

Critical Care CME Program

Module 3

CSA's Critical Care CME Program will consist of eight modules. The third module appears in this issue of the *Bulletin*, and Modules 4 through 8 will appear in upcoming consecutive issues of the *Bulletin*. The test questions and evaluation for this module are at the end of this article. Submit answers to the ten questions to the CSA office with the registration page to receive the CME credit. Your CME certificate will be mailed from the CSA office. Alternatively, the full text of each module of this CME program will be accessible through the CSA Web Site, www.csahq.org, in the Online CME Program section, and as part of the online *CSA Bulletin*. Instructions to complete Module 3 online are given in the "Information" pages. After completing the assessment, print your CME certificate. Members will need their usernames and passwords to do the modules online.

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Important Information about Critical Care Module 3

The following information must be read and acknowledged before proceeding to the rest of the module. Check the acknowledgement box on the registration page.

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Any faculty participating in continuing medical education activities sponsored by the CSA is required to disclose any real or apparent conflict(s) of interest related to the content of their presentation(s) or any of the industry sponsors of the meeting. In addition, speakers must disclose when a product is not labeled for the use under discussion or when a product is still investigational.

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Tight Glucose Control (cont'd)

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Registration/Instructions

Method of Participation: The physician will read and study the materials and complete a quiz and evaluation of the module. Some modules may have slides available online. To register for and complete this module: Read and study all of the module pages; complete the registration page; go to the test questions that can be found after the article; complete the quiz and the evaluation that follows; submit your quiz to the CSA office by mail or fax (650-345-3269); and your CME certificate will be mailed to you

Estimated Time to Complete the Module: One hour

Availability

Module 3: Tight Glucose Control in Critically Ill Patients

Release Date: September 30, 2008

Expiration Date: September 30, 2011

CME Sponsor/Accreditation

The California Society of Anesthesiologists is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

The California Society of Anesthesiologists Educational Programs Division designates this critical care educational activity for a maximum of 8 AMA PRA Category 1 Credit(s)[™]. Physicians should claim credits commensurate with the extent of their participation in the activity.

Fees

The modules are free to CSA members. Nonmembers pay \$30 for each module. Each module is worth one AMA PRA Category 1 Credit[™].

Tight Glucose Control (cont'd)

Target Audience

This program is intended for all licensed physicians, including residents.

Evaluation

An evaluation of each module of this series is offered after the test questions.

Privacy Policy

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Acknowledgement

To proceed with this module, please acknowledge that you have read everything on these introductory pages by checking the box on the registration page.

Objectives

Upon completion of this CME activity, participants will be able to:

- Describe the pathophysiological basis for the concept of maintaining normoglycemia in critically ill patients
- Classify the benefits on morbidity and mortality
- Identify patients with a potential benefit of tight glucose control
- Determine risks and complications of tight glucose control
- Develop concepts for glucose control in clinical practice

Tight Glucose Control in Critically Ill Patients

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For over 30 years, various pathophysiological mechanisms described how hyperglycemia may lead to cellular and organ damage.^{1,2} In 2001, Van den Berghe and colleagues first reported that tight glucose control reduced intensive care unit (ICU) mortality in surgical patients from 8.0% to 4.6%.³ As a consequence tight glucose control protocols were implemented in many ICUs.⁴ However, subsequent studies were not consistent.⁵⁻⁷

Background

Hyperglycemia is commonly observed in critically ill patients, and appears to be an epiphenomenon that is part of the stress response. Elevated levels of cortisol, catecholamines, glucagon and growth hormone, increased pro-inflammatory cytokine release, and signals from the nervous system during critical illness all affect glucose metabolism. These chemical mediators produce ongoing gluconeogenesis and glycogenolysis, and thus elevate blood glucose levels. This incites accelerated insulin release as well as increased insulin resistance in such a proportion as to engender relative insulin deficiency, which in turn aggravates hyperglycemia, frequently to excessive levels. These metabolic changes, the so-called "diabetes of injury," were for many years thought to be beneficial for the patient because it was believed that this was a compensatory mechanism which could generate adequate glucose supply in non-insulin-dependent tissues such as the nervous system and blood cells.⁸

Current Evidence for Tight Glucose Control

The first large randomized controlled trial in this area, performed by Van den Berghe and colleagues in Leuven, Belgium, showed the benefit of tight glucose control in mechanically ventilated patients admitted to a surgical ICU.³ Their protocol targeted a glucose level of 80 to 110 mg/dl, and this was maintained with an insulin infusion pump and blood glucose measurements at intervals of one to four hours. The trial compared a treatment group receiving intensive

Tight Glucose Control (cont'd)

insulin therapy (mean blood glucose level 98 mg/dl) with a control group receiving insulin therapy only if blood glucose levels exceeded 215 mg/dl and with a target of 180 to 200 mg/dl (mean blood glucose levels 158 mg/dl). ICU mortality was reduced from 8.0% to 4.6% overall in the tight glucose control group, independent of the duration of treatment (Table 1). Furthermore, ICU mortality decreased from 20.2% to 10.6% in patients receiving the treatment for more than five days. Additionally, the treatment group showed a significant reduction in overall hospital morbidity and mortality (10.9% vs. 7.2%).

This same group conducted a second large randomized clinical trial in medical ICU patients, and reproduced these results with the same study protocol. Patients who received treatment for more than three days had a significantly reduced in-hospital morbidity and mortality. Intensive insulin therapy also reduced morbidity among all medical ICU patients.⁹ However, in contrast to the results of the first study, there was no benefit in survival for patients receiving treatment for less than three days.

Moreover, these studies showed a reduction in overall health care costs (due to a shorter ICU stay) and reduced dependency on mechanical ventilation in patients receiving tight glucose control.⁹

A comparative data analysis from the Van den Berghe studies indicated that the risk of death was highly correlated with blood glucose levels, with no clearly delineated cut-off level.¹⁰ The highest benefit regarding mortality and morbidity (acute renal failure, critical illness polyneuropathy) was observed in patients in the tight glucose control group with glucose levels \leq 110 mg/dl. This post hoc data analysis also showed that patients in the conventional glucose control group were at a higher risk of death after hyperglycemia developed with mean values between 150 and 200 mg/dl when compared to patients in the conventional group who developed only moderate hyperglycemia (110 – 150 mg/dl).

The benefit of long-term glucose control in diabetic patients is well known. A strictly normoglycemic metabolism prevents diabetic nephropathy, retinopathy, and micro- and macro-angiopathy. Furthermore, evidence that the short-term treatment of hyperglycemia in acute illness is beneficial is consistent across a number of patient populations. Insulin treatment targeting a lower blood glucose concentration significantly reduces long-term mortality following myocardial infarction and lowers the risk of cardiovascular events in diabetic patients.^{11,12} A meta-analysis evaluating 35 randomized controlled trials of insulin therapy in critically ill hospitalized patients found a beneficial effect of insulin therapy on mortality. The benefit was limited to trials in which insulin was administered with the goal of achieving a pre-determined blood glucose target.¹³

Patho-Physiological Basis for Maintaining Normoglycemia

For years, the administration of the “GIK” metabolic cocktail—glucose plus insulin plus potassium—was taught to be beneficial in patients with acute myocardial infarction or stroke. However, recent randomized trials were unable to show the expected benefit. It is interesting to note that these studies were not designed to control blood glucose levels and/or did not reach the targeted normal glucose levels.¹⁴⁻¹⁶ These results indicate that GIK infusion without glucose control has no benefit in the outcome of patients after myocardial infarction or stroke. Additionally a post hoc analysis of the Van den Berghe studies revealed a linear correlation between the degree of hyperglycemia and the risk of death. These results suggested that insulin-mediated normoglycemia improved the outcome—not the insulin infusion itself, and that hyperglycemia has toxic effects in critically ill patients.

These clinical findings are supported by our current, albeit incomplete, understanding of the pathophysiological mechanisms described below.

Pathophysiology

Pathological conditions at play in critical illness cause significant metabolic changes, such as alterations in energy substrate metabolism. The release of classic counter-regulatory hormones—glucagon, epinephrine, and cortisol, all of which oppose the normal action of insulin—leads to an increase in both adipose tissue lipolysis and skeletal muscle proteolysis. The resultant increase in gluconeogenic substrates—such as glycerol, alanine, and lactate—contribute to enhanced hepatic glucose production that often occurs in spite of the hyperinsulinemia associated with critical illness. Catecholamine-mediated enhancement of hepatic glycogenolysis, as well as direct sympathetic stimulation of glycogen breakdown, also leads to hyperglycemia.¹⁷

Cells of the central and peripheral nervous system, hepatocytes, and endothelial, epithelial, and immune cells each take up glucose independently of insulin, mediated by the $GLUC_{1/2/3}$ transporter. High levels of mediators of the stress response components (angiotensin II, cytokines, hypoxia) seem to up-regulate the $GLUC$ transporter, leading to glucose overload at the cellular level in non insulin dependent tissues.⁸ Then, glucose undergoes glycolysis in the cytosol, generating pyruvate, which is further transformed into acetyl-CoA and, in the presence of oxygen, oxidative phosphorylation generates ATP. Concomitant with the generation of ATP by the mitochondrial respiratory chain, a small amount of superoxide is produced. Normally, 2% to 5% of the oxygen used in the mitochondria is metabolized into superoxide, and this is detoxified by manganese superoxide dismutase (MnSOD, Figure 1). When

Tight Glucose Control (cont'd)

more glucose enters the cell, mass action increases pyruvate, which then is the substrate for enhanced oxidative phosphorylation, and in turn more superoxide is generated. Superoxide interacts with nitric oxide (NO) to form peroxynitrite, and this nitrates proteins such as mitochondrial complexes I and IV, MnSOD and the voltage-dependent anion channel (VDAC). Nitration of proteins presumably degrades them and reduces their enzymatic efficiency.

A unifying theoretical model was proposed by the Van den Berghe study group to explain the pathophysiology of glucose toxicity during critical illness, as contrasted with normal physiology, as follows. More peroxynitrite may be generated as a consequence of cytokine-induced NO synthase activation and hypoxia/reperfusion-associated superoxide production. Therefore, when cells of critically ill patients are overloaded with glucose, the production of even more superoxide and peroxynitrite is only to be expected. The ensuing nitration of mitochondrial complexes, MnSOD, and VDAC may theoretically suppress the activity of the mitochondrial electron transfer chain, impair detoxification of superoxide, shuttle glucose into toxic pathways, and increase apoptosis, respectively.

According to this model, prevention of hyperglycemia-induced mitochondrial dysfunction in insulin-independent cellular systems, such as immune cells, endothelial cells, and in the central and peripheral nervous system, theoretically would explain some of the protective effects of insulin therapy in critically ill patients. To date, this model of glucose toxicity in critically ill patients is still debated, but basic research has confirmed two aspects of the model: 1) NO synthase is activated in glucose overloaded cells and, 2) hypoxia/reperfusion induces superoxide production.

Because the diabetes of injury coincides with increased insulin resistance, it seems surprising that exogenous insulin infusion can lower blood glucose levels. Analysis of liver and skeletal muscle biopsies, obtained immediately after death from nonsurvivors in the Van den Berghe studies, revealed that the classical insulin-regulated metabolic pathways in the liver (gluconeogenesis, glycogenolysis) did not respond to intensive insulin therapy and confirmed severe hepatic insulin resistance. However, skeletal muscle tissue showed an up-regulation of its glucose transporter. Additionally, a glucose turnover study in a canine model confirmed a more severe insulin-resistance in the liver as compared with other peripheral tissue. In conclusion, adipose tissue and skeletal muscle remain relatively responsive to insulin; whereas, the liver is much more insulin resistant in critically ill patients.⁸

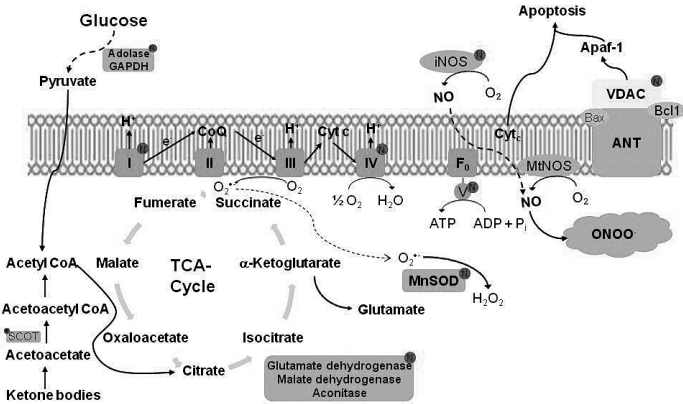


Figure 1. A diagrammatic representation of energy production in mitochondria and the mechanism of peroxynitrite generation. Excessive glycolysis and oxidative phosphorylation may result in more peroxynitrite generation in the critically ill. The ensuing nitration of mitochondrial complexes I and IV, MnSOD, GAPDH, and VDAC may suppress the activity of the mitochondrial electron transfer chain, impair detoxification of superoxide, shuttle glucose into toxic pathways, and increase apoptosis, respectively. These toxic effects may explain organ and cellular system failure related to adverse outcome in the critically ill. Proteins that are nitrated are indicated by the letter N in a red circle. Figure adapted from (8). TCA, tricarboxylic acid cycle; CoQ, coenzyme Q; Cyt c, cytochrome c; mtNOS, mitochondrial NO synthase; ANT, adenine nucleotide translocase; SCOT, succinyl-CoA: 3-oxoacid CoA-transferase, ONOO⁻, peroxynitrite; F₀, the portion of the mitochondrial ATP synthase that channels protons through the membrane.

Limitations

Although past clinical trials and basic research data seem to support tight glucose control, a meta-analysis published in August 2008 was unable to show a benefit of tight glucose control on hospital mortality in critically ill patients.¹⁸ Data from this meta-analysis were derived from 29 randomized controlled trials involving 8,432 patients comparing tight glucose control vs. usual glucose control. Hospital mortality was 21.6% in the tight glucose control group and 23.3% in the conventional treatment group (RR 0.93, 95% CI 0.85-1.03). Subgroup analyses stratifying trials by ICU setting (surgical vs. medical) and glucose goal in the treatment group (very tight glucose control ≤110 mg/dl vs. moderately tight glucose control ≤ 150 mg/dl) also did not provide significant differences between the groups. However, the tight glucose control group was associated with a lower rate of sepsis (10.9% vs. 13.4%, RR 0.76, 95% CI 0.59-0.97). After stratifying for ICU setting, the benefit was seen in surgical ICU settings but not in medical ICUs. The risk of hypoglycemia was

Tight Glucose Control (cont'd)

significantly higher in the tight glucose control group (13.7% vs. 2.5%, RR 5.13, 95% CI 4.09-6.43).

This meta-analysis failed to show a significant risk reduction in mortality in the tight glucose control group, but it also does not provide any evidence for an increased mortality risk due to tight glucose control. Indeed, there appears to be a trend to beneficial effects of tight glucose control (RR 0.93, 95% CI 0.85-1.03). This meta-analysis might not have enough power to show small differences in mortality between the tight glucose control group and the conventional group.

In the following two paragraphs, we introduce two recently conducted multi-center trials that also were included in the previously elaborated meta-analysis. These trials are often cited in the discussion about both the effectiveness and the potential harm of tight glucose control.

The “Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis” trial (VISEP, Table 1) compared a tight glucose control regimen (mean blood glucose level 112 mg/dl) with a control group (mean glucose levels 151 mg/dl) using the same protocol as the Van den Berghe studies.^{6,7} This trial was stopped after a planned interim analysis for safety reasons because they found a significantly higher rate of severe hypoglycemia events (≤ 40 mg/dl) in the tight glucose control group while there was no significant difference in the rate of death or the mean score of organ failure between the groups.

The results of the European multicenter trial GLUCONTROL (A Multi-Center Study Comparing the Effects of Two Glucose Control Regimens by Insulin in Intensive Care Unit Patients) has yet to be published in its entirety. Again, this trial also was stopped early due to a higher rate of hypoglycemia (≤ 40 mg/dl) in the treatment group without any difference in mortality.¹⁵

A possible explanation for the inconsistent results might be the different sepsis rates at admission. On the one hand, tight glucose control reduced the risk for the development of sepsis which might have been one reason for the impressive benefit described in the first van den Berghe study (surgical ICU). On the other hand, tight glucose control appears to be of limited value in patients that are already septic, possibly because of increased glycemic instability (and thus associated higher risks for hypoglycemia), which would explain why there was no survival benefit in the second van den Berghe study (medical ICU) or VISEP.

Discussion

Because of the conflicting results of the clinical trials, many concerns have been raised regarding efficacy and safety of tight glucose control in ICU

Tight Glucose Control (cont'd)

	V. d. Berghe 2001		V. d. Berghe 2006		GLUCONTROL		VISEP		Meta-analysis	
	Tight glucose therapy	Control group	Tight glucose therapy	Control group	Tight glucose therapy	Control group	Tight glucose therapy	Control group	Tight glucose therapy	Control group
Site numbers	1		1		19		18		29 trials	
Enrollment	02/2000-01/2001		03/2002-05/2005		NA		04/2003-06/2005		1991-2008	
Patients	surgical ICU patients		medical ICU patients		ICU patients		ICU patients with severe sepsis/septic shock		ICU patients	
No. of enrolled patients	765	783	605	595	550	551	247	241	overall 8432	
Targeted glucose level (mg/dl)	80 - 110	180-200 (treated if >215)	80 - 110	180-200 (treated if >215)	80 - 110	140-180	80-110	180-200 (treated if >200)		
Mean glucose level (mg/dl)	103	153	~ 102	~158	119	147	112	151		
Rate of hypoglycemia	5.1%	0.8%	12.5%	4.5%	9.8%	2.7%	17.0%	4.1%	13.7%	2.5%
ICU stay (days)	3	3	Earlier hazard ratio: 1.15				16	14		

Tight Glucose Control (cont'd)

patients. A major concern is the significantly increased rate of hypoglycemia in patients treated with intensive insulin therapy. In the Van den Berghe studies, the risk of hypoglycemia in patients receiving intensive insulin therapy increased from 0.8% to 5.1% in the surgical trial and from 3.1% to 18.7% in the medical trial. The VISEP and the GLUCONTROL studies and the meta-analysis from Wiener-Soylemez and colleagues show comparable rates of hypoglycemia.

Prolonged or severe hypoglycemia (blood glucose ≤ 40 mg/dl) is a serious complication and can be associated with seizures, coma, brain damage, and cardiac arrhythmias. Although the Van den Berghe trials did not report any obvious major complications associated with short-term hypoglycemic episodes, the risk of hypoglycemia was associated with a higher risk of death independent of the study group allocation. A retrospective cohort study examined the association between predefined circumstances and the occurrence of hypoglycemia in ICU patients.¹⁹ They found an association between hypoglycemic events (blood glucose ≤ 45 mg/dl) and the use of bicarbonate-based (as opposed to lactate-based) substitution fluid during continuous venovenous hemofiltration (OR 14.0, 95% CI 1.8-106); a change in parenteral or enteral nutrition without adjustment for insulin infusion (OR 6.6, 95% CI 1.9-23); a prior diagnosis of diabetes mellitus (OR 2.6, 95% CI 1.5-4.7); sepsis (OR 2.2, 95% CI 1.2-4.1); shock or need for inotropic support (OR 1.8, 95% CI 1.1-2.9); and female gender.

Because factors such as renal insufficiency, sepsis, and cardiac insufficiency are associated with an adverse outcome by themselves, it remains unclear whether hypoglycemia plays a causative role for increased mortality or vice versa; that is, hypoglycemia in and of itself reflects a more severe pathophysiologic state.

Further analysis of these data showed no increased mortality in patients with hypoglycemic episodes.²⁰ However, the number of events in this study is too small to exclude the possibility that hypoglycemia is associated with a higher mortality. Additionally, two patients developed coma and one patient had seizures that were likely to have been associated with the hypoglycemic event.

Another often-discussed critical point of the Van den Berghe trials is the high amount of parenteral glucose infusion and the high number of patients with predominantly parenteral nutrition. According to the on-site parenteral nutrition concept, all patients received 22-30 kcal/kg/day balanced between lipid (20%- 40%), protein (0.08-0.25 g nitrogen/kg/day) and glucose leading to a daily average glucose infusion of about 200-250 g. Although this concept often is described and recommended in the literature,²¹ parenteral glucose input usually is lower in clinical practice. Data analysis from the Van den Berghe trials

Tight Glucose Control (cont'd)

indicated that the benefit of tight glucose control was independent of parenteral glucose load because mortality was lowered in the lowest as well as the highest third of parenteral glucose infusion. One might hypothesize that differing parenteral nutrition strategies and metabolic conditions influence in differing ways and to variable extents the complex relationship between glucose administration, glycemic control, and outcome.

A frequent critique of the Van den Berghe trials is that it was conducted in a single center. However, while single-center trials may not have the external validity that multicenter trials have, they usually do allow for better internal validity. Moreover, when one considers the high number of patients enrolled, these results do provide convincing evidence.

A new multicenter trial in Australia is planned to enroll 5,000 critically ill ICU patients, comparing a tight glucose control regimen with a conventional regimen (NICE-SUGAR) with a 90-day mortality outcome. The results of this large multicenter trial are awaited eagerly worldwide.

Conclusion

Tight glucose control is a promising concept to improve the outcome of critically ill patients. However, its general applicability has yet to be proved, especially because hypoglycemia may be associated with adverse events. Considerations for establishing a standardized glucose control strategy should take the following issues into consideration:

Tight glucose control was only beneficial in a few studies. However, in those studies that showed a benefit, patients with an ICU stay of ≥ 3 days appeared to benefit most.

Tight glucose control was generally associated with an increased risk for hypoglycemia that itself is associated with an increased risk for mortality. This suggests that the benefit of tight glucose control that focuses on the avoidance of hyperglycemia might be counter-balanced by the risk for hypoglycemia.

Therefore, technical equipment for glucose control, and the training and workload of the ICU staff is critical for a safe implementation of a tight glucose control concept. Furthermore, it might be safer to implement a glucose control concept with a somewhat higher glucose target in the beginning and decrease it once the concept is clinically established with positive results.

We are grateful to Dr. Stephen Jackson for his valuable comments that have undoubtedly improved this manuscript.

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Questions

1. Which statement is not correct? "Diabetes of injury":
 - a. Results from increased levels of epinephrine, glucagon, and cortisol, leading to ongoing gluconeogenesis and glycogenolysis
 - b. Describes a diabetic metabolism in consequence of pancreatic surgery
 - c. Results as part of the stress response
 - d. Implies relative insulin deficiency in critically ill patients
 - e. Describes hyperglycemic conditions in critically ill patients
2. Glucose uptake is non-insulin-dependent in all of the following tissues, except:
 - a. Central nervous system
 - b. Epithelial cells
 - c. Skeletal muscle tissue
 - d. Peripheral nervous system
 - e. Immune cells
3. Which statement is not correct?
 - a. High levels of stress response components down-regulate the glucose uptake in non-insulin-dependent tissue and consequently lead to hyperglycemia.
 - b. High levels of stress response components lead physiologically to an up-regulation of GLUT transporters in insulin independent tissue
 - c. Physiological by-products of ATP generation by the mitochondrial respiratory chain are superoxide and peroxynitrite.
 - d. Peroxynitrite nitrates proteins such as mitochondrial complexes I and IV, manganese superoxide dismutase (MnSOD), and the voltage-dependent anion channel (VDAC).
 - e. Elevated levels of peroxynitrite in critical ill patients might suppress the activity of the mitochondrial electron transfer chain, impair detoxification of superoxide, shuttle glucose into toxic pathways, and increase apoptosis.

Tight Glucose Control (cont'd)

4. A risk of tight glucose control in critically ill patients is:
 - a. Decreased risk of hypoglycemia
 - b. Increased mortality
 - c. Increased risk for acute renal failure
 - d. Increased risk of hypoglycemia
 - e. Decreased risk of bleeding

5. Tight glucose control seems to be most beneficial when the following glucose levels are targeted:
 - a. 40-80 mg/dl
 - b. 80-110 mg/dl
 - c. 110-150 mg/dl
 - d. 150-200 mg/dl
 - e. To have a glucose/insulin infusion is more important than any blood glucose target.

6. Possible benefits of tight glucose control does NOT include:
 - a. Reduced ICU stay
 - b. Reduced mortality
 - c. Reduced duration of mechanical ventilation
 - d. Reduced hypoglycemic events
 - e. Reduced health care costs

7. Which statement is correct?
 - a. Only diabetic patients can benefit from tight glucose control.
 - b. Short-term medical ICU patients benefit most from tight glucose control.
 - c. Critically ill patients receiving intensive insulin therapy for three days and more seem to benefit from tight glucose control.
 - d. Only patients with severe sepsis or septic shock benefit from tight glucose control.
 - e. Patients after myocardial infarction do not benefit from tight glucose control.

8. Glucose-Insulin-Potassium infusion (GIK):
 - a. Is able to reduce morbidity and mortality in diabetic patients
 - b. Is shown as not effective without lowering blood glucose levels
 - c. Is beneficial for patients after stroke
 - d. Is an evidence-based concept in medical ICU patients
 - e. Reduces health care costs

9. Tight glucose control in critically ill patients
 - a. Turned out not to be effective
 - b. Harms more than benefits
 - c. Is proven to reduce mortality
 - d. Has no side effects
 - e. May improve survival if hypoglycemia can be avoided

Tight Glucose Control (cont'd)

10. Which statement is not correct?
- Diabetes of injury coincides with increased insulin resistance.
 - The increase in gluconeogenic substrates, such as glycerol, alanine, and lactate, contribute to enhanced hepatic glucose production.
 - The catecholamine-mediated reduction of hepatic glycogenolysis leads to hyperglycemia.
 - Glucose undergoes glycolysis in the cytosol.
 - Glucagon, epinephrine, and cortisol oppose the normal action of insulin.

Critical Care CME Program

In this issue of the *Bulletin*, Module 3 of the new Critical Care CME Program is available. There will be eight modules for this program. After each module is published in the *CSA Bulletin* (one per season), it is posted on the CSA Web Site at www.csahq.org. Each online module uses a self-assessment and evaluation; once these are completed, you may print your CME certificate. You may also contact the CSA office at 800-345-3691 to obtain the materials by fax or mail.

ABA Numbers for Reporting CME credits!

New benefit! CSA will report CME credits earned to the American Board of Anesthesiology. These credits will be counted as Lifelong Learning and Self-Assessment activities toward your Maintenance of Certification in Anesthesiology (MOCA) requirement. In order to report these credits, doctors need to provide their ABA number. To obtain an ABA number, visit www.theABA.org and create a personal portal account.

Tight Glucose Control (cont'd)

Registration

Complete this form, the test, and the evaluation, and **mail or fax** all three to the CSA office at 951 Mariner's Island Boulevard #270, San Mateo, CA 94404 or FAX to 650-345-3269. The CSA CME journal courses are also available on the CSA Web Site at www.csahq.org.

Critical Care CME Course, Module 3

Available September 30, 2008, to September 30, 2011

Name _____ M.D. D.O.

Address _____

City/State/Zip _____

Phone () _____

E-mail _____

CSA Member No Fee

Non-CSA Physician \$30

Total \$ _____

Please charge my:

MasterCard

Visa

Card # _____

Exp. Date _____

I authorize the California Society of Anesthesiologists to charge my account for the registration.

Signature: _____

OR

Mail with check payable to California Society of Anesthesiologists

I acknowledge that I have read the Important Information about Module 3.