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MODEL-BASED DECISION SUPPORT FOR NUTRITION AND INSULIN TREATMENT OF HYPERGLYCAEMIA IN THE ICU

BY
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AALBORG UNIVERSITY
DENMARK

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LIST OF ABBREVIATIONS

ICU	Intensive Care Unit
IIT	Intensive Insulin Therapy
BG	Blood Glucose
EE	Energy Expenditure
SIRS	Systemic Inflammatory Response Syndrome
HPA	Hypothalamic-Pituitary-Adrenal
CRH	Corticotrophin-Releasing Hormone
ACTH	Adrenocorticotropic Hormone
FFA	Free Fatty Acids
PID	Proportional-Integral-Derivative
MPC	Model Predictive Control
RMSE	Root Mean Square Error
SF	Stress Factor
O_2	Oxygen
VO_2	Oxygen consumption
CO_2	Carbon Dioxide
VCO_2	Carbon Dioxide production
IC	Indirect Calorimetry
RQ	Respiratory Quotient
FiO_2	Fraction of inspired Oxygen
ET-CO_2	End Tidal CO_2
MV	Minute Volume
IBM	Ideal Body Mass

ENGLISH SUMMARY

Stress-induced hyperglycaemia commonly occurs during critical illness and has been associated with increased morbidity and mortality. The results in the literature concerning glycaemic control and nutritional support are, to some extent, conflicting and do not provide consensus about optimal protocols for treatment. Concerning the control of blood glucose (BG), this thesis hypothesizes that mortality can be reduced by reducing BG and/or by reducing the frequency of hypoglycaemic events. It also hypothesizes that in clinical practice reduction of BG and hypoglycaemic events is best achieved by using model-based decision support systems. Concerning nutrition the thesis hypothesizes that nutrition should target the patient's energy expenditure (EE), except for the first few days following the insult to the patient, where the caloric target should be below the patients EE. The thesis also hypothesizes that in clinical practise accurate estimation of EE cannot be done by predictive equations that use anthropometric data, but can be done by a novel method, CO_2-based calorimetry.
Evidence from the literature, including the four papers that are the basis of this thesis, will be used to examine each of the six hypotheses.

Most of the controlled studies using intensive insulin therapy (IIT) to reduce BG have succeeded in lowering BG, but almost all of them resulted in increasing the number of patients with hypoglycaemic events. The studies have shown different results in terms of mortality, with about half of the studies having resulted in reduced mortality and the other half resulting in increased mortality. Lowered mortality was not associated with the reduction in BG ($p=0.40$), nor with the reduction in the percentage of patients with severe (BG < 2.2 mmol/l) hypoglycaemia ($p=0.83$).
A two-dimensional regression analysis with changes in BG and hypoglycaemia as independent variables indicated that reduced mortality was associated with reduced BG ($p=0.05$) and reduced frequency of hypoglycaemic events ($p=0.07$). That supports the notion that hyperglycaemia should be reduced to normal BG concentrations while avoiding hypoglycaemic events. Clinical studies support the hypothesis that a safe reduction in BG is best achieved with the use of a model based decision support system. While there are many different systems to do so, both rule-based and model-based, the Glucosafe system (using the Glucosafe model) has, compared to other systems, shown either bigger or similar reduction in BG with no hypoglycaemic events.
Glucosafe has two major components: the advice module and the model. The quality of these two components determines Glucosafe's ability to safely lower BG. The model's predictive accuracy can be tested and improved on retrospective data, but testing of the advice module in principle requires a clinical trial. To reduce the need for clinical trials, a method based on virtual patients was developed. The

virtual patients were based on insulin sensitivity profiles from real patients and were used to evaluate different settings of the penalty functions that govern Glucosafe's treatment advice. An example showed how this method can be used to select settings of the penalty functions, likely to produce a desired outcome in terms of mean BG and frequency of hypoglycaemic events. Glucosafe with these modified settings may then be worthy of a new clinical trial.
To improve the Glucosafe model's ability to predict BG, a model of pancreatic insulin release was constructed. The pancreas model introduces a feedback loop in the Glucosafe model, which may produce instability. The model was found to be stable but also to produce damped oscillation after sudden changes in BG. An early version of the pancreas model showed a non-significant improvement in predictive accuracy, presumably because it was tested on critically ill patients with high BG and administration of large insulin doses. Further clinical testing is needed to investigate if the pancreas model improves predictive accuracy in patients who are recovering from critical illness.

The literature on nutritional support for critically ill patients is still not in consensus. While there is support for not feeding the patient more than 100% of EE, as studies have shown this to have deleterious effects, some studies suggest targeting 100% of EE and some suggest targeting less. The hypothesis that the target should be 100% of EE stems from studies showing that a large caloric debt increases morbidity and/or mortality. Although there are studies advocating underfeeding patients, the American, European, and Canadian guidelines for the nutrition supports the hypothesis that nutritional support should target 100% of a patient's EE to avoid or lessen caloric debt. With regards to restricting feeding in the first few days, there is no counter indication to the hypothesis that nutrition should be reduced in the first few days where the body catabolism provides the necessary substrates to cover energy needs. Regardless of the nutritional target being 100% of EE or less, an accurate estimation of a patient's EE is needed. Predictive equations for estimating EE are not accurate and over- or underestimate patients' EE compared to indirect calorimetry as shown in literature reviews and in the research presented in this thesis. VCO_2-based calorimetry is the estimation of EE based on a patient's VCO_2, using a formula incorporating a Respiratory Quotient (RQ) value. The VCO_2-based calorimetry results presented here show that VCO_2-based calorimetry gives EE estimates significantly better than predictive equations. There are some problems in using only VCO_2 as a measure for EE, as changes in ventilation which result in VCO_2 not matching metabolically produced CO_2, results in EE estimation errors lasting up to 20 min. due to the CO_2 equilibration time constant. Solutions to this is either the application of a running average of 5 min. or more to the measurements if the measurement period is short, or the use of the mean values from 24 hour measurements if possible.

In conclusion there seems to be support for, or no direct evidence to oppose, the 6 hypotheses stated.

DANSK RESUME

Stress induceret hyperglykæmi ses ofte i kritisk sygdom og er blevet associeret med øget morbiditet og mortalitet. Litteraturen om glykæmisk kontrol og ernæring er i et vist omfang modstridende, og der er ikke konsensus om optimale protokoller for behandling. Angående kontrol af blod glukose (BG) fremsætter denne afhandling hypoteser som siger at mortalitet kan reduceres ved at reducerer BG og/eller ved at reducerer frekvensen af hypoglykæmiske tilfælde. En yderligere hypotese er at i klinisk praksis er reduktionen af BG og hypoglykæmiske tilfælde bedst opnået ved brugen af model-baserede beslutningsstøtte systemer. Angående ernæring er det denne afhandlings hypotese, at der skal sigtes efter at administrere ernæring tilsvarende patientens energi forbrug (EE), undtagen i de første få dage efter skade, hvor der sigtes lavere end patientens EE. Afhandlingen hypoteserer også, at i klinisk praksis kan nøjagtig estimering af EE ikke udføres med prædikative ligninger, der anvender antropometriske data, men kan estimeres med en ny metode, CO_2-baseret kalorimetri. Evidens fra litteratur, og de fire artikler som er basis for denne afhandling, bliver anvendt til at undersøge hver af de seks hypoteser.

De fleste kontrollerede studies som anvender intensiv insulin terapi (IIT) har været succesfulde i at reducere BG men næsten alle resulterede i stigninger i antallet af patienter med hypoglykæmiske tilfælde. Studierne har vist forskellige resultater angående mortalitet, hvor ca. halvdelen af dem har resulteret i reduceret mortalitet og den anden halvdel har resulteret i øget mortalitet. Reduceret mortalitet var ikke associeret med reduktion i BG ($p=0.40$) eller med reduktion i procentdelen af patienter med alvorlig (BG > 2.2 mmol/l) hypoglykæmi ($p=0.83$).

En todimensionel regressionsanalyse med ændringer i BG og hypoglykæmi som uafhængige variabler indikerede, at reduceret mortalitet var associeret med reduceret BG ($p=0.05$) og reduceret frekvens af hypoglykæmiske tilfælde ($p=0.07$). Dette støtter ideen, at hyperglykæmi burde reduceres, mens hypoglykæmiske tilfælde undgås. Kliniske studies understøtter hypotesen som siger at en reduktion af BG, uden hypoglykæmiske tilfælde, bedst opnås ved brugen af et model-baseret beslutningsstøttesystem. På trods af at der er mange forskellige sådanne systemer, både regel-baserede og model-baserede, har Glucosafe systemet (som anvender Glucosafe modellen), sammenlignet med andre systemer, vist enten større elle lignende reduktion i BG uden hypoglykæmiske tilfælde.

Glucosafe har to overordnede komponenter: rådgivningsmodulet og modellen. Kvaliteten af disse to komponenter bestemmer Glucosafe's evne til at sinke BG og undgå hypoglykæmi. Modellens prædiktive nøjagtighed kan testes og forbedres ved brug af retrospektiv data, men testning af rådgivningsmodulet kræver i princippet et klinisk studie. For at mindske nødvendigheden af kliniske studier blev en metode baseret på virtuelle patients udviklet. De virtuelle patienter var baseret på insulinsensitivitetsprofiler fra rigtige patients og blev anvendt til at evaluere

forskellige indstillinger af straffunktionerne, som styrer Glucosafe's behandlingsrådgivning. Et eksempel viste, hvorledes denne metode kan anvendes til at vælge de indstillinger af straffefunktionerne, som sandsynligvis vil give et ønsket resultat, i form af gennemsnitlig BG og frekvens af hypoglykæmiske tilfælde. Med disse modificerede indstillinger vil det muligvis være fordelagtigt med et nyt klinisk studie af Glucosafe.
For at kunne forbedre Glucosafemodellens evne til at prædiktere BG blev en model af insulinfrigivelse fra bugspytkirtlen konstrueret. Modellen introducerer et feedback-loop i Glucosafe modellen, hvilken kan give ustabilitet. Modellen fandtes at være stabil, men også at producere dæmpede oscillationer efter pludselige ændringer i BG. En tidlig udgave af bugspytkirtelmodellen viste en ikke signifikant forbedring i prædiktiv nøjagtighed, formentlig fordi den blev testet på kritisk syge patients med højt BG og indgift af store doser insulin. Ydereligere klinisk testning er nødvendigt for at undersøge om bugspytkirtelmodellen forbedre den prædiktive nøjagtighed hos patienter som er i bedring fra kritisk sygdom.

Litteraturen om ernæring til kritisk syge er stadig ikke i konsensus. Mens der er støtte for ikke at ernære patienter mere en 100% af EE, da studier har vist, at det har en skadelig virkning, har nogle studier forslået at sigte efter 100% af EE og nogle har forslået at sigte lavere. Hypotesen om at målet skulle være 100% af EE stammer fra studier, der har vist at en større kaloriegæld øger morbiditet og/eller mortalitet. På trods af at der findes studier som advokerer for at underernære patienter, så støtter de amerikanske, europæiske, og canadiske retningslinjer for ernæring, hypotesen om at sigte efter 100% af EE for at undgå eller mindske kaloriegæld. Men hensyn til begrænset ernæring i de første dage er der ingen kontraindikation til hypotesen om at ernæring skal reduceres i de første dage, hvor kroppens katabolisme giver de nødvendige substrater til at dække kroppen energibehov. Uanset om ernæringsmålet er 100% af EE eller lavere, så er en nøjagtig estimering af patientens EE nødvendig. Prædiktive ligninger til at estimerer EE er ikke nøjagtige og over- eller undervurderer patienters EE sammenlignet med indirekte kalorimetri, som vist i litteraturgennemgange og i forskningsresultater præsenteret i denne afhandling. I VCO_2-baseret kalorimetri er estimeringen af EE baseret på en patients VCO_2, ved brug af en formel indeholdende en Respiratorisk Kvotient (RQ). Resultaterne viser at VCO_2-baseret kalorimetri giver EE estimater signifikant bedre end prædiktive ligninger. Der er dog nogle problemer ved brugen af VCO_2-baseret kalorimetri til estimering af EE, da ændringer i vejrtrækning kan resulterer i et VCO_2 som ikke stemmer med den metaboliske producerede CO_2, hvilket resulterer i EE estimationsfejl varende op til 20 min. grundet ligevægtstidskonstanten for CO_2. Løsninger på dette er enten anvendelsen af et løbende gennemsnit på 5 min. eller mere, hvis måleperioden er kort, eller brugen af gennemsnitsværdier fra 24 timers målinger, hvis det er muligt.

Konklusionen er at der er støtte for, eller ingen beviser imod, de 6 fremsatte hypoteser.

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LIST OF PAPERS

This thesis is based primarily on the following four peer-reviewed journal papers.

I. Pielmeier, Ulrike; Rousing, Mark Lillelund; Andreassen, Steen; Steenfeldt Nielsen, Birgitte; Christensen, Pernille Haure. 2012. Decision support for optimized blood glucose control and nutrition in a neurotrauma intensive care unit: preliminary results of clinical advice and prediction accuracy of the Glucosafe system. *Journal of Clinical Monitoring and Computing*, 2012; 26(4): 319-328.

II. Rousing, Mark Lillelund; Pielmeier, Ulrike; Andreassen, Steen. 2014. Evaluating modifications to the Glucosafe decision support system for tight glycemic control in the ICU using virtual patients. *Biomedical Signal Processing and Control*, 2014; 12: 54-61.

III. Rousing, Mark Lillelund; Pielmeier, Ulrike; Andreassen, Steen. 2015. Stability of the insulin-glucose feedback loop in Glucosafe: a comparison of pancreas models. *Biomedical Signal Processing and Control*, 2015; 22: 155-160

IV. Rousing, Mark Lillelund; Hahn-Pedersen, Mie Hviid; Andreassen, Steen; Pielmeier, Ulrike; Preiser, Jean-Charles. 2015. Energy expenditure in critically ill patients estimated by population-based equations, indirect calorimetry and CO_2-based indirect calorimetry. *Annals of Intensive Care*, 2016; 6(1): 1-11.

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CHAPTER 1. INTRODUCTION

Stress-induced hyperglycaemia commonly occurs during critical illness and has been associated with increased morbidity and mortality [1,2]. Treatment of hyperglycaemia by Intensive Insulin Therapy (IIT) has been shown to reduce mortality [3]. At the same time patients should receive adequate nutrition but both overfeeding and underfeeding with accumulation of large caloric debt has been shown to increase morbidity and or mortality [4,5].
To some extent the results in the literature concerning glycaemic control and nutritional support are conflicting and do not provide consensus about optimal protocols neither for glycaemic control nor for nutrition. The six hypotheses formulated below reflect many of the issues currently discussed in the literature. In their actual formulation they also embed our view of what may be a reasonable interpretation of the literature.

Concerning glycaemic control our hypotheses are that:
G1: The mortality of the critically ill patient can be lowered by reducing average blood glucose (BG) to the upper end of the normal range
G2: The mortality of the critically ill patient can be lowered by reducing the variability of BG and in particular reducing the incidence of hypoglycaemia
G3: Reducing both BG and the incidence of hypoglycaemia is best achieved through the application of decision support systems based on physiological models

Concerning nutritional support our hypotheses are that:
N1: The nutritional support should target the patients' Energy Expenditure (EE) without overfeeding
N2: During the first few days of critical illness where catabolism dominates, the nutritional target should be less than the patient's EE
N3: The patient's EE can be estimated with sufficient accuracy by a novel method, VCO_2-based calorimetry, but not from predictive equations using anthropometric data.

In the following chapters we seek to support the hypotheses through published literature and our own research.

Chapter 2 provides an introduction to the physiology and pathophysiology of critical illness. The chapter also includes a review of the treatment of stress-induced hyperglycaemia and clinical studies of glycaemic control. The purpose is to provide a basis of knowledge for the rest of the thesis but also to support hypothesis G1, G2, N1, and N2. There have been studies which have shown reduced mortality when lowering hyperglycaemia towards normoglycaemia using insulin [3,6,7]. However some of these studies have resulted in increased hypoglycaemic events and have been criticized for this.

There have also been studies on how best to feed critically ill patients, however there is still some discussion as to the optimal nutritional strategy. In this chapter we examine the literature and seek to support our hypotheses on when and how much to feed the patients.

Chapter 3 is based primarily on Paper I and introduces the concept of modelling. This includes a short review of different types of modelling, including physiological modelling, but primarily presents the Glucosafe model of insulin-glucose metabolism that is central to the work presented in this thesis. The purpose of this chapter is to show that decision support systems based on physiological models perform well compared to other forms of decision support, supporting hypothesis G3. This is done by examining some of the published models and decision support systems, evaluating how they preform, and comparing their performance with our own Glucosafe model and system.

Chapter 4 is based primarily on Paper II and describes the development of a method to assess the likely treatment outcome of changes made to the advice module part of the Glucosafe system, without the need for a clinical trial. The chapter describes the use of virtual patients, based on real patients, to estimate treatment outcomes. If model-based decision support systems are to be the best tool to optimize treatment of critically ill patients then there needs to be a method of adapting the model/system to different patient cohorts. The purpose of this chapter is to present a method of adapting the Glucosafe system to offer optimal treatment advice for different patient cohorts or in line with different clinical guidelines.

Chapter 5 is based primarily on Paper III and presents the work done to develop a model of pancreatic insulin release for the Glucosafe model. If the Glucosafe system is to prove hypothesis G3 correct it should be based on a model with physiologically correct assumptions. The Glucosafe model was initially not constructed to incorporate the variable insulin release from the pancreas, using instead a constant, fixed insulin release (as shown in chapter 3). The goal was to develop a model of pancreatic insulin release to improve the physiological correctness of the model and to possibly improve the model's ability to predict BG and offer treatments advice.

Chapter 6 is based primarily on Paper IV and presents work on optimizing patient nutrition in the ICU. In order to fulfil hypotheses N1 and N2 an accurate assessment of a patient's nutritional needs is required as the question of how much to feed the patients is based on a patient's EE, it becomes necessary to accurately estimate the EE. The work presented in chapter 6 is the work done to evaluate the accuracy with which a patient's EE can be estimated and to support hypothesis N3, to present a simple and accurate method (VCO_2-based calorimetry) to estimate EE using measurements of carbon dioxide production (VCO_2).

CHAPTER 2. THE PATHOPHYSIOLOGY OF CRITICAL ILLNESS

The human body controls the blood glucose balance using two negative feedback systems, insulin and glucagon. In the healthy person, if BG increases from normoglycaemia, the β-cells of the pancreas increase the release of insulin to the bloodstream to lower BG. If the BG concentration decreases from normoglycaemia, α-cells in the pancreas release glucagon in order to increase BG [8].
However in critical illness, the body's response to injury results is, amongst others, the BG being increased despite the release of insulin.

2.1. THE METABOLIC PHASES IN CRITICAL ILLNESS

The body has a metabolic stress response to injury (be it from trauma, major surgery, burns, or sepsis). It involves a neuroendocrine and an immune component and includes increased catabolism and anabolism. Over time the body's response to critical illness occurs in three phases: the acute phase and two more prolonged phases, the catabolic and the anabolic phases [9].

2.1.1. THE ACUTE PHASE

The first phase is the acute response, which often lasts <12 hours but in extreme cases up to 24 hours [9]. The patient develops the Systemic Inflammatory Response Syndrome (SIRS), which acutely is dominated by hemodynamic changes. Neurally mediated stress factors such as pain or hypovolemia activate the Hypothalamic-Pituitary-Adrenal (HPA) axis. The hypothalamus releases corticotrophin-releasing hormone (CRH), which stimulates pituitary secretion of adrenocorticotropic hormone (ACTH). Acutely, this results in increased adrenal secretion of epinephrine which in turn increases pancreatic glucagon production and suppresses the pancreatic insulin production when plasma epinephrine is above 2.2 nmol/l. This effect is powerful enough to inhibit insulin secretion despite hyperglycaemia [10,11]. In liver and muscles, the combination of high epinephrine and low insulin results in a rapid mobilization of the glycogen stores which in the liver is further enhanced by the elevated plasma glucagon concentration. This leads to elevated blood glucose, i.e. hyperglycaemia.
In the muscles, the increased glycogenolysis (the breakdown of glycogen stores into glucose-6-P) increases the intracellular availability of glucose-6-P. Oxidative metabolism is in the acute phase not elevated despite the availability of substrates. This is possibly due to lack of oxygen caused by reduced blood pressure [9]. Reduced blood pressure due to for instance hypovolemia is a common feature of

sepsis, severe burn and trauma. This means that glucose will be channelled through glycolysis and anaerobic lactic acid metabolism. The resulting lactate can diffuse out of the cell into the plasma, resulting in hyperlactatemia [9].

2.1.2. THE CATABOLIC PHASE

The acute phase is followed by a catabolic phase, which, as the acute phase, is also dominated by SIRS, but with more metabolic than hemodynamic changes [12]. Through cytokines produced by immune cells [13] the HPA-axis is activated causing CRH-release from the hypothalamus which again stimulates pituitary ACTH secretion. In this phase, the hormonal response is different from the response in the acute phase as ACTH release leads to secretion of cortisol from the adrenal gland [14-17]. The plasma levels of epinephrine return to normal or near normal in the catabolic phase and only cortisol levels remain elevated throughout the catabolic phase [11]. The disappearance of the elevated epinephrine levels allows the pancreas to respond normally to hyperglycaemia, and therefore, due to the elevated blood glucose the patient enters a state of hyperinsulinaemia [11]. Insulin interacts with receptors in the cell membrane (primarily in skeletal muscles) triggering translocation of so-called GLUT-4 transporters to cell membranes, resulting in increased uptake of glucose. Insulin also induces the cells to store the glucose by converting it to glycogen and thus the increased glucose uptake and storage should result in the BG decreasing [18]. In general, the higher the BG the larger the insulin release, to a point where the pancreatic insulin release reaches a plateau. During times where BG is rising, the insulin release is also mediated by the rate of change in BG [8,19]. This physiological response is the basis of the modelling of a pancreatic insulin release model, shown in chapter 5.

Both in the tissues and in the liver cortisol drives the catabolism. In the tissues, the catabolic effects of cortisol cause lysis of triglycerides into glycerol and free fatty acids (FFA). FFA can diffuse into the blood stream causing hyperlipidaemia [14]. In muscle tissues, cortisol also causes lysis of proteins into amino acids and hereby causes muscle wasting [20]. In both tissues and liver, cortisol causes glycogenolysis. Increased intracellular availability of glucose-6-P (from mobilization of the muscular glycogen stores due to cortisol and increased glucose uptake due to hyperinsulinaemia) results in hyperlactatemia as mitochondrial respiration cannot match the supply of glucose-6-P and therefore a large proportion may be metabolized anaerobically into lactate [10]. These catabolic effects counteract the anabolic effects of insulin, but during the catabolic phase it is apparent that the catabolism caused by cortisol is dominating: plasma levels of FFA rise [10], as do levels of amino acids [9,21]. BG also increases due to the increased concentration of glucagon and cortisol which return to normal 7-10 days after the initial injury [11,22]. Both glucagon and cortisol stimulates glycogenolysis, and gluconeogenesis (the synthesis of glucose from substrates such as fatty acids,

glycerol, lactate, and amino acids) [23]. The catabolism of proteins may cause substantial loss of muscle mass over the duration of the catabolic phase [24].

2.1.3. THE ANABOLIC PHASE

The catabolic phase overlaps with the anabolic phase and initially the elevated cortisol level keeps the catabolic response dominant. However as cortisol levels decrease so does the strength of the catabolic response. As the catabolic response lessens, the anabolic phase starts to dominate.
The catabolic phase leaves the patient in a condition with an acute need for tissue repair due to the original insult and in addition a need for replenishing of the intracellular energy stores, which have been depleted by the catabolism. Presumably tissue repair has started already during the catabolic phase, such that there in reality is an overlap between the catabolic and anabolic phases – a situation where catabolism and anabolism coexist and the metabolism is increased. Thus tissue repair contributes to the duration of increased metabolism which typically lasts for a couple of weeks [25,26]. Often patients develop an energy debt during the first week of their stay in the intensive care unit due to slow progression to feeding target. The slow progression may be due to poor absorption by the patients of enteral nutrition, supplemented by fear of aspiration pneumonia or by cessations in feeding due to elective procedures [27]. This energy debt is mostly not compensated for during the latter part of the patient's stay in the ICU and is correlated to worse clinical outcome [5,28].

2.2. TREATMENT OF STRESS HYPERGLYCAEMIA

As stated our hypotheses is that mortality can be lowered by reducing stress-hyperglycaemia (G1) and by reducing hypoglycaemic events (G2). We also hypothesize that nutrition should target the patients' EE (N1), except during the first few days of critical illness where the nutritional target should be less than the patient's EE (N2). The support in the literature for G1 and G2 will be reviewed in section 2.2.1 and the support for N1 and N2 in section 2.2.2.

2.2.1. GLYCAEMIC CONTROL WITH INSULIN THERAPY

There have been several studies done using IIT to lower BG and investigating the effect on mortality. Studies have shown both reduced mortality and increased mortality, with most studies resulting in increased number of patients with hypoglycaemic events. This section reviews the studies and presents a regression analysis of the association between changes in mortality, BG and hypoglycaemia.

Studies with reduced mortality

In 2001, in a landmark randomized controlled study (known as the Leuven study) of 1548 critically ill patients (970 cardiac surgery patients and 578 non-cardiac surgery or trauma patients), Greet Van den Berghe et al. tested IIT to decrease hyperglycaemia in an attempt to reach normoglycaemia and reduce mortality. Using insulin infusions to target a BG concentration of 4.4 – 6.1 mmol/l, the study achieved a mean morning blood glucose of 5.7 mmol/l in the group receiving IIT, and 8.5 mmol/l in the conventionally treated control group. However the IIT resulted in 39 patients (5.1%) in the IIT group having severe hypoglycaemic events (BG < 2.2 mmol/l) compared to six patients (0.8%) in the control group. The reduction in hospital mortality was 9.5%, from 26.3% to 16.8%, a relative reduction in mortality of 45% [3].

A second Leuven study in a medical ICU resulted in BG being lowered from 8.5 mmol/l to 6.2 mmol/l but also a significant increase in patients with hypoglycaemic events (3.1% versus 18.7%) in the IIT group. The study showed no significant difference in mortality between the IIT group and the control group (28-day mortality of 29.9% versus 30.0%).

There have been subsequent studies also showing reduced hospital mortality using IIT (see Table 2.1 for a summary of data from the studies).

Krinsley et al. [6] showed a BG reduction from 8.5 mmol/l to 7.3 mmol/l with no significant increase in the percentage of patients with hypoglycaemic events (0.34%) compared to the historic controls (0.35%), and a 6.1% reduction in hospital mortality.

Chase et al. [7] showed a reduction in BG (6.0 mmol/l in the intervention group and 7.2 mmol/l in the retrospective comparison) with 5.2% of patients in the intervention group having hypoglycaemic events. The number of patients with hypoglycaemic events in the control group was not reported, but the study did show a modest but significant decrease in the number of hypoglycaemic measurements, from 0.2% of measurements in the control group to 0.1% in the intervention group. The study showed a 11.3% reduction in hospital mortality (in patients being in the ICU for 5 days or more) compared to historic controls.

Arabi et al. showed a reduction in BG from 9.5 mmol/l to 6.4 mmol/l and despite a significant increase in patients with hypoglycaemic events (3.1% in the conventional treatment group versus 28.6% in the IIT group), showed a reduction in ICU mortality (17.1% in the conventional treatment group versus 13.5% in the IIT group).

These studies indicate that lowering BG reduces hospital mortality, despite the failure in these studies to reduce hypoglycaemic events. This provides support for the G1 hypothesis.

Studies with increased mortality

However there have also been studies where IIT increased mortality: VISEP [29], NICE-SUGAR [30], Glucontrol [31], and a study by De La Rosa et al. [32]. All

resulted in lowered BG and increased number of patients with hypoglycaemic events, but increased mortality.
The VISEP study was a multicentre, controlled two-by-two factorial trial, in patients with severe sepsis. The trial tested IIT versus conventional treatment and showed a reduction in BG from 8.4 mmol/l in the conventional treatment group to 6.2 mmol/l in the IIT group. However the VISEP study was stopped early due to a large increase in the percentage of patients with hypoglycaemic events (17% vs. 4.1%) and higher (10.9% vs. 5.2%) 90-day mortality in the IIT group.
The NICE-SUGAR study randomized ICU patients into two groups, targeting a BG of 4.5 to 6.0 mmol/l in the intervention group and less than 10.0 mmol/l in the control group, resulting in a reduction in BG from 8.1 mmol/l to 6.6 mmol/l but an increase in patients with hypoglycaemic events (0.5% vs. 6.8%) and in 90-day mortality (24.9% vs. 27.5%).
The Glucontrol study randomized ICU patients into two groups targeting a BG of either 4.4-6.1 mmol/l or 7.8-10-0 mmol/l and showed a BG reduction from 8.0 mmol/l to 6.5 mmol/l but also an increase in patients with hypoglycaemic events (2.7% vs. 8.7%) and in 28-day mortality (15.3% vs. 18.7%).
The De La Rosa study [32] reduced BG from 8.3 mmol/l to 6.7 mmol/l, but had an increase in patients with hypoglycaemic events (0.8% vs. 8.3%) and an increase in 28-day mortality (32.4% vs. 36.6%).

Regression analysis
A linear regression analysis on how the reduction of BG (ΔBG) may reduce mortality (ΔMortality) shows no significant correlation (p=0.40). This shows that a conclusion on the effect of IIT on mortality cannot be drawn from the data on reduction of BG alone.
A study by Preiser et al. [31] in a multi-centre trial with medical and surgical intensive care patients showed that the occurrence of hypoglycaemia coincided with a twofold increased risk of death independent of the blood glucose target range. Other studies [30,33] have also showed a similar association. These studies do not prove a causal connection between hypoglycaemic events and increased risk of death, but they are compatible with hypothesis G2: reducing hypoglycaemias reduces mortality. Table 2.1 shows that the studies with increases in mortality are also the studies with the largest increase in number of patients with hypoglycaemic events. A linear regression analysis between percentage of patients with severe (BG < 2.2 mmol/l) hypoglycaemia (ΔHypo) and mortality (ΔMortality) showed no significant correlation (p=0.83).

To explore how a reduction in BG (ΔBG) and a reduction in the percentage of patients with severe (BG < 2.2 mmol/l) hypoglycaemia (ΔHypo) may reduce mortality (ΔMortality) a two-dimensional linear regression model was formulated:

$$\Delta\text{Mortality} = a \cdot \Delta\text{BG} + b \cdot \Delta\text{Hypo} \qquad \text{Eq. 2.1}$$

The regression was performed on the data in Table 2.1, which gave the resulting regression equation (SPSS, 23.0.0.0):

$$\Delta\text{Mortality} = 3.2 \cdot \Delta\text{BG} + 0.51 \cdot \Delta\text{Hypo} \qquad \text{Eq. 2.2}$$

with the p-values of a and b being 0.05 and 0.07, respectively.

Table 2.1 Reduction in mortality, BG, and percentage of patients with severe hypoglycaemia (BG < 2.2 mmol/l) in the IIT group versus the control group.

Study	ΔBG (mmol/l)	ΔHypo (BG<2.2 mmol/l)	ΔMortality (%)	Residuals
Leuven	2.8	-4.3	9.5	-2.2
Leuven-2	2.3	-15.6	0.1	-0.5
Krinsley	1.2	0.0	6.1	-1.9
SPRINT[a]	1.2	5.2	11.3	-4.3
Arabi et al.	3.1	-25.5	3.6	-6.7
VISEP	2.2	-12.9	-4.3	4.9
NICE-SUGAR	1.6	-6.3	-2.6	4.6
Glucontrol	1.5	-6.0	-3.4	5.2
De La Rosa et al.	1.6	-7.5	-4.2	5.7
Mean (SD)	1.9 (0.7)	-8.1 (9.0)	1.8 (6.1)	0.6 (4.7)

[a] The number of patients in the control group with hypoglycaemic events was not reported, but the percentage of hypoglycaemic measurements was twice that of the intervention group. For the purpose of this regression we therefore assumed that 10.4% of patients in the control group had hypoglycaemic events, twice that of the intervention group.

Despite the a and b values in the regression formula being a little less than significant, the regression does lend some support to both the G1 and G2 hypothesis that lowering stress-hyperglycaemia improves patient care in terms of lowering mortality, in so far as hypoglycaemic events are avoided or not increased to a large degree. G2 is further supported by studies [34,35] which have shown that BG variability is a strong predictor of hospital mortality.

2.3. ENSURING ADEQUATE CALORIC INTAKE

American, European, and Canadian guidelines for the nutrition of critically ill patients recommend eucaloric feeding, i.e. that the caloric intake should match the individual patient's EE [36-38], based on studies which have shown that overfeeding by as little as 10% relative to EE can adversely affect organ function, leading to e.g. hypercapnia, metabolic acidosis, and fatty liver [4]. It has also been shown that in critically ill patients, a high caloric debt, calculated as the difference between caloric intake and the patient's actual EE, is associated with an increased

rate of adverse outcome in terms of increased number of infections [5]. This supports our N1 hypothesis, that nutrition should target 100% of patient's EE.

Despite the negative effects of caloric debt, the guidelines are more flexible concerning underfeeding than overfeeding, by allowing delayed initiation of enteral feeding by 24 hours [37] or by 24-48 hours [36,38] and by recommending a seven day delay in initiation of parenteral feeding in case the nutritional target cannot be achieved by enteral feeding alone [36]. This acceptance of a delay of supplementary parenteral nutrition may be justified by the observation that early parenteral feeding increases the rate of infection [39] but contrasts with the desire to avoid a large caloric debt.

There is still some disagreement on the subject of whether or not to underfeed the patients and whether to initiate early feeding or late feeding of the patients. Arabi et al. showed that hypocaloric feeding (approximately 60% of EE) may be associated with lower hospital mortality [40]. Artinian et al [41] and Khalid et al. [42] both showed that initiation of enteral nutrition within 48 hours of mechanical ventilation was associated with reduced ICU and hospital mortality. While the nutritional guidelines support our N1 hypothesis on eucaloric feeding and no overfeeding, there are studies [40,43] which suggest permissive underfeeding as optimal and that the early use of parenteral nutrition should be avoided. It is intuitively appealing to restrict caloric intake in the catabolic phase where plasma concentrations of glucose, lipids and amino acids is already high. It may be however that the detrimental effects of early parenteral nutrition does not reflect negatively on parenteral nutrition but on the fact that the early parenteral nutrition results in early eucaloric feeding which according to our hypothesis (N2) should be avoided, although more evidence from randomized trial is still needed to properly support the hypothesis.

CHAPTER 3. DECISION SUPPORT SYSTEMS FOR GLYCAEMIC CONTROL

Decision support systems have been developed to assist medical staff with the management of stress induced hyperglycaemia, while avoiding hypoglycaemia, in critically ill patients. These decision support systems have ranged from rule-based systems and protocols, to complex physiological mathematical models. It is our hypothesis, G3, that the use of decision support systems based on physiological models is the best method for glycaemic control.

This chapter is based primarily on Paper I which describes the Glucosafe decision support system. In addition this chapter contains descriptions of physiological models and decision support systems, including a comparison of systems.

3.1. TYPES OF DECISION SUPPORT SYSTEMS

3.1.1. RULE BASED SYSTEMS

These systems are also known as expert systems as the rules used are often set by experts in the field [44]. A type of rule based protocol is the sliding scale system which administers a set a predetermined amount of insulin at different ranges of BG (e.g. 1U/h if BG is 6-8 mmol/l and 2U/h if BG is 8-9 mmol/l). Another type is the dynamic scale which adjusts the insulin dosage by a predetermined size of change depending on the range the BG is in (e.g. if BG is 6-8 mmol/l the insulin is increased by 1U/h, if BG is 8-9mmol/l the insulin is increased by 2U/h).
Examples of rule based systems include the SPRINT system [7], which developed a set of rules based on simulations with a physiological model. Examples also include the eProtocol-insulin system which uses a set of rules to determine the rate of insulin infusion: For BG < 3.3mmol/l the rules state that the insulin infusion is discontinued. For BG ≥ 3.3mmol/l the insulin infusion rate is adjusted based on the difference between the BG target (set by clinicians) and the current BG, modulated by the rate of change in BG between the current and previous BG measurement. [45]. In section 3.4 the rule-based eProtocol-insulin system is compared to the Glucosafe system, which is based on a physiological model.

3.1.2. PHYSIOLOGICAL MODELS

In physiological models it is attempted to let the structure of the model reflect the physiology of the biological system being modelled. The majority of these systems have been based on compartmental models of insulin-glucose metabolism, using differential equations [44].

Perhaps the best known physiological model is the minimal model by Bergman et al. which was constructed with two compartments for insulin pharmacokinetics and an equation for insulin-glucose pharmacodynamics [46,47].

$$\frac{dX}{dt} = -p_2 X(t) + p_3(I(t) - I_b) \quad \text{Eq. 3.1}$$

$$\frac{dG}{dt} = -X(t)G(t) + p_1\big(G_b - G(t)\big) + P(t) \quad \text{Eq. 3.2}$$

G(t) is the plasma glucose concentration at time t, I(t) is the plasma insulin concentration, and X(t) is the interstitial insulin. G_b is the basal plasma glucose concentration, P(t) is the appearance rate of glucose from exogenous input and I_b is the basal plasma insulin concentration. Patient specific parameters p_1, p_2 and p_3 are transport rates between the various compartments with the ratio p_3/p_2 representing insulin sensitivity.

The minimal model captures the three basics of models for glycaemic control; 1) insulin pharmacokinetics and distribution, 2) Glucose appearance, and 3) the effect of insulin on removal of plasma glucose.
Most compartment models used for studies of glycaemic control have their basis in the minimal model, with compartments or equations added as necessary to improve the patient specific simulation and prediction of BG [48]. This has led to increases in physiological accuracy of the models [48].

A more complex model was developed by Hovorka et al [49] for the purpose of controlling type-1 diabetes. The model was multi-compartmental and included subsystems for insulin and glucose absorption, including subcutaneous insulin absorption, distribution, and disposal, as well as insulin action on glucose transport, disposal and endogenous insulin production. The model was designed to control insulin delivery in artificial pancreas systems. There are other models [50,51] developed for use in artificial pancreas systems [52].

Based on the minimal model but further incorporating saturation effect of plasma insulin disappearance and insulin-dependent glucose uptake a model was developed by Chase et al. and further developed into the Intensive Control Insulin-Nutrition-Glucose (ICING) model [53]. Like the Hovorka et al. model, the ICING model incorporates insulin and glucose absorption, distribution, and disposal, as well as insulin action on glucose transport and endogenous insulin production. However the ICING model was constructed for use in the ICU with intravenous insulin delivery, not subcutaneous boluses.

Prior to the development of the Hovorka et al. model and the ICING model, the Diabetes Insulin Advisory System (DIAS) model [54], was constructed to predict BG and advice on insulin dosing to manage type-1 diabetes. The DIAS model was constructed to model the uptake of glucose from the intestines, facilitated diffusion of glucose mediated by glucose transporters (GLUT-1, GLUT-3, and GLUT-4), and renal clearance of glucose. The DIAS model was constructed to incorporate insulin

saturation effects and included a patient specific parameter to model the effects of insulin sensitivity [55]. The DIAS model parameters were optimized using literature data on hepatic and endogenous glucose balance. From the DIAS model a multi-compartment model of insulin-glucose metabolism was constructed, the Glucosafe model [56]. The Glucosafe model is similar to the DIAS model but uses a more explicit compartment model of plasma and peripheral insulin concentrations and removal. And like DIAS the Glucosafe model incorporates the modelling of the non-linear effect of insulin on glucose uptake, but also models reduced gastric uptake of glucose and (as shown in chapter 5) now includes a model of pancreatic insulin secretion.

The chosen focus of this thesis is the Glucosafe model and the Glucosafe system incorporating the model.

3.1.3. MODEL PREDICTIVE CONTROL

Decision support systems for insulin therapy based on physiological mathematical models can be used to predict the outcome of a treatment. By simulating several treatments, the treatment resulting in the optimal outcome can be recommended to the decision maker. In the context of glycaemic control, the simulations are performed using a model of the insulin-glucose metabolism with the input parameters being current and previous insulin treatment, nutritional status, and BG measurements.

There are several methods to evaluate model output and adjust input where the model is used to generate an output, based on an input. One method is the proportional-integral-derivative (PID) control where the output is compared to a predetermined target output and the input is changed based on the difference between output and target. However PID control has several limitations to its use. The use of PID control presupposes linearity and, as the input is adjusted based on the output, has only a single input and a single output. Less restrictive is the Model Predictive Control (MPC) [44], where the output is compared to a predetermined target output and the input is adjusted stepwise until the model output matches the target. An example would be adjusting the insulin infusion rate until the resulting BG matches a predetermined target. However MCP is limited by only being able to evaluate the outputs of the model relative to a set target and then optimize the output by changing the input. MCP however is not capable of optimizing both inputs and outputs or compromising between several targets.

One method to manage multiple inputs and outputs (such as both insulin and nutrition inputs influencing the simulated BG) or having multiple objectives to resolve (such as wanting to lower BG to a specific target while also targeting a certain nutritional goal, for example 100% of a patients energy expenditure), is the use of utilities. Utilities can take the form of a set of equations used to evaluate both input and output and finding the best compromise between multiple objectives.

The Glucosafe system, incorporating the Glucosafe model, uses (negative) utilities in the form of a set of penalty functions to control the generation of treatment advice [57]. The penalty functions balance the administration of insulin and nutrition in an attempt to compromise between achieving normoglycaemia while neither starving nor overfeeding the patient.

3.2. THE GLUCOSAFE MODEL

The Glucosafe decision support system is based on the Glucosafe model [56] of insulin-glucose metabolism. The model and equations are shown in Fig. 3-1.
The Glucosafe model uses a two-compartment insulin kinetics model to simulate plasma insulin (I) and peripheral insulin (Q) concentrations. This is based on the endogenous production (U) and exogenous infusions (P) of insulin and the removal of insulin by the kidneys and by insulin degradation in the liver and peripheral tissue. In Glucosafe the pancreatic insulin release is a constant rate, unless the patient is a type-1 diabetic in which case the insulin release is zero.
The insulin sensitivity (s) scales the effect of insulin (a) on hepatic removal and peripheral absorption of glucose. The insulin sensitivity is a dimensionless normalized parameter so a value of one indicates normal insulin sensitivity and values below one indicate insulin resistance. In the model the estimated insulin sensitivity is assumed to be a time-varying, patient-specific parameter, which is independent of the treatment the patient is receiving.

The Glucosafe model takes patient height, weight, age, and gender into account to determine patient-specific parameters such as distribution volumes. Following the initial determination of patient-specific parameters, the variables gut content, plasma and interstitial insulin concentrations, and BG are continually modelled based on user specified inputs (i.e. BG measurements, insulin dosing, and amount and composition of nutrition), however the only parameter used to fit the model to the data (i.e. BG measurements) is the insulin sensitivity which is re-estimated every time a new BG measurement is input to the system, thus making it the only patient specific parameter allowed to vary over time.

The simulated BG concentration is a model variable that depends on insulin-mediated and insulin-independent glucose clearance from plasma and glucose uptake from intravenous infusions and carbohydrate uptake from nutrition. The insulin-mediated glucose clearance is affected by the non-linear insulin saturation function [56], and the uptake of bioavailable glucose from nutrition is scaled by a carbohydrate absorption factor (m_{gut}) to model reduced nutrient absorption in critical illness. The C-peptide/insulin kinetics parameters; k_1, A_{BSA}, V_P, and V_Q are calculated using the method presented by Van Cauter et al. [58] and the moving average function, f(.), for renal clearance is taken from Rave et al. [59]. Further information on parameters, variables, and values can be found in [56].

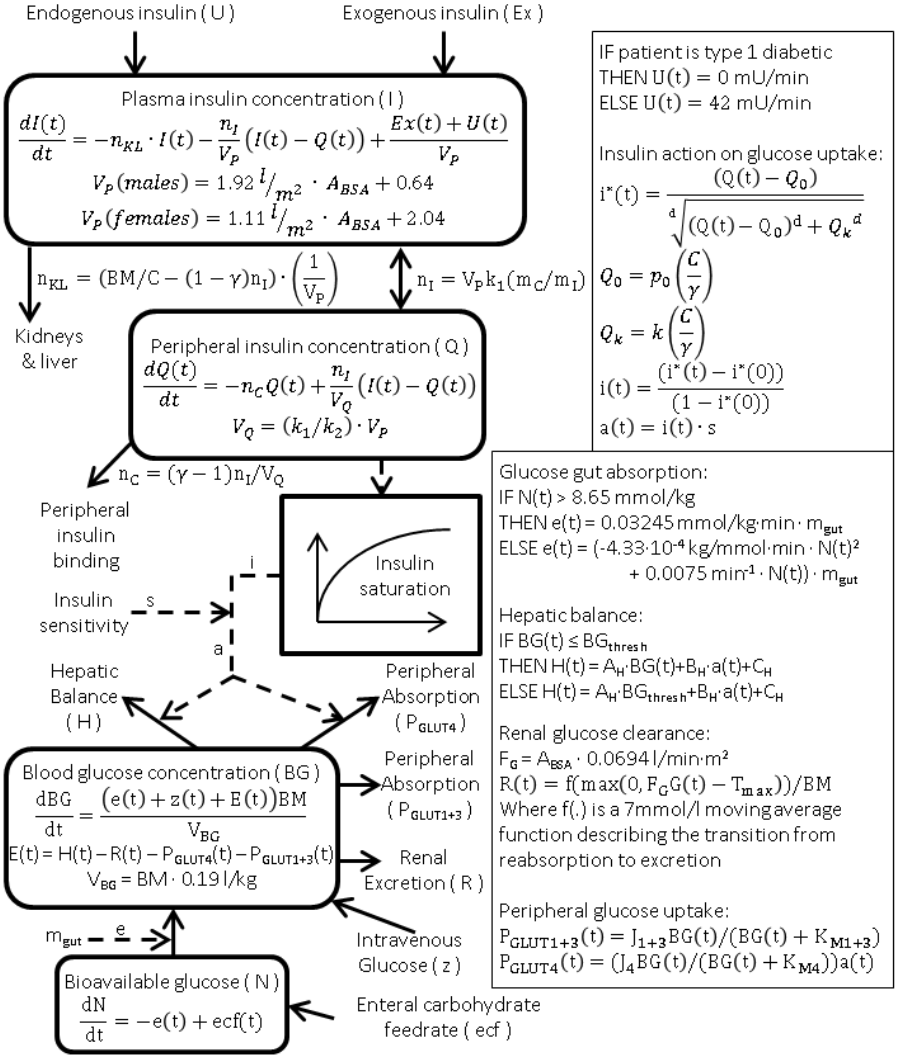

Figure 3-1 *The Glucosafe model of insulin-glucose metabolism. Solid lines indicate flows and dashed lines indicate effects of variables or parameters on other variables.*

3.2.1. VALIDITY OF THE GLUCOSAFE MODEL

To determine the validity of the model it can be tested for the ability to predict future BG concentration. This is done retrospectively using data on nutrition, insulin, and BG from patient, by having the model predict BG from one real

measurement to the next, for all measurements and all patients used. The predictive accuracy is then calculated. The relative error, $e(\Delta t_{ik})$, is calculated as:

$$e(\Delta t_{ik}) = \left| \frac{m(t_i + \Delta t_{ik}) - G(ti; \Delta t_{ik})}{m(t_i + \Delta t_{ik})} \right| \quad \text{Eq. 3.3}$$

$$\Delta t_{ik} = t_{i+k} - t_i \quad \text{Eq. 3.4}$$

$$\forall i | 1 \leq i \leq N - 1 \quad \text{Eq. 3.5}$$

$$\forall k | \Delta t_{ik} < PH \quad \text{Eq. 3.6}$$

N is the total number of BG measurements for the patient, PH is the prediction horizon (i.e. the maximum forward prediction time the prediction error is to be calculated for), Δt_{ik} is the time between two BG measurements (t_i and t_{i+k}), $G(t_i;\Delta t_{ik})$ is the model-predicted blood glucose from time point t_i and Δt_{ik} forward, and $m(t_i + \Delta t_{ik})$ is the measured BG value at Δt_{ik} time from t_i. Note that the prediction error is expected to increase with longer prediction times. Thus, the individual errors are sorted by Δt_{ik} in ascending order, and the absolute mean prediction error is calculated for two intervals of t: (1) 1 min $\leq \Delta t_{ik} \leq$ 90 min; (2) 91min $\leq \Delta t_{ik} \leq$ 180min.

The result of testing the predictive accuracy on a cohort of 12 critically ill patients in a neuro-ortho-trauma intensive care unit (NOTIA) at Aalborg University Hospital in Denmark [60] was a mean prediction error of 8.7% (1-90 min.) and 13.9% (91-180 min.). The total mean prediction error (0-180 min.) was 11.9%.

The Glucosafe model had its predictive accuracy tested and compared to a paper-based protocol from Christchurch, New Zealand [61]. Both were tested on retrospective patient data from two cohorts, one from Denmark and one from New Zealand.

The results showed very similar predictive accuracy, with the Christchurch protocol more accurately predicting the New Zealand patients and the Glucosafe model more accurately predicting the patients from Denmark.

3.3. THE GLUCOSAFE SYSTEM

The Glucosafe system uses the Glucosafe model to simulate a patient and from there, predict the patient's future BG. The main control window of the Glucosafe system is shown in Fig. 3-2.

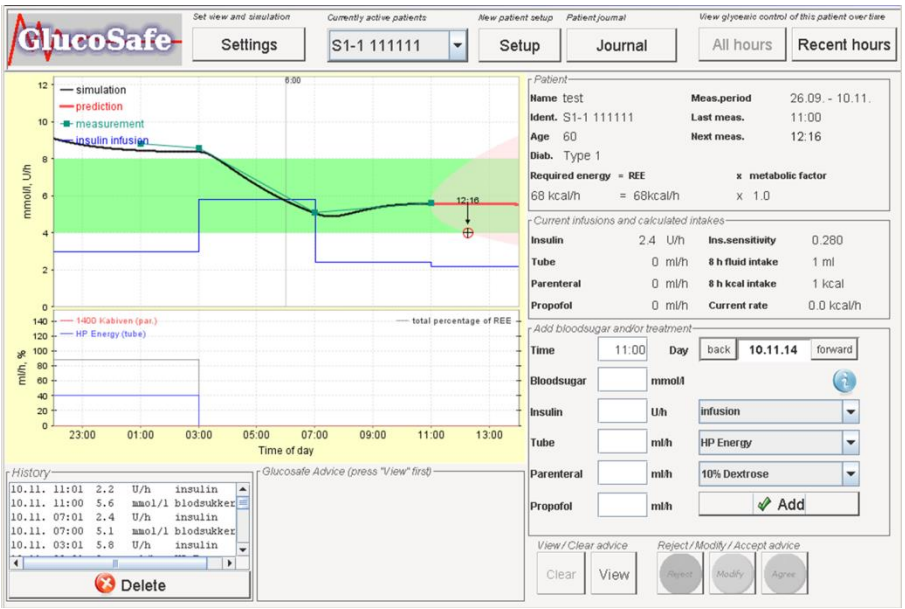

Figure 3-2 *The main control screen of the Glucosafe system with a window on the left hand side displaying measured and predicted BG, current and previous insulin infusions and nutrition. On the right hand side of the screen is information on the patients and the current treatment and several boxes for inputting changes to the current and previous treatment and BG measurements. At the bottom of the right hand side are buttons for requesting treatment advice and accepting, modifying, or rejecting the advice.*

3.3.1. TREATMENT ADVICE

Advice is shown upon user request, typically after a new blood glucose measurement. Upon a request for advice, the model predicts the blood glucose trajectory for different treatments consisting of a continuous insulin infusion rate (or insulin infusion rate and bolus size if the BG is above ten mmol/l) and either an enteral feed rate, an intravenous feed rate, or a combination of the two feed types. A penalty score rates the tested treatments and the treatment with the lowest penalty score is deemed the optimal treatment and is shown to the user. Users can either accept or reject the advice, or modify it (Fig. 3-2). In case of a modification the user overrules the advice manually, setting one or both of the recommended feed rates (enteral and intravenous) and asking for new advice based on these settings. If both feed rates have been manually set by the user, Glucosafe adjusts only the insulin to minimize the penalty score, and recommends only insulin along with the user specified nutrition.

As previously mentioned, Glucosafe uses a set of four penalty functions which evaluate the treatment objectives to determine the optimal treatment advice. Fig. 3-3 shows plots of the penalty functions used in the Glucosafe system.

Glycaemic Penalty – The penalty increases for treatments which result in the predicted BG above or below the target. The penalty increases more rapidly for BG concentrations that are below the target, in order to minimize the occurrence of hypoglycaemia. The BG target (G_0) can be set by the user. The penalty (Fig. 3-3A) is defined as:

$$f_G(G) = \left(\ln\left(\frac{G}{G_0}\right)\right)^2 \times P_G \qquad \text{Eq. 3.7}$$

where G is the predicted BG, $G_0$is the specific BG where the penalty is zero [62] (standard setting is 5.5 mmol/l), and $P_G = 22.6$ is a dimensionless scaling factor. The BG penalty used is the mean of penalties calculated from the predicted BG at one, two, three, and four hours.

Insulin Consumption Penalty – To decrease the use of excessive insulin, the use is penalized with the following function (Fig 3-3B):

$$f_I(P) = \left(\frac{(P \times C + K_m)^2}{{K_m}^2} - 1\right) \times P_I \qquad \text{Eq. 3.8}$$

where P is the insulin infusion rate (mU/(kg×min.), $C = 98.1$ kg/min.×L is a factor for converting insulin infusion rate to steady state plasma concentrations [55], $K_m = 28$ mU/L is a Michaelis-Menten saturation constant [63], and $P_I = 0.00916$ is a dimensionless scaling factor.

Mucosal Damage Penalty – To maintain functional intestinal mucosa, the amount of nutrition administered enterally is maximized using the following function (Fig. 3-3C):

$$f_D = (N_{enteral} - 1)^2 \times P_D \qquad \text{Eq. 3.9}$$

where $N_{enteral}$ is the fraction of the EE that is administered enterally and $P_D = 1$ is a dimensionless scaling factor. EE is the caloric intake needed to cover 100% of the patient's energy expenditure.

Nourishment Penalty – In Glucosafe the EE of the patient is estimated using the Mifflin St Jeor equation based on height, weight, age, and gender, multiplied by a user selected Stress Factor (SF) to accommodate the hypermetabolism usually seen in the critically ill. The following function (Fig. 3-3D) is used to penalize under- or over-feeding relative to the estimated EE:

$$f_C(N_{total}) = (N_{total} - 1)^2 \times P_N \qquad \text{Eq. 3.10}$$

where N_{total} is the total nutrition administered, as a percentage of EE, and $P_N = 1$ is a dimensionless scaling factor. The values of the scaling factors shown here are different from those previously published [57], though the ratio between them are the same. This is because the values here have been normalized so that P_D and P_N are equal to one.

The dimensionless scaling factors used in the four equations were derived by a simulation of steady state BG from combinations of insulin and nutrition, over a range on insulin sensitivities. From there a treatment target was set for each insulin sensitivity and then minimizing the sum of squares of the difference between Glucosafe advice and the set advice targets [57].
A grid search of the possible treatment combinations of insulin and nutrition is used to minimize the sum of these penalties and the treatment advice on nutrition and insulin resulting in the lowest combined penalty is shown to the user.

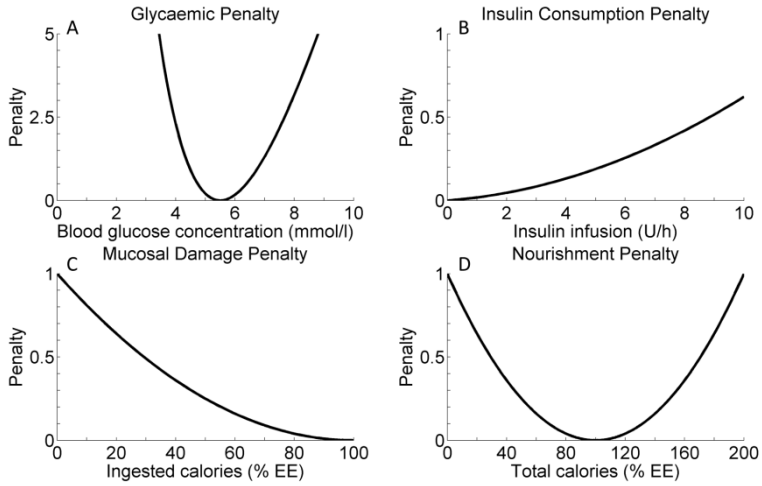

Figure 3-3 *The four penalty functions used by the Glucosafe system to determine the treatments advice resulting in the lowest combined penalty.*

3.4. PERFORMANCE OF THE GLUCOSAFE SYSTEM

To examine if our hypothesis (G3) that decision support systems based on physiological models is the best method to lower hyperglycaemia while avoiding hypoglycaemic events the Glucosafe system has been tested in three different clinical studies (including Paper I of this thesis, which this chapter is based upon) and compared to other models and systems. Glucosafe is compared to both other computer based systems and paper based systems, some of which are model-based and some of which are not.

As seen from Table 3.1, the Glucosafe system has, in all three clinical trials, been able to lower BG without any hypoglycaemic events.

Table 3.1. Comparison of glucose control trials. Above the thick line are trials using computer-based decision support, below the line are paper based trials.

	BG (mmol/l) Mean (SD) Median (IQR)		Patients with hypoglycaemia Mild (BG < 3.3 mmol/l) Severe (BG < 2.2 mmol/l)	
Trial	Intervention	Control	Intervention	Control
Glucosafe 1 [60]	7.0 (± 1.2) 7.1 (6.3-7.9)	8.0 (± 1.2) 8.0 (7.0-9.1)	0.0% 0.0%	0.0% 0.0%
Glucosafe 2 [62]	7.0 (± 1.1) 7.2 (6.6-8.2)[a]	8.6 (± 2.4) 8.0 (6.9-6.9)[a]	0.0% 0.0%	0.0% 0.0%
Glucosafe 3 [64]	5.8 (± 1.0)[a] 5.6 (5.0-6.6)	7.8 (± 1.8)[a] 7.8 (6.6-8.7)[a]	0.0% 0.0%	0.0% 0.0%
LOGIC-1 [65]	5.9 (± 0.5)	--	14.1% 0.0%	17.9% 3.3%
STAR-Liege 2 [66]	-- 7.4 (6.5-8.4)	-- 8.6 (6.9-9.5)	0.0% 0.0%	0.0% 0.0%
Leuven 1 [3]	5.7 (±1.0) --	8.5 (± 1.8) --	-- 5.1%	-- 0.8%
SPRINT [7]	6.0 (±1.5) --	7.2 (± 2.4) --	-- 5.2%	-- --
Glucontrol [31]	-- 6.5 (6.0-7.2)	-- 8.0 (7.1–9.0)	-- 8.7%	-- 2.7%
NICE-SUGAR [30]	6.6 (± 1.4) --	-- --	74.2% 6.8%	15.8% 0.5%
Krinsley [6]	7.3 (±3.1) 6.6 (5.5-8.2)		1.02% 0.34%	

[a] Unpublished data

Table 3.1 shows a comparison of Glucosafe and two other trials using computer based systems, the LOGIC-1 trial and the STAR-liege 2 trial. While the LOGIC-1 trial achieved lower BG than two of the Glucosafe trials it also had 14.1% of patients experiencing mild hypoglycaemic events (defined as BG < 3.3 mmol/l). The STAR-Liege-2 trial avoided hypoglycaemic events but was inferior to Glucosafe in terms of lowering BG. This indicates that Glucosafe performs better than the other computer-based systems in terms of lowering BG while avoiding hypoglycaemic events.

With reference to hypothesis G3, that model-based systems are better able to lower hyperglycaemia while avoiding hypoglycaemia, Table 3.1 clearly indicates this, as all the trials using paper-based systems show the occurrence of hypoglycaemic events. Further support to the hypothesis is a direct comparison of Glucosafe and the rule-based eProtocol-insulin system [45]. The Glucosafe system consistently provided more favourable recommendations on insulin use based on data from 408

critically ill patients treated using the eProtocol-insulin system, supporting hypothesis G3.

Overall Glucosafe has shown the ability to lower BG while avoiding any hypoglycaemic events. The Glucosafe 3 study was the most successful in lowering BG, reaching BG concentrations similar to the Leuven 1 study (5.7 mmol/l), but where the Leuven study had 5.1% of patients with hypoglycaemic events, the Glucosafe 3 study had no hypoglycaemic events. That the third Glucosafe study achieved lower BG than the previous two Glucosafe studies is most likely because the patients were fed very little, some only receiving intravenous glucose, and as Glucosafe was not allowed to advise on nutrition the patients continued to receive little nutrition when treated with Glucosafe.
These studies evaluating the Glucosafe system, and the comparison to other studies, supports our hypothesis (G3) that the use of physiological models and decision support systems can be beneficial in glycaemic control and a better tool than non-model based systems. However if model-based decision support systems are to be the best tool to optimize treatment of critically ill patients then there needs to be a method of adapting the model/system to different patient cohorts.

CHAPTER 4. EVALUATING MODIFICATIONS TO THE GLUCOSAFE SYSTEM

Glucosafe has two major components: the model and the advice module. As previously mentioned the Glucosafe model can be (and has been) evaluated by determining its predictive accuracy, i.e. its ability to minimize the distance between predicted and measured blood glucose concentrations. This can be done from retrospectively collected data and the effects of modifications to the model can conveniently be tested by evaluating the modified model on the same retrospective data. Evaluation of the Glucosafe system's ability to control BG (i.e. how good is the advice offered by Glucosafe) is more complicated. This is (and has been) done by conducting a clinical trial, where the Glucosafe system is allowed to recommend insulin and nutrition to a patient cohort and then determining the performance of the system on this cohort in terms of the clinical goals for blood glucose, nutrition, and insulin.

As stated in chapter 2, hyperglycaemia is treated using insulin to lower the BG. While Glucosafe has been shown to reduce hyperglycaemia in clinical trials [60,62], in two of those studies the goal of reducing the mean BG into the target band of 4.4 – 6.1 mmol/l was not achieved, even though G_0 in the glucose penalty function was set to 5.5 mmol/l (section 3.3.1, Eq. 3.7). This happens because the Glucosafe advice minimizes the sum of all four penalty functions, which necessitates compromises in each of the four penalty functions. For example, increasing the insulin dosing will lower the BG, thus simultaneous reducing the BG penalty and increasing the insulin consumption penalty. If the user of Glucosafe actually prefers to reduce BG, even at the expense of a higher insulin consumption penalty, this can practically be achieved by changing the balance between the two penalties, for example by scaling down the insulin consumption penalty. Since there are four interacting penalty functions, finding out which modifications to make to the penalty functions to achieve a specific treatment target, in order to optimize the treatment of a patient cohort or to best accommodate department guidelines, could be problematic as this would require further clinical trials which are expensive and time consuming. The purpose of this chapter is to describe a method for adjusting the relative scaling of the penalty functions without clinical trials. The chapter is primarily based on Paper II, though with some results omitted for brevity.

4.1. VIRTUAL PATIENTS

It is possible to test and compare the outcome of changes to the advice generator using virtual patients constructed from actual patients treated by Glucosafe.
Virtual patients have been used in the design and testing of IIT protocols [67,68]. Others have developed them for evaluating type-1 diabetes treatments [69,70] and in critical care [71].

As previously mentioned a study using Glucosafe in an ICU achieved a significantly lower BG compared to the control group (see Table 3.1, Glucosafe 1). However the study failed to achieve the targeted 4.4 – 6.1 mmol/l BG range [60]. As an example of how the virtual patients can be used to select settings of the penalty functions likely to produce a desired outcome in terms of mean BG and frequency of hypoglycaemic events, several modifications to the penalty functions were tested to find the settings resulting in a mean BG in the 4.4 – 6.1 mmol/l range. The virtual patients were constructed from six patients treated according to Glucosafe advice (intervention group) and six control subjects from the previously mentioned study [60]. The virtual patients were constructed with the same model and penalty functions as used during the clinical study.

4.2. VIRTUAL PATIENTS AND THE GLUCOSAFE SYSTEM

The virtual patients are based on insulin sensitivity profiles from patients previously treated using Glucosafe. The profiles are generated from the insulin sensitivity estimated for every BG measurement entered into the Glucosafe system. As the insulin sensitivity is assumed to be independent of the treatment the patient is receiving it can be used to describe a specific patient's insulin responsiveness over time. An example of an insulin sensitivity profile is given in Fig. 4-1, where insulin sensitivity is recalculated whenever a new blood glucose measurement is entered into the Glucosafe system.

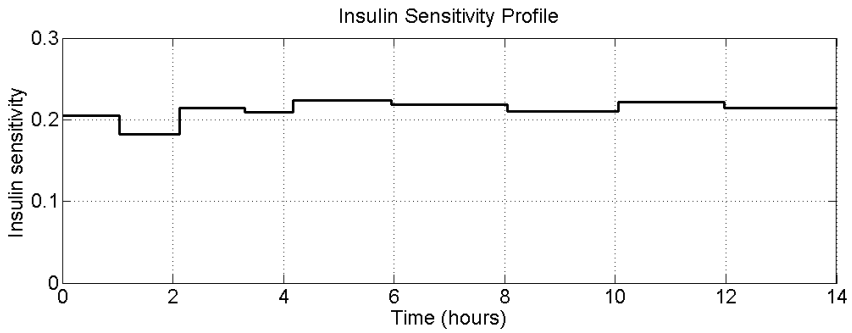

Figure 4-1 *Example of a 14 hour insulin sensitivity profile from a patient.*

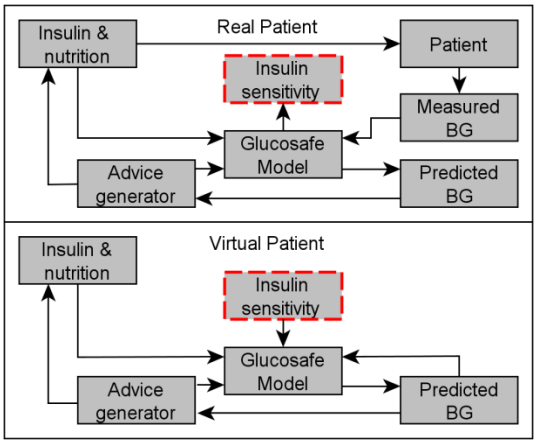

Figure 4-2 *Diagram of the Glucosafe system when used for advice generation with real patients and when used for testing with virtual patients. Insulin sensitivity is estimated by Glucosafe during real-time use, based on the patient's measured BG and the amount of nutrition and insulin the patient has been receiving. The insulin sensitivity estimated during real patient use is then forced upon the system during virtual patient generation.*

Fig. 4-2 shows a diagram of Glucosafe when used in real-time with patients and when using virtual patients. In real-time, an amount of insulin and nutrition is given to the patient with a resulting measured BG. The measured BG and administered insulin and nutrition amounts are used by the Glucosafe model to estimate the insulin sensitivity at that specific time. As previously mentioned, a grid search of the possible treatment combinations of insulin and nutrition, and the resulting predicted BG four hours ahead, is input into the penalty functions, to generate an advice for new insulin and nutrition amounts.

In the virtual patient the insulin sensitivity profile previously estimated from the real patient is used by the Glucosafe model to simulate BG during subsequent testing. With the insulin sensitivities read from the insulin sensitivity profile, a single BG measurement from the patient is used as a starting point and Glucosafe is asked for an advice on insulin and nutrition. The advice is followed and at the time-point for the next BG measurement, the BG predicted by the model is used instead of the measured BG. Using the predicted BG as a starting point the insulin sensitivity is read from the insulin sensitivity profile, and a new advice is requested.

This method results in a cohort of virtual patients, based on real patients, where model predicted BG is used in lieu of measured BG, and as the insulin sensitivity profile is meant as a profile of patient behaviour independent of treatment, the treatment advice given by Glucosafe is what determines the patients BG over time. This means that different settings for the penalty function governing advice generation can be compared by analysing the outcome of the virtual patient cohort, e.g. the mean BG, or which settings result in a desired treatment outcome.

4.3. EVALUATING MODIFICATIONS USING VIRTUAL PATIENTS

A patient cohort was managed with Glucosafe [60] with the penalty function settings listed in section 3.3.1, (G_0 = 5.5 mmol/l) seeking to reduce the cohort mean BG to between 4.4 and 6.1 mmol/l. A mean BG of 7.0 mmol/l was achieved. Several different modifications were made to the penalty functions which govern treatment advice and then the modifications were tested for their influence on glycaemic control on the set of virtual patients derived from the cohort. The purpose of testing several modifications was to determine which set of modifications was required to achieve a mean BG between 4.4 and 6.1 mmol/l in the cohort of virtual patients.

The following modifications were tested:

Glycaemic Penalty – The BG where the penalty is zero (G_0), was lowered from 5.5 mmol/L to 5.25 mmol/L, which is the middle of the 4.4 – 6.1 mmol/l band. This results in higher penalties for BG above the target (Fig. 4-3A).

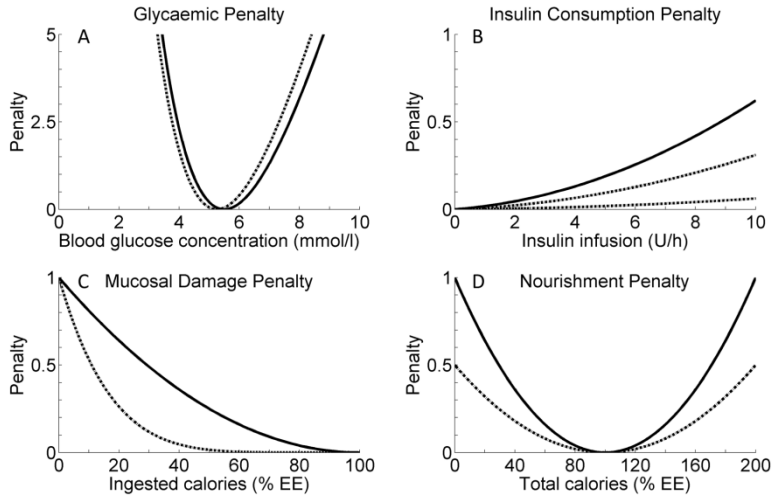

Figure 4-3 The penalty functions used in the Glucosafe system to find the treatment advice. The solid lines are the original penalty functions. The dashed lines are the modified penalty functions.

Insulin Consumption Penalty – Two different changes were made to the insulin dose penalty function by lowering P_I (section 3.3.1, Eq. 3.8) with a factor of two and ten (Fig. 4-3B).

Mucosal Damage Penalty – The function was modified to be raised to the sixth power instead of the second power:

$$f_D = (N_{enteral} - 1)^6 \times P_D \qquad \text{Eq. 4.1}$$

This changes the shape and overall lowers the Mucosal Damage Penalty (Fig. 4-3C).

Nourishment penalty – P_N (section 3.3.1, Eq. 3.10) was reduced by a factor of two which lowers the penalty for over and underfeeding the patient (Fig. 4-3D).

4.4. RESULTS

As the use of virtual patients rests on the assumption that the underlying model is sufficiently accurate in predicting BG, first the real and virtual patients were compared in order to validate the virtual patients. This was done by determining if virtual patients, using the same treatment advice setting as used on the real patients, would result in a similar outcome in terms of BG, insulin use, and nutrition. There were some deviations between the virtual patients and the real patients, primarily due to the real patients having cessations of insulin and nutrition administration that the virtual patients did not replicate. Despite this there were no significant differences between the real and the virtual patients in insulin use or nutrition nor in the log-normally distributed BG. As such, all 12 virtual patients were deemed usable to evaluate modifications. The virtual patient cohort had a mean BG of 6.5 mmol/l before any modifications were tested. Modifying the penalty functions gave the results:

- Lowering G_0 to 5.25 mmol/l reduced BG to 6.3 mmol/l.
- Reducing the insulin dose penalty by a factor of 2 had no impact on BG; reducing the insulin dose penalty by a factor 10 lowered BG to 6.4 mmol/l.
- Reducing the mucosal damage penalty lowered BG to 6.3 mmol/l.
- Reducing the nourishment penalty lowered BG to 6.4 mmol/l.

As none of the modifications tested resulted in decreasing the BG for the cohort into the 4.4-6.1 mmol/l band, combinations of modifications were tested.

The full results of the accuracy testing and the results of the individual modifications can be found in Paper II.

The modifications of the penalty functions were evaluated by comparing results from the 12 virtual patients before and after the modifications. The biggest effects on mean BG were seen by lowering the glycaemic target and by lowering the mucosal damage and nourishment penalties. Combining these three modifications resulted in a mean BG of 5.9 mmol/l for the cohort with 54% of BG measurements in the target BG band, compared to 39% without any modifications. The consequence was a lowering of the administered nutrition (from 79% to 60% of estimated EE) and a 0.6 U/h decrease in insulin usage, from 5.4 U/h to 4.8 U/h. The combined modifications resulted in a mean BG of 5.9 mmol/l, which is within the 4.4-6.1 mmol/l band, with seven of the twelve virtual patients having a mean BG in the band.

This compares well with the Leuven study [3] which achieved a mean BG of 5.7 mmol/l, considering that the study reported only morning BG which has been shown to be lower than BG measured later in the day [72].

The lowest BG in the virtual patient cohort was 3.6 mmol/l reduced to 3.3 mmol/l with the combined modifications. Using the definitions of hypoglycaemia from Table 3.1, this measurement touches the limit of mild hypoglycaemia. There were no events of severe hypoglycaemia compared to the 5% of patients (39 out of 765 patients) in the Leuven study which experienced hypoglycaemic events.

The results show that the use of virtual patients as a tool, is suited to optimize treatment in a clinical study after an initial pilot study or as a tool to continually optimize treatment in a clinical setting, although it will remain necessary to verify in a new set of real patients that the proposed modifications of the advice algorithm produce similar results in real patients as in virtual patients.

CHAPTER 5. MODELLING PANCREATIC INSULIN RELEASE

The Glucosafe model has previously been tested for accuracy and performed well, both in clinical trial and while testing the accuracy of the virtual patients. However as mentioned, the cornerstone of the usability of virtual patients is the predictive accuracy of the underlying model and while Glucosafe may perform well in its current configuration, it does not model pancreatic insulin release other than as a constant release.
The body's own method of managing hyperglycaemia is by releasing variable amounts of insulin from the pancreas, and the relationship between BG and pancreatic insulin secretion is complex. In the Glucosafe model the pancreatic insulin release was modelled as a constant release regardless of the patient's BG concentration [56]. This was not a problem as the patients treated with Glucosafe had high BG's resulting in a high and almost constant endogenous insulin release. However if Glucosafe is to model patients during their recovery phase, where they may have lower BG, a model of BG dependent insulin release must be included. To do this a model of pancreatic insulin release was constructed. This chapter gives the results from Paper III, with some results omitted for brevity.

5.1. PANCREATIC INSULIN RELEASE

The pancreas model was based partly on previous studies and models of pancreatic insulin release. Cerasi and Luft [19] found a dual-phase insulin release (i.e. a phase-1 and phase-2 response) in healthy humans during glucose infusion tests and Porte and Pupo [73] found evidence of a two-pool insulin system.
Their findings indicate that pancreatic insulin release is a dual-compartment, dual-phase process, with the phase-1 insulin response being dependent on the rate of rise of BG (dBG/dt) and the phase-2 response being dependent on the BG concentration, in a sigmoidal relationship.

There have previously been constructed models of insulin secretion; Grodsky [74] built a model of pancreatic insulin secretion with two insulin compartments. The compartments were modelled with a larger stable compartment containing 98% of the stored insulin and a smaller labile compartment containing 2% of the stored insulin. Transport between the compartments was governed by the BG with insulin secretion occurring from the labile compartment only. Hovorka et al. [75] also constructed (as part of a model of glucose regulation) a model of insulin secretion. Like the Grodsky model, the model by Hovorka et al. only modelled the phase-2 response, using a linear relationship between BG and endogenous insulin release.

Inclusion of a pancreatic model with insulin release being dependent on BG, creates a negative feedback loop. In any system, a feedback loop with an absolute value of

the loop gain (|LG|) larger than one has the potential to make the system unstable, resulting in oscillations or damped oscillations. While neither the Grodsky nor the Hovorka model was tested for stability, Steil et al. [76] performed stability tests with models of insulin secretion by combining them with a one-compartment insulin kinetics model and a minimal model of glucose kinetics [47].
Previous Glucosafe simulations with a pancreas model with only a phase-2 response, showed that if the BG of a person with normal insulin sensitivity was perturbed by a glucose injection over a 10 min. period, then BG and insulin release responded by a damped oscillation [77].

If a pancreas model is to be included in the Glucosafe model, then it needs to be stable before any testing of prediction accuracy can be performed. Thus further testing was performed on the inclusion of a pancreas model in the Glucosafe system, evaluating the stability of Glucosafe with a dual-phase, dual compartment, pancreas model including both a phase-1 and phase-2 response (the Phase 1+2 model).

5.2. THE PANCREAS MODEL

The new pancreas Phase 1+2 model, incorporated into the Glucosafe model, is shown in Fig. 5-1, with the pancreas model highlighted in red.

The total endogenous insulin release is both the phase-1 (P_1) and phase-2 (P_2) response with the exception of type-1 diabetes patients, where endogenous insulin production is assumed to be zero.
The phase-1 response is proportional to the rate of change of BG, and to the amount of insulin in insulin reservoir 2 (R_2). K_2 is a constant.
The phase-2 response is a sigmoid curve that describes the rate of endogenous insulin release as a non-linear dependency on the BG concentration, BG(t). The sigmoid relationship between BG and insulin secretion has been shown experimentally by Henquin et al. [78].

The curve was fitted to the data shown in Fig. 5-3. The negative insulin release modelled at low BG concentrations is not indicative of negative insulin release, but can be seen as a glucagon release as this has the effect of increasing BG. R_{1max} and R_{2max} are the maximum contents of the respective reservoirs and R_{total} is the maximum amount of stored insulin. As in the Grodsky model [74], R_{1max} and R_{2max} limits the maximum content of compartments R_1 and R_2 to 98% and 2% of R_{total}, respectively.

With this model the endogenous insulin production is dependent on the BG through a negative feedback loop. An increase in BG results in increasing endogenous insulin production that counteracts the rise in BG.

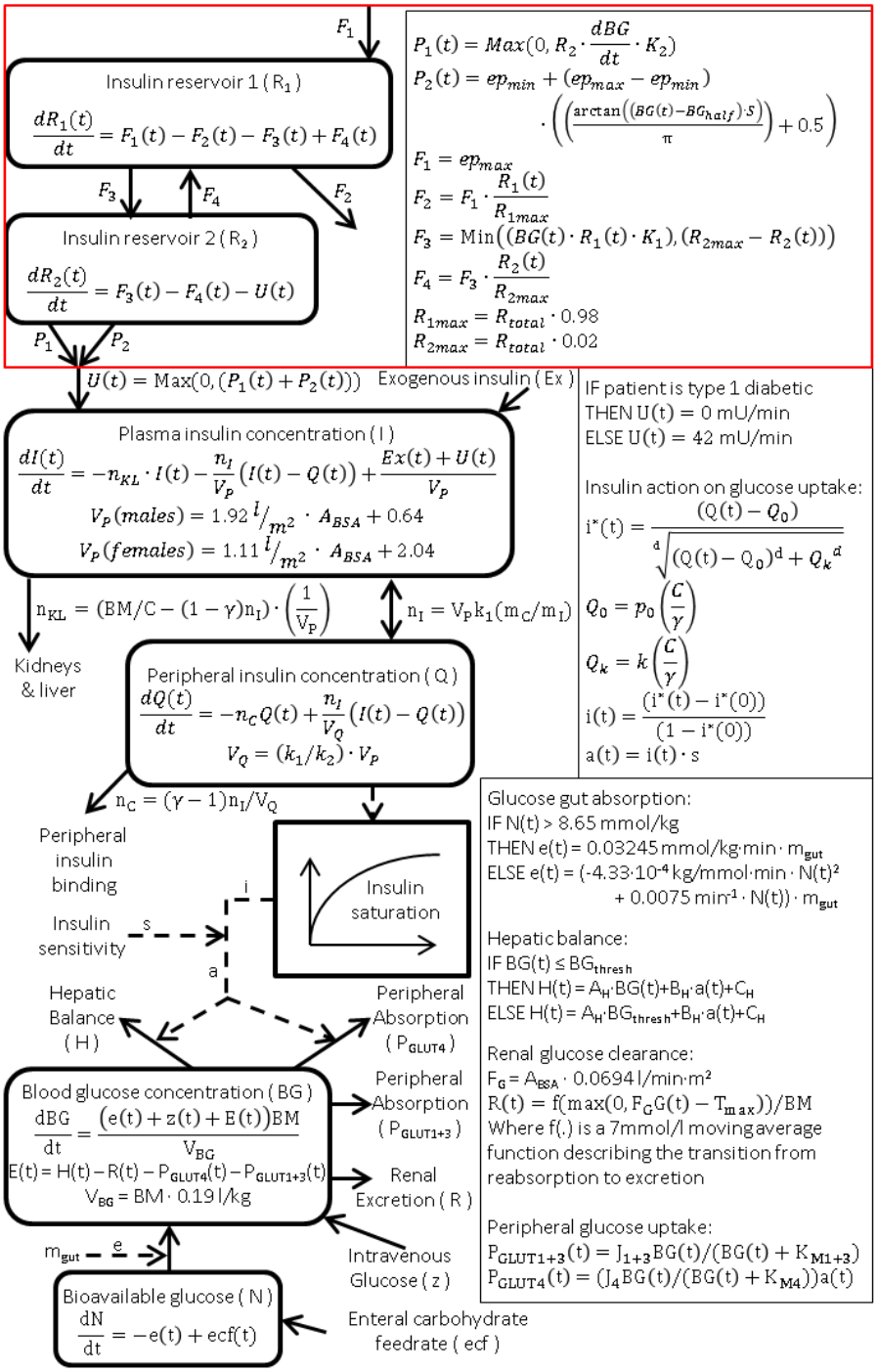
F1
Insulin reservoir 1 (R1)
dR1(t)/dt = F1(t) − F2(t) − F3(t) + F4(t)
F3
F4
F2
Insulin reservoir 2 (R2)
dR2(t)/dt = F3(t) − F4(t) − U(t)
P1
P2
U(t) = Max(0, (P1(t) + P2(t)))
Exogenous insulin (Ex)
P1(t) = Max(0, R2 · dBG/dt · K2)
P2(t) = epmin + (epmax − epmin) · ((arctan((BG(t) − BGhalf) · S))/π + 0.5)
F1 = epmax
F2 = F1 · R1(t)/R1max
F3 = Min((BG(t) · R1(t) · K1), (R2max − R2(t)))
F4 = F3 · R2(t)/R2max
R1max = Rtotal · 0.98
R2max = Rtotal · 0.02
IF patient is type 1 diabetic
THEN U(t) = 0 mU/min
ELSE U(t) = 42 mU/min
Plasma insulin concentration (I)
dI(t)/dt = −nKL · I(t) − nI/VP (I(t) − Q(t)) + (Ex(t) + U(t))/VP
VP(males) = 1.92 l/m² · ABSA + 0.64
VP(females) = 1.11 l/m² · ABSA + 2.04
nKL = (BM/C − (1 − γ)nI) · (1/VP)
nI = VP k1 (mC/mI)
Kidneys & liver
Peripheral insulin concentration (Q)
dQ(t)/dt = −nC Q(t) + nI/VQ (I(t) − Q(t))
VQ = (k1/k2) · VP
nC = (γ − 1)nI/VQ
Insulin action on glucose uptake:
i*(t) = (Q(t) − Q0) / ∜((Q(t) − Q0)⁴ + Qk⁴)
Q0 = p0 (C/γ)
Qk = k (C/γ)
i(t) = (i*(t) − i*(0))/(1 − i*(0))
a(t) = i(t) · s
Peripheral insulin binding
Insulin sensitivity
s
i
a
Insulin saturation
Hepatic Balance (H)
Peripheral Absorption (PGLUT4)
Glucose gut absorption:
IF N(t) > 8.65 mmol/kg
THEN e(t) = 0.03245 mmol/kg·min · mgut
ELSE e(t) = (-4.33·10⁻⁴ kg/mmol·min · N(t)² + 0.0075 min⁻¹ · N(t)) · mgut
Hepatic balance:
IF BG(t) ≤ BGthresh
THEN H(t) = AH·BG(t)+BH·a(t)+CH
ELSE H(t) = AH·BGthresh+BH·a(t)+CH
Blood glucose concentration (BG)
dBG/dt = (e(t) + z(t) + E(t))BM / VBG
E(t) = H(t) − R(t) − PGLUT4(t) − PGLUT1+3(t)
VBG = BM · 0.19 l/kg
Peripheral Absorption (PGLUT1+3)
Renal Excretion (R)
Renal glucose clearance:
FG = ABSA · 0.0694 l/min·m²
R(t) = f(max(0, FG G(t) − Tmax))/BM
Where f(.) is a 7mmol/l moving average function describing the transition from reabsorption to excretion
mgut
e
Intravenous Glucose (z)
Bioavailable glucose (N)
dN/dt = −e(t) + ecf(t)
Enteral carbohydrate feedrate (ecf)
Peripheral glucose uptake:
PGLUT1+3(t) = J1+3 BG(t)/(BG(t) + KM1+3)
PGLUT4(t) = (J4 BG(t)/(BG(t) + KM4))a(t)

Figure 5-1 *The Glucosafe model of insulin-glucose metabolism, including the model of pancreatic insulin release (marked in red). Solid lines indicate flows and dashed lines indicate effects of variables or parameters on other variables. The model differs from the model in Fig. 3-1 with the addition of the pancreas model which changes the insulin release (U) from a constant to being determined by P1 and P2 as shown (i.e. dependent on BG concentration and rate of change in BG).*

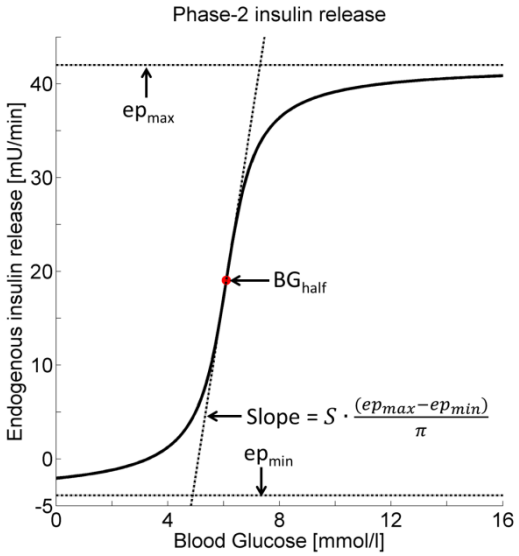

Figure 5-2 *The phase-2 response of the pancreas model, illustrating the sigmoid relationship between BG and insulin secretion. The equation for the phase-2 response curve is shown in Fig. 5-1 (P_2) where ep_{min} and ep_{max} are asymptotes to $P_2(t)$ and together with S, determine the slope at BG_{half}. Parameter values are shown in Table 5.1.*

5.3. TESTING THE PANCREAS MODEL

The pancreas model was fitted to BG and plasma insulin data from 14 healthy adults (mean age 38.5 ±3.7, mean weight 70.1 kg), using a grid search programmed in Matlab. The subjects received three meals over the course of one day, and Polonsky et al. [79,80] collected 58 BG and plasma insulin measurements from each subject over a 24 hour period. The mean values of the BG and plasma insulin measurements from the 14 subjects were used to optimize the shape of the sigmoid curve (phase-2), the magnitude of the phase-1 response (K_2), the dependence of insulin movement from R_1 to R_2 on BG (K_1), and R_{total}. Using the BG changes from the data, the resulting plasma insulin calculated by Glucosafe was compared to the mean values from the patient data and the model was fitted to minimize the Root Mean Square Error (RMSE) between the 58 measured and modelled plasma insulin concentrations.

5.3.1. LOOP GAIN

The steady-state loop gain of Glucosafe with each of the two pancreas models was calculated in the following manner:

(1) Using either insulin infusions or intravenous glucose infusions a specific steady-state BG_0 was obtained and the steady-state endogenous insulin production U_0 was noted.
(2) A new steady-state endogenous production rate (U_0 + ε) with ε = U_0/10 was set as a fixed insulin release and the steady-state BG and the resulting endogenous insulin production (U_0 + δ) was simulated.
(3) The loop gain was then calculated as: LG = |δ/ε|.

5.3.2. POST-PERTURBATION OSCILLATIONS

At the BG resulting in the largest loop gain, and thus where the model is potentially the least stable, the model was tested for the occurrence of oscillations in BG and insulin secretion following an initial perturbation of BG (post-perturbation oscillations). The post-perturbation oscillations were examined for two insulin sensitivities representing the "insulin-resistant" state and the "insulin-normal" state. For the "insulin-resistant" state a reduced insulin sensitivity of 0.3 was chosen as is often seen in critically ill patients [77]. For the "insulin-normal" state a value of 1.0 for insulin sensitivity was chosen. The perturbation was an intravenous glucose infusion over ten min. resulting in a one mmol/l increase in BG. The subsequent oscillations in BG and endogenous insulin production were simulated by the Glucosafe model and described by the period and the time constant (τ) for the decay of the oscillations.

5.4. RESULTS

5.4.1. FITTED MODEL PARAMETERS

The plasma insulin data from the healthy subjects and the fitted pancreas model can be seen in Fig. 5-3.
The fitting of the pancreas model to plasma insulin data resulted in parameter values as shown in Table 5.1.

Table 5.1. Fitted parameter values for the Phase 2 and Phase 1+2 models

Parameter	Value Phase 1+2 model	Unit
ep_{min}	-3.9	mU/min.
ep_{max}	42	mU/min.
BG_{half}	6.1	mmol/l
S	1.3	mU/min.·(mmol/l)$^{-1}$
K_1	0.0009	l·mmol^{-1}·min.$^{-1}$
K_2	0.57	l·mmol^{-1}
R_{total}	16800	mU

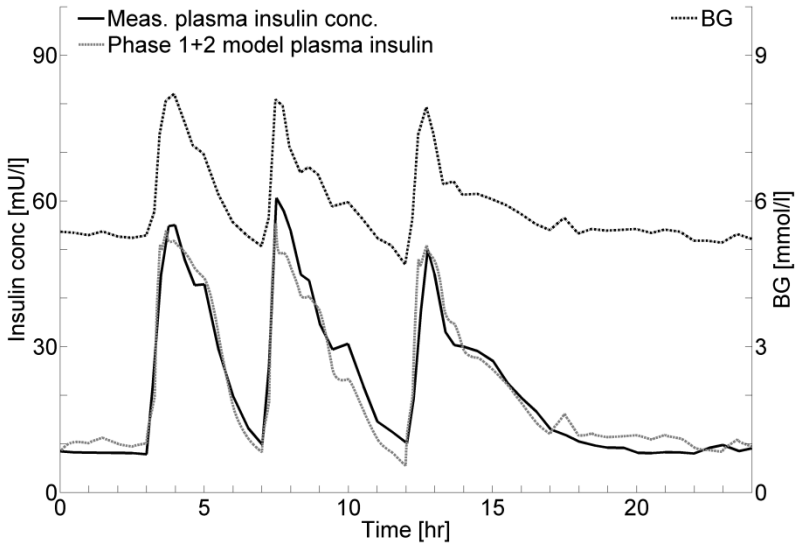

Figure 5-3. *24-hour profile of mean BG and mean plasma insulin concentrations from 14 healthy subjects receiving meals* [79], *and the plasma insulin concentrations simulated with the Glucosafe model using the optimized Phase 1+2 pancreas model. Figure adapted from* [81].

5.4.2. LOOP GAIN RESULTS

The loop gain of the phase 1+2 model was calculated for steady state BG concentrations of 3.0 mmol/l to 10 mmol/l, for the two different levels of insulin sensitivity. The maximal LG with an insulin sensitivity of 0.3 was 4.0 at a BG of 6.3 mmol/l and with an insulin sensitivity of 1.0 the maximal loop gain was 6.6 at a BG of 6.0 mmol/l. Fig. 5-4 shows the change in loop gain for the model.

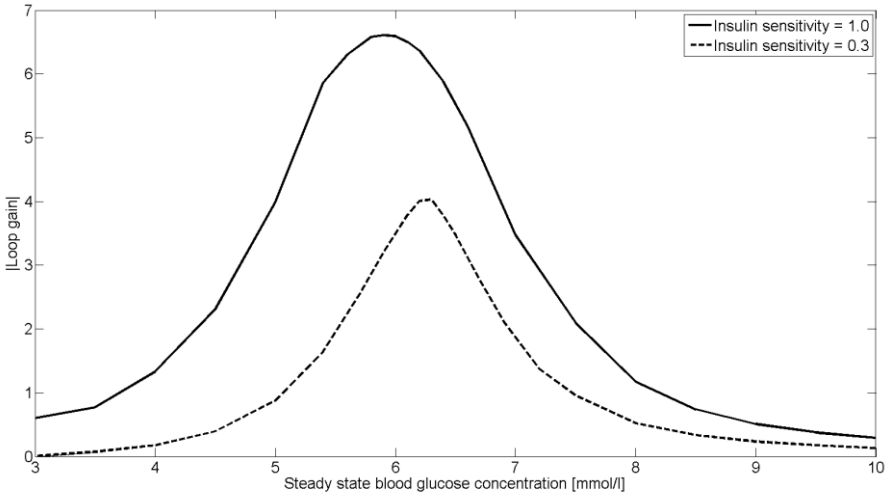

Figure 5-4 *Calculated loop gain at different pairs of steady state blood glucose and insulin sensitivity. Figure adapted from* [81].

5.4.3. POST PERTURBATION OSCILLATIONS

As the maximal loop gain (i.e. where the model is potentially most unstable) was observed at a steady state BG of 6.0 mmol/l and an insulin sensitivity of 1.0, the model was tested for post perturbation oscillations from that steady state BG. The result was an occurrence of damped oscillations. Fig. 5-5 shows a comparison of the post-perturbations oscillations in BG and insulin release for the model (with an insulin sensitivity of 1.0 and 0.3).
The damping of post-perturbation BG oscillations was described by fitting an exponential function to the envelope of the first two oscillations. Using the following equation:

$$E(t) = -1.30\ \text{mmol/l} \cdot \exp^{-t/40\ \text{min.}} + 6.0\ \text{mmol/l} \qquad \text{Eq. 5.1}$$

The time constant τ of the envelope was 40 min. for the pancreas model, at a normal insulin sensitivity of 1.0. The envelope is plotted along with the post perturbation BG oscillations in Fig. 5-5.

As seen in Fig. 5-5, the BG perturbation resulted in damped oscillations, but despite a loop gain greater than one, the pancreas model proved stable with a time-constant of the damping of 40 min. In Paper III the model shown here was compared to a model with only a phase-2 response. The Phase 2 model resulted in longer lasting oscillations compared to the Phase 1+2 model shown here and had an envelope time constant of 92 min.

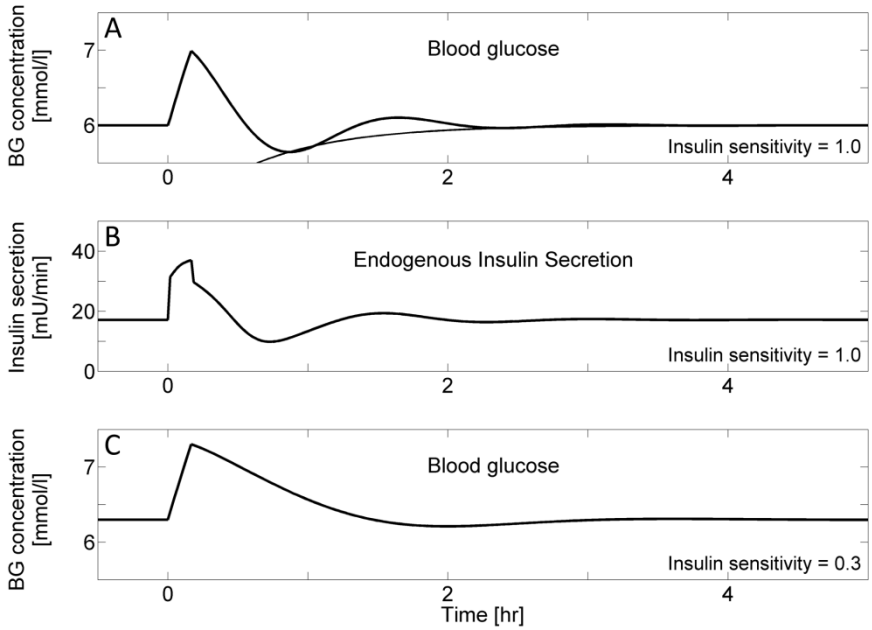

Figure 5-5 *Post-perturbation curves for blood glucose (A with insulin sensitivity of 1.0 and C with insulin sensitivity of 0.3) and (B) endogenous insulin release for the Phase 1+2 pancreas model with insulin sensitivity of 1.0. The thinner line (A) is the envelope fitted to the first two oscillations. The initial perturbation was a one mmol/l increase in BG over ten min., from a steady state BG of 6.0 mmol/l. Figure adapted from* [81].

What remains to be investigated is to which extent the Phase-1+2 model improves the accuracy of BG predictions. In Paper I [60] an early version of the Phase 2 model was tested for improvement in predictive accuracy compared to a constant insulin release. The result was only a marginal improvement, likely because the patient cohort was critically ill and over 60% had a BG above 7 mmol/l and thus there was little difference between the constant release and the phase-2 release. As stated in the beginning of this chapter the Phase 1+2 model is expected to improve predictive accuracy of the Glucosafe system in patients with lower BG.

CHAPTER 6. ENERGY EXPENDITURE IN THE ICU

Glucosafe has thus far been constructed to offer advice on insulin and nutrition in order to achieve normoglycaemia in critically ill patients. The system has been tested for its ability to lower BG and has proven that capability and using virtual patients has shown the possibility of achieving normoglycaemia in a patient cohort, through increased insulin usage and a decrease in the amount of nutrition administered. As stated previously, Glucosafe estimates the EE of the patient using the Mifflin St Jeor equation, multiplied by a user selected SF. However if Glucosafe is to offer advice on nutrition then the estimation of EE should be accurate. With regard to hypothesis N1 and N2 of this thesis, studies have shown that overfeeding by as little as 10% relative to actual EE can adversely affect organ function, leading to e.g. hypercapnia, metabolic acidosis, and fatty liver [4] and conversely a high caloric debt, calculated as the difference between caloric intake and the patient's actual EE, has been associated with a high rate of complications and adverse outcome [5]. If the goal is not to overfeed the patient (N1) and in the first day of critical illness not to feed the patient 100% of EE (N2), then the EE needs to be accurately determined. The N3 hypothesis states that predictive equations cannot accurately determine EE but that VCO_2-based calorimetry can. To test this hypothesis some commonly used predictive equations and the VCO_2-based calorimetry is compared to indirect calorimetry (IC) measurements and the results compared to other results from literature.

6.1. DETERMINATION OF ENERGY EXPENDITURE

The determination of a patient's EE can aid clinicians when they prescribe nutrition as caloric needs differ from person to person and with type (sepsis, trauma/surgery, burns) of insult [25,26,82]. The reference method to determine EE is IC [83], which estimates EE using measurements of oxygen consumption (VO_2) and VCO_2. However, the use of IC is limited both by cost of equipment and by demand on resources (e.g. time, equipment and staff) [84,85].

The use of a caloric intake based on EE determined by predictive equations is recommended when IC cannot be used. However reviews by Tatucu-Babet et al. [86] and Frankenfield et al. [87] of the extensive body of literature, which compares various predictive equations to IC, conclude that predictive equations are often inaccurate. Both reviews found that 12% of the reviewed predictive equations overestimated EE by more than 10% and underestimation was even more frequent with 38% of the equations underestimating EE by more than 10%. Most of the studies evaluating the Harris-Benedict equation use an SF ranging from 1.13 to 1.6.

This large range of SF may partially be due to interindividual differences, but also to systematic variations of SF due to the severity and type (sepsis, trauma/surgery, burns) of insult [25,26,82] as well as the time elapsed since the insult [25,26].

Hence, there is a need for an accurate and easy method to estimate EE, as it can help clinicians prescribe caloric intake during the late phase of critical illness [88]. A possible suitable option is the calculation of EE from VCO_2 alone, "VCO_2-based calorimetry", routinely measured by capnometers connected to the ventilatory circuit in mechanically ventilated patients [89]. VCO_2-based calorimetry has previously been tested using a modified Weir equation [90], to make the EE estimation dependent on VCO_2 and the Respiratory quotient (RQ) and then individualized by estimating the patient RQ from nutritional intake [91,92].

As there is evidence that both over- and under-feeding is harmful, accurate determination of EE becomes vital, if Glucosafe is to offer nutritional advice. However the predictive equation Glucosafe uses may not be accurate in estimating EE. As such there are two questions relevant to hypothesis N3:

1) Can the poor performance of predictive EE equations be confirmed in our cohort of patients?
2) Can the estimation of EE be based on VCO_2?

6.2. COMPARISON OF PREDICTIVE EQUATIONS, VCO_2-BASED CALORIMETRY, AND INDIRECT CALORIMETRY

As IC is considered the reference method for estimating EE, the predictive equations and the VCO_2-based calorimetry, were compared to IC measurements. Both IC and VCO_2-based calorimetry rely on the assumption that the rates of ventilated O_2 and CO_2 reflect the rate of O_2 consumption and CO_2 production, respectively. However, EE(IC) and EE(VCO_2) calculated from instantaneous values of VO_2 and VCO_2 may be erroneous in situations where respiratory VO_2 and VCO_2 are not equal to the metabolically consumed O_2 or produced CO_2, respectively. Therefore VCO_2-based calorimetry and IC was assessed for possible sources of error in EE estimation, both qualitatively and quantitatively, and as VCO_2-based calorimetry is based on the choice of an RQ value, a sensitivity analysis was performed.

The comparison was performed using measurements from patients at a mixed medical/post-surgical ICU at Erasme University Hospital of Brussels, Belgium. Eighteen mechanically ventilated patients, 18 years or older, were included as soon as possible after ICU admission. Height, gender, body mass, temperature, diagnosis, mode of ventilation, APACHE 2 score at admission [93], and mode of sedation were recorded. VO_2, VCO_2, End Tidal CO_2 (ET-CO_2), Fraction of inspired O_2 (FiO_2), Minute Volume (MV), and RQ were measured over a 30-min. period. The metabolic monitor used was a Compact Airway Module, E-CAiOVX mounted in a

Compact Anaesthesia Monitor (GE Healthcare, Little Chalfont, Buckinghamshire, UK), which offers breath-by-breath VCO_2 and VO_2 measurements [94]. The Compact Airway Module determines VCO_2 and VO_2 within ±10% when FiO_2 < 65% [95].
EE was determined, using the Weir equation (3):

$$EE(IC)=(5.5\ \text{min/ml} \cdot VO_2 + 1.76\ \text{min/ml} \cdot VCO_2 - 1.99\ \text{day/g} \cdot N)\ \text{kcal/day} \quad \text{Eq. 6.1}$$

with a standard setting of N = 13 g/day [95], as ureic nitrogen was not measured in the study, yielding:

$$EE(IC) = (5.5\ \text{min/ml} \cdot VO_2 + 1.76\ \text{min/ml} \cdot VCO_2 - 26)\ \text{kcal/day} \quad \text{Eq. 6.2}$$

In this study this was used as the reference method, against which other EE estimates were compared.

6.2.1. PREDICTIVE EQUATIONS AND VCO_2-BASED CALORIMETRY

The equation for estimating EE based on VCO_2 was constructed from Eq. 6.2, with VO_2 substituted by:

$$VO_2 = VCO_2/RQ \quad \text{Eq. 6.3}$$

This gives the modified Weir equation:

$$EE(VCO_2) = \left((5.5\ \text{min/ml} \cdot RQ^{-1} + 1.76\ \text{min/ml}) \cdot VCO_2 - 26\right)\text{kcal/day} \quad \text{Eq. 6.4}$$

VCO_2 measurements used in the EE(IC) and EE(VCO_2) estimations are both derived from the metabolic monitor. Differences between EE(IC) and EE(VCO_2) must either be due to an incorrect assumption about RQ or due to variations in ventilation. Variations in ventilation will cause different variations in EE(IC) and EE(VCO_2) because the time constant for VCO_2 equilibration is much longer (10-20 min.) [96,97] than the time constant for VO_2 equilibration (2-3 min.) [98].

The accuracy of the EE(VCO_2) estimates and of some commonly used predictive equations (Table 6.1) were compared to EE(IC).
The value of SF, used for the cohort with the Harris-Benedict equation (b, Table 6.1) was calculated using the following equation:

$$SF = \text{mean EE(IC)} / \text{mean EE(HB)} \quad \text{Eq. 6.5}$$

The SF for methods c and d (Table 6.1) were similarly determined using their respective mean EE. The result is that the mean EE for the 18 patients determined by each method equals the mean EE(IC) determined by Eq. 6.2 (the reference method).

The ideal body mass (IBM) was calculated from the Hamwi equations [99]:

$$\text{Men: IBM} = 48.0\ \text{kg} + 2.7\ \text{kg} \cdot (\text{height} - 1.524\ \text{m}) / 0{,}0254\ \text{m} \quad \text{Eq. 6.6}$$
$$\text{Women: IBM} = 45.5\ \text{kg} + 2.2\ \text{kg} \cdot (\text{height} - 1.524\ \text{m}) / 0.0254\ \text{m} \quad \text{Eq. 6.7}$$

Table 6.1: Predictive equations for estimation of EE		
	Method	Equation
a	ACCP	The ACCP equation [36-38] using BM as the only variable EE(ACCP) = 25 kcal/kg/day · BM
b	Harris-Benedict	The Harris-Benedict equation from 1919 [100] multiplied by a SF Men: EE(HB) = (66.5 + 13.75 kg^{-1} · BM + 5.003 cm^{-1} · height - 6.775 yr^{-1} · age) kcal/day · SF Women: EE(HB) = (655.1 + 9.563 kg^{-1} · BM + 1.85 cm^{-1} · height - 4.676 yr^{-1} · age) kcal/day · SF
c	Harris-Benedict IBM	The Harris-Benedict equation with ideal body mass (IBM) multiplied by a SF Men: EE(HBI) = (66.5 + 13.75 kg^{-1} · IBM + 5.003 cm^{-1} · height - 6.775 yr^{-1} · age) kcal/day · SF Women: EE(HBI) = (655.1 + 9.563 kg^{-1} · IBM + 1.85 cm^{-1} · height - 4.676 yr^{-1} · age) kcal/day · SF
d	Mifflin St Jeor	The Mifflin St Jeor equation [101] multiplied by a SF Men: EE(MSJ) = (9.99 kg^{-1} · BM + 6.25 cm^{-1} · height - 4.92 yr^{-1} · age + 166) kcal/day · SF Women: EE(MSJ) = (9.99 kg^{-1} · BM + 6.25 cm^{-1} · height - 4.92 yr^{-1} · age – 161) kcal/day · SF
e	Penn State 1	The original Penn State equation from 1998 [102] EE(PS1) = 1.1·HB + (32 min·l^{-1}· MV + 140 C^{-1}·T_{Max} – 5340) kcal/day
f	Penn State 2	Version 2 of the Penn State equation from 2003 [103] EE(PS2) = 0.85·HB + (33 min·l^{-1}·MV + 175 C^{-1}·T_{Max} – 6433) kcal/day
g	Penn State 3	Version 3 of the Penn State equation from 2003 [103] EE(PS3) = 0.96·MSJ + (31 min·l^{-1}·MV + 167 C^{-1}·T_{Max} – 6212) kcal/day
ACCP: American College of Chest Physicians, T_{Max}: Maximum body temperature in 24 hours [°C].		

6.2.2. STATISTICAL ANALYSIS

To assess the bias of each method (the predictive equations and EE(VCO_2)), the difference in percent between mean EE for the method and mean EE(IC) was calculated. The significance was tested by a two-tailed paired t-test. The assumption of normal distribution of tested variables was assessed with the Shapiro-Wilk test.

RMSE was used to describe the quality of the predictions for each method. A comparison of EE(VCO_2) and each predictive equation was performed by an F-test over the prediction errors relative to EE(IC).

To determine the how often the methods resulted in accurate predictions of EE, the number of patients with accurate predictions was compared between EE(VCO_2) and each predictive equation, with per-patient EE estimates defined as accurate if the estimate was within ±10% of the IC measurement. Testing for significant differences was performed using Fisher's exact test. Significance level for all tests was $p < 0.05$.

6.2.3. SENSITIVITY ANALYSIS OF RQ

The practical use of VCO_2-based calorimetry relies on a choice of RQ. A sensitivity study of the effect of the choice of RQ was conducted. In six studies [82,103-108] the average reported cohort values for RQ ranged from 0.76 to 0.89. These minimum and maximum values and the extreme range of the physiological range (0.7 to 1.0) [92] were used in the sensitivity analysis.

6.2.4. QUALITATIVE ANALYSIS OF DYNAMIC ERRORS

As mentioned both IC and VCO_2-based calorimetry rely on the assumption that the rate of ventilated O_2 and CO_2 is reflecting the rate of O_2 consumption and CO_2 production, respectively. A mismatch however may occur when the patient's metabolism changes rapidly, or due to changes in the patient's ventilation. The VCO_2-based calorimetry should only be used if the patients EE is constant over the measurement period. To determine if a patient had constant EE, the trend line for the VO_2 recording was compared with the average VO_2 over the recording period. If the absolute difference between the trend line and the average was less than 10% of the average VO_2, the patient was considered to have constant EE throughout the recording period.

From the patients with constant EE, an example patient was selected and a descriptive analysis of the reasons for errors was performed by inspection of the 30 min. recordings of MV, VCO_2, VO_2, and ET-CO_2 and comparing these to the changes in EE(IC), and EE(VCO_2).

Quantitative analysis of dynamic errors
As the EE(IC) and EE(VCO_2) estimation may be affected by changes in ventilation, the two methods' vulnerability to changes in ventilation was analyzed and compared. For each patient the maximum deviation of EE from the mean EE was calculated for both EE(IC) and EE(VCO_2). The effect of a five min. moving average on the calculated EE was explored by comparing the maximum EE deviations from mean EE, for both EE(IC) and EE(VCO_2), before and after its application.

6.3. RESULTS

The 18 patients included had a mean age 61±17 years, five were women. Average VO_2 for the 18 patients was 343±77 ml/min. and average VCO_2 was 273±63 ml/min, giving an average RQ of 0.81. The mean FiO_2 was 42% with no patient exceeding 50%. All patients received intravenous glucose during the measurement period and patients 1, 2, 3, 14, 17, and 18 received enteral nutrition. The mean RQ for the patients receiving enteral nutrition (0.86) was significantly higher ($p<0.05$; t-test, unpaired, two-tailed) than the mean RQ (0.79) for the patients not receiving enteral nutrition. Individual patient specifics can be found in Paper IV upon which this chapter is based [109].

Table 6.2. Comparison of EE estimates to IC including sensitivity of EE(VCO_2) reliance on RQ.
The bias in percent is relative to the mean EE(IC). The range of estimation differences is the maximum and minimum difference between the equations and individual mean EE(IC). The RMSE of EE difference is the root mean square error of EE difference between the equations and the IC measurements. Accurate EE estimates are defined as per-patient EE within ±10% of EE(IC).

Equation	Mean EE (Bias) kcal/day	Range of estimation differences	RMSE of EE difference	# of patients with accurate EE estimates (%)
ACCP	1889 (-20%)*	[-49 %; 22 %]	28 %†	6 (33 %)‡
Harris-Benedict	2347 (0%)	[-20 %; 61 %]	16 %†	9 (50%)‡
Harris-Benedict, IBM	2347 (0%)	[-23 %; 76 %]	18 %†	8 (35 %)‡
Mifflin St Jeor	2347 (0%)	[-18 %; 68 %]	15 %†	9 (50 %)‡
Penn State 1	1782 (-24%)*	[-41 %; 0 %]	27 %†	1 (6 %)‡
Penn State 2	1572 (-33%)*	[-49 %; -10%]	35 %†	1 (6 %)‡
Penn State 3	1637 (-30%)*	[-43 %; -9%]	32 %†	1 (6 %)‡
EE(VCO_2) RQ=0,81	2332 (-1%)	[-13 %; 14 %]	7 %	16 (89 %)
EE(IC)	2347 (0%)	-	-	-
Sensitivity analysis of RQ				
EE(VCO_2) RQ=0,70	2626 (12%)*	[-2 %; 30 %]	12 %	9 (50 %)‡
EE(VCO_2) RQ=0,76	2455 (5%)*	[-8 %; 20 %]	8 %	14 (78 %)
EE(VCO_2) RQ=0,85	2244 (-4%)	[-16 %; 10 %]	6 %	16 (89 %)
EE(VCO_2) RQ=0,89	2163 (-8%)*	[-19 %; 6 %]	10 %	10 (56 %)
EE(VCO_2) RQ=1,00	1976 (-16%)*	[-26 %; -3 %]	17 %	4 (22 %)‡

* Significantly different from mean EE(IC).
† Significantly greater variance than EE(VCO_2) RQ=0.81.
‡ Significantly different from EE(VCO_2) RQ=0.81.

All predictive equations, a through g, largely over- and underestimated the reference EE value (see Fig. 6-1). The Penn State equation and the ACCP equation had the largest bias, while the ranges of estimation difference were largest for the ACCP, Harris-Benedict, and Mifflin St Jeor equations (Table 6.2). The SF values

used in the Harris-Benedict (1.55 for actual body mass, 1.67 for IBM) and Mifflin St Jeor (1.59) equations resulted in these equations having no bias, but the quality of prediction was poor for all predictive equations, as shown by a 15% or greater RMSE. The accuracy was also poor for all predictive equations with all of them having 50% or less of patients with accurate EE estimates.

The EE(VCO_2) was significantly better than the predictive equations. The mean EE(VCO_2), with an RQ value of 0.81, was not significantly different from mean EE(IC) and the EE(VCO_2) had a lower RMSE compared to the other predictive equations. The EE(VCO_2) had accurate estimates in 89% of the patients, significantly better than the predictive equations.
The sensitivity analysis showed that as long as the RQ is chosen within the range of published cohort values, 0.76 to 0.89, the VCO_2-based calorimetry performs better than the predictive equations.

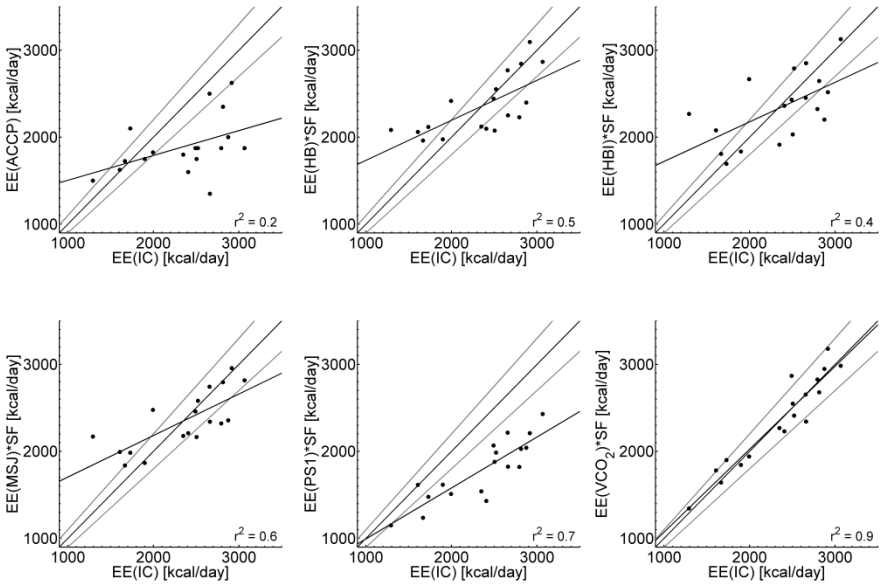

Figure 6-1 *Scatterplots for the predictive equations and the VCO_2-based calorimetry, comparing them to IC.*

6.3.1. QUALITATIVE ANALYSIS OF DYNAMIC ERRORS

Of all 18 patients, 17 were found to have constant EE during the recording period.

Fig. 6-2 shows ten min. of data from an example patient with constant EE during the 30 min. recording period (patient 16). In the figure a change in ventilation is clearly visible. The MV is a steady state until 7.5 min. when the MV is lowered and

the measurement fluctuates until 10.5 min. when the MV reaches a lower steady state (fig 6-2A). The measurements of VCO_2 and VO_2 also fluctuate leading to changes in estimated EE for both the IC and the VCO_2-based calorimetry (Fig. 6-2B), however there is no reason to suspect that the patient's EE changes during this period, so the fluctuations of EE(IC) and EE(VCO_2) must be ascribed to the fluctuations of MV. In the 7.5 min. to 10.5 min. period, MV increases to 36% higher than the steady-state value at 7.5 min. This results in increases in VO_2 and VCO_2 of 22% and 34%, respectively and similar increases in EE(IC) and EE(VCO_2) of 24% and 35%, respectively.

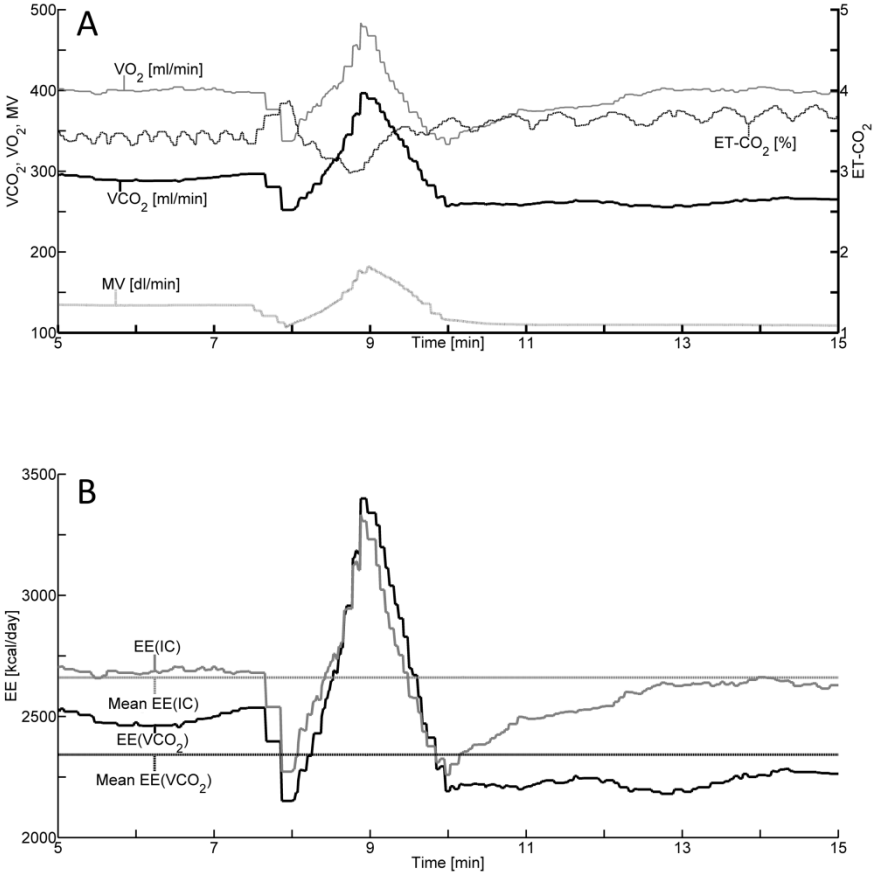

Figure 6-2 A: *Recorded values from patient 16 of VCO_2, ET-CO_2, VO_2, and MV. B: EE(VCO_2) and EE(IC) calculated from recorded VO_2 and VCO_2, including means of EE(VCO_2) and EE(IC). Modified from (*[109]*, Fig. 3).*

From 10.5 min. until 13.5 min. VO_2 returns to the steady state value seen before the change in ventilation, and similarly the EE(IC) returns almost the steady state in the

same timeframe. However VCO_2 does not return to steady state due to the 10-20 min. equilibration time constant and as such the EE(VCO2) does not return to its original steady state value either. This shows that changes in MV results in similar changes in EE(IC) and EE(VCO_2) but EE(VCO_2) takes 10-20 min. or more to recover.

6.3.2. QUANTITATIVE ANALYSIS OF DYNAMIC ERRORS

The effects of changes in ventilation were determined for each patient with stable EE in the recording period. Individual values can be found in Paper IV upon which this chapter is based.
Both EE(IC) and EE(VCO_2) are vulnerable to changes of ventilation with a maximum deviation of up to 42% for instantaneous values of EE(IC) and 46% for instantaneous values of EE(VCO_2). Both methods are equally vulnerable with no significant differences (t-test) between the mean of the max values for the two methods. This implies that instantaneous values of EE(IC) and EE(VCO_2) cannot safely be used to assess EE.

However the application of a five min. running average to the calculated EE(IC) reduced the max deviation to 18% and the Standard Deviation (SD) of the mean to 7.5%. For EE(VCO_2) the max deviation was reduced to 14% and the SD of the mean to 7.3%.
Thus the introduction of a five min. running average reduced the dynamic error of the EE(VCO_2) to a size comparable to the RMSE of EE difference.
If practical another solution is the use of mean values from 24 hour measurements as this will smooth out short term errors.

The results seem to confirm hypothesis N3: The predictive EE equations tested here (including the Mifflin St. Jeor equation used in Glucosafe) were all inaccurate (± 10%) compared to IC measurements in more than 50% of the patients. In contrast VCO_2-based calorimetry was accurate in 89% of the patients, though some caution should be taken when using short measurement periods.

CHAPTER 7. DISCUSSION AND CONCLUSION

The pathophysiology of critical illness is complex and often results in stress-hyperglycaemia which can be treated using IIT to reduce the BG to normal (or near-normal) levels, though at the risk of hypoglycaemic events.

In the introduction of this thesis a set of hypotheses regarding the treatments of stress-hyperglycaemia (hypotheses G1, G2, and G3) and nutritional support (hypotheses N1, N2, and N3) for the critically ill patient was formulated. Evidence concerning these hypotheses in published literature and the research presented in this thesis was examined.

With regards to hypothesis G1 and G2, stating that reducing hyperglycaemia while avoiding hypoglycaemia is beneficial to critically ill patients, there is some literature support. All studies using IIT have shown reduced BG, but some have resulted in reduced mortality and some in increased mortality. In the studies showing increased mortality, it is likely due to the negative effect of substantially increased frequency of patients with hypoglycaemic events, overshadowing the positive effects of lowering the BG. A regression analysis of the studies, while not significant, indicates support for hypothesis G1 and G2, that reducing hyperglycaemia correlates with reduced mortality and that hypoglycaemia should be avoided as this increases mortality.

Hypothesis G3 states that the best way to lower BG while avoiding hypoglycaemia is the use of a model-based decision support system. Several studies using decision support systems were compared and in all studies the group treated using decision support had lower BG, although some had increased numbers of hypoglycaemic events. Comparison of model-based systems and rule-based systems showed the model-based system to have better results, with Glucosafe showing the best results with lowered BG and no hypoglycaemic events, lending support to the G3 hypothesis. In addition, clinical testing of Glucosafe has showed it to reduce variability of BG compared to departmental guidelines.

Glucosafe has two major components, the model and the advice module. The model's predictive accuracy can be tested and improved on retrospective data, but testing of the advice module in principle requires a clinical trial. To reduce the need for clinical trials, a method based on virtual patients was developed. The virtual patients were based on insulin sensitivity profiles from real patients and were used to evaluate different settings of the penalty functions that govern Glucosafe's treatment advice. As an example of how this method can be used several different modification to the penalty functions was evaluated to find the settings, likely to produce a desired outcome in terms of mean BG and frequency of

hypoglycaemic events. Glucosafe with these modified settings may then be worthy of a new clinical trial.

A pancreas model of endogenous insulin release was developed for the purpose of improving Glucosafe's ability to predict BG and thus improving the support for the G3 hypothesis. As the pancreas model introduced a feedback loop into the Glucosafe model it was tested for stability and found to produce damped oscillation after sudden changes in BG. An early version of the pancreas model, the results of which can be found in Paper I, showed no improvement in predictive accuracy, but was tested on critically ill patients with high BG and with administration of large insulin doses. Further clinical testing is needed to investigate if the pancreas model improves predictive accuracy in patients who are recovering from critical illness.

The hypotheses stated that nutritional support should target 100% of the patient's EE (N1) without overfeeding, to avoid or lessen caloric debt, except in the first few days (N2) where the body catabolism provides the necessary substrates to cover energy needs. There is support for not overfeeding patients as this has been shown this to have deleterious effects and although there are studies advocating underfeeding patients, the American, European, and Canadian guidelines for nutrition support the N1 hypothesis that nutritional support should target 100% of a patient's EE to avoid or lessen caloric debt. With regards to restricting feeding in the first few days, there is no counter indication to the N2 hypothesis that nutrition should be reduced in the first few days where the body catabolism provides the necessary substrates to cover energy needs.
However, regardless of the nutritional target being 100% of EE of less, an accurate estimation of a patient's EE is needed.

Both literature reviews of predictive equations and the results shown in Paper IV shows that predictive equations are often inaccurate and over- or underestimate patients' EE compared to IC, which is considered the golden standard of estimating EE. The VCO_2-based calorimetry results presented here shows that VCO_2-based calorimetry gives EE estimates significantly better than predictive equations. A sensitivity analysis showed that as long as the RQ value used in the equation for VCO_2-based calorimetry is within the published range of average cohort values, 0.76 to 0.89, the VCO_2-based calorimetry performs better than the predictive equations. There are some problems in using only VCO_2 as a measure for EE, as changes in ventilation which result in VCO_2 not matching metabolically produced CO_2, results in EE estimation errors lasting up to 20 min. due the CO_2 equilibration time constant. Solutions to this is either the application of a running average of five min. or more to the measurements if the measurement period is short, or the use of the mean values from 24 hour measurements if possible.

The use of VCO_2-based calorimetry has been shown in other studies to work in children [110] and adults [91] with patients specific RQ values estimated from the nutrition. The results presented here and those in literature support the N3

hypothesis and indicate that VCO_2-based calorimetry should be favoured over predictive equations when estimating a patient's EE.

In conclusion there seems to be support for, or no direct evidence to oppose, the 6 hypotheses stated in the introduction, either through published literature or the work presented in the thesis.

7.1. FUTURE WORK

There are three major points of future work to be addressed, all of which involve clinical testing of Glucosafe. Glucosafe has thus far been clinically tested for the ability to safely lower BG but the hypotheses and modification to Glucosafe presented in this thesis has not been clinically tested yet. There is a need for clinical testing to prove that using Glucosafe lowers mortality, the clinical testing of the pancreas model, and Clinical testing of hypothesis N1 and N2 to find the optimal nutritional treatment for the critically ill.

The regression analysis performed on several studies indicated that lowering BG without increasing hypoglycaemic events decreases mortality. While clinical studies of Glucosafe have not evaluated mortality, Glucosafe has been shown to lower BG without any hypoglycaemic events and therefore the expectation is that using Glucosafe results in lowered mortality. There is however a need to clinically test this, to prove the expectations. In addition such clinical testing may also show computer-based system have the added benefit of making it easier to keep track of current and previous treatment, both in terms of glycaemic control, but also for nutritional support. A computerized system would also make it easier to track nutritional inputs, patient EE, and caloric debt, on a continuous basis, compared to paper-based systems.

There is also a need to clinically validate the pancreas model on patients that are recovering from critical illness. The model has thus far been tested for stability but there is need of a study to test if the addition of the pancreas model, not just improves the predictive capabilities of Glucosafe, but if Glucosafe is able to model less critically ill patients.

As hypotheses N1 and N2 has not been proven and as there is not a consensus on the optimal nutritional treatment for critically ill, there is a need to clinically test the hypotheses, if permissive underfeeding in the early state of critical illness and then targeting the patients EE later improves patient outcome, including an accurate estimation of patient EE using either IC or VCO_2-based calorimetry.

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