Cardiac abnormalities in type 1 diabetes

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Background. **Left ventricular (LV) structural and hemodynamic consequences of type 1 diabetes mellitus are not fully understood.**

Methods. **To evaluate LV geometry, systolic and diastolic function in type 1 diabetes, Doppler echocardiograms were performed in 40 normotensive, type 1 diabetic patients without coronary heart disease or valvular lesions (22 men, 18 women, mean age 43 ± 6 years, body mass index 24.7 ± 2.8 kg/m^2) and in 40 age and sex-matched non-diabetic normotensive controls (22 men, 18 women, mean age 43 ± 5 years, body mass index 23.2 ± 2.8 kg/m^2), in a case-control design.**

Results. **Patients had higher systolic blood pressure than controls ($p < 0.03$) and comparable diastolic blood pressure and heart rate. LV dimension and mass were higher in patients than in controls (both $p < 0.0001$) whereas relative wall thickness did not differ. For comparable levels of end-systolic stress, patients exhibited a higher ejection fraction than controls ($p < 0.01$) and normal mid-wall shortening. Cardiac output was also higher ($p < 0.001$), whereas total peripheral resistance was lower in patients than in controls ($p < 0.0001$). Isovolumic relaxation time and E deceleration were prolonged in patients and peak A velocity was greater than in controls (all $p < 0.01$), whereas the difference in duration between A and pulmonary vein peak reverse flow at atrial contraction was comparable. In subgroup analyses, all reported features were independent of a) presence of target organ damage; b) duration of disease; c) levels of glycosylated hemoglobin.**

Conclusions. **In normotensive patients with type 1 diabetes: 1) there was a moderate increase in LV mass; 2) LV chamber function was supernormal and wall mechanics was normal; 3) LV active relaxation was impaired but chamber stiffness was normal.**

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Cardiovascular complications are the most common cause of morbidity and mortality in diabetic patients[1]. Alteration of myocardial substrate delivery to the mitochondria is impaired in diabetes, which may lead to the energy depleted state observed in heart failure[2].

As opposed to type 2 diabetes, in type 1 diabetes there is no evident association with hypertension and obesity[3] and cardiac changes are less clearly understood[4-6]. Modifications of right ventricular geometry and function have been reported in fetuses of type 1 diabetic mothers, suggesting a volume overload[7-9], and left ventricular (LV) geometry is altered in children and adolescents with type 1 diabetes, independently of the effect of blood pressure[10]. In adults, the association of type 1 diabetes with increased LV mass is less clear[11-13], and a number of abnormalities of LV function and diastolic filling have been reported in different combinations with LV geometric abnormalities[14-17]. The presence of a peculiar diabetic "cardiomyopathy" is frequently postulated in the medical literature[1,18,19], although never definitively proven.

The present analysis is a case-control study designed to characterize LV geometry and function in patients with long-duration type 1 diabetes.

Methods

Population. Forty normotensive patients with type 1 diabetes mellitus (22 men, 18 women, mean age 43 ± 6 years) were studied by Doppler echocardiography, 2 to 3 hours after insulin administration. Forty age (2-year matching), and sex-matched normotensive, non-diabetic individuals (22 men, 18 women, mean age 43 ± 5 years), who were part of a screening program involving the staff of the Hospital, served as controls. All participants had given informed consent prior the study.

Onset of diabetes was dated at least 10 years before (range 10-33 years). Insulin-dependence was defined as documented history of cheto-acidosis or fasting serum c-peptide < 0.2 nmol/l. All eligible patients were free from symptoms or signs of cardiovascular diseases or overt renal disease (i.e. macroproteinuria or serum creatinine > 1.3 mg/dl), and were in acceptable glycemic control (glycosylated hemoglobin 8.2 ± 1.3%).

Coronary heart disease was excluded on the basis of a negative clinical history and the absence of symptoms (Rose questionnaire on myocardial infarction and angina), a negative clinical examination (including rest 12-lead ECG), a normal LV wall motion evaluated by two-dimensional echocardiography in multiple standard projections, and a negative bicycle exercise stress test with recording of 12-lead ECG. No patient was taking medication other than insulin and none had significant mitral or aortic regurgitation.

Blood pressure was normal (< 140/90 mmHg) during repeated visits to the Hospital and all patients had a negative history of arterial hypertension. Blood pressure was also measured at the end of the echocardiographic study, in supine position, using a mercury sphygmomanometer. These values were used for analysis.

Target organ damage. Albumin excretion was measured by radioimmunoassay on spot urine collection. Microalbuminuria was defined as the ratio of urinary albumin to creatinine ≥ 30 μg/mg[20]. Retinopathy was assessed by stereoscopic fundus photographs performed and evaluated according to a standard protocol[21].

Echocardiography. Doppler echocardiographic examinations were performed on patients in partial left decubitus position. Echocardiograms were recorded on videotape using a commercially available machine equipped with a 2.5 to 3.5 MHz annular-array transducer. M-mode tracings obtained from the parasternal LV short-axis view were printed out on strip-chart paper at the velocity of 50 m/s and read by two independent observers, blinded to the knowledge of the subjects' condition, blood pressure and body size[22], by a graphic tablet interfaced with a personal computer, using a home-made acquisition program. LV chamber dimensions, septum and posterior wall thickness were measured according to the recommendations of the American Society of Echocardiography[23]. LV end-diastolic dimension was also normalized for body height. The Penn Convention[24] was used to calculate LV mass. LV eccentric or concentric geometric patterns were evaluated by computation of relative wall thickness (posterior wall thickness divided by LV end-diastolic radius)[25]. LV hypertrophy was defined as a LV mass index ≥ 51 g/m$^{2.7}$ of height, according to a prognostically validated method[26]. Indexation of LV mass for body surface area was also reported.

LV end-diastolic and end-systolic volumes were calculated from M-mode tracings, using a validated method (Z-derived method), showing a high accuracy for echocardiographic M-mode LV volume calculation even in the presence of dilated LV cavities[27]. Thereafter, stroke volume and cardiac output were calculated and peripheral resistance also generated as 80 times the ratio of mean pressure to cardiac output.

End-ejection LV chamber function was evaluated by ejection fraction as the ratio of stroke volume to end-diastolic volume. Wall mechanics was assessed by computing the shortening of LV minor axis at the midwall, taking into account the epicardial migration of midwall during systole[28]. Midwall shortening was also corrected by circumferential end-systolic wall stress (σ_c), calculated at the midwall level using a cylindrical model[28,29], as previously reported[30].

Doppler signals were recorded and measurements performed as previously reported[31,32], to obtain E and A flow velocities, E flow deceleration time, duration of A velocity and isovolumic relaxation time. Atrial filling fraction was calculated as the ratio of the velocity-time integral of A to total diastolic flow.

Pulmonary venous flow velocities were recorded from the apical 4-chamber view, by pulsed-wave Doppler interrogation of the right upper pulmonary vein, using a 3 to 5 mm sample volume placed 1 to 2 cm into the vein lumen, as previously recommended[33,34], in order to record a clear laminar flow pattern[35]. Measures of the peak systolic and diastolic forward flow velocities and relative velocity-time integrals, as well as peak velocity and velocity-time integral of reverse flow at atrial contraction were obtained. The duration of pulmonary vein reverse flow at atrial contraction was measured and the difference from the duration of transmitral A velocity was used as a raw estimate of passive filling pressure.

Statistical analysis. All data were expressed as mean ± 1 SD. One-factor analysis of variance was used to compare measures of LV geometry, systolic function, relaxation and filling between diabetic and normal individuals. Analysis of covariance was used to adjust for confounders. In order to evaluate the potential effect of the presence of organ damage, duration of diabetes or levels of glycosylated hemoglobin, appropriate subgroup analyses were also carried out using one-factor ANOVA and the Ryan-Einot-Gabriel-Welsch step-down post-hoc F test. For this purpose, the presence or absence of organ damage was evaluated by microalbuminuria and/or funduscopic abnormalities, duration of diabetes was divided according to the median values of the distribution in the present study population (14.5 years), and glycosylated hemoglobin was considered abnormal when > 7.5%[36]. Least squares linear regression was used for univariate comparisons.

The null hypothesis was rejected at a two-tailed $p \leq 0.05$.

Results

Six diabetic patients (15%) exhibited microalbuminuria and 16 (40%) had funduscopic abnormalities (8 with background and 8 with proliferative retinopathy).

Table I shows that age, diastolic blood pressure and heart rate were identical in patients and controls. Although hypertensive patients were excluded from the study, systolic blood pressure was higher in diabetic patients ($p < 0.0001$) and so was body mass index ($p < 0.03$). As a consequence of the increased isolated systolic pressure, also pulse pressure was higher in patients than in controls ($p < 0.001$). Due to the differences in blood pressure and body mass index, the following comparisons were controlled for these potential confounders. No differences were observed in relation to either the duration of the disease or the presence of target organ damage.

Left ventricular geometry (Table II). After adjusting for body mass index and systolic blood pressure, LV end-diastolic dimension was significantly greater in patients than in controls, yielding a parallel, remarkable average 14 g/m$^{2.7}$ difference in LV mass (all $p < 0.001$). LV wall thickness increased in proportion to the increase in LV chamber dimension, maintaining the relative wall thickness within the normal range. These geometric characteristics were confirmed when analyzing only the 15 patients with normal fundus and without microalbuminuria (LV mass dimension 3.31 ± 0.33 cm/m; LV mass index 44.69 ± 9.78 g/m$^{2.7}$; relative wall thickness 0.33 ± 0.06). No differences were observed in relation to either the duration of the disease or the levels of glycosylated hemoglobin. In a model of multiple linear regression analysis including age, body mass index, systolic blood pressure, presence or absence of diabetes, duration of the disease and levels of glycosylated hemoglobin, LV mass was independently associated only with diabetes ($\beta = 0.46$, $p < 0.0001$) and high body mass index ($\beta = 0.31$, $p < 0.001$; multiple $R = 0.63$, SEE 36 g, $p < 0.0001$), and not with age, systolic blood pressure, duration of diabetes and glycosylated hemoglobin.

Clear-cut LV hypertrophy was present in 12 of 40 diabetic patients (30%) as opposed to none of the normotensive controls.

Left ventricular end-ejection performance and pump function (Table III). LV ejection fraction, as a measure of LV chamber function, was significantly higher in patients than in normal controls ($p < 0.009$), whereas midwall shortening was similar. There was an inverse relation between midwall shortening and end-systolic stress both in controls ($p < 0.0001$) and, less closely, in patients with diabetes (Fig. 1), who had similar stress-corrected values. Stroke volume and cardiac output were markedly higher in patients than in controls, either as a raw value or normalized for body surface area (all $p < 0.0001$). Although mean blood pressure was normal, peripheral resistance was significantly lower in patients than in normal controls ($p < 0.0001$). All the above differences were confirmed when analyzing only the 15 patients with normal fundus and without microalbuminuria (all $p < 0.001$). Stratification for glycosylated hemoglobin did not reveal any difference between the groups of patients.

Left ventricular active relaxation (Table IV). Isovolumic relaxation time and E deceleration time were prolonged in patients compared to controls (both $p < 0.001$) even after controlling for body mass index and systolic blood pressure. While peak E velocity was similar, the E velocity-time integral was greater in patients than in controls ($p < 0.0001$). Since relaxation depends on loading conditions, comparison between patients and controls was also carried out controlling for end-diastolic volume (a measure of load imposed at end-diastole), systolic blood pressure (a measure of load imposed during contraction) and end-systolic stress (a measure of load

Table I. General characteristics of type 1 diabetic patients and controls.

	Diabetics	Controls
Age (years)	43 ± 6	43 ± 5
Body mass index (kg/m^2)	24.7 ± 2.8*	23.2 ± 2.8
Systolic blood pressure (mmHg)	123 ± 13*	117 ± 10
Diastolic blood pressure (mmHg)	74 ± 7	74 ± 7
Mean blood pressure (mmHg)	90 ± 8	88 ± 7
Pulse pressure (mmHg)	49 ± 10*	43 ± 9
Heart rate (b/min)	71 ± 9	71 ± 11

Data are expressed as mean ± SD. * $0.03 < p < 0.001$.

Table II. Left ventricular (LV) geometry in type 1 diabetic patients and controls.

	Diabetics	Controls
LV end-diastolic dimension (cm)	5.37 ± 0.49*	4.80 ± 0.37
LV dimension index (cm/m)	3.27 ± 0.29*	2.89 ± 0.22
LV mass (g)	166.01 ± 45.93*	117.9 ± 29.79
LV mass index (g/m^2)	95.94 ± 26.95*	68.51 ± 14.89
LV mass index (g/m$^{2.7}$)	43.69 ± 14.89*	29.79 ± 6.73
Posterior wall thickness (cm)	0.87 ± 0.12*	0.76 ± 0.11
Septal thickness (cm)	0.96 ± 0.14*	0.83 ± 0.12
Relative wall thickness	0.32 ± 0.05	0.32 ± 0.05

Data are expressed as mean ± SD. * $0.03 < p < 0.0001$.

Table III. Left ventricular (LV) systolic function and systemic hemodynamics in type 1 diabetic patients and controls.

	Diabetics	Controls
Ejection fraction (%)	67.22 ± 6.02*	63.91 ± 4.96
Midwall shortening (%)	18.93 ± 2.86	18.07 ± 2.67
Stress-corrected midwall shortening (%)	101.77 ± 14.68	97.89 ± 13.74
Stroke volume (ml)	87.31 ± 16.14*	66.78 ± 11.12
Stroke index (ml/m^2)	50.78 ± 11.14*	39.15 ± 7.12
Cardiac output (l/min)	6.25 ± 1.32*	4.71 ± 0.89
Cardiac index (l/m^2)	3.63 ± 0.8600*	2.77 ± 0.57
Heart rate	71.63 ± 8.98	71.15 ± 10.97
Peripheral resistance (dynes•s•cm^{-5})	1209.58 ± 297.26*	1561.66 ± 374.45
Peripheral resistance index (dynes•s•cm^{-5}•m^2)	2113.17 ± 620.45*	2686.23 ± 718.51

Data are expressed as mean ± SD. * 0.03 < p < 0.0001.

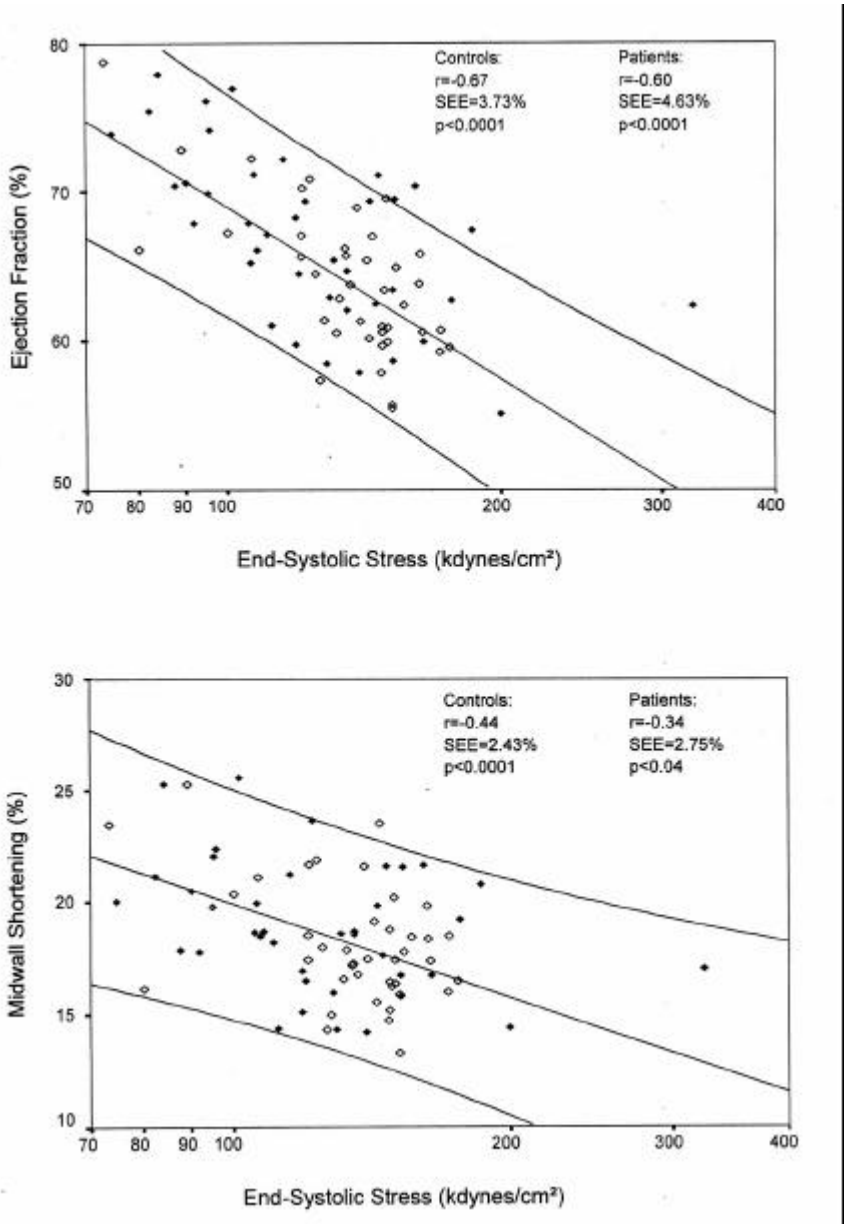

Figure 1. *Relation of midwall shortening (y axis) to circumferential end-systolic stress (x axis) in patients with type 1 diabetes (closed squares) and non-diabetic controls (open squares). Continuous lines are the regression line and 95% confidence interval of dependent variables.*

Table IV. Left ventricular active relaxation and early filling in type 1 diabetic patients and controls.

	Diabetics	Controls
Isovolumic relaxation time (ms)	99.50 ± 20.13*	67.99 ± 12.56
Time of deceleration of E flow velocity (ms)	180.57 ± 41.76*	143.66 ± 24.22
Peak E flow velocity (cm/s)	67.37 ± 12.27	64.66 ± 11.76
Integral of E flow velocity (cm)	9.07 ± 2.56*	7.91 ± 1.94

Data are expressed as mean ± SD. * $0.03 < p < 0.0001$.

imposed at beginning of relaxation). The differences in isovolumic relaxation time and E deceleration were only slightly attenuated by the above hemodynamic control (adjusted means: 70 ms and 142 ms in controls; 98 ms and 183 ms in patients, respectively; both $p < 0.0001$). The same abnormalities (both prolonged isovolumic relaxation time and E deceleration) were also confirmed when analyzing only the 15 patients with normal fundus and without microalbuminuria (both $p < 0.001$). No effect was detected when analyzing subgroups clustered on the basis of glycosylated hemoglobin.

Left ventricular passive filling (Table V). A velocity was higher in diabetic patients than in controls ($p < 0.002$), with a consequent reduction of the E/A ratio ($p < 0.01$), but without any appreciable difference in A velocity-time integral and atrial filling fraction. This increased peak velocity at atrial contraction paralleled the increased left atrial dimension (3.57 ± 0.50 vs 3.21 ± 0.46 cm in controls, $p < 0.001$).

No significant differences were found in the pulmonary velocity pattern, during systolic, diastolic and reverse flow phases. The difference from the duration of transmitral A velocity was also similar in patients with diabetes and in controls. Subgroup classification for target organ damage, glycosylated hemoglobin or duration of diabetes, did not modify this result.

Discussion

Results of this study indicate that in type 1 diabetes changes in LV geometry and function occur in the absence of concomitant arterial hypertension and coronary heart disease. These changes were also independent of the mild increase in body mass index. The exclusion of clinically overt coronary heart disease and hypertension, as well as consideration by design or analysis of other potential confounders (including age, sex, body mass index), allowed us to infer that deviations from normal found in this case-control study are mostly related to the presence of type 1 diabetes. Duration of the disease, concomitant target organ damage and levels of glycosylated hemoglobin did not substantially influence the cardiac effects directly attributable to diabetes. The young age, the good glycemic control and the intensive insulin treatment of our diabetic patients could account for the relative low prevalence of target organ damage (i.e. microalbuminuria or proliferative retinopathy) in this study population.

The LV pattern emerging in our type 1 diabetic patients is characterized by mild LV enlargement with a hypertension-independent 30% prevalence of volume-dependent LV eccentric hypertrophy, associated with supranormal LV chamber function, normal wall mechanics, impaired LV active relaxation but normal LV chamber filling properties. The information of a high cardiac output state is a major characteristic of these patients, and has never been reported with the evidence displayed in our study.

The LV enlargement found in our patients is consistent with findings in fetuses and children of diabetic mothers[8-10], suggesting some degree of volume overload. This possibility is indeed also supported by the evidence of higher stroke volume and cardiac output in oth-

Table V. Left ventricular passive filling in type 1 diabetic patients and controls.

	Diabetics	Controls
Peak A flow velocity (cm/s)	60.82 ± 11.27*	51.02 ± 11.08
E/A velocity ratio	1.14 ± 0.27*	1.31 ± 0.30
Atrial filling fraction	0.33 ± 0.08	0.31 ± 0.07
PV systolic peak velocity (cm/s)	44.54 ± 9.04	46.63 ± 6.67
PV diastolic peak velocity (cm/s)	41.94 ± 11.94	43.50 ± 12.97
PV reverse peak velocity (cm/s)	-17.91 ± 3.94	-20.81 ± 3.71
Duration of PV reverse flow (ms)	111.92 ± 23.75	111.18 ± 23.56
Difference between PV reverse flow and transmitral A (ms)	-18.38 ± 36.44	-13.24 ± 29.31

Data are expressed as mean ± SD. PV = pulmonary vein. * $0.03 < p < 0.0001$.

er diabetic patients. In a previous study of 107 young type 1 diabetic patients, a similar LV enlargement was reported[37], but other authors have documented a concentric LV geometry[13], or absence of any LV geometric abnormality in the absence of microvascular complications[38]. In a cross-sectional analysis, Lo et al.[11] reported no geometric abnormalities in 40 young type 1 diabetic patients as compared with their non-diabetic monozygotic twins, but did report abnormalities in LV diastolic pattern similar to those described in our patients. A number of differences among studies may account for these apparent discrepancies, including control for confounders, age of participants and duration of exposure, presence of matched control groups, methods for assessing LV geometry but excluding concomitant coronary heart disease. Notably, age of participants and duration of exposure might be particularly important for detectable LV geometric changes to take place, as suggested by the Lo study[11]. A volume overload might be induced in type 1 diabetes by exogenous insulin administration because of its documented acute effect on both peripheral resistance[39] and sodium retention[40]. The possible role of exogenous insulin in determining the reported LV geometric remodeling also makes type 1 diabetes very different from non-insulin-dependent diabetes, mainly characterized by insulin-resistance and associated with predominant LV concentric geometry[5,41]. Analyses of relations between cardiac abnormalities and average insulin doses over a prolonged time in which metabolic control is achieved could help in defining the role of exogenous insulin, in appropriately prospective studies.

The evidence of enlarged left ventricle in our study also parallels the increased LV pump function and the supranormal LV chamber performance, indicating that a recruitment of Starling forces, in the presence of normal myocardial contractility (as indicated by analysis of stress-adjusted wall mechanics) might be operating in these patients also in rest conditions.

Finally, in the absence of systolic dysfunction at rest, or even in the presence of supranormal LV chamber dynamics, active relaxation was confirmed abnormal in these patients, consistent with a number of previous findings[17,18,42]. However, no changes were detected in the duration of pulmonary reverse flow in relation to the duration of forward transmitral flow at atrial contraction, suggesting that the passive properties of the LV chamber might be still preserved. The peculiarity of this finding, i.e. matching a normal (or even supranormal) systolic function with abnormal LV relaxation, suggests that diastolic dysfunction may precede and be independent of the progression toward systolic pump dysfunction, a possibility recently demonstrated also in arterial hypertension[43]. This observation is also made more striking by the evidence that impairment of LV relaxation can be detected independently of both hemodynamic or demographic confounders.

The association of LV eccentric hypertrophy with supranormal LV chamber function and impaired LV relaxation does not appear to be distinctive of type 1 diabetes, having been also described in obesity and hypertension[31,32,43]. Similar to obesity, because relaxation is an active, energy-consuming process, a metabolically-dependent alteration of myocyte inactivation may be proposed as the underlying mechanism of this dysfunction[44,45].

This study demonstrates that, in type 1 diabetes, the first functional abnormality concerns diastole, and even marked abnormalities of active relaxation can be detected in the presence of preserved or even exaggerated systolic performance.

In conclusion, type 1 diabetes in the absence of arterial hypertension and coronary heart disease is associated with eccentric LV hypertrophy, normal or even supranormal pump function and impaired LV active relaxation with possible normal chamber stiffness, that are independent of body mass index and loading conditions. These features are consistent with a mild volume overload with consequent recruitment of Starling forces in the presence of normal myocardial function and abnormal cardiomyocyte inactivation.

References

1. Mahgoub MA, Abd-Elfattah AS. Diabetes mellitus and cardiac function. Mol Cell Biochem 1998; 180: 59-64.
2. Seymour AM, Chatham JC. The effects of hypertrophy and diabetes on cardiac pyruvate dehydrogenase activity. J Mol Cell Cardiol 1997; 29: 2771-8.
3. Resnick LM. Ionic basis of hypertension, insulin resistance, vascular disease, and related disorders. The mechanism of "syndrome X". Am J Hypertens 1993; 6 (Suppl 2): 123S-134S.
4. Nielsen FS, Ali S, Rossing P, et al. Left ventricular hypertrophy in non-insulin-dependent diabetic patients with and without diabetic nephropathy. Diabet Med 1997; 14: 538-46.
5. Devereux RB, Roman MJ, de Simone G, et al, for the Strong Heart Study Investigators. Relations of left ventricular mass to demographic and hemodynamic variables in American Indians: The Strong Heart Study. Circulation 1997; 96: 1416-23.
6. Celentano A, Vaccaro O, Tammaro P, et al. Early abnormalities of cardiac function in non-insulin-dependent diabetes mellitus and impaired glucose tolerance. Am J Cardiol 1995; 76: 1173-6.
7. Gandhi JA, Zhang XY, Maidman JE. Fetal cardiac hypertrophy and cardiac function in diabetic pregnancies. Am J Obstet Gynecol 1995; 173: 1132-6.
8. Rizzo G, Arduini D, Romanini C. Accelerated cardiac growth and abnormal cardiac flow in fetuses of type I diabetic mothers. Obstet Gynecol 1992; 80: 369-76.
9. Weber HS, Copel JA, Reece EA, Green J, Kleinman CS. Cardiac growth in fetuses of diabetic mothers with good metabolic control. J Pediatr 1991; 118: 103-7.
10. Theochari MA, Vyssoulis GP, Giannakopoulou AE, Paleologos AA, Bartsocas CS, Toutouzas PK. Myocardial trophic effects of blood pressure in children with insulin-dependent diabetes mellitus. J Hum Hypertens 1995; 9: 633-6.
11. Lo SS, Leslie RD, Sutton MS. Effects of type 1 diabetes mellitus on cardiac function: a study of monozygotic twins. Br Heart J 1995; 73: 450-5.

12. Schmidt A, Grossmann G, Hauner H, et al. Left ventricular function and wall thickness in long-term insulin dependent diabetes mellitus: an echocardiographic study. J Intern Med 1991; 229: 527-31.
13. Semplicini A, Lusiani L, Marzola M, et al. Erythrocyte Li^+/Na^+ and Na^+/H^+ exchange, cardiac anatomy and function in insulin-dependent diabetics. Eur J Clin Invest 1992; 22: 254-9.
14. Cerutti F, Vigo A, Sacchetti C, et al. Evaluation of left ventricular diastolic function in insulin dependent diabetic children by M-mode and Doppler echocardiography. Panminerva Med 1994; 36: 109-14.
15. Kelbaek H, Jensen T, Feldt-Rasmussen B, et al. Impaired left ventricular function in insulin dependent diabetic patients with increased urinary albumin excretion. Scand Clin Lab Invest 1991; 51: 467-73.
16. Illan F, Valdes-Chavarri M, Tebar J, et al. Anatomical and functional cardiac abnormalities in type I diabetes. Clin Investig 1992; 70: 403-10.
17. Hausdorf G, Rieger U, Koepp P. Cardiomyopathy in childhood diabetes mellitus: incidence, time of onset, and relation to metabolic control. Int J Cardiol 1988; 19: 225-36.
18. Fein FS, Sonnenblick EH. Diabetic cardiomyopathy. Cardiovasc Drugs Ther 1994; 8: 65-73.
19. Galderisi M, Anderson KM, Wilson PWF, Levy D. Echocardiographic evidence for the existence of a distinct diabetic cardiomyopathy (the Framingham Heart Study). Am J Cardiol 1991; 68: 85-9.
20. American Diabetes Association. Diabetic nephropathy. Position Statement. Diabetes Care 1997; 20 (Suppl 1): S24-S27.
21. Aiello LP, Gardner TW, King GL, et al. Diabetic retinopathy. Diabetes Care 1998; 43: 143-56.
22. de Simone G, Mureddu GF, Greco R, et al. Relations of left ventricular geometry and function to body composition in children with high casual blood pressure. Hypertension 1997; 30: 377-82.
23. Sahn DH, DeMaria A, Kisslo J, Weyman A. The Committee on M-Mode Standardization of the American Society of Echocardiography: recommendations regarding quantitation in M-mode echocardiography. Results of a survey of echocardiographic measurements. Circulation 1978; 58: 1072-83.
24. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man: anatomic validation of the method. Circulation 1977; 56: 613-8.
25. Ganau A, Devereux RB, Roman MJ, et al. Patterns of left ventricular hypertrophy and geometric remodeling in arterial hypertension. J Am Coll Cardiol 1992; 19: 1550-8.
26. de Simone G, Devereux RB, Daniels SR, Koren MJ, Alderman MH, Laragh JH. Effect of growth on variability of left ventricular mass: assessment of allometric signals in adults and children and of their capacity to predict cardiovascular risk. J Am Coll Cardiol 1995; 25: 1056-62.
27. de Simone G, Devereux RB, Ganau A, et al. Estimation of left ventricular chamber and stroke volume by limited M-mode echocardiography: validation by two-dimensional and Doppler-echocardiography. Am J Cardiol 1996; 78: 801-7.
28. de Simone G, Devereux RB, Roman MJ, et al. Assessment of left ventricular function by midwall fractional shortening-end-systolic stress relation in human hypertension. J Am Coll Cardiol 1994; 23: 1444-51.
29. Gaasch WH, Zile MR, Hosino PK, Apstein CS, Blaustein AS. Stress-shortening relations and myocardial blood flow in compensated and failing canine hearts with pressure-overload hypertrophy. Circulation 1989; 79: 872-3.
30. de Simone G, Devereux RB, Mureddu GF, et al. Influence of obesity on left ventricular midwall mechanics in arterial hypertension. Hypertension 1966; 28: 276-83.
31. Mureddu GF, de Simone G, Greco R, Rosato GF, Contaldo F. Left ventricular filling pattern in uncomplicated obesity. Am J Cardiol 1996; 77: 509-14.
32. Mureddu GF, de Simone G, Greco R, Rosato GF, Contaldo F. Left ventricular filling in arterial hypertension: influence of obesity, hemodynamic and structural confounders. Hypertension 1997; 29: 544-50.
33. Rossvoll O, Hatle LK. Pulmonary venous flow velocities recorded by transthoracic Doppler ultrasound: relation to left ventricular diastolic pressures. J Am Coll Cardiol 1993; 21: 1687-96.
34. Appleton CP, Galloway JM, Gonzales MS, Gaballa M, Basnight MA. Estimation of left ventricular filling pressures using two dimensional and Doppler echocardiography in adult patients with cardiac disease (additional value of analyzing left atrial size, left atrial ejection fraction and the difference in duration of pulmonary venous and mitral flow velocity at atrial contraction. J Am Coll Cardiol 1993; 22: 1972-82.
35. Mureddu GF, Celentano A, Pasanisi F, et al. Pulmonary venous flow and mitral inflow velocity pattern in uncomplicated obesity: evidence for late diastolic dysfunction. Ital Heart J 2000; 1: 194-9.
36. The Diabetes Control and Complications Trial Study Group. The effect of intensive treatment of diabetes in the development and progression of long-term complications in insulin dependent diabetes mellitus. N Engl J Med 1993; 329: 304-7.
37. Lababidi ZA, Goldstein DE. High prevalence of echocardiographic abnormalities in diabetic youths. Diabetes Care 1983; 6: 18-22.
38. Fisher BM, Cleland JG, Dargie HJ, Frier BM. Non-invasive evaluation of cardiac function in young patients with type 1 diabetes. Diabet Med 1989; 6: 677-81.
39. Zemel MB. Insulin resistance vs hyperinsulinemia in hypertension: insulin regulation of Ca^{2+} transport and $Ca^{(2+)}$-regulation of insulin sensitivity. J Nutr 1995; 125: 1738S-1743S.
40. Quinones-Galvan A, Ferrannini E. Renal effects of insulin in man. J Nephrol 1997; 10: 188-91.
41. Lind L, Andersson PE, Andren B, Hänni A, Lithell HO. Left ventricular hypertrophy in hypertension is associated with the insulin resistance metabolic syndrome. J Hypertens 1995; 13: 433-8.
42. Zarich SW, Arbuckle BE, Cohen LR, Roberts M, Nesto RW. Diastolic abnormalities in young asymptomatic diabetic patients assessed by pulsed Doppler echocardiography. J Am Coll Cardiol 1988; 12: 114-2.
43. de Simone G, Greco R, Mureddu GF, et al. Relation of left ventricular diastolic properties to systolic function in arterial hypertension. Circulation 2000; 101: 152-7.
44. Brutsaert DL, Rademakers FE, Sys SU. Triple control of relaxation: implications in cardiac disease. Circulation 1984; 69: 190-8.
45. Mureddu GF, Greco R, Rosato GF, et al. Relation of insulin resistance to left ventricular hypertrophy and diastolic dysfunction in obesity. Int J Obes 1998; 22: 363-8.