Cardiovascular Status in Young Patients With Insulin-Dependent Diabetes Mellitus

Thomas R. Kimball, MD; Stephen R. Daniels, MD, PhD; Philip R. Khoury, MS; Ralph A. Magnotti, PhD; Angela M. Turner, RN; Lawrence M. Dolan, MD

Background Although the existence of diabetic cardiomyopathy in adults is firmly established, the presence of cardiac abnormalities in young diabetic patients is not universally accepted. We sought to determine the early stages of cardiac derangement and whether they are associated with renal dysfunction.

Methods and Results Thirty-nine patients (29 boys; mean age, 17.6±3.4 years) with insulin-dependent diabetes mellitus underwent echocardiography and timed overnight urine collection. Echocardiographic evaluation consisted of left ventricular mass, performance (shortening fraction, velocity of circumferential fiber shortening, stroke volume, and cardiac index), preload (end-diastolic dimension and volume), afterload (end-systolic wall stress and systemic vascular resistance), and contractility (velocity of fiber shortening relative to wall stress). Creatinine clearance and albumin excretion were measured from the urine sample. Glycosylated hemoglobin levels were measured; height and weight were measured; and Quetelet index (weight/height²) was calculated. These data were compared with control data. Left ventricular mass (26±6 versus 22±6 g/m², P<0.01), the indexes of performance, blood pressure, and contractility (0.14±0.14 versus 0.003±0.03 circumference/s, P<0.003) were significantly higher in the diabetic patients than in control subjects. To evaluate the correlates of left ventricular mass and contractility in the diabetic patients, univariate and multiple regression analyses were performed. Significant univariate correlations of mass included albumin excretion (r=.36, P<.02), glycosylated hemoglobin (r=.35, P<.04), and stroke volume (r=.34, P<.03). A multivariate model included Quetelet index, albumin excretion, and duration of diabetes. Significant univariate correlations of contractility included insulin dosage (r=-.36, P<.02), creatinine clearance (r=.40, P<.02), and Quetelet index (r=.34, P<.03). A multivariate model included insulin dosage and creatinine clearance.

Conclusions Early onset of diabetes mellitus is associated with increased left ventricular mass, performance, contractility, and blood pressure. These cardiovascular findings are correlated with increased creatinine clearance and microalbuminuria. These relations suggest that alterations in cardiovascular and renal function may occur in parallel in adolescents with insulin-dependent diabetes mellitus. (Circulation. 1994;90:357-361.)

Key Words • diabetes • creatinine • microalbuminuria • kidneys • contractility

The existence of a diabetic cardiomyopathy, independent of atherosclerotic and hypertensive heart disease, has been firmly established in the adult population.1-4 The presence of cardiac abnormalities in younger patients with insulin-dependent diabetes mellitus (IDDM) is controversial.5-10 Most investigators have found that cardiac function is normal at rest in young patients with diabetes mellitus. Unfortunately, these studies have measured ejection-phase indexes in the assessment of ventricular performance that are dependent not only on myocardial contractility but also on loading conditions. Therefore, the specific level of cardiac contractility has not been determined in this patient population.

Longitudinal studies of renal function in patients with IDDM have demonstrated that in the early stages of disease there is increased glomerular filtration. Over time, this progresses to diminished renal function and end-stage diabetic nephropathy.11,12 We hypothesized that a parallel sequence of events may occur in the heart of patients with IDDM, ie, initially increased cardiac contractility that progresses over time to a chronic cardiomyopathy.

The purposes of this study were to compare left ventricular mass, systolic performance, contractility, preload, and afterload in young patients with IDDM with those of healthy subjects, to evaluate the correlates of left ventricular mass and contractility in young patients with IDDM, and to evaluate possible associations between ventricular performance and renal function.

Methods

Study Population

The study population consisted of 39 patients with IDDM (29 boys and 10 girls; mean±1 SD age, 17.6±3.4 years) and 40 healthy individuals (29 boys and 11 girls; age, 17.7±3.4 years) of comparable age and sex. IDDM was defined as requiring daily insulin administration to prevent the metabolic cascade of diabetic ketoacidosis. The range of duration of IDDM was 3.5 to 23 years (mean, 9±5 years). The patients with IDDM represented the spectrum of albumin excretion without evidence of clinical nephropathy (mean albumin excretion, <200 µg/min in three timed overnight urine collections) at the time of the study.11,12 One of the patients with IDDM was hypothyroid and taking ethyroxine sodium, and another was taking oral contraceptives. No participant was taking antihypertensive medications, including angiotensin-converting enzyme inhibitors, at the time of the study. The control subjects were

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healthy volunteers who were recruited primarily from families of employees of Children’s Hospital Medical Center.

Protocol

After giving written informed consent according to the guidelines established by the Institutional Review Board at Children’s Hospital Medical Center, the participants underwent a medical history and physical examination. All subjects had an echocardiogram performed. Resting blood pressure was obtained with subjects in a sitting position. Blood pressure was measured by individuals trained in the method of blood pressure measurement as defined by the second National Heart, Lung, and Blood Institute Task Force. All of the IDDM patients and 18 of the control subjects provided three timed overnight urine collections for creatinine and albumin excretion with a minimum of 7 days between each collection. The patients with IDDM also had a blood sample obtained for serum creatinine and hemoglobin A1 determinations. None of the participants had clinical or echocardiographic evidence of coronary artery disease or structural heart disease.

Echocardiographic Examination

Each patient and control subject underwent echocardiography, phonocardiography, ECG, and indirect carotid pulse-tracing examination using a Hewlett Packard ultrasound imaging system (model 77020A or 77030A).

Left ventricular end-diastolic and end-systolic dimensions and thicknesses and end-diastolic septal thickness were measured and indexed to account for differences in body size by dividing by body surface area raised to the 0.5 power. End diastole was defined by the Q wave, and end systole was defined by the first component of the second heart sound. Left ventricular mass was calculated and indexed by dividing by the patient’s height raised to the power of 2.7. Left ventricular end-diastolic and end-systolic volumes were calculated and indexed by dividing by body surface area raised to the 1.5 power.

Shortening fraction, heart rate–corrected velocity of circumferential fiber shortening, stroke volume, cardiac output, and cardiac index were calculated. Mean blood pressure and indexed systolic and diastolic blood pressures were recorded. Systemic vascular resistance was calculated. Because systemic vascular resistance may be a less reliable index of afterload, end-systolic meridonal wall stress was also calculated.

Contractility was assessed by determining the relation between heart rate–corrected velocity of circumferential fiber shortening and end-systolic wall stress. Specifically, the difference between measured and predicted velocity of circumferential fiber shortening for the measured wall stress served as a quantitative index. Velocity of circumferential fiber shortening was plotted against wall stress for each patient and then compared with the normal velocity of circumferential fiber shortening, wall stress relation to determine how many patient data pairs (velocity of circumferential fiber shortening, wall stress) were outside the 95th percentile confidence limits. The frequency of elevated contractility was then compared between patients with diabetes and control subjects.

Laboratory Procedures

Serum and urine creatinine concentrations were measured using the picric acid method. The interassay and intra-assay coefficients of variation are <2% for each assay. To ensure that the timed urine collection was accurate, the creatinine value reported by the laboratory (mg/min) was extrapolated to milligrams per 24 hours. Adequate urine collections have a creatinine concentration of 10 to 30 mg/kg per 24 hours. Urine collections with values outside of this range were excluded, and the subject provided another sample.

Urinary albumin concentration was measured using an ELISA technique described previously. All subjects also had a negative urine culture to rule out an occult urinary tract infection that might interfere with the albumin assay.

Glycosylated hemoglobin concentration was measured using the Glycoscreen assay kit (Curtin Matheson Sci). The interassay and intra-assay coefficients of variation are each <2.4%.

Statistical Analysis

Body surface area and Quetelet index were calculated using the following equations:

Body Surface Area = 71.84 (wt0.425) (ht0.725)/10 000

Quetelet Index = wt/ht2

Because blood pressure varies with sex and age during childhood and adolescence, both systolic and diastolic blood pressures were indexed by dividing by the age and sex-appropriate 90th percentile blood pressure value.

Creatinine clearance was determined from the serum and urine creatinine concentration and adjusted to 1.73 m2. The mean albumin excretion rate of the three timed overnight urine collections was used in the analysis. Microalbuminuria was defined as ≥13 μg/min by calculating the 95% confidence limit for albumin excretion obtained from timed overnight urine collections (as described above) in 98 healthy subjects of the same age as the study population (unpublished results). The frequency of microalbuminuria was compared between the diabetic patients and control subjects.

Values are presented as mean±SD. Variables were tested for normality, and appropriate variance-stabilizing transformations were used. Unpaired Student’s t tests were performed to compare continuous variables between the diabetic patients and control subjects. χ2 analysis was used to compare categorical variables between groups.

The univariate associations between relevant independent variables and left ventricular mass index and velocity of circumferential fiber shortening difference were assessed in the diabetic patients using Spearman rank-order correlation. Stepwise multiple regression techniques and analysis of covariance were used to evaluate the independent effect of the relevant variables in explaining the variance of left ventricular mass index and velocity of circumferential fiber shortening difference. Variables that have been previously shown to have a relation with the dependent variable or had a significant univariate relation were first allowed into the model. The best regression model was determined from the significance of regression coefficients and the ability of the model to explain the variance of the dependent variable to the model. A potential independent variable was considered to have an independent and important contribution if the regression coefficient for that variable was significantly different from zero and the addition of the variable to the multiple regression model increased the multiple R2 by >10% compared with the regression model without that variable. Statistical significance was set at a P value of <.05. Statistical tests with a P value <.10 and >.05 were considered to be of borderline significance.

Results

Patient Characteristics

The average height and body surface area in the patients with IDDM were 170±13 cm and 1.8±.2 m2, respectively, and not significantly different from those of the control subjects. The average weight and Quetelet index in the patients with IDDM were 68±12 kg and 2.4±.5 kg/m2, respectively. These values were both significantly higher than those for the control subjects (60±13 kg and 2.0±.3 kg/m2, P<.01). The average insulin dosage for the diabetic patients was 0.9±0.2
TABLE 1. Hemodynamic Data for Diabetic Patients and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Diabetic Patients (n=39)</th>
<th>Control Subjects (n=40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indexed left ventricular mass, g/ht^{2.7}</td>
<td>26±6</td>
<td>22±6</td>
<td>≤.01</td>
</tr>
<tr>
<td><strong>Left ventricular performance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>75±19</td>
<td>64±19</td>
<td>≤.01</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>5.4±1.5</td>
<td>4.1±1.1</td>
<td>≤.001</td>
</tr>
<tr>
<td>Cardiac index, L/min per m^2</td>
<td>3.0±0.8</td>
<td>2.4±0.7</td>
<td>≤.006</td>
</tr>
<tr>
<td>Shortening fraction</td>
<td>0.36±0.05</td>
<td>0.32±0.06</td>
<td>≤.004</td>
</tr>
<tr>
<td>VCF, circumference per second</td>
<td>1.16±0.16</td>
<td>1.03±0.18</td>
<td>≤.001</td>
</tr>
<tr>
<td><strong>Left ventricular preload</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indexed diastolic dimension, cm/BSA^{0.5}</td>
<td>3.6±0.3</td>
<td>3.5±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Indexed diastolic volume, cm^3/BSA^{1.5}</td>
<td>88±15</td>
<td>83±17</td>
<td>NS</td>
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<tr>
<td><strong>Left ventricular afterload</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-systolic wall stress, g/cm^2</td>
<td>60±13</td>
<td>58±23</td>
<td>NS</td>
</tr>
<tr>
<td>Systemic vascular resistance, dyne·s·m^{-2}·cm^{-5}</td>
<td>1328±321</td>
<td>1626±563</td>
<td>≤.005</td>
</tr>
<tr>
<td>Indexed systolic blood pressure</td>
<td>0.93±0.06</td>
<td>0.87±0.07</td>
<td>≤.001</td>
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<tr>
<td>Indexed diastolic blood pressure</td>
<td>0.78±0.08</td>
<td>0.73±0.1</td>
<td>≤.03</td>
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<tr>
<td><strong>Left ventricular contractility</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VCF difference, circumference per second</td>
<td>0.14±0.14</td>
<td>0.003±0.03</td>
<td>≤.0003</td>
</tr>
</tbody>
</table>

VCF indicates velocity of circumferential fiber shortening; BSA, body surface area. Data are expressed as mean±SD.

U/kg per day. The mean glycosylated hemoglobin level was 11.3±1.8%.

**Urine Protein Excretion**

The median average rate of albumin excretion for the 39 patients with IDDM was 8.43 µg/min (range, 3.66 to 71.19 µg/min). Ten of the patients with IDDM had microalbuminuria (≥13 µg/min). The median rate of albumin excretion for patients with IDDM with microalbuminuria was 19.20 µg/min (range, 13.90 to 71.19 µg/min). None of the 18 control subjects who underwent urine collection had microalbuminuria.

**Hemodynamic Data**

Table 1 demonstrates that the diabetic patients had increased left ventricular mass, performance, contractility, and systolic and diastolic blood pressures compared with the control subjects. The diabetic patients had left ventricular diastolic dimension similar to that of control subjects, indicating that the increase in left ventricular mass observed in the diabetic patients is due primarily to an increase in thickness. Furthermore, when the diabetic patients' velocities of circumferential fiber shortening and wall stress data pairs were plotted against the normal velocity of circumferential fiber shortening/wall stress relation, 6 of the 39 were at a point above the 95th percent confidence limits for the normal relation. Three of the 6 who were above the 95th percent confidence limits were from the group of 10 microalbuminuric patients (30%). On the other hand, only 2 of the 29 diabetic patients without microalbuminuria (7%) were higher than the upper 95th percent confidence limits (P=.03). Preload was not significantly different between diabetic patients and control subjects.

End-systolic wall stress, a measure of afterload, also was not significantly different between the two groups.

**Relation of Mass to Independent Variables**

Left ventricular mass index was significantly correlated with stroke volume, albumin excretion, and glycosylated hemoglobin level in diabetic patients (Table 2). The univariate correlation of left ventricular mass index to duration of diabetes and Quetelet index were of borderline significance.

The best multiple regression model (Table 3) for explaining the variance of left ventricular mass index in patients with diabetes mellitus included Quetelet index, albumin excretion, and the duration of diabetes.

**Relation of Contractility to Independent Variables**

Left ventricular contractility was independently associated in diabetic patients with the Quetelet index, corrected creatinine clearance, and insulin dosage (Table 4). The relations with indexed diastolic dimension and volume were of borderline significance. Duration of diabetes, glycosylated hemoglobin, and albumin excretion did not have significant univariate correlation with left ventricular contractility.

The best multiple regression model for explaining the variance of left ventricular contractility in diabetic patients included creatinine clearance and insulin dosage (Table 5).

**Discussion**

The major findings of this study are that in young patients with IDDM, left ventricular mass, performance, contractility, and blood pressure are elevated compared with healthy individuals. These relations are
important because they may reflect a cardiac condition that, if persistent over time, could result in future morbidity in these patients. These cardiovascular findings are also associated with increased creatinine clearance and microalbuminuria, which are thought to be the earliest abnormalities in the pathogenesis of renal dysfunction and ultimate renal failure in diabetic patients. This suggests the possibility that increased left ventricular contractility and blood pressure may result in increased glomerular pressure and filtration rate, which, over time, could have adverse consequences for renal structure and function, resulting in first, microalbuminuria and, later, frank proteinuria. These renal alterations may also be associated with further elevation of blood pressure and left ventricular mass, setting up a cycle of cardiovascular and renal changes in the development of diabetic complications.

| Table 3. Multivariate Analysis of Determinants of Left Ventricular Mass Index |
|---------------------------------|-----------------|-----------------|
| Variable                        | Regression Coefficient | Standard Error  |
| Intercept                       | 4.5              | 4.1             | ≤.28            |
| Quetelet index                  | 3.5              | 1.5             | ≤.03            |
| Albumin excretion               | 4.0              | 1.3             | ≤.004           |
| Duration of diabetes            | 0.50             | 0.18            | ≤.01            |

Multiple $R^2 = .51$.}

Most previous studies have shown that left ventricular performance in young insulin-dependent diabetic patients is normal at rest. However, few studies have focused on diabetic subjects early in the course of their disease, and no studies have investigated the components of performance including preload, afterload, and contractility to determine if contractility is different in young diabetic patients than in control subjects. In our study, there were no significant differences in left ventricular preload or afterload between diabetic patients and control subjects. Our results demonstrate that left ventricular contractility at rest is significantly increased in diabetic patients. Diabetic patients also had significantly elevated left ventricular mass and blood pressure compared with control subjects.

Because the development of left ventricular hypertrophy may be important in the pathogenesis of cardiovascular disease, the correlates of left ventricular mass are important. Our multiple regression results demonstrated that increased mass was associated with increased Quetelet index (a measure of obesity), urinary albumin excretion, and duration of diabetes. The relation of left ventricular mass to obesity has been well documented. The relation between left ventricular mass index and duration of diabetes indicates that mass

| Table 5. Multivariate Analysis of Determinants of Left Ventricular Contractility |
|---------------------------------|-----------------|-----------------|
| Variable                        | Regression Coefficient | Standard Error  |
| Intercept                       | .10              | .10             | ≤.20            |
| Insulin dosage                  | −.20             | .09             | ≤.02            |
| Creatinine clearance            | .002             | .0006           | ≤.003           |

Multiple $R^2 = .31$.}
increases with longer duration of disease. The relation of cardiac hypertrophy with increased urinary albumin excretion is particularly intriguing; it suggests a clinical link or possible common pathogenic mechanism for derangements in these two end organs.

Because enhanced left ventricular performance in diabetic patients is due to higher contractility, the correlates of contractility in this population are important. Multiple regression analysis in our study demonstrated that increased contractility was associated with insulin dosage and creatinine clearance, an estimate of glomerular filtration rate. The inverse relation between insulin dose and cardiac contractility is unexplained. The relation of increased contractility with increased creatinine clearance suggests the possibility that the changes in the heart and the kidney are related and supports the hypothesis that abnormalities in these two important organ systems may develop in parallel. The association of cardiac and renal function adds credence to the concept that the observed relations have biological as well as statistical significance. Longitudinal studies will be necessary to better delineate the temporal relation of the development of these abnormalities.

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References

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