Early detection of left ventricular dysfunction in diabetes

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Abstract
Patients with type 2 diabetes are at risk of developing left ventricular (LV) dysfunction and heart failure. Symptoms associated with LV dysfunction in these patients, especially in the early stages, may be minimal or attributed to other noncardiac factors. LV dysfunction in diabetes is multifactorial, but there is evidence of the specific entity of diabetic cardiomyopathy. Although a direct relationship between glycemic control and LV function has not been firmly established, there is increasing evidence to suggest that poor glycemic control is associated with LV dysfunction and that improving glycemic control improves LV function. A high index of suspicion is necessary in managing these patients. Echocardiography is a noninvasive, widely available imaging tool that provides comprehensive assessment of cardiac structure and function. Exercise echocardiography allows detection of coronary disease and assessment of LV diastolic reserve. A multifaceted approach targeting all vascular risk factors in the management of LV dysfunction in these patients is essential. A specific treatment for diabetic cardiomyopathy is still lacking, but optimizing glycemic control and aldosterone antagonism may be beneficial, and trials are currently underway. Early detection of LV dysfunction allows identification of at-risk patients and timely intervention, which could ultimately improve patient outcome in this condition, which is associated with significant morbidity and mortality. Heart Metab. 2017;73:18-23

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Introduction
The prevalence of obesity is skyrocketing in both developing and developed countries. This is accompanied by a corresponding increase in the prevalence of type 2 diabetes. Patients with type 2 diabetes have a high prevalence of heart failure, both undiagnosed and diagnosed, and left ventricular (LV) dysfunction. In these patients, although LV dysfunction and heart failure may be attributed to common comorbidities, such as hypertension, obesity, and coronary disease, there is evidence for the distinct clinical entity of diabetic cardiomyopathy. The spectrum of the disease may range from LV diastolic dysfunction in the early stage to systolic dysfunction and overt LV dysfunction and advanced heart failure. The diagnosis of heart failure and LV dysfunction in these patients is often delayed. LV diastolic and systolic dysfunction may be subclinical, and early symptoms of exercise intolerance may be subtle and attributed to lack of physical fitness. Nevertheless, early detection of LV dysfunction in these high-risk
Fig. 1 Evaluation of a 66-year-old man with type 2 diabetes who complained of dyspnea on exertion found left ventricular (LV) hypertrophy, but normal LV ejection fraction. LV global longitudinal strain (GLS) was impaired at -13.2% (Panel A). The patient had grade 1 diastolic dysfunction with a mitral E/A ratio < 0.5 at rest (Panel B) and a septal e’ velocity of 6 cm/s (Panel C).

Abbreviations: 4-ch, 4-chamber view; ANT_SEPT, anteroseptal; APLAX, apical long axis view; AVC_AUTO, aortic valve closure detected automatically; GLPS_A4C, global longitudinal peak strain, apical 4-chamber view; GLPS_LAX, global longitudinal peak strain, apical long axis view; HR, heart rate; HR_ApLAX, heart rate during acquisition of the apical long axis view; INF, inferior; LAT, lateral; POST, posterior; SEPT, septal.
patients is important; timely, aggressive, multifaceted management is the key to ameliorating the otherwise devastating consequences of diabetic heart disease.

**Echocardiography in detection of left ventricular dysfunction**

Echocardiography is a versatile, noninvasive, and widely available imaging tool for the assessment of LV structure and function and has been most commonly used in the detection of LV dysfunction. LV ejection fraction is an insensitive marker for early detection of LV dysfunction. Mitral E- and A-wave, and tissue Doppler e’-wave velocities are measures of LV diastolic function. An elevated mitral E/e’ velocity ratio is a reliable marker of elevated LV filling pressures, commonly seen in patients with LV dysfunction and heart failure. Echocardiographic strain deformation imaging allows a sensitive, angle-independent, and site-specific assessment of LV systolic function, and assessment of LV global longitudinal strain is superior to ejection fraction in the detection of early diabetic heart disease. Moreover, LV global longitudinal strain has incremental prognostic value over ejection fraction in a wide range of cardiovascular diseases. Exercise echocardiography is a well-accepted, accurate, and noninvasive test for inducible ischemia, allowing detection of coronary artery disease. It also allows assessment of LV filling pressures at rest and after exercise. As an example, Figure 1 and Figure 2 depict an exercise echocardiographic evaluation of a type 2 diabetes patient with dyspnea on exertion.

**Left ventricular dysfunction in diabetes**

The Strong Heart Study demonstrated that heart failure was very prevalent in patients with diabetes despite normal ejection fraction. Fang et al found subclinical LV systolic and diastolic dysfunction in a large proportion of patients with type 2 diabetes without ischemia or hypertrophy. Compared with age-matched controls, asymptomatic patients with type 2 diabetes had impaired LV longitudinal systolic, as well as diastolic, function. In a recent study of 105 patients with poorly controlled type 2 diabetes, we found that these patients have impaired LV diastolic and systolic function and elevated LV filling pressures despite normal LV ejection fraction and LV mass.

The underlying pathophysiological mechanisms of diabetic cardiomyopathy are multifactorial and may include microvascular disease, endothelial dysfunction, autonomic dysfunction, hyperglycemia, hyperinsulinemia, insulin resistance and other metabolic disturbances, myocardial interstitial fibrosis, and myocardial steatosis. Obesity, common in patients with diabetes, may also lead to LV dysfunction. We have demonstrated impaired coronary microvascular function in patients with diabetes in the absence of epicardial coronary stenosis. As cardiac extracellular matrix plays an active role in modulating cardiac function, myocardial fibrosis has been suggested as one of the important mechanisms of LV dysfunction in diabetes.

Although hyperglycemia is the primary metabolic disturbance in diabetes, the relationship between glycemic control and cardiac function is unclear. Some studies have shown poor glycemic control to be associated with abnormal LV relaxation, elevated filling pressures, and impaired systolic contraction. Patients who had poorly controlled diabetes in the Strong Heart Study were found to have abnormal LV relaxation. In 120 patients with type 2 diabetes, peak systolic strain was independently associated with glycated hemoglobin (HbA1c) levels, whereas septal e’ velocities were related more to age and hypertension and not to glycemic control. However, a number of other studies have demonstrated no association between glycemic control and ventricular function. The relationship between prevailing glycemic control and LV function may be more complicated and affected by multiple factors, including duration of diabetes, presence and control of other vascular risk factors, medications, body weight, and others that are known to have an impact on LV function.

**Impact of improving glycemic control on left ventricular function**

A few studies have examined the effect that improved glycemic control has on LV function. von Bibra et al showed that intensive glycemic control with insulin improved LV diastolic, but not systolic, function. However, others did not demonstrate improvements, despite better glycemic control. Most of these studies examined improved glycemic control over short periods of time, which may not have been sufficient to effect any detectable changes in LV function. We
Fig. 2 Evaluation of a 66-year-old man with type 2 diabetes who complained of dyspnea on exertion (see also Fig. 1) found a dilated left atrium (Panel A), with a maximum left atrial volume of 51 mL/m². On exercise echocardiography, no inducible ischemia was found. Immediately after exercise, the mitral E/A ratio reversed and became >1 (Panel B). The septal e’ velocity decreased to 5 cm/s, leading to a significantly higher E/e’ ratio; this indicates elevated LV filling pressures and limited LV diastolic reserve, explaining the exertional dyspnea.

Abbreviations: A2C, apical 2-chamber; A-L, area-length; LAEDV, left atrial end diastolic volume; LAAd, left atrial area; LALd, left atrial longitudinal dimension.
recruited 105 patients with suboptimally controlled type 2 diabetes; during a 12-month follow-up period, we optimized treatment aimed to improve their metabolic control. Improved glycemic control led to improvement in LV diastolic and systolic function, and both the magnitude of the improvement and the final glycemic control affected LV function at follow-up. Worsened glycemic control actually led to further deterioration of LV systolic function. Patients with diabetes are often overweight and obesity itself is also linked to LV dysfunction. In support of this concept, weight loss has been shown to lead to improved LV function. The impact of improving glycemic control on LV function may be mediated through the beneficial effects of weight loss on LV function. However, in another study, we demonstrated that both improved glycemic control and weight loss had incremental additive benefits on LV function.

**Effort intolerance in diabetes**

Early stages of LV dysfunction in diabetes may be associated with little or no symptoms. Effort intolerance is usually the first manifestation. Unfortunately, effort intolerance may be attributed to body weight or lack of physical fitness. Coronary artery disease may be another underlying cause. Evaluation of LV function at rest may not be adequate in patients with diabetes. Therefore, examining the response of the left ventricle to exercise may yield further diagnostic information. Diastolic reserve is the ability of LV filling pressures to remain normal with exercise and tachycardia. Impaired diastolic reserve is seen in the early stages of LV diastolic dysfunction in diabetes. Patients with diabetes have an impaired diastolic reserve, and elevated LV filling pressures with exercise manifest an exertional dyspnea even without inducible myocardial ischemia. Exercise echocardiography, by allowing assessment of LV diastolic reserve, is a useful tool to unmask diastolic and systolic dysfunction to evaluate patients with exertional dyspnea. Improving glycemic control is also associated with an improvement in exercise tolerance in these patients.

**Treatment of left ventricular dysfunction in diabetes**

Treatment of LV dysfunction in diabetes requires a multifaceted approach. Early detection of LV dysfunction in these patients allows identification of at-risk patients and early intervention. As these patients often have multiple comorbidities, a comprehensive approach to the management of all vascular risk factors is essential. Aggressive blood pressure lowering, treating hypercholesterolemia to target, and optimization of body weight are all important parts of management. Optimization of glycemic control may also lead to improvement in LV systolic and diastolic function and exercise tolerance.

A specific therapeutic agent for diabetic cardiomyopathy is still lacking. Aldosterone antagonism, which reduces cardiac extracellular matrix turnover, improves symptoms and outcomes in advanced systolic heart failure and after acute myocardial infarction. Aldosterone antagonism has also been shown to improve LV function in dilated and hypertensive cardiomyopathy and metabolic syndrome with regression in markers of myocardial fibrosis. Trials evaluating the impact of specific aldosterone antagonism on LV systolic and diastolic function in patients with type 2 diabetes are ongoing.

**Conclusions**

LV dysfunction and heart failure are prevalent in patients with diabetes. Hypertension, coronary artery disease, and obesity are common comorbidities and may also cause LV dysfunction. Diabetic cardiomyopathy is considered a distinct entity. LV dysfunction in these patients may be associated with little or no symptoms, with exertional dyspnea a common, though nonspecific, symptom. LV function is linked to glycemic control, and early detection of LV dysfunction is important. Echocardiography, combined with exercise testing, allows comprehensive assessment of LV morphology, systolic and diastolic function at rest and after stress, and exclusion of coronary artery disease. A multifaceted approach targeting all vascular risk factors in the management of LV dysfunction in these patients is essential. A specific treatment for diabetic cardiomyopathy is still lacking, but aldosterone antagonists may be beneficial. Timely intervention may improve patient outcome for such a condition, which is associated with significant morbidity and mortality.

**REFERENCES**


