Perioperative diabetic and hyperglycemic management issues

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Objective and Design: **To review and discuss selected literature, expert opinion, and conventional care of the hyperglycemic perioperative or critically ill patient.**

Main Points: **Diabetes mellitus, the most commonly encountered perioperative endocrinopathy, continues to increase dramatically in prevalence. Diabetes is the sixth most common cause of death in the United States and significantly affects other more common causes of death such as cardiac disease and stroke. Diabetic patients commonly have microvascular and macrovascular pathology that influences their perioperative course and critical illness and increases morbidity and mortality rates during hospitalization. Since diabetics require more surgeries and receive critical care more frequently than their nondiabetic counterparts, preemptive identification and anticipation of diabetic complications and comorbidities, along with an optimized treatment plan, are the foundation for the proper intensive care of this growing patient population. Hyperglycemia occurs commonly in critically ill diabetic patients but also is frequent in those who have a history of normal glucose homeostasis. The new onset of hyperglycemia in critically ill patients is driven by excessive counterregulatory stress hormone release and high tissue and circulating concentrations of inflammatory cytokines. Aggressive glycemic management improves short- and long-term outcomes in diabetic patients with acute myocardial infarction and cardiac surgical patients. Most recently, "tight" glycemic control in both diabetic and nondiabetic hyperglycemic intensive care unit patients resulted in improved survival in selected surgical patients without excessive consequences related to hypoglycemia. The mechanisms of benefit of euglycemia appear to be multifactorial.**

Conclusions: **Up to 25% of patients admitted to the intensive care unit have previously diagnosed diabetes. Diabetics are most commonly admitted for treatment of complications of comorbid diseases. New-onset hyperglycemia also is common in critically ill patients, and it affects patient morbidity and mortality rates. A growing body of literature supports the benefits of tight glycemic control in certain patient populations. However, further data are needed about the optimal concentration of blood glucose, the role of maintaining euglycemia in a broader group of patients (including the medically critically ill), and the mechanisms of benefit of infused glucose and insulin. (Crit Care Med 2004; 32[Suppl.]:S116–S125)**

KEY WORDS: diabetes mellitus: outcome; risk stratification; critical illness; acute myocardial infarction; postcardiac surgery; stroke; acute management; hyperglycemia: insulin; critical care; length of hospital or intensive care unit stay; complications

Glycemic control is increasingly recognized as an important goal for perioperative patients and the critically ill (1–6). However, it remains open to speculation whether euglycemia, in a broad spectrum of medical and surgical adult and pediatric patients, results in less morbidity and improved survival (6, 7). Even in the absence of prior diagnosis of diabetes mellitus, hyperglycemia was reported previously to be an independent risk factor for poor outcome for patients sustaining sudden cardiac death, myocardial infarction, cerebrovascular accident, or closed head injury (2, 3, 8–12). Patients who undergo cardiac surgery with concurrent perioperative hyperglycemia have increased morbidity rates (including wound and sternal infection) and perioperative mortality rates when they remain in the intensive care unit (ICU) for ≥5 days (1, 13, 14). The exact role of hyperglycemia, insulin resistance/insufficiency, or both that results in increased morbidity and mortality rates during acute stress or illness remains under intense investigation (4, 15–20). This review focuses on diabetes mellitus since it is the most common cause of abnormal glucose homeostasis, but we also address the risk of hyperglycemia in the nondiabetic acutely ill patient and the potential benefits of maintaining euglycemia.

Diabetes Mellitus and Critical Illness-Induced Hyperglycemia

Epidemiology. Diabetes mellitus is a progressive endocrinopathy associated with carbohydrate intolerance and insulin dysregulation and is the sixth most common cause of death in the United States (21–26). Diabetics also suffer an increased incidence of cardiac complications, the leading cause of death, and cerebrovascular pathology, the third leading cause of death in the United States (24, 26). The National Diabetes Data Group recently revised guidelines for the diagnosis of diabetes to provide uniform terminology and a functional working classification of the disease. This led to the current system based on disease etiology instead of pharmacologic treatment (21).

Diabetics suffer from insulin deficiency, insulin resistance, excessive hepatic gluconeogenesis, or a combination of these factors (25). The vast majority of diabetics fall into two broad etiopathogenetic categories (23). The presence of type 1 or 2 diabetes should be differentiated in the critically ill patient to facilitate patient management and recognition of comorbid pathologies. Type 1 diabetics have an obligate need for insulin as a result of their severe, usually absolute, insulin deficiency (23). The presence of type 1 diabetes is often identified by various genetic markers and serologic evidence of an autoimmune process directed against pancreatic islet cells (23). Since

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type 1 diabetes is an autoimmune process, other autoimmune endocrinopathies such as thyroid dysfunction or hypoadrenalism should be considered, particularly in unstable ICU patients with unexplained altered mental status, weakness, hypotension, tachydysrhythmias, or abnormal thermoregulation (26). Type 1 diabetes frequently develops during childhood, but a third of type 1 patients present as adults. Diabetic ketoacidosis is far more common in type 1 than type 2 diabetics and is commonly present at the time of initial diagnosis of diabetes mellitus (27). The type 1 patient tends to require lower insulin doses than insulin-treated type 2 diabetic because the type 1 patient usually has less insulin resistance. However, type 1 patients tend to have more fluctuation in their blood glucose concentrations during the course of a procedure or illness than type 2 diabetics.

Type 2 diabetes may be controlled with diet, oral hypoglycemic agents, and/or insulin depending on the degree of glucose intolerance secondary to excessive hepatic gluconeogenesis and insulin deficit or hyporesponsiveness that are the common causes of this entity (22, 25). Although type 2 diabetes usually develops in older adults, it is being diagnosed increasingly in younger patients, particularly those from certain ethnic groups, including Native Americans, African-Americans, Hispanics, and those from the Pacific Islands (26). Perioperative or critically ill type 2 diabetics may be first diagnosed at the time of their procedure or illness, and some type 2 patients require insulin for the first time during this event. Unfortunately, type 2 diabetes may be present for prolonged periods before diagnosis, and as many as 50% of patients may develop significant target organ compromise without clinical symptoms before disease recognition (23).

The incidence of type 1 diabetes remains fairly fixed at 0.4% of the population, whereas type 2 diabetes has doubled in the past decade (22). Type 2 represents approximately 95% of all diabetics and currently affects 8–10% of Americans (22). The prevalence is projected to double again within the next several decades and will affect a quarter to a third of the U.S. population if interventions are not successful in slowing this growth (22, 28).

Narayan et al. (28) recently projected that 32.8% of males and 38.5% of females born after 2000 in America will develop diabetes during their lifetime. The highest likelihood of developing diabetes is in obese, inactive, low-income persons and those of selected ethnicity, being highest among Hispanic females, where it approaches 50% (28). This disquieting projection compares with the lifetime risk of developing breast cancer (one in eight for U.S. women), coronary disease (one in two for men and one in three for women), or dementia (one in ten for U.S. men) (28). Narayan et al. emphasized that their data are likely an underestimation of the lifetime risk for diabetes as the study was based on self-reporting. Since a third of diabetics are unaware of their diagnosis, self-reporting likely underestimates the risk. They also did not factor in the predicted ongoing increase of obesity and the projected increase in life expectancy in the U.S. population, both of which will further increase lifetime risk for diabetes development. Narayan et al. also estimated the quality adjusted life years that will be lost for those men and woman developing diabetes during their lives. This is projected to represent a disturbingly high 18–22 yrs. This loss in quality adjusted life years is exacerbated when the diagnosis of diabetes is made at a younger age, a trend that is ongoing (28).

The dramatic increase in diabetes appears to be multifactorial but most heavily affected by the aging of the population and the expanding epidemic of obesity and inactivity. Other factors affecting the development of diabetes appear to be related to chronic inflammatory processes, therapies that result in glucose intolerance, and an increase in the amount and composition of carbohydrate in the modern American diet.

Diabetics require more hospitalizations, have greater lengths of stay, and cost more to manage than nondiabetics (29). Hospitalized diabetics are usually older, are less active, and control their disease less aggressively, as evidenced by higher hemoglobin-A1C concentrations at the time of admission (29). Diabetics undergo various procedures and surgeries more commonly than their nondiabetic counterparts and have increased morbidity and mortality rates when acutely compromised or ill (30). Since a third or more of perioperative diabetics are unrecognized or untreated before surgery or critical illness, the clinician must be vigilant in the identification of diabetes, glucose intolerance, and associated pathologies (21, 28). Perioperative glycemic control was previously dominated by a passive approach, driven in large part because of concerns over the systemic effects of unrecognized hypoglycemia, particularly the neuroglycopenic sequelae. Severe hypoglycemia may result in somnolence, unconsciousness, seizures, and, if sustained for a sufficient period, irreversible neurologic insult or death (30). Recognition of these events while a patient is under general anesthesia or receiving sedatives and analgesics with or without neuromuscular blocking agents in the ICU is problematic, potentially leaving the hypoglycemic state unappreciated for a critical period before treatment (30). Furthermore, until the past decade or so, there were only modest data substantiating the benefits of euglycemia.

Although diabetics sustain greater perioperative morbidity and mortality rates than nondiabetics, there is a surprising paucity of accepted and codified guidelines to aid in their risk stratification, to minimize complications, and to optimize perioperative care (31). This is in contradistinction to the broad-based and widely disseminated guidelines for patients with known or suspected myocardial compromise (32).

Identification of the suspected diabetic during preoperative assessment or critical illness is crucial. The diagnosis is established through evaluation of the patient history and physical and complemented with judicious laboratory investigation, including blood glucose monitoring and urinalysis (with focus on glycosuria, ketonuria, and proteinuria), serum electrolytes, hemoglobin-A1C, and electrocardiogram.

Critical illness-induced hyperglycemia, defined previously as a blood glucose $\geq$200 mg/dL (11 mmol/L) in the absence of known diabetes, occurs frequently, particularly in the elderly (1, 4, 7, 33–35). Since many diabetics remain unaware of their diagnosis, the measurement of a hemoglobin-A1C should be routinely considered in a critically ill patient with newly identified hyperglycemia. Stress-induced hyperglycemia results mainly from counterregulatory hormone release (catecholamines, glucocorticoids, growth hormone, and glucagon) and excessive release of inflammatory cytokines, such as tumor necrosis factor-α, interleukin-1, and interleukin-6 (4, 33, 34, 36) (Table 1). Along with this, immobility itself is associated with reduced skeletal muscle insulin sensitivity (4, 37). Interestingly, Takala et al. (38) reported the deleterious

Table 1. Risk factors associated with critical illness-induced hyperglycemia

Etiology	Major Mechanism of Hyperglycemia
Known diabetes mellitus	Relative or absolute insulin deficiency, resistance or increased hepatic gluconeogenesis
Catecholamine infusion, particularly epinephrine and norepinephrine	Insulin resistance Inhibition of insulin release
Elderly	Insulin deficiency
Obesity	Insulin resistance
Increase severity of illness	Excess counterregulatory hormone concentrations
Excess carbohydrate ingestion or infusion	Inadequate uptake of glucose
Acute or chronic pancreatitis	Insulin deficiency
Severe inflammation or infection	Insulin resistance
Hypothermia	Insulin deficiency
Uremia	Insulin resistance
Cirrhosis	Insulin resistance
Hypoxemia	Insulin deficiency

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effects on glucose control and survival in critically ill patients treated with growth hormone. This study and others raise the question of the impact of counterregulatory hormone response to survival in the critically ill and the potential role of modulating outcome in hyperglycemic patients (4, 8–10, 38).

Krinsley (7) recently reported that ICU admission and mean and maximal blood glucose concentrations during critical illness were independent predictors of outcome. Stress-induced hyperglycemia occurs most often shortly after ICU admission, but it should also be sought when nutritional supplementation is initiated and when patients acutely deteriorate (e.g., from a nosocomial infection or gastrointestinal hemorrhage) (1, 4). Protracted hyperglycemia in a critically ill patient may be associated with ongoing inflammation or inadequately treated infection (4).

The goals for the diabetic or stress-induced hyperglycemic patient are minimal metabolic disruption, avoidance of untoward events, and return to stable glycemic control as soon as possible (26).

Organ-Specific Evaluation and Care

Neurologic. Stroke remains the third leading cause of death in the United States, following cardiac disease and cancer (24). Diabetic patients have an increased incidence of cerebral vascular disease and stroke that results in greater morbidity and mortality rates (39). This is related to their greater frequency of underlying hypertension, dyslipidemia, accelerated atherosclerosis, and abnormal endothelial proliferation (39). These pathologies are exacerbated by diabetes-induced alteration in red blood cell deformability, increased platelet adhesion and aggregation, and diminished fibrinolytic activity.

Increasing recognition of the effect of acute and chronic hyperglycemia on outcome of patients with brain ischemia has evolved over the past decade (3, 40). Various reports demonstrated that hyperglycemic diabetics and nondiabetics have a worsened outcome after stroke than normoglycemic patients (3, 8, 40). Experimental data suggest that this may be related to hyperglycemia causing intracellular acidosis and an exacerbation of the neuronal edema that was initiated by anoxia (41, 42). In a study of stroke patients who had continuous blood glucose measurements after presentation, the level of premorbid chronic glycemic control, as assessed by hemoglobin-A1C, did not correlate with stroke outcome (43). Glucose control during the hospitalization correlated with better outcome after stroke and was more reflective of outcome than the blood glucose at admission (43).

There is some debate whether the worsened prognosis in hyperglycemic patients is secondary to the increased brain glucose or to the intensity of the stress hormone response. The glucose insulin in stroke trial attempted to prospectively address the role of glycemic control in hyperglycemic stroke patients by controlling blood glucose with a glucose/insulin/potassium infusion (44). The study failed to show a benefit with normalization of blood glucose, but several issues about the study design call into question the applicability of the results (44). Finally, in a retrospective review of 138 stroke patients treated with acute lytic therapy, blood glucose concentration was the only positive predictor of risk of hemorrhagic transformation associated with fibrinolysis (45).

Similar to the data from stroke patients, closed head injury patients with admission hyperglycemia have a poorer prognosis than euglycemic patients (4). Unfortunately, there are no data prospectively establishing the role of normalization of hyperglycemia in this patient population. The current recommendations in brain-injured and acute stroke victims are to provide careful glycemic control, avoiding concentrations >150–180 but limiting the potential deleterious neurologic effects of hypoglycemia (4).

Cardiac. The diabetic patient has an increased risk of various cardiovascular pathologies, including hypertension, coronary artery disease, peripheral arterial disease, systolic and diastolic dysfunction, and congestive heart failure (39). Cardiovascular pathology is the cause of death in 80% of diabetic patients. The American College of Cardiology and American Heart Association recognize the increased risk of atherosclerotic disease in diabetics and list it as a major risk factor along with a history of smoking, hyperlipidemia, and hypertension. The recent American College of Cardiology/American Heart Association updated guidelines on perioperative cardiac assessment of patients undergoing noncardiac surgery place diabetics, especially those receiving insulin, at a minimum of intermediate risk (32, 39). They also state that the vast majority of diabetic patients >65 yrs of age have significant symptomatic or asymptomatic coronary artery disease, with the incidence of silent ischemia increased because of associated diabetic autonomic neuropathy.

Hypertension develops more commonly in diabetics than nondiabetics and increases in frequency over time. Hypertension is closely related to the development of progressive nephropathy (46). Hypertension usually develops within 3 yrs of the onset of microalbuminuria. The risk for hypertension and renal insufficiency is greatest in African Americans.

In contrast to type 1 diabetics, a larger number of type 2 diabetics are hypertensive at the time of diagnosis. In a follow-up evaluation of the appropriate blood pressure control in diabetes (ABCD trial) of 3,500 newly diagnosed type 2 diabetics, Schrier and Estacio (47) reported that 39% of patients were hypertensive (diastolic blood pressure >90 mm Hg) at the time of diagnosis. This probably reflects, in part, greater age and inci-

dence of obesity, less activity, and increased comorbidities.

In type 2 diabetics, modest blood pressure control may be even more important than chronic glycemic control (48). In this trial, the U.K. Prospective Diabetes Study Group reported that blood pressure control using an angiotensin converting enzyme inhibitor (ACEI) or β-blocker significantly reduced the risk of death from diabetic-induced macrovascular pathology. Whether this chronic study extrapolates to the acute care setting remains open to speculation (48). Current recommendations are to target blood pressure control to <130/80 in the hypertensive diabetic. This frequently requires two or more drugs to achieve (49, 50).

The ABCD trial reported an increased incidence of fatal and nonfatal myocardial infarctions in those diabetic patients treated with a calcium channel blocker compared with those treated with an ACEI (51), but this has not been substantiated by subsequent studies (51).

In addition to renal vascular disease, the development of hypertension appears to be accelerated in diabetics because of long-term effects of hyperinsulinemia, arterial vascular noncompliance, and chronic extravascular hypervolemia. Hyperinsulinemia and insulin resistance in type 2 diabetics are associated with increasing obesity and accelerated atherosclerosis, which increase the evolution of hypertension ("syndrome X" or the "insulin resistance syndrome") (26). Increased arterial vessel stiffness is hypothesized to be secondary to increased protein glycosylation, altered nitric oxide production and metabolism, and advancing atherosclerosis (26).

Left ventricular dysfunction occurs commonly in diabetics, at about four to five times the rate of the general population. Left ventricular dysfunction results in diabetics having twice the rate of congestive heart failure compared with nondiabetics. The increased rate of systolic and diastolic dysfunction is related to a) concurrent macro- and microvascular coronary artery disease; b) hypertension; c) left ventricular hypertrophy; d) endothelial dysfunction; e) obesity; f) autonomic neuropathy; and g) various metabolic complications secondary to hyperglycemia and hyperlipidemia (46).

Cardiac compromise in the diabetic must be identified before major surgery and during critical illness. Since ischemia may be silent in the diabetic, noninvasive or invasive cardiac testing may be warranted preoperatively, particularly for the diabetic undergoing major noncardiac and vascular surgery. A recent position paper—by the American College of Cardiology/American Heart Association on risk stratification of the diabetic—reviews current evidence for evaluation of high-risk patients and provides general guidelines but also calls for additional studies to identify the optimal means of evaluating the diabetic patient (31).

In patients with acute myocardial infarction, it has been shown that the sicker the patient, the more likely he or she is to be hyperglycemic (52). Acute glycemic control results in marked improvement in cardiac survival in hyperglycemic nondiabetic and diabetics with acute coronary syndromes and myocardial infarction and those who have undergone recent cardiac surgery. Even modest glucose elevations during acute myocardial infarction result in increased mortality rates (2, 53–55). The Scandinavian Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction trial reported a nearly linear relationship between blood glucose concentrations in type 1 and 2 diabetics at the time of admission and long-term mortality rate after acute myocardial infarction. The authors prospectively randomized 620 patients to receive glucose/insulin/potassium infusion to maintain a blood glucose concentration <180 mg/dL (10 mmol/L) or to a control group with the aim of conventional therapy to achieve a blood glucose <215 mg/dL (12 mmol/L). Patients were followed for up to 3.4 yrs. The group that had better glucose control showed an 11% improvement in long-term survival (54).

In a nonrandomized study performed over a 15-yr time period in 3,554 diabetics undergoing coronary artery bypass surgery, Furnary et al. (13) reported a marked improvement in survival when patients had their blood glucose controlled using a continuous insulin infusion started on the day of surgery and continued for 2 days postoperatively. The study group was sequentially compared with the previous regime based on subcutaneous insulin injections to control blood glucose. The reported mortality rate was 2.5% in the infusion group vs. 5.3% in the subcutaneous group (13). This was in follow-up to a previous study where Furnary et al. (14) reported a lower incidence of sternal wound infection in diabetic patients undergoing coronary artery bypass surgery when continuous insulin infusions were used to control perioperative blood glucose. Although there is potential for statistical bias in this study as well as change in technique and patient care during the study period, multivariable analysis substantiated blood glucose control as a powerful independent factor (13, 56).

The nonischemic myocardium normally is mainly dependent on fatty acid metabolism as its energy source (56). Although widely debated, therapeutic interventions that switch myocyte metabolism from free fatty acid to glucose during ischemia have been shown to be beneficial in experimental animals. What remains under discussion is the exact role of glucose, insulin, and potassium in this scenario. Recent reports show that the cardioprotective benefits of insulin may be independent of glucose and more closely related to reduction in circulating free fatty acid. Insulin infusion appears to be most beneficial after reperfusion and not during on-going ischemia (57, 58).

Renal. Diabetes is the leading cause of end-stage renal disease in the United States. Risk factors associated with end-stage renal disease in diabetics include hypertension, dyslipidemias, and anemia (59, 60). Exceeding a threshold value of a creatinine of 1.5 has been found to be associated with a linear increase in risk of cardiovascular morbidity and death. Developing acute renal failure after coronary artery bypass surgery increases one's mortality rate from 1–2%, in the absence of renal failure, to 20% with moderate acute renal failure and 60% for patients who require dialysis (61).

Recently, a number of potential genetic markers predisposing some diabetics to the development of diabetic nephropathy have been identified (62, 63). Chew et al. (63) also noted an association of the apolipoprotein epsilon 4 allele with an increased likelihood for the development of acute renal failure after cardiac surgery. Future rapid genomic screening modalities may enhance the ability of intensivists to stratify those at greatest risk for development of progression of renal insufficiency (64).

The 5-yr survival rate for diabetics with end-stage renal disease is reportedly only 20%. This increased mortality rate is largely because of associated cardiovascular disease. Chantrel et al. (65) demonstrated the poor prognosis of diabetics

who progress to dialysis in a study of 84 patients, 32% of whom were dead within 8 months. Higher mortality rates were noted in patients who had symptomatic coronary artery disease, had advanced peripheral vascular disease, or had undergone amputation. Surprisingly, in this high-risk group, only 10% of patients were treated with β-blockers, 23% with ACEIs, and 25% with aspirin, reflecting the lack of acceptance of the beneficial effects of such therapies in those at risk. The authors also noted that iatrogenic exposure to nephrotoxins and cardiac surgery were responsible for precipitating renal failure in almost a third of their patients (65). Emergency dialysis was associated with the greatest mortality rate.

A moderate number of diabetics are clinically anemic before chronic renal insufficiency progresses to end-stage disease. Similar to ongoing investigation of the role of erythropoietin therapy in the critically ill and patients with congestive heart failure, the effect of increased hemoglobin on quality of life and disease progression in those with renal insufficiency before onset of dialysis remains under investigation (66–68)

The natural history for the development of renal insufficiency in diabetics is similar in type 1 and 2 patients (59). Glomerular hyperfiltration occurs early in the course of evolving diabetic nephropathy due to dilation of the afferent more than the efferent arteriole of the kidney. This is mediated, in part, by increased vasodilatory prostanoid production and hyperglycemic induced expression of inducible nitric oxide synthase. The resultant increase in glomerular hydrostatic pressure results in glomerular damage and microalbuminuria. The latter starts about 5 yrs after onset of diabetes and progresses over the subsequent decade in some patients to overt macroalbuminuria. This represents significant anatomical injury to the kidneys and portends a linear diminution in renal function. Interestingly, over time diabetic patients with significant cardiovascular and renovascular compromise develop impaired endothelium-dependent vasodilation. Furthermore, uremia is associated with hyperlipidemia, which further impairs nitrovasodilator activity and increases white cell adhesion to endothelium, both of which play a role in endothelial injury and progression of cardiac and renal compromise (59).

The Heart Outcomes Prevention Evaluation trial reported the long-term benefits of ACEI in slowing the progression of renal insufficiency and improving cardiovascular function, despite producing only modest reduction in blood pressure in hypertensive diabetic patients (69). The use of cholesterol-lowering agents may also slow the progression of diabetic nephropathy. Continuing ACEI and statin drugs during critical illness remains uncertain because of concerns over cardiovascular stability and potential for evolving renal and hepatic dysfunction, respectively. Both agents appear to play potentially acute and long-term beneficial roles in diabetic patients who have sustained acute myocardial infarction. ACEIs alter nitric oxide and free radical formation and improve myocardial remodeling. Statins may be beneficial through acute anti-inflammatory mechanisms as well as long-term cholesterol-lowering effects (70). The hemodynamic state, renal reserve, and serum potassium concentrations help determine the use of ACEI in the ICU.

It is increasingly recognized that one of the goals of critical care is the avoidance of acute renal failure, necessitating dialytic support (71). The diabetic more commonly has premorbid renal compromise and may be at greater risk to develop acute renal compromise, and thus limiting hypovolemia, avoiding nephrotoxins, and judicious use of high-risk interventions such as angioplasty and contrast-based radiographic procedures should be attempted. The pathogenesis of contrast media-induced acute renal failure, which diabetics are prone to develop, is hypothesized to result from release of renal vasoconstrictors, free radical release, and altered nitric oxide availability (72).

Various interventions and pharmacologic agents have been used as "renal protectants." With the exception of appropriate volume replacement, administration of iso-osmotic dyes during contrast, n-acetyl-cysteine, and selected use of hemofiltration in high-risk patients, there are no data to support therapies such as renal dose dopamine, osmotic diuresis, or calcium channel blockade (71, 73). However, other agents including selective adenosine A1 receptor antagonists, vasodilatory prostanoids (alprostadil), and fenoldopam—a dopamine A1 agonist—are being investigated as prophylactic measures (74, 75).

Specific Recommendations for ICU Care of the Diabetic

General Considerations. Diabetics are occasionally admitted to the ICU for management of an acute diabetic related process such as life-threatening hypoglycemia, hyperglycemia, diabetic ketoacidosis, or nonketotic hyperosmolar state, which were recently reviewed elsewhere (27). However, most diabetics are admitted to the ICU because of comorbid pathologies or infection. Various studies report that 13–26% of ICU patients have a history of diabetes mellitus at the time of ICU admission (1, 7, 20).

The type 1 diabetic always requires basal amounts of insulin. At least 1 day before elective surgery or at the time of ICU admission of type 2 diabetics, discontinuation of all oral hypoglycemic agents is recommended (30). This is done to avoid reactive hypoglycemia, particularly with sulfonylurea compounds, and associated drug-induced toxicities and interactions. These toxicities include the development of lactic acidosis in patients treated with the biguanide metformin. Patients with renal insufficiency are at increased risk of this complication. Thiazolidinedione compounds precipitate volume expansion and may exacerbate congestive heart failure in patients at risk (76).

Discontinuing patient-controlled insulin pumps to avoid hypoglycemia and problems with insulin preparations and pump technology is often advised in the critically ill. Although sliding scale regular insulin is used on occasion, it is increasingly common to initiate regular insulin infusions, particularly if lower blood glucose concentrations are desired. Newer shorter acting insulins such as lispro and aspart have little to no role in the ICU patient and are not available for intravenous infusion. Subcutaneous insulin may be unpredictably absorbed during critical illness, and protocols that administer intermittent sliding scale regular insulin without a basal longer acting preparation do not consistently control hyperglycemia (26).

The risk of aspiration is increased in diabetics because of autonomic neuropathy and the decreased ability to coordinate swallowing and/or gastroparesis. Autonomic neuropathy may be associated with hemodynamic lability, particularly with change in patient position and initiation of positive pressure ventilation. Appropriate patient positioning and use

of gastric acid secretion suppressants, gastric motility medications, vasoactive drugs, and volume replacement may be required to limit the risk of aspiration and maintain hemodynamic stability (30).

The "stiff joint" syndrome may be seen in patients with long-standing type 1 diabetes and manifests with joint rigidity (most significantly affecting joints supporting the airway such as the temporomandibular, atlanto-occipital, and cervical spine joints), short stature, and tight, waxy skin. These changes appear secondary to chronic hyperglycemia resulting in nonenzymatic glycosylation of proteins and abnormal cross-linking of collagen in joints and other tissues. Joint limitation may result in a difficult intubation and should be identified before airway manipulation. A positive "prayer sign" (inability to approximate the fingers and palms while pressing the hands together with the fingers extended) has been reported as a marker (30, 77). About one third of patients with long-term type 1 diabetes are reported to undergo a difficult laryngoscopy. Therefore, appropriate equipment should be available when intubating high-risk diabetics. Medications to facilitate intubation and to blunt ischemia should be administered judiciously on a case-by-case basis.

Glycemic Management in the Critically Ill. Historically, perioperative physicians and intensivists took a less aggressive approach to glycemic control in the acutely ill. Blood glucose concentrations were maintained at 150–250 mg/dL (8.3–14 mmol/L). This approach was based on several factors: the lack of knowledge of deleterious effects of acute hyperglycemia, the inability to readily measure blood glucose at the bedside, limitations in nutritional support, and fear of reactive hypoglycemia. This was particularly of concern in sedated, analgesed, paralyzed, or unconscious patients who received multiple medications that might blunt the response to low blood sugars (30). Current and evolving technology may provide continuous noninvasive measurement of blood glucose and rapid adjustment in continuous insulin infusions. Initiation of enteral and parenteral nutritional support raises the specter of secondary hyperglycemia and need for insulin supplementation.

In a single-center, retrospective study of >1,800 medical and surgical adult patients, Krinsley (7) reported the predictive value of blood glucose on patient survival. This study represents the broadest population of critically ill patients reported to date that focused on the association of glucose concentrations and outcome. In contradistinction to other recent reports of glucose control and outcome, cardiac surgery patients were excluded from Krinsley's study. It is uncertain whether Krinsley's report represents a causal event or an epiphenomenon such as previously reported for patients with loss of heart rate variability during critical illness (7, 78).

Recent studies suggest that aggressive glucose control may benefit some patients (1, 13, 14, 20, 54) (Table 2). Most of the data showing benefits of euglycemia or limitation of hyperglycemia are from cardiac patients, either those sustaining a recent myocardial infarction or those undergoing a recent cardiac surgical procedure (1, 13, 14, 20, 54). The potential cardiovascular benefits of glycemic control in the diabetic were well reviewed by Gu et al. (79). Table 3 presents accepted and proposed mechanisms of myocardial ischemia in diabetics secondary to hyperglycemia (79). Current recommendations to limit ischemic episodes in high-risk diabetics include glycemic control (<150 mg/dL [8.3 mmol/L] perioperatively and <120 [6.7 mmol/L] in the ICU), appropriate β-1 blockade, statin medications, and the use of thiazolidinediones and α-glucosidase inhibitors in place of sulfonylurea oral hypoglycemic drugs. The former drugs have been shown to poten-

Table 2. Studies evaluating glycemic control in the critically ill

Study and Type	Population	Protocol	Outcome	Issues
Van Den Berghe et al. (1) PRCT	1,548 patients; surgical, mainly CT surgery	Control—start insulin infusion if blood glucose >215 mg/dL, goal 180–200 mg/dL Study group—use insulin infusion to maintain blood glucose between 80 and 110 mg/dL	Improved outcome, particularly if longer duration in the ICU Lower morbidity rate in study group No major hypoglycemic episodes in study patients	Mainly CV surgery No benefit in others Few if any medical patients
Finney et al. (20) PRCT	523 surgical patients (85% CT surgery)	Treated with insulin infusions Stratified by level of glucose control and insulin infused	Lower glucose better outcome, but more insulin worse outcome	Mainly CT surgery, No medical patients
Malmberg et al. (54) PRCT	620 AMI patients	Randomized diabetics to tight blood glucose control with an initial insulin/glucose infusion or conventional therapy. Tight control group treated subsequently with aggressive subcutaneous insulin 4 times/day	Improved survival, most notable in patients with lowest risk and least previous insulin use	Only diabetics Acute and chronic glycemic control beneficial
Furnary et al. (13) Comparative	3,554 cardiac surgery patients	Done over 15 years. Initial study patients treated with subcutaneous insulin; second half treated with insulin infusion initiated on day of surgery and for 2 days afterward	Halved mortality rate in patients treated with prolonged continuous insulin infusion	Since comparative study, possibility of bias

PRCT, prospective randomized control trial; CT, cardiac surgery; ICU, intensive care unit; CV, cardiovascular; AMI, acute myocardial infarction.

Table 3. Mechanisms of acute and long-term hyperglycemic induced adverse cardiovascular effects

CV Effect	Proposed Mechanism
Altered cell signal transduction	↓ K+ATP channel activation ↓ IPC ↓ APC
Alteration in the coronary microcirculation	↓ Ischemia-induced dilation ↓ Dilation in response to increased cardiac oxygen consumption
Diminished coronary vasodilatory reserve	↓ Responsiveness to coronary vasodilators
Coronary collateral flow compromise	↓ Flow in existing vessels ↓ Development of collaterals
Biochemical	↑ Reactive oxygen species ↑ Advanced glycosylation end products ↓ Nitric oxide production
Endothelial	Dysfunction from ↓ vasodilation
Hematologic	↓ Responsiveness to endogenous and exogenous fibrinolytics

IPC, ischemic preconditioning; APC, anesthetic preconditioning.
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Diabetes mellitus is an increasingly common pathology that affects patients of all ages and results in significant morbidity and mortality rates.

tially be cardioprotective via K_{ATP} channel modulation, whereas sulfonylureas limit ischemic preconditioning through K_{ATP} channel blockade (79).

The recent single-center Flemish study by Van Den Berghe et al. (1) sheds new light on the issue of glucose control in critically ill patients using intensive insulin therapy. This group hypothesized that hyperglycemia, relative insulin deficiency, or both that occurred during critical illness directly or indirectly predisposed patients to complications and potentially greater mortality rates. They further hypothesized that "tighter" glucose control that resulted in euglycemia would reduce morbidity and mortality rates. They reported that glucose control could be maintained using insulin infusions, even in patients who received early nutritional support via the enteral or parenteral route, and that improved glucose control resulted in fewer complications and better survival (1). The data from this sentinel work were widely disseminated, generated significant commentary, and stimulated the common goal of achieving euglycemia in many ICUs (1, 6, 7, 20).

This prospective study randomized patients to strict or traditional blood glucose control. Greater than 60% of the 1,548 adult patients were postoperative cardiac patients, and all required mechanical ventilation. Thirteen percent of patients were known to be diabetic at the time of study entry, 5% required insulin, and 8% were treated with diet and/or oral agents, although hemoglobin-A1C concentrations were not reported, which may have facilitated the identification of previously undiagnosed diabetes mellitus. Conventional therapy consisted of using insulin infusions only if the blood glucose was 215 mg/dL (12 mmol/L) with the therapeutic end point being a blood glucose of 150–180 mg/dL (8.3–10 mmol/dL). More than 98% of the tightly controlled group received an insulin infusion to maintain a blood glucose in the range of 80–110 mg/dL (4.5–6.1 mmol/L). All patients routinely received glucose infusions at the time of admission and were started on enteral, combined enteral-parenteral, or parenteral nutritional support within the first day after ICU admission according to a standardized schedule (1, 80). If patients remained in the ICU for 5 days, there was a significant improvement in overall hospital mortality rate in the tight control group. There was also a lowered ICU mortality rate and far fewer morbidities, including a decreased development of renal failure, a decrease in bloodstream infection, fewer transfusions, a shorter duration of mechanical ventilation, and a lower incidence of developing critical illness polyneuropathy (1).

The incidence of hypoglycemia in the Van Den Berghe report (1) was low, only 5% of the study group and 0.7% of the control group, and there were no reported neuroglycopenic complications. The authors concluded that well-educated staff using a standard insulin infusion protocol could minimize hypoglycemic events. A significant body of additional information from the Van Den Berghe study is now available via the Web site of the *New England Journal of Medicine* (80). The use and timing of nutritional support and required adjustment in insulin infusion are extensively discussed (80).

In a subsequent report on their 1,548-patient database, Van Den Berghe et al. (17) proposed that the main benefit was related to glycemic control and not insulin alone (Table 4). They also speculated about the role of early feedings in their study group and the potential advantages of timely nutritional support in the ICU. In an accompanying editorial, Annane and Melchior (81) argued that insulin may still play an important role in improving outcome of critically ill patients. They proposed multiple potential benefits related to insulin infusion during acute illness (81), including decreased hepatic glucose production, positive influences on immune function with alteration in inflammatory cytokines and chemokines, enhanced glucose transport to intracellular sites, and beneficial adipokinin-mediated neuroendocrine modulation (81).

In a single-center British study from the Royal Brompton Hospital in London, Finney et al. (20) further complemented the insights of Van Den Berghe et al. (17). Finney et al. attempted to discern whether blood glucose concentration or the quantity of insulin required to control hyperglycemia contributed to mortality in 523 consecutively admitted critically ill patients admitted over a 6-month period. Similar to Van Den Berghe's patient population, the study group consisted of adults, a majority of whom were postoperative cardiac surgical patients (85% of admissions and 16.4% were known diabetics, overwhelmingly type 2). Patients had 40 blood glucose measurements taken during a median ICU stay of 1.8 days. The authors followed their routine practice of maintaining blood glucose concentrations between 90 and 145 mg/dL (5.0 and 8.0

Table 4. Potential benefits of glycemic control and/or insulin infusion during acute illness

Controls hyperglycemia-induced osmotic diuresis
Enhances wound healing
Enhances balance of pro- and anti-inflammatory mediators
Insulin infusion
Suppresses tumor necrosis factor-α concentrations
Decreases intranuclear nuclear factor-κB concentrations
Decreases free radical formation
Decreases concentrations of P-47 protein
Decreases number of plasma soluble intercellular adhesion molecules
Decreases monocyte chemoattractant protein-1
Decreases plasminogen activator inhibitor-1 concentrations
Enhances nitric oxide formation
Enhances vasodilatory prostanoid formation
Glucose normalization
Decreases free radical production
Modulates nitric oxide formation
Maintenance of macrophage and neutrophil function
Alters white blood cell binding protein and human leukocyte antigen expression
Insulin-induced beneficial trophic changes on mucosal and skin barriers
Enhances erythropoiesis
Reduces hemolysis
Reduces cholestasis
Improves liberation from mechanical ventilation secondary to a direct anabolic effect of insulin on respiratory muscle function and less hyperglycemic injury of neuronal axons
Reduces axonal dysfunction and degeneration

mmol/L) using regular insulin infusions adjusted at the discretion of the bedside practitioner. Patients were routinely fed as soon as possible (20).

The relationship between ICU survival and concentration of blood glucose control and insulin administration was modeled with multivariable logistic regression analysis. Interestingly, at all blood glucose concentrations, increased insulin administration was associated with a significantly increased risk of death. Patients with a blood glucose concentrations <180 mg/dL (10 mmol/L) had improved survival rates. The authors concluded that glucose control rather than administration of exogenous insulin was the key to improving mortality rates (20). However, the interrelationship of insulin, stress-induced counterregulatory hormone responsiveness, and outcome remains incompletely defined.

Five important questions remain open to investigation as a result of the studies of Van Den Berghe et al. and others. First, is glycemic control applicable in a wider range of critically ill adult and pediatric patients including medical, surgical, neurologic, neurosurgical, and trauma patients? Second, does the duration of ICU stay and severity of illness correlate with the need for tighter glycemic control in critically ill patients? Third, is benefit derived from glycemic control, infused insulin, or a combination of both? Fourth, what is the role of early feeding in the studies of Van Den Berghe et al. (1) and Finney et al. (20)? Fifth, does insulin resistance increase mortality rate and if so, what can been done to ameliorate this effect?

To answer these and other questions, adequately powered prospective, randomized, controlled, multiple-center trials in heterogeneous pediatric and adult populations (e.g., medical, surgical, and neurologic) are needed to establish potential benefit of enhanced glucose control. Without adequately designed and conducted studies, we will continue to empirically extrapolate the current literature and uniformly initiate euglycemic control without identifying the ideal target level of glucose control and without fully appreciating the mechanisms of any potential benefit.

SUMMARY

Diabetes mellitus is an increasingly common pathology that affects patients of all ages and results in significant morbidity and mortality rates. Diabetics require procedural intervention including surgery, hospitalization, and critical care more frequently than their nondiabetic counterparts. An increasing number of patients who require hospitalization and critical care will present to our practices. Identification of the diabetic patient with timely, cost-effective, and comprehensive preoperative evaluation and risk stratification may facilitate appropriate implementation of therapies and procedures that may enhance outcome and limit perioperative complications. An expanding body of literature suggests that improved glycemic control may limit morbidity, mortality, and use of ICU and hospital resources. However, more information is needed from well-designed prospective, randomized, controlled clinical trials that determine the impact of tighter glycemic control in a heterogeneous group of adult and pediatric patients. In particular, we need more data on medical, general surgery, trauma, transplant, neurologic, and neurosurgical patients. We must identify the ideal degree of glycemic control. Are Finney and colleagues (20) correct that the threshold should be <145 mg/dL, and would one glucose threshold apply to all patient populations? What is the incidence of untoward side effects with intense glucose control? What are the mechanisms of benefit of euglycemia: the control of glucose itself, the addition of insulin, or both? To answer these and other questions germane to the optimal metabolic care of the hyperglycemic acutely ill or stressed patient will require a multidisciplinary approach that will clearly benefit from longitudinal multiple-center trials.

REFERENCES

1. Van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; 345:1359–1367
2. Capes SE, Hunt D, Malmberg K, et al: Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: A systematic overview. *Lancet* 2000; 355:773–778
3. Wass CT, Lanier WL: Glucose modulation of ischemic brain injury: Review and clinical recommendations. *Mayo Clin Proc* 1996; 71: 801–812
4. McCowan KC, Malhoota A, Bistrian BR: Endocrine and metabolic dysfunction syndromes in the critically ill. *Crit Care Clin* 2001; 17:107–124
5. Mesotten D, Van den Berghe G: Clinical potential of insulin therapy in critically ill patients. *Crit Care Med* 2001; 29:1714–1719
6. Coursin DB, Murray MJ: How sweet is euglycemia in the critically ill? *Mayo Clinic Proc*, In Press
7. Krinsley JS: Hyperglycemia is strongly associated with increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proceed*, In Press
8. Weir CJ, Murray GD, Dyker AG, et al: Is hyperglycaemia an independent predictor of poor outcome after acute stroke? Results of a long-term follow up study. *BMJ* 1997; 314: 1303–1306
9. Bruno A, Levine SR, Frankel MR, et al: Ad-

mission glucose level and clinical outcomes in the NINDS rt-PA Stroke Trial. *Neurology* 2002; 59:669–674
10. Capes SE, Hunt D, Malmberg K, et al: Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients. *Stroke* 2001; 32:2426–2432
11. Williams LS, Rotich J, Qi R, et al: Effects of admission hyperglycemia on mortality and costs in acute ischemic stroke. *Neurology* 2002; 59:67–71
12. Coutinho M, Gerstein HC, Wang Y, et al: The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95, 783 individuals followed for 12.4 years. *Diabetes Care* 1999; 22:233–240
13. Furnary AP, Gao G, Grunkemeier GL, et al: Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2003; 125:1007–1021
14. Furnary AP, Zerr KJ, Grunkemeier GL, et al: Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. *Ann Thorac Surg* 1999; 67:352–362
15. Das UN: Is insulin an anti-inflammatory molecule? *Nutrition* 2001; 17:409–413
16. Das UN: Insulin and the critically ill. *Crit Care* 2002; 6:262–263
17. Van den Berghe G, Wouters PJ, Bouillon R, et al: Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. *Crit Care Med* 2003; 31:359–366
18. Groeneveld ABJ, Beishuizen A, Visser FC: Insulin: A wonder drug in the critically ill? *Crit Care* 2002; 6:102–105
19. Hansen TK, Thiel S, Wouters PJ, et al: Intensive insulin therapy exerts anti-inflammatory effects in critically ill patients and counteracts the adverse effect of low mannose-binding lectin levels. *J Clin Endocrinol Metab* 2003; 88:1082–1088
20. Finney SJ, Zekvaeld C, Elia A, et al: Glucose control and mortality in critically ill patients. *JAMA* 2003; 290:2041–2047
21. Centers for Disease Control and Prevention (CDC): Prevalence of diabetes and impaired fasting glucose in adults—United States, 1999–2000. *MMWR Morbid Mortal Wkly Rep* 2003; 52:833–837
22. Weinstock RS: Treating type 2 diabetes mellitus: A growing epidemic. *Mayo Clin Proc* 2003; 78:411–413
23. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2003; 26(Suppl 1):S5–S20
24. Arias E, Anderson RN, Kung H-C, et al: Deaths: Final data for 2003. *National Vital Statistics Report* 2003; 52:1–116
25. Gerich JE: Contributions of insulin-resistance and insulin-secretory defects to the pathogenesis of type 2 diabetes mellitus. *Mayo Clin Proc* 2003; 78:447–456
26. Boord JB, Graber AL, Christman JW, et al: Practical management of diabetes in critically ill patients. *Am J Respir Crit Care Med* 2001; 164:1763–1767
27. Magee MF, Bhatt BA: Management of decompensated diabetes—diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome. *Crit Care Clin* 2001; 17:75–106
28. Narayan KM, Boyle JP, Thompson TJ, et al: Lifetime risk for diabetes mellitus in the United States. *JAMA* 2003; 290:1884–1890
29. Umpierrez GE, Isaacs SD, Bazargan N, et al: Hyperglycemia: An independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 2002; 87:978–982
30. Ketzler JT, Angelini GA, Coursin DB: Perioperative care of the diabetic. *ASA Refresher Courses in Anesthesiology* 2001; 29:1–9
31. Redberg RF, Greenland P, Fuster V, et al: Prevention conference VI: Diabetes and cardiovascular disease: Writing group III: Risk assessment in persons with diabetes. *Circulation* 2002; 105:144–152
32. Eagle KA, Berger PB, Calkins H, et al: ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation* 2002; 105:1257–1267
33. O'Neill PA, Davies, Fullerton KJ, et al: Stress hormone and blood glucose response following acute stroke in the elderly. *Stroke* 1991; 22:842–847
34. Mizock BA: Alterations in carbohydrate metabolism during stress: A review of the literature. *Am J Med* 1995; 98:75–84
35. Dessai D, March R, Water JM: Hyperglycemia after trauma increases with age. *J Trauma* 1989; 29:719–723
36. Hotamisligil GS, Spiegelman BM: Tumor necrosis factor alpha: A key component of the obesity-diabetes link. *Diabetes* 1994; 43: 1271–1278
37. Stuart CA, Shangraw RE, Prince MJ, et al: Bed-rest induced insulin resistance occurs primarily in muscle. *Metabolism* 1988; 37: 802–806
38. Takala J, Ruokonen E, Webster NR, et al: Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med* 1999; 341:785–792
39. Grundy S, Benjamin I, Burke G, et al: Diabetes and cardiovascular disease: A statement for healthcare professionals from the American Heart Association. *Circulation* 1999; 100:1134–1146
40. Melamed E: Reactive hyperglycaemia in patients with acute stroke. *J Neurol Sci* 1976; 29:267–275
41. Anderson RE, Tan WK, Martin HS, et al: Effects of glucose and Pa02 modulation on cortical intracellular acidosis, NADH redox state, and infarction in the ischemic penumbra. *Stroke* 1999; 30:160–170
42. De Crespigny AJ, Rother J, Beaullieu C, et al: Rapid monitoring of diffusion DC potential, and blood oxygenation changes during global ischemia: Effects of hypoglycemia, hyperglycemia, and TTX. *Stroke* 1999; 30:2212–2222
43. Tracey BA, Parsons MW, Phanh G, et al: Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. *Stroke* 2003; 34:2208–2214
44. Scott JF, Robinson GM, French JM, et al: Glucose potassium insulin infusions in the treatment of acute stroke patients with mild to moderate hyperglycemia: The glucose insulin in stroke trial (GIST). *Stroke* 1999; 30:793–799
45. Demchuk AM, Morgenstern LB, Krieger DW, et al: Serum glucose level and diabetes predict tissue plasminogen activator-related intracerebral hemorrhage in acute ischemic stroke. *Stroke* 1999; 30:34–39
46. Bonow RO, Mitch WE, Nesto RW, et al: Prevention conference VI diabetes and cardiovascular disease writing group V: Management of cardiovascular-renal complications. *Circulation* 2002; 105:e159–e164
47. Schrier RW, Estacio RO: Additional follow-up from the ABCD Trial in patients with type 2 diabetes and hypertension. *N Engl J Med* 2000; 343:1969
48. UK Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998; 317: 703–13
49. Chobanian AV, Bakris GL, Black HR, et al: The Seventh Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: The JNC 7 Report. *JAMA* 2003; 289: 2560–2571
50. Estacio RO, Jeffers BW, Hiatt WR, et al: The effect of nisoldopine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med* 1998; 338:645–652
51. Staessen JA, Wang JG, Thijs L: Calcium-channel blockade and cardiovascular prognosis: Recent evidence from clinical outcome trials. *Am J Hypertension* 2002; 15:85S–93S
52. Oswald GA, Smith CC, Betteridge DJ, et al: Determinants and importance of stress hyperglycaemia in non-diabetic patients with myocardial infarction. *BMJ* 1986; 293: 917–922
53. Bolk J, van der Ploeg T, Cornel JH, et al: Impaired glucose metabolism predicts mortality after a myocardial infarction. *Int J Cardiol* 2001; 79:207–214
54. Malmberg K, Norhammar A, Wedel H, et al: Glycometabolic state at admission: Important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: Long-term results from the Diabetes and Insulin-

Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. *Circulation* 1999; 99: 2626–2632
55. Gerstein HC, Pais P, Pogue J, et al: Relationship of glucose and insulin levels to the risk of myocardial infarction: A case-control study. *J Am Coll Cardiol* 1999; 33:612–619
56. Jesson ME: Glucose control during cardiac surgery: How sweet it is. *J Thorac Cardiovascular Surg* 2003; 125:985–987
57. Jonassen AK, Sack MN, Mjos AD, et al: Protection by insulin at reperfusion requires early administration and is mediated via Akt and p70s6 kinase cell-survival signaling. *Circ Res* 2001; 89:1191–1198
58. McNulty PH: Comparison of local and systemic effects of insulin on myocardial glucose extraction in ischemic heart disease. *Am J Physiol Heart Circ Physiol* 2000; 278: 1208–1212
59. Ritz E, Orth SR: Nephropathy in patients with type 2 diabetes mellitus. *N Engl J Med* 1999; 341:1127–1133
60. Gaede P, Vedel P, Larsen N, et al: Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003; 348:383–393
61. Mangano CM, Diamondstone LS, Ramsay JG, et al: Renal dysfunction after myocardial revascularization: Risk factors, adverse outcomes, and hospital resource utilization. The Multicenter Study of Perioperative Ischemia Research Group. *Ann Inter Med* 1998; 128: 194–203
62. Lovati E, Richard A, Frey BM, et al: Genetic polymorphisms of the renin-angiotensin-aldosterone system in end-stage renal disease. *Kidney Int* 2001; 60:46–54
63. Chew ST, Newman MF, White WD, et al: Preliminary report of the association of apolipoprotein E polymorphisms with postoperative peak serum creatinine concentrations in cardiac surgical patients. *Anesthesiology* 2000; 93:325–331
64. Hogan KJ: Genomics in perioperative care. *In:* Critical Care Medicine–Perioperative Management. Second Edition. Murray MJ, Coursin DB, Pearl RG, et al (Eds). Philadelphia, Lippincott, Williams & Wilkins, 2002, pp 63–69
65. Chantrel F, Enache I, Bouiller M, et al: Abysmal prognosis of patients with type 2 diabetes entering diabetes. *Nephrol Dial Transplant* 1999; 14:129–136
66. Corwin HL, Gettinger A, Pearl RG, et al: Efficacy of recombinant human erythropoietin in critically ill patients: A randomized trial. *JAMA* 2002; 288:2827–2835
67. Mancini DM, Kaz SD, Lang CC: Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. *Circulation* 2003; 107:294–299
68. Provenzano R, Lorber D, MaClellan W: Prevalence of anemia in diabetic patients with chronic kidney disease and treatment with epoetin. *Am J Kidney Dis* 2002; 39:A26
69. Yusuf S, Sleight P, Pogue J, et al: Effects of angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. *N Engl J Med* 2000; 342:145–153
70. Ritz E: Albuminuria and vascular damage—the vicious twins. *N Engl J Med* 2003; 348: 2349–2352
71. Lee HT, Sladen RN: Perioperative Renal Protection. *In:* Critical Care Medicine—Perioperative Management. Murray MJ, Coursin DB, Pearl RG, et al (Eds). Second Edition. Philadelphia, Lippincott, Williams & Wilkins, 2002, pp 503–520
72. Tepel M, van Der Giet M, Schwarzfeld C, et al: Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med* 2000; 343: 180–184
73. Marenzi G, Marana I, Lauri G, et al: The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. *N Engl J Med* 2003; 349:1333–1340
74. Koch J-A, Plum J, Grabensee B, et al: Prostaglandin E1: A new agent for the prevention of renal dysfunction in high risk patients caused by radiocontrast media? *Nephrol Dial Transplant* 2000; 15:43–49
75. Pflueger A, Larson TS, Nath KA et al: Role of adenosine in contrast media-induced acute renal failure in diabetes mellitus. *Mayo Clin Proceed* 2000; 75:1275–1283
76. Kermani A, Garg A: Thiazolidonedione-associated congestive heart failure and pulmonary edema. *Mayo Clinic Proceed* 2003; 78:1088–1091
77. Hogan KJ, Rusy DA, Springman SR: Difficult laryngoscopy and diabetes mellitus. *Anesth Analg* 1988; 67:1162–1165
78. Stein PK, Schmieg RE Jr, El-Foudy A, et al: Association between heart rate variability recorded on post operative day 1 and length of stay in abdominal aortic surgery patients. *Crit Care Med* 2001; 29:1738–1743
79. Gu W, Pagel PS, Warltier DC, et al: Modifying cardiovascular risk in diabetes mellitus. *Anesthesiology* 2003; 98:774–779
80. Available online at: http://content.nejm.org/cgi/content/full/346/20/1586/DC1. Accessed October 25, 2003
81. Annane D, Melchior JC: Hormone replacement therapy for the critically ill. *Crit Care Med* 2003; 31:634–635

NOTE ADDED IN PROOF

Krinsley recently completed a prospective study evaluating the use of an insulin infusion in 800 adult medical-surgical (noncardiac surgery) intensive care unit patients. Patients who had two consecutive blood glucose readings of >200 mg/dL (11.1 mmol/L) had an insulin infusion initiated, with the subsequent goal blood glucose concentration being <140 mg/dL (7.7 mmol/L). He compared the results with the previous 800 consecutively treated patients in his unit. He reported an almost 30% decrease in mortality in the more tightly controlled cohort, as well as lower frequency of new onset of renal insufficiency, a lower transfusion requirement, and shorter ICU length of stay (James S. Krinsley, MD, personal communication). This is the first such study reporting the benefit of glucose control in a large heterogeneous general ICU population.

In addition, a recent study and state-of-the-art commentary review advances the understanding of the potential associated genetic alteration in mitochondrial oxidative phosphorylation and the development of type 2 diabetes (82, 83).

REFERENCES

82. Peterson KF, Dufour S, Befroy D, et al: Impaired mitochondrial activity in the insulin-resistant offspring of patients with type-2 diabetes. *N Engl J Med* 2004; 350:664–671
83. Taylor R: Causation of type 2 diabetes–The Gordian knot unravels. *N Engl J Med* 2004; 350:639–641