

Impact of Autonomic Neuropathy on Left Ventricular Function in Normotensive Type 1 Diabetic Patients

A tissue Doppler echocardiographic study

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Cardiovascular autonomic neuropathy (CAN) is one of the most serious complications of diabetes and has been weakly linked with left ventricular (LV) diastolic dysfunction. Previous studies that explored this association either suffer from inadequate definition of CAN or have mainly used conventional Doppler or nuclear techniques to investigate LV diastolic function. Tissue Doppler imaging (TDI) has evolved as a new quantitative tool for the assessment of cardiac systolic function, diastolic function, and the hemodynamics of LV filling. We sought to investigate conventional and TDI-derived indexes of LV systolic and diastolic function in type 1 diabetic patients with and without CAN and also in normal control subjects. Our findings suggest that the presence of CAN seems to have an additive effect on LV diastolic dysfunction in type 1 diabetes.

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There is growing evidence to support the existence of diabetic cardiomyopathy as a distinct clinical entity that may lead to heart failure independent of coronary artery disease or hypertension (1). Although there is general agreement that left ventricular (LV) diastolic dysfunction may be present in diabetic patients (2,3), recent studies using tissue Doppler imaging (TDI) also support the presence of subtle systolic abnormalities in the longitudinal axis (4).

Cardiovascular autonomic neuropathy (CAN) is one of the most serious complications of diabetes and has been weakly linked with LV diastolic dysfunction (5). Many previous studies that have explored this association suffer from inadequate definitions of CAN and have used conventional Doppler or nuclear techniques to investigate LV diastolic function (6,7). TDI is a new quantitative tool for the assessment of cardiac systolic

function, diastolic function, and the hemodynamics of LV filling (8). TDI-derived diastolic velocities are less influenced by preload and do not pseudo-normalize in the same way as transmitral flow.

We sought to investigate conventional and TDI-derived indexes of LV systolic and diastolic function in type 1 diabetic patients with and without CAN and also in normal control subjects.

RESEARCH DESIGN AND METHODS

Altogether, 44 type 1 diabetic patients and 21 healthy normal volunteers comprised the study population. The study was approved by the institutional ethics committee, and all subjects gave written informed consent. All diabetic patients were asymptomatic, had normal electrocardiogram (sinus rhythm), and were normotensive (blood pressure <130/85 mmHg) without mi-

crovascular complications. They also had normal renal function, without microalbuminuria, and took no medication other than insulin. Coronary artery disease was excluded on the basis of a normal thallium-201 myocardial stress test. Other exclusion criteria were poor-quality echocardiographic imaging, valvular heart disease, and conduction or rhythm disturbances. Autonomic nervous function (ANF) was assessed according to the consensus statement of the American Diabetes Association and the American Academy of Neurology (9), taking into account various factors such as drug use, concomitant illness, and lifestyle issues (exercise, smoking, and caffeine intake). The following tests were performed as previously described (6):

- Beat-to-beat variation of R-R interval assessed by 1) expiration/inspiration index, 2) mean circular resultant vector analysis, and 3) SD of R-R intervals.
- Valsalva index.
- Variation of R-R interval during postural change (30:15 index).
- Variation of systolic blood pressure during postural change (standing).

The presence of definite CAN was established if at least two of the above-mentioned ANF tests were abnormal. The normal values we adopted were those set by Ziegler (10). Nondiabetic control subjects were healthy asymptomatic subjects with no history of cardiac disease, hypertension, or other cardiac risk factors who had normal resting and exercise 12-lead electrocardiogram.

Each subject underwent echocardiographic examination using a standard commercial ultrasound machine (Vivid 7; GE Vingmed, Horten, Norway) with a 1.7–3.4 MHz phased array transducer. The evaluation included measurements of LV ejection fraction by modified Simpson's biplane method as well as conventional Doppler parameters of diastolic function (early [E] and late [A] peak transmitral diastolic flow velocities) and pulsed

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Abbreviations: ANF, autonomic nervous function; CAN, cardiovascular autonomic neuropathy; LV, left ventricular; TDI, tissue Doppler imaging

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Table 1—Clinical and echocardiographic data in diabetic patients and control subjects

| | CAN ⁺ | CAN [−] | Control | P |
|--|------------------|------------------|-------------|--------|
| n | 18 | 24 | 21 | |
| Age (years) | 40 ± 8 | 38 ± 7 | 37 ± 10 | NS |
| Sex (M/F) | 5/13 | 8/16 | 7/14 | NS |
| Duration of diabetes (years) | 24 ± 7 | 21 ± 6 | — | NS |
| Heart rate (bpm) | 76 ± 9 | 74 ± 11 | 75 ± 9 | NS |
| Systolic blood pressure (mm/Hg) | 125 ± 10 | 122 ± 9 | 120 ± 6 | NS |
| Diastolic blood pressure (mm/Hg) | 80 ± 5 | 80 ± 6 | 82 ± 3 | NS |
| A1C (%) | 7.8 ± 0.8*† | 7.1 ± 0.9*† | 4.9 ± 0.3 | <0.001 |
| Microalbuminuria (mg/24 h): normal values (0–30) | 21 ± 6 | 17 ± 7 | — | NS |
| Creatinine plasma (mg/dl): normal values (0.5–1.4) | 1.18 ± 0.16 | 1.09 ± 0.18 | 1.06 ± 0.20 | NS |
| Ejection fraction (%) | 68.2 ± 5.6 | 69.5 ± 5.1 | 67.7 ± 5.5 | NS |
| E (m/s) | 0.78 ± 0.2 | 0.83 ± 0.1 | 0.81 ± 0.1 | NS |
| A (m/s) | 0.72 ± 0.2* | 0.67 ± 0.2* | 0.53 ± 0.1 | <0.001 |
| E/A | 1.1 ± 0.3* | 1.3 ± 0.3* | 1.5 ± 0.2 | <0.001 |
| S _m (cm/s) | 7.0 ± 1.6 | 6.9 ± 1.6 | 7.7 ± 1.2 | NS |
| E _m (cm/s) | 8.9 ± 2.5*† | 10.1 ± 2.7*† | 11.1 ± 1.9 | 0.015 |
| A _m (cm/s) | 7.7 ± 2.6*† | 6.6 ± 2.5*† | 5.4 ± 1.5 | 0.007 |
| E _m /A _m | 1.3 ± 0.7*† | 1.8 ± 0.9*† | 2.2 ± 0.8 | 0.003 |

Data are means ± SD. A, peak late mitral velocity; A_m, lateral mitral annulus velocity in late diastole; E, peak early mitral velocity; E_m, lateral mitral annulus velocity in early diastole; NS, no significant difference; S_m, lateral mitral annulus velocity in systole. *P < 0.05 for comparison with normal control subjects. †P < 0.05 for comparison between diabetic subjects with and without autonomic neuropathy.

TDI to assess longitudinal myocardial function in the lateral mitral annulus as previously described (3,11). The following TDI variables were evaluated: peak systolic velocity (S_m), peak early diastolic velocity (E_m), and peak late diastolic velocity (A_m).

Comparisons between the three groups were carried out with ANOVA, with post hoc analysis (Bonferroni). An unpaired *t* test was used to compare continuous variables (duration of diabetes, microalbuminuria) between the diabetic groups. Correlations between the number of ANF tests and continuous variables were tested by Spearman's correlation coefficient (*r_s*). All analyses were performed using SPSS 14 (SPSS, Chicago, IL). A *P* value <0.05 was considered significant.

RESULTS — A total of 18 diabetic patients had at least two abnormal ANF tests. There were no significant differences among the three groups with regard to age, sex, duration of diabetes, heart rate, and systolic and diastolic blood pressure (Table 1). Similarly, there were no significant differences in LV systolic function as measured by either two-dimensional echocardiography (ejection fraction) or TDI (S_m). Glycemic control as assessed by A1C was worse in diabetic patients with definite CAN. There were also significant differences between the three groups in measures of LV diastolic function, both conventional (mitral A ve-

locity, E/A ratio) and TDI-derived indexes (E_m, A_m, E_m/A_m ratio). From post hoc analysis, only the TDI-derived E_m/A_m ratio differed between CAN⁺ and CAN[−] diabetic patients. Again, diabetic subjects with definite CAN showed the greatest diastolic impairment. There was a significant correlation between the number of abnormal ANF tests and duration of diabetes (*r_s* = 0.44, *P* = 0.004), E/A ratio (*r_s* = −0.38, *P* = 0.014), and E_m/A_m ratio (*r_s* = −0.41, *P* = 0.007).

CONCLUSIONS — Our study demonstrates an association between the existence of CAN and LV diastolic dysfunction. The principal finding is that diabetic subjects with CAN have a greater impairment of diastolic function than subjects without CAN or nondiabetic control subjects. Importantly, the significant difference in LV diastolic performance between the two groups of diabetic subjects was identified only with TDI. On the contrary, LV systolic function in type 1 diabetic subjects seems to be unimpaired compared with normal control subjects, irrespective of the presence of CAN. Therefore, compared with other echocardiographic approaches in the evaluation of LV myocardial function in diabetic patients, TDI seems to be the preferred modality, as it is more sensitive and less dependent on confounders such as preload or respiratory variation. The pres-

ence of CAN seems to have an additive effect on the impairment in LV diastolic function in type 1 diabetes. It is tempting to speculate that since age and duration of diabetes did not differ in our diabetic groups, the further deterioration in LV diastolic function could be attributed to CAN. Nevertheless, metabolic control comes also into play, and it is difficult to exclude the poorer glycemic control in CAN⁺ diabetic patients as a possible explanation of the greater degree of LV diastolic dysfunction. In any case, strict glycemic control, careful testing for CAN, and frequent echocardiographic assessment for the presence of LV diastolic dysfunction are imperative in type 1 patients.

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