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Modifying Cardiovascular Risk in Diabetes Mellitus

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DIABETES mellitus affects an estimated 35 million people in the United States, and the disease prevalence is predicted to increase by nearly 200% in the next several decades. As a result, anesthesiologists will be confronted with an increasing population of patients undergoing anesthesia and surgery who are at risk for ischemic heart disease.

Hyperglycemia Predicts Cardiovascular Risk

Diabetes is a significant predictor of perioperative cardiovascular morbidity and mortality, but few studies have evaluated methods to modify this risk. Compelling evidence indicates that aggressive management of diabetes may substantially decrease the adverse consequences of myocardial ischemia and infarction. The direct impact of hyperglycemia on cardiovascular mortality in patients with and without diabetes is a central theme of current research, and several investigations conducted during the past 20 yr demonstrated that mortality resulting from acute myocardial infarction (AMI) is increased if blood glucose concentration is elevated at the time of hospital admission.[1] These findings were confirmed in a recent prospective analysis of 336 consecutive patients admitted with AMI.[2] One-year mortality was 9% for patients with AMI and normal admission blood glucose values. In contrast, patients with hyperglycemia (blood glucose concentrations of 121 ± 15, 168 ± 13, and 282 ± 65 mg/dl) on admission demonstrated substantial increases ($P < 0.005$) in mortality to 13, 30, and 44%, respectively.[2] The Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial addressed the prognostic significance of hyperglycemia in patients with type 1 and 2 diabetes and AMI.[3] A nearly linear relationship between blood glucose concentration on admission and long-term mortality was observed in conventionally treated patients in this randomized clinical trial (mortality rates of 35, 40, and 55% at blood glucose concentrations of < 235, 235–298, and > 298 mg/dl, respectively).

A direct relationship between fasting blood glucose concentration and the risk of sustaining a cardiovascular event (*e.g.*, sudden cardiac death, AMI, or cerebrovascular accident) has been demonstrated in a meta-regression analysis of data from 20 studies involving more than 95,000 patients.[4] The risk associated with fasting blood glucose concentrations was linear and extended below the threshold used to define diabetes. A fasting blood glucose value of only 110 mg/dl was associated with an increased relative risk of a cardiovascular event. Similarly, the odds ratio of AMI was increased to 1.5, 3.4, and 6.0 at fasting blood glucose concentrations of approximately 90, 110, and greater than 115 mg/dl, respectively.[5] Another large cohort study indicated that glycosylated hemoglobin (HbA_{1c}) concentration, but not the presence of diabetes, predicted an increase in mortality.[6] The risk of all-cause mortality increased by a factor of 1.46 for every 1% increase in HbA_{1c} when male patients with diabetes, those with HbA_{1c} concentrations greater than 7%, or patients with a history of heart disease or stroke were excluded from the multivariate regression model. Similarly, creatinine kinase concentrations were higher in patients with hyperglycemia admitted with AMI compared with those with normal blood glucose levels.[2] These data demonstrate a striking relationship between mild increases in blood glucose concentration and cardiovascular risk. As a result of such findings, the definition of diabetes has been revised, and diabetes is diagnosed at a lower fasting plasma glucose concentration (≤ 126 mg/dl) than previously recommended.

Data obtained from experimental animals support the clinical findings relating to hyperglycemia and cardiovascular risk, and also indicate a direct relationship between the severity of hyperglycemia and the extent of myocardial infarction. For example, myocardial infarct size was linearly related to blood glucose concentration, and further, this relationship was similar whether hyperglycemia was produced by chemical induction of diabetes or by acute infusion of intravenous dextrose.[7] Taken together, these data indicate a strong correlation between

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blood glucose concentration and outcome for patients with coronary artery disease. The data suggest that aggressive control of blood glucose concentration may decrease cardiovascular morbidity and mortality in these patients.

The impact of tight control of blood glucose concentration on the microvascular consequences of diabetes has long been recognized, but the importance of this therapeutic objective on the incidence and severity of macrovascular complications of diabetes (*e.g.*, AMI) is not as clearly appreciated. The United Kingdom Prospective Diabetes Study provided evidence that this approach was clearly beneficial. The risk of myocardial infarction was directly related to fasting blood glucose and HbA_{1c} concentrations in this study.[8] Furthermore, intensive insulin treatment of patients instituted within hours of admission after AMI significantly decreased long-term mortality compared with a less aggressive management approach.[3] Although blood glucose concentrations were similar at randomization in this study, blood glucose levels measured 24 h after admission or immediately before discharge were lower in the aggressively treated patients compared with the conventionally treated patients. Also, mortality rate was not related to severity of hyperglycemia at hospital admission in intensively treated patients. These data suggested that the deleterious effects of hyperglycemia on outcome during AMI were mitigated in part by tight control of blood glucose concentration with administration of insulin.

The potential benefit of aggressive perioperative control of blood glucose concentrations in patients with or without diabetes has not been adequately evaluated, but the results of several recent investigations suggest that mortality may be decreased with intensive glycemic control in these patients. In a prospective trial of more than 2,000 patients with diabetes undergoing coronary artery bypass graft surgery, blood glucose concentration averaged for the first 2 postoperative days was an independent predictor of operative mortality. Mortality rate increased from 1.4% in patients with blood glucose concentrations less than 150 mg/dl to 8.6% for patients with average blood glucose levels greater than 250 mg/dl. A decrease in morbidity resulting from infection was also observed in patients with diabetes who were treated with a continuous infusion of insulin to maintain blood glucose concentration less than 200 mg/dl after cardiac surgery.[9] Aggressive insulin treatment (*i.e.*, maintenance of blood glucose concentrations between 80 and 110 mg/dl with insulin) significantly decreased in-hospital deaths from 26% to 17% in critically ill patients (13% had a history of diabetes) admitted to the intensive care unit (60% were cardiac surgical patients) compared with conventional therapy (*i.e.*, maintenance of blood glucose concentration between 180 to 200 mg/dl).[10] Few patients developed hypoglycemia requiring treatment, and none developed hemodynamic instability or neurologic complications. These provocative results suggest that aggressive control of blood glucose concentrations with insulin may provide substantial improvements in outcome.

Sulfonylurea Hypoglycemic Agents and Ischemic Preconditioning

Sulfonylurea hypoglycemic agents are also frequently used to decrease blood glucose concentration in patients with type 2 diabetes, but the impact of these drugs on cardiovascular complications is controversial. In 1970, the University Group Diabetes Program Study reported that cardiovascular mortality was greater for patients with diabetes receiving tolbutamide compared with those treated with insulin or placebo.[11] The results of this important trial were initially criticized, in part, because the physiologic basis or pharmacologic mechanism for the findings was not understood. The target of sulfonylurea drugs is now known to be the adenosine triphosphate-regulated potassium (K_{ATP}) channel in pancreatic islet cells. Closure of the K_{ATP} channel causes insulin release. K_{ATP} channels are also present in sarcolemmal and mitochondrial membranes of cardiac myocytes, and activation of these channels protects myocardium against ischemic injury. Myocardium subjected to brief episodes of ischemia before a prolonged coronary artery occlusion is resistant to infarction. This ischemic preconditioning process depends on activation of K_{ATP} channels. Sulfonylurea oral hypoglycemic drugs block this process by interfering with K_{ATP} channel opening.

Ischemic preconditioning is not only a laboratory phenomenon but also occurs clinically in humans. For example, patients who experience prodromal anginal symptoms within 24 h before subsequent AMI demonstrate more rapid recovery of left ventricular function and improved survival.[12] The warm-up phenomenon, during which exercise tolerance improves after repeated episodes of exercise in patients with chronic stable angina, may also reflect a beneficial effect of preconditioning.[13] Ischemic preconditioning can also be elicited during percutaneous coronary angioplasty or cardiac surgery. Sulfonylurea oral hypoglycemic agents (*e.g.*, glyburide) and other K_{ATP} channel antagonists abolish ischemic preconditioning in experimental animals and in human myocardium *in vitro* and *in vivo*. Early mortality after angioplasty for AMI was increased in patients with diabetes treated with sulfonylurea agents.[14] Glyburide also blocked ischemic preconditioning in patients without diabetes undergoing angioplasty.[15] Glyburide pretreatment eliminated the electrocardiographic and functional benefit of the warm-up phenomenon in patients with diabetes undergoing sequential exercise testing[13] and exacerbated dipyridamole-induced myocardial ischemia measured with echocardiography.[16]

Diabetes or acute hyperglycemia decreases the salutary actions of ischemic preconditioning in the presence or absence of sulfonylurea therapy. For example, myocardium harvested from patients with diabetes treated with sulfonylurea agents could not be preconditioned *in vitro*.[17] The presence of diabetes also eliminated the beneficial effects of prodromal angina on mortality observed in patients with AMI.[12] Evidence from animal studies indicates that acute and chronic hyperglycemia block reductions of infarct size in response to ischemic preconditioning, volatile anesthetic agents, and direct pharmacologic activation of mitochondrial K_{ATP} channels.[18,19] The severity of hyperglycemia and the degree of K_{ATP} channel activation achieved with pharmacologic agonists are interactive determinants of infarct size. Thus, a higher dose of a K_{ATP} channel agonist is required to reduce infarct size in the presence of severe compared with moderate hyperglycemia.[18,19] In summary, considerable evidence suggests that the presence of diabetes, uncontrolled hyperglycemia, or management with sulfonylurea agents impairs K_{ATP} channel activation and decreases the usefulness of or completely abolishes the beneficial effect of ischemic preconditioning. These actions may ultimately contribute to increases in mortality for patients with ischemic heart disease. In contrast, preliminary data suggest that management of diabetes with other hypoglycemic drugs that act *via* alternative mechanisms (*e.g.*, thiazolidinediones, α-glucosidase inhibitors) may protect against ischemia–reperfusion injury, in part through activation of K_{ATP} channels. However, improvement of cardiovascular outcome in patients with diabetes with these new drugs remains to be established.

Insulin and Glucose

Insulin has been shown to exert myocardial protection in experimental animals and humans. Insulin activates cell survival pathways including the phosphatidylinositol 3'-kinase–Akt-dependent pathway, decreasing infarct size and apoptotic myocyte death.[20] Interestingly, the salutary actions of insulin appear to occur only at reperfusion and may not be observed when insulin is administered before ischemia.[21] The protective effects of insulin also do not require concomitant administration of glucose.[20,21] These recent results have begun to clarify the large body of apparently contradictory evidence examining the usefulness of glucose, insulin, and potassium (GIK) infusions in patients after AMI or cardiac surgery. For example, a recent clinical trial randomized 407 patients with AMI (~18% with diabetes) to receive GIK or conventional treatment.[22] Mortality decreased with GIK only in patients who also received reperfusion therapy (relative risk 0.34 compared with control subjects) despite similar control of blood glucose concentrations between groups. In contrast, an older study performed before the advent of thrombolytic drugs demonstrated increased mortality for patients without diabetes receiving GIK compared with placebo.[23] This negative result may have been observed because myocardium was not reperfused before GIK therapy was instituted and because blood glucose concentrations were poorly controlled. GIK administered as a component of cardioplegia during cardiac surgery also failed to improve outcome in a recent randomized, blinded trial of more than 1,000 patients (~20% with diabetes).[24] However, severe hyperglycemia (defined as a blood glucose concentration $>$ 360 mg/dl) or hyperkalemia requiring management with intravenous insulin occurred in 32 and 12% of the control and experimental subjects, respectively. Thus, hyperglycemia may have mitigated any beneficial effect of insulin in these patients. These data suggest that aggressive control of blood glucose concentration with a continuous infusion of insulin may be a primary strategy to decrease cardiovascular mortality, but provision of exogenous glucose alone, particularly before or during an episode of ischemia, may actually increase the risk of myocardial injury.

Mechanisms and Risk Modification

Acute and chronic hyperglycemia appear to increase the risk of ischemic injury through several mechanisms (fig. 1). Endogenous protective signal transduction pathways are impaired, and coronary blood flow to ischemic myocardium is adversely affected during hyperglycemia. Hyperglycemia decreases coronary collateral blood flow, impairs coronary microcirculatory responses to ischemia, and causes endothelial dysfunction, in part by increasing reactive oxygen species and decreasing nitric oxide availability. Coronary vasodilator reserve is attenuated in patients with diabetes with angiographically normal coronary arteries. Flow reserve measured with positron emission tomography is inversely related to average fasting blood glucose or HbA_{1c} concentration.[25] Diabetes inhibits the development of coronary collateral vessels,[26] and this effect may be related to impairment of nitric oxide signaling during hyperglycemia. Diabetes is also associated with abnormalities of myocardial contraction and relaxation, and its presence may differentially increase mortality in the presence of ischemic compared with nonischemic cardiomyopathy.

Despite the clear experimental evidence indicating that hyperglycemia adversely alters endogenous cardiac signal transduction and impairs regulation of coronary hemodynamics, no clinical trials have been specifically designed to date to modify perioperative cardiovascular risk in patients with diabetes. Aggressive perioperative control of blood glucose concentration may prove to be beneficial for these patients based on the evidence accumulated in the management of AMI. Nevertheless, this hypothesis has yet to be rigorously tested. Several studies have demonstrated that perioperative administration of a β_1-adrenoceptor antagonist decreases mortality in patients

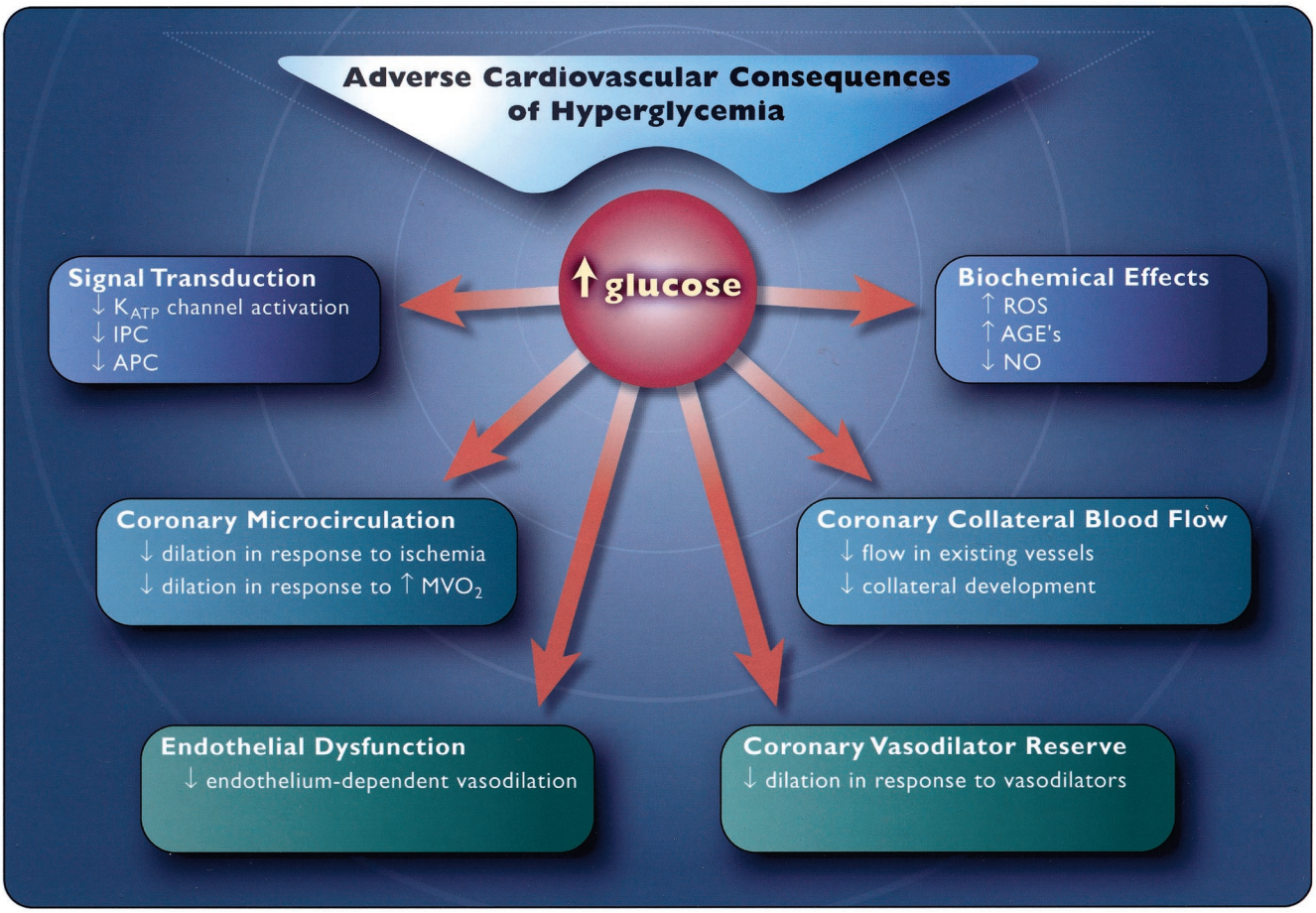

Fig. 1. The adverse cardiovascular effects of acute and chronic hyperglycemia contributing to increases in morbidity and mortality for patients with diabetes are summarized. APC and IPC = anesthetic and ischemic preconditioning, respectively; AGEs = advanced glycosylation end products; K_{ATP} = adenosine triphosphate-regulated potassium channel; NO = nitric oxide; ROS = reactive oxygen species.

with coronary artery disease undergoing noncardiac surgery,[27] but whether similar benefits are attainable for patients with diabetes is unknown. Several randomized clinical trials have evaluated whether β_1-adrenoceptor antagonists decrease mortality in patients with diabetes when administered within hours to days after AMI. In this setting, β_1-adrenoceptor blockers decrease the risk of death by approximately 35%, and further, the magnitude of this decrease in mortality is similar to or greater than that observed for patients without diabetes.[28] Unawareness of hypoglycemia (as a result of blockade of increases in sympathetic tone), insulin resistance, and dyslipidemia have not been shown to be significant clinical problems for patients with diabetes treated with β_1-selective adrenergic receptor blockers. Thus, these data clearly do not support the previously held assumption that β blockers should be routinely withheld from patients with diabetes[29] because such a decision may deny these patients an important therapeutic benefit.

Primary or secondary prevention of AMI is also enhanced in patients with diabetes who receive hydroxymethylglutaryl-CoA (HMG-CoA) reductase[28,30] or angiotensin-converting enzyme (ACE) inhibitors.[31,32] In one trial, pravastatin decreased the absolute risk of sustaining a new coronary event by 25% in patients with diabetes who had a previous myocardial infarction, and the relative risk reduction was greater for patients with diabetes compared with patients without diabetes.[30] The beneficial actions of HMG-CoA reductase inhibitors are not solely attributed to decreases in cholesterol. These drugs also independently enhance nitric oxide production, decrease oxidant stress, suppress inflammatory responses, enhance angiogenesis, and decrease myocardial ischemia–reperfusion injury.[33] Similarly, ACE inhibitors may produce favorable actions in the cardiac myocyte by decreasing oxidant stress, enhancing bioavailability of nitric oxide, potentiating ischemic preconditioning, and improving glycemic control.[32] In the Heart Outcomes Prevention Evaluation (HOPE) Study of 3,577 patients with diabetes, the risk of myocardial infarction, stroke, cardiovascular mortality, and all-cause mortality was reduced by 22, 33, 37, and 24%, respectively, in patients receiving the ACE inhibitor ramipril compared with placebo.[31] These results confirmed the findings of several

Strategies to Modify Cardiovascular Risk of Diabetes

INTERVENTION	SUPPORTING EVIDENCE
• Aggressive control of blood glucose concentration (< 150 mg/dl perioperatively; < 120 mg/dl in ICU)	↓ mortality in setting of myocardial ischemia
• Avoidance of non-selective sulfonylurea oral hypoglycemic agents (e.g., glyburide)	Blocks IPC and APC in human and animal myocardium
• Administration of β_1-selective adrenergic receptor antagonists	↓ mortality in high risk surgical patients
• Administration of HMG-CoA reductase and ACE inhibitors	↓ overall cardiovascular risk; ? perioperative benefit
• Novel antidiabetic drugs (e.g., thiazolidinediones and alpha-glucosidase inhibitors)	Possible cardioprotective effects via K_{ATP} channels

Abbreviations:
APC and IPC = anesthetic and ischemic preconditioning, respectively;
K_{ATP} = adenosine triphosphate-regulated potassium channel.

other trials demonstrating the beneficial effects of ACE inhibitors for the secondary prevention of AMI in patients with diabetes. However, whether HMG-CoA reductase or ACE inhibitors specifically modify cardiovascular risk for patients with diabetes undergoing anesthesia and surgery remains to be investigated.

Conclusions

In conclusion, although substantial evidence indicates that cardiovascular risk may be favorably modified for patients with diabetes, risk modification has not been prospectively studied in the perioperative setting. Nonetheless, several strategies to improve cardiovascular outcome for patients with diabetes are suggested (table 1). Hyperglycemia has clearly been identified as an independent predictor of cardiovascular mortality. Although the benefit of tight glycemic control perioperatively has not been specifically investigated, available evidence suggests that the primary therapeutic objective to decrease cardiac risk for patients with diabetes should be aggressive control of blood glucose concentration using a constant infusion of insulin. Based on clinical trials of cardiac surgical patients,[9,10,34] blood glucose concentration should be maintained at less than 150 mg/dl perioperatively and at less than 120 mg/dl in the intensive care unit. This aggressive approach requires frequent monitoring of blood glucose concentrations to avoid hypoglycemia. Although further study is needed, sulfonylurea hypoglycemic agents that block myocardial K_{ATP} channels responsible for ischemic and anesthetic-induced preconditioning should probably be discontinued 24–48 h before elective surgery and avoided perioperatively. Instead, insulin should be used as an alternative means to maintain normoglycemia. β_1-Adrenoceptor antagonists are first-line agents that decrease perioperative cardiovascular mortality for patients with coronary artery disease who do not have an absolute contraindication to their use. Patients with diabetes may achieve a particular benefit from β_1-adrenoceptor blockade. Finally, perioperative risk may be modified by treatment of patients with HMG-CoA reductase and ACE inhibitors, although the role of short-term or long-term administration of these drugs and perioperative risk reduction are unknown. Additional investigation is clearly required to identify other effective strategies to decrease cardiovascular morbidity and mortality for patients with diabetes undergoing anesthesia and surgery.

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