Relationship Between Early Diastolic Dysfunction and Abnormal Microvolt T-Wave Alternans in Patients With Type 2 Diabetes

Stefano Bonapace, MD; Giovanni Targher, MD; Giulio Molon, MD; Andrea Rossi, MD; Alessandro Costa, MD; Luciano Zenari, MD; Lorenzo Bertolini, MD; Debora Cian, MD; Laura Lanzoni, MD; Enrico Barbieri, MD

Background—Abnormal microvolt T-wave alternans (MTWA), a marker of ventricular arrhythmic risk, is a highly prevalent condition in patients with type 2 diabetes mellitus (T2DM) and is correlated with glycemic control. However, there is uncertainty as to whether central or peripheral hemodynamic factors are associated with abnormal MTWA in T2DM individuals.

Methods and Results—We studied 50 consecutive, well-controlled T2DM outpatients without a history of ischemic heart disease and with normal systolic function. All patients underwent a complete echocardiographic Doppler evaluation with spectral tissue Doppler analysis. MTWA analysis was performed noninvasively during submaximal exercise. Effective arterial elastance, arterial compliance, and heart rate variability were also measured. Compared with patients with MTWA negativity (n=38), those with MTWA abnormality (n=12, 24%) had significantly lower e’ (7.6±1.3 versus 9.1±1.7 cm/s; P<0.01), a’ (10.2±1.6 versus 12.7±1.9 cm/s; P<0.001) and s’ velocities (8.7±1.1 versus 10.2±1.5 cm/s; P=0.001) and higher indexed left ventricular mass (121.3±16.4 versus 107.5±16.5 g/m²; P=0.016), indexed left atrial volume (33.5±11.9 versus 23.6±5.6 mL/m²; P<0.001), and E/e’ ratio (8.8±1.4 versus 6.5±1.3; P<0.001). Multivariable logistic regression analysis revealed that higher E/e’ ratio was the only independent correlate of abnormal MTWA (adjusted odds ratio, 3.52; 95% confidence interval, 1.19 to 10.6; P=0.02) after controlling for glycemic control and other potential confounders.

Conclusions—In this pilot study, we found that early diastolic dysfunction, as measured by tissue Doppler imaging, is independently associated with MTWA abnormality in T2DM individuals with normal systolic function. Further larger studies are needed to examine the reproducibility of these results. (Circ Cardiovasc Imaging. 2011;4:408-414.)

Key Words: T-wave alternans ■ diastolic dysfunction ■ type 2 diabetes

Type 2 diabetes mellitus (T2DM) is an established risk factor for cardiovascular disease and is associated not only with an increased risk of all-cause and cardiovascular mortality but also with an increased risk of ventricular tachyarrhythmias and sudden cardiac death.1

The risk of ventricular arrhythmias and sudden cardiac death is significantly increased in T2DM individuals.1 Previous studies reported a greater prevalence of T2DM among patients with left ventricular (LV) systolic dysfunction who had abnormal MTWA than among those with normal MTWA.8–10 Recently, we found that the prevalence of abnormal MTWA was ≈5-fold greater in T2DM patients without a history of myocardial infarction than in matched nondiabetic control subjects and it was strongly correlated with glycemic control.13

It has been reported that MTWA is influenced by myocardial ischemia,14 increased sympathetic tone,15 emotional arousal,16 LV hypertrophy,17 and LV end-diastolic volume (EDV) in dilated cardiomyopathy.18 However, there is uncertainty as to whether central or peripheral hemodynamic

Clinical Perspective on p 414

Microvolt T-wave alternans (MTWA) analysis is a noninvasive diagnostic test for detecting beat-to-beat fluctuations in the ECG T-wave morphology.2–4 Several observational studies suggested that MTWA is a marker of arrhythmic risk in relevant primary prevention populations,5–10 whereas some other studies have not.11 MTWA is appealing because it noninvasively probes the underlying electrophysiological substrate and has been linked to cellular mechanisms for arrhythmias.12

Received December 14, 2010; accepted April 13, 2011.
From the Division of Cardiology, Sacro Cuore Hospital, Negrar (VR), Italy (S.B., G.M., A.C., D.C., L.L., E.B.); the Section of Endocrinology and Metabolism, Department of Medicine, University of Verona, Italy (G.T.); the Section of Cardiology, Department of Medicine, University of Verona, Italy (A.R.); and the Diabetes Unit, Sacro Cuore Hospital, Negrar (VR), Italy (L.Z., L.B.).
Correspondence to Giovanni Targher, MD, Section of Endocrinology and Metabolism, Department of Medicine, University of Verona, Piazzale A. Stefani, 1, 37126 Verona, Italy. E-mail giovanni.targher@univr.it © 2011 American Heart Association, Inc.
Circ Cardiovasc Imaging is available at http://circimaging.ahajournals.org DOI: 10.1161/CIRCIMAGING.110.962951

408
Factors are associated with MTWA abnormality in T2DM individuals without LV systolic dysfunction. The purpose of the present study was to assess the relationships between MTWA abnormality and several cardiac and vascular function indexes in a sample of well-controlled T2DM individuals without a history of ischemic heart disease and with normal LV systolic function.

Methods
We studied 50 T2DM outpatients who consecutively attended the Diabetes Unit at “Sacro Cuore” Hospital of Negrar (Verona) during a period of 18 months. We excluded (1) patients who had a history of ischemic heart and valvular disease (eg, annular calcification and mitral regurgitation, aortic stenosis, aortic regurgitation), cirrhosis, and overt nephropathy; (2) patients with atrial fibrillation, atrial flutter, and bundle-branch block; (3) patients taking medications that might affect MTWA analysis (eg, β-blockers and other antiarrhythmic drugs); and (4) patients with poor and unstable glycemic control. The study was approved by the local ethics committee, and all participants gave written informed consent for participation in medical research.

Clinical and Biochemical Measurements
Body mass index was calculated by dividing weight in kilograms by height in meters squared. Blood pressure was measured with a standard mercury manometer. In all participants, the presence of microvascular complications such as diabetic retinopathy (by ophthalmoscopy), sensory neuropathy (by biothesiometer), and nephropathy (by serum creatinine and urinary albumin excretion measurements) was also recorded.

Blood samples were drawn in the morning after an overnight fast. Serum lipids, creatinine, and other biochemical blood measurements were determined by standard laboratory procedures (DAX 96, Bayer Diagnostic, Milan, Italy). Low-density lipoprotein cholesterol was calculated using the Friedewald equation. Hemoglobin A1c (HbA1c) was measured by a high-performance liquid chromatography analyzer (HA-8140, Menarini Diagnostics, Florence, Italy); the upper limit of normal for the laboratory was 5.6%. Albuminuria was determined by standard laboratory procedures (DAX 96, Bayer Diagnostic, Milan, Italy): The standard deviation of normal-to-normal intervals (SDNN), the root-mean-square of difference of successive R-R intervals (rMSSD), and the percentage of adjacent R-R intervals varying by 50 ms (pNN50) are specific for the parasympathetic limb.3

Heart Rate Variability Analysis
Heart rate variability (HRV) analysis was performed by measuring the following time-domain parameters of 24-hour HRV that were automatically calculated during Holter monitoring (Mortara Ran- goni, Bologna, Italy): The standard deviation of normal-to-normal R-R intervals (SDNN), the root-mean-square of difference of successive R-R intervals (rMSSD), and the percentage of adjacent R-R intervals varying by >50 ms (pNN50). SDNN is thought to represent joint sympathetic and parasympathetic modulation of HRV, and rMSSD and pNN50 are specific for the parasympathetic limb.3

MTWA Analysis
Before MTWA measurements, a 12-lead standard resting ECG, 24-hour Holter monitoring, bicycle ergometry, and conventional Doppler echocardiography were performed to exclude the presence of myocardial ischemia or significant disturbances of sinus rhythm; no participants had any abnormal test results. Stress echocardiography during exercise or administration of pharmacological agents was not performed.

The MTWA analysis was performed noninvasively during submaximal exercise with the subject sitting on a bicycle ergometer, by use of the CH-2000 system (Cambridge Heart Inc, Bedford, MA). The test was considered as positive if there was sustained MTWA (with a voltage >1.9 μV and signal/noise ratio >3) for >1 minute and with a heart rate at onset ≥110 bpm; the MTWA test was classified as negative if the criteria for positivity were not met and if there was 1 minute of data without significant noise, bad beats, or nonsustained alternans, with an interval heart rate ≥105 bpm; the MTWA test was classified as indeterminate if the criteria for positivity and negativity were not met.3,4,13,19

All MTWA tests were performed and interpreted by an expert cardiologist who was blinded to echocardiographic characteristics of patients.

Echocardiographic Evaluation
Conventional Doppler echocardiography was used to measure LV diameters, wall thickness, and mass according to standard criteria.20 LV end-diastolic and end-systolic volumes and ejection fraction at rest were measured at the apical 2-chamber and 4-chamber views (by modified Simpson rule).20 Left atrial (LA) maximal volume was measured at the end of LV systole from the apical 2-chamber and 4-chamber views (by modified Simpson rule). The ratio between IVRT/Tdt was then indexed to body surface area when appropriate. Pulsed-wave Doppler was used to measure transmitral peak early diastolic velocity (E), peak late diastolic velocity (A), and E/A ratio. LV end-diastolic volume (EDV) was estimated as follows: EDV = 11.96 +0.596 × E/e′ ratio.23

Tissue Doppler Imaging
Pulsed-wave tissue Doppler (TD) echocardiography of the septal and lateral mitral annulus was used to measure the early peak (e′) and late (a′) annular diastolic velocities, and the mean values of septal and lateral annulus measurements were used for analysis.21,22 The e′ velocity is relatively preload-independent and is correlated inversely with the time constant of isovolumic relaxation (τ), which is derived from the following formula: τ = [(14.70 – 100 e′)/(0.15)].23,24 LV end-diastolic pressure (EDP) was estimated as follows: LVEDP = 11.96 + 0.596 × E/e′ ratio.23 The time interval between the QRS complex and the onset of mitral E-wave velocity was subtracted from the time interval between the QRS complex and e′ onset to derive T Pe−w, which strongly depends on the time constant of LV relaxation and is considered as a better index of diastolic properties.7,8 The ratio between IVRT/Tdt was then calculated; this ratio provides incremental information to the E/e′ ratio on LV filling pressure in subjects with normal ejection fraction and E/e′ ratio between 8 and 15.25

Myocardial deformation measurements were also performed offline in patients with adequate apical windows (n = 38) with the use of a standard EchoPac PC workstation application for 2-dimensional strain analysis. Global longitudinal strain and strain rate curves were obtained including all 6 LV myocardial segments from 4-chamber, 2-chamber, and long-axis apical views.26 The average values of peak systolic longitudinal strain and peak systolic strain rate from the 3 apical views were calculated as global longitudinal strain (LSe,g) and global strain rate (SRe,g), respectively. Similarly, the global strain rate during the early (SRPe) and late (SRa) phases of diastole was also calculated. The ratio of transmural E-wave velocity to SRPe as an index of LV filling pressure was calculated as previously proposed.27 Standard echocardiographic views were obtained using frequency, depth, and sector width adjusted for frame-rate optimization (between 60 and 100 fps). TD imaging was performed in all patients by a single experienced cardiologist who was blinded to MTWA details of participants. Eighteen TD imaging signals were remeasured by the same observer; the mean absolute differences (±SD) in tissue velocities within the same observer were 0.10 ±0.02 cm/s for s′ velocity, 0.19 ±0.17 cm/s for e′ velocity, and 0.23 ±0.20 cm/s for a′ velocity, respectively (P = NS for all differences). Eighteen TD imaging signals were also remeasured by a second observer; the mean absolute differences in tissue velocities between the 2 observers were 0.11 ±0.09 cm/s for s′ velocity, 0.30 ±0.25 cm/s for e′ velocity, and 0.36 ±0.28 cm/s for a′ velocity (P = NS for all). No significant differences were also found in the intraobserver and interobserver variabilities for global longitudinal strain (0.79 ±0.60% and 1.07 ±0.80%), SRe,g (0.08 ±0.04 s−1 and 0.11 ±0.07 s−1), and SRPe (0.08 ±0.06 s−1 and 0.12 ±0.08 s−1).
Vascular Function

Effective arterial elastance was estimated as end-systolic pressure divided by stroke volume.\textsuperscript{28} End-systolic pressure was estimated as systolic pressure$\times(0.9)^{29}$ Systemic arterial compliance was estimated by the stroke volume–to–pulse-pressure ratio\textsuperscript{30} and systemic vascular resistance index by mean arterial pressure$\div$cardiac index$\times80$.

Statistical Analysis

Statistical analyses were performed using a commercially available statistical software package (Stat-View 5.0, Abacus Concept, Inc.). Data are presented as mean$\pm$SD or medians and interquartile ranges or percentages. Comparisons between groups were made using the unpaired $t$ test (for variables normally distributed), the Mann-Whitney test (for variables not normally distributed), and the $\chi^2$ test with Yates correction for continuity (for categorical variables). Univariable linear regression analysis was performed to examine the associations of MTWA or HbA1c with echocardiographic parameters. Multivariable logistic or linear regression analysis was also performed to identify the factors independently associated with MTWA. Two forced-entry multivariable regression models were performed. In the logistic regression model, the presence of abnormal MTWA, included as a categorical variable, was considered as a composite measure inclusive of those with positive and indeterminate MTWA test results, on the basis of previously published reports.\textsuperscript{7,9,10,19} In the linear regression model, MTWA was included as a continuous variable. The following covariates were included in the 2 multivariable regression models: s’ velocity, a’ velocity, E/e’ ratio, and HbA1c. The covariates were chosen as potential confounders, based on their biological plausibility and statistical association with MTWA in univariate analyses. LVEDP was not included in these regression models because LVEDP was not directly measured but derived from the E/e’ ratio. Probability values <0.05 were considered statistically significant.

Results

The MTWA test was negative in 38 (76%) patients, positive in 10 (20%) patients, and indeterminate in 2 (4%) patients. Clinical and biochemical characteristics of T2DM patients stratified by their MTWA status are summarized in Table 1. Patients with abnormal MTWA ($n=12$, 24%) had higher HbA1c than those with normal MTWA, although the glycemic control of participants was fairly good (mean HbA1c, 7.3%). Age, sex, body mass index, smoking status, heart rate, blood pressure, plasma lipids, fasting glucose, duration of diabetes, status of microvascular complications (ie, retinopathy, nephropathy and sensory neuropathy), and treatments for diabetes, hypertension and dyslipidemia were not significantly different between the groups.

Table 2 shows the echocardiographic characteristics of participants grouped according to MTWA status. Compared with those with MTWA normality, patients with MTWA abnormality had lower e’, s’, and a’ tissue velocities, lower IVRT/TE$\div$e ratio, higher E/e’ ratio, higher indexed LV mass, and higher indexed LA volume. Among the measurements of global LV strain and strain rate, those with abnormal MTWA also had lower LS$_{SYS}$, lower SR$_{E}$, and higher E/SR$_{E}$. No significant differences were found in LV ejection fraction, E and A transmitial wave velocities, E/A ratio, Dte, arterial elastance, systemic arterial compliance, and 24-hour HRV parameters between the groups.

Notably, when patients were categorized into 2 groups according to an E/e’ ratio $\geq$8 (ie, if $\leq$8, LA pressure is normal), only $\approx$8% of those with normal MTWA had an E/e’ ratio $>$8, whereas 67% of those with abnormal MTWA had an E/e’ ratio $>$8 ($P=0.005$ for the difference between the groups). No patients had an E/e’ ratio $>$15.

Multivariable logistic regression analysis (Table 3) revealed that an increased E/e’ ratio was the only independent correlate of MTWA abnormality (adjusted odds ratio, 3.52; 95% confidence interval, 1.19 to 10.6; $P=0.02$) after controlling for HbA1c, s’, and a’ velocities. Results did not change after additional adjustment for age, sex, hypertension, and microvascular complication status (adjusted odds ratio, 3.65, 1.1 to 12.9; $P=0.03$). Almost identical results were also obtained in multivariable logistic regression models in which participants who had indeterminate MTWA test results ($n=2$) were excluded from analysis (data not shown). However, it is important to note that the results of multivariable logistic regression analyses should be interpreted with caution, given the very low number of patients with abnormal MTWA.
Table 2. Echocardiographic and Hemodynamic Characteristics of T2DM Patients Grouped by MTWA Status

<table>
<thead>
<tr>
<th></th>
<th>Normal MTWA (n=38)</th>
<th>Abnormal MTWA (n=12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDV, mL</td>
<td>85.2±11.8</td>
<td>82.3±6.0</td>
<td>0.42</td>
</tr>
<tr>
<td>ESV, mL</td>
<td>23.2±7.4</td>
<td>23.0±5.8</td>
<td>0.93</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>72.9±7.1</td>
<td>71.8±7.3</td>
<td>0.67</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>107.5±16.5</td>
<td>121.3±16.4</td>
<td>0.016</td>
</tr>
<tr>
<td>LA maximal volume index, mL/m²</td>
<td>23.6±5.6</td>
<td>33.5±11.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E, m/s</td>
<td>0.61±0.13</td>
<td>0.66±0.11</td>
<td>0.11</td>
</tr>
<tr>
<td>A, m/s</td>
<td>0.85±0.12</td>
<td>0.89±0.16</td>
<td>0.34</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.69±0.11</td>
<td>0.75±0.11</td>
<td>0.15</td>
</tr>
<tr>
<td>Dte, ms</td>
<td>266.3±65</td>
<td>293.1±95</td>
<td>0.34</td>
</tr>
<tr>
<td>s' velocity, cm/s</td>
<td>10.2±1.5</td>
<td>8.7±1.1</td>
<td>0.001</td>
</tr>
<tr>
<td>a' velocity, cm/s</td>
<td>12.7±1.9</td>
<td>10.2±1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>e' velocity, cm/s</td>
<td>9.1±1.7</td>
<td>7.6±1.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>E/e ratio</td>
<td>6.5±1.3</td>
<td>8.8±1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>90.8±15</td>
<td>93.8±17</td>
<td>0.57</td>
</tr>
<tr>
<td>IVRT/Tau, ms</td>
<td>2.23±1.0</td>
<td>1.35±0.5</td>
<td>0.012</td>
</tr>
<tr>
<td>Tau, ms</td>
<td>37.7±11.4</td>
<td>47.4±8.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>15.6±1.1</td>
<td>17.2±0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDP/EDV, mm Hg/mL</td>
<td>0.19±0.03</td>
<td>0.21±0.01</td>
<td>0.018</td>
</tr>
<tr>
<td>Ea, mm Hg/mL</td>
<td>0.98±0.26</td>
<td>1.01±0.22</td>
<td>0.79</td>
</tr>
<tr>
<td>SAC, mL/mm Hg</td>
<td>1.53±0.39</td>
<td>1.40±0.31</td>
<td>0.28</td>
</tr>
<tr>
<td>LSYS, %</td>
<td>−16.6±2.7</td>
<td>−14.4±3.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SRsys, s⁻¹</td>
<td>−1.03±0.13</td>
<td>−0.96±0.13</td>
<td>0.10</td>
</tr>
<tr>
<td>SRc, s⁻¹</td>
<td>0.95±0.18</td>
<td>0.78±0.19</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>E/SRc, s⁻¹</td>
<td>0.98±0.20</td>
<td>0.87±0.18</td>
<td>0.08</td>
</tr>
<tr>
<td>24-h HRV by SDNN, ms</td>
<td>118 (109–136)</td>
<td>115 (109–154)</td>
<td>0.79</td>
</tr>
<tr>
<td>24-h HRV by r-MSSD, ms</td>
<td>30 (20–39)</td>
<td>33 (20–39)</td>
<td>0.58</td>
</tr>
<tr>
<td>24-h HRV by p-NN50, %</td>
<td>3.5 (0.7–6.7)</td>
<td>4.3 (1.7–10.0)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

MTWA indicates end-diastolic volume; ESV, end-systolic volume; Dte, E-wave deceleration time; Ea, arterial elastance; HRV, heart rate variability; IVRT, isovolumic relaxation time; LSYS, global longitudinal strain during systole; LVEF, left ventricular ejection fraction; LVEDP, left ventricular end-diastolic pressure; pNN50, percentage of beats with a consecutive R-R interval difference of >50 ms; r-MSSD, root-mean-square of difference for successive R-R intervals; SAC, systemic arterial compliance; SDNN, standard deviation of normal-to-normal R-R intervals; SRc, global longitudinal strain rate during early diastole; SRsys, global strain rate during late diastole; and SV, stroke volume.

Data are expressed as mean±SD or medians (interquartile range) or percentages. Measurements of global longitudinal strain and strain rate were available in 38 patients (10 with normal MTWA and 28 with normal MTWA).

In univariable linear regression analysis (Table 4), HbA1c and MTWA—which was considered as a continuous variable and expressed in microvolt—were correlated with each other as well as with various echocardiographic parameters. Among these, the E/e' ratio was found to be the strongest positive correlate of both MTWA and HbA1c.

Table 3 shows the results from a multivariable linear regression analysis, in which MTWA was included as a continuous variable. Also in this case, the E/e' ratio was found to be the only independent correlate of MTWA (standardized coefficient, 0.47; P<0.01).

Table 3. Multivariable Logistic Regression Analysis: Independent Predictors of Abnormal MTWA in T2DM Patients

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio(s)</th>
<th>95% Confidence Intervals</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin A₁c,%</td>
<td>2.20</td>
<td>0.46–10.8</td>
<td>0.32</td>
</tr>
<tr>
<td>s’ velocity, cm/s</td>
<td>0.53</td>
<td>0.16–1.75</td>
<td>0.51</td>
</tr>
<tr>
<td>a’ velocity, cm/s</td>
<td>0.45</td>
<td>0.21–1.01</td>
<td>0.06</td>
</tr>
<tr>
<td>E/e’ ratio</td>
<td>3.52</td>
<td>1.19–10.6</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Sample size, n=50. In this regression model, MTWA was included as a categorical variable.

Discussion

In this pilot study, we have shown for the first time that early LV diastolic dysfunction, as measured by TD imaging, is independently associated with MTWA abnormality, which is a marker of arrhythmic risk, in a sample of well-controlled T2DM patients without a history of ischemic heart disease and with normal LV systolic function. In addition, because diastolic dysfunction was not detected by conventional echocardiography, our results also provide further evidence that TD imaging is more accurate and sensitive than conventional echocardiography for detecting early alterations in LV diastolic function in people with T2DM.

We found that compared with patients with normal MTWA, those with abnormal MTWA had an early, subclinical impairment of LV diastolic (impaired relaxation) and systolic function, as reflected by lower e' and s' tissue velocities. Measurements of global longitudinal strain and strain rate further confirmed these findings (ie, those with abnormal MTWA had lower LSsys, lower SRc, and higher E/SRc). Interestingly, the reduction in e' and s' velocities has been shown to reflect the degree of myocardial fibrosis, which represents the main structural abnormality of diabetic cardiomyopathy. This might also be of pathophysiological relevance in the explanation of our findings because increased myocardial fibrosis may favor the cellular uncoupling.

Table 4. Univariable Linear Regression Analyses: Associations of Hemoglobin A1c or MTWA With Echocardiographic Parameters in T2DM Patients

<table>
<thead>
<tr>
<th></th>
<th>Hemoglobin A₁c,%</th>
<th>MTWA</th>
</tr>
</thead>
<tbody>
<tr>
<td>E, m/s</td>
<td>0.17 (P=0.43)</td>
<td>0.34 (P=0.02)</td>
</tr>
<tr>
<td>s’ velocity, cm/s</td>
<td>−0.33 (P=0.02)</td>
<td>−0.34 (P&lt;0.02)</td>
</tr>
<tr>
<td>a’ velocity, cm/s</td>
<td>−0.30 (P=0.04)</td>
<td>−0.36 (P&lt;0.01)</td>
</tr>
<tr>
<td>E/e’ ratio</td>
<td>0.36 (P=0.01)</td>
<td>0.55 (P&lt;0.001)</td>
</tr>
<tr>
<td>IVRT/Tau, ms</td>
<td>−0.35 (P=0.01)</td>
<td>0.15 (P=0.45)</td>
</tr>
<tr>
<td>LA maximal volume index, mL/m²</td>
<td>0.23 (P=0.27)</td>
<td>0.62 (P&lt;0.001)</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>0.35 (P=0.01)</td>
<td>0.47 (P=0.01)</td>
</tr>
<tr>
<td>LVEDP/EDV, mm Hg/mL</td>
<td>0.34 (P=0.02)</td>
<td>0.26 (P=0.16)</td>
</tr>
<tr>
<td>HbA1c,%</td>
<td>Not applicable</td>
<td>0.30 (P=0.04)</td>
</tr>
</tbody>
</table>

Sample size, n=50. Data are presented as correlation coefficients and P values (in parentheses).

No other echocardiographic parameters were significantly associated with either HbA1c or MTWA in univariable regression analysis.
that leads to diastolic electric repolarization instability and subsequent MTWA abnormality.

Compared with patients with normal MTWA, those with abnormal MTWA also had a slightly higher indexed LV mass, despite no significant differences found either in the frequency and drug treatment of hypertension or in total vascular load (neither in terms of arterial stiffness nor in terms of systemic vascular resistance) between the groups. This finding provides further support to the concept of a distinct diabetic cardiomyopathy as earlier reported in other studies showing that LV hypertrophy and increased myocardial stiffness are both strongly correlated with poor glycemic control.32

Because in our study the E/e’ ratio, that is, an index of LV filling pressure, was found to be the only independent correlate of MTWA abnormality, it is possible to speculate that chronic changes in LV filling pressures might also play a part in the occurrence of MTWA abnormality. Most of our MTWA-positive patients (~70%) had an E/e’ ratio ranging from 8 to 14, which is considered a “gray” zone for the diagnosis of increased LV filling pressures in patients with normal LV systolic function.37 However, our MTWA-positive patients had echocardiographic parameters suggesting that their LVs are likely to work at higher LV filling pressure. First, they had a slightly enlarged LA volume, which is an index of chronic diastolic dysfunction.37 A significant positive relationship between LA volume, E/e’ ratio, and glycemic control has been previously reported in T2DM patients.38 Second, they had a lower a’ velocity, which reflects LA systolic performance and is inversely correlated with LV filling pressure.39 Third, the IVRT/TiE/e’ ratio, which provides incremental information to the E/e’ ratio on LV filling pressure in subjects with normal ejection fraction and E/e’ ratio between 8 and 15,21.25 was lower in patients with abnormal MTWA than in those with normal MTWA, thus further supporting a raised LVEDP among these patients. Finally, they also had a higher LVEDP/EDV ratio, suggesting the presence of elevated LV diastolic stiffness. Experimental observations in animals with diabetic cardiomyopathy documented that a higher LVEDP/EDV ratio is strongly associated with increased collagen deposition in the myocardium and elevated LV diastolic stiffness.40 It has been also previously demonstrated that T2DM patients might have LV diastolic dysfunction (as estimated by the E/e’ ratio), which is identified only during exercise echocardiography.41,42 This latter observation may be relevant for our findings because MTWA is mainly elicited by exercise,43 and it further suggests that also in our sample those subjects with a higher E/e’ ratio at rest might further worsen their LV filling pressure during exercise.

However, we must be cautious in making any causal inferences because of the cross-sectional design of the study. Although the frequency and treatment of hypertension did not significantly differ between the 2 groups of patients, a plausible explanation for our findings could be that the significant positive association between the E/e’ ratio and MTWA simply reflects the coexistence of LV hypertrophy (hypertensive heart disease) and, possibly, subclinical myocardial ischemia, which cannot be completely excluded on the basis of patients’ clinical history, Holter monitoring, and standard bicycle ergometry. We did not perform a stress echocardiography during exercise or administration of pharmacological agents. In addition, although there were no significant differences in the frequency of sensory neuropathy in the lower extremities (by biothesiometer) as well as in various indexes of the autonomic nervous system drive (eg, 24-hour HRV parameters on Holter monitoring) between patients with normal and with abnormal MTWA, we cannot exclude that cardiac autonomic neuropathy might also play a role in the relationship between early diastolic dysfunction and MTWA abnormality. Unfortunately, cardiovascular reflex tests analyzing heart rate and blood pressure variations during lying to standing, deep breathing, and Valsalva maneuver were not performed in our patients.

Our study has important limitations that should be kept in mind. First, the cross-sectional design of the study precludes the establishment of causal or temporal relationships between early diastolic dysfunction and MTWA abnormality. Second, given the small sample size of the study and the very small number of patients with abnormal MTWA, our results must be interpreted with caution and must be verified in a larger cohort of patients. Third, a stress echocardiography was not performed to exclude the presence of subclinical ischemic heart disease. Fourth, invasive measurements of LV filling pressure were not also performed in our study. However, when compared with invasive reference methods, TD imaging has been shown to accurately estimate LV filling pressures in patients with normal systolic function.21 Moreover, because MTWA is elicited by exercise, the detection of central and peripheral hemodynamic data during exercise might also be helpful for better stratification of patients with MTWA abnormality. Last, in the absence of large, prospective studies, it remains uncertain whether MTWA is a marker of diabetic heart disease, whether MTWA predicts arrhythmic events, or whether it is merely a false-positive marker in people with T2DM.

In conclusion, our findings suggest that early diastolic dysfunction, as measured by TD imaging, is associated with MTWA abnormality in well-controlled T2DM patients without LV systolic dysfunction. We believe that these cross-sectional findings, although not conclusive, are sufficiently provocative and hypothesis-generating to warrant further study. Future larger studies are needed to examine the

| Table 5. Multivariable Linear Regression Analysis: Independent Predictors of MTWA in T2DM Patients |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Coefficient(s) | Standard Error | Standardized Coefficient(s) | Value | Value |
| Hemoglobin A1c, % | 0.16 | 0.54 | 0.09 | 0.30 | 0.72 |
| S’ velocity, cm/s | 0.03 | 0.38 | 0.02 | 0.10 | 0.93 |
| A’ velocity, cm/s | -0.27 | 0.24 | -0.16 | -1.11 | 0.27 |
| E/e’ ratio | 1.0 | 0.36 | 0.47 | 2.76 | <0.01 |

Sample size, n=50. In this regression model, MTWA was included as a continuous variable.
reproducibility of these results and to elucidate the underlying biological mechanisms that link early diastolic dysfunction and abnormal MTWA in T2DM individuals.

Disclosures
None.

References
24. Sohn DW, Chai IH, Lee DJ, Kim HC, Kim HS, Oh BH, Lee MM, Park YB, Choi YS, Seo JD, Lee YW. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. J Am Coll Cardiol. 1997;30:1267–1272.
38. Shishhebhor MH, Hoogwerf BJ, Schoenhagen P, Marso SP, Sun JP, Li, Klein AL, Thomas JD, Garcia MJ. Relation of hemoglobin A1c to left


---

**CLINICAL PERSPECTIVE**

In this pilot study, we have shown for the first time that early left ventricular diastolic dysfunction, as detected by tissue Doppler imaging, is independently associated with abnormal microvolt T-wave alternans, a marker of ventricular tachyarrhythmic events, in well-controlled type 2 diabetic patients without ischemic heart disease and left ventricular systolic dysfunction. Ventricular tachyarrhythmia episodes and the factors potentially responsible for triggering them are poorly understood, usually occur without warning or provocation, and result almost invariably in death. Therefore, efforts aimed at predicting and preventing sudden cardiac death have emerged as the major paradigm for addressing this significant unresolved public health dilemma.
Relationship Between Early Diastolic Dysfunction and Abnormal Microvolt T-Wave Alternans in Patients With Type 2 Diabetes
Stefano Bonapace, Giovanni Targher, Giulio Molon, Andrea Rossi, Alessandro Costa, Luciano Zenari, Lorenzo Bertolini, Debora Cian, Laura Lanzoni and Enrico Barbieri

_Circ Cardiovasc Imaging_. 2011;4:408-414; originally published online April 18, 2011; doi: 10.1161/CIRCIMAGING.110.962951
_Circulation: Cardiovascular Imaging_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/4/4/408

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Cardiovascular Imaging_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Cardiovascular Imaging_ is online at:
http://circimaging.ahajournals.org//subscriptions/