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REVIEW ARTICLE

Essential Elements of the Native Glucoregulatory System, Which, If Appreciated, May Help Improve the Function of Glucose Controllers in the Intensive Care Unit Setting

Leon DeJournett, M.D.

Abstract

In 2001, Van den Berghe and colleagues were able to show that tight glucose control decreases morbidity and mortality rates in the intensive care unit (ICU) setting. Several large, prospective, randomized controlled trials have failed to confirm these results. All of these studies attempted tight glucose control using expert-designed algorithms to adjust the rate of intravenous insulin. Unfortunately, these studies each had high rates of hypoglycemia, a high percentage of glucose values outside of the target range, and increased glucose variability. These three measurements have been shown to increase mortality rates in ICU patients. In order to achieve a high rate of success with regards to tight glucose control, a closed-loop system will need to be created. The two main elements of such a system are a continuous glucose sensor and a recursive glucose control algorithm. This review highlights the important elements of the native glucoregulatory system, which, if utilized, may help create a successful glucose control algorithm for a closed-loop system.

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Introduction

The importance of glucose control in postoperative patients was first demonstrated by Furnary and associates[1] and later confirmed by Van den Berghe and coworkers[2] in a large, prospective, randomized control study. Numerous other studies have confirmed these findings in both surgical and medical intensive care unit (ICU) patients.[3–7] In addition, an analysis of over 200,000 Veterans Administration ICU patients confirmed that mean glucose values greater than 110 mg/dl led to increased morbidity and mortality rates.[8] However, the Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial[9] cast doubt as to the validity of tight glucose control. This large, prospective study of adult medical/surgical ICU patients showed that aggressive glucose control may actually increase overall mortality rates, although there seemed to be a benefit in the subgroup of trauma patients. Other studies have delineated the risks and called into question the importance of tight glucose control,[10–12] and as a result of all the available data, the American Association of Clinical Endocrinologists and the American Diabetes Association have issued a new consensus statement.[13] The new recommendation states that insulin therapy should be initiated for glucose values that exceed 180 mg/dl and that the old tight glucose control range of 80–110 mg/dl be replaced with a more modest range of 140–180 mg/dl, so as to lessen the risk of hypoglycemia.

Author Affiliation: Neurocath, Asheville, North Carolina

Abbreviations: (ICU) intensive care unit, (MPC) model predictive control, (NICE-SUGAR) Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation

Keywords: algorithm, closed loop, control, fuzzy logic, glucose, hyperglycemia, intensive care unit

Corresponding Author: Leon DeJournett, M.D., Neurocath, 18 N. Kensington Road, Asheville, NC 28804; email address leondejnc@bellsouth.net

The one common element of the NICE-SUGAR trial and other large prospective studies[14,15] that failed to demonstrate a benefit of tight glucose control was a high rate of hypoglycemia. It is well-known that hypoglycemia itself can be correlated with adverse outcomes.[16–18] Other studies have shown that increased glucose variability, which is often seen with inadequate glucose control, also adversely affects mortality rates.[19–22] The common occurrence of hypoglycemia and increased glucose variability in tight glucose control trials makes it difficult to discern the potential benefits of this new therapy. In addition, no large prospective study published to date has been able to keep blood glucose in the desired range more than 65% of the time, once again making it difficult to discern the true benefits of this therapy.

Glucose Control

One possible reason studies have not been able to achieve tight glucose control without untoward side effects is that absolute control over the extremely complicated glucose homeostatic system has not yet been achieved. In order to achieve tight glucose control with no hypoglycemia and with minimal glucose variability, a process that works in unison with the body's endogenous glucose control system will need to be created. Previous reviews describing the endogenous factors that affect blood glucose levels have been published,[23–26] thus this paper will focus solely on the elements of the native glucoregulatory system that may be incorporated into, and potentially enhance, exogenous glucose control systems. Ultimately, for such systems to be successful, they should mirror the natural endogenous system with regards to (1) timing of insulin response to changing glucose levels, (2) insulin secretion pattern, (3) insulin mass delivered per each discrete delivery period, and (4) altered insulin delivery mass in states of hyperglycemia. They should also control (1) the rate of glucose change per minute, (2) the insulin response to states of hypoglycemia, and (3) delivery of exogenous dextrose in a fashion that mimics the glycogenolytic/gluconeogenic responses to hypoglycemia.

This review incorporates information from basic physiology studies of both normal and diabetic subjects who were studied as outpatients. The use of data from non-ICU patients is necessary, as most of our current knowledge of the native glucoregulatory system comes from these sources. Data from ICU patients are utilized when available. In addition, a brief review of glucose sensors, existing glucose controllers, and logistic concerns will be included, as these are all important elements of a complete ICU-based glucose control system.

Glucose Curve

The glucose curve is nonlinear in nature and thus requires frequent monitoring to track effectively. Prior work has shown that a sampling frequency of at least every 10 min is needed to characterize the glucose curve adequately.[27,28] However, tracking the glucose value every 30–60 s would allow for a moving average to be calculated every 5 to 10 min, which would help to attenuate the affect of white noise on the glucose data.[29] Existing amperometric glucose sensors[30] and proposed photoluminescent sensors[31] are capable of this sampling frequency. These sensors would preferably be in an intravascular position so as to avoid the adverse effects of lag time and poor tissue perfusion that are associated with interstitial glucose sensor use in the ICU setting.[32,33] Alternatively, proposed glucose sensors could be used that automatically withdraw blood via an indwelling catheter and then analyze the blood once it is in the extracorporeal position. These sensors are capable of a sampling interval of every 5–15 min and have low coefficient of variances compared to amperometric sensors.[34,35] However, they have not yet been approved by the Food and Drug Administration. In addition, the effects of these sensors on central venous catheter patency, infection rates, and thrombus formation will need to be studied thoroughly before they can be recommended for routine use.

It has been shown that the current glucose value is only dependent on glucose values that fall within the last 60 min of the glucose curve,[36] thus implying that only the most recent 60 min of glucose data should be used in making predictions of future insulin needs. Most current ICU-based glucose control algorithms/systems measure blood glucose levels with a maximal frequency of once every hour, with a more typical range of once every 1 to 4 h. This rate of sampling does not allow for adequate characterization of the glucose curve and promotes utilization of glucose values that are not relevant to predicting future insulin needs.

Insulin Release

The insulin response to rapidly changing glucose levels needs to occur within 5–10 min to effectively deal with released hyperinsulinemic euglycemic clamps (as used in study protocols), sudden initiation of intravenous glucose loads/enteral feeds, or an acute change in insulin sensitivity as may be seen with acute dysrhythmias. An example of an unintended released hyperinsulinemic euglycemic clamp would be a patient who has been on a high-dextrose solution for an extended period of

time and requires exogenous insulin to keep his blood glucose in the normal range. If the high-dextrose solution is suddenly stopped (released) and the insulin rate is not adjusted, this patient will experience a sudden and potentially dangerous fall in his glucose level. If the standard glucose measurement cycle interval was 10 min, with an ongoing intermediate analysis every 5 min, a rapid change of the blood glucose level as seen in this scenario would be quickly noted, providing the clinician or glucose control software of a closed-loop system a chance to intervene in an appropriate fashion. This real-time analysis and intervention is consistent with the actions of the native pancreas/liver.

A study of isolated human islets showed that the insulin response to increasing glucose levels is marked by an immediate and rapid rise in insulin secretion.[37] Older, *in vivo* studies of systemic blood samples have shown that insulin is released in a pulsatile manner, with an interval of 10–15 min.[38–40] However, a later study using more sensitive assays and a sampling frequency of every minute has shown that insulin is released in a Gaussian distribution, with an interval of every 5 min.[41] These results have been confirmed in a study that involved direct sampling from the portal vein.[42] This interval does not change in states of hyperglycemia, as the natural mechanism of dealing with hyperglycemic states is to increase the mass of insulin released with each pulse while keeping the frequency of pulsations the same. The proportion of total insulin that is released by the pancreas in each pulsation remains steady at 70–85% in euglycemic states but may increase to as much as 90% during hyperglycemia.[41] The balance of insulin would be released during the basal period between pulsations. It has also been shown in type 1 diabetes patients that brief pulsatile insulin delivery is more effective than continuous delivery in reducing blood glucose levels[43–47] and in terms of improving other metabolic parameters.[48,49] Furthermore, an early study that used a deconvolution analysis, which is a technique used to measure the insulin secretion rate, revealed that transitioning from a hyperglycemic state to one of euglycemia brings about a rapid decrease in the insulin release rate, even though the glucose level was still elevated.[50]

Insulin secretion rates have been evaluated in hyperglycemic clamp studies using the deconvolution technique.[41,42,51,52] These studies consistently reveal a response characterized by a steady increase in the insulin mass released with each pulse, while at the same time showing a steady increase in the basal rate of insulin release. The quantity of insulin released per pulse in hyperglycemic states is often 300–600% greater than that released during euglycemic states. The time required to go from a basal rate of insulin release in a euglycemic state to a maximal rate of insulin release during a hyperglycemic challenge can be as short as 10–20 min. Data from these and other studies also reveal that, once the glucose curve begins to decline, there is an immediate decrease in the insulin release rate, even though the absolute glucose level remains elevated. If the rate of glucose decline begins to level off, there is again an immediate increase in the insulin mass released per pulse until the rate of decline is accelerated or the glucose level is brought back to the normal range.

Even during steady state euglycemic conditions, the insulin mass that is released with each pulse can vary by as much as 150%.[41,42] This would suggest that future software-based controllers should not hold the insulin dose steady in euglycemic states, rather they should continuously alter the insulin dose released based on the slope of the glucose curve within the euglycemic zone. This strategy could help to keep the glucose level from drifting out of the normal range with no attempts at altering the insulin dose in a manner that would prevent this drift.

Another advantage of using a shorter cycle interval between insulin adjustments is the short half-life of insulin. Studies have shown that intravenous insulin has a half-life of 3–7 min.[53–55] Standard pharmacokinetic principles would thus imply that 10–20 min are needed before a new steady state of insulin is reached after each change of a continuous intravenous insulin infusion. However, when the intravenous rate of insulin is increased in states of hyperglycemia, the full pharmacodynamic effect will be delayed at least 10 min from the time the new steady state is achieved.[56] This delay would be a potential source of error with regards to over-adjusting the insulin dose in states of hyperglycemia. It will thus be important for future algorithms/controllers that use short cycle intervals to take this into consideration and provide for an expeditious lowering of the insulin dose once an appropriate rate of lowering of blood glucose has been achieved.

A reasonable starting point for future closed-loop glucose controllers would be a cycle interval of every 10–20 min, with the capability of changing the cycle interval to every 5–10 min in extreme hypoglycemic/hyperglycemic states. If steady state conditions were to develop, the cycle interval could be decreased to every

20–60 min, so long as an ongoing intermediate analysis of the glucose data existed. Recommendations for insulin dosing cannot be given, as each patient will require individualized dosing based on the insulin volume of distribution, clearance rate, sensitivity factor, and the enteral/intravenous glucose load. In the NICE-SUGAR study, if a body weight of 80 kg per patient is assumed, 95% of patients were covered by insulin dosing of 0–126 U/day, which averages out to 0–0.07 U/kg/h.

Hepatic Glucose Output

The normal hepatic glucose production rate is 1–2 mg/kg/min, with 30–50% coming from glycogenolysis and the balance from gluconeogenesis.[57] In fasted states or states of critical illness, liver glycogen stores may be depleted,[58,59] and the overall hepatic glucose production rate will fall toward the lower limit of normal as glycogenolytic rates become negligible. The loss of glycogenolysis as a contributing factor toward hepatic glucose output renders the ICU patient particularly vulnerable to hypoglycemic events, as the normal response to hypoglycemia is an immediate rise in the rate of glycogenolysis followed by a delayed increase in gluconeogenesis.[60–62] Although rates of gluconeogenesis may actually be increased in critically ill patients,[63,64] this rise tends to accentuate the elevated basal glucose level of these patients rather than provide for any immediate rise in hepatic glucose output in states of severe hypoglycemia.

The glycogenolytic response to hypoglycemia is immediate and capable of increasing the hepatic glucose output from a basal rate of 1 mg/kg/min to as much as 2.5 mg/kg/min within a period of 60 min. If the hypoglycemic state persists, the glycogen stores will be depleted and the overall rate of hepatic glucose output may fall secondary to a lowering of the rate of glycogenolysis. However, the glucose output will tend to remain toward the upper limits of normal due to increased rates of gluconeogenesis. Spectral analysis of the glucose curve has shown that glycogenolysis/gluconeogenesis may begin at glucose values as high as 90–100 mg/dl if the rate of decline of glucose is great enough.[28] Future controllers that take this fact into consideration may be more capable of avoiding hypoglycemic states that are the result of a rapid fall of the glucose curve through the normal range. **Table 1** gives an illustrative example of the natural response to a hypoglycemic challenge.

Although insulin therapy is necessary to normalize blood sugar levels in critically ill diabetes patients, one potential side effect of increased blood insulin levels in these patients is a blunting of the gluconeogenic response to states of hypoglycemia.[65] This is one reason future controllers should seek to duplicate the natural response of glycogenolysis/gluconeogenesis to hypoglycemic states. One possibility would be to initiate a dextrose infusion in the range of 0.25 to 1 mg/kg/min during periods of hypoglycemia, with the capability to increase this rate up to 3 mg/kg/min over a period of 60 min should there be a persistence of hypoglycemia.

Rate of Glucose Change

An early study of the isolated perfused pancreas showed that the rate of glucose change was important in determining the amount of insulin released by the pancreas.[66] Incorporating the rate of change into a control algorithm has been shown to be effective with regards to glucose control in the ICU setting;[67] therefore,

Table 1.
Example of Expected Response to Hypoglycemic Challenge with an Average Rate Glucose Fall of –1 mg/dl/min[a]

Glucose (mg/dl)	Time (min)	Glycogenolysis	Gluconeogenesis	Hepatic glucose output (mg/kg/min)	Counterregulatory hormone response	Neuroglycopenic symptoms
80	0	Normal	Normal	1	None	None
70	10	Normal	Normal	1	None	None
60	20	↑[b]	Normal	1.5	G, C, GH	None
50	30	↑↑	Normal	2	G, C, GH, E, NE	+[c]
40	40	↑↑↑	↑	2.5	G, C, GH, E, NE	++

[a] G, glucagon; C, cortisol; GH, growth hormone; E, epinephrine; NE, norepinephrine. Refer to References 60–62.
[b] Degree of increase from basal rate: ↑ mild, ↑↑ moderate, ↑↑↑ significant.
[c] Severity of neuroglycemic symptoms: + mild, ++ moderate.

it is important to understand the normal range of the rate of change of glucose. Healthy individuals with no history of diabetes and normal body mass indices have normal rates of glucose change that are <±1 mg/dl/min, although, in the immediate postprandial period, the rate of rise can be as high as 2 mg/dl/min.[68] In contrast, individuals with type 1 diabetes can have normal rates of glucose change as high as ±3 mg/dl/min.[68,69]

In early studies of the affects of insulin on gastric acid output in normal individuals, after a single intravenous dose of 0.4 U/kg of insulin, rates of change as high as -3 mg/dl/min were seen.[70] A rate of change as high as -6 mg/kg/min can be seen in the early treatment phase of diabetic ketoacidosis[71] as a consequence of rehydration therapy or in the first 30 min after release of a hyperglycemic clamp study.[72] This rate of fall can also be seen with intravenous glucose tolerance tests.[73]

Data on the rate of change of blood glucose levels in ICU patients is limited, as continuous glucose monitors have not been routinely utilized in this setting. The few studies that have utilized a continuous interstitial glucose monitor do not contain sufficient data to determine average per minute rates of change.[74–77] Extrapolating rates of change from hourly glucose data will result in some underestimation of maximal rates. However, when a line of best fit technique is applied to hourly data from ICU studies, the maximal rates of change are <±1 mg/dl/min.[78,79] This is consistent with an outpatient study of type 2 diabetes patients, which is another group of patients with relative insulin resistance, whereby the rate of change of blood glucose was <±1 mg/dl/min a majority of the time.[68] **Table 2** summarizes this data.

Frequent adjustment of the intravenous insulin dose—by a controller in a closed-loop system—has the potential to minimize the rate of change of blood glucose, which, in turn, should decrease the risk of hypoglycemia and lower glucose variability. Future controllers should be capable of managing routine rates of glucose change up to ±1 mg/dl/min and have the capability to rapidly adjust the rates of intravenous insulin/dextrose should the glucose rate of change exceed ±1 mg/dl/min. Appropriate digital signal processing should help to minimize overreaction to sensor error.

Logistic Concerns

One important aspect of glucose control that is often overlooked is the effect of intravenous line dead space. Several studies have shown that both the dead space volume of the intravenous catheter and the carrier rate are important with regards to achieving a steady state.[80–83] The optimal setup would infuse insulin via the peripheral venous catheter or central venous catheter lumen with the smallest dead space volume, while at the same time fixing the carrier solution rate at a minimum of 20 ml/h. In order to minimize the effect of dead space, the insulin infusion line should be connected to the carrier solution line in a position as close to the intravenous catheter as is physically possible. In addition, before use, the intravenous tubing that carries the insulin should be primed with 20 ml of insulin solution in order to minimize insulin absorption to the tubing.[84] The intravenous pump used for insulin infusions should be capable of delivering flow rates with accuracy down to 0.1 ml/h. Furthermore, adopting a standardized insulin concentration of 1 U/ml would help to unify care across different ICUs. However, as standardization of both insulin and dextrose solutions will be difficult to achieve, future closed-loop controllers should have the flexibility of allowing the user to determine the concentrations of both insulin and dextrose as they pertain to glucose control in a closed-loop setting.

Table 2.
Summarized Glucose Rates of Change[a]

Rate glucose change (mg/min)	Patient type	Stimuli producing change
>+1	NGT, AGT, T1DM, Non-ICU, ICU	Postprandial; IV medications mixed in dextrose; push IV glucose; initiation of IV dextrose solutions
±1	NGT, AGT, T1DM, Non-ICU, ICU	All
-1 to -3	AGT, T1DM, Non-ICU, ICU, DKA	Postprandial, postabsorptive, insulin therapy; cessation of enteral feeds/IV dextrose; released HEC; hydration; IVGTT; OGTT
<-3	TIDM, DKA, HC	Insulin therapy; hydration; release of HC

[a] NGT, normal glucose tolerance; AGT, abnormal glucose tolerance; T1DM, type 1 diabetes mellitus; DKA, diabetic ketoacidosis; HC, hyperglycemic clamp; HEC, hyperinsulinemic euglycemic clamp; IVGTT, intravenous glucose tolerance test; OGTT, oral glucose tolerance test.

Controllers

Various control techniques have been utilized in an attempt to stabilize blood sugar levels in ICU patients. The Glucocommander is one of the oldest, simplest, and most effective controllers ever employed. This is

a proportional controller with a variable gain that is able to achieve good glucose control in less than 6 h, with a low rate of hypoglycemia.[85] More sophisticated proportional integral derivative controllers have been tested in both pediatric[86] and adult[87] ICU settings, with variable results. Model predictive control (MPC) is well-known in industrial applications[88] and has been used in both diabetic[89] and ICU patients.[90] In MPC, a model of each patient's glucoregulatory system is created and then continually optimized in order to maintain the best fit model. A randomized control study using enhanced MPC was carried out on 60 cardiac surgery patients for a period of 24 h.[91] This study showed that enhanced MPC was superior to a standard glucose management protocol, as evidenced by 60% of all glucose values being within the desired range of 80–110 mg/dl, with no episodes of hypoglycemia. The Endotool™ system also uses MPC (personal communication with Endotool) and, in a small postoperative study, was able to keep blood glucose in the range of 90–150 mg/dl 84% of the time, while keeping the hypoglycemic rate less than 2%.[92]

Another potential control methodology for glucose regulation is fuzzy logic.[93] A previous paper has commented on its potential applicability in the ICU setting.[94] Fuzzy logic has been used successfully in the ICU for control of glucose[95] and norepinephrine.[96] The potential of this control technique for diabetes patients has also been commented on.[97–99]

Tight glucose control in the ICU setting will require development of a closed-loop system, as the rapidly fluctuating insulin requirements of each patient make successful manual control unlikely in the fast-paced environment of the ICU. While progress is being made on development of continuous glucose sensors, much work remains to be done to create the equally important control arm of a closed-loop system.

Conclusion

Tight glucose control in the ICU setting has yet to be achieved. Although current treatment techniques permit some control over hyperglycemia, and represent an improvement over the past strategy of ignoring hyperglycemia, there are still unacceptably high rates of hypoglycemia, percentage of glucose values outside of the desired range, and glucose variability. Future efforts at developing a controller for a closed-loop system should pay homage to the native glucoregulatory system. This system cycles itself every 5 min, reacts instantly to rapidly changing glucose concentrations, can change the insulin mass released per pulse by as much as 300% within 20 min of a rapid change in blood glucose levels, and does not keep the insulin release rate constant during euglycemia. In addition, during states of hypoglycemia, it quickly adjusts the insulin output to near zero, while at the same time increasing the rate of hepatic glucose output. By incorporating some elements of the native glucoregulatory system into future glucose controllers, we may find ourselves closer to the realization of a safe and effective closed-loop system.

Disclosures:

Leon DeJournett is chief executive officer of Neurocath.

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