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Diabetic Cardiomyopathy and Anesthesia

Bench to Bedside

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DIABETES mellitus is a growing public health concern, affecting 170 million individuals worldwide. The incidence of diabetes is increasing, not only in the aging population but also in young adults and children, in large measure as a result of escalating rates of obesity and adoption of a sedentary lifestyle. The World Health Organization estimates that the incidence of diabetes will increase to 300 million affected individuals by 2025, representing 5.4% of the world's population.[1] Cardiovascular disease is the leading cause of death in diabetes, and the presence of diabetes increases the risk of perioperative morbidity and mortality by twofold to threefold.[1,2] Diabetes predisposes to the development of atherosclerotic heart disease and to the development of a specific cardiomyopathy that contributes to increasing cardiovascular risk.[2,3] The aim of this article is to review the characteristics of diabetic cardiomyopathy and its consequences on anesthetic management.

Epidemiology of Diabetes and Heart Failure

The association between diabetes and adverse cardiovascular outcomes, such as heart failure (HF) with or without preserved systolic ventricular function, is well known. Overall, 36–47% of all patients with clinical HF and 32–33% of those with HF and a normal ejection fraction (EF) have diabetes.[4] Although they are frequently associated, the cardiomyopathy of diabetes seems to develop independently of coronary artery disease, valvular heart disease, or hypertension. Diabetic cardiomyopathy progresses from impaired ventricular relaxation to diastolic dysfunction, with high left ventricular filling pressures, and finally to overt HF. It should be recognized that HF with low EF is accompanied by abnormalities in diastolic function; however, in the setting of diabetes, HF most frequently occurs with preservation of left ventricular systolic function, defined as an EF of greater than 50%. Evidence suggests that as many as 60–75% of asymptomatic, well-controlled, patients with type II diabetes demonstrate diastolic dysfunction, and 28% develop severe impairment of diastolic function with increased left ventricular filling pressures.[5] The risk of HF in diabetes is sex dependent, with the relative risk increased threefold in women compared with men. The overall prevalence of preserved systolic function in individuals with HF is 31–47%.[4] Despite the presumed benefits of preserved systolic function, however, there were no differences in mortality rates (22% at 1 yr after a first episode of congestive HF) reported in patients with either decreased or preserved left ventricular EF.

Multifactorial Etiology of Diabetic Cardiomyopathy

The etiology of diabetic cardiomyopathy is incompletely understood. This disorder develops after 4–5 yr of clinical diabetes and seems to be related to chronic hyperglycemia. Increases in blood glucose concentration are known to induce oxidative stress, contribute to abnormalities in excitation–contraction coupling,[1,6,7] and increase myocardial fibrosis and cardiomyocyte apoptosis.[3,8] Hyperglycemia increases production of advanced glycosylation end products and enhances angiotensin II and free fatty acid synthesis (fig. 1).[8] Both advanced glycosylation end products and angiotensin II promote reactive oxygen species production that leads to protein kinase C and A activation. Reactive oxygen species and protein kinases C and A have each been implicated in the adverse structural collagen alterations and extracellular matrix remodeling that occur in diabetes.[8] Diabetes or hyperglycemia decreases the production of vascular endothelium growth factor, and this action is suggested to play an important role in the development of diabetic cardiomyopathy. Vascular en-

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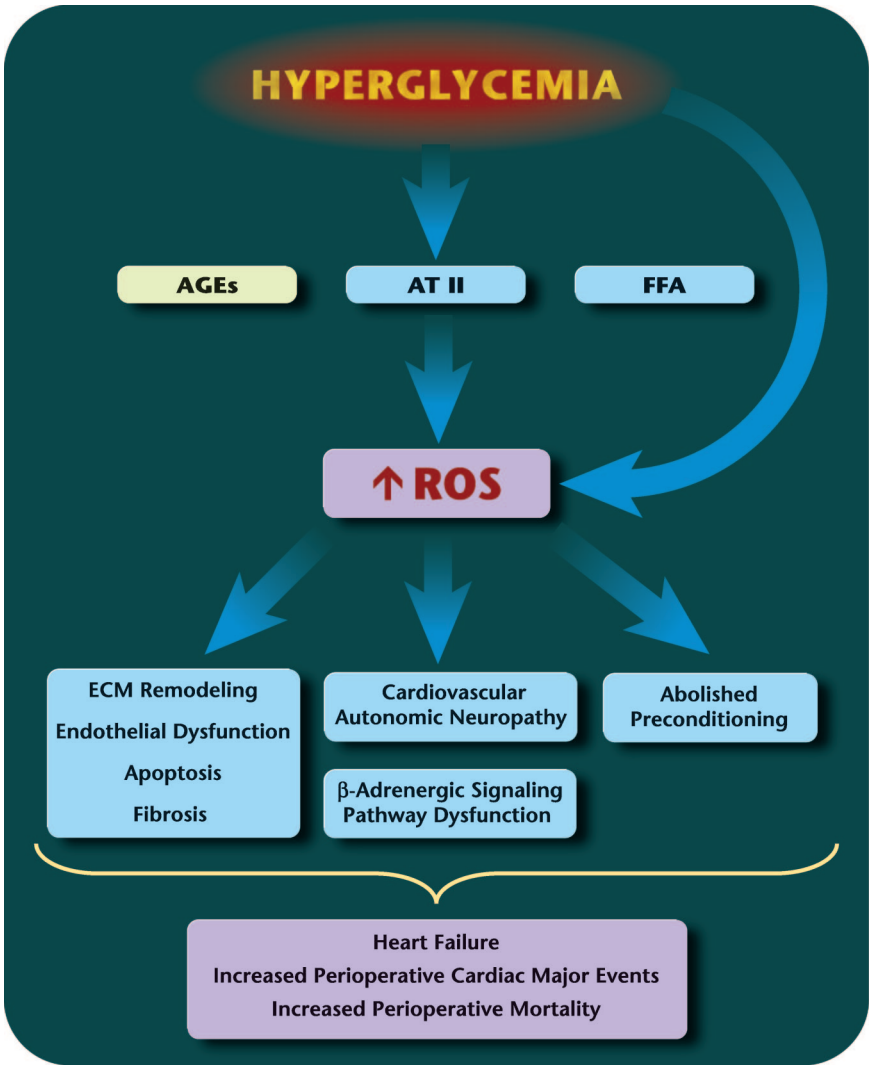

Fig. 1. Multifactorial etiology of diabetic cardiomyopathy. AGE = advanced glycosylation end product; AT II = angiotensin II; ECM = extracellular matrix; FFA = free fatty acids; ROS = reactive oxygen species.

dothelium growth factor is a critical mediator of angiogenesis and arteriogenesis, and decreases in these proangiogenic proteins are associated with microvascular endothelial cell apoptosis and endothelial dysfunction.[8] In an animal model, hyperglycemia attenuates coronary collateral development, and this action occurs concomitantly with increased production of the antiproliferative protein angiostatin.[9]

At the level of the cardiomyocyte, diabetes causes altered regulation of adenosine 5′-triphosphate hydrolysis, sarcoplasmic reticulum proteins, calcium channels, intracellular Ca^{2+} handling, Na^{+}–Ca^{2+} exchange, mitochondrial function, and contractile proteins that manifests as inotropic and lusitropic abnormalities in diabetic cardiomyopathy.[8] Contraction and relaxation velocities are decreased without significant change in developed active force.[1,6,7]

Diabetes and acute hyperglycemia abolish the cardioprotective effects of ischemic, anesthetic, and pharmacologic preconditioning,[3] but whether abnormal cardioprotective signaling specifically contributes to the development of diabetic cardiomyopathy remains unclear. Myocardial infarct size, functional recovery of myocardium, and mortality are directly related to blood glucose concentration in patients with acute myocardial infarction with or without diabetes. In contrast, aggressive control of blood glucose concentrations seems to mitigate this risk.[3] Moreover, hyperglycemia is highly associated with adverse perioperative cardiovascular events (adjusted odds ratio, 7.5), and patients with poorly controlled intraoperative blood glucose (>200 mg/dl) demonstrate an increased risk for perioperative mortality.[3,10] Similarly, hyperglycemia has been shown to increase complication rates in critically ill patients in the intensive care unit.[3,10,11] Variability of blood glucose concentrations is also an important factor that influences outcomes in critically ill patients. Increased fluctuations of blood glucose concentrations are predictive of mortality in the intensive care unit and hospital, and this occurs independently of maximum blood glucose level.[11]

Cardiovascular autonomic neuropathy significantly contributes to morbidity and mortality in diabetic patients and

may play a role in the development of diabetic cardiomyopathy.[2] Autonomic neuropathy is characterized by changes in heart rate variability. Resting tachycardia occurs early, but with disease progression and involvement of both the sympathetic and parasympathetic nervous systems, heart rate becomes fixed and unresponsive to exercise, stress, or sleep. These findings indicate complete sympathetic and parasympathetic cardiac denervation.[2] Loss of parasympathetic innervation leads to a relative predominance of sympathetic nervous system activity, and this autonomic imbalance is implicated in impairment of coronary vasodilator reserve. Defects in microcirculatory blood flow regulation contribute to the development of diastolic dysfunction and to the occurrence of silent myocardial ischemia.[2] Diabetic patients with cardiovascular autonomic neuropathy demonstrate greater hemodynamic instability during anesthesia and an increased requirement for vasoactive drugs.[2] For example, diabetic patients with autonomic neuropathy may demonstrate more profound decreases in heart rate and arterial blood pressure during induction of anesthesia and less tachycardia and hypertension after tracheal intubation and extubation compared with nondiabetic subjects.[2] Normal compensatory responses to the vasodilating effects of anesthesia may not occur in cardiovascular autonomic neuropathy.[2] These patients are also at an increased risk for intraoperative hypothermia and demonstrate impairment of hypoxic ventilatory drive.[2] Noninvasive evaluation of cardiovascular autonomic neuropathy can be accomplished with spectral analysis of heart rate variability using sequential R–R intervals.[2] However, the impact of preoperative identification of patients with autonomic nervous system neuropathy on perioperative outcomes is unknown.

Adrenergic pathways, an important mechanism for maintaining cardiac output, are also altered in diabetic myocardium. The positive inotropic effect of β-adrenoceptor stimulation induced by catecholamines is altered in diabetic heart.[1,6] At least three types of β adrenoceptors potentially modulate cardiac function. Stimulation of β_1 and β_2 adrenoceptors induces a positive inotropic effect, whereas β_3-adrenoceptor stimulation produces negative inotropic effect. β-Adrenoceptor equilibrium is disturbed in diabetic cardiomyopathy, as β_1 and β_2 adrenoceptors are down-regulated and β_3 adrenoceptors are up-regulated.[1] The β_3-adrenoceptor pathway stimulates the production of nitric oxide *via* cardiac neuronal nitric oxide synthase, and subsequent activation of phosphodiesterases decreases cyclic adenosine monophosphate concentrations. Therefore, enhanced β_3-adrenoceptor stimulation—relative to β_1- and β_2-adrenoceptor stimulation—contributes to a blunted inotropic response to sympathetic nervous system activation in diabetic myocardium.[1] Similar to changes in β-adrenoceptor regulation, the expression of α_1 adrenoceptors is decreased in diabetes. However, the positive inotropic effect of α_1-adrenoceptor stimulation seems to be preserved in diabetic myocardium.[6] Nevertheless, the role of α adrenoceptors to modulate contractile function in humans is unclear.

Clinical and Echocardiographic Predictors of Diabetic Cardiomyopathy

Specific criteria for the diagnosis of diabetic cardiomyopathy have not been developed, in part because HF in diabetes is also frequently associated with coronary artery disease, valvular heart disease, or hypertension and because the diagnosis of diastolic dysfunction with echocardiography lacks specific criteria. Clinical reports of diabetic cardiomyopathy are relatively heterogeneous, and few large clinical trials have been conducted in this population. The presence of clinical symptoms alone is insufficient to identify all individuals with diabetic cardiomyopathy. In fact, fewer than 50% of patients with moderate to severe systolic or diastolic dysfunction have symptoms of congestive HF. In the initial stages, patients with diabetic cardiomyopathy may be asymptomatic or may have only mild exercise intolerance that eventually progresses to HF.[4]

An abnormal glycosylated hemoglobin A_{1c} level reflects chronically poor glycemic control that is associated with an increased rate of development of cardiomyopathy and is an independent predictor of increased rates of hospitalization for congestive HF.[3] Retinopathy coexists in 50% of patients with diabetic cardiomyopathy.[12] Increases in urinary albumin excretion, as observed in diabetic nephropathy, are correlated with the development of coronary endothelial dysfunction[13] and may indicate the presence of altered ventricular mechanics. Although chronic hyperglycemia, renal abnormalities, autonomic nervous system dysfunction, and clinical symptoms may alert the physician to the presence of diabetic cardiomyopathy, echocardiography remains the accepted standard for the assessment of alterations in systolic and diastolic function that occur in diabetes. Nevertheless, there is no consensus on the specific criteria to be used to confirm the diagnosis of diabetic cardiomyopathy. However, it is suggested that the combination of two or more Doppler criteria may be sufficient,[14] and the tissue Doppler imaging of mitral annular motion may be particularly helpful to make the diagnosis.[5]

Impaired ventricular relaxation is the earliest manifestation of diastolic dysfunction and is characterized by decreases in the peak early filling velocity of mitral inflow (E). The rate of decrease of velocity following the E velocity (deceleration time) is also prolonged. As diastolic dysfunction progresses and left atrial pressures increase, the pressure gradient between the left atrium and ventricle rises and the E velocity returns toward normal, producing a "pseudo-normal" mitral filling pat-

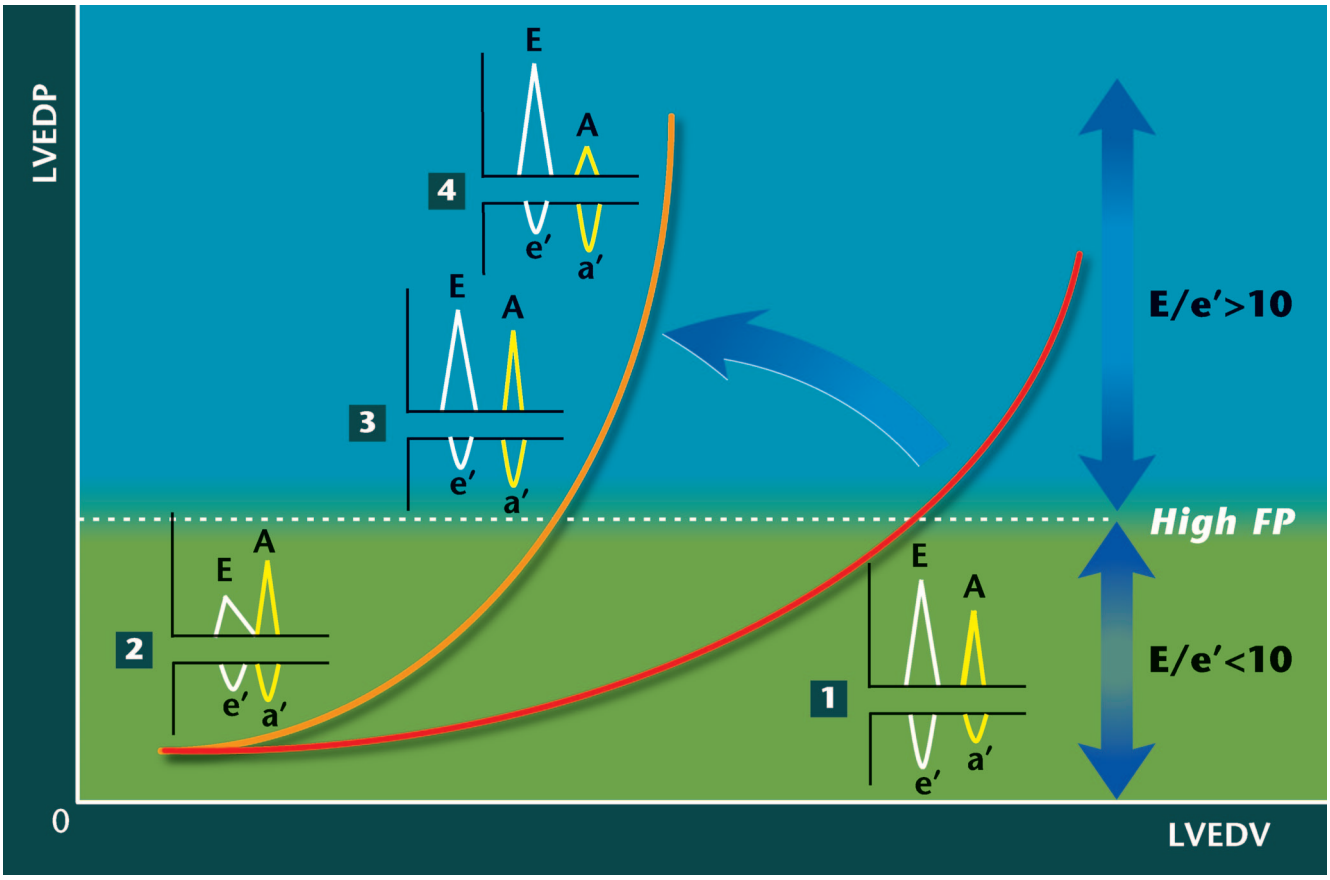

Fig. 2. Doppler criteria for classification of diastolic dysfunction correlate with pressure–volume curves. The correlation between Doppler mitral inflow (A = velocity at atrial contraction; E = peak early filling velocity) and Doppler tissue imaging of mitral annular motion (a′ = velocity of mitral annulus motion with atrial systole; e′ = velocity of mitral annulus early diastolic motion) is shown in a healthy patient compared with the leftward shift of diastolic dysfunction observed in a diabetic patient: (1) normal Doppler mitral inflow and Doppler tissue imaging of mitral annular motion, (2) impaired relaxation, (3) pseudo-normal filling pattern, (4) restrictive filling pattern. High FP = high filling pressure; LVEDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume. This figure is adapted from several articles.[14–16]

tern. During later stages of the disease, as symptoms of HF appear, left ventricular chamber compliance decreases further and causes a "restrictive" filling pattern to emerge. This pattern is manifested by a high E velocity and lower velocity during atrial (A) contraction. A limitation in interpreting transmitral flow patterns is that alterations in flow velocities are dependent on the loading conditions of the heart. Among other criteria, tissue Doppler imaging of mitral annular motion to determine the ratio of mitral annulus velocity during early diastole (e′) to the velocity of mitral annulus motion during atrial systole (a′) can provide a relatively preload-independent assessment of diastolic function.[14] The ratio of E/e′ has been proposed as a sensitive index of left ventricular filling pressures. E/e′ greater than 10 in spontaneously ventilated and greater than 7.5 in mechanically ventilated patients is both sensitive and specific for the presence of increased filling pressures, and changes in left ventricular filling pressures after volume expansion are accurately assessed by repeated E/e′ determinations.[15] Acute changes in loading conditions may have a profound effect on overall ventricular performance in patients with diabetic cardiomyopathy.[15,16] Even relatively small increases in afterload may provoke increases in left ventricular filling pressures and lead to congestive HF despite preservation of systolic function (fig. 2).[16] Precipitation of myocardial ischemia during the perioperative period may also exacerbate diastolic dysfunction.[16]

In summary, patients with diabetes should be carefully evaluated for the presence of coexisting cardiomyopathy. If abnormalities in diastolic ventricular function are detected, consideration should be given to intraoperative monitoring of intravascular volume status, particularly in those patients who are also at risk for large volume shifts that may occur during major surgery or during conditions that predispose to rapid decompensation, such as sepsis, atrial fibrillation, and pulmonary hypertension.

Treatment of Diabetic Cardiomyopathy

Given the complexity of HF and the paucity of studies in patients with HF and preserved systolic function,

more specifically diabetic cardiomyopathy, guidelines for the treatment of diabetic cardiomyopathy are still a matter of some debate. Nevertheless, the available evidence suggests that treatment of diabetic cardiomyopathy should focus on control of risk factors. The appropriate treatment of hypertension, dyslipidemia, obesity, and insulin resistance reduces the risk of developing HF. Aggressive control of blood glucose concentrations may reverse early abnormalities in diastolic function; however, as diabetes progresses, increases in interstitial collagen deposition may not be attenuated by improvements in metabolic control. Nevertheless, control of blood glucose concentrations with a continuous infusion of insulin to maintain blood glucose less than 150 mg/dl during the perioperative period is recommended.[3,10,17] The impact of this management strategy on outcome in patients with diabetic cardiomyopathy has not been specifically investigated, however.

Guidelines for the management of HF have been published recently.[18] Treatment recommendations for patients with HF and impaired systolic function are clearly supported by the results of randomized clinical trials, but there is a lack of data on which to base treatment recommendations for patients with HF and preserved EF, more specifically for diabetic cardiomyopathy. In experimental studies, the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers attenuates global cardiac dysfunction, hypertrophy, extracellular matrix remodelling, and apoptosis in diabetic myocardium.[19] The results of a recent study in asymptomatic diabetic patients demonstrated that inhibition of the renin–angiotensin system reversed early diastolic dysfunction. The combined treatment with the angiotensin-converting enzyme inhibitor ramipril and the angiotensin receptor blocker telmisartan produced additive effects to reverse diastolic dysfunction in diabetic cardiomyopathy.[20] In the Heart Outcomes Prevention Evaluation (HOPE) trial, ramipril decreased the incidence of HF in a subgroup of diabetic patients independently of actions to alter cardiac ischemic events.[19] In contrast, the Candesartan in Heart Failure–Assessment of Reduction in Mortality and Morbidity Study (CHARM-Preserved) did not demonstrate a significant improvement in all-cause or cardiovascular mortality in patients with HF and normal EF treated with candesartan, but the incidence of hospitalization was decreased in accord with the Reduction of Endpoints in Non–Insulin-dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) and the Losartan Intervention for Endpoint (LIFE) trials evaluating the efficacy of losartan.[19] The benefits of continuing angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in the perioperative period in patients with diabetic cardiomyopathy and preserved ventricular function are unknown. The use of these drugs may exacerbate hypotension during induction or maintenance of general anesthesia and during abrupt changes in intravascular volume such as during blood loss. Alterations in cardiovascular autonomic nervous system regulation and blunted responses to β-adrenergic stimulation predispose these patients to hemodynamic instability and impede rapid correction of hypotension with sympathomimetic drugs. In the absence of compelling data to suggest otherwise, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should probably be held preoperatively in patients with compensated diabetic cardiomyopathy to avoid refractory intraoperative hypotension.

Updated guidelines for the perioperative use of β-blockers have been published recently.[17] However, the benefits of β-blocker therapy specifically in patients with diabetic cardiomyopathy and normal EF are not entirely clear. The Study of Effect of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) suggests that nebivolol may be beneficial in elderly patients with HF and preserved systolic function.[21] β-Blockers may be advantageous in this setting by decreasing heart rate and prolonging left ventricular filling time. Control of heart rate is particularly important in patients with diastolic dysfunction, and sinus rhythm should be maintained if at all possible. Another potential benefit of β-blockers in HF is decreased neurohormonal stimulation. Abrupt changes in afterload can exacerbate left ventricular dysfunction.

Therefore, the prevention and treatment of perioperative hypertension is an important goal in the management of diabetic cardiomyopathy, although there is insufficient evidence to recommend a specific class of antihypertensive agent. Calcium channel blockers could have a theoretical advantage in that they produce positive lusitropic effects. In experimental studies, calcium channel blockers improved global abnormalities observed in diabetic cardiomyopathy, and this action was associated with increased insulin sensitivity.[22] Nitrates may also be useful; however, care must be exercised because patients with diastolic dysfunction may be quite sensitive to decreases in preload.

A growing body of evidence indicates that statin drugs decrease mortality in patients with diabetes. Statins produce a variety of favorable effects to enhance endothelial function, to promote coronary angiogenesis, and to reduce ventricular remodelling that are independent of cholesterol lowering.[3] Statin therapy decreased the risk of major cardiovascular events, death, and hospitalization in a large subgroup of diabetic patients with HF and preserved EF.[23] Recent evidence also demonstrates that statins improved outcomes in patients undergoing vascular surgery. Therefore, it is recommended that patients taking statin drugs should continue these preoperatively, and statins that have been withheld should be reinstituted as soon as possible in the postoperative period.

Anesthetic Considerations in Diabetic Cardiomyopathy

The effects of anesthetic agents on diabetic myocardium have been incompletely elucidated, and investigations conducted in humans are limited. A majority of the evidence cited has been derived from animal studies conducted in different species and using various models of chemically induced and genetic diabetes.[24] These considerations taken into account; halogenated anesthetic agents produced greater negative inotropic effects in diabetic compared with normal myocardium.[7] Myofilament Ca^{2+} sensitivity was not altered by diabetes at baseline; however, volatile anesthetics produced more profound decreases in myofilament calcium sensitivity in diabetic compared with normal myocardium. These results suggested that diabetes exacerbates anesthetic-induced alterations in troponin–tropomyosin complex activity.[7] The inotropic response to β-adrenoceptor stimulation is markedly decreased in diabetic ventricular papillary muscle, whereas that to α-adrenoceptor stimulation is preserved. Isoflurane, halothane, and sevoflurane have been shown to potentiate the positive inotropic effect of α_1-adrenoceptor stimulation in normal myocardium, but this action was abolished in diabetes. In contrast to these findings, the potentiation of β-adrenergic stimulation by volatile anesthetics observed in healthy myocardium is preserved in diabetes during isoflurane and sevoflurane, but not halothane. Abnormalities in intracellular signaling dependent on G proteins and alterations in sarcoplasmic reticulum may be responsible for some of these observations.[6]

Propofol has been shown to impair diastolic left ventricular filling in experimental models of cardiomyopathy and to produce negative lusitropic effects in diabetic cardiomyocytes.[25] There are few reports describing the effects of propofol on ventricular performance in patients with diastolic dysfunction or diabetic cardiomyopathy. Propofol or midazolam did not have an adverse effect on left ventricular diastolic performance in patients with diastolic dysfunction and preserved EF who were sedated with these drugs before noncardiac surgery.[26] In another study, neither propofol nor sevoflurane substantially altered abnormal diastolic filling parameters in patients with diastolic dysfunction.[27] The effects of barbiturates on diastolic function are not entirely clear, but these drugs cause differential effects on intracellular calcium handling. Thiopental seems to induce greater negative inotropic effects than pentobarbital in diabetic myocardium.[28] Evidence also suggests that induction or maintenance of anesthesia with a combination of etomidate and opioids may reduce hemodynamic instability in diabetic patients with coexisting cardiovascular autonomic neuropathy.[29] However, no single anesthetic drug has clearly been shown to be superior for the induction of anesthesia in patients with diabetic cardiomyopathy. Careful attention should be paid to the hemodynamic consequences of anesthetic induction, institution of positive-pressure ventilation with concomitant changes in preload, and impaired responses to sympathetic nervous system activation that occur in these challenging patients.

The treatment of perioperative hemodynamic instability in patients with diabetic cardiomyopathy may necessitate administration of intravenous fluids, catecholamines, or pressors. The value of intraoperative transesophageal echocardiography to guide therapy in these patients has not been specifically investigated but might be helpful in assessing left ventricular filling, preload responsiveness, and overall performance. Overly aggressive fluid resuscitation should be avoided. The judicious use of diuretics may be helpful in case pulmonary congestion develops perioperatively. Postoperatively, continuous positive-airway pressure by facemask may be useful to improve oxygenation resulting from increases in left ventricular filling pressures.[30] In a large retrospective study, anemia less than 13 g/dl in men or less than 12 g/dl in women was an independent predictor of mortality in HF with preserved systolic function and should be avoided.[31] Intravenous vasodilators such as nitroglycerin or nesiritide, a recombinant brain natriuretic peptide, are efficacious in decreasing ventricular filling pressures, although excessive decreases in preload can compromise cardiac output and may cause hypotension. In some cases, the use of positive inotropic drugs, such as dobutamine, milrinone, or levosimendan, may be required. Levosimendan has been approved for the treatment of HF in several European countries but is not yet approved in the United States. This drug is a myofilament calcium sensitizer that promotes Ca^{2+} binding to troponin C during systole, but allows calcium to dissociate during diastole. Therefore, levosimendan does not cause adverse effects on ventricular relaxation, and in contrast to phosphodiesterase inhibitors and β-adrenoceptor agonists, it does not increase myocardial oxygen consumption.[32] Levosimendan has been shown to produce antiischemic effects by directly preconditioning myocardium against infarction *in vivo* through the activation of adenosine 5′-triphosphate–sensitive potassium channels.[32] In the Levosimendan Infusion *versus* Dobutamine in Severe Low-Output Heart Failure (LIDO) study, levosimendan produced favorable hemodynamic effects and decreased mortality in patients with acute HF and low EF as compared with dobutamine.[32] Levosimendan, in combination with dobutamine, improved cardiac performance, reduced the requirement for additional vasopressors, and hastened extubation in cardiac surgical patients with poor left ventricular function as compared with patients receiving milrinone and dobutamine.[32,33] These findings suggested that levosimendan might be beneficial in the setting of diabetic cardiomyopathy; however, this hypothesis remains to be tested in randomized clinical trials.

In conclusion, diabetic cardiomyopathy is a significant cause of overall cardiovascular morbidity and mortality, and this disease substantially contributes to perioperative risk. Diabetic cardiomyopathy is characterized by abnormal diastolic ventricular performance with preserved systolic function that progresses to overt HF. Risk factor modification, such as adequate control of blood glucose concentrations, treatment of hypertension and dyslipidemia, and weight control, is the focus of medical treatment. Diabetic patients with HF are at particular risk for intraoperative hemodynamic instability, and these patients require careful management of intravascular fluid volume and vasoactive drug use to avoid complications of anesthesia and surgery.

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