Diabetes is a risk factor for the development of symptomatic heart failure, particularly in elderly patients with type 2 diabetes (1,2). Heart failure that occurs as the result of impaired myocardial relaxation and compliance has been termed diastolic heart failure (3). Diastolic heart failure develops despite normal left ventricular systolic contractile function and leads to significant morbidity, medical costs, and mortality. Typically, patients with type 2 diabetes who are symptomatic from diastolic heart failure have superimposed hypertension, coronary artery disease, left ventricular hypertrophy, atrial fibrillation, or renal insufficiency (4). Alterations in diastolic function are also frequently observed in asymptomatic individuals with type 1 diabetes (5,6), although their contribution to the development of clinical heart failure later in life remains uncertain.

In this issue of Diabetes Care, Suys et al. (7) provide new evidence that children and adolescents with type 1 diabetes have altered cardiac structure and function compared with age-matched individuals without diabetes. Subjects included in the study had no cardiac signs or symptoms or diabetes complications and were not taking medications known to modify cardiac structure or function (presumably including ACE inhibitors). The most striking findings were in the girls with type 1 diabetes, who had greater left ventricular size and reduced diastolic function compared with control subjects. The fact that they were otherwise healthy young individuals without hypertension makes these observations all the more noteworthy. The findings in boys with type 1 diabetes were somewhat less dramatic and consistent.

A number of conventional echocardiographic parameters were evaluated. Left ventricular wall thickness was 10% greater, and there was a trend toward increased left ventricular mass and left ventricular mass index (corrected for BMI) in the girls (but not boys) with type 1 diabetes. The study did not address the important issue of how many of these girls would be considered as having frank left ventricular hypertrophy. It is interesting that the Framingham Study also reported that women (more than men) with diabetes (mostly type 2) had increases in left ventricular mass (8). Left ventricular cavity dimensions and fractional systolic shortening were similar in subjects with and without type 1 diabetes, indicating the absence of more advanced cardiomyopathy. However, the study did not assess more sensitive indexes of systolic dysfunction, such as left ventricular strain or the increment in ejection fraction during exercise, which are abnormal in patients with type 2 diabetes (9,10).

Cardiologists have studied and reported numerous parameters of diastolic function in the literature, resulting in confusion among diabetes care providers. Diastolic parameters are also highly influenced by changes in volume status, blood pressure, and heart rate (11), further complicating their interpretation in patients with diabetes. In addition, more exacting analysis of left ventricular diastolic function requires direct left ventricular pressure measurements (12), which are not appropriate for clinical studies in healthy individuals. Noninvasive echocardiography with Doppler measurements of transmural blood flow, together with more recently developed myocardial tissue Doppler measurements, have become the preferred means to evaluate diastolic function noninvasively (13,14). These latter measurements have been helpful in the study of patients with type 2 diabetes (15).

Suys et al. utilized conventional echocardiography/Doppler as well as tissue Doppler techniques and found abnormalities in diastolic function in both girls and boys with type 1 diabetes. Both had prolonged isovolumic relaxation times, which reflect the rate of active left ventricular diastolic relaxation between aortic valve closure and the opening of the mitral valve. Relaxation of the myocardium is an energy-dependent process requiring calcium sequestration from the cytosol into the sarcoplasmic reticulum, and it is altered in diabetes (2). Interestingly, recent magnetic resonance studies have correlated changes in myocardial high-energy phosphates and parameters of diastolic function in patients with type 2 diabetes (16). Experimental studies have also shown abnormalities in the calcium pump activity in diabetic animals (2).

Girls, but not boys, with type 1 diabetes in this study had additional evidence for reduced diastolic function with a low transmural E/A ratio, a commonly reported index that represents the ratio of early diastolic velocity (E) to late diastolic velocity associated with left atrial contraction (A). E is a function of ongoing myocardial relaxation after mitral valve opening, left ventricular chamber compliance, and the left atrial pressure (13,14). In the presence of mild diastolic dysfunction, early filling is often blunted, leading to an exaggerated atrial contribution to left ventricular filling and a low E/A ratio (13,14). In more advanced heart failure, this pattern is often lost due to high left atrial and left ventricular pressure and the E/A ratio pseudo-normalizes or increases, complicating interpretation (13,14).

Most novel in the study by Suys et al. were the tissue Doppler findings that myocardial relaxation velocity during early diastolic filling (E’, sometimes termed Em) was reduced in girls, but not boys, with type 1 diabetes. Tissue Doppler tracks the left ventricular myocardium and provides information on diastolic function, making it less dependent on preload or volume status than traditional echo/Doppler techniques (13,14). The mean E’ velocities were lower in the diabetic girls, and a similar trend was observed for the more commonly measured maximal E’ velocities. Somewhat surprisingly, there were no clear relationships between parameters of diastolic function and diabetes duration, BMI, or HbA1c. Prior studies have shown a correlation between HbA1c and diastolic function in older individuals with type 1 diabetes, suggesting that glycemic control may be an important determinant of diastolic function (17).

These results further our understanding of cardiac function in girls and boys with type 1 diabetes, but also introduce a number of questions for further investigation. In particular, why do girls have more consistently reduced parameters of dia-
stolic function than boys? If altered diastolic function was related simply to hormonal status, one might have expected to see greater differences in the older adolescent girls. Are diastolic abnormalities related to glycemic control? It is noteworthy that the girls in this study had higher HbA$_1c$ values than boys (8.4 vs. 7.8%), although there was no apparent correlation between the HbA$_1c$ measured at the time of the study and diastolic parameters. Further study is needed to determine whether intensification of glycemic control improves diastolic parameters. Hyperglycemia influences heart metabolism, the production of advanced glycosylation end products, oxidative stress, and protein kinase C activation (18), and these factors could potentially contribute to the development of myocardial diastolic dysfunction.

Do more subtle alterations in arterial stiffness in patients with type 1 diabetes influence myocardial structure and function? While this study excluded subjects with hypertension, more subtle hemodynamic alterations could play a role in myocardial remodeling and diastolic function. This study also excluded individuals who had complications of their diabetes. While this approach was helpful in teasing out the impact of “diabetes alone” on cardiac function, diastolic abnormalities would be expected to be more prominent in patients with neuropathy, retinopathy, microalbuminuria, or nephropathy (10, 19, 20).

Perhaps the most important clinical question raised by these results is whether the alterations in cardiac function observed have long-term clinical impact in subjects with type 1 diabetes. Unfortunately, a cross-sectional study of this nature does not address this issue directly, and prospective follow-up of these patients is critical in this regard. Until this information is available, it is difficult to advocate that all asymptomatic individuals with type 1 diabetes should have routine echocardiography. In addition, it should be noted that although the left ventricular wall thickness and diastolic parameters differed in subjects with and without type 1 diabetes, it is likely that the vast majority of studies in those with type 1 diabetes would not show left ventricular hypertrophy or overt diastolic dysfunction. In addition, tissue Doppler measurements are technically exacting and age-related normal values for children and adolescents have not been established in most laboratories. Thus, the routine search for asymptomatic alterations in cardiac function in children and adolescents with type 1 diabetes would be premature at the current time.

What are the therapeutic implications of this study? One obvious point is that aggressive blood pressure control should be adhered to in all patients with type 1 diabetes, since hypertension is known to have adverse impact on diastolic function and to contribute to the development of heart failure in diabetes (4, 6). ACE inhibitors and angiotensin receptor blockers prevent or reverse cardiac hypertrophy and are preferred for patients with hypertension or microalbuminuria. Clinical trials are underway to determine whether these agents improve outcomes in older patients with diastolic heart failure. With further information on the mechanisms and outcomes associated with diastolic dysfunction, diabetes caregivers will better understand how best to evaluate and treat patients with type 1 diabetes. Until then, optimization of glycemic control continues to be the primary mandate for treatment of children and adolescents with type 1 diabetes.

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