Alterations in Left Ventricular Structure and Function in Type-1 Diabetics: A Focus on Left Atrial Contribution to Function

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This study was designed to determine the effects of type 1 diabetes mellitus (T1DM) on left ventricular (LV) and particularly left atrial (LA) structure and function. We evaluated 88 non-obese subjects: 44 with T1DM, 44 age- and gender-matched normal controls (age 39 ± 11 years). LV and LA structure and function were quantified using two-dimensional echocardiography, pulse-wave Doppler, and tissue Doppler imaging, including early and late diastolic myocardial velocities (Em global and Am global, respectively). The T1DM subjects averaged higher heart rate, relative wall thickness, and ejection fraction, and lower indexed end-systolic volume than normal controls (P < .001, P < .05, P < .01, and P < .05, respectively). T1DM was related to A wave velocity, Am global, A wave integral, LA ejection fraction, and LA systolic ejection fraction (P < .01, P < .05, P < .0005, P < .001, and P < .0005, respectively). In multivariate analyses, T1DM was an independent predictor of the A wave integral, LA ejection fraction, and LA systolic ejection fraction (P < .01, P < .01, and P < .005, respectively). Thus, despite increased relative wall thickness, LV systolic function is increased and early diastolic filling is normal in T1DM subjects; however, they possess changes in LA transport function suggesting increased reliance on LA contribution to LV filling. (J Am Soc Echocardiogr 2006;19:749-755.)

The effects of type 1 diabetes mellitus (T1DM) on left ventricular (LV) structure and function are controversial. Some studies have shown that there is no change in LV structure, whereas others demonstrate an increase in LV mass index or concentric remodeling. There are also conflicting reports regarding the effect of T1DM on LV diastolic function with some studies showing decreased peak early filling velocities, increased atrial filling velocities, and prolongation of deceleration and isovolumic relaxation time intervals, but others showing either no abnormalities or isolated increases in late diastolic filling velocities. In addition, few studies have focused specifically on the effect of T1DM on the left atrial (LA) function and contribution to LV filling.

From the Cardiovascular Division, Division of Geriatrics and Nutritional Sciences, Department of Medicine; Division of Biostatistics; Division of Endocrinology and Metabolism; Department of Radiology, Washington University School of Medicine. This work was supported by NIH grants R01HL58878, S10RR14778, K24HL67002, HL13581, AG154666, HL69100, RR00036 (General Clinical Research Center), and by a grant from the Barnes-Jewish Hospital Foundation to the Cardiovascular Imaging and Clinical Research Core Laboratory. Reprint requests: Linda R. Peterson, MD, Washington University School of Medicine, 660 S Euclid Avenue, Campus Box 8086, St. Louis, MO 63110 (E-mail: lpeterso@im.wustl.edu). 0894-7317/$32.00 Copyright 2006 by the American Society of Echocardiography. doi:10.1016/j.echo.2006.01.009

METHODS

Subjects
Forty-four patients (ages 18-56 years, with T1DM or insulin-dependent diabetes, were evaluated at the Cardiovascular Imaging and Clinical Research Core Laboratory and met the following entry criteria for this study: a body mass index (BMI) greater than 18 and less than 30 kg/m², systolic blood pressure (SBP) less than 140 mm Hg, diastolic blood pressure (DBP) less than 90 mm Hg, and no
history of major systemic disease (e.g., cancer, lupus) other than T1DM or its related complications, a stress echocardiogram negative for inducible ischemia or systolic dysfunction (defined as an LV ejection fraction <55%), pericardial or valvular disease, and no subject was pregnant or lactating. Five T1DM subjects were taking angiotensin-converting enzyme inhibitors; no other subjects were taking any other vasoactive medications. The T1DM patients had measurements of serum glycated hemoglobin (%HbA1c) and creatinine levels obtained within 1 month of study. Heart rate was measured after 10 minutes in the supine position. The resting 12-lead electrocardiogram (lead II or III) was used to measure the QT and RR intervals, and corrected for the cardiac cycle length (QTc) according to Bazett's formula (QTc = QT/ [RR]^{1/2}). Values were averaged over three consecutive beats. Peripheral complications were determined by a patient’s self-reported history of and/or evidence of retinopathy, nephropathy, or peripheral neuropathy. Echocardiographic results from a group of 44 age- and gender-matched normal controls (NC) who also had normal stress echocardiograms and met the above-listed entry criteria were used for comparison. All subjects signed an informed consent, which was approved by the Institutional Review Board at Washington University School of Medicine.

**Two-dimensional and Pulsed-wave Doppler Echocardiography**

All subjects underwent a complete two-dimensional and pulsed-wave Doppler (PWD)-echocardiographic examination using a commercially available ultrasound system (Sequoia-C256, Acuson-Siemens, Mountain View, CA) equipped with second harmonic imaging software. Quantitative measurements at rest included LV volumes (method of discs) at end-diastole and end-systole indexed for body surface area; the LV ejection fraction was calculated as (LV end-diastolic volume – LV end-systolic volume)/LV end-systolic volume at end-diastole, end-systole, and late diastole (before atrial contraction, determined from the onset of the P wave on the surface electrocardiogram).15 Total LA ejection fraction was determined by the following equation: LA ejection fraction = (LA end-diastolic volume – LA end-systolic volume)/LA end-systolic volume (Fig. 1 A and C). The LA systolic ejection fraction (i.e., the fractional volume ejected during atrial systole) was determined as the ratio of (LA late-diastolic volume – LA end-diastolic volume)/LA late-diastolic volume (Fig. 1 B and C).

PWD-derived transmitral velocities were obtained at the mitral leaflet tips per the American Society of Echocardiology guidelines.16 Measurements included the early diastolic E-wave and atrial A-wave velocities, E/A ratio, isovolumic relaxation and deceleration time intervals, and integral of the area under the A-wave (Fig. 1, D). Both two-dimensional echocardiographic and PWD-derived transmitral indices were measured by one observer and averaged over three to five consecutive cardiac cycles. Interobserver variability in measurements of PWD, LV mass, and TDI-derived Em global has been reported.19

**Tissue Doppler Imaging and Color M-Mode Flow Propagation**

TDI was performed in the apical four- and two-chamber views by placement of a 3-mm sample gate at the lateral, septal, anterior, and inferior mitral annulus. Measurements of Em and Am velocities were obtained at each annular site, as described in a previous study from our laboratory (Fig. 1E).19 The Em global and Am global velocities were derived by averaging the velocities from the four annular sites. The ratios of the PWD-derived E wave to the TDI-derived Em global velocity (E/Em) were calculated to provide an estimation of LV filling pressures.20

The early diastolic flow propagation velocities were obtained in the apical four-chamber view by positioning an M-Mode cursor within the color flow velocity profile of mitral inflow.18 The slope (cm/s) of the early diastolic velocities was measured at the mitral leaflets to a distance of 4 cm into the LV chamber.

**Statistical Analysis**

Statistical analyses were performed using the SAS software version 8.2 (SAS Institute, Cary, NC). All continuous variables are expressed as mean ± standard deviation. Comparisons of echocardiographic variables of T1DM subjects and NC were performed using Student t test for unpaired data. Chi-square tests were used for comparison of categoric variables. Pearson’s correlation coefficients were used to assess the strength of the relationship between continuous variables. All predetermined independent variables that correlated with the dependent measures of diastolic function (Am, A, the time velocity integral of the mitral valve A-wave, the LA ejection fraction, and the LA systolic ejection fraction) with a P value of less than .1 in the Pearson’s correlations were inserted into a stepwise, multiple regression analysis. To determine the covariate-adjusted effect of T1DM on the dependent variables, all multivariate analyses required that diabetes be included in the model. Statistical significance was determined as a P value of less than .05; this was not corrected for the performance of multiple analyses.

**RESULTS**

The demographic and hemodynamic variables of T1DM subjects and NC are shown in Table 1. The majority of patients in both groups were women. The average duration of T1DM was 22 ± 11 years. There was no significant difference between the racial compositions of the two groups, but the absolute numbers of non-white subjects was small (five in the NC and two in the T1DM group, respectively). The resting heart rate was significantly higher and QTc was longer in T1DM compared with
Of the T1DM patients, the mean %HbA1c of the T1DM patients was 8.2 ± 2.0%; 19% of T1DM subjects had peripheral vascular complications, including seven with retinopathy, three with neuropathy, and one with nephropathy, defined as a serum creatinine level greater than 0.115 mmol/L (1.3 mg/dL).

Left Ventricular Structure and Systolic Function

Table 2 shows the LV end-systolic volume index was lower, and the relative wall thickness was higher (P < .05 for both) in T1DM subjects compared with NC. The increased relative wall thickness with normal LV mass index is consistent with a pattern of concentric LV remodeling.21 The LV ejection fraction was increased in the T1DM subjects compared with NC (P = .01). However, the TDI-derived measure of LV systolic longitudinal shortening, Sm global, was not different between the two groups.

Left Ventricular Early Relaxation and Filling

As shown in Table 3, mean mitral E-wave velocity, E/A ratio, deceleration time, isovolumic relaxation time, color M-Mode flow propagation velocity, and Em velocity were similar in T1DM and NC. The mitral E/Em ratios were also not different between the two groups. T1DM did not correlate with the relatively load-independent measure of early LV relaxation, Em global. Em was negatively correlated with BMI (r = −0.25, P < .05), SBP (r = −0.22, P < .05), DBP (r = −0.35, P = .001), and diabetes duration (r = −0.31, P < .05); of these only DBP was an independent predictor in the multivariate model (P = .001).
Table 1 Baseline characteristics and hemodynamics

<table>
<thead>
<tr>
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<th>NC</th>
<th>TIDM</th>
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<tbody>
<tr>
<td>Age (y)</td>
<td>39</td>
<td>38</td>
</tr>
<tr>
<td>Gender (% F)</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>Race (% white)</td>
<td>89</td>
<td>95</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>24</td>
<td>24</td>
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<tr>
<td>DM duration (y)</td>
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<td>N/A</td>
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<tr>
<td>HbA1C (%)</td>
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<tr>
<td>Heart rate (bpm)</td>
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<tr>
<td>QTIc (msec)</td>
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<td>42</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
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<td>115</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>71</td>
<td>73</td>
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</tbody>
</table>

NC, Normal control; T1DM, type 1 diabetes mellitus; BMI, body mass index; DM, diabetes mellitus; HbA1C, hemoglobin A1C; SBP, systolic blood pressure; DBP, diastolic blood pressure.

*P < .001, †P = .001 vs. NC.

Table 2 Left ventricular structure and systolic function

<table>
<thead>
<tr>
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<th>NC</th>
<th>TIDM</th>
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<tbody>
<tr>
<td>LV mass index (g/m²)</td>
<td>81</td>
<td>80</td>
</tr>
<tr>
<td>Relative wall thickness</td>
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<td>0.43</td>
</tr>
<tr>
<td>LV end-diastolic volume index (mL/m²)</td>
<td>51</td>
<td>49</td>
</tr>
<tr>
<td>LV end-systolic volume index (mL/m²)</td>
<td>18</td>
<td>16</td>
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<tr>
<td>LV ejection fraction (%)</td>
<td>65</td>
<td>68</td>
</tr>
<tr>
<td>Sm global (cm/s)</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

LV, Left ventricular.

*P < .05, †P = .01, ‡P < .005, §P < .0005 vs. NC.

Left Atrial Structure and the Contribution of Left Atrial Systole to Left Ventricular Filling

The PWD-derived A-wave velocities and the time velocity integral of the A-wave were significantly higher in T1DM subjects compared with NC (P = .01, P < .0005, respectively; Table 4). TDI-derived Am global, was also higher in T1DM subjects compared with NC (P < .05). LA end-systolic volumes were similar between T1DM and NC. Total LA ejection fraction and LA systolic ejection fraction were also significantly higher in T1DM compared with NC (P < .005 and P < .0005, respectively).

Predictors of Left Atrial Function

As shown in Table 5, the presence of T1DM significantly correlated with all of the measures of LA function: the integral of the mitral valve A-wave, LA ejection fraction, LA systolic ejection fraction, A-wave velocity, and Am global (P < .0005, P < .001, P = .0005, P < .01, P < .05, respectively). Moreover, in Table 6 the presence of T1DM is shown to be an independent predictor of the mitral valve A-wave integral, LA ejection fraction, and LA systolic ejection fraction. There were no other independent predictors of the time velocity integral for the mitral valve A-wave or LA systolic ejection fraction, and the only other independent predictor of LA ejection fraction was SBP. Heart rate was the only variable other than the presence of T1DM that correlated significantly in the univariate analyses with all of the measures of LA function; however, like the presence of T1DM, it was not an independent predictor of all LA function measures. Other variables correlating with A-wave velocity in univariate analyses, in addition to T1DM and heart rate, were BMI (r = 0.25, P < .05), SBP (r = 0.31, P < .005), and DBP (r = 0.23, P < .05). Of these, only heart rate and SBP were independent predictors of A-wave velocity. The measures that significantly correlated with Am global (in addition to T1DM) in the univariate analyses were BMI (r = 0.23, P < .05) and heart rate (r = 0.35, P < .001); both were also independent predictors of Am global in the stepwise multivariate model.

DISCUSSION

Our results suggest that in patients with T1DM, there is evidence of concentric LV remodeling with preserved LV systolic function (LV ejection fraction and TDI-derived Sm velocity), and an increased reliance on LA transport function for LV filling but no change in LV early relaxation as assessed using PWD mitral inflow and TDI-derived measures. Our finding of LV concentric remodeling is consistent
with some previous studies in which non-hypertensive T1DM patients had an increase in wall thickness, relative wall thickness, and/or LV mass. In contrast, a study in children and adolescents (mean age 11 years) did not show a difference between T1DM patients and NC, suggesting that the LV remodeling in T1DM may be a progressive process requiring years to evolve. The current study also shows that in T1DM patients free of clinically evident coronary disease, LV ejection fraction and longitudinal systolic function (i.e., TDI-derived Sm velocity) are either increased or similar to NC, suggesting no adverse effect of T1DM on systolic performance.

The finding that the primary abnormality of LV diastolic function in T1DM patients without optimal glycemic control was the increased requirement for atrial contribution to LV filling was supported by all of our TDI, PWD, and two dimensional measures of LA function. T1DM and heart rate were the only two variables that were significantly related to all of the measures of LA function studied. However, the increased heart rate in T1DM group did not account for all of the effect of T1DM on LA function; T1DM was an independent predictor of the time velocity integral of the A-wave, LA ejection fraction, and LA systolic ejection fraction. Thus, our data suggest that the LV of patients with T1DM is dependent on an increased atrial contribution to LV filling. This is consistent with a study in T1DM patients in which LA transport function, determined using acoustic quantification, is increased during late diastolic LV filling, but peak early diastolic filling (indexed for LV size) was normal.

The current investigation found that measures of early LV relaxation, both load-dependent PWD-derived indices (E-wave velocity, E/A ratio, deceleration time, isovolumic relaxation time, and color M-Mode flow propagation velocities) and a relatively load-independent measure (TDI-derived Em velocity), remain normal in moderately controlled T1DM patients; these findings suggest that active relaxation by the LV is preserved. This is in contrast with a smaller study that also used TDI to investigate the effects of T1DM on LV diastolic function. In that study, Em was lower in the T1DM group than in the NC group. Differences in TDI methods, patient populations, screening procedures, and numbers of patients may explain some of the differences between the results of our TDI-derived measures and those of the previous study. To our knowledge, these are the only studies to use TDI to investigate the load-independent effects of T1DM on LV diastolic function. Interestingly, in that study and in the Cardiovascular Health Study, atrial function defined by PWD-derived measures of A-wave velocity was altered in the T1DM patients, which is concordant with our findings.

### Proposed Mechanisms of Increased Left Atrial Function in Type 1 Diabetes Mellitus

Abnormalities of the balance between sympathetic input and parasympathetic tone, which are often present in T1DM subjects, may contribute to the observed alterations in the LA contribution to LV filling. The increased resting heart rate and prolongation of the QTc interval in the T1DM patients

### Table 5 Univariate correlations with left atrial function

<table>
<thead>
<tr>
<th></th>
<th>A-wave integral</th>
<th>LA ejection fraction</th>
<th>LA systolic ejection fraction</th>
<th>A-wave velocity</th>
<th>Am global</th>
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<tbody>
<tr>
<td>T1DM (r = .05)</td>
<td>P &lt; .0005</td>
<td>P &lt; .001</td>
<td>P &lt; .001</td>
<td>P &lt; .005</td>
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<tr>
<td>HbA1c</td>
<td>r = .32, P &lt; .05</td>
<td>r = .28, P &lt; .07</td>
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<tr>
<td>T1DM duration</td>
<td>r = .20, P = .07</td>
<td>r = .23, P &lt; .05</td>
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<tr>
<td>BMI</td>
<td>r = .06, P = .59</td>
<td>r = .06, P = .59</td>
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<tr>
<td>HR</td>
<td>r = .23, P &lt; .05</td>
<td>r = .20, P = .28</td>
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<tr>
<td>SBP</td>
<td>r = .03, P = .28</td>
<td>r = .03, P = .28</td>
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<tr>
<td>DBP</td>
<td>r = .06, P = .54</td>
<td>r = .06, P = .54</td>
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### Table 6 Independent predictors of left atrial function

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<tr>
<th></th>
<th>A-wave integral</th>
<th>LA ejection fraction</th>
<th>LA systolic ejection fraction</th>
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<tr>
<td>T1DM (P &lt; .01)</td>
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<td>SBP (P &lt; .05)</td>
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<td>BMI (P &lt; .05)</td>
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LA, Left atrial; T1DM, type 1 diabetes mellitus; HbA1c, hemoglobin A1C; BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

*Variables in bold type* are statistically significantly related to the measures of LA function.
suggest that the balance between parasympathetic and sympathetic systems is not the same as in nondiabetic subjects. T1DM may cause a relative increase in sympathetic stimulation and decrease in parasympathetic tone, which may contribute to smaller LV end-systolic volumes and shorter LV filling time (resulting from the increased resting heart rate), thus resulting in increased reliance on the LA contribution to LV filling because less space and time are available for early LV filling. However, because T1DM is an independent predictor of many of the measures of LA contractility, the association between T1DM and LA contractility does not seem to be exclusively mediated by an increased heart rate.

The increases in TDI Am velocities and other measures of late LV filling may also, in part, reflect increases in LV end-diastolic pressures because of increased passive stiffness that would require augmented LA transport function. Alternations in passive LV stiffness may result from increased myocardial collagen formation, which has been suggested by studies using ultrasonic integrated backscatter to characterize the myocardium of T1DM patients.

Limitations of the Study
This study is not longitudinal and, thus, cannot determine causation but rather demonstrates the strength and independence of the associations between T1DM and measures of LA contractility. This study assessed LV systolic and diastolic function in a relatively young, healthy population of T1DM patients with few peripheral complications. The data from this study cannot necessarily be used to predict outcomes in patients whose profiles do not fit the entry criteria used in this study. Also, given the relatively small numbers of non-white subjects in this study, the possible effect of race on the outcome variables cannot be assessed in this study. More invasive and/or expensive measures for quantifying either LV wall compliance (from catheterization-derived LV pressure-volume loops) or the balance between sympathetic outflow and parasympathetic tone were not used in this study. The study by Stevens et al. highlights the complexity of studying the effects of the sympathetic nervous system in patients with T1DM, that is, there seems to be heterogeneity in the effects of this system on different regions of the myocardium.

CONCLUSIONS
Relatively healthy T1DM patients without evidence of coronary artery disease or heart failure have LV concentric remodeling, normal LV systolic function, normal early diastolic LV relaxation, but increased LA transport function. This reliance on increased LA transport cannot be completely accounted for by increases in resting heart rate.

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REFERENCES


