

**The Impact of Autonomic Neuropathy on Left Ventricular Function
in Normotensive Type 1 Diabetic Patients: a Tissue Doppler
Echocardiographic Study**

¹Theodoros D. Karamitsos PhD, ²Haralambos I. Karvounis MD,
³Triantafyllos Didangelos MD, ²Georgios E. Parcharidis MD,
³Dimitrios T. Karamitsos MD

¹Cardiovascular Medicine, University of Oxford, Oxford, UK; ²First Cardiology,
AHEPA University Hospital, Thessaloniki, Greece; and ³First Propedeutic, Internal Medicine,
AHEPA University Hospital, Thessaloniki, Greece

Running Title: TDI on Type 1 Diabetes with Autonomic Neuropathy

Corresponding Author:

Dr. Theodoros D. Karamitsos
Cardiovascular Medicine
University of Oxford
Oxford, UK, OX3 9DU
theo.karamitsos@cardiov.ox.ac.uk

Received for publication 19 August 2007 and accepted in revised form 7 November 2007.

ABSTRACT

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 indices of LV systolic and diastolic function in type 1 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.

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 utilizing 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 indices of LV systolic and diastolic function in type 1 patients with and without CAN, and also in normal control subjects.

RESEARCH DESIGN AND METHODS

Forty-four type 1 patients and twenty-one healthy normal volunteers comprised the study population. The study was approved by our Institutional Ethics Committee and all subjects gave written informed consent. All diabetic patients were asymptomatic, had normal ECG (sinus rhythm) and were selected to be normotensive (blood pressure < 130/85 mmHg) without microvascular 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 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) standard deviation 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 and colleagues(10). Non-diabetic controls were healthy asymptomatic subjects with no history of cardiac disease, hypertension, or other cardiac risk factors, who had normal resting and exercise 12-lead ECG.

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; conventional Doppler parameters of diastolic function [early (E) and late (A) peak transmitral diastolic flow velocities] and pulsed 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 3 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 Inc., Chicago,IL,USA). A p-value < 0.05 was considered significant.

RESULTS

Eighteen diabetic patients had at least two abnormal ANF tests. There were no significant differences amongst the three groups with regard to age, sex, duration of diabetes, heart rate, systolic and diastolic blood pressure (Table 1). Similarly, there were no significant differences in LV systolic function as measured by either 2-D echocardiography (ejection fraction) or TDI (S_m). Glycemic control as assessed by HbA1c 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 velocity, E/A ratio) and TDI derived indices (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 non-diabetic controls. 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 to normal controls, 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 presence 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.

REFERENCES

1. Boudina S, Abel ED: Diabetic cardiomyopathy revisited. *Circulation* 115:3213-3223, 2007
2. Karvounis HI, Papadopoulos CE, Zaglavara TA, Nouskas IG, Gemitzis KD, Parharidis GE, Louridas GE: Evidence of left ventricular dysfunction in asymptomatic elderly patients with non-insulin-dependent diabetes mellitus. *Angiology* 55:549-555, 2004
3. Karamitsos TD, Karvounis HI, Dalamanga EG, Papadopoulos CE, Didangelos TP, Karamitsos DT, Parharidis GE, Louridas GE: Early diastolic impairment of diabetic heart: the significance of right ventricle. *Int J Cardiol* 114:218-223, 2007
4. Fang ZY, Leano R, Marwick TH: Relationship between longitudinal and radial contractility in subclinical diabetic heart disease. *Clin Sci (Lond)* 106:53-60, 2004
5. Debono M, Cachia E: The impact of Cardiovascular Autonomic Neuropathy in diabetes: is it associated with left ventricular dysfunction? *Auton Neurosci* 132:1-7, 2007
6. Didangelos TP, Arsos GA, Karamitsos DT, Athyros VG, Karatzas ND: Left ventricular systolic and diastolic function in normotensive type 1 diabetic patients with or without autonomic neuropathy: a radionuclide ventriculography study. *Diabetes Care* 26:1955-1960, 2003
7. Taskiran M, Rasmussen V, Rasmussen B, Fritz-Hansen T, Larsson HB, Jensen GB, Hilsted J: Left ventricular dysfunction in normotensive Type 1 diabetic patients: the impact of autonomic neuropathy. *Diabet Med* 21:524-530, 2004
8. Yu CM, Sanderson JE, Marwick TH, Oh JK: Tissue Doppler imaging a new prognosticator for cardiovascular diseases. *J Am Coll Cardiol* 49:1903-1914, 2007
9. American Diabetes Association and American Academy of Neurology: Proceedings of a consensus development conference on standardized measures in diabetic neuropathy. Autonomic nervous system testing. *Diabetes Care* 15:1080-1107, 1992
10. Ziegler D: Diabetic cardiovascular autonomic neuropathy: prognosis, diagnosis and treatment. *Diabetes Metab Rev* 10:339-383, 1994
11. Karamitsos TD, Karvounis HI, Didangelos TP, Papadopoulos CE, Kachrimanidou MK, Selvanayagam JB, Parharidis GE: Aortic Elastic Properties Are Related to Left Ventricular Diastolic Function in Patients with Type 1 Diabetes Mellitus. *Cardiology* 109:99-104, 2007

TABLE 1. Clinical and echocardiographic data in diabetic patients and control subjects

	CAN(+)	CAN(-)	Controls	P value
	n= 18	n= 24	n= 21	
Age (years)	40 ± 8	38 ± 7	37 ± 10	NS
Gender (M/F)	5/13	8/16	7/14	NS
Duration of diabetes (years)	24 ± 7	21 ± 6	-	NS
Heart rate (b/min)	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
HbA1c (%)	7.8 ± 0.8*†	7.1 ± 0.9*†	4.9 ± 0.3	<0.001
Microalbuminuria (mg/24h) 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
Sm (cm/s)	7.0 ± 1.6	6.9 ± 1.6	7.7 ± 1.2	NS
Em (cm/s)	8.9 ± 2.5*†	10.1 ± 2.7*†	11.1 ± 1.9	0.015
Am (cm/s)	7.7 ± 2.6*†	6.6 ± 2.5*†	5.4 ± 1.5	0.007
Em/Am	1.3 ± 0.7*†	1.8 ± 0.9*†	2.2 ± 0.8	0.003

Data are means ± SD.

A, peak late mitral velocity; Am, lateral mitral annulus velocity in late diastole; E, peak early mitral velocity; Em, lateral mitral annulus velocity in early diastole; NS, no significant difference; Sm, lateral mitral annulus velocity in systole.

* p < 0.05 for comparison with normal controls

† p < 0.05 for comparison between diabetic subjects with and without autonomic neuropathy