

A Simple Insulin-Nutrition Protocol for Tight Glycemic Control in Critical Illness: Development and Protocol Comparison

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ABSTRACT

Background: Hyperglycemia is prevalent in critical care, and tight control can significantly reduce mortality. However, current protocols have been considered taxing to administer and may require extra staff. In addition, increased insulin resistance and saturation effects limit the level of control possible using insulin alone. Thus, regulating both insulin and exogenous nutritional inputs is required to control blood glucose.

Methods: A robust, easy-to-use protocol ["SPRINT" (Specialized Relative Insulin Nutrition Tables)] that employs both insulin and feed modulation is developed and analyzed using retrospective data from 19 patients with average Acute Physiology and Chronic Health Evaluation II score of 21.8. Results are compared with several published protocols in simulation, and verified in a proof-of-concept trial.

Results: In simulation, 61.7% of measurements were in the 75–110 mg/dL band and 83.5% in the 75–140 mg/dL band. Results from the simulation of published protocols agreed with published results. Clinically, for two patients, 64% and 85% of measurements were between 75 and 110 mg/dL during the two proof-of-concept trials. Total enteral feeding was similar to, or exceeded, retrospective data.

Conclusions: Tight control was achieved in simulation using a protocol that is easy to implement in an intensive care unit. Similarly tight control was also maintained during the two proof-of-concept clinical trials. Measurement frequency of 1–2 h is seen to be critical to achieving and maintaining tight control. The overall SPRINT protocol is easy to use for clinical staff and effective in achieving and maintaining normoglycemia in critical illness.

INTRODUCTION

STRESS-INDUCED HYPERGLYCEMIA is prevalent in critical care, and can occur in patients with no history of diabetes.^{1–4} Critically ill pa-

tients exhibit increased endogenous glucose production, reduced insulin production, and increased insulin resistance. Therefore, enteral feeding of glucose and administration of glucocorticoids can further enhance the onset of

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hyperglycemia and insulin resistance, respectively.

Hyperglycemia worsens outcomes leading to risk of further complications, particularly sepsis,⁵ myocardial infarction,¹ and polyneuropathy and multiple organ failure.² Van den Berghe et al.^{2,6} showed that tight glucose control averaging 6.1 mmol/L reduced cardiac intensive care unit (ICU) patient mortality up to 45%. Krinsley^{7,8} showed a 17–29% reduction in mortality over a wider ICU population with a higher glucose average of 140 mg/dL.

Adaptive model-based protocols for insulin-mediated glucose control in critical care have shown promise, but have limitations.^{9–12} Because of increased levels of insulin resistance and the insulin effect saturation,¹³ only limited glycemic reductions can be made using insulin alone.^{9,14} Hence, the only avenue left to control blood glucose is to also control the exogenous nutritional input that exacerbates stress-induced hyperglycemia.^{15–17}

This paper presents a robust, table-based protocol [“SPRINT” (Specialized Relative Insulin Nutrition Tables)] for safe, predictable regulation of glucose levels under elevated insulin resistance. The goal is to maintain blood glucose levels in the target band of 75–110 mg/dL. This protocol has been developed based on computerized glycemic control trials and patient simulations using a physiologically verified insulin–glucose system model.^{11,12} The secondary goal is an easy-to-use system for clinical staff with performance equivalent to the computerized AIC4 protocol of Chase et al.¹¹ and Wong et al.¹² Simulations are used to compare the SPRINT protocol with published glucose management protocols, and to demonstrate the impact of measurement frequency. Finally, the results of two proof-of-concept trials are presented from an ongoing pilot study.

SUBJECTS AND METHODS

System patient modeling

Tight glucose control requires capturing the fundamental dynamics of the glucose regulatory system. Chase et al.^{9,10} and Hann et al.¹⁴ used the system defined:

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

$$\dot{Q} = -kI + kQ \quad (2)$$

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

where $G(t)$ (in mmol/L) is the plasma glucose above an equilibrium level, G_E (in mmol/L), and $I(t)$ (in mmol/L) is the plasma insulin resulting from exogenous insulin input, $u_{ex}(t)$ (in mU/min). The effect of previously infused insulin being utilized over time is represented by $Q(t)$ (in mU/L), with k (in 1/min) accounting for the effective life of insulin in the system. Patient endogenous glucose clearance and insulin sensitivity are p_G (in 1/min) and S_I (in L/mU/min), respectively. The parameter V (in L) is the insulin distribution volume, and n (in 1/min) is the constant first-order decay rate for insulin from plasma. Total plasma glucose input is denoted $P(t)$ (in mmol/L/min). Michaelis-Menten functions are used to model saturation, with α_I (in L/mU) used for the saturation of plasma insulin disappearance, and α_G (in L/mU) for the saturation of insulin-dependent glucose clearance.^{18,19} For the simulations in this study, k , n , α_G , α_I , and V are set to generic population values.^{9,19}

Patient-specific profiles for time-varying S_I and p_G can be generated from retrospective data using this model to create virtual patients^{10,14} to test trial protocols. Virtual trials use these profiles to determine patient-specific blood glucose levels for different insulin and feed inputs. Hence, different protocols can be compared for the same patient, a significant advantage in developing new protocols.

Patient cohort and feed rate data

Long-term virtual trials were performed using retrospective data from 17 patients in a 201-patient data audit.^{14,19} This subset of patients was selected based on the density of available retrospective blood glucose measurements, in an effort to capture most fundamental patient dynamics in simulation. A bias towards diagnosed diabetes is due to the 3-h data density required, as they were closely monitored from admission. Retrospective data from two clini-

cal control trial patients¹¹ prior to their participation were also included for a total of 19. Each record took glucose measurements every 3 h or less, giving adequate data density for model fitting. The average length is 3.9 days (range, 1.4–18.8 days).

The cohort, shown in Table 1, represents a general cross-section of ICU population, Acute Physiology and Chronic Health Evaluation (APACHE II) score (average, 21.8; range, 8–36), age, sex, and mortality. It is worth noting that the APACHE II scores in Table 1 have a much higher mean and range than the larger cohorts in the glycemic control research of Van den Berghe et al.^{2,6} and Krinsley.⁷ Hence, these patients are more critically ill and therefore likelier to exhibit severe stress-induced hyperglycemia stemming from high effective insulin resistance. This effect can also be seen comparing the glycemic limits of (110, 140) mg/dL and the median APACHE II scores of (9.0, 16.9) between Van den Berghe et al.⁶ and Krinsley,⁷ respectively. Ethical consent was granted by the Canterbury Ethics Committee for this retrospective analysis.

The SPRINT protocol is a simplified paper-based implementation of a computerized AIC4 protocol developed by Chase et al.^{11,20} and Wong et al.¹² The computerized AIC4 protocol

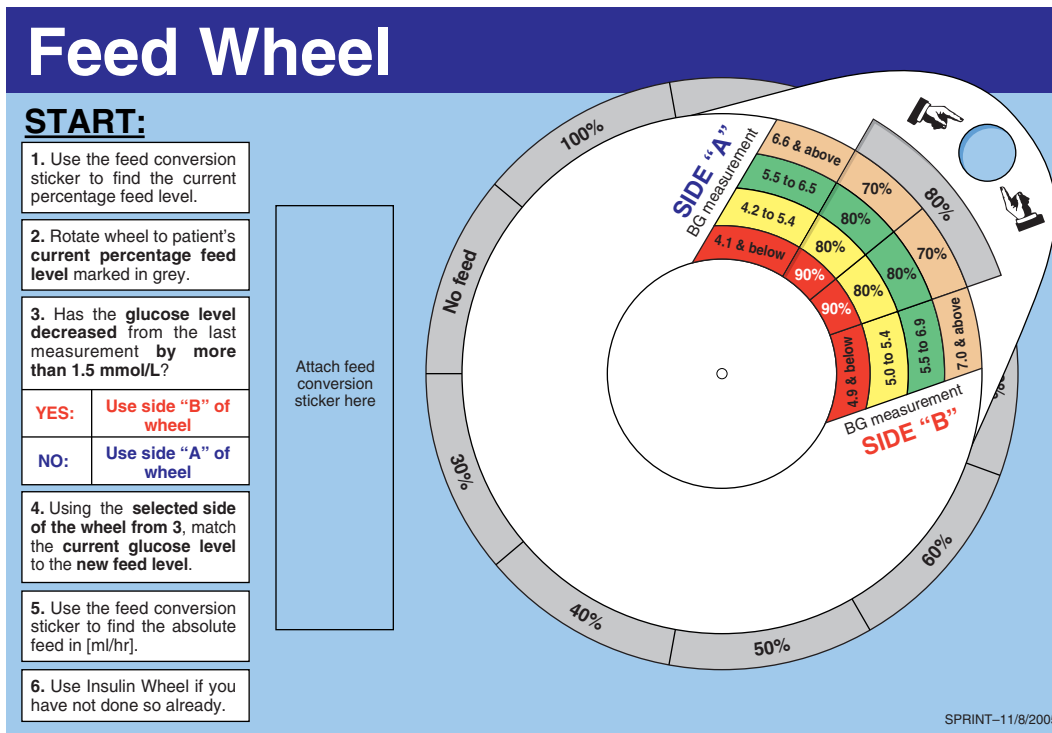
optimizes Eqs. 1–3 to regulate both nutritional and insulin inputs for each hour of patient care. The paper-based SPRINT protocol was developed from the results of simulated patient trials based on the same mathematical model. To compare with protocols that use insulin only, the nutritional inputs used were obtained from the retrospective feed data. Many feed rate variations in ICU are not explicitly intended for maintaining normoglycemia. For variable feed protocols the initial feed rate was the starting value of the retrospective data. The permissible range of feed variation was 280–1,000 kcal/day from glucose. At the 280 kcal/day minimum, the total caloric intake is still 778 kcal/day,²¹ which exceeds the level found to avoid an increased risk of bloodstream infections.²²

SPRINT PROTOCOL

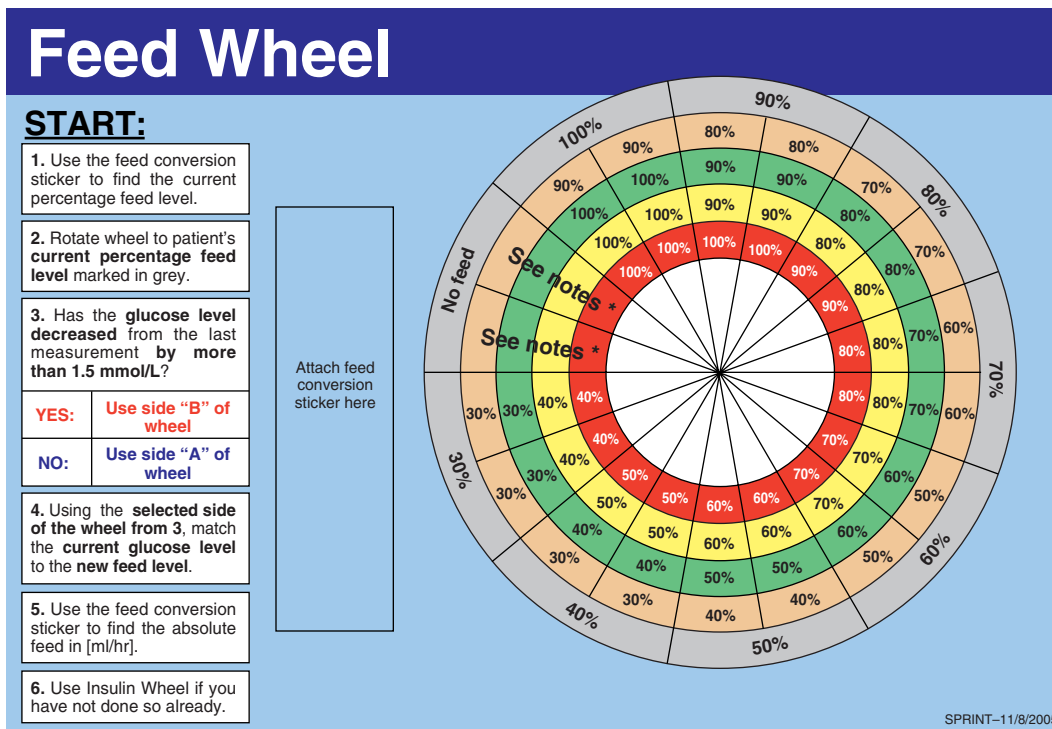
Computerized protocols are effective but require portable computing power, making them difficult to implement in some ICUs. The SPRINT system is designed to provide an easy-to-use equivalent in ICUs where blood glucose measurements are not automated. SPRINT offers a clinically realistic and cost-effective in-

TABLE 1. LONG-TERM VIRTUAL TRIAL PATIENT COHORT

Patient number	Medical subgroup	APACHE II score	Age (years)	Sex	Mortality	Diabetes
1	Sepsis	17	56	M		Type 2
2	Sepsis	24	64	M		
24	Other medical	25	47	M	Yes	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	Yes	
1125	Other medical	Unknown	72	F	Yes	
Average (range)		23 (8–36)	52 (20–76)			

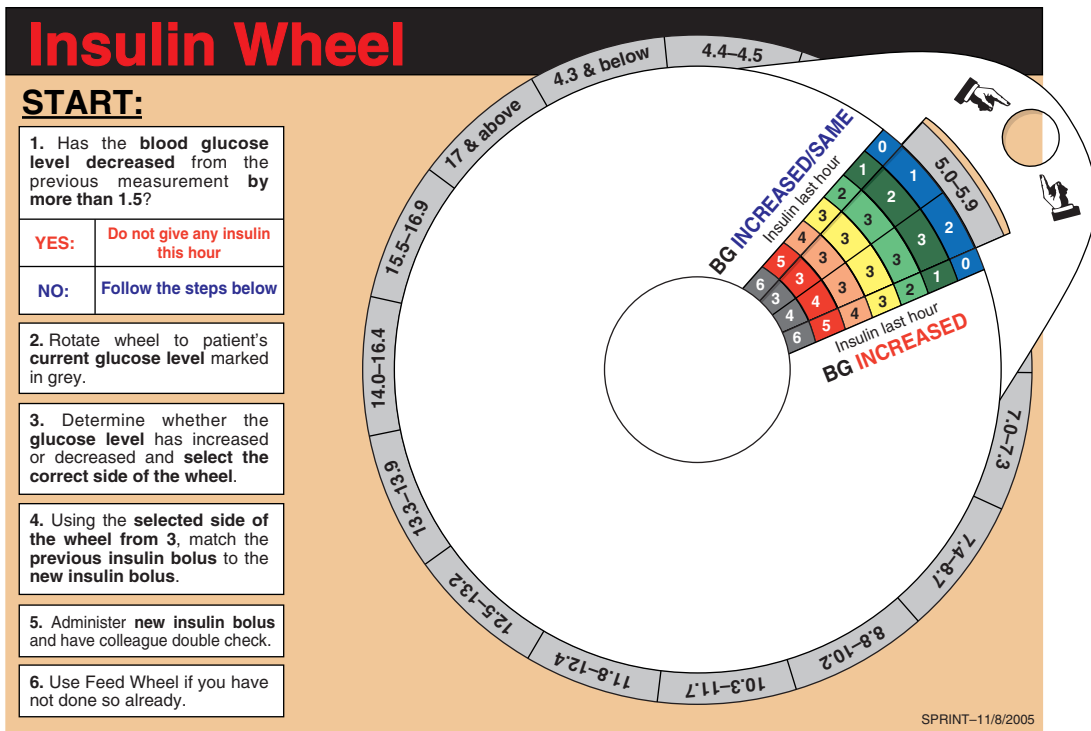


(a)

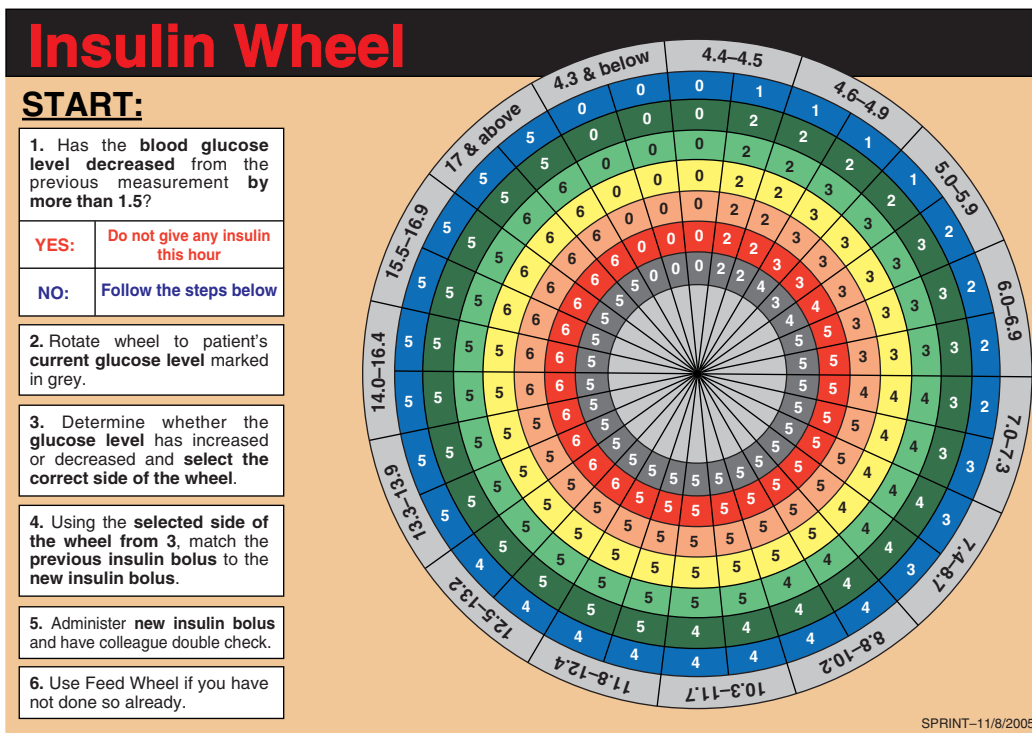


(b)

FIG. 1. The SPRINT feed wheel with dial (a) and with dial removed (b). [Blood glucose (BG) values are in mmol/L; to convert to mg/dL multiply by 18.]



(a)



(b)

FIG. 2. The SPRINT insulin wheel with dial (a) and with dial removed (b). [Blood glucose (BG) values are in mmol/L; to convert to mg/dL multiply by 18.]

intermediate solution until a fully automated system arrives. The protocols for controlling feed and insulin inputs were developed through virtual patient trials of the 19-patient cohort to maintain blood glucose levels within the 75–110 mg/dL band. The goal is to achieve equal overall glycemic control to the computerized method using Eqs. 1–3.^{10–12}

The SPRINT protocol consists of two wheels dedicated to enteral nutrition optimization (specifically RESOURCE[®] Diabetic, Novartis Medical Nutrition, Minneapolis, MN) and insulin bolus administration (Actrapid[™], Novo Nordisk, Baegsverd, Denmark), and is shown in Figures 1 and 2. Instructions are printed directly on the tables, and a more detailed guide is located at each patient workstation. The starting criterion is currently set to blood glucose greater than 144 mg/dL for two consecutive

hours. Blood glucose is measured hourly using Glucocard[™] II sensors (Arkray, Inc., Kyoto, Japan), and this measurement used to determine the next hour's intervention. Criteria for 2-h-interval measurement and stopping the protocol are given in Figure 3.

The instructions on the “Feed Wheel” in Figure 1 are used to determine the rate of feed as a percentage of the patient's clinically determined goal feed. The result is based on the previous hour's feed level, the current blood glucose concentration, and whether blood glucose is rising or falling. The percentage goal feed is converted into an absolute feed rate (in mL/h) using a patient-specific conversion sticker attached to the table. Clinical staff enter patient parameters such as age, weight, and sex into a computer program to generate the sticker, which lists percentage feeds and absolute feed

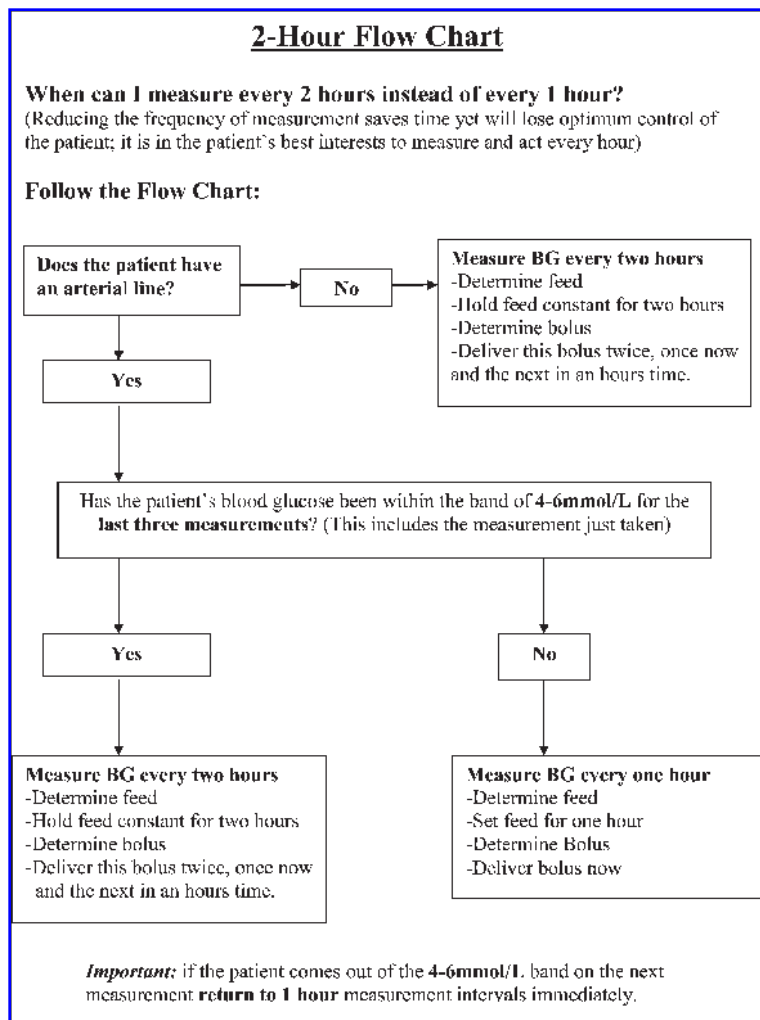


FIG. 3. Flow chart specifying guidelines for measuring blood glucose level at 2-h intervals. [Blood glucose (BG) values are in mmol/L; to convert to mg/dL multiply by 18.]

rates side-by-side to facilitate easy adjustment. The "Insulin Wheel" is then used to determine the insulin bolus size based on the previous insulin bolus size, the current blood glucose level, and whether the blood glucose has decreased by more than 27 mg/dL. The feed and insulin inputs are also recorded on the patient's chart. Hence, the method is effectively fully automated.

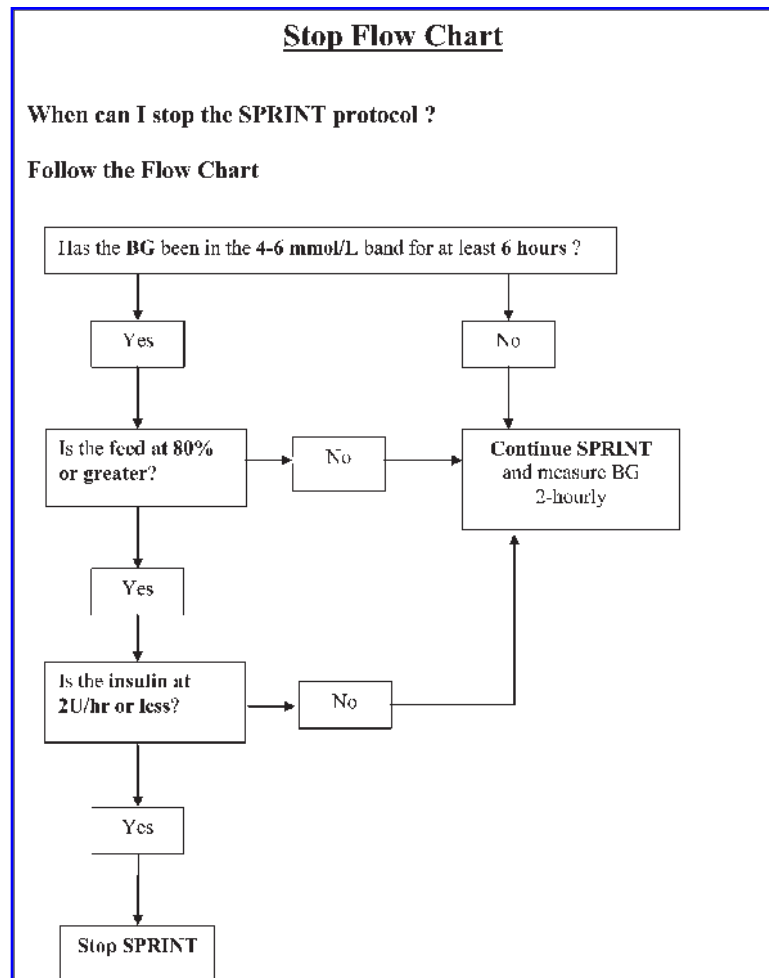
Hourly blood glucose measurements are used to ensure tight control. Measurements at 2-h intervals are used when the patient is stable, defined in Figure 3 as three consecutive measurements in the 75–110 mg/dL (4–6 mmol/L) range. Note that in clinical implementation the limits of 4–6 mmol/L were used to make the target band as easy as possible for nursing staff to remember. For 2-h-interval measurements, the feed rate is maintained constant, and the same insulin bolus is adminis-

tered again on the hour between measurements. Measurements at 2-h intervals are continued until the patient leaves the band of 75–110 mg/dL or SPRINT is stopped.

SPRINT is stopped when the patient is stable, normoglycemic, and adequately self-regulating. Figure 4 defines this state as ≥ 6 h in the 75–110 mg/dL band, with over 80% of goal feed rate and a maximum of 2 U/h of insulin. Finally, insulin is always administered via bolus for patient safety, thus avoiding infusions being left on.

The specific layout of the tables/wheels resulted from extensive consultation with ICU staff. Clinical staff became proficient in minutes and have reported the system is easy to use. In an evaluation survey completed by nursing staff, 24 of 26 respondents rated the ease of use of the SPRINT system as "satisfactory" or better, with 15 respondents rating the system as

FIG. 4. Flow chart specifying guidelines for stopping the SPRINT protocol. [Blood glucose (BG) values are in mmol/L; to convert to mg/dL multiply by 18.]



“good” to “very good.” In clinical implementation, nurses take approximately 2–5 min to use the SPRINT system to determine their hourly actions. The covered wheel concept reduces table complexity, which reduces error. The SPRINT system is simple enough to readily integrate with any typical ICU practice.

OTHER PUBLISHED PROTOCOLS

SPRINT is compared with the published protocols listed in Table 2. The Mayo, Leuven, Bath, and Yale protocols were selected from studies available through PubMed that had a target average glucose level less than 140 mg/dL. SPRINT and AIC4 modulate both feed and insulin, while the remaining protocols utilize insulin only. The Mayo protocol was designed to maintain blood glucose below 140 mg/dL.⁸ The Leuven protocol is from the landmark study by Van den Berghe et al.⁶ with a 110 mg/dL target average. The Bath and Yale protocols are from other recent ICU glycemic control studies.^{23,24} The “Canterbury District Health Board (CDHB) Standard Insulin Sliding Scale” is a standard insulin sliding scale previously used in the Christchurch ICU, and the “Aggressive Insulin Sliding Scale” protocol is a more aggressive form. The “Standard” and “Aggressive” sliding scales are defined in Table 3. Performance is measured by the ability to maintain blood glucose within the 75–110 mg/dL band⁶ or the 75–140 mg/dL band⁸ used in prior studies.

Protocols selected from publications required assumptions where detail was lacking. Specifically, the Leuven, Bath, and Yale protocols made use of glucose shots when hypoglycemia was experienced, which were as-

TABLE 2. PROTOCOLS COMPARED IN VIRTUAL PATIENT SIMULATIONS

SPRINT Protocol
AIC4 Protocol ¹⁰
Mayo Clinic Protocol ⁸
Leuven Protocol ²
Bath University Protocol ²³
Yale University Protocol ²⁴
CDHB Standard Insulin Sliding Scale Protocol
Aggressive Insulin Sliding Scale Protocol

TABLE 3. CDHB STANDARD AND AGGRESSIVE INSULIN SLIDING SCALES

Blood glucose level	Insulin rate	
	Standard	Aggressive
<72 mg/dL	0 U/h	0 U/h
75–106 mg/dL	1 U/h	1 U/h
107–142 mg/dL	2 U/h	2 U/h
143–179 mg/dL	3 U/h	4 U/h
180–215 mg/dL	4 U/h	6 U/h
216–252 mg/dL	5 U/h	6 U/h
>252 mg/dL	6 U/h	6 U/h

sumed to be administered over a 5-min period. No other changes were made from the published protocols.

RESULTS

Each protocol is run over all 19 patients including random measurement errors, simulated as a normally distributed 7% error. Figure 5 shows the resulting distribution density of blood glucose measurements for all of the protocols. SPRINT provided performance comparable with the computerized AIC4 protocol. SPRINT and AIC4 both display much tighter control within the target bands and less incidence of hypoglycemia. The goal of these two protocols is to maximize time within a band, not just a limit or average at the edge of the band. Both protocols avoid insulin saturation, deal with measurement error, and account for inter-patient variability.

The noticeable outlying protocol was from the Mayo Clinic.⁸ However, it was designed to be less intensive with a target average of 140 mg/dL, which it essentially meets. The results in Figure 5 are summarized in Table 4 using log-normal distributions as the best fit to the resulting data ($P < 0.005$).

A two-sample Kolmogorov-Smirnov Test was carried out on all permutations of simulation data sets. The results of these non-parametric tests indicate that none of the data sets can be drawn from the same distribution ($P < 0.005$). Hence any further valid statistical analysis was not possible.

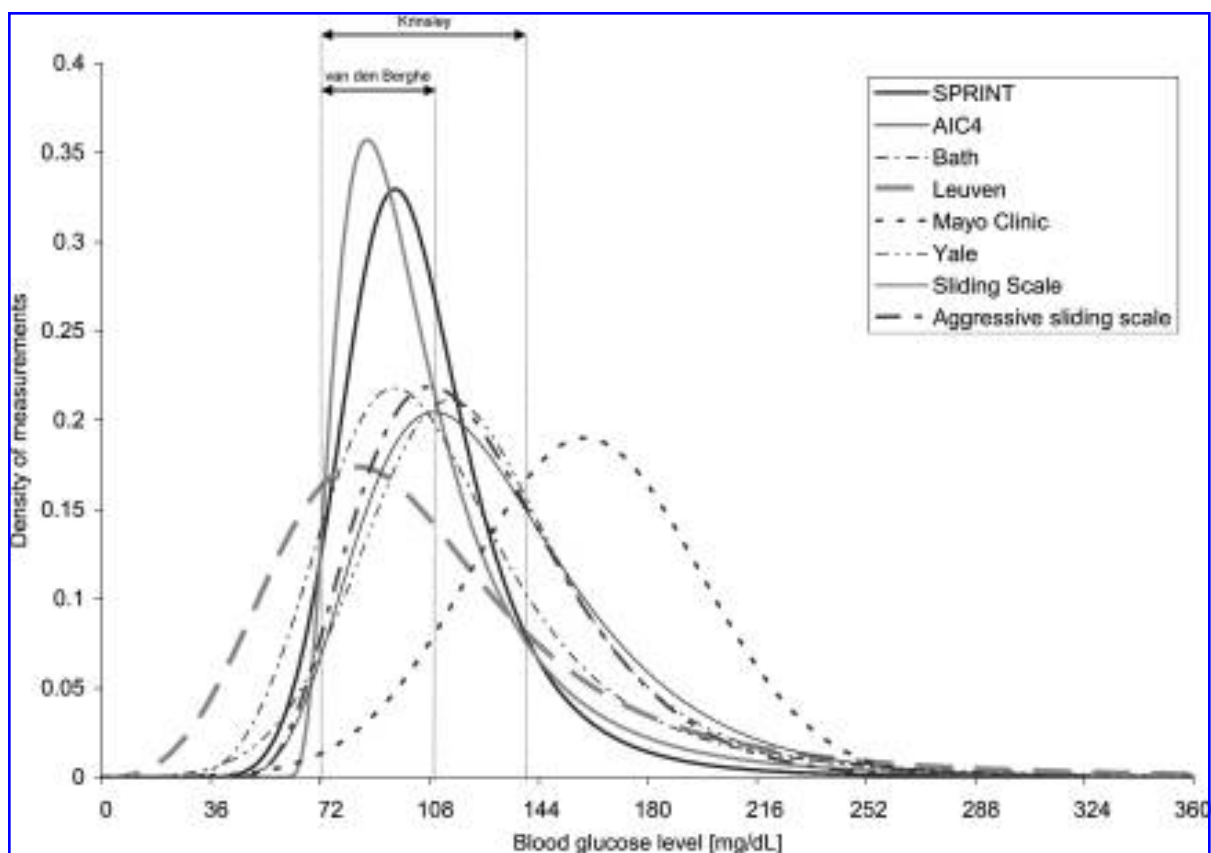


FIG. 5. Distribution of blood glucose measurements, indicating target bands by Van den Berghe et al.⁶ and Krinsley.⁷

The log median blood glucose values for SPRINT and the AIC4 protocol are comparable with the Leuven protocol.^{2,6} However, the 2 SD range of 63.0–172.4 mg/dL for SPRINT compared with that of 37.1–274.3 mg/dL for the Leuven protocol shows much tighter control, with similar results for the 1 SD range. The other insulin-only protocols gave similar larger spreads with higher average levels compared with SPRINT and AIC4, as seen in Table 4. This result shows that SPRINT and AIC4 can tightly regulate blood glucose without significant risk of hypoglycemia, with 0.50% and 0.057% of patient time, respectively, spent at a blood glucose level less than 60 mg/dL, shown in Table 4. The study by Van den Berghe et al.² details the clinical significance of maintaining normoglycemia, and indicates that averages outside the target range are associated with poorer outcomes.⁶ This is significant as many of the protocols in Table 4 had simulated averages above the 110 mg/dL target limit.

All virtual patients were on the same goal feed. SPRINT had the lowest feed at 61.9% of goal feed; however, there was no evidence to suggest that feeding patients at this level is associated with adverse outcomes. In particular, Krishnan et al.²⁵ showed that feeding at a level of 33–66% of the American College of Chest Physicians goal feed (approximately 9–18 kcal/kg/day) was associated with improved mortality and outcomes compared with the 67–100% rate.

The simulated results compare well with reported average values as shown in Table 5, suggesting that the computer simulation method produced realistic results. It is worth noting that the statistical measures presented in Table 5 are not uniform as they are drawn from each respective study. Differences, such as the 2.7% of measurements below 40 mg/dL in the simulated Leuven protocol compared with 1.0% in the reported results,^{2,6} may be due to a more severely ill patient cohort. This virtual cohort

TABLE 4. SUMMARY OF VIRTUAL PATIENT TRIALS OVER THE COHORT OF 19 PATIENTS

	SPRINT	AIC4 ¹⁰	Mayo Clinic ⁸	Leuven ²	Bath ²³	Yale ²⁴	Sliding scale	
							Standard	Aggressive
Log median	104.2	106.7	154.6	100.8	111.8	120.6	124.0	119.0
Multiplicative SD	23.2	24.3	23.2	29.7	26.1	25.2	24.5	23.9
1 SD range	(81.0–134.1)	(79.0–144.2)	(120.2–199.0)	(61.2–166.3)	(76.9–162.5)	(86.0–169.2)	(91.4–167.9)	(89.8–157.9)
2 SD range	(63.0–172.4)	(58.5–194.8)	(93.6–255.6)	(37.1–274.3)	(52.9–236.3)	(61.4–237.2)	(67.5–227.7)	(67.9–209.2)
Blood glucose time								
In 75–110 band	61.7%	62.2%	11.2%	35.8%	45.5%	22.3%	41.9%	43.8%
In 75–140 band	83.5%	82.9%	27.4%	51.0%	70.0%	64.8%	60.0%	65.2%
Less than 70	4.4%	1.1%	0.6%	23.6%	7.1%	5.9%	2.4%	2.8%
Less than 60	0.50%	0.057%	0.15%	11.6%	1.9%	3.3%	0.34%	0.34%
Higher than 140	12.1%	16.1%	72.0%	25.3%	22.9%	29.3%	37.5%	32.0%
Average insulin (U/h)	2.4	2.6	1.6	3.0	5.8	4.6	1.9	2.1
Average % feed of goal	61.9%	75.8%	67.7%	67.7%	71.8%	71.4%	67.7%	67.7%

All blood glucose values are in mg/dL.

has an average APACHE II score of 21.8 versus 9 for the Leuven protocol² and 16.9 for the Mayo protocol.⁷

Another explanation for differences between the simulated and reported results may be due to the assumptions made where the protocols referred to specialized clinical input. The insulin dosages recommended by the Leuven protocol were intended as “directives, rather than strict numerical instructions.”⁶ Insulin dose adjustments in the Leu-

ven 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/h. The advantage of the AIC4 and SPRINT protocols, in all of these cases, is that they are essentially fully automated. Overall, the results are qualitatively similar to the reported values adding weight to these simulation results.

TABLE 5. COMPARISON BETWEEN PERFORMANCE METRICS FOR REPORTED AND SIMULATED RESULTS

Study	Reported			Sliding scale		
	μ (mg/dL)	2σ range (mg/dL)	APACHE II (average)	μ (mg/dL)	2σ range (mg/dL)	APACHE II
Mayo Protocol ⁸						
Survivors	137.9 (range, 54.0–642.3)	—	16.9	154.6	93.6–255.6	23 ± 8.0 ^a
Non-survivors	172.0 (range, 27.0–1,183.0)	—	—	—	—	—
Leuven Protocol ²	103 ± 19 ^a	95–141	9 (IQR, 6–13)	100.8	61.2–166.32	23 ± 8.0 ^a
Bath Protocol ²³	111.6 (IQR, 106.2–127.8)	—	16 (range, 13–21)	111.8	52.9–236.3	23 ± 8.0 ^a
Yale Protocol ²⁴						
Diabetic	125 ± 12 ^a	101–149	23.9 ± 9.2 ^a	120.6	61.2–237.24	23 ± 8.0 ^a
Non-diabetic	121 ± 18 ^a	85–157	—	—	—	—

IQR, interquartile range.

^aData are average ± SD.

IMPACT OF MEASUREMENT FREQUENCY

Frequent glucose measurement is desirable to obtain tight control.²⁶ Practically, to optimize the clinical effort on glucose regulation, frequent measurement must be balanced with outcome, patient comfort, and clinical effort. Measurement intervals of 1, 2, and 4 h are examined using SPRINT and the “Standard” and “Aggressive” insulin sliding scales. The remaining protocols in Table 2 were omitted from this study as they contained strict measurement interval guidelines that could not be altered without deviating significantly from the protocol prescription. All insulin and feed actions are administered every hour as determined by the protocols at the last measurement. Table 6 summarizes the results.

Increased measurement interval time decreases performance for all three protocols. Time in the 75–110 mg/dL band dropped from 61.7% to 44.0% for SPRINT, with a lesser reduction for the poorer-performing insulin sliding scales. A noticeable increase in hypoglycemic events is also observed for larger

measurement intervals, particularly for the aggressive sliding scale and SPRINT. The primary cause is the maintenance of aggressive insulin and/or nutrition interventions determined at a hyperglycemic level over the subsequent 2–4 h between measurements. The result is poor titration, overshoot, and hyperglycemia, highlighting the importance of frequent measurement in obtaining and maintaining tight control. Similar effects have been reported elsewhere.²⁷ Note that 2-h-interval measurement had less effect and is included in the SPRINT protocol for stable patients. Hence SPRINT had fewer total measurements for the 1-h time interval in Table 6, as this simulation represented conditions where the *maximum* frequency of measurement is hourly.

All these results are due to poor control, an example of which is shown in Figure 6. Figure 6 shows a simulated trial for the SPRINT protocol when measuring at 1- and 4-h intervals. The 4-h-interval trace exhibits excessive oscillations, because of less frequent measurement and adjustment. As a result, control is less tight. However, note that the average glucose result-

TABLE 6. SUMMARY RESULTS FOR MEASUREMENT INTERVAL COMPARISON

	<i>Sliding scale</i>	<i>Aggressive sliding scale</i>	<i>SPRINT</i>
1-h time interval			
Time in 75–110 mg/dL	41.9%	43.8%	61.7%
Time above 110 mg/dL	57.3%	54.8%	36.7%
Average BG level	126.0	120.6	110.0
Number of measurements below 55 mg/dL	4	5	1
Total number of measurements	1,700	1,700	1,334
Average feed	67.7%	67.7%	61.9%
2-h interval			
Time in 75–110 mg/dL	41.7%	44.2%	60.3%
Time above 110 mg/dL	56.6%	54.2%	35.7%
Average BG level	127.8	122.4	110.0
Number of measurements below 55 mg/dL	5	5	7
Total number of measurements	812	812	812
Average feed	67.7%	67.7%	57.6%
4-h interval			
Time in 75–110 mg/dL	37.2%	38.8%	44.0%
Time above 110 mg/dL	60.3%	56.1%	40.2%
Average BG level	129.6	124.2	110.0
Number of measurements below 55 mg/dL	6	16	19
Total number of measurements	368	368	368
Average feed	67.7%	67.7%	54.5%

BG, blood glucose.

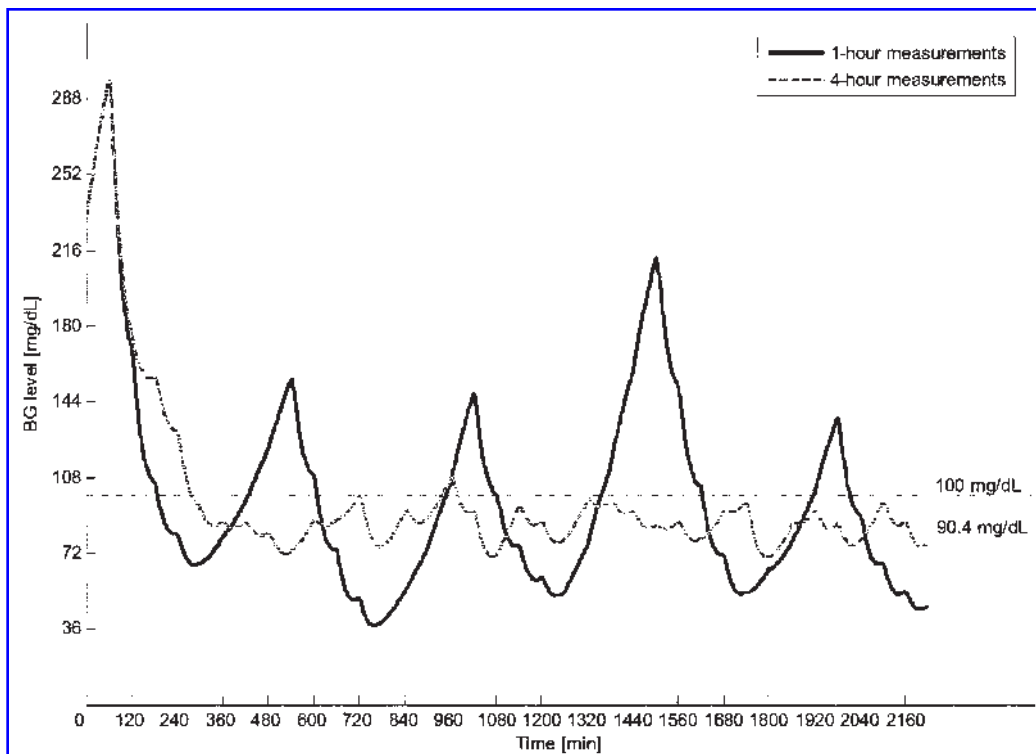


FIG. 6. Loss of tight control with increase in measurement interval, showing average blood glucose (BG) level increasing only slightly from 90.4 mg/dL to 100 mg/dL while peak-to-peak variation increases significantly.

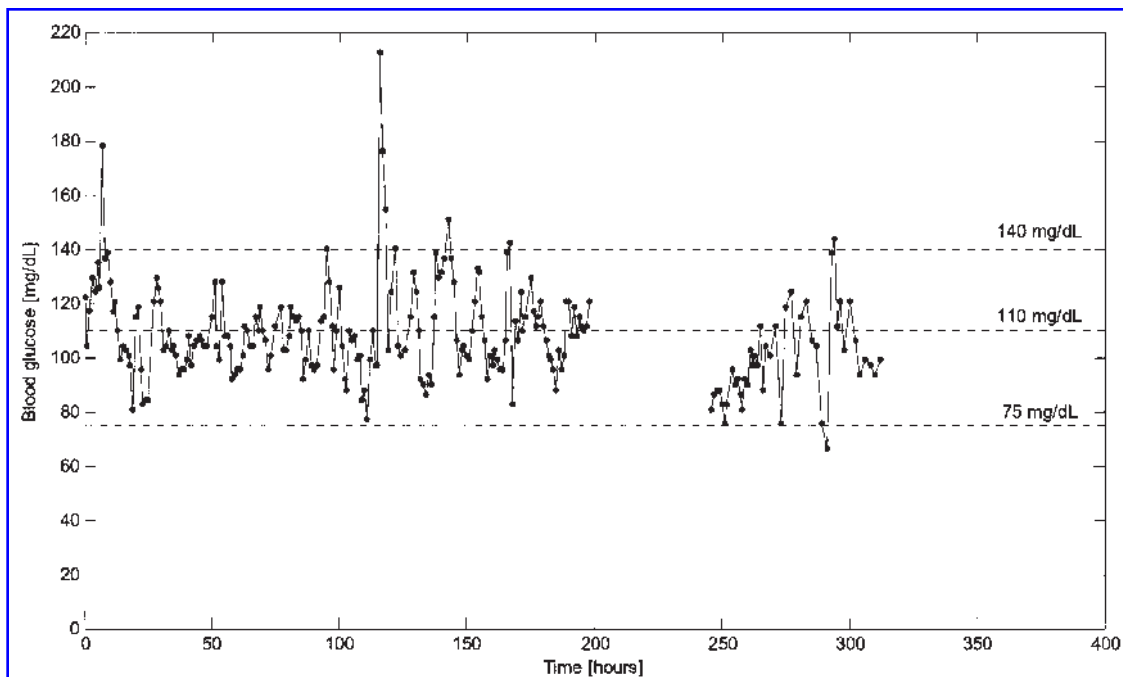


FIG. 7. Blood glucose measurements for clinical patient 5001 on SPRINT. The gap between 200 and 247 h represents a break from the SPRINT protocol due to a surgical procedure.

TABLE 7. SUMMARY STATISTICS FOR SPRINT PATIENT 5001

	<i>Before surgery</i>	<i>After surgery</i>	<i>Total</i>
Number of measurements	189	44	233
Time in			
75–110 mg/dL band	61%	75%	64%
75–125 mg/dL band	85%	93%	87%
75–140 mg/dL band	96%	98%	96%
Average feed (percentage of goal feed)	56%	57%	56%
Average insulin (U/h)	3.1	2.8	3.0
Average blood glucose level (mg/dL \pm SD)	110 \pm 17	99 \pm 16	108 \pm 17

ing from 4-h-interval measurements is only an 11%, increase from hourly control, a significant qualitative result that might impact outcome.²⁶ The averages would suggest that the protocols are within the target range in both cases; however, this misses the significant amount of time outside the 75–110 mg/dL band experienced during 4-h-interval measurements. For this reason we view time within a band as a more suitable performance indicator than an average value.

These results are also significant because some protocols use 4-h-interval measurements at least part of the time, while other studies have found more frequent measurement “taxing.”²⁷ Note that Bland et al.²⁷ recommended the need for extra staff as in the Leuven study.⁶ The simplicity of the SPRINT design allows glycemic control without a significant increase in clinical effort.

CLINICAL PROOF-OF-CONCEPT

SPRINT has been implemented as a clinical practice change in the Christchurch Hospital ICU, and the Canterbury Ethics Committee has approved the audit, analysis, and publication

TABLE 8. SUMMARY STATISTICS FOR SPRINT PATIENT 5008

Number of measurements	112
Time in	
75–110 mg/dL band	85%
75–125 mg/dL band	92%
75–140 mg/dL band	97%
Average feed (percentage of goal feed)	85%
Average insulin (U/h)	3.4
Average blood glucose level (mg/dL \pm SD)	97.2 \pm 14

of these data. The first patient was a 77-year-old man in the ICU following cardiac surgery with an APACHE II score of 22. The blood glucose level of this patient during the 266 h is shown in Figure 7. Table 7 summarizes the overall results.

The patient’s condition changed rapidly primarily because of the evolution of sepsis. The administration of rifampicin with glucose also may have had an effect.²⁸ These issues are evident especially at 8 and 115 h around otherwise tight control. Such outlying data readings may occur also when the Glucocard II sensor falls out of calibration or from contamination. Despite these typical difficulties and variations, the results show that SPRINT maintained patient safety and tight control.

Overall, the patient spent 64% of the trial in the 75–110 mg/dL band at an average blood glucose level of 108 \pm 17 mg/dL. Blood glucose levels were in the 75–125 mg/dL range 87% of the trial, and 96% of measurements were within the 75–140 mg/dL band. The average feed was 56% of the goal feed, which is comparable with retrospective hospital feed rates and simulation.^{14,26}

Data for the second clinical patient, a 44-year-old woman with an APACHE II score of 21, is shown in Table 8, and blood glucose values are shown in Figure 8. SPRINT was used for 163 h, achieving an average blood glucose level of 97.2 \pm 14 mg/dL. During the trial, 112 measurements of blood glucose were taken, showing 2-h-interval measurements were utilized when the patient was stable. In summary, the blood glucose levels spent 85% of the time in the 75–110 mg/dL band, 92% of the time in the 75–125 mg/dL range, and 97% of the time

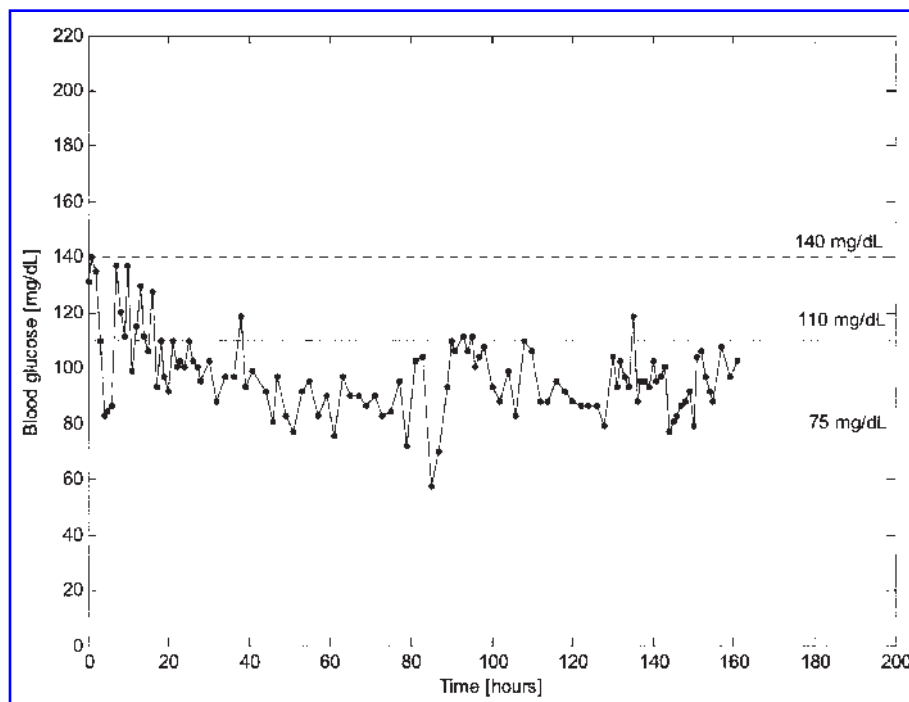


FIG. 8. Blood glucose measurements for clinical patient 5008 on SPRINT.

within the 75–140 mg/dL band with an average feed level of 85% of goal feed.

CONCLUSIONS

This study examines the ability of several clinical glycemic control algorithms to accurately reduce and tightly regulate glucose levels, despite significant inter-patient variability and time-varying physiological condition. The virtual trial results compare well with reported targeted averages, indicating realistic results. Results indicate that the tightest control for this cohort is achieved via modulating both insulin and nutritional feed rate. Insulin-only protocols gave distributions with a larger spreads and higher average levels compared with insulin- and feed-modulating protocols because of the increased insulin resistance of this cohort, which is more critically ill by APACHE II score than those examined in previous studies.

The SPRINT protocol presented modulates both nutritional and insulin inputs to achieve tight control, and achieves results comparable to a similar computerized control proto-

col. The two proof-of-concept trials show that the SPRINT algorithm can provide safe yet tight glycemic control to reduce ICU mortality, and the risk of severe complications with relatively limited clinical effort and labor. This system was easily implemented by the regular nursing staff and is part of an ongoing pilot study.

Finally, frequent glucose measurement is shown to improve control. In simulation the level of control decreased with the increase in measurement interval. The SPRINT protocol presented uses 1- and 2-h-interval measurements to optimize clinical effort, outcome, and patient comfort.

Future work for the SPRINT protocol, and other similar glycemic control methods, would depend on blood glucose sensor technology. Currently the SPRINT system uses nurses to take blood glucose measurements to close the control loop. The ultimate goal for glycemic control would be to develop a fully automated system. In this case the computerized AIC4 protocol would be the ideal algorithm to control such a system. Until sensors are automated it will be difficult to significantly reduce clinical effort. SPRINT offers a clinically realistic

and reliable intermediate solution until a fully automated system arrives.

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