar, fibre, and the recommended daily intake of carbohydrate, upper (65% of calorie intake) and lower (45% of calorie intake)*

Table 14.5 Summary table of measured physical and metabolic variables, where PBF = Percent Body Fat, FFM = Fat Free Mass, FBG = Fasting Blood Glucose, FPI = Fasting Plasma Insulin, FIS = Fasting Insulin Secretion, TIB –MR = Time in Band, with meals removed, Maxppg = the maximum blood glucose value reached after a meal, PPG = the blood glucose value 2 hours after a meal. Body composition analysis results were not available for Ath02 and Ath03 hence PBF and FFM values are missing.

Subject	Sex	Age	BMI	PBF (%)	FFM (kg)	FBG (mmol/L)	FPI (mU/L)	FIS (mU/L.min)	TIB- MR (%)	Mean PPGR (mmol/L.hr)	Mean PPG (mmol/L)	Exercise (min/day)	VO2max (mL/kg/ min)
ATH01	F	23	21.6	25.3	45	5.2	9	1319	86.6	1.1	6.1	84	39
ATH02	M	23	21.9	-	-	5.1	6.3	913	90.7	0.5	6	41	60
ATH03	M	50	26.4	-	-	4.7	11.8	1878	76.1	1.9	6	68	39
ATH04	M	23	20.4	5.1	64.8	4.6	6.5	832	99.2	0.5	5.5	93	67
ATH05	M	28	24.2	14.1	60.6	6	6.3	820	30.7	0.9	6.8	158	59
ATH06	M	36	22.4	15.5	63.3	4.4	8.3	1844	94.3	1.2	5.9	28	59
ATH07	M	37	26	19.7	65.3	6.7	10.5	1553	23.9	1.1	7.1	20	42
ATH08	M	22	24.5	13.2	70.6	5.5	11	1550	31.7	0.2	5.5	24	37
ATH09	F	37	21.1	17.8	46.7	6	6	936	9.7	2	7.4	102	47
ATH10	F	27	22.2	28.3	47.7	5.2	9.5	1344	86.6	1	6.7	42	44

In particular, 4/10 subjects spent more than ~70% of the total monitoring period with SG > 6.0 mmol/L, even with the two hour period after meals removed. Only one athlete experienced a significant time below 4.0 mmol/L and this behaviour appears largely due to a considerably decreased calorie intake compared to recommended guidelines.

Ath09 and Ath05 undertook the most exercise during the monitoring period, averaging 102 and 158 min/day respectively. This high training load could have contributed to the low time in the 4.0 – 6.0 mmol/L band, as exercise is known to increase blood glucose and induce hyperglycaemia and hyperinsulinemia as a result of this catecholamine response (Bloom et al., 1976, Ivy et al., 1988, Marliss et al., 2002). Both subjects had the lowest fasting plasma insulin and insulin secretion recorded suggesting efficient glucose uptake. In addition, both achieved VO2max values that put them in the *excellent* category based on their gender and age.

Ath07 and Ath08 carried out the least amount of exercise during the monitoring period only averaging 20 and 24 min/day of exercise, while over consuming added sugars (World Health Organisation, 2006) and Ath08 over consuming on the recommended carbohydrate intake. Lowering physical activity is known to impact the glycaemic control of healthy individuals and the increased insulin sensitivity witnessed due to training wanes with 5 days of detraining (Borghouts et al., 2000, Mikus et al., 2012, Heath et al., 1983, Mikines et al., 1989). The large amount of time spent out of band by Ath07 and Ath08 is likely to be attributed to these diet and lifestyle choices. This conclusion is supported by Ath07 and Ath08 showing the highest fasting plasma insulin levels and fasting insulin secretion and only achieving *average* or *above average* category VO2max levels based on gender and age.

An individual's tolerance of carbohydrate is highly variable and is related to a number of factors including age and genetics (Zeevi et al., 2015, Vrolix et al., 2010). A differing ability to tolerate carbohydrates in this cohort is demonstrated with the wide range of cohort values of mean PPGR and mean PPG, 0.2 – 2.0 mmol/L.h and 5.5 – 7.4 mmol/L, respectively. Also PPGR and PPG do not necessarily correlate with time in band or FBG. A subject can achieve good overall control or even experience low BG, such as Ath03, but still demonstrate a high mean PPGR indicating a high sensitivity to carbohydrates. A subject like ATH09 also appears to have a very high sensitivity to carbohydrates achieving high PPGR and low time in band while under consuming on the recommended carbohydrate intake. However, a subject like Ath04 displays a very high tolerance of carbohydrates, achieving the greatest time in band and very low PPGR, while still over consuming added-sugars. It is interesting to note that normalising results by grams of carbohydrate consumed did not change the trends seen.

Athletes are traditionally encouraged to consume high carbohydrate diets to replenish muscle glycogen stores and improve performance, with a particular focus on post exercise carbohydrate consumption (IOC, 2010, 2000, Jacobs et al., 1999). However, this advice may be negatively impacting the blood sugar levels of athletes predisposed to have a low tolerance of carbohydrates. In addition it is unlikely that low BG in day to day life is a real concern for athletes, unless they are significantly under consuming calories. Hence, the potential for a more personalised nutrition plan aided by CGM to optimise the BG levels during different phases of athletes training is highlighted by these results.

This study warrants further investigation on the recommend diets and the blood glucose levels of athletes, in particular those in the sub-elite category studied here. Sub-elite athletes are unlikely to have the same

nutritional and dietary support from trained professionals as elite athletes. Hence, their nutritional intakes are more perhaps likely to be sub-optimal, as demonstrated in this study.

14.4.1 Limitations

This study is limited by the small cohort size. However, this initial pilot investigation has highlighted some interesting points where there is potential to optimise an athlete's diet. Hence, it has raised questions where further studies are thus justified.

A second limitation is that activity was only monitored by self-reporting in future studies it would be much better to use a specific activity monitoring device to capture energy expenditure more accurately. Equally, activity could be directly controlled in a more homogenous cohort, in a more strictly controlled study than this pilot investigation.

14.5 Summary

Physical training is known to significantly increase insulin sensitivity and improve PPG and PPGR. Therefore, it could be expected sustained high BG during free living would not be frequently seen in athletes and low BG would be of greater concern due to increased energy expenditure. However, this hypothesis does not appear to be the case in the data we have collected.

When the sensor glucose profiles of 10 trained, sub-elite athletes were analysed over a 6 day monitoring period 4/10 athletes studied spent more than 70% of the total monitoring time above 6 mmol/L even with

the 2hour period after meals removed. FBG was also in the range of pre-diabetes for 3/10 athletes, as defined by the ADA. Only one participant spent substantial time below 4 mmol/L and this was largely due to a significantly lower overall calorie intake compared to recommendations.

A differing ability to tolerate carbohydrates in this cohort is demonstrated with the wide range of cohort values of mean PPGR and mean PPG, which were 0.2 – 2.0 mmol/L.h and 5.5 – 7.4 mmol/L, respectively. Therefore, a diet rich in carbohydrates may not be beneficial in some athletes. This outcome is particularly valid considering low BG is unlikely to be of concern to an athlete consuming adequate calorie intake.

Chapter 15. Summary Glucose Metabolism and CGM in Athletes

The glucose metabolism of athletes is not fully defined in current literature and neither are the effects of exercise on the overall glucose metabolism of athletes. Studies comparing the metabolic and hormonal response to exercise between trained and untrained normal glucose tolerant individuals have found significant differences in the metabolism of athletes. However, there are only a few studies investigating how metabolic parameters, such as EGP change with exercise, and none that attempt to quantify endogenous insulin secretion or insulin sensitivity during exercise.

Additionally, an individual's tolerance of carbohydrate is highly variable and is related to a number of factors including age and genetics. CGM devices have the potential to personalise nutrition based on glucose response. Such research using CGM devices has not been undertaken in athletic subjects before. However, real time knowledge of blood variables, such as glucose, is noted as the "future' of sports technology (Gizmag Team, 2007, Metz, 2014). The second half of this thesis examined the glucose metabolism of athletes further, and investigated the potential of CGM to provide accurate information and personalise nutritional strategies for athletes.

In a study of 10 sub-elite athletes, it was found that after race simulation exercise test hyperglycaemia persists >60 mins post exercise. Plasma insulin and insulin secretion both peaked 60 mins post intense exercise to median [IQR] cohort values of 256 [193 586] pmol/L and 1150 [817 1482] pmol/min, respectively. These median peak values of plasma insulin and insulin secretion were approximately 5 and 9 times higher than the median fasting levels in this cohort, respectively. In general, this response greater and more prolonged than reported in previous metabolic studies. The most likely reason is the subjects

received two boluses, one during exercise and one immediately one post exercise, as per recommended nutritional guidelines for competition, while in other studies, the athletes remained fasted. Therefore, the main outcome of this chapter was to highlight the potential for a re-examination of the post exercise feeding protocol used by many athletes to achieve both optimal glycogen recovery and optimal blood glucose levels in a manner more representative of how athletes train and race.

Using data collected from the 10 subjects during and immediately after the exercise test, a simple 1-dimensional model of endogenous insulin secretion was created, with a coefficient of determination, R^2 = 0.53 and a glucose coefficient (a_1) of 2559 mU.l/mmol.hr. The proposed model of endogenous insulin secretion, based on physiological measurements, provides a simple estimate of insulin secretion with comparable physiological parameters to existing literature. Overall, this endogenous insulin secretion model provides a valuable addition to glucose-insulin modelling, particularly for athletic individuals during exercise and immediately after.

The next step was to attempt to adapt the successful ICING model to allow insulin sensitivity to be identified during and after exercise in a well-trained cohort. The ICING model was simplified to remove the unnecessary plasma insulin compartment as plasma insulin was measured regularly during exercise in this study. All other parameters were adjusted to be values from athletic or lean, healthy cohorts where possible

The model appeared to be best able to identify insulin sensitivity during steady state periods of exercise as SI trends in these periods match known physiology. However, when boluses are delivered non-

physiological jumps in SI occur due to under-modelling of gut dynamics and glucose appearance, as well as necessary assumptions of constant endogenous glucose production and non-insulin mediated glucose uptake. SI was often negative, indicating the model was not able to accurately capture the BG dynamics with current parameter values and assumptions. While an improved understanding insulin sensitivity levels during and after exercise has potential, further research is needed to understand how to model the ingestion of glucose, endogenous glucose production and non-insulin mediated glucose uptake, in a way that does not over-complicate the model, while remaining physiologically realistic.

CGM devices have the potential to provide important feedback to athletes to aid in the optimisation of blood glucose levels during training, racing and recovery. However, these devices are designed for use in T1DM and T1DM, who typically experience different glycaemic ranges, and have not been tested in this cohort before. Therefore, their performance in athlete subjects during intense physical exercise is unknown.

The performance of CGM during exercise was investigated by comparing reference measurements to CGM data collected form the 10 subjects during the exercise test. For all athletes, the Ipro2 CGM devices were both inserted in to the left side of the abdomen and the Guardian real-time in the right side. These devices are referred to as sensor 1 (SG1), the lower left abdomen sensor, sensor 2 (SG2), the upper left abdomen sensor and real-time sensor, the right abdomen sensor (SGrealtime).

During steady state exercise, all sensors performed better than results reported for diabetes cohorts, with median MARD of 9.7%, 9.6% and 11.1% for SG1, SG2 and SGrealtime, respectively. However, there

was increased error after an oral glucose bolus likely due to the gradient of BG change being higher, so the delay in transport to interstitial fluid and sensor results in a larger discrepancy to measured blood based reference values.

CGM devices agree very well with each other during rigorous exercise with median zero-lag cross-correlation coefficients between 0.88 and 0.97 for the different sensor pairings. The good correlation between all three signals suggests the error between glucose measured by CGM and from blood is not random. The error is likely due to transport/uptake effects differing between the blood and CGM values. Overall these results demonstrate the good accuracy and performance of CGM devices in active athletes while exercising, confirming the applicability of these monitors to this new domain.

Physical training is known to significantly increase insulin sensitivity and improve both PPG and PPGR metrics. CGM devices provide an opportunity to examine what effect this increased insulin sensitivity has over a much longer time period. In addition, it is well-documented that athletes, especially those in the sub-elite category, do not meet nutritional recommendations for their level of energy expenditure. Therefore, CGM devices have the potential to highlight the effect of not meeting these recommendations on blood glucose levels and the subsequent potential impact on recovery.

When the sensor glucose profiles of 10 trained, sub-elite athletes were analysed over a 6 day monitoring period 4/10 athletes studied spent more than 70% of the total monitoring time above 6 mmol/L even with the 2hour period after meals removed. Only one participant spent substantial time below 4 mmol/L and this was largely due to a significantly lower overall calorie intake compared to recommendations.

A differing ability to tolerate carbohydrates in this cohort is demonstrated with the wide range of cohort values of mean PPGR and mean PPG, which were 0.2 – 2.0 mmol/L.h and 5.5 – 7.4 mmol/L, respectively. Therefore, a diet rich in carbohydrates maybe benefical in some athletes and not others. This outcome appears particularly valid considering low BG is unlikely to be of concern to an athlete consuming adequate caloric intake.

This study provides a unique insight in to the day to day glucose levels of athletes that could only be achieved through the use of CGM devices highlighting the need for further investigation on the recommend diets of athletes to better determine the causes and impact of the hyperglycaemia seen on health and performance.

Overall the work presented in Chapters 8 – 15 provides unique insight in to the glucose metabolism of athletes. The glucose metabolism has not attempted to be quantified in this way before, considering both the engineering and clinical perspective. The results presented provide a significant advancement to the body of knowledge surrounding glucose metabolism during and immediately after exercise. In addition, the proof of concept trials of CGM in athletes show promise and potential for this device to work accurately in this cohort and capture a much different insight that expected of glucose levels of athletes

Chapter 16. Future Work

The work presented in this thesis show the potential and pitfalls of using CGM to optimise blood glucose levels in ICU patients and athletes. In particular, it highlights areas that need to be improved before they can be relied upon to guide glycaemic control protocols in ICU. In addition, the ability to examine blood glucose trends over a longer period highlighted several aspects of the athlete metabolism that are contradictory to current literature. Overall, the results are promising for these devices in both fields. However, improvements in sensor technology and further research are needed before the maximum benefits of CGM can be realised. This chapter outlines aspects of future work that could be investigated to allow the advancement of CGM in these areas.

16.1 CGM in ICU Future Work

Chapters 2-7 highlighted that before CGM can be successful in reducing nurse workload and increasing patient safety sensor technology must improve to cope with the challenging ICU environment. The following recommendations were made to advance the technology to allow more reliable sensor glucose outputs:

- Waterproof CGM sensors
- Reconsider insertion technique to lessen the risk of capillary damage
- Wireless transmission between sensor and monitor unit for ease of patient mobility

Once these recommendations have been addressed in a device, a large scale trial such as this would need to be repeated to prove the performance of the device once again. Another option for CGM technology in the ICU is devices which sample continuously from existing arterial lines which are currently being developed and refined (Schierenbeck et al., 2013, Hage et al., 2010). These devices remove the need for

subcutaneous sensors and eliminating the difficulties of translating subcutaneous glucose levels to blood glucose levels accurately. However, these devices face their own challenges, but if they are able to meet the above criteria, they show much promise to aid in the reduction of nurse workload and increase of patient safety with in the ICU.

With an improved sensor other future work in this area could include the addition of adaptive guardrails. These adaptive guardrails would provide flexibility to allow targets and tolerances to be adjusted based on how the sensor is performing and observed patient variability. Further reducing nurse workload and alarm fatigue. To implement adaptive alarms there would need to additional functionality in the CGM device, something that is not currently available with the Sentrino or other similar devices. Another option with guardrails would be to investigate only having a lower bound, to ensure patient safety but prevent alarm fatigue.

Another future study that would aid in the development of sensor technology, would be to use the CGM model from Chapter 6 and virtual trial method in Chapter 7, to investigate the level of drift that could be present in the sensor and still achieve acceptable performance. This way, device manufacturers would have a better idea of what performance is needed before a device will be successful in a clinical setting.

The overall aim of future studies should be to create the technology and develop the protocols to allow a fully automated closed loop system for ICU patients. These protocols need to be able modulate insulin and/or nutrition with little input from nurses while still maintaining good blood glucose control and high patient safety. With the promise of emerging sensors specifically designed for this environment this closed loop system could be achieved in the not too distant future.

16.2 The Glucose Metabolism and CGM in Athletes

The research presented in Chapters 8 – 15 provides novel insight into the athlete metabolism that would not be achievable without the long term sensing capability of CGM. In addition, the athlete metabolism has not been quantified thoroughly in this manner before. To the author's knowledge, no studies have attempted to identify insulin sensitivity in athletes during and immediately after exercise. This research holds much promise to aid in personalising nutritional guidelines for athletes to improve recovery, training, and race performance.

It was noted that hyperglycaemia and hyperinsulinemia are prolonged post intense exercise to a far greater extent than previously noted in literature when following current nutritional guidelines. However, this study is limited by the lack of catecholamine analysis to assess or segregate inflammation induced effects from other metabolic impacts and not having glycogen measurements to confirm the amount of glycogen storage post exercise. Therefore, considering the glycaemic dysregulation seen post exercise and there is potential for a re-examination of the post exercise feeding protocol used by many athletes to achieve both optimal glycogen recovery and optimal blood glucose levels

The adapted and simplified ICING model developed for athletes is currently unable to deal with the rapid and transient effects of boluses. In particular, the gut model parameters, *d1* and *d2*, may not be suitable during exercise. Conducting an experiment to improve the gut model during exercise and under bolus conditions would be the first step to allowing the model to better cope with the dynamics induced when glucose is consumed.

Another important step to improving the model, to make it more physiologically realistic, would be to model EGP and/or non-insulin mediated glucose uptake (p_g) rather than holding these constant. This could be potentially be achieved by making p_g, and EGP dependent on heart rate or some other suitable marker of effort. However, it is difficult to capture the dynamics of these parameters in a non-invasive manner and it may have to wait until technological advancements allow such parameters to be measured non-invasively.

Finally, while CGM in athletes proved to be successful as a proof-of-concept analysis further investigation is needed in to the recommended dietary intakes and resulting blood glucose levels of athletes. A larger study with more detailed nutritional intake data and specific activity monitoring is necessary before sweeping conclusions can be made. Equally, activity could be directly controlled in a more homogenous cohort, in a more strictly controlled study than this pilot investigation. In particular, those in the sub-elite category as studied here are of interest. Sub-elite athletes are unlikely to have the same nutritional and dietary support from trained professionals as elite athletes. Hence, their nutritional intakes are perhaps more likely to be sub-optimal, as demonstrated in this study.

Ultimately, it is anticipated that CGM could prove interesting insights into the metabolism of athletes not yet captured due to their long duration of data collection. However, generating a metabolic model that can then use this data to recommend optimal, personalised, nutrition is still a long way off. Further advancements of technology, including better non-invasive measurement of metabolic parameters such as EGP are likely necessary before this can be achieved.

“What we call the beginning is often the end. And to make an end is to make a beginning. The end is where we start from.”

T.S. Eliot

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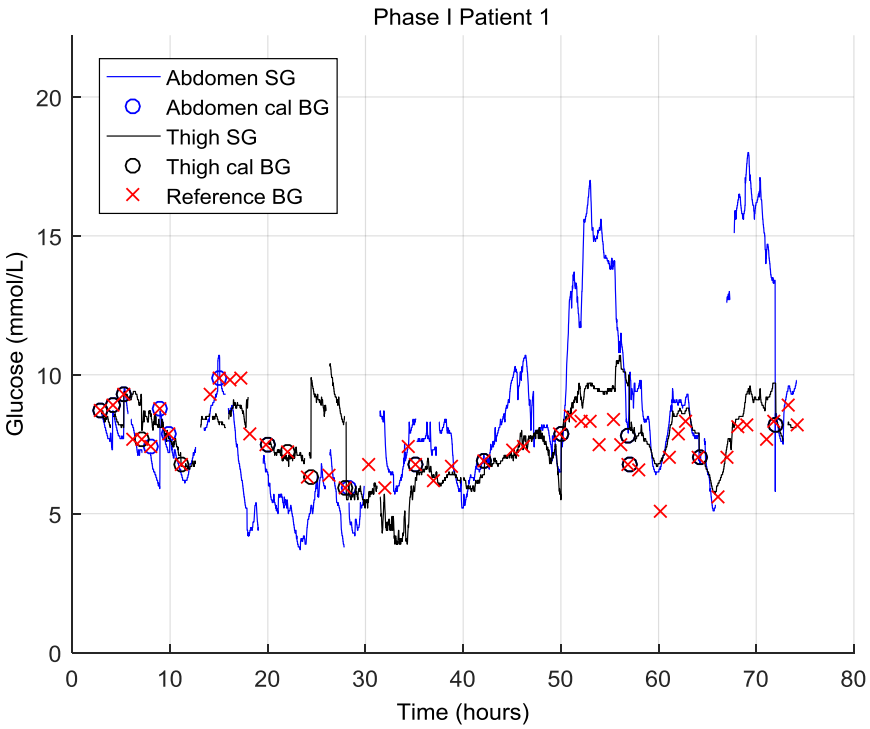
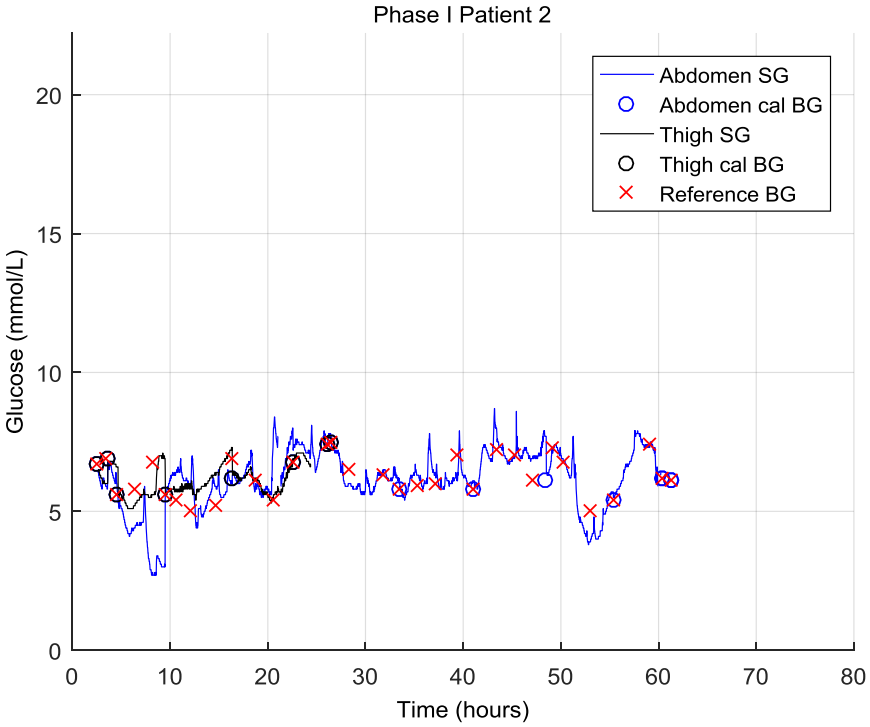
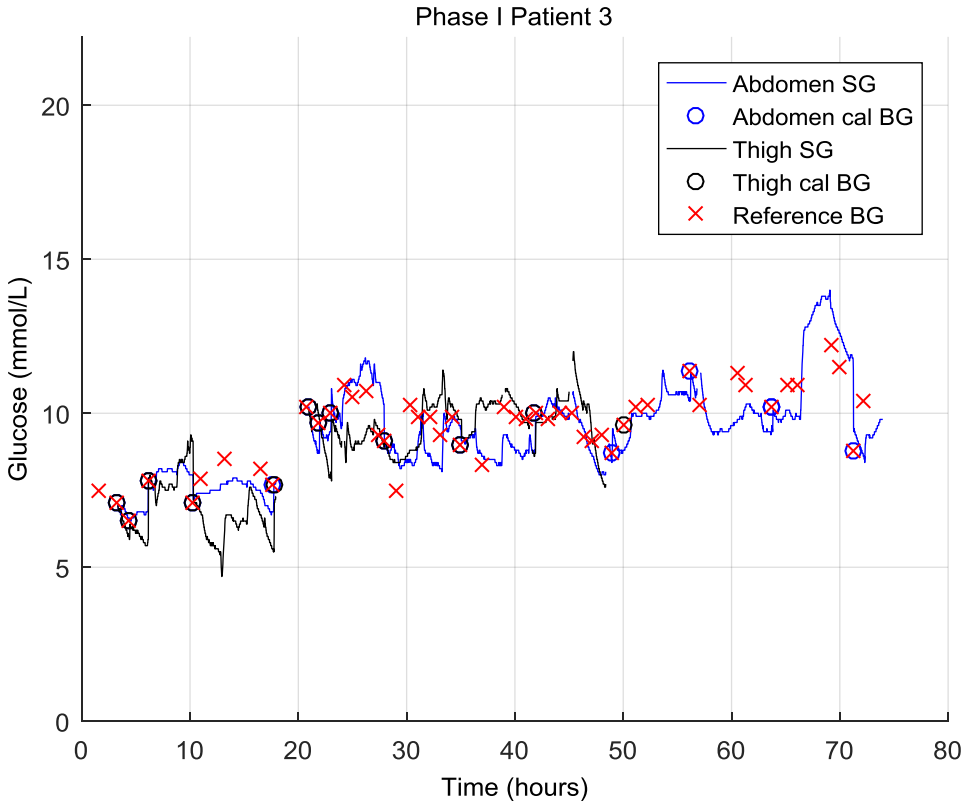
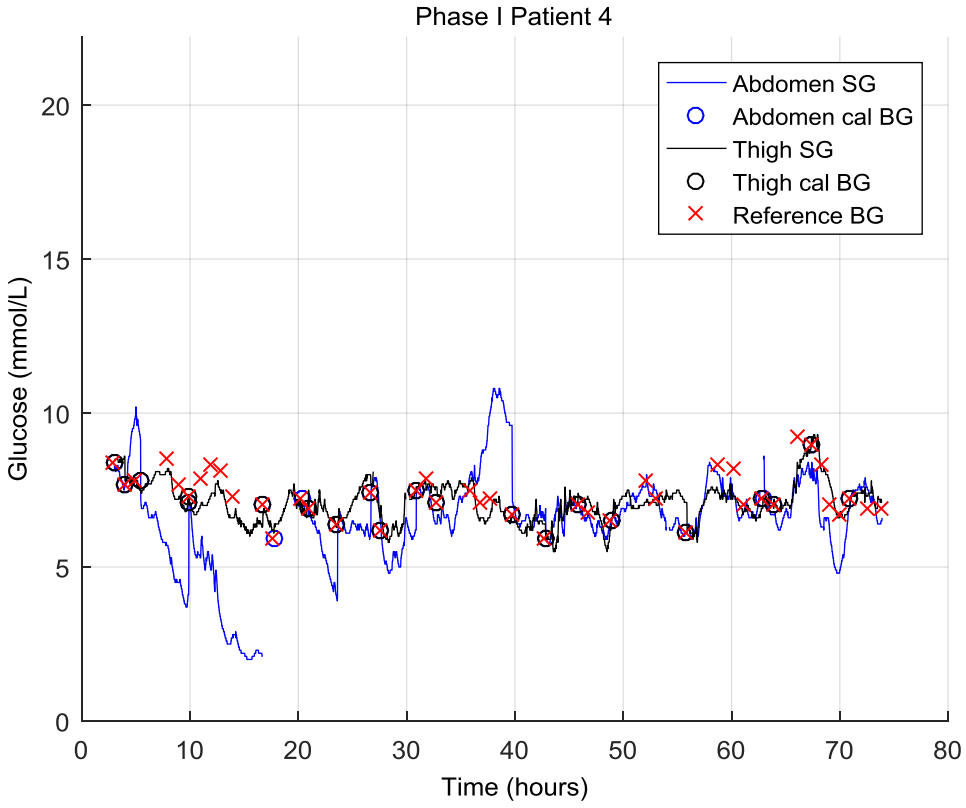
Appendix A: Phase 1 Sentrino CGM Data






Phase I Patient 3
Abdomen SG
Abdomen cal BG
Thigh SG
Thigh cal BG
Reference BG
Glucose (mmol/L)
Time (hours)
0
5
10
15
20
0
10
20
30
40
50
60
70
80


Phase I Patient 4
Abdomen SG
Abdomen cal BG
Thigh SG
Thigh cal BG
Reference BG
Glucose (mmol/L)
Time (hours)
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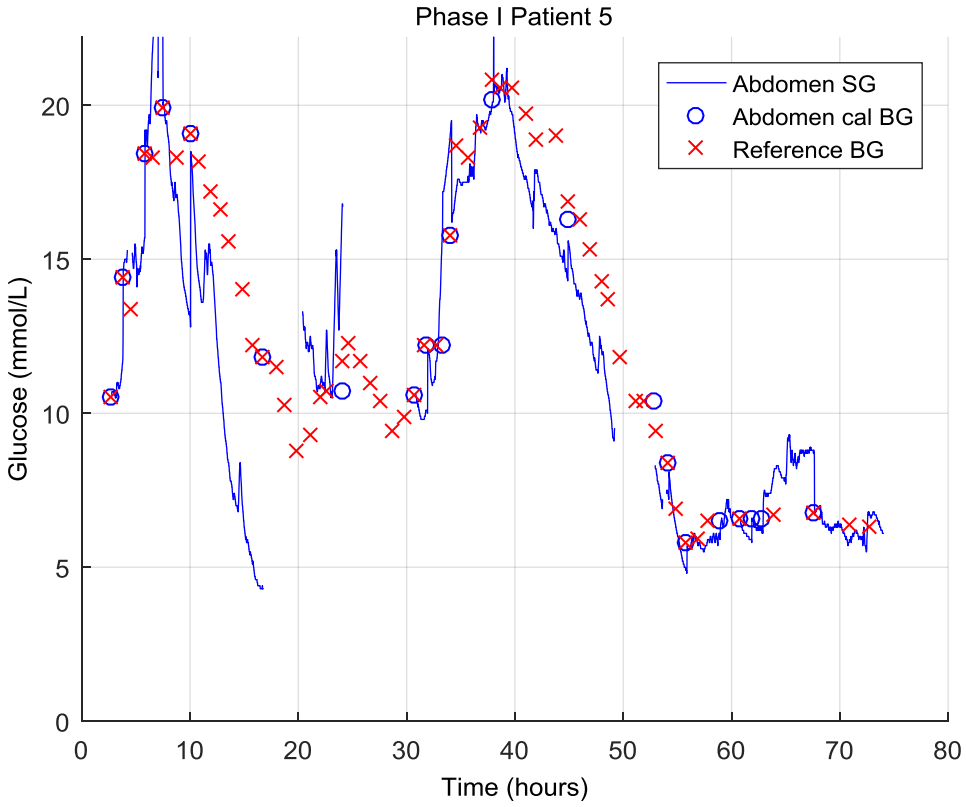
5
10
15
20
0
10
20
30
40
50
60
70
80


Phase I Patient 5
Abdomen SG
Abdomen cal BG
Reference BG
Glucose (mmol/L)
Time (hours)
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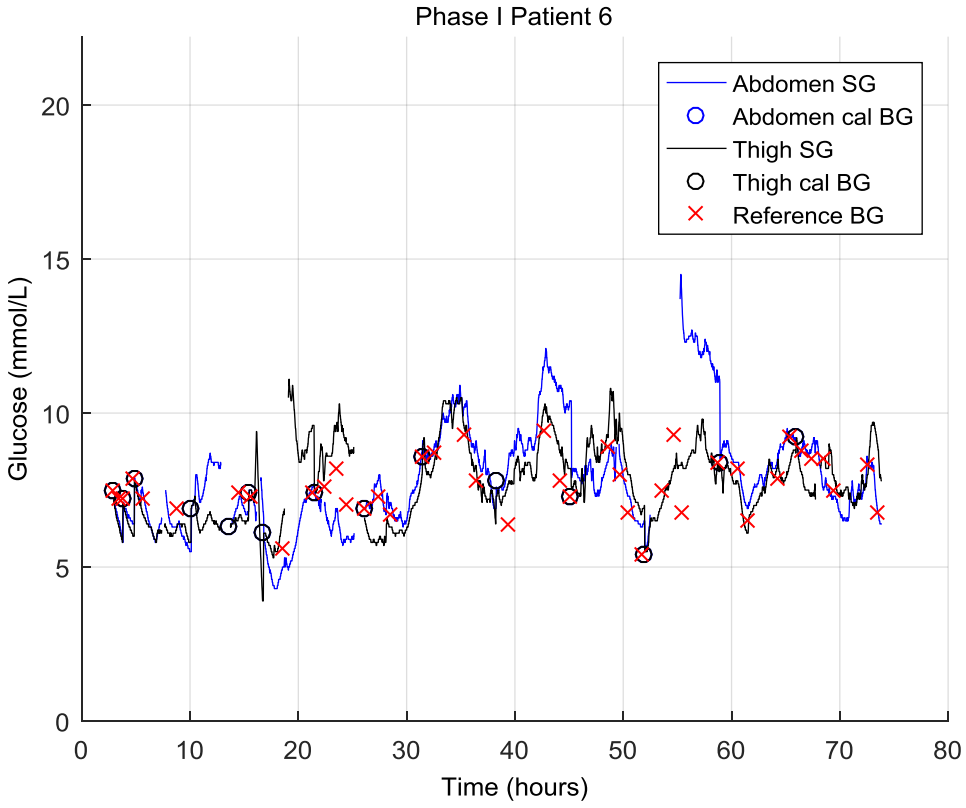
5
10
15
20
0
10
20
30
40
50
60
70
80


Phase I Patient 6
Abdomen SG
Abdomen cal BG
Thigh SG
Thigh cal BG
Reference BG
Glucose (mmol/L)
Time (hours)
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15
20
0
10
20
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40
50
60
70
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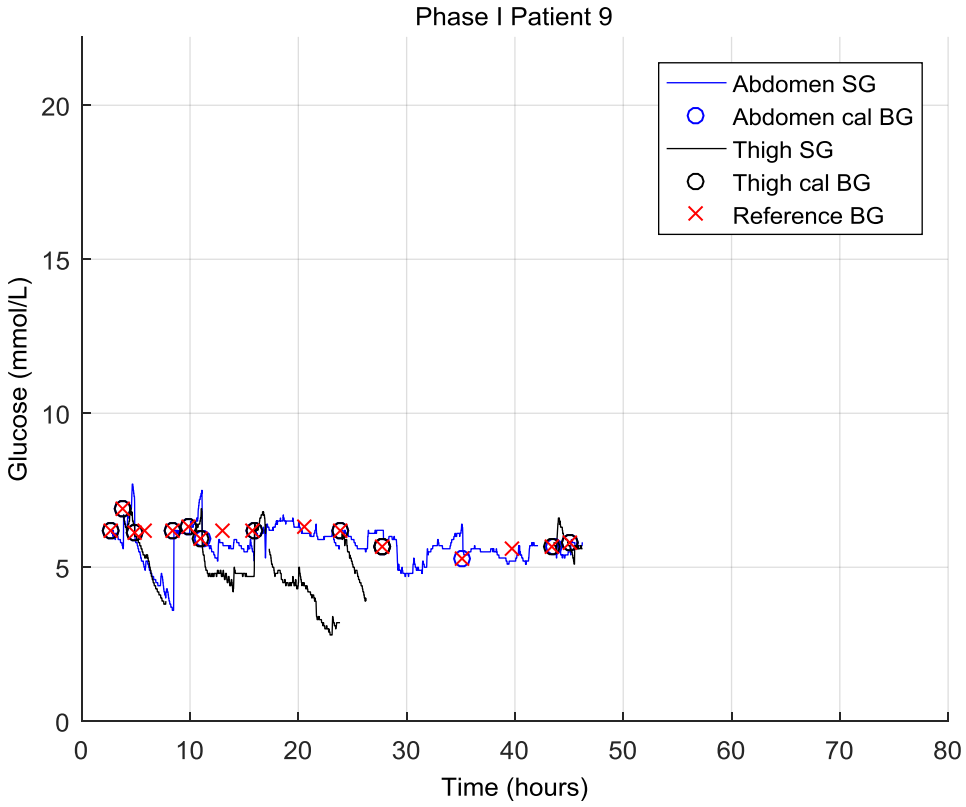
Phase I Patient 9
Abdomen SG
Abdomen cal BG
Thigh SG
Thigh cal BG
Reference BG
Glucose (mmol/L)
Time (hours)
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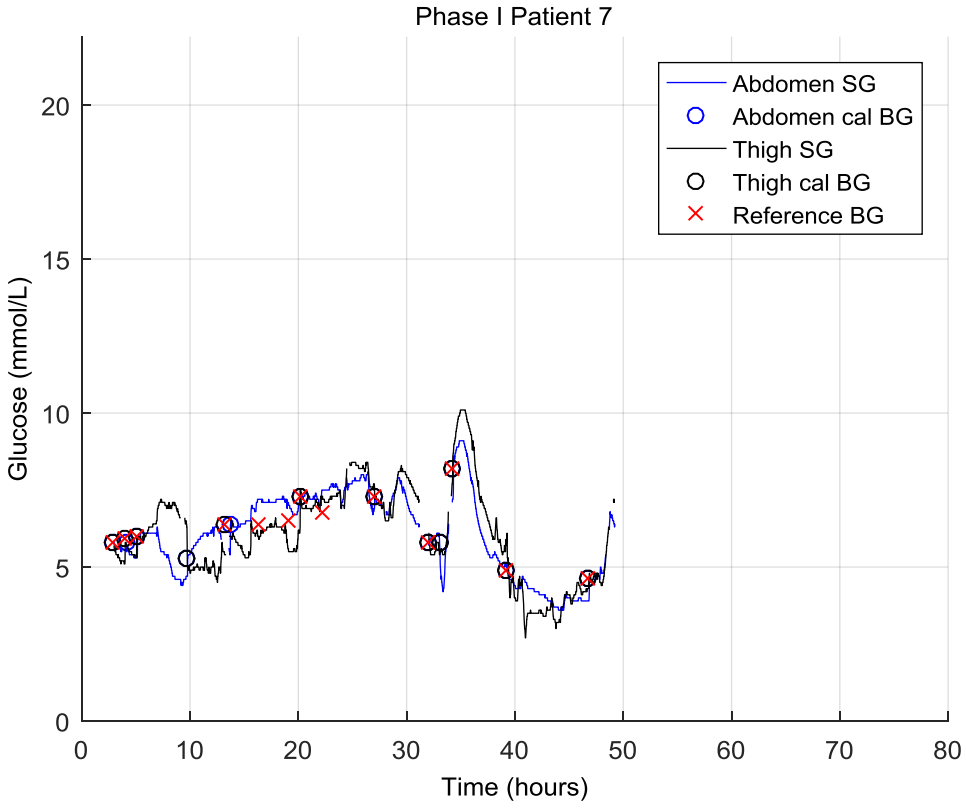
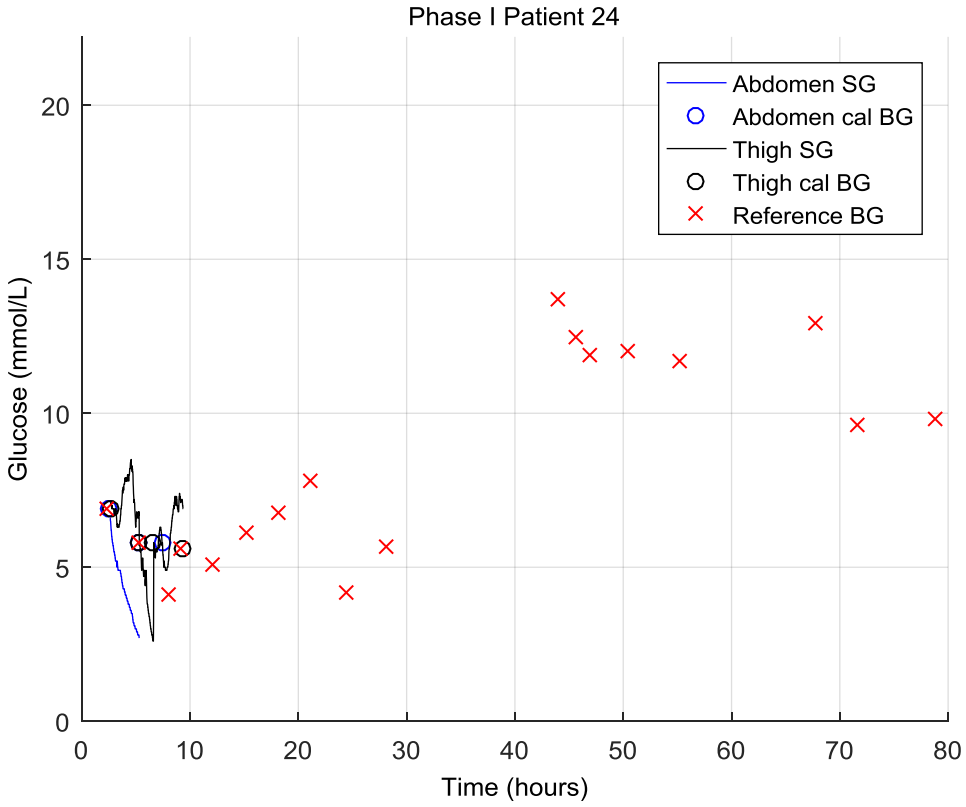
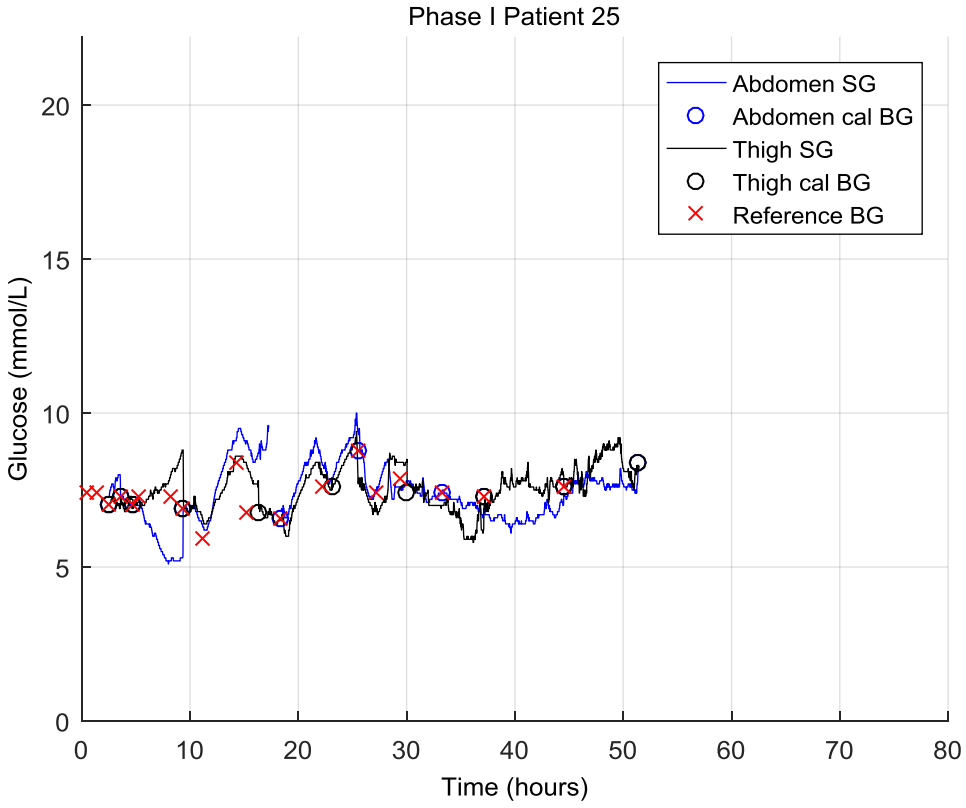
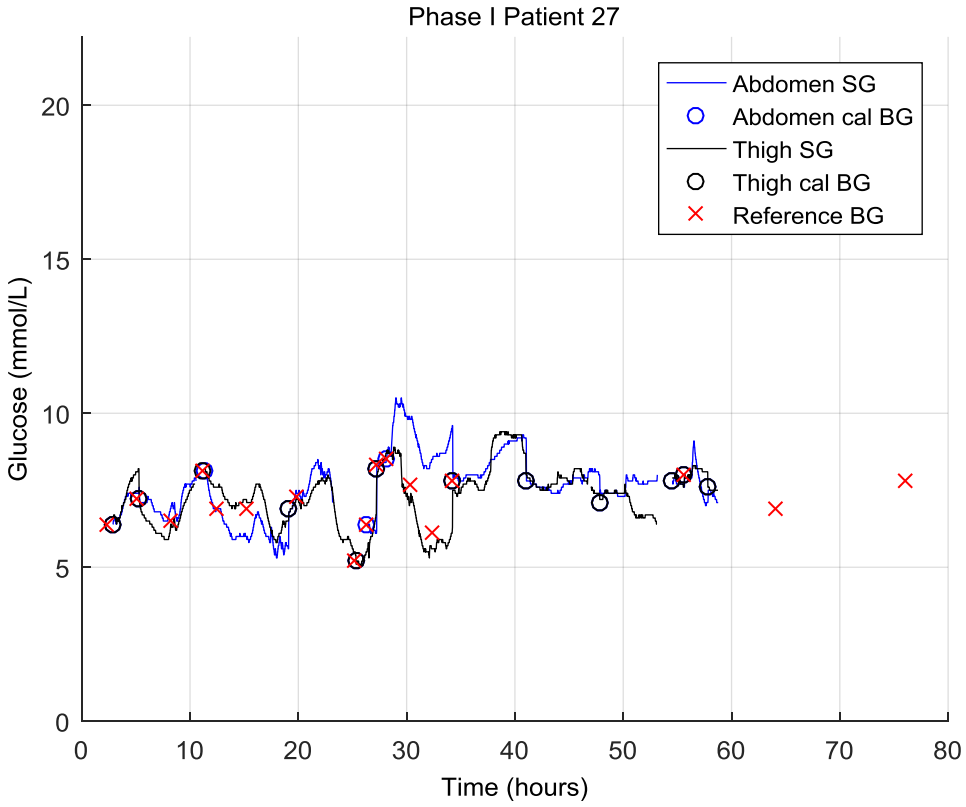
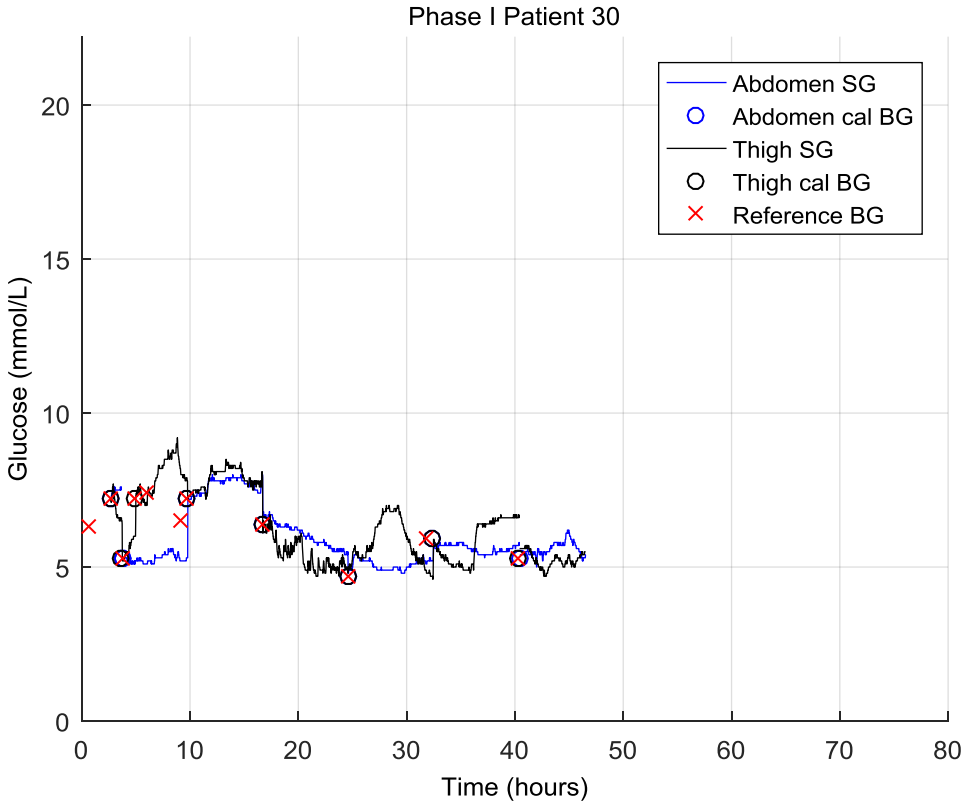
5
10
15
20
0
10
20
30
40
50
60
70
80


Phase I Patient 7
Abdomen SG
Abdomen cal BG
Thigh SG
Thigh cal BG
Reference BG
Glucose (mmol/L)
Time (hours)
0
5
10
15
20
0
10
20
30
40
50
60
70
80


Phase I Patient 24
Abdomen SG
Abdomen cal BG
Thigh SG
Thigh cal BG
Reference BG
Glucose (mmol/L)
Time (hours)
0
5
10
15
20
0
10
20
30
40
50
60
70
80


Phase I Patient 25
Abdomen SG
Abdomen cal BG
Thigh SG
Thigh cal BG
Reference BG
Glucose (mmol/L)
Time (hours)
0
5
10
15
20
0
10
20
30
40
50
60
70
80


Phase I Patient 27
Abdomen SG
Abdomen cal BG
Thigh SG
Thigh cal BG
Reference BG
Glucose (mmol/L)
Time (hours)
0
5
10
15
20
0
10
20
30
40
50
60
70
80


Phase I Patient 30
Abdomen SG
Abdomen cal BG
Thigh SG
Thigh cal BG
Reference BG
Glucose (mmol/L)
Time (hours)
0
5
10
15
20
0
10
20
30
40
50
60
70
80