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Anesthetic implications of diabetes*

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INTRODUCTION

Patients undergoing surgery move through a continuum of medical care to which a primary care physician, an internist or pediatrician, an anesthesiologist, and a surgeon or radiologist or obstetrician-gynecologist contribute to ensure the best outcome possible. No aspect of medical care requires greater cooperation among physicians than does the performance of a surgical operation or complex procedure involving multiple specialists and the perioperative care of a patient. The importance of integrating physicians' expertise is even greater within the context of the increasing life span of our population[1]. As the number of the elderly and the very old (those > 85 years of age) grows, so does the need of surgical patients for preoperative consultation that helps plan for comorbidity and multiple drug regimens, knowledge of which is crucial to successful patient management. At a time when medical information is encyclopedic, it is difficult if not impossible for even the most conscientious anesthesiologist to keep abreast of the medical issues relevant to every aspect of perioperative or periprocedure patient management. This chapter reviews such issues.

As with "healthy" patients, it is the history and physical examination of these patients that most accurately predict not only the associated risks but also the likelihood that a monitoring technique or change in therapy will be beneficial or necessary for survival. This chapter emphasizes those instances in which specific information should be sought in history-taking, physical examination, or laboratory evaluations. Although controlled studies designed to confirm that optimizing a patient's preoperative or preprocedure physical condition would result in lower morbidity have not been performed for most diseases, it is logical to assume that such is the case. Studies showing the benefits of optimizing specific preoprocedure conditions are highlighted. The fact that such preventive measures would cost less than treating the morbidity that would otherwise occur is an important consideration in a cost-conscious environment.

Recent data indicates that minimally invasive procedures such as cataract extraction, magnetic resonance imaging, or diagnostic arthroscopy performed in conjunction with the best current anesthetic practices, pose no greater risk than that of daily living, and thus might not be considered an opportunity for special evaluation. Nonetheless, preanesthetic and preprocedure evaluations were found to provide information that led to changes in health care plans for more than 15 percent of all American Society of Anesthesiologists (ASA) I and II patients (and for > 20 percent of all patients in general) at the University of Florida (Gibby GL et al., personal communication). Although these changes in care plans were attributable to data found on history and observation (the most common being gastric reflux, diabetes mellitus requiring insulin, asthma, and suspected difficult intubation), no data show that patient outcome was improved by such changes. Nevertheless, logic caused practitioners to alter plans for such patients in ways that would delay operating room schedules and increase costs. Examples would be administering a beta adrenergic blocking drug and/or aspirin and/or a statin the night before rather than delaying surgery to do so on the morning of surgery, administering a histamine type-2 antagonist 1 to 2 hours before, and an oral antacid immediately before, entry to the operating room; obtaining equipment to measure blood glucose levels; obtaining a history of the patient's diabetic course and treatment from the primary care doctor as well as from the patient; and obtaining a fiberoptic laryngoscopic examination or additional skilled attention. Thus even if preoperative and preprocedure evaluation were not to alter outcome in an important way, its ability to reduce costs by reducing unwarranted laboratory testing and delays in obtaining treatment and equipment perceived to be beneficial (and medicolegally required) would be substantial and would warrant its use.

ROLE OF THE PRIMARY CARE PHYSICIAN OR CONSULTANT

The role of the primary care physician or consultant is not to select or suggest anesthetic or surgical methods but rather to

* Much of this review is taken from The Upcoming 6th Edition of Miller's Anesthesia, with permission of the author.

optimize the patient's preoperative and preprocedure status regarding those conditions that increase the morbidity and mortality associated with surgery.

Quotations and a table in a recent Medical Knowledge Self-Assessment Program published by the leading organization representing internists, the American College of Physicians, highlight this role for the consultant[2]:

Consultation practice is an important component of virtually every internist's professional activity and in some specialties accounts for up to 50 percent of patient care time. Effective interaction with colleagues in other specialties requires a thorough grounding in the language and science of these other disciplines as well as an awareness of basic guidelines for consultation. The consulting internists' role in perioperative care is focused on the elucidation of medical factors that may increase the risks of anesthesia and surgery.

Selecting the anesthetic technique for a given patient, procedure, surgeon, and anesthetist is highly individualized and remains the responsibility of the anesthesiologist rather than the internist.

Optimizing a patient's preoperative and preprocedure condition is a cooperative venture between the anesthesiologist and the internist, pediatrician, surgeon, or family physician. If the primary care physician cannot affirm that the patient is in the very best physical state attainable (for that patient) by that physician and his or her consultants, the anesthesiologist and the physician should do what is necessary to optimize that condition. Failing to consult with the primary care physician preoperatively or before a complex is as risky as not checking the oxygen in the spare tanks. In fact, statements that describe the preoperative and preprocedure physical condition of the patient (e.g., "This patient is in optimum shape" and "I believe the mitral stenosis is more severe than the slight degree of mitral insufficiency") are much more useful to the anesthesiologist than are statements that suggest overall clearance ("cleared for surgery") or perioperative processeds ("prevent hypoxia and hypotension").

Primary care physicians can prepare and treat a patient for optimal conditions for daily life. However, they do not have the depth of understanding of the anesthesiologist regarding the physiologic changes brought on by surgery and the manipulations of functioning that must be made to facilitate surgery and procedures and optimize perioperative and periprocedure outcome. One example would be the primary care physician's induction of some degree of prerenal azotemia for the patient with congestive heart failure. The volume depletion associated with prerenal azotemia may make the cardiac patient more comfortable in daily life but would predispose him or her to hypovolemic disaster during and after surgery and complex procedures. Thus although it would be desirable for the primary care physician to start the process of preparing the patient for the needs of surgery or complex procedures, this activity would not be compatible with the current state of knowledge or functioning of the vast majority of primary care physicians. Although such education is more available and of better quality than in prior decades[3-7], and although Fleisher, Goldman, Charlson, and their co-workers and even cardiologic organizations have provided considerable data regarding the importance of this aspect of care[6-10], the training, knowledge, and ability of primary care physicians are still very deficient in this aspect of consultation. Without understanding the physiologic changes that occur perioperatively, it is difficult to prescribe the appropriate therapy. It is therefore part of the anesthesiologist's job to educate the patient's consultants as to what information is needed from the preoperative and preprocedure consultation.

PREOPERATIVE AND PREPROCEDURE DIABETES MELLITUS

This section makes nine major points regarding diabetes:

1. Diabetes itself may not be as important to perioperative outcome as its end-organ effects (see point no. 3 for exceptions). Although the presence of diabetes has long been assumed to increase perioperative risk, results from epidemiologic studies may not support this assumption for patients not requiring intensive care unit stays. These studies segregated the effects of diabetes per se on the organ system, from the effects of the complications of diabetes (e.g., cardiac, nervous system, renal, and vascular disease) and the effects of old age and the accelerated aging that diabetes causes. Surgical mortality rates for the diabetic population are on average five times higher than those for the nondiabetic population[11,12]. However, in epidemiologic studies in which diabetes itself was segregated from the complications of diabetes (including cardiac and vascular disease) and old age, this finding was questioned[12,13]. Similarly, if diabetics undergoing major vascular surgery are compared with nondiabetics who are matched for type of surgery, age, sex, weight, and complicating diseases, there is no difference in the mortality rate or the number of postoperative complications[13]. Even in patients requiring the intensive care unit, longstanding diabetes does not appear to be as important an issue as end organ dysfunction that exists and degree of glucose control in the perioperative and periprocedure periods and in the intensive care unit period[13A,13B,13C].
2. Because diabetes represents at least two disease processes, its perioperative management may differ between these.

3. The Diabetes Control and Complication Trial for Type I diabetics, the UKPDS for Type II diabetetics, and the Kumamoto studies all show that chronic tight control of blood sugar and blood pressure combined with physical activity in diabetes results in a major delay in microvascular complications and maybe indefinite postponement for Type II patients[14,14A]. However, current debate centers on the benefit associated with tight control in the perioperative period and on the benefit-risk ratio. The evidence indicates that tight control of blood glucose might be a benefit for the pregnant diabetic (and her future offspring)[15] (also see Ch. 59), for the diabetic undergoing cardiopulmonary bypass, for those undergoing (global) CNS ischemia[16], and for those requiring postoperative or postprocedure care in an intensive care unit. Little evidence indicates that tight control is of substantial benefit to any other group; the benefit-risk ratio of tight control has not been examined for any other group of patients[13A,B,C].
4. Different regimens permit almost any degree of perioperative control of blood glucose levels, but the tighter the control desired, the more frequently blood glucose levels must be monitored. Three treatment regimens are outlined below.
5. The major risk factors for diabetics undergoing surgery are the end-organ diseases associated with diabetes: cardiovascular dysfunction, renal insufficiency, joint collagen tissue abnormalities (limitations of neck extension(18), poor wound healing), inadequate granulocyte production, and neuropathies[11,13,13A,B,C,18,19]. Thus a major focus of the anesthesiologist should be the preoperative and preprocedure evaluation and treatment of these diseases to ensure optimal preoperative and preprocedure conditions.
6. Regional anesthesia may be indicated to facilitate some procedures. The following considerations should be kept in mind regarding the use of regional anesthesia for diabetic patients. Local anesthetic requirements are lower and the risk of nerve injury is higher in diabetic patients[20,21]. Also, combining local anesthetics with epinephrine may pose even greater risk of ischemic and/or edematous nerve injury in the diabetic.
7. Nosocomial infection rates are probably decreased with outpatient surgery; complications may be decreased in those diabetics most at risk by either tight control of blood glucose or intense postoperative care, or both.
8. The United States and the world has been experiencing a great and progressive growth in the number of people who are known to be diabetic. That growth parallels a gain in weight in the adult population that causes type II diabetes.
9. Both forms of diabetes cause accelerated aging. Thus the risks involved in caring for someone with diabetes is similar to the risks for someone much older, i.e., someone who has a much higher physiologic age (or "RealAge"[22,22A].

Non-insulin-dependent (type II) diabetics constitute more than 90 percent of the more than 18 million diabetics in the United States[23], sixty percent of whom are diagnosed. The medical costs for these patients was over 150 billion dollars in 2002, and has increased at more than 10 percent per year since 1996 At the current rate of growth, there will be 250 million diabetics in the world in 2010. These individuals tend to be elderly, overweight, and relatively resistant to ketoacidosis and susceptible to the development of a hyperglycemic-hyperosmolar nonketotic state. The diagnosis of diabetes is made with a fasting blood gluicose greater than 125 mg/dl (7.0 mmol/l), and impaired glucose if the fasting level is below 125mg/dl (7.0 mmol/l), but greater than 110 (6.1). Plasma insulin levels are normal or elevated in type II diabetetics, but are relatively low for the level of blood glucose. This hyperinsulinemia by itself is postulated to cause accelerated cardiovascular disease[23A].

Insulin originates in the pancreas. Pancreatic islets are composed of at least three cells: $\propto$-cells that secret glucagon, β-cells that secrete insulin, and δ-cells that contain secretory granules. Insulin is first synthesized as proinsulin, converted to insulin by proteolytic cleavage, and then packaged into granules within the β-cells. A large quantity of insulin, normally about 200 units, is stored in the pancreas; continued synthesis is stimulated by glucose. There is a basal, steady-state release of insulin from the β-granules and additional release controlled by stimuli external to the β-cell. Basal insulin secretion continues in the fasted state and is crucial to the inhibition of catabolism and ketoacidosis. Glucose and fructose are the primary regulators of insulin release. Other stimulators of insulin release include amino acids, glucagon, GI hormones (gastrin, secretin, cholecystokinin-pancreozymin, and enteroglucagon), and acetylcholine. Epinephrine and norepinephrine inhibit insulin release by stimulating $\propto$-adrenergic receptors and stimulate insulin release at β-adrenergic receptors.

Diabetes mellitus is a heterogeneous group of disorders that have the common feature of a relative or absolute lack of insulin. The disease is characterized by a multitude of hormone-induced metabolic abnormalities, by a diffuse microvascular lesion, and by long-term end-organ complications. Diabetes can be divided into two very different diseases that share these end-organ abnormalities. Type I diabetes is associated with autoimmune diseases and has a concordance rate of 40 to 50 percent (i.e., if one of a pair of monozygotic twins had diabetes, the likelihood that the oth-

er twin would have diabetes is 40 to 50 percent). In type I, the patient is insulin-deficient and is susceptible to ketoacidosis if insulin is withheld. For type II diabetes, the concordance rate is 100 percent (i.e., the genetic material is both necessary and sufficient for the development of type II diabetes). The patients are not susceptible to the development of ketoacidosis in the absence of insulin, and they have peripheral insulin resistance. Gestational diabetes develops in more than 2 percent of all pregnancies, and increases the risk for type II diabetes to 17 to 63 percent within 15 years.

Type I and type II diabetes differ in other ways as well. Contrary to a long-standing belief, patient age does not allow a firm distinction between type I and type II diabetes; an older person can develop type I diabetes. A diabetes-producing variant of coxsackie B4 virus has been isolated from the pancreas of a patient who died of diabetic ketoacidosis (type I diabetes). This virus was also recovered from mice bred to be diabetes-prone after inoculation of the virus had produced hyperglycemia and pancreatic β-cell necrosis coincident with rising antibody titers[24]. Thus the intrinsic genetic "vulnerability" in insulin-dependent type I diabetes mellitus may consist of diminished capacity of β-cells to survive exposure to potentially damaging extrinsic agents.

Type I diabetes is associated with a 15 percent prevalence of other autoimmune diseases, including Graves' disease, Hashimoto's thyroiditis, Addison's disease, and myasthenia gravis.

Currently, therapy for type II diabetes usually begins with exercise and dietary management. A diet rich in fiber and less saturated fat, and daily physical activity of 30 minutes, is often associated with normalization of fasting blood glucose and delay of glucose intolerance by more than 50 percent of subjects[25]. The nextr stage of therapy is use of oral hypoglycemic medications that act by stimulating release of insulin by pancreatic β-cells and by improving the tissue responsiveness to insulin by reversing the postbinding abnormality. The common orally administered drugs are tolazamide (Tolinase), tolbutamine (Orinase), and the newer sulfonylureas glyburide (Micronase), glipizide (Glucotrol), and Glimperide. These last drugs have a longer blood glucose-lowering effect, which persists for 24 hours or more, and fewer drug-drug interactions. Oral hypoglycemic drugs may produce hypoglycemia for as long as 50 hours after intake (chlorpropamide [Diabinese] has the longest half-life). Other drugs include metformin, which decreases hepatic glucose output and may increase peripheral responsiveness to glucose (and is associated with lactic acidosis if the patient becomes dehydrated) ; acarbose, which decreases glucose absorption; and the thiaolidinediones (rosiglitazone and pioglitizone) which increase peripheral responsiveness to insulin[26]. Troglitazone, another drug of this latter class, has been taken off the market due to 61 cases of acute renal failure after its use. Progressively, physicians advocating tight control of blood sugar levels give insulin to "maturity onset" insulin-dependent diabetic patients twice a day, or even more frequently[27,28].

Insulin-dependent diabetics tend to be young, nonobese, and susceptible to the development of ketoacidosis. Plasma insulin levels are low or nonmeasurable, and therapy requires insulin replacement. Patients with insulin-dependent diabetes experience an increase in their insulin requirements in the postmidnight hours; this may result in early-morning hyperglycemia (dawn phenomenon). This accelerated glucose production and impaired glucose utilization are due to nocturnal surges in growth hormone secretion[29]. Normal patients and diabetics taking insulin have steady-state levels of insulin in their blood. (Unfortunately, traditional values for insulin pharmacokinetics derive from studies designed as though the diabetic received only one shot of insulin in a lifetime). Absorption of insulin is highly variable and is dependent on the type and species of insulin, the site of administration, and subcutaneous blood flow. Nevertheless, the steady state is dependent on periodic administration of the preparations received by the patient. Thus it seems logical to continue perioperatively the combinations of preparations the patient has been receiving chronically, after examining the patient's blood-glucose monitoring logbook for the degree of control. (In my clinical experience, erratic control can foreshadow perioperative hypoglycemia).

Acute complications for the diabetic patient include hypoglycemia and diabetic ketoacidosis, as well as hyperglycemic, hyperosmolar, nonketotic coma. Diabetic patients are also subject to a series of long-term complications, including cataracts, neuropathies, retinopathy, and angiopathy involving peripheral and myocardial vessels, that lead to considerable morbidity and premature mortality. The leading cause of blindness of renal failure in the United States is diabetes. Many of these complications will bring the diabetic patient to surgery. The evidence that hyperglycemia itself accelerates these complications or that tight control of blood sugar levels decreases the rapidity of the progression of microangiopathic disease is becoming more definitive[14,14A].

Glucose itself may be toxic because high levels can promote nonenzymatic glycosylation reactions, leading to the formation of abnormal proteins that may decrease elastance and wound-healing tensile strength. The decrease in elastance is responsible for the stiff joint syndrome and for fixation of the atlanto-occipital joint that makes intubation difficult[17,32,33]. Furthermore, elevations in glucose may increase production of macroglobulins by the liver, thereby increasing blood viscosity, and may promote intracellular swelling by favoring the production of nondiffusible, large molecules (e.g., sorbitol). Newer drug therapies (e.g., aldose-reductase

inhibitors) aim to decrease intracellular swelling by inhibiting formation of such large molecules.

Studies relating to the long-term outcome for type I and type II diabeticsindicate tight control of blood glucose and blood sugar substantially prevents such complications.

Perioperative management of the diabetic patient may affect surgical outcome. Physicians advocating tight control of blood glucose levels point to the evidence of increased wound-healing tensile strength and decreased wound infections in animal models of diabetes (type I) under tight control and in infections, renal failure, other serious complications and death in patients requining intensive care[13A,B,C,34].

Infections account for two-thirds of postoperative complications and about 20 percent of perioperative deaths in diabetic patients. Experimental data suggest many factors that can make the diabetic patient vulnerable to infection. Many alterations in leukocyte function have been demonstrated in hyperglycemic diabetics, including decreased chemotaxis and impaired phagocytic activity of granulocytes, as well as reduced intracellular killig of pneumococci and staphylococci[35,36]. When diabetic patients are treated aggressively and blood glucose levels are kept below 270 mg/dl, the phagocytic function of granulocytes is improved and intracellular killing of bacteria is restored to near-normal levels[37].

Diabetic patients have been thought to experience more infections in clean wounds than nondiabetics. In a review of 23,649 surgical patients, the rate of wound infection in clean incisions was 10.7 percent for diabetics versus 1.8 percent for nondiabetics[38]. However, when age is accounted for, the incidence of wound infection for diabetic surgical patients does not differ significantly from that for nondiabetic patients. In addition, hyperglycemia may worsen neurologic outcome after intraoperative cerebral ischemia.

Blood glucose levels may affect neurologic recovery after a global ischemic event. In a study of 430 consecutive patients resuscitated after out-of-hospital cardiac arrest, mean blood glucose levels were higher in patients who never awakened (341 ± 13 mg/dl) than in those who did awaken (262 ± 7 mg/dl)[39]. Among patients who awakened, those with persistent neurologic deficits had higher mean glucose levels (286 ± 15 mg/dl) than patients without deficits (251 ± 7 mg/dl). These results are consistent with the finding that hyperglycemia during a stroke is associated with poorer short- and long-term neurologic outcomes. Although several questions remain, the likelihood that blood glucose is a determinant of brain damage following global ischemia is supported by the vast majority of animal studies after global CNS ischemia[16], and by most but not all studies after focal CNS ischemia[16]. The preponderance of data after CNS ischemia indicates that levels of glucose higher than 150 or 250 mg/dl have an adverse effect on CNS recovery. Until better data are available, many will argue that the diabetic patient about to undergo surgery in which hypotension or reduced cerebral flow may occur should have a blood glucose level below 200 mg/dl during a period of cerebral ischemia. Some special situations may also influence how tightly one should manage the patient's glucose level, such as surgery requiring cardiopulmonary bypass, surgery for pregnant patients, and emergency surgery on patients with diabetic ketoacidosis or hyperosmolar nonketotic coma.

Diabetics undergoing coronary artery bypass graft (CABG) surgery in 1980 had a perioperative mortality rate of 5 percent, compared with 1.5 percent for nondiabetics. In this study, and in most other studies of diabetic patients undergoing CABG surgery, important additional risk factors or confounding variables were not considered, including the incidence and extent of hypertension, ventricular dysfunction, congestive heart failure, or severity of coronary artery disease.

The above study of 340 diabetics and 2,522 nondiabetics undergoing CABG surgery in 1980 demonstrated only a moderate increase in the operative mortality for diabetics (1.8 percent versus 0.6 percent). In the postbypass phase, patients with diabetes were found to require inotropic therapy and intraaortic balloon pump support five times more frequently than nondiabetics. There are several possible reasons. Diabetics with angina have more extensive coronary artery disease than do nondiabetic patients. They are also more likely to have hypertension, cardiomegaly, diffuse hypokinesis, and prior myocardial infarction. Insulin-dependent diabetics with coronary artery disease, impaired stress responses, and autonomic nerve dysfunction appear to have stiffer ventricles with greater elevation of left ventricular end-diastolic pressure than do matched nondiabetic controls[40-42]. During cardiopulmonary bypass, hypothermia and stress reactions decrease the response to insulin and result in marked hyperglycemia (even when the perfusate and intravenous solutions do not contain glucose). Administration of washed cells has been advocated for small individuals, as acid citrate dextrose (ACD) or adenine-supplemented (AS) blood can result in significant hyperglycemia. These changes are exaggerated in the diabetic patient, and insulin administration may have little effect until rewarming is achieved. In a number of recently reported cases, inotropic agents were ineffective in maintaining cardiac contractility, although filling pressures, sinus rhythm, serum electrolytes, and arterial blood gases were adequate. Blood sugar levels were elevated in each case. After intravenous infusion of insulin, effective myocardial contractions returned, allowing easy and rapid bypass weaning. The effect of glucose levels during cardiopulmonary bypass on neurologic outcome is both unclear and controversial.

Many diabetics requiring emergency surgery for trauma or infection have significant metabolic decompensation, including ketoacidosis. Often little time is available for stabilization of the patient, but even a few hours may be suffi-

cient for correction of fluid and electrolyte disturbances that are potentially life-threatening. It is futile to delay surgery in an attempt to eliminate ketoacidosis completely if the underlying surgical condition will lead to further metabolic deterioration. The likelihood of intraoperative cardiac arrhythmias and hypotension resulting from ketoacidosis will be reduced if volume depletion and hypokalemia are at least partially treated.

Insulin therapy is initiated with a 10-unit intravenous bolus of regular insulin, followed by continuous insulin infusion. The rate of infusion is determined most easily if one divides the last serum glucose value by 150 (or 100 if the patient is receiving steroids, has an infection, or is considerably overweight). The actual amount of insulin administered is less important than regular monitoring of glucose, potassium, and pH. Because the number of insulin-binding sites is limited, the maximum rate of glucose decline is fairly constant, averaging 75 to 100 mg/dl/h regardless of the dose of insulin[43]. During the first 1 to 2 hours of fluid resuscitation, the glucose level may fall more precipitously. When serum glucose reaches 250 mg/dl, the intravenous fluid should include 5 percent dextrose.

The volume of fluid required for therapy varies with overall deficits, ranging from 3 to 5 liters and as high as 10 liters. Despite losses of water in excess of losses of solute, sodium levels are generally normal or reduced. Factitious hyponatremia caused by hyperglycemia or hypertriglyceridemia may result in this seeming contradiction. The plasma sodium concentration decreases by about 1.6 mEq/l for every 100-mg/dl increase in plasma glucose above normal. Initially, normal saline is infused at the rate of 250 to 1,000 ml/h, depending on the degree of volume depletion and on cardiac status. Some measure of left ventricular volume should be monitored in diabetics who have a history of myocardial dysfunction. About one-third of the estimated fluid deficit is corrected during the first 6 to 8 hours, and the remaining two-thirds over the next 24 hours.

The degree of acidosis present is determined by measurement of arterial blood gases and an increased anion gap:

$$Na+ \quad (Cl- + HCO3-)$$

Acidosis with an increased anion gap ($\geq$ 16 mEq/l) in the acutely ill diabetic may be caused by ketones in ketoacidosis, lactic acid in lactic acidosis, increased organic acids from renal insufficiency, or all three problems. In ketoacidosis, plasma levels of acetoacetate, $\beta-$hydroxybutarate, and acetone are increased. Plasma and urinary ketones are measured semiquantitatively with Ketostix and Acetest tablets. The role of bicarbonate therapy in diabetic ketoacidosis is controversial. Myocardial function and respiration are known to be depressed at a blood pH below 7.0 to 7.10, yet rapid correction of acidosis with bicarbonate therapy may result in alterations in CNS function and structure. This may be caused by (1) paradoxical development of cerebrospinal fluid and CNS acidosis resulting from rapid conversion of bicarbonate to carbon dioxide and diffusion of the acid across the blood-brain barrier, (2) altered CNS oxygenation with decreased cerebral blood flow, and (3) the development of unfavorable osmotic gradients. After treatment with fluids and insulin, β-hydroxybutarate levels decrease rapidly, whereas acetoacetate levels may remain stable or may even increase before declining. Plasma acetone levels remain elevated for 24 to 42 hours, long after blood glucose, β-hydroxybutarate, and acetoacetate levels have returned to normal; the result is continuing ketonuria[43]. Persistent ketosis, with a serum bicarbonate level of less than 20 mEq/l in the presence of a normal glucose level, represents a continued need for intracellular glucose and insulin for reversal of lipolysis.

The most important electrolyte disturbance in diabetic ketoacidosis is depletion of total body potassium. The deficits range from 3 to 10 mEq/kg body weight. Rapid declines in serum potassium level occur, reaching a nadir within 2 to 4 hours after the start of intravenous insulin administration. Aggressive replacement therapy is required. The potassium administered moves into the intracellular space with insulin as the acidosis is corrected. Potassium is also excreted in the urine with the increased delivery of sodium to the distal renal tubules that accompanies volume expansion. Phosphorus deficiency in ketoacidosis caused by tissue catabolism, impaired cellular uptake, and increased urinary losses may result in significant muscular weakness and organ dysfunction. The average phosphorus deficit is approximately 1 mmol/kg body weight. Replacement is needed if the plasma concentration falls below 1.0 mg/dl[43].

Glucotoxicity

Chronic tight control of blood glucose has been motivated by a theoretic concern about five potential glucotoxicities, plus the results from threemajor randomized outcome studies involving diabetic patients[14,14A].

Glucose itself may be toxic because high levels can promote nonenzymatic glycosylation reactions that lead to the formation of abnormal proteins. These proteins may decrease elastance—which is responsible for the stiff joint syndrome (and the fixation of the atlanto-occipital joint that makes intubation difficult)—and wound-healing tensile strength. Furthermore, elevations in glucose may increase production of macroglobulins by the liver (which would increase blood viscosity) and promote intracellular swelling by favoring production of nondiffusible, large molecules (such as sorbitol). Some drug therapies (e.g., aldose-reductase inhibitors) aim to decrease intracellular swelling by inhibiting formation of such large molecules.

Glycemia also disrupts autoregulation. Glucose-induced vasodilation prevents target organs from protecting against increases in systemic blood pressure. A glycosylated hemoglobin level of 8.1 percent is the threshold at which the risk of microalbuminuria increases logarithmically. A person with type I diabetes who has microalbuminuria of more than 29 mg/day has an 80 percent chance of experiencing renal insufficiency. The threshold for glycemic toxicity differs for various vascular beds. For example, the threshold for retinopathy is a glycosylated hemoglobin value of 8.5 to 9.0 percent (12.5 mmol/l or 225 mg/dl); and, for cardiovascular disease, an average blood glucose value of 5.4 mmol/l (96 mg/dl). Thus different degrees of hyperglycemia may be required before different vascular beds are damaged, or certain degrees of glycemia are associated with other risk factors for vascular disease. Another view is that perhaps severe hyperglycemia and microalbuminuria are simply concomitant effects of a common underlying cause. Diabetics in whom microalbuminuria develops are more resistant to insulin; insulin resistance is associated with microalbuminuria in first-degree relatives of type II diabetics; and persons who are normoglycemic but subsequently have clinical diabetes have atherogenic risks before onset of disease.

Tight control retards all of these glucotoxicities, and may have other benefits in retarding the severity of diabetes itself[14,14A,44].

Thus management of intraoperative glucose might be influenced by specific situations, such as type of operation, pregnancy[45,46], and expected global CNS insult; bias of the patient's primary care physician; or type of diabetes. Type I diabetic patients definitely need insulin and might be considered candidates for tight control of blood glucose levels. Type II diabetic patients have insulin, and current data indicate they do not benefit from tight perioperative control, unless they need intensive care[13A,B,C,47].

The key to managing blood glucose levels in diabetic patients perioperatively is to set clear goals and then to monitor blood glucose levels frequently enough to adjust therapy to achieve those goals. Three regimens that afford various degrees of perioperative control of blood glucose levels are discussed below.

Classic "Nontight Control" Regimen

Aim: To prevent hypoglycemia. To prevent ketoacidosis and hyperosmolar states.

Protocol:

1. Day before surgery: Patient should be given nothing by mouth after midnight; a 13-ounce glass of clear orange juice should be at the bedside or in the car for emergency use.
2. At 6 AM on day of surgery, institute intravenous fluids using plastic cannulae and a solution containing 5 percent dextrose, infused at the rate of 125 ml/h/70 kg body weight.
3. After institution of intravenous infusion, give one-half the usual morning insulin dose (and usual type of insulin) subcutaneously.
4. Continue 5 percent dextrose solutions through operative period, giving at least 125 ml/h/70 kg body weight.
5. In recovery room monitor blood glucose concentrations and treat on a sliding scale.

Such a regimen has been found to meet its goals.

"Tight Control" Regimen 1

Aim: To keep plasma glucose levels at 79 to 120 mg/dl; this practice may improve wound healing and prevent wound infections, improve neurologic outcome after global or focal CNS ischemic insult, or improve weaning from cardiopulmonary bypass.

Protocol:

1. Evening before operation, determine preprandial blood glucose level.
2. Through a plastic cannula, begin intravenous infusion of 5 percent dextrose in water at the rate of 50 ml/h/70 kg body weight.
3. "Piggyback" to the dextrose infusion an infusion of regular insulin (50 units in 250 ml or 0.9 percent sodium chloride) and an infusion pump. Before attaching this piggyback line to the dextrose infusion, flush the line with 60 ml of infusion mixture and discard the flushing solution. This approach saturates insulin-binding sites of the tubing[48].
4. Set the infusion rate, using the following equation: Insulin (U/h) = plasma glucose (mg/dl)/150. (Note: This denominator should be 100 if patient is taking corticosteroids, e.g., 100 mg of prednisolone a day or its equivalent, not to include inhaled steroids.)
5. Repeat measurements of blood glucose levels every 4 hours as needed, and adjust insulin appropriately to obtain blood glucose levels of 100 to 200 mg/dl.
6. The day of surgery, intraoperative fluids and electrolytes are managed by continuing to administer non-dextrose-containing solutions, as described in steps 3 and 4.
7. Determine plasma glucose level at the start of operation and every 1 to 2 hours for the rest of the 24-hour period. Adjust insulin dosage appropriately.

Although I have not found the need to treat hypoglycemia (i.e., blood glucose levels of < 50 mg/dl), I have been prepared to do so with 15 ml of 50 percent dextrose in water. Under such circumstances, the insulin infusion would be terminated. Such a regimen has been found to accomplish its goals, with the exception of such tight goals for blood glu-

cose, even in very "brittle" diabetics (i.e., those extremely resistant to treatment) given high doses of steroids[49].

"Tight Control" Regimen 2

Aim: Same as for Tight Control Regimen 1

Protocol:

1. Obtain a "feedback mechanical pancreas" and set the controls for the desired plasma glucose regimen.
2. Institute two appropriate intravenous lines.

This last regimen may well supersede all others if the cost of a mechanical pancreas can be reduced and if control of hyperglycemia is shown to make a meaningful difference perioperatively; it has superseded all others in many intensive care units, and for good reason (Table XXVII-IIB)[13A,B,C,].

Diabetes and accelerated physiologic aging

Adverse perioperative outcomes have repeatedly and substantially correlated with age of the patient[7,9,12,22,22A,50,51,52], and diabetes does cause physiologic aging. When one translates the results of the Diabetes Control and Complications Trials into age-induced physiologic changes, the type I diabetic who has poor control of blood sugar ages approximately 1.75 years physiologically for every chronologic year of the disease, and 1.25 years if blood sugar has been controlled tightly[22]. The type II diabetic ages about 1.5 years for every chronologic year of the disease, and about 1.06 years with tight control of blood sugar and blood pressure[22,22A,14A,25]. Thus when providing care for a diabetic patient, one must consider the associated risks to be those of a person who is much older physiologically. That is, the diabetic's physiologic age ("RealAge") is considerably higher than his or her calendar age just by virtue of having the disease[1].

The increased prevalence of obesity and lack of physical exercise seem to be major contributors to the increased prevalence of type II diabetes. As with type I diabetes, tight control of blood sugar, increased physical activity, and reduction in weight appear to reduce the accelerated aging of type II diabetes, and even to delay substantially the appearance of the disease. Although such a reduction in aging should reduce the perioperative risk for diabetic patients, no controlled trials have confirmed this theory.

Other conditions associated with diabetes

Diabetes is associated with microangiopathy (in retinal and renal vessels), peripheral neuropathies, autonomic dysfunction, and infection. Diabetics are often treated with angiotensin-converting enzyme inhibitors even in the absence of gross hypertension, in an effort to prevent the effects of disordered autoregulation, including renal failure[53,14,14A].

Before surgery, assessment and optimization of treatment of the potential and potent end-organ effects of diabetes are at least as important as an assessment of the diabetic's current overall metabolic status. Information about a diabetic patient that might merit special attention before surgery includes the therapeutic, dietary, and exercise or physical activity regimens; adequacy of glucose control; prior surgical and anesthetic responses; and the presence of the end-organ effects of diabetes. In this clinician's experience, many diabetic patients pay extreme attention to glucose control, expect each physician to ask about it, and are annoyed (and probably rightly so) if the physicians treating them in the perioperative period are not at least as concerned about glucose level as the patient has had to be. Thus if just to avoid making the patient angry (and, I believe, for more value than that), the anesthesiologist should inquire in some depth about the diabetic's control of blood glucose levels. Basic laboratory examinations might include determination of fasting blood sugar levels, electrolytes, blood urea nitrogen (BUN) or creatinine levels, and an electrocardiogram (ECG). Scheduling the operative procedure early in the day avoids prolonging the catabolic state and minimizes the risk of preoperative hypoglycemia.

If one is to believe the few studies we have, the presence of autonomic neuropathy makes the operative period more hazardous and the postoperative period crucial to survival. Evidence of autonomic neuropathy might be routinely sought prior to surgery. Patients with diabetic autonomic neuropathy are at increased risk of gastroparesis (and consequent aspiration) and of intraoperative and postoperative cardiorespiratory arrest. Data indicate that diabetics who exhibit signs of autonomic neuropathy, such as early satiety, lack of sweating, lack of pulse rate change with inspiration or orthostatic maneuvers, and impotence, have a very high incidence of painless myocardial ischemia[42,48-50,54,55] and of gastroparesis. Some investigators have successfully used 10 mg of metoclopramide preoperatively to facilitate gastric emptying of solids. Interference with respiration or sinus automaticity by pneumonia or by anesthetics, pain medications, or sedative drugs appears to be the precipitating cause in most cases of sudden cardiorespiratory arrest. Measuring the degree of sinus arrhythmia or beat-to-beat variability provides a simple, accurate test for significant autonomic neuropathy. The difference between maximum and minimum heart rate on deep inspiration is normally 15 beats/min but was found to be 5 beats/min or less in all patients who sustained cardiorespiratory arrest[54].

Other characteristics of patients with autonomic neuropathy include postural hypotension with a decrease in blood pressure of more than 30 mmHg, resting tachycardia, nocturnal diarrhea, and dense peripheral neuropathy. Diabetics with significant autonomic neuropathy may have impaired respirato-

ry responses to hypoxia and are particularly susceptible to the action of drugs that have depressant effects. Such patients may warrant very close, continuous cardiac and respiratory monitoring for 24 to 72 hours postoperatively, although such logical treatment has not been tested in a rigorous, controlled trial(19A). In the absence of autonomic neuropathy. I would favor outpatient surgery for the diabetic.

Anticipated newer treatments for diabetes

At least four major changes in care for the diabetic patient have made it to the clinical trial stage include:

Implanted (like a pacemaker) glucose analyzer with electronic transmission to a surface (watch) monitor

A glucagon like peptide receptor antagonist like

New islet transplantation medication that makes islet cell transplants much more successful and rejection medication less hazardous

Medication like INGAP peptide that may cause regrowth of normally functioning islet cells (without needing transplantation)

You can imaging how some of these may radically change therapies used in the perioperative period-if regrowth of islets becomes common, type I diabetes could all but disappear; if implanted minute to minute glucose reading is possible, tight control may be much easier and more expected.

Current focus for diabetes perioperatively

Perhaps as important as arranging for tight control in the diabetic needing intensive care is active memory that diabetic patients have an increased incidence of atherosclerosis and all its complications. These patients are particularly susceptible to episodes of painless myocardial ischemia and cardiovascular instability[57-59]. In fact, over 80 percent of the ischemic episodes that occur in both patients who have myocardial ischemia and in those who are diabetic are "silent." However, a 65-year-old diabetic is as likely to die of a cardiovascular event in the next several years as is a person who has just had a heart attack[60]. These data dramatically illustrate the increased risk of cardiovascular disease in the diabetic who does not have symptoms. As with other endocrinopathies, the cardiovascular system should be a focus for the anesthetist's attention for the diabetic patient.

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