Model-based Insulin and Nutrition Administration for Tight Glycaemic Control in Critical Care

J. Geoffrey Chase[1], Geoffrey M. Shaw[2], Thomas Lotz[1], Aaron LeCompte[1], Jason Wong[1], Jessica Lin[1], Timothy Lonergan[1], Michael Willacy[1], Christopher E. Hann[1]

[1] University of Canterbury, Department of Mechanical Engineering, Centre for Bio-Engineering, Private Bag 4800, Christchurch, New Zealand

[2] Christchurch School of Medicine and Health Sciences, University of Otago, Christchurch, New Zealand; and Dept of Intensive Care Medicine, Christchurch Hospital, Christchurch, New Zealand

Objective: Present a new model-based tight glycaemic control approach using variable insulin and nutrition administration.

Background: Hyperglycaemia is prevalent in critical care. Current published protocols use insulin alone to reduce blood glucose levels, require significant added clinical effort, and provide highly variable results. None directly address both the practical clinical difficulties and significant patient variation seen in general critical care, while also providing tight control.

Methods: The approach presented manages both nutritional inputs and exogenous insulin infusions using tables simplified from a model-based, computerised protocol. Unique delivery aspects include bolus insulin delivery for safety and variable enteral nutrition rates. Unique development aspects include the use of simulated virtual patient trials created from retrospective data. The model, protocol development, and first 50 clinical case results are presented.

Results: High qualitative correlation to within +/-10% between simulated virtual trials and published clinical results validates the overall approach. Pilot tests covering 7358 patient hours produced an average glucose of 5.9 +/- 1.1 mmol/L. Time in the 4-6.1 mmol/L band was 59%, with 84% in 4.0-7.0 mmol/L, and 92% in 4.0-7.75 mmol/L. The average feed rate was 63% of patient specific goal feed and the average insulin dose was 2.6U/hour. There was one hypoglycaemic measurement of 2.1 mmol/L. No departures from protocol or clinical interventions were required at any time.

Summary: Modulating both low dose insulin boluses and nutrition input rates challenges the current practice of using only insulin in larger doses to reduce hyperglycaemic levels. Clinical results show very tight control in safe glycaemic bands. The approach could be readily adopted in any typical ICU.

1.0 INTRODUCTION

1.1 Hyperglycaemia in Critical Care

Stress induced hyperglycaemia is prevalent in critical care, and can occur in patients with no history of diabetes [1-6]. Critically ill patients exhibit increased endogenous glucose production, antagonised and erratic insulin production, and increased insulin resistance. Enteral feeding of glucose and administration of glucocorticoids can further enhance the onset of hyperglycaemia and insulin resistance, respectively. In addition, increased secretion of counter-regulatory hormones stimulates endogenous glucose production and increases effective insulin resistance [2-4], further exacerbating elevated glycaemic levels. Studies also indicate that high glucose nutritional regimes often result in excess blood glucose [7-13], representing another source or cause of hyperglycaemia.

Hyperglycaemia worsens outcomes, increasing the risk of severe infection [14], sepsis and septic shock [15-17], myocardial infarction [1], and critical illnesses such as polyneuropathy and multiple-organ failure [5, 18]. Evidence also exists of significant reductions in other therapies, such as mechanical ventilation, dialysis and blood transfusions, with aggressive glycaemic control [5, 19-22]. More importantly, van den Berghe et al. [5, 22, 23] and Krinsley et al. [20, 21] showed that tight glucose control to limits of 6.10 and 7.75mmol/L respectively, reduced ICU mortality 9-45%, depending on cohort. These relative reductions in mortality were achieved primarily in those patients with length of stay greater than 3 days, with the implicit hypothesis being that these patients are most likely to benefit from glycaemic control while recovering from the initial insult. Perhaps equally importantly, further examination of both clinical studies showed significant cost savings per patient [24, 25].

Other clinical studies have examined glycaemic control in critical care using ad-hoc sliding scales or protocols [26-28]. Most focused on the management of glucose levels and were limited in duration or

patient numbers, and thus did not extend to clinical endpoints such as mortality. However, Thomas et al [28] achieved an average glucose reduction of approximately 15% to 6.2 mmol/L (SD: 1.3 mmol/L) over the course of their study using the protocol based on that of van den Berghe et al [5], but, in contrast, saw no change in mortality over their cohort. Laver et al [27] achieved a similar glycaemic result to the clinical studies noted, reporting a median value of 6.2 mmol/L (IQR: 5.9-7.2 mmol/L). All were developed based primarily on clinical experience and the fundamental utilisation of titration to adjust insulin dose based on pre-determined glycaemic levels and/or other factors.

1.2 Impact of Patient Cohort

However, a major confounding factor in comparing these initial studies is the impact of the cohort, and specifically their level of critical illness. The more critically ill the cohort the more likely it is to exhibit the severe stress-induced hyperglycemia stemming from higher effective insulin resistance [6, 22, 29-31]. This effect may be evident in the fact that van den Berghe et al's initial cohort had had a glycaemic limit of 6.1 mmol/L that was achieved with a median APACHE II score of 9.0 [5], while Krinsley's higher glycaemic limit of 7.75 mmol/L was achieved on a cohort with median APACHE II score of 16.9 [20, 21]. It is further supported by the more recent results of van den Berghe et al [23] on a cohort with average APACHE II score of 24, which achieved similar average glycaemic levels to the original study. However, only a 9% reduction in mortality was observed, versus the 45% achieved in the original study with a much less critically ill cohort.

Thus, cohort is a critical factor in assessing glycaemic control results achieved in comparing different studies. It is also a major confounding factor in assessing the efficacy of different protocols for use in different settings or cohorts. This problem is exacerbated by each study reporting glycaemic control results using different metrics, illustrating the lack of a consistent, accepted metric or method of comparison [32].

1.3 Model-based Control

Regulating blood glucose levels in critical care using simple model-based protocols and insulin alone has been moderately successful in limited clinical testing [33-40], where sliding scales and other ad-hoc methods have not always been consistently effective [37, 41-48]. Additionally, some studies find intensive insulin therapy protocols "taxing" [49-53], noting that van den Berghe et al [5, 23] required additional specialised staff. Clinical burden thus creates another constraint in protocol design. Hence, despite the potential, many intensive care units do not use fixed protocols or necessarily agree on what constitutes acceptable or desirable glycaemic management and performance [2, 19, 32, 50, 51, 53].

Models offer the chance to create patient specific drug delivery, as model parameters can be fit to observed or measured behaviour. They are thus attractive for their potential to aggregate clinical measurements into a direct assessment of patient glycaemic status and resulting patient specific intervention. Both of these outcomes are beyond typical sliding scale oriented titration protocols, but require adequate models of a complex and non-linear metabolic system. While this topic is outside the scope of this paper, the most comprehensive review of this topic may be the recent work of Carson and Cobelli [54].

Nonlinear, model-based control protocols for insulin-mediated glycaemic control have been developed and clinically tested [33-35, 37, 38, 40, 55, 56]. Plank et al [39] use a model predictive controller (MPC) to provide tight control over a series of 48-hour trials for post-cardiac surgery patients, achieving average glycaemic levels of 6.1-6.8 mmol/L across three centres with 42-56% of time spent in a target band of 4.5-6.1 mmol/L for patients with average APACHE II scores ranging from 10-12. Chee et al [35, 38] used PID control, and sliding scale [37] control with CGMS sensors, in an automated closed loop feedback system to achieve average glucose values of 11.5 mmol/L across 9 patients in short term trials less than 2 days. However, their tests were focused primarily on automating the system using

emerging sensors, which had issues with sensor reliability and accuracy for this application. Finally, Vogelzang et al [40], used a simple estimator-predictor model to control glycaemic levels for 179 patients in a surgical intensive care unit, and achieved glucose levels in a 4.0-7.5 mmol/L target range for 78% of the time. All of these methods used only insulin for glycaemic control and left the provision of nutrition to local clinical standards.

By using only insulin to reduce glucose levels, all of these protocols are also challenged to differing extents, based on the cohort they examined, and by the significantly elevated insulin resistance often encountered in broad critical care cohorts. In particular, insulin effect saturates at high concentrations [57-60], limiting the achievable glycaemic reductions in the presence of significant insulin resistance when using only insulin [33, 59]. Different nutritional provision methods and significantly different cohorts makes further comparison of results between the existing clinical tests very difficult.

However, when insulin effect saturates, effective glycaemic control may still be enabled by controlling the exogenous nutritional inputs that may otherwise be exacerbating the original problem [7-13]. Research that specifically lowered glucose nutrition in critical care significantly reduced average blood glucose levels without added insulin [7, 10, 12, 61, 62]. Further, Krishnan et al [12] showed that feeding 33-66% of the ACCP guidelines [63] minimised mortality and hyperglycaemia when compared to the 67-100% or 0-33% tertiles of this nutritional guideline that specifies approximately 25kcal/kg/day [12, 63] with typically 50% (or more) from carbohydrate in most enteral and parenteral nutrition formulas.

1.4 Glycaemic Control Requirements and Preface

Overall, any glycaemic control protocol must reduce elevated blood glucose levels in a controlled, predictable manner, and hold them in a tight range in the presence of any perturbations. It must also account for inter-patient variability, conflicting drug therapies and varying physiological condition as

patient status evolves over time in the critical care unit. Hence, it must be adaptive and/or able to identify changes in patient metabolic status, particularly with respect to insulin sensitivity. It must also be simple enough to be easily implemented and effective enough to be essentially automated to minimise the consumption of clinical time and expertise.

More generally, what is required is a "one method fits all approach" that works, given the difficulty experienced by ad-hoc clinical protocols to provide successful control with a "one protocol fits all" approach, as evidenced by the variable results reported. The difference is in the semantic of a "method" versus a "protocol", where in clinical practice the requirement for protocol simplicity significantly limits the ability of the protocol to adapt to widely different patients or complex time-varying changes in response to therapy, as patient condition evolves. In contrast, a control "method", model-based or otherwise, can overcome these difficulties by providing an adaptable, computationally-based means to determine optimal, time-varying, yet patient-specific, interventions to optimise drug delivery in the presence of this variation.

This paper presents the model based development of a robust, table-based protocol ("SPRINT" – Specialized Relative Insulin Nutrition Tables) to maintain blood glucose levels in the target band of 4-6.1 mmol/L. This protocol has been developed from computerized, model-based glycaemic control trials and extensive virtual trial patient simulations using a physiologically verified insulin-glucose system model. Virtual trials enable the testing of new glycaemic control approaches prior to clinical use, offering the potential to safely optimise the method before implementation. They also offer the ability to directly compare different protocols on the same "cohort".

Published clinical results are compared to these simulations in this paper to validate the virtual trial design approach and provide a better comparison between published clinical protocols and the methods

presented here. Results and some brief discussion are presented together where necessary for clarity. Hence, this paper presents the virtual trial methods and resulting SPRINT protocol, and validates the methods by comparison to published clinical results. Comparison of virtual trial results using other protocols to their published clinical results is used to validate the overall design method. The comparison of SPRINT virtual trials to clinical results for the first fifty patients is used to further validate the design approach and the protocol itself. The paper concludes with an overall discussion and conclusions.

2.0 METHODS

2.1 System Model

Tight Glucose control requires capturing the fundamental dynamics of the glucose regulatory system. Chase et al. [34, 47, 64-66] used a metabolic system model defined:

$$\dot{G} = -p_G G - S_I (G + G_E)\frac{Q}{1+\alpha_G Q} + P(t) \tag{1}$$

$$\dot{Q} = -kI + kQ \tag{2}$$

$$\dot{I} = -\frac{nI}{1+\alpha_I I} + \frac{u_{ex}}{V} \tag{3}$$

$$P(t_i < t < t_{i+1}) = \overline{P}_{i+1} + (\overline{P}_i - \overline{P}_{i+1})e^{-k_{pd}(t-t_i)} \text{ where } \overline{P}_{i+1} < \overline{P}_i \tag{4}$$

$$P(t_i < t < t_{i+1}) = \overline{P}_{i+1} + (\overline{P}_i - \overline{P}_{i+1})e^{-k_{pr}(t-t_i)} \text{ where } \overline{P}_{i+1} > \overline{P}_i \tag{5}$$

where $G(t)$ [mmol/L] is the plasma glucose above an equilibrium level, G_E [mmol/L]. $I(t)$ [mU/L] is plasma insulin concentration resulting from exogenous insulin input, $u_{ex}(t)$ [mU/min]. $Q(t)$ [mU/L] is interstitial insulin concentration and k [1/min] accounts for the effective life of insulin in the system. Patient endogenous glucose clearance and insulin sensitivity are p_G [1/min] and S_I [L/(mU.min)], respectively. V [L] is the insulin distribution volume and n [1/min] is the constant first order decay rate for insulin from plasma. Total plasma glucose input is denoted $P(t)$ [mmol/(L.min)]. k_{pr} is the rise rate of rate of plasma glucose input from enterally administered feed [1/min]. k_{pd} is the decay rate of rate of glucose input into plasma from enterally administered feed [1/min]. $\overline{P}_i$, $\overline{P}_{i+1}$ are stepwise consecutive enteral glucose feed rates [mmol/L.min]. Michaelis-Menten functions are used to model saturation, with α_I [L/mU] used for the saturation of plasma insulin disappearance, and α_G [L/mU] for the saturation of insulin-dependent glucose clearance. For the simulations in this study, k, n, G, I and V are set to generic population values [34, 64, 67, 68].

With this model, patient specific profiles for time-varying S_I and p_G can be generated by fitting retrospective glucose, insulin and nutritional input data. Virtual patients can thus be created [34, 42, 47, 64, 65], which can be used to test insulin delivery protocols. Virtual trials can then use these profiles to determine patient specific blood glucose levels for different insulin and nutrition inputs. More importantly, different protocols can be compared for the same patient, a significant advantage in developing and validating new protocols.

This virtual trials approach of designing more optimal drug delivery methods to achieve clinical outcomes is markedly different than typical clinical protocol development, in particular for glycaemic control. The first requirement is a clinically validated control model that can be combined with retrospective clinical data to create these virtual patient profiles. However, it offers significant patient safety advantages by providing a consistent validated simulation test environment, as well as the ability

to trial many different approaches to dosing and measurement frequency. It also reduces the potential likelihood of having to modify a protocol mid-trial, or for specific patients, if undesirable results arise.

2.2 The SPRINT Protocol

SPRINT is based on a computerized protocol [65, 66, 69] that regulates both nutritional and insulin inputs. This computerized protocol determines optimal feed and insulin inputs to achieve tight glucose control and has been shown to be effective in 10-24 hour clinical trials [42, 65]. However, its complexity makes it difficult to implement for long term testing or use in ICUs that do not already possess bedside computing power and/or trained computer support personnel.

The SPRINT system was designed to provide an easy-to-use equivalent and achieve equal overall glycaemic control to the computerised protocol, thus providing a simple means of large-scale testing of this approach. SPRINT automatically determines the required hourly enteral nutrition rate and insulin bolus to minimise hyperglycaemia. It aims to keep the blood glucose between 4.0 – 6.1 mmol/L with minimal excursion. An insulin average of 3U/hr and nutrition rates of 60-70% of the calculated patient-specific total caloric intake of approximately 25kcal/kg/day [12, 47, 66] are the heuristic ideal for highly insulin resistant, high APACHE II score, critically ill patients [47, 48]. Ease of use is paramount to ensure minimal clinical burden and maximum clinical compliance with the protocol.

The SPRINT protocol consists of two wheels dedicated to enteral nutrition optimisation and insulin bolus administration, as shown in Figures 1. SPRINT is used hourly. Every hour a blood glucose measurement is taken using a bedside Glucocard™ Test Strip II glucose testing kit (Arkray, Inc., Kyoto, Japan). All blood samples are taken from the arterial cannula, to maximize patient comfort. If no arterial cannula is present, blood is taken via pin-stick from the toes or fingers, but only every two hours.

The SPRINT algorithm requires the current and previous blood glucose measurements, previous hour's nutrition feed rate and previous hour's insulin bolus size to determine the nutrition and insulin interventions for the coming interval. The insulin bolus and feed rate for the next hour are then obtained with the wheels and instructions in Figures 1. Note that feed rates move in increments of 10% to a minimum of 30% of patient specific goal feed rate. Insulin is given in bolus form for safety and in increments of 1U to a maximum of 6U/hr, which is a level that minimises insulin saturation [57, 59]. The concentration of insulin used in the bolus was 1U/ml. Bolus administration avoids high rates of insulin infusion being left running if clinical staff become occupied elsewhere, reducing the risk of unintended hypoglycemia. This issue is especially evident in situations where high insulin infusion rates coupled with infrequent measurement intervals lead to higher rates of hypoglycaemic events, with up to 25% reported in some clinical studies [23, 28].

Any patient with a random blood glucose measurement over 8 mmol/L is put on the SPRINT protocol. At entry a patient specific feed level sticker is attached to the feed wheel in Figure 1. This sticker relates absolute percentage goal feed (e.g. 30-100%) requested by SPRINT to an absolute enteral feed pump rate in mL/hr. These feed rates are patient specific and thus the wheel is patient specific. The values on the feed conversion sticker are computed based on the patient's age, body frame size and gender. Weighting factors are assigned to each group of each variable (eg: "Male" = 1.0, "Female" = 0.8, "Large body size" = 1.1, "Small body size" = 0.8), which are then multiplied together to scale the feed rates on a per-patient basis [47, 48]. These overall guidelines are very similar to the ACCP guidelines [63]. The range of patient-specific goal nutrition rates is 50 mL/hr to 100 mL/hr.

The permissible range of feed variation amounts to approximately 280-700kcal/day from glucose for an 80kg male, based on an ideal patient-specific rate of 25kcal/kg/day with 35% of kilo-calories from

dextrose. At the 280kcal/day minimum from glucose, the total caloric intake is still 778kcal/day [48, 70, 71], which exceeds the level found to avoid an increased risk of bloodstream infections [72-74]. Note that the reduced percentage from dextrose of 35%, from a more typical 50%, can be found in commercially available formulations that are designed and marketed for diabetic patients [70].

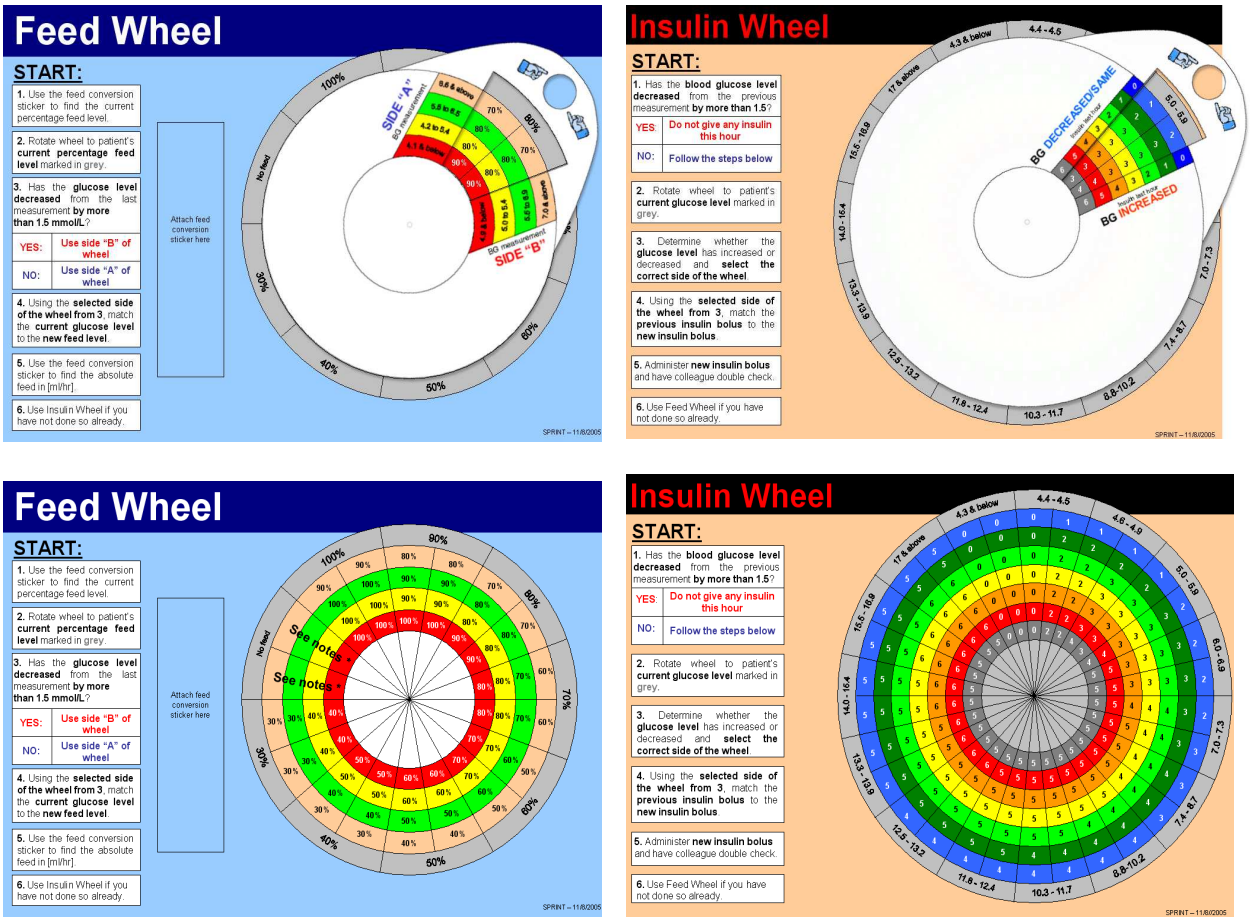


Figure 1: SPRINT feed and insulin wheels: covered for use (top) and uncovered to show full data (bottom). These wheels are available in soft or hardcopy from the authors or on the internet [47].

Figure 2 shows the simple decision tree for going to measurements every two hours when the patient is glycaemically stable. Glycaemic stability is defined as 3 hours in the 4.0-6.1 mmol/L band with 3U or less insulin per hour and 60% or more of total feed rate. Such a patient is thus not significantly insulin resistant and is in the target band, making sudden changes potentially less likely and allowing less

frequent measurements for patient comfort and to reduce the clinical burden. When measuring two-hourly, in the hour between measurements the nurse administers the same size insulin bolus administered the previous hour, and leaves the feed rate unchanged.

SPRINT may be stopped when the patient is exhibiting normoglycaemia, and is adequately self regulating their glucose system. This state is characterized as being stable within the 4-6.1mmol/L band for the last 6 hours, with an 80% rate of goal feed or higher and an insulin bolus of 2 U/hr or less. The protocol stopping decision tree is shown in Figure 3.

Importantly, the method is effectively fully automated, aside from the patient specific feed rate, as it relies on no other external clinical inputs or modifications for any patient. The wheels mimic the model-based controller, thus accounting for the highly dynamic evolving patient by regulating insulin and nutrition hour-to-hour, based on response. More specifically, a highly resistant patient will see SPRINT increase insulin administration, while also reducing feed rates. As a patient recovers from a given illness and/or insult the protocol gradually removes insulin and increases feed. A highly dynamic patient may theoretically see several such cycles. Hence, SPRINT represents a method of determining the proper inputs in a patient specific fashion that accounts for the natural variability of the critical care patient – a potentially one method fits all, or most, solution.

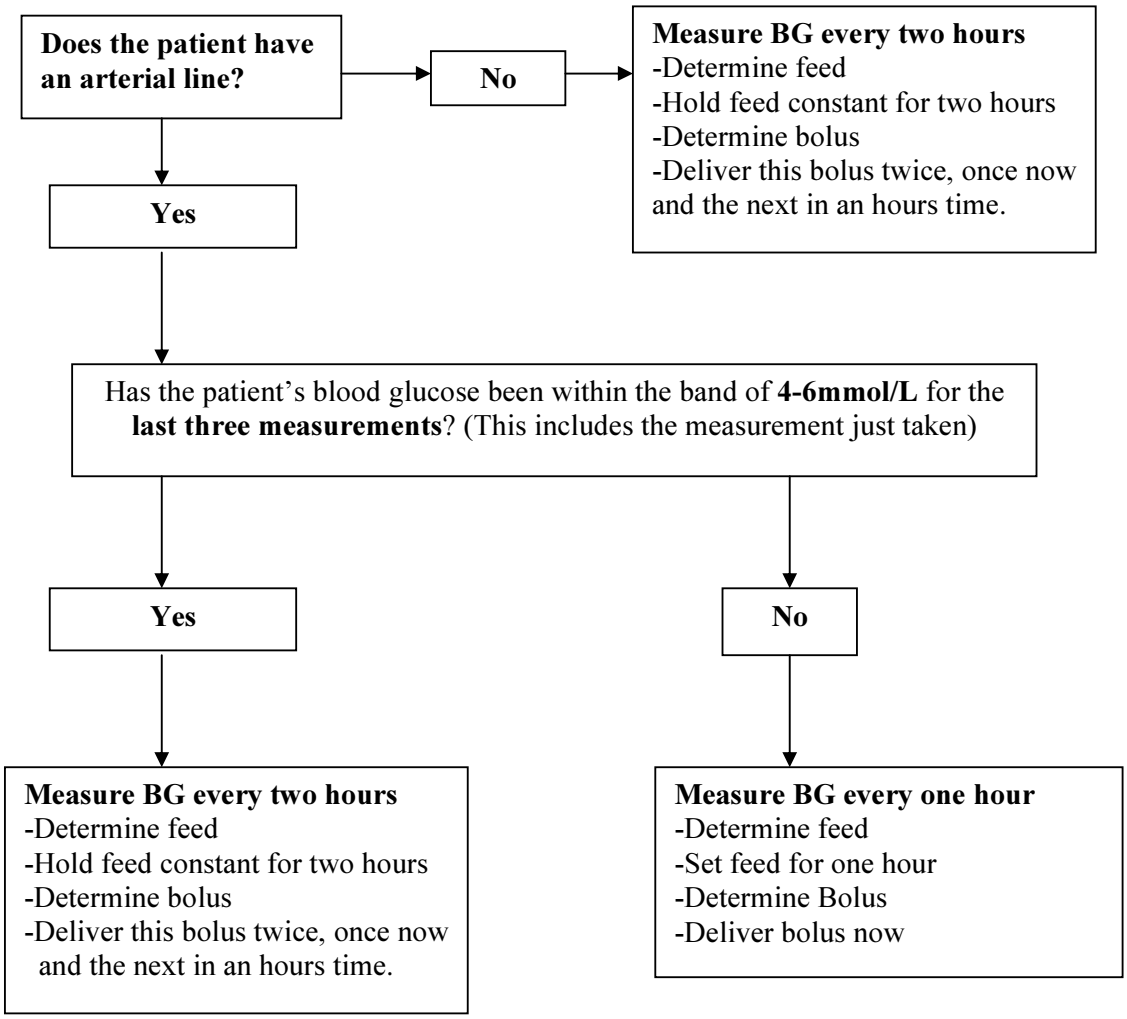
Finally, the layout of the SPRINT wheels resulted from extensive consultation. Clinical staff reported the system as very easy to use in clinical pilots before full-scale implementation as a clinical practice change. The covered wheel concept is designed to reduce complexity and thus reducing user error. Overall, SPRINT should be simple enough to integrate with any typical ICU practice.

SPRINT 2-Hour Flow Chart

When can I measure every 2 hours instead of every 1 hour?

(Reducing the frequency of measurement saves time yet will lose optimum control of the patient; it is in the patient's best interests to measure and act every hour)

Follow the Flow Chart:



Important: if the patient comes out of the **4-6mmol/L** band on the next measurement **return to 1 hour** measurement intervals immediately.

Figure 2: Decision tree used by nurses to determine when to measure blood glucose two-hourly.

SPRINT Stop Flow Chart

When can I stop the SPRINT protocol ?

Follow the Flow Chart

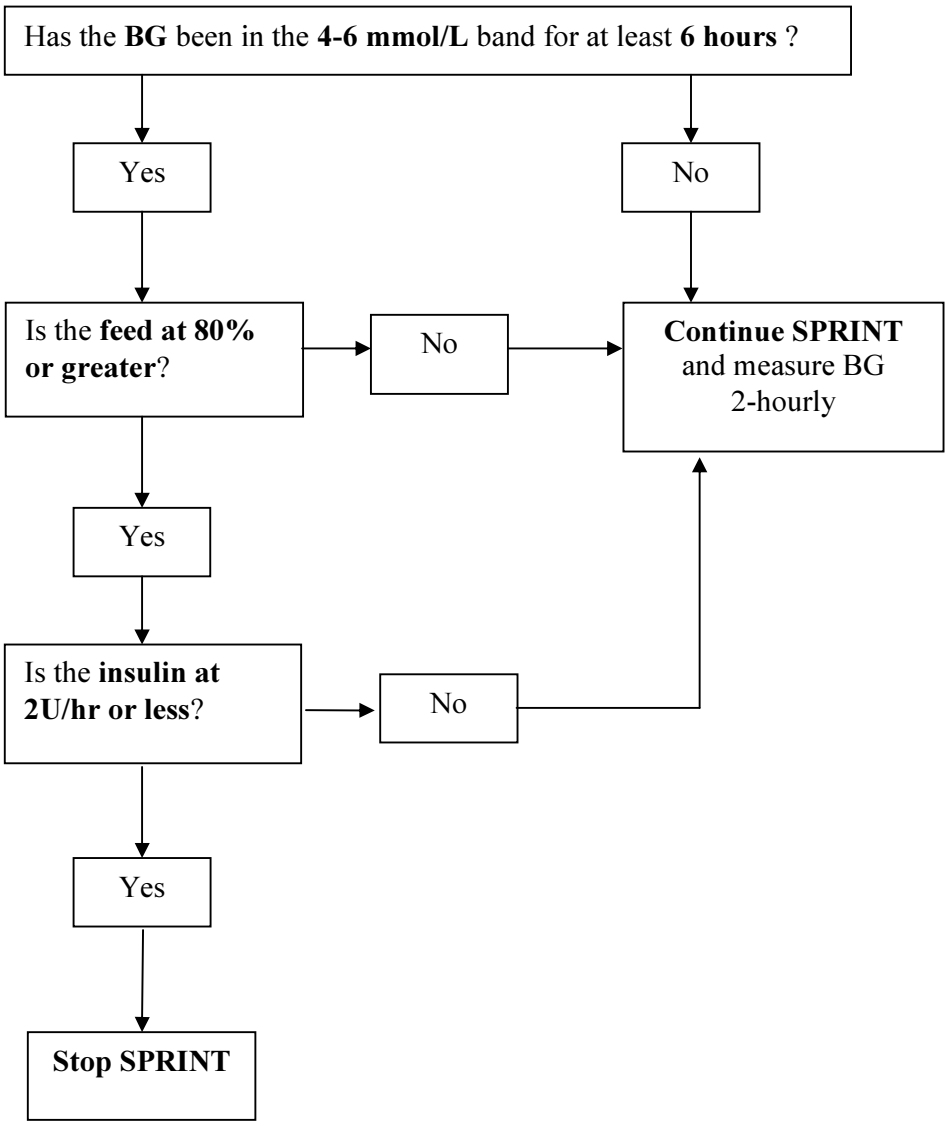


Figure 3: Decision tree used by nurses to determine when to stop SPRINT protocol

2.3 Virtual Trial Protocol Comparison

Virtual trials are used to evaluate the performance of SPRINT before clinical implementation. Those results can then be compared with published protocols [5, 20-23], as simulated on the same cohort and as published on their specific cohort. Hence, it is possible to validate the model and design approach by comparing virtual trial results with published results using the same protocol [41, 48]. Differences between virtual trial results for SPRINT and these published protocols can then be put into better context. The computerised AIC4 protocol [65, 66] provides another comparison.

Protocols that utilised glucose shots for hypoglycaemic events, modelled the glucose administered at the same value and assumed they were administered over 5 minutes. No other changes were made from the published protocols. Performance is measured by time spent in the 4-6.1mmol/L band [5, 22, 23], or the 4-7.75 mmol/L [20, 21] band, rather than a simple average value that does not assess the tightness of the control or distribution of glucose values [47, 75]. Hence, glycaemic levels and the tightness with which they are maintained are assessed for a more complete analysis of control efficacy, as it may also impact on clinical outcome [48, 67, 76, 77].

Monte Carlo simulations of each virtual patient are used to include the effects of reported measurement errors. In this study, measurement errors range from 7-12% as a function of glucose level per standard bedside glucometers [78-81]. Each protocol is run 20 times for all 19 virtual patients. The results are stored for every glucose measurement the specific protocol required, rather than reporting a morning average or other surrogate. Finally, to validate the comparison and overall design approach the clinical results from SPRINT are compared with its Monte Carlo simulation results.

2.4 Virtual Trial Patient Cohort

The patient cohort used to create the virtual cohort for simulation, development and testing covers a general cross-section of ICU population, APACHE II score (Average: 21.8, Range: 8-36), age, sex and mortality [64, 67]. The average stay is 3.9 days (Range: 1.4-18.8 days). It is worth noting that the APACHE II scores have a much higher mean and range than the larger cohorts in the glycaemic control research of van den Berghe et al [5, 22], and Krinsley [20, 21], but are more similar to van den Berghe et al's more recent study [23]. The patient details are shown in Table 1 and are developed from the retrospective cohort used by Hann et al [64] and computerised glycaemic control clinical trial patients prior to their trial [34, 65]. Note that diagnosed diabetes is somewhat over-represented as they had more retrospective data due to the greater monitoring they tended to receive in the ICU.

Table 1: Long-term virtual trial patient cohort

Patient number	*Medical subgroup*	*APACHE II score*	*Age*	*Sex*	*Mortality*	*Diabetes*
1	Sepsis	17	56	M		Type 2
2	Sepsis	24	64	M		
24	Other medical	25	47	M	Y	Type 1
87	Other medical	26	62	F		
130	Trauma	11	21	M		Type 1
229	Cardiac	15	73	F		
289	Cardiac	18	70	M		
468	General surgical	32	76	M		
484	Other medical	34	30	F		
486	General surgical	22	76	F		Type 2
519	General surgical	29	69	M		Type 2
554	Other medical	26	20	F		Type 1
666	Cardiac	8	44	F		Type 2
847	Other medical	17	67	F		
1016	General surgical	20	37	F		Type 2
1025	Pulmonary	36	48	M		Type 2
1090	General surgical	Unknown	37	F		
1099	Pulmonary	Unknown	24	M	Y	
1125	Other medical	Unknown	72	F	Y	
Average (range)		*23 (8-36)*	*52 (20-76)*			

3.0 RESULTS AND VALIDATION

Results and brief discussion are presented for the virtual trial development of SPRINT followed by its validation in comparison to other published protocols and results in the literature. Results showing the impact of controlling nutritional inputs on glycaemic levels are then presented. Finally, the SPRINT clinical results are presented for the first 50 patients followed by results validating the overall approach in comparing the clinical SPRINT results and the virtual trial SPRINT results used in developing the protocol and justifying its initial implementation.

3.1 Virtual Trial Results

Table 2 shows the Monte Carlo simulated virtual trial results for SPRINT, the computerized "AIC4" method that it mimics, and the two landmark clinical protocols. The clinical protocols are denoted by primary author as "Krinsley" for [20, 21] and abbreviated "vdB" for [5]. The glucose results in all cases are lognormal ($p < 0.005$), instead of the often assumed normal distribution. The 68.3% and 95.5% ranges thus represent 1 and 2 multiplicative standard deviations respectively. The time in band values are percentages of the total trial time. The average insulin and average percentage of goal feed are presented to show the level of interventions. Finally, the glucose results are shown graphically in Figure 4 as probability density functions, which clearly illustrate the differences in the tightness and variability of the glycaemic control provided by the different methods.

Table 2: Monte Carlo virtual patient clinical trial results

	SPRINT	Krinsley [20]	vdB [5]	AIC4 [65, 66]
50th Percentile	5.79	8.59	5.60	5.93
Mult. STD	1.29	1.29	1.65	1.35
68.3% range	(4.5-7.5)	(6.7-11.1)	(3.40-9.24)	(4.4-8.0)
95.5% range	(3.5-9.6)	(5.2-14.2)	(2.1-15.2)	(3.3-10.8)
Time in 4-6.1	61.7%	11.2%	35.8%	62.2%
Time in 4-7.75	83.5%	27.4%	51.0%	82.9%
Time < 4	4.4%	0.6%	23.6%	1.1%
Time < 2.2	0.5%	0%	2.7%	0.1%
Time > 7.75	12.1%	72.0%	25.3%	16.1%
Avg insulin (U/hr)	2.4	1.6	3.0	2.6
Avg % goal feed	61.9%	67.7%	67.7%	75.8%

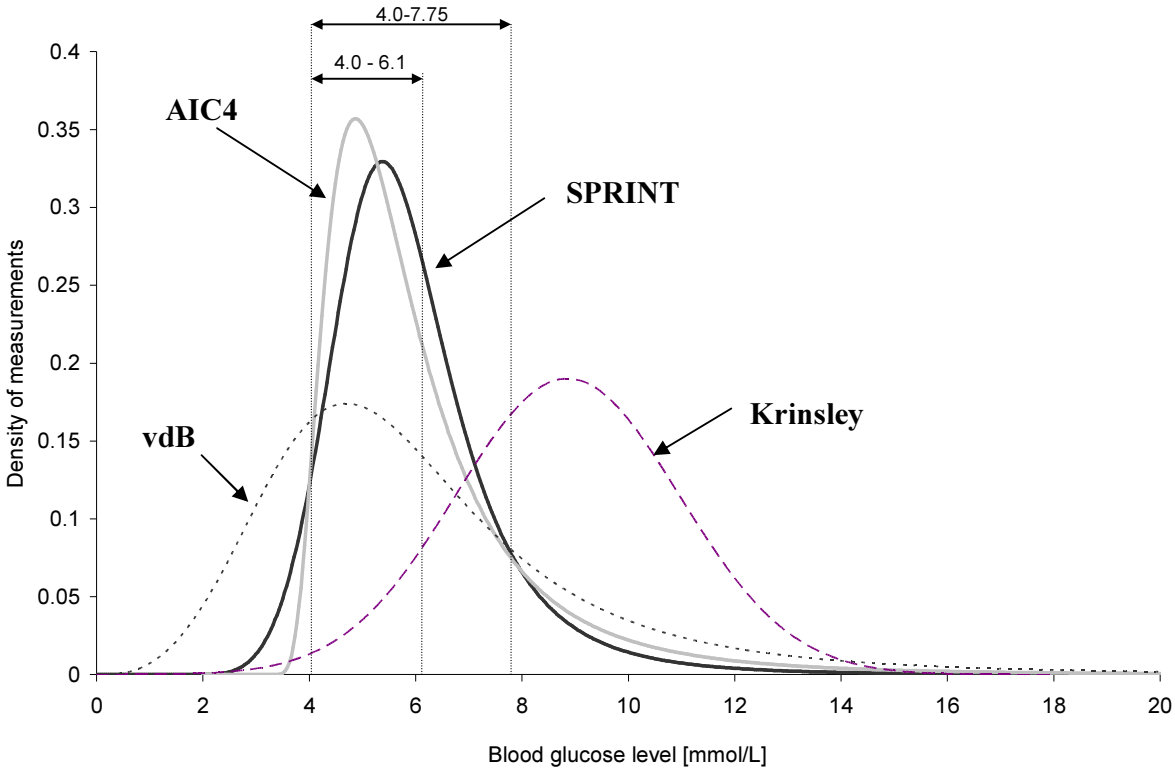


Figure 4: Probability density functions of glucose results for Monte Carlo simulation of different protocols showing tightness of control and glycaemic bands.

The results in Table 2 and Figure 4 also compare well with reported clinical values, particularly for average glucose levels, suggesting that the computer simulation method produced realistic results. Differences, such as the 2.7% of measurements below 2.2 mmol/L in the simulated van den Berghe et al protocol compared to 1.0% in the reported results [5, 22], may be due to the more severely ill virtual patient cohort simulated here. Specifically, this virtual cohort has an average APACHE II score of 21.8 versus 9 for the van den Berghe et al protocol [5] and 16 for the Krinsley protocol [20]. Note that van den Berghe et al's [23] later study with an average APACHE II score of 24 reported that 18.7-25.1% of patients experienced at least 1 hypoglycaemic event. Similarly, in the virtual trials with a similar mean APACHE II score, 5 of 19 virtual patients experienced at least 1 hypoglycaemic event, qualitatively matching the published clinical result.

3.2 The Impact of Also Using Nutrition for Glycaemic Control

A more telling comparison can be made by comparing the AIC4 computerized method to both the retrospective hospital control [64, 67] and the same AIC4 protocol where the ability to modulate nutritional inputs is removed. This "insulin only" version of the AIC4 computerized protocol is thus more directly comparable to the other model-based insulin only approaches tested elsewhere [34-36, 39, 40]. Figure 5 plots the percentage time in the 4.0-6.61 mmol/L band as a function of the average model-based insulin sensitivity parameter, S_I, fitted over the given patients stay, where this value is considered to be broadly indicative of a patient's level of critical illness as represented by resulting insulin resistance. More specifically, S_I directly represents the ability to reduce glycaemic levels using exogenous insulin.

As seen in Figure 5, at low average insulin sensitivity values the percentage time in band is very low for all protocols that do not also modulate nutritional inputs. This result occurs because at low insulin

sensitivity, insulin saturation effects limit the ability to reduce glycaemic levels, as also seen clinically in short clinical studies using this insulin-only model-based approach [33, 34, 59]. At high insulin sensitivity levels, insulin alone is more effective, as expected. Importantly, this result clearly highlights the need to attack high glycaemic levels via this additional avenue, as well as providing the means, with a computerized protocol, to directly identify the patient who might benefit most from controlling both the nutritional and insulin inputs. Finally, these results qualitatively serve as further validation of the underlying models and methods when making the decision to implement a protocol clinically.

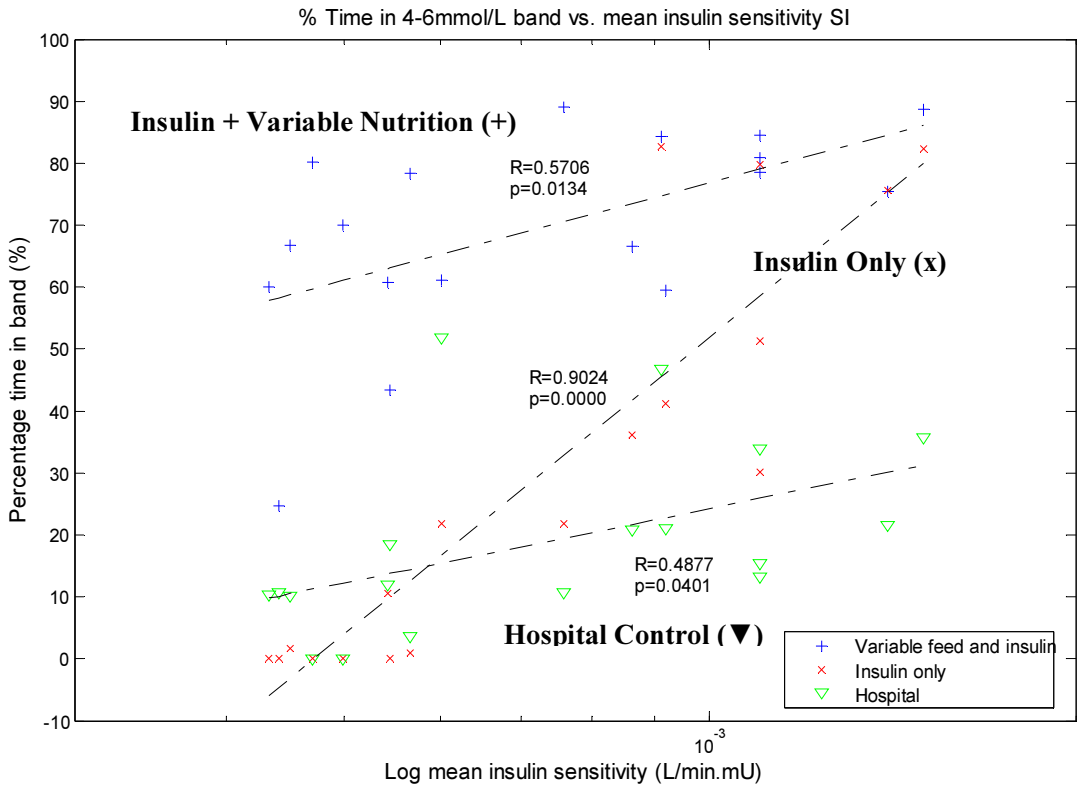


Figure 5: Mean Insulin Sensitivity, S_I, versus Time in the 4-6mmol/L Band

3.3 SPRINT Clinical Results

Summarized clinical results in Table 3 indicate that SPRINT is achieving tight glucose control for the first 50 patients tested. There have been 7358 hours of control with 5359 measurements. Thus, approximately 54% of the time is on 2-hourly measurements per the protocol requirements, representing a significant reduction in clinical burden, as well as the stability of many patients on the control.

Table 3: Summary of SPRINT patient results.

Total patients	*50*	
Total trial hours	*7352*	*hours*
Total measurements	*5359*	
Average length of stay on SPRINT	*147*	*hours*
Blood glucose average	*5.9*	*mmol/L*
Blood glucose standard deviation	*1.1*	*mmol/L*
Blood glucose range	*(2.1-16.4)*	*mmol/L*
Average time in 4-6.1	*58%*	
Average time in 4-7	*84%*	
Average time in 4-7.75	*92%*	
Number of Measurements < 4	*112 (2.1%)*	
Number of Measurements < 2.5	*3 (0.06%)*	
Minimum Blood glucose	*1.9*	*Mmol/L*
Average hourly insulin bolus	*2.6*	*U*
Average percentage of goal feed	*63%*	
Average feed rate	*47.3*	*ml/hr*
(assuming 1.06 Kcal/ml for feed)	*1204*	*Kcal/day*
Percentage of time >= 50% goal feed	*68%*	
Percentage of time >= 60% goal feed	*61%*	

Only 1 instance of hypoglycaemia, defined as less than 2.2 mmol/L, was recorded over all 7358 hours of control, and no clinical manifestations of hyperglycaemia were observed in any of the trial patients. The next minimum blood glucose measurement was 2.3 mmol/L. Only 3 of 5359 blood glucose readings were less than 2.5 mmol/L. Hence, the safety, with respect to hypoglycaemia is well documented, and exceeds other published studies, where some report up to 25% of patients experiencing at least one hypoglycaemic event [23].

The average blood glucose over all patients was 5.9 ± 1.1 mmol/L with an average feed rate of 63% of goal feed rate using RESOURCE® Diabetic (Novartis), which equates to approximately 1204 Kcal/day in total (35% from dextrose). The average hourly insulin bolus was 2.6 U. Time in the 4-6.1 mmol/L band was 58%, with 84% in a slightly wider 4-7.0 mmol/L band, and 92% of all measurements in the 4-7.75 mmol/L band. Only 2.1% of all measurements were below 4 mmol/L and 0.06% were less than 2.5 mmol/L. Finally, only 6% of all measurements were above 7.75 mmol/L with a maximum over all patients of 16.4 mmol/L, which was recorded for a diabetic ketoacidosis admission.

The cohort represented was relatively critically ill with an average APACHE II score of 21 (range: 6-43). The average age was 62 (range: 18-86) and 62% of all patients were male. More importantly, there was never any clinical intercession in the protocol operation, no required departures from protocol were taken, and no reported adverse events were reported.

Table 4 summarises this patient cohort in terms of age, sex, risk of death (ROD), APACHE II and III, and SAPS II scores. It is evident from the table that the cohort is fairly broad covering most potential diagnoses and situations typical of a critical care unit, as reflected in the APACHE scores and ranges shown, noting that APACHE II score ROD tends to be slightly overstated for some levels but a better analogue than SAPS II [82-85]. In addition, considering primary diagnosis, 19 patients (38%) had sepsis and 15 (30%) had some form or cardiac diagnosis including myocardial infarction, ruptured aorta, AAA surgery and 4 (8%) valvular surgery patients. A further 3 were primary diagnosed with respiratory failure and another 2 with acute renal failure. Overall, this group is generically representative of this medical ICU, and has a broad cross section of patient types and level of critical illness.

Table 4: Cohort summary for first 50 patients on SPRINT. Ranges are 100% unless noted with an added inter-quartile range (IQR) as noted.

	Average	Ranges	Average ROD (%)
Age	62	18-86 IQR: 59-75	--
APACHE II	21	6-43 IQR: 14-23	39.8
APACHE III	64	20-136 IQR: 44-70	--
SAPS II	43	9-75 IQR: 29-50	34.7

Finally, clinical burden in such a protocol is also an important consideration. An evaluation survey of nursing staff opinion of the SPRINT system was therefore conducted. Of 27 respondents to 3 questions, 72 of the 76 total responses, or 95%, rated SPRINT as satisfactory or better, with 74% rating it good or very good. There were 5 questions left unanswered on those surveys returned. Thus, once implemented, the burden was not considered to outweigh the clinical benefits observed. In addition, analysis of all intervention and glucose data shows less than 0.3% was in error, with most cases recognizable as minor user error, rather than non-compliance with the protocol. Finally, these results also reflect the simplicity of SPRINT, which should be simple enough to readily integrate with any typical ICU practice

3.4 Clinical Validation of Simulation Results and Design Approach

Figure 6 shows the probability density functions for all clinical SPRINT blood glucose measurements over the first 50 patients. It also shows these results for the Monte Carlo SPRINT virtual trial simulations. This figure thus compares the virtual trial simulation used to develop the protocol to the clinical results obtained after implementation. The clinical cohort has an average APACHE II score of 21, which is very similar to the average 21.8 for the virtual cohort. Finally, the virtual trial results from

Figure 4 for the van den Berghe et al [5] and Krinsley [20] protocols are repeated for comparison, and the primary glycaemic control bands are shown to provide context.

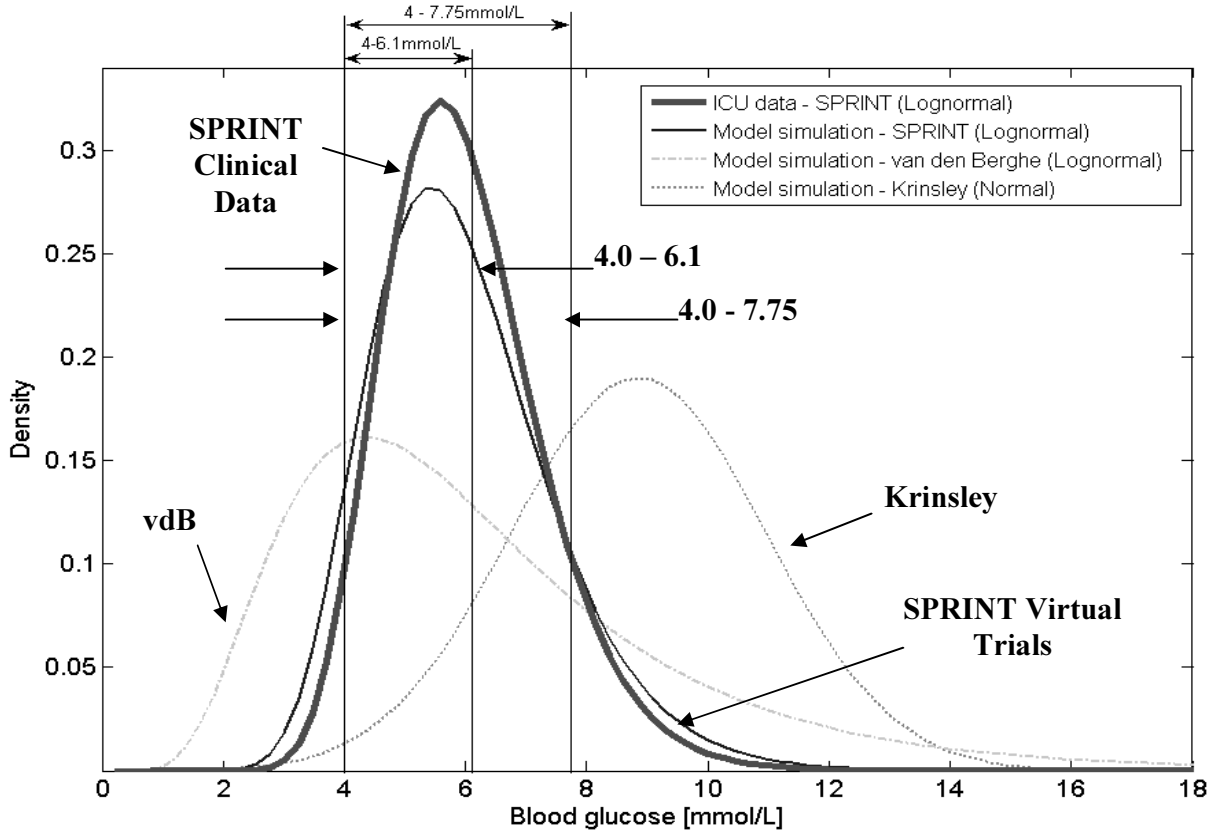


Figure 6: Probability density functions based on both virtual and clinical glycaemic control trial results

The simulated and clinical SPRINT results in Figure 6 are very similar, particularly with respect to their width through the 4.0-6.1 mmol/L and 4.0-7.75 mmol/L tight control ranges. The differences between these two curves indicate that less than 10% of all simulated measurements are outside the clinical density function results. Note that the slightly tighter clinical results indicates that the virtual trial are both accurate and clinically, slightly conservative, as this approach delivered a result that was slightly tighter, or better, in clinical practice than in the virtual trials.

In the low and hypo- glycaemic ranges there are significant differences comparing SPRINT results to other protocols. The van den Berghe protocol has 3.5% of measurements below 2.5 mmol/L in comparison to 0.1% for clinical SPRINT results and 0.16% for virtual trial SPRINT results. Below 4.0 mmol/L, the results are 23.6% for the van den Berghe protocol versus 2.6% for clinical SPRINT and 0.6% for Krinsley's protocol. Hence, the clinical results validate the simulations with respect to low and hypoglycaemic levels.

With regard to high blood glucose levels, there are also significant differences due to the differing levels of tight control achieved. Specifically, 25.3% of the van den Berghe protocol results are above 7.75 mmol/L versus 10% for SPRINT and 70% for the more conservative protocol used by Krinsley. Note that of the 10% above 7.75 mmol/L from SPRINT 2% occur in the first 12-24 hours of patient stay due to initially elevated blood glucose levels.

4.0 DISCUSSION

4.1 Virtual Trials Development Approach

Both the computerized AIC4 and SPRINT protocols were developed using the virtual trial method presented in this work. This virtual development approach is novel in this field, which typically relies primarily on experience and/or intuition. The SPRINT table-based version, and the computerised AIC4 method it mimics, also deliver very similar results, justifying the conversion to a more easily used system for large-scale clinical validation.

The virtual trial approach also allows a more apples-to-apples comparison to other published protocols by removing differences in cohort that confounds direct comparison of published clinical results. Note

that some differences will still exist for the as-modeled published protocols. More specifically, the protocols compared here utilise unspecified and unreported patient-specific clinical modification of treatment that cannot be modeled without more complete information. Regular or significant patient-specific protocol modification by clinicians is also important because it increases clinical burden and illustrates a lack of adaptability to the variation in patient needs that is a hallmark of highly dynamic and complex critical care patients.

For specific results and validation, examining Table 2 and Figure 4, the noticeable outlying protocol was from Krinsley [20, 21]. However, it is also a less intensive protocol with a target average glycaemic level of 7.75 mmol/L. The 50^{th} percentile blood glucose levels for SPRINT and AIC4 are comparable with those of van den Berghe et al [5, 22, 23]. However, the 95.5% range of 3.50-9.58 mmol/L for SPRINT and a similar value for AIC4 are much narrower than the 2.06-15.24 mmol/L from van den Berghe et al. Similar results are seen over the 68.3% range. Thus, SPRINT and its computerized version (AIC4) more tightly regulate blood glucose with much less risk of hypoglycaemia, as shown by the percentage time less than 4 and 2.2 mmol/L. Note that the percentage of goal feed values in Table 2 are all less than 100% as the retrospective data contains clinical stoppages of nutritional input for other clinical causes.

In general, the more critically ill the cohort, the potentially more insulin resistant and dynamic the metabolic response, and thus the more variable the results seen in these virtual trials when compared to published clinical results for less critically ill cohorts. Another reason for difference between virtual trial results and published clinical data might be measurement method, where van den Berghe et al reported only the morning average glucose level using normal statistics, and Krinsley reported the average over all measurements (as above). Both used normal statistics for data that is, in this case, more lognormally distributed. Hence, the right shifted lognormal distribution shown in Figure 4 for Krinsley's protocol

would report the higher 50^{th} percentile lognormal mean than the normal distribution mean, thus potentially accounting for some of the difference when compared to the published value.

A final difference in results may be due to the assumptions made where the protocols referred to specialised clinical input. The insulin dosages recommended by the protocol of van den Berghe et al were intended as "directives, rather than strict numerical instructions" [5, 22]. Insulin dose adjustments in this study were also guided by factors, such as body temperature and infection. Retrospective data for these parameters were not available for simulation and the protocol was run on a strict numerical basis, with insulin doses capped at 15 U/hr. The comparative advantage of the AIC4 and SPRINT protocols, in these cases, is that they are essentially fully automated. However, the overall fundamental results do clearly indicate the differences and variability of the control obtained for each protocol, and in particular relative to other approaches. A brief, yet similar comparison of these and other protocols is also presented by Lonergan et al [48].

Overall, despite these differences, the glycaemic results for the Monte Carlo simulations are qualitatively very similar to the reported values for these protocols in the literature. This result should add a significant measure of validation to these simulation results. With regard to developing better drug delivery methods, a protocol designer should gain confidence that good virtual trial performance would do similarly well in clinical practice. Hence, these results indicate how the virtual patient approach can increase safety in drug delivery protocol design by validating the decision for clinical implementation before any pilot clinical testing, as was the case for the SPRINT protocol presented here.

4.2 SPRINT Glycaemic Control

The goal of this protocol is to maximize time within a band, not just a limit or average at the edge of the band, a significant difference from prior clinical results. Hence, the overall goal is to effectively clamp patients in a tight glycaemic band. For the first 50 patients, the SPRINT protocol maintained tight glycaemic control over all patients in the study with an overall blood glucose average of 5.9 ± 1.1mmol/L. Patients spent 58% and 92% of time in the 4.0-6.1 mmol/L and 4.0-7.75 mmol/L bands, respectively. However, these time in band results cannot be directly compared to other published results, as no other long term clinical studies have reported them.

More importantly, this control was achieved using an average of 2.6 U/hour of insulin and providing 63% of patient specific goal feed. These insulin dosage values are relatively low compared to other clinical results and show the impact of also modulating the nutritional inputs. The enteral nutritional feed rates are lower than those in some studies [5, 20-22] and similar to others [23], where this latter study by van den Berghe et al used significantly less nutritional input with the more critically ill cohort for reasons that were not directly discussed. Overall, the feed rates are higher, as a percentage of patient specific goal feed rate, than average retrospective data for the same unit [48, 64, 65, 67].

For patient specific results, Figure 7 shows Patient 5005 (APACHE II score = 21) who experienced three sudden glucose peaks from within the 4-6.1 mmol/L band between 100 and 145 hours. The first two peaks may be due to contaminated measurements or other errors, as the resulting strong control response drove glucose values in the next hour to below the value prior to the peak. In contrast, the third peak at approximately 155 hours is likely a real event, as glucose level only dropped relatively marginally following a strong control response to the glycaemic rise and took 4-5 hours to return to the 4.0-6.1 mmol/L band. This third peak was thus likely due to a sudden large change in insulin resistance,

perhaps due to the onset of an adrenergic event [42, 65]. Similar behaviors with low glycaemic measurements are also indicated in Figure 7. All of these peak values are included in the performance statistics. However, the overall tight control results for this patient indicates that, whatever the cause, the protocol is able to safely handle both types of behavior.

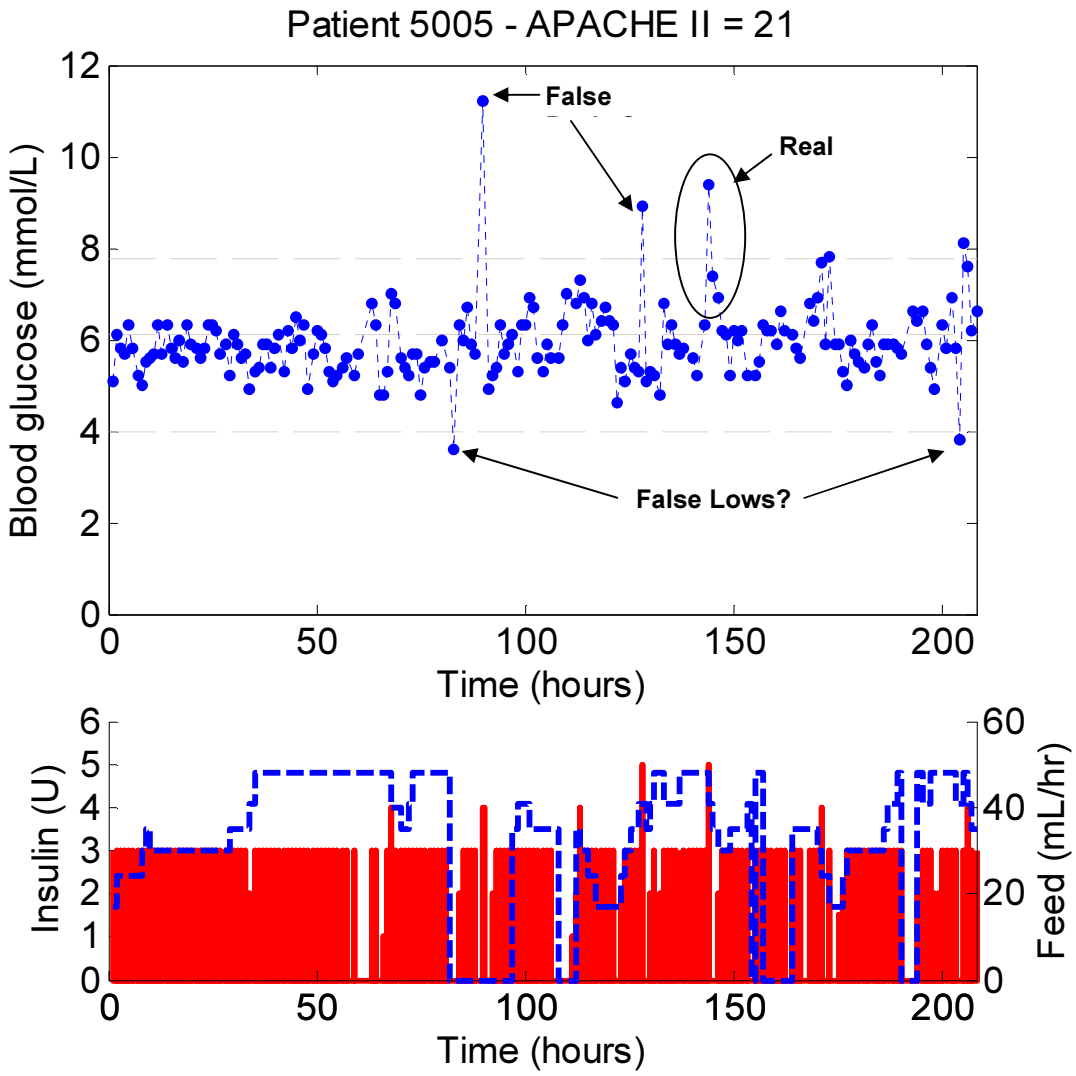


Figure 7: Blood glucose measurements for patient 5005 on SPRINT. Feed rates are plotted as dashed lines and insulin boluses are plotted as solid lines.

Figure 7 also shows the insulin boluses and feed rate over the 200 hour length of stay. The average insulin administered was 2.6 U/hour and relatively constant. The feed rate was modulated more extensively with an average of 52% of goal feed, which is lower than the cohort average but is slightly biased, as seen in Figure 7, by the periods at 0% feed rate where the nutritional input was turned off for other clinical reasons. The overall result was an average glucose level of 5.9 mmol/L with 66% of time spent in the 4-6.1 mmol/L band, 94% in the 4-7 mmol/L band, and 96% in the 4-7.75 mmol/L band.

Overall, high levels of control were achieved on a patient cohort with relatively severe medical conditions compared to other studies. The average APACHE II score was 21, as compared to previous intensive insulin clinical studies whose APACHE II medians or averages were 9 [5, 22],16.9 [20], and 24 [23], respectively. Higher APACHE II scores are a general indicator of increased insulin resistance [6, 29-31]. Hence, the overall glycaemic average of 5.9 ± 1.1 mmol/L compares very well with van den Berghe et al's 5.7 ± 1.0 mmol/L [5], which had a much less ill cohort, and the 6.0 ± 1.45 mmol/L morning average in their second study with much more critically ill cohort [23]. Similarly, it exceeds the 7.3 ± 3 mmol/L reported by Krinsley [20].

Finally, to provide further clarity, the summary results for the first 10 patients on SPRINT are shown in Table 5, where patients 5003 and 5007 were excluded as they had less than 10 hours on the protocol. These results show both the tight control achieved as well as the inter-patient variability in control outcome across the cohort. However, the individual results are relatively tightly grouped and the overall results for these 10 patients match those for the first 50 patients reasonably well.

Table 5: Summary of results for first 10 SPRINT patients

Patient Number	5001	5002	5004	5005	5006	5008	5009	5010	5011	5012	Average/Total
Trial Length (hours)	261	163	251	206	41	162	366	184	107	362	210 [(a)]
Num. Measurements	234	154	167	190	32	112	224	114	100	252	158 [(a)]
Avg. BG (mmol/L)	6.0	6.2	5.3	5.9	5.5	5.4	5.4	5.9	6.5	6.0	5.8 [(b)]
Time in 4-6.1	63%	44%	84%	66%	78%	85%	75%	68%	24%	57%	64% [(b)]
Time in 4-7	87%	81%	94%	94%	91%	92%	88%	89%	82%	91%	89% [(b)]
Time in 4-7.75	96%	95%	98%	96%	94%	97%	95%	96%	98%	99%	97% [(b)]
Num < 4	1	0	3	2	1	2	11	2	0	1	23 [(c)]
Num < 3	0	0	0	0	0	0	0	0	0	0	0 [(c)]
Goal Feed (ml/hr)	75	80	75	60	60	60	85	90	90	90	79 [(d)]
Avg. Feed (%)	54%	42%	88%	52%	75%	85%	81%	66%	33%	54%	65% [(d)]
Avg. Feed (ml/hr)	40.3	33.6	66.3	31.2	44.7	50.9	68.4	59.3	29.9	48.5	50.3 [(d)]
Avg. Feed (kcal/day)	1025	855	1687	794	1137	1295	1740	1506	761	1234	1280 [(d)]
Avg. Insulin (U/hr)	2.7	3.3	1.8	2.6	2.0	2.3	2.0	2.7	3.5	2.8	2.5 [(d)]

[(a)] = arithmetic mean
[(b)] = mean weighted by number of measurements
[(c)] = total for all patients
[(d)] = mean weighted by trial length

4.3 Insulin and Nutrition Control Approach

One major conclusion to draw from this limited, initial, and ongoing, study is that modulating nutritional rates in addition to insulin can achieve very tight control, with potentially less drug delivery effort and more success than using insulin alone. For example, van den Berghe et al [5] used an average of ~3U/hr where this trial achieved equally tight or tighter control with a much more critically ill cohort using 2.6 U/hr. Modulating nutrition also provides a potentially safer method, as seen by the single (1.9 mmol/L) hypoglycaemic measurement below 2.2 mmol/L, out of 5359 total measurements (0.02%). Note that

5.2% of patients experienced at least 1 hypoglycaemic measurement in van den Berghe et al's original study [5, 22] and at least 25% of patients in their later study on a more critically ill cohort [23]. More specifically, as patient condition evolves, feed reductions allow less insulin to be used for the same or greater glycaemic reduction, avoiding saturation and/or sudden changes in glycaemic level due to excessive insulin,.

In this study, dynamic increases and reductions in enteral glucose administration rates were used to assist glycaemic control. Impaired splanchnic and peripheral glucose uptake implies a slow decay in the rate at which glucose appears in the bloodstream following a reduction in nutritional feed [86, 87]. Conversely, the rate of peripheral appearance of oral glucose is approximately equal to the intestinal absorption rate, implying a rapid rise following a nutritional feed increase [88]. Both aspects provide a more sure level of control as glucose drops are relatively slow and, in contrast, sudden low glycaemic levels can be raised relatively rapidly by increasing the feed rate.

Modulating nutritional dextrose inputs also provides a physiologically non-saturable path to reduce plasma glucose, at least to the point of eliminating nutritional input entirely. It is important to note that this approach is focused on controlling the dextrose carbohydrate content exacerbating hyperglycaemia, rather than the overall nutritional profile. This last issue could be practically addressed, for example, by separating the dextrose and protein-fat nutritional inputs infused, or by providing more specifically designed nutritional inputs based on more in-depth clinical study, as has been done with neonatal nutrition [89, 90]. Thus, nutritional delivery in critical care, in this light, could be seen to constitute a form of drug delivery problem.

Overall, this approach of modulating nutrition in addition to exogenous insulin is a significant departure from other approaches in this field, which use insulin alone. It is supported by recent studies that show

low-calorie (or low dextrose) nutritional inputs reduce hyperglycaemia [7, 10, 13, 61, 62], and above ~30% of standard goal feed rates do not increase infectious complications [12, 72-74]. Specifically, Krishnan et al [12] showed that feeding over 66% of the ACCP recommended rates increased the likelihood of ICU mortality, and suggested that the ACCP caloric targets may thus be set too high. More importantly, the 30-100% goal feed rate range in this study exists within that middle tertile of the ACCP guidelines, given the use of low dextrose content enteral nutrition formulations.

In this study, the first 50 patients spent on average 61% of the time at or above the 60% of goal feed rate. The average feed rate of 63% of goal feed would equate to 460kcal/day from dextrose (1204 kcal/day total) for an 80kg male. This value is in the middle of the more optimal middle tertile of the ACCP guidelines [63] that Krishnan et al [12] reported as having the lowest mortality. This last point provides some further measure of confidence that the results of this approach are supported by other clinical evidence.

In addition, hyperglycaemia has also been shown to exacerbate muscle protein catabolism in burn patients [91] indicating that excessive nutrition should be avoided in this instance, as well. Similarly, reduced caloric nutritional support has been effective in paediatric and neonatal care and for the obese [61, 73, 92]. Thus, there is reasonable evidence that moderate reductions in nutrition may increase critical care survival and will not reduce other clinical outcomes. However, extreme or long-term underfeeding should be avoided [93].

4.4 The Effect of Insulin in Glycemic Control

The approach presented here is in somewhat stark contrast to the original hypotheses behind tight control with intensive insulin therapy [5, 94]. Specifically, an initial goal of tight control was to

maximize the amount of insulin given, counterbalanced by nutritional inputs, to maximize the potential anti-inflammatory benefits of insulin outside the metabolic considerations. The fundamental idea was that the anti-inflammatory effects of insulin would ameliorate the inflammatory pathways that feature prominently in sepsis, infection and multi-organ failure [94]. In particular, it has been shown that insulin does exert anti-inflammatory effects in the critically ill, which has been shown to have influence on the inflammation and infection/sepsis encountered as a result [15, 18, 95, 96]. However, it has also been shown that the primary outcome benefit of tight control is in the tight glucose levels achieved although the contribution of insulin in a non-metabolic manner has been noted but not fully apportioned, suggesting that over broad cohort studies it does not outweigh the metabolic effects [22, 96].

Therefore, it should be noted that insulin plays multiple roles that are both metabolic and non-metabolic. As a result, an insulin plus nutrition approach as presented here may have a lesser effect on mortality in a longer randomized trial due to using reduced levels of insulin that are, in this case, approximately 65% of those utilized in van den Berghe's two studies. These results would be particularly apparent in sepsis or infection, and represent a potential limitation of this approach that will require further study.

4.5 Study Limitations

This study is initial and ongoing. It also has limitations in its scope as the primary endpoint is the tightness of control. In this regard, it considers the weight of evidence for tight control and its outcome benefits [5, 18, 20-23] to be enough justification to examine primarily the tightness that can be achieved, preparatory to determining its global impact in a randomized trial. In particular, recent analyses have indicated that the tighter the control obtained, the lower the standardized mortality [97]. Hence, the primary measurements to date that are of statistical significance are based on glycemic time in band and

variability, the latter of which is also becoming well related to inflammatory cascade and reduced insulin sensitivity seen in critical care [16, 98-100], and the resulting poor response to infection [101, 102].

A second potential limitation is that this study reduces glucose in part by modulating nutritional inputs, which are almost entirely an enteral with total parenteral nutrition (TPN) used in some cases. In addition, it focuses its control on the modulation of carbohydrate content in adjusting dextrose. This approach presents two primary potential difficulties in being generalised. First it does not address the differences in type of feeding. However, enteral feeding is the most variable given the absorption rates required, as outlined in Equations (4)-(5), where, in contrast, TPN would see more dramatic and predictable changes in plasma appearance. Finally, the use of intravenous glucose would be similar to TPN, but more difficult to modulate, given the fixed concentration, except by modulating the drip rate itself, which would present difficulties in terms of clinical ease of use.

Potentially more limiting is the assumption is that the nutrition be comprised of approximately 35% of calories by carbohydrate. This limitation does not affect the wheels or system in Figures 1-3 directly. However, if an enteral feed of 50% carbohydrate content were given, which is approximately 30% greater than assumed, the percentage feed rates used in SPRINT would have to be adjusted downward accordingly in creating the feed stickers. This approach does not limit efficacy and in turn provides the same expected carbohydrate load, making the system fully general. Where it is a limitation, is in the use of high carbohydrate feeds reducing the total caloric intake to potentially quite low levels that may not be locally or clinically acceptable. Longer term this issue would have to be addressed in either how nutrition formulas are implemented, perhaps separately for carbohydrate, or in the formulation used. Note that for a fully computerized approach as in Wong et al and Chase et al [65, 66, 75, 103], these issues could be more directly accounted for in the controller, versus the use of the relatively fixed and less general SPRINT wheels. However, it should also be noted that the SPRINT wheels were created

primarily as a means of obtaining widespread clinical results at minimal effort, and not entirely as an end-point solution.

Finally, there is potentially debate about the use of nutrition as a reliable control input, which may be a limitation of the method. In particular, different enteral nutrition formulations will absorb at different rates depending on the form of the carbohydrate used to provide nutrition. For example, longer chained saccharides will appear from the gut at slower rates than smaller chain carbohydrates like dextrose, and as a result more variability in appearance may also be seen. In addition, the ability of the gut to digest enteral feed may be quite variable across critically ill cohorts.

The formulation used in this study, Diabetic RESOURCE™ by Novartis utilizes Dextrin, Fructose, Corn Syrup Solids, covering a typical range of carbohydrate chain sizes [70]. In all computerized trials, hourly target accuracy utilizing this formulation and nutrition as a control input was 94% with differences explained by physiological changes in patient condition, such as atrial fibrillation [65, 66].These results were obtained using very standard population models for the two compartment model of Equations (4)-(5) as discussed earlier. More specifically, the current evidence of this limited, initial trial is that this potential variability is not evident beyond changes in patient condition over the same 1-2 hour timeframe. However, further evidence with specific study would be required to prove this point conclusively, and/or to delineate those cases or situations where it was not applicable.

4.6 Glycaemic Performance and Clinical Burden

This study also raises the question of what is the best measure of blood glucose control. van den Berghe et al [5, 22, 23] used mean morning glucose, and thus did not include several daily measurements. Krinsley [20, 21], Laver et al [27], Goldberg et al [26] and others [39, 40] have used average glucose

over all treatment, even if, or when, the glucose distribution may not be normal. This study proposes that time in a relevant tight glucose range, such as 4.0-6.1 mmol/L or 4.0-7.75 mmol/L, provides more complete information. In particular, maximizing time in band tightens control, while still allowing variation with condition within the band.

More specifically, this approach seeks any glucose level in the desired 4.0-6.1 mmol/L band as long as variation is also restricted. By reducing variability, it decreases the risk of hypoglycaemia. In addition, evidence is showing that minimizing exposure to hyperglycaemia has a significant effect on a variety of cell functions and immune response [16, 22, 94, 100, 101, 104, 105]. Hence, tight control may also have positive impact on clinical outcomes by minimising exposure to hyperglycaemic levels.

With respect to clinical burden, SPRINT is effectively automated as currently implemented by nursing staff. It has not required any form of additional clinical input, modification or intervention. The frequent blood glucose measurement required by SPRINT has been accepted by nurses in this initial study, as the protocol prescribes definitive actions without the need for consultation. Hence, it has been found to reduce concerns experienced using ad-hoc methods that produce variable results and require additional input or modification. Specifically, the tight control reported in these results has anecdotally further encouraged nursing staff, as it provides tight, predictable control without the need to constantly analyse or revise the protocol for specific patients when variable results are encountered.

As a result, there is currently a high level of support for the SPRINT protocol among clinical staff at this first site, and minimal non-compliance (<0.2%) is seen in the data recorded for each patient. In an informal survey of the nursing staff all reported the system easy to use and believed the improved glycaemic control justified the additional effort of 1-2 hourly measurement. These last results stand in contrast to several studies [5, 20, 49, 50, 52, 53, 106] that report the need for extra staffing and/or note

the burdensome extra effort that may be required to provide intensive insulin therapy protocols in a critical care setting.

Finally, it must be noted that this pilot with 7358 hours of control represents only approximately 10-15% of the patient days in van den Berghe [5, 23] and Krinsley [20, 21]. Overall, these initial pilot trial results indicate that extremely tight control can be achieved for a critically ill cohort with relatively high APACHE II scores and concomitantly significant insulin resistance. More importantly, it can be achieved with relatively minimal clinical effort and a high level of automation using the simple protocol presented that varies both nutritional and insulin inputs.

5.0 CONCLUSIONS

There are two main results from this overview of the model-based and ad-hoc clinical treatment of hyperglycaemia in critical care. First, the virtual patient trial simulation and design approach is validated as an effective means of developing clinical protocols for tight glycaemic control. The virtual trial results are very close to reported clinical results from other studies, with differences attributable to differences in patient cohort and level of critical illness. In addition, the first 50 cases on SPRINT had high correlation to the virtual trial simulations further validating the approach taken. However, the main advantage offered is the ability to determine the potential glycaemic control outcome before clinical implementation, significantly enhancing the supporting data for clinical implementation decisions. They also save significant development time as they can be performed much more rapidly than clinical pilot testing, and offer more certainty of the eventual outcome. Second, the variable insulin and nutrition glycaemic control approach, as seen with the SPRINT protocol, provides a long term, stable method of tightly controlling blood glucose for a very critically ill cohort.

Thus, this paper presents a different design approach based on model-based systems and control theory, as well as a novel method of improving or optimizing the delivery of insulin for tight glycaemic control in a critical care environment. The virtual trials approach can also be readily generalised to similar drug delivery problems. Finally, this study also raises the opportunity to begin asking several new clinical questions. In particular, the ability to tightly and consistently clamp patient glycaemic levels offer the potential to examine the level of tight glucose control required to achieve more optimal clinical outcomes, the optimal glycaemic performance targets for best clinical outcome, and the impact of different types of critically ill cohort.

REFERENCES

1. Capes, S. E.; Hunt, D.; Malmberg, K.; Gerstein, H. C. *Lancet* **2000,** *355*, (9206), 773.
2. McCowen, K. C.; Malhotra, A.; Bistrian, B. R. *Crit. Care Clin.* **2001,** *17*, (1), 107.
3. Mizock, B. A. *Best Pract. Res. Clin. Endocrinol. Metab.* **2001,** *15*, (4), 533.
4. Thorell, A.; Rooyackers, O.; Myrenfors, P.; Soop, M.; Nygren, J.; Ljungqvist, O. H. *J. Clin. Endocrinol. Metab.* **2004,** *89*, (11), 5382.
5. Van den Berghe, G.; Wouters, P.; Weekers, F.; Verwaest, C.; Bruyninckx, F.; Schetz, M.; Vlasselaers, D.; Ferdinande, P.; Lauwers, P.; Bouillon, R. *N. Engl. J. Med.* **2001,** *345*, (19), 1359.
6. Krinsley, J. S. *Mayo Clin. Proc.* **2003,** *78*, (12), 1471.
7. Patino, J. F.; de Pimiento, S. E.; Vergara, A.; Savino, P.; Rodriguez, M.; Escallon, J. *World J. Surg.* **1999,** *23*, (6), 553.
8. Weissman, C. *Crit. Care* **1999,** *3*, (5), R67.
9. Woolfson, A. M. *Intensive Care Med.* **1980,** *7*, (1), 11.
10. Ahrens, C. L.; Barletta, J. F.; Kanji, S.; Tyburski, J. G.; Wilson, R. F.; Janisse, J. J.; Devlin, J. W. *Crit. Care Med.* **2005,** *33*, (11), 2507.
11. Kim, H.; Son, E.; Kim, J.; Choi, K.; Kim, C.; Shin, W.; Suh, O. *Am. J. Health Syst. Pharm.* **2003,** *60*, (17), 1760.
12. Krishnan, J. A.; Parce, P. B.; Martinez, A.; Diette, G. B.; Brower, R. G. *Chest* **2003,** *124*, (1), 297.
13. Elia, M.; Ceriello, A.; Laube, H.; Sinclair, A. J.; Engfer, M.; Stratton, R. J. *Diabetes Care* **2005,** *28*, (9), 2267.
14. Bistrian, B. R. *JPEN J. Parenter. Enteral Nutr.* **2001,** *25*, (4), 180.
15. Das, U. N. *J. Assoc. Physicians India* **2003,** *51*, 695.
16. Marik, P. E.; Raghavan, M. *Intensive Care Medicine* **2004,** *30*, (5), 748.
17. Oddo, M.; Schaller, M. D.; Calandra, T.; Liaudet, L. *Rev. Med. Suisse Romande* **2004,** *124*, (6), 329.
18. Langouche, L.; Vanhorebeek, I.; Vlasselaers, D.; Vander Perre, S.; Wouters, P. J.; Skogstrand, K.; Hansen, T. K.; Van den Berghe, G. *J. Clin. Invest.* **2005,** *115*, (8), 2277.
19. Diringer, M. N. *Neurology* **2005,** *64*, (8), 1330.
20. Krinsley, J. S. *Crit. Care Med.* **2003,** *31*, A19.
21. Krinsley, J. S. *Mayo. Clin. Pro.c* **2004,** *79*, (8), 992.
22. Van den Berghe, G.; Wouters, P. J.; Bouillon, R.; Weekers, F.; Verwaest, C.; Schetz, M.; Vlasselaers, D.; Ferdinande, P.; Lauwers, P. *Crit. Care Med.* **2003,** *31*, (2), 359.
23. Van den Berghe, G.; Wilmer, A.; Hermans, G.; Meersseman, W.; Wouters, P. J.; Milants, I.; Van Wijngaerden, E.; Bobbaers, H.; Bouillon, R. *N. Engl. J. Med.* **2006,** *354*, (5), 449.
24. Krinsley, J. S.; Jones, R. L. *Chest* **2006,** *129*, (3), 644.
25. Van den Berghe, G.; Wouters, P. J.; Kesteloot, K.; Hilleman, D. E. *Crit. Care Med.* **2006,** *34*, (3), 612.
26. Goldberg, P. A.; Siegel, M. D.; Sherwin, R. S.; Halickman, J. I.; Lee, M.; Bailey, V. A.; Lee, S. L.; Dziura, J. D.; Inzucchi, S. E. *Diabetes Care* **2004,** *27*, (2), 461.
27. Laver, S.; Preston, S.; Turner, D.; McKinstry, C.; Padkin, A. *Anaesth. Intensive Care* **2004,** *32*, (3), 311.
28. Thomas, A. N.; Marchant, A. E.; Ogden, M. C.; Collin, S. *Anaesthesia* **2005,** *60*, (11), 1093.
29. Basi, S.; Pupim, L. B.; Simmons, E. M.; Sezer, M. T.; Shyr, Y.; Freedman, S.; Chertow, G. M.; Mehta, R. L.; Paganini, E.; Himmelfarb, J.; Ikizler, T. A. *American Journal of Physiology-Renal Physiology* **2005,** *289*, (2), F259.
30. Lind, L.; Lithell, H. *Clin. Intensive Care* **1994,** *5*, (3), 100.

31. Christiansen, C.; Toft, P.; Jorgensen, H. S.; Andersen, S. K.; Tonnesen, E. *Intensive Care Medicine* **2004,** *30*, (8), 1685.
32. Gale, S. C.; Gracias, V. H. *Critical care medicine* **2006,** *34*, (6), 1856.
33. Chase, J. G.; Shaw, G. M.; Lin, J.; Doran, C. V.; Hann, C.; Robertson, M. B.; Browne, P. M.; Lotz, T.; Wake, G. C.; Broughton, B. *Med. Eng. Phys.* **2005,** *27*, (1), 1.
34. Chase, J. G.; Shaw, G. M.; Lin, J.; Doran, C. V.; Hann, C.; Lotz, T.; Wake, G. C.; Broughton, B. *Diabetes Technol. Ther.* **2005,** *7*, (2), 274.
35. Chee, F.; Fernando, T. L.; Savkin, A. V.; van Heeden, V. *IEEE Trans. Inf. Technol. Biomed.* **2003,** *7*, (4), 419.
36. Blaha, J.; Hovorka, R.; Matias, M.; Kotulak, T.; Kremen, J.; Sloukova, A.; Svacina, S.; Haluzik, M. *Intensive Care Med.* **2005,** *31*, (S1), S203.
37. Chee, F.; Fernando, T.; van Heerden, P. V. *Anaesth. Intensive Care* **2002,** *30*, (3), 295.
38. Chee, F.; Fernando, T.; van Heerden, P. V. *IEEE Trans. Inf. Technol. Biomed.* **2003,** *7*, (1), 43.
39. Plank, J.; Blaha, J.; Cordingley, J.; Wilinska, M. E.; Chassin, L. J.; Morgan, C.; Squire, S.; Haluzik, M.; Kremen, J.; Svacina, S.; Toller, W.; Plasnik, A.; Ellmerer, M.; Hovorka, R.; Pieber, T. R. *Diabetes Care* **2006,** *29*, (2), 271.
40. Vogelzang, M.; Zijlstra, F.; Nijsten, M. W. *BMC Med. Inform. Decis. Mak.* **2005,** *5*, (38), 10-pages.
41. Chase, J. G.; Lonergan, T.; LeCompte, A.; Willacy, M.; Shaw, G. M.; Wong, X. W.; Lin, J.; Lotz, T.; Hann, C. E. In *Tight glucose control in critically ill patients using a specialized insulin-nutrition table*, Proc. of the 12th International Conf. on Biomedical Engineering (ICBME 2005), Singapore, Dec 7-10, 2005; IFMBE 'Ed.' Singapore, 2005; pp 4-pages.
42. Wong, X. W.; Chase, J. G.; Shaw, G. M.; Hann, C. E.; Lin, J.; Lotz, T. In *Comparison of Adaptive and Sliding-Scale Glycaemic Control in Critical Care and the Impact of Nutritional Inputs*, Proc. of the 12th International Conf. on Biomedical Engineering (ICBME 2005), Singapore, Dec. 7-10, 2005; IFMBE 'Ed.' Singapore, 2005; pp 4-pages.
43. Kletter, G. G. *Arch. Intern. Med.* **1998,** *158*, (13), 1472.
44. Radack, H. B. *Arch. Intern. Med.* **1997,** *157*, (15), 1776.
45. Sawin, C. T. *Arch. Intern. Med.* **1997,** *157*, (5), 489.
46. Chant, C.; Wilson, G.; Friedrich, J. O. *Pharmacotherapy* **2005,** *25*, (3), 352.
47. Shaw, G. M.; Chase, J. G.; Wong, J.; Lin, J.; Lotz, T.; Le Compte, A. J.; Lonergan, T. R.; Willacy, M. B.; Hann, C. E. *Crit. Care. Resusc.* **2006,** *8*, (2), 90.
48. Lonergan, T.; LeCompte, A.; Willacy, M.; Chase, J. G.; Shaw, G. M.; Wong, X. W.; Lotz, T.; Lin, J.; Hann, C. E. *Diabetes Technol. Ther.* **2006,** *8*, (2), 191.
49. Waeschle, R.; Moerer, O.; Wahaha, D.; Neumann, P.; Quintel, M. *Intensive Care Med.* **2005,** *31*, (S1), S203.
50. Mackenzie, I.; Ingle, S.; Zaidi, S.; Buczaski, S. *Intensive Care Med* **2005,** *31*, (8), 1136.
51. Bland, D. K.; Fankhanel, Y.; Langford, E.; Lee, M.; Lee, S. W.; Maloney, C.; Rogers, M.; Zimmerman, G. *Am. J Crit. Care* **2005,** *14*, (5), 370.
52. Di Nardo, M. M.; Korytkowski, M. T.; Siminerio, L. S. *Crit. Care Nurs. Q.* **2004,** *27*, (2), 126.
53. Schultz, M. J.; Spronk, P. E.; Moeniralam, H. S. *Intensive Care Med.* **2006,** *32*, (4), 618.
54. Carson, E. R.; Cobelli, C., *Modelling methodology for physiology and medicine*. ed.; Academic Press: San Diego, 2001; xiv, 421.
55. Chase, J. G.; Lam, Z. H.; Lee, J. Y.; Hwang, K. S. In *Active Insulin Infusion Control of the Blood Glucose Derivative*, Proc. of the 7th International Conf. on Control, Automation, Robotics and Vision (ICARCV 2002), Singapore, Dec. 2-5, 2002; NTU 'Ed.' Singapore, 2002; pp 1162.
56. Chase, J. G.; Shaw, G. M.; Doran, C. V.; Hudson, N. H.; Moorhead, K. T. In *Derivative Weighted Active Insulin Control Algorithms and Trials*, IFAC Symposium, Melbourne, Australia, August 21-23, 2003; E.R. Carson 'Ed.' Melbourne, Australia, 2003; pp 83.

57. Prigeon, R. L.; Roder, M. E.; Porte, D., Jr.; Kahn, S. E. *J. Clin. Invest.* **1996,** *97*, (2), 501.
58. Natali, A.; Gastaldelli, A.; Camastra, S.; Sironi, A. M.; Toschi, E.; Masoni, A.; Ferrannini, E.; Mari, A. *Am. J. Physiol. Endocrinol. Metab.* **2000,** *278*, (5), E794.
59. Chase, J. G.; Shaw, G. M.; Lin, J.; Doran, C. V.; Bloomfield, M.; Wake, G. C.; Broughton, B.; Hann, C.; Lotz, T. *International Journal of Intelligent Systems Technologies and Applications (IJISTA)* **2004,** *1*, (1/2), 79.
60. Rizza, R. A.; Mandarino, L. J.; Gerich, J. E. *Am. J. Physiol.* **1981,** *240*, (6), E630.
61. Dickerson, R. N. *Curr. Opin. Clin. Nutr. Metab. Care* **2005,** *8*, (2), 189.
62. McCowen, K. C.; Friel, C.; Sternberg, J.; Chan, S.; Forse, R. A.; Burke, P. A.; Bistrian, B. R. *Crit Care Med* **2000,** *28*, (11), 3606.
63. Cerra, F. B.; Benitez, M. R.; Blackburn, G. L.; Irwin, R. S.; Jeejeebhoy, K.; Katz, D. P.; Pingleton, S. K.; Pomposelli, J.; Rombeau, J. L.; Shronts, E.; Wolfe, R. R.; Zaloga, G. P. *Chest* **1997,** *111*, (3), 769.
64. Hann, C. E.; Chase, J. G.; Lin, J.; Lotz, T.; Doran, C. V.; Shaw, G. M. *Comput. Methods Programs Biomed.* **2005,** *77*, (3), 259.
65. Wong, X.; Chase, J. G.; Shaw, G. M.; Hann, C.; Lotz, T.; Lin, J.; Singh-Levett, I.; Hollingsworth, L.; Wong, O.; Andreassen, S. *Medical Engineering & Physics* **2006,** *28*, (7), 665.
66. Wong, X. W.; Singh-Levett, I.; Hollingsworth, L. J.; Shaw, G. M.; Hann, C. E.; Lotz, T.; Lin, J.; Wong, O. S.; Chase, J. G. *Diabetes Technol. Ther.* **2006,** *8*, (2), 174.
67. Doran, C. V. Modelling and Control of Hyperglycemia in Critical Care Patients. Masters of Engineering (ME), University of Canterbury, Christchurch, New Zealand, 2004.
68. Wong, X. W.; Shaw, G. M.; Hann, C. E.; Lotz, T.; Lin, J.; Singh-Levett, I.; Hollingsworth, L.; Wong, O. S.; Chase, J. G. *Diabetes Technol. Ther.* **2006,** *8*, (2), 174.
69. Wong, X. W.; Chase, J. G.; Shaw, G. M.; Hann, C.; Lin, J.; Lotz, T. In *Comparison of adaptive and sliding scale glycaemic control in critical care and the impact of nutritional inputs*, 12th Intl. Conf. on Biomedical Engineering (ICBME), Dec 7-10, 2005; IFMBE 'Ed.' 2005; 4-pages.
70. Novartis, RESOURCE® Diabetic Nutrition Information. In Novartis Medical Nutrition: US, 2005; Technical Sheet, 1-page.
71. Lonergan, T.; LeCompte, A.; Willacy, M.; Chase, J.; Shaw, G.; Hann, C.; Lotz, T.; Lin, J.; Wong, X. *Diabetes Technol. Ther.* **2006,** *84*, (4), 449.
72. Rubinson, L.; Diette, G. B.; Song, X.; Brower, R. G.; Krishnan, J. A. *Crit. Care Med.* **2004,** *32*, (2), 350.
73. Iyer, P. U. *Indian J Pediatr.* **2002,** *69*, (5), 405.
74. Jeejeebhoy, K. N. *Nutr. Clin. Pract.* **2004,** *19*, (5), 477.
75. Chase, J.; Shaw, G. M.; Wong, X. W.; Lotz, T.; Lin, J.; Hann, C. E. *Biomedical Signal Processing & Control* **2006,** *1*, (1), 3.
76. Hirsch, I. B.; Brownlee, M. *J Diabetes Complications* **2005,** *19*, (3), 178.
77. Shaw, G. M.; Chase, J. G.; Lee, D. S.; Bloomfield, M.; Doran, C. V.; Lin, J.; Lotz, T. *Critical Care Medicine* **2005,** *32*, (12), A125.
78. Klonoff, D. C. *Diabetes Care* **2004,** *27*, (3), 834.
79. Klonoff, D. C. *Diabetes Technol. Ther.* **2002,** *4*, (6), 763.
80. Solnica, B.; Naskalski, J. W.; Sieradzki, J. *Clin. Chim. Acta* **2003,** *331*, (1-2), 29.
81. Weitgasser, R.; Gappmayer, B.; Pichler, M. *Clinical Chemistry* **1999,** *45*, (10), 1821.
82. Knaus, W. A.; Draper, E. A.; Wagner, D. P.; Zimmerman, J. E. *Crit. Care Med.* **1985,** *13*, (10), 818.
83. Ledoux, D.; Finfer, S.; McKinley, S. *Anaesthesia and intensive care* **2005,** *33*, (5), 585-90.
84. Del Bufalo, C.; Morelli, A.; Bassein, L.; Fasano, L.; Quarta, C. C.; Pacilli, A. M.; Gunella, G. *Respiratory Care* **1995,** *40*, (10), 1042.
85. Sleigh, J. W.; Brook, R. J.; Miller, M. *Anaesthesia and intensive care* **1992,** *20*, (1), 63-5.

86. Kiwanuka, E.; Barazzoni, R.; Tessari, P. *Diabetes Nutrition & Metabolism* **2001,** *14*, (6), 315.
87. Ludvik, B.; Nolan, J. J.; Roberts, A.; Baloga, J.; Joyce, M.; Bell, J. M.; Olefsky, J. M. *Journal of Clinical Investigation* **1997,** *100*, (9), 2354.
88. Radziuk, J.; McDonald, T. J.; Rubenstein, D.; Dupre, J. *Metabolism-Clinical and Experimental* **1978,** *27*, (6), 657.
89. Agus, M. S.; Javid, P. J.; Ryan, D. P.; Jaksic, T. *Journal of pediatric surgery* **2004,** *39*, (6), 839-44; discussion 839.
90. Poindexter, B. B.; Karn, C. A.; Denne, S. C. *The Journal of pediatrics* **1998,** *132*, (6), 948-53.
91. Gore, D. C.; Chinkes, D. L.; Hart, D. W.; Wolf, S. E.; Herndon, D. N.; Sanford, A. P. *Crit Care Med* **2002,** *30*, (11), 2438.
92. Dickerson, R. N.; Boschert, K. J.; Kudsk, K. A.; Brown, R. O. *Nutrition* **2002,** *18*, (3), 241-6.
93. Villet, S.; Chiolero, R. L.; Bollmann, M. D.; Revelly, J. P.; Cayeux, R. N. M.; Delarue, J.; Berger, M. M. *Clin. Nutr.* **2005,** *24*, (4), 502.
94. Van den Berghe, G. *J Clin Invest* **2004,** *114*, (9), 1187.
95. Dandona, P.; Mohanty, P.; Chaudhuri, A.; Garg, R.; Aljada, A. *The Journal of clinical investigation* **2005,** *115*, (8), 2069.
96. Hansen, T. K.; Thiel, S.; Wouters, P. J.; Christiansen, J. S.; Van den Berghe, G. *The Journal of clinical endocrinology and metabolism* **2003,** *88*, (3), 1082.
97. Chase, J. G.; Hann, C. E.; Shaw, G. M.; Wong, X. W.; Lin, J.; Lotz, T.; Le Compte, A. J.; Lonergan, T. *Journal of Diabetes Science and Technology (http://www.journalofdst.org)* **2006,** *1*, (1), 82.
98. Fernandez-Real, J. M.; Broch, M.; Richart, C.; Vendrell, J.; Lopez-Bermejo, A.; Ricart, W. *The Journal of clinical endocrinology and metabolism* **2003,** *88*, (4), 1780.
99. Vozarova, B.; Weyer, C.; Lindsay, R. S.; Pratley, R. E.; Bogardus, C.; Tataranni, P. A. *Diabetes* **2002,** *51*, (2), 455.
100. Gubern, C.; Lopez-Bermejo, A.; Biarnes, J.; Vendrell, J.; Ricart, W.; Fernandez-Real, J. M. *Diabetes* **2006,** *55*, (1), 216.
101. Monnier, L.; Mas, E.; Ginet, C.; Michel, F.; Villon, L.; Cristol, J. P.; Colette, C. *JAMA* **2006,** *295*, (14), 1681.
102. Krogh-Madsen, R.; Moller, K.; Dela, F.; Kronborg, G.; Jauffred, S.; Pedersen, B. K. *Am. J. Physiol. Endocrinol. Metab.* **2004,** *286*, (5), E766.
103. Chase, J.; Shaw, G.; LeCompte, A.; Lee, D.; Lonergan, T.; Willacy, M.; Wong, X.; Lin, J.; Lotz, T.; Hann, C. In *Tight Glycaemic Control in Critical Care Using Insulin and Nutrition – the SPRINT Protocol*, 6th Annual Diabetes Technology Meeting, Atlanta, GA, November 2-4, 2006; Klonoff, D., 'Ed.' Diabetes Technology Society: Atlanta, GA, 2006; pp 1-page.
104. Van den Berghe, G.; Schoonheydt, K.; Becx, P.; Bruyninckx, F.; Wouters, P. J. *Neurology* **2005**, 1348.
105. Lin, Y.; Kohn, F. R.; Kung, A. H.; Ammons, W. S. *Biochemical pharmacology* **1994,** *47*, (9), 1553.
106. Bland, D.; Fankhanel, Y.; Langford, E.; Lee, M.; Lee, S.; Maloney, C.; Rogers, M.; Zimmerman, G. *American Journal of Critical Care* **2005,** *14*, (5), 370.