The left ventricular function was assessed in 70 diabetics under 60 years of age without clinically evident heart disease using established non-invasive methods, these include systolic time interval method and echocardiography. The ratio of pre-ejection period to left ventricular ejection time (PEP/ET) was remarkably elevated in diabetics with severe microangiopathy (0.431 ± 0.037). Even in diabetics without microangiopathy PEP/ET ratio was significantly higher (0.374 ± 0.037) compared with that in controls (0.331 ± 0.023, P < 0.01). Most of diabetics with a PEP/ET value of higher than 0.40 were not under proper care with regard to diabetic control. A tendency toward normalization of PEP/ET values was often observed with the improvement in diabetic control during six to twelve months among the inadequately controlled diabetics. Isovolumic relaxation time in diabetics was longer than in controls (80 ± 14 msec, 59 ± 11 msec, P < 0.005).

Our results suggest that abnormalities of left ventricular function in diabetics may be related to not only severity of microangiopathy but also the state of diabetic control. The maintenance of adequate control of diabetes seems to play an important role in the prevention of congestive heart failure in patients with diabetes mellitus.

Key Words: Systolic time interval, Echocardiography, Diabetic complication.

Cardiac disease has been found to be one of the major complications of diabetes mellitus and for many years was attributed to coronary atherosclerosis. However, the Framingham study showed that diabetics suffered an incidence of heart failure in excess of that predicted from atherogenic risk factors, and suggested that some form of cardiomyopathy was associated with diabetes mellitus. Recently, there is increasing evidence that diabetics have abnormalities of left ventricular function in the absence of clinical heart disease. Whether this result from small vessel disease of the myocardium or metabolic effect of diabetes is unknown.

This study was undertaken to investigate the left ventricular function as a potential myocardial involvement in diabetic patients without clinical evidence of myocardial ischemia using established non-invasive method. The relationship between the left ventricular function and the clinical features of diabetes mellitus were also investigated.

PATIENTS AND METHODS

The left ventricular function was assessed in 70 diabetic patients and 31 healthy controls. According to the severity of diabetic retinopathy and the existence of persistent proteinuria, the diabetics were classified to three groups: patients with no retinopathy and persistent proteinuria (Group I, n = 35), those with simple retinopathy and no persistent proteinuria (Group II, n = 26), and those with proliferative retinopathy and persistent

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Left Ventricular Function in Diabetics

Table 1. Clinical Details of Diabetics

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Case</td>
<td>35</td>
<td>26</td>
<td>9</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>(M:15,F:16)</td>
<td>(M:8,F:8)</td>
<td>(M:7,F:2)</td>
</tr>
<tr>
<td></td>
<td>46.1±11.1</td>
<td>46.6±11.2</td>
<td>49.4±9.2</td>
</tr>
<tr>
<td>Duration of diabetes (yrs)</td>
<td>(11–16)</td>
<td>(16–16)</td>
<td>(11–16)</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>194±60</td>
<td>211±47</td>
<td>208±47</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>188±39(3)</td>
<td>192±38</td>
<td>233±43</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>103±52</td>
<td>85±41</td>
<td>128±62</td>
</tr>
<tr>
<td>%Body weight</td>
<td>101±14</td>
<td>103±11</td>
<td>105±13</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>119/71</td>
<td>118/73</td>
<td>132/81</td>
</tr>
</tbody>
</table>

a) vs III : p<0.005, b) vs II, c) vs III : p<0.01, d) vs III : p<0.05
I : Retinopathy (−), Proteinuria (−)
II : Simple retinopathy, Proteinuria (−)
III : Proliferative retinopathy, Proteinuria (+)

![Fig. 1. Measurement of systolic time interval](image1)

Simultaneous recording of the carotid arterial pulse, phonocardiogram and electrocardiogram at 100 mm/sec, paper speed illustrating the measurement of QS2, S1S2, ET and calculation of PEP.

PEP = QS2 - ET

Fig. 1. Measurement of systolic time interval
Simultaneous recording of electrocardiogram, phonocardiogram and carotid arterial pulse at 100 mm/sec, paper speed illustrating the measurement of QS2, S1S2, ET and calculation of PEP.

QS2: electromechanical systole
S1S2: heart sound interval
ET: left ventricular ejection time
PEP: pre-ejection period

proteinuria (Group III, n = 9). Clinical characteristics of diabetics are shown in Table 1. None of the patients had cardiorespiratory symptoms, any

![Fig. 2. Echocardiographic measurement](image2)

Simultaneous recording of echocardiogram, electrocardiogram (ECG) and phonocardiogram (PCG) at 50 mm/sec paper speed.

IVS: interventricular septum
MV: mitral valve
LVPW: left ventricular posterior wall
*: isovolumic relaxation time (IRT)

clinical, electrocardiographic, or X-ray evidence of cardiac abnormality. Furthermore none of the patients were heavy drinker and had taken digitals, β-blocker, or diuretics. In addition, individuals were excluded if they had an arterial pressure above 160/95 mmHg or presented clinical evidence of renal failure.

Systolic time intervals7) were obtained by simultaneous recordings of the carotid arterial pulse, phonocardiogram and electrocardiogram at 100 mm/sec paper speed. The electromechanical systole (QS2) was measured from beginning of the Q-wave in Lead II to the first rapid deflection of the second heart sound. Left ventricular ejection time (ET) was measured from the onset of the rapid upstroke of the carotid pulse to the nadir of the dicrotic notch. Pre-ejection period (PEP) was calculated as the difference between QS2 and ET. The ratio of the pre-ejection period to the left ventricular ejection time (PEP/ET) was calculated (Fig. 1).
Echocardiography was performed with a simultaneous recordings of electrocardiogram and phonocardiogram. The isovolumic relaxation time (IRT) was determined from the onset of the aortic component of second heart sound to the time of initial separation of mitral valve leaflets (Fig. 2).

Statistical analysis were performed according to student’s t-test.

RESULT

PEP/ET ratio was significantly higher in Group III (0.431 ± 0.037) compared with that in Group I (0.374 ± 0.037, P < 0.005), and in Group II (0.366 ± 0.025, P < 0.005). However, PEP/ET ratio in Group I and II were significantly higher than in the controls (0.331 ± 0.023, P < 0.01) respectively (Fig. 3).

The mean fasting blood sugar levels during one year before examination were significantly correlated with PEP/ET ratios ($r = 0.414$, $P < 0.05$). Furthermore, most of diabetics with a PEP/ET value of higher than 0.4 were not under proper care with regard to diabetic control (Fig. 4). Remarkably high values of PEP/ET were found in the inadequately controlled diabetics (above 200 mg/dl in mean fasting blood sugar) with the duration of over ten years (0.410 ± 0.042).

![Fig. 3](image-url)  
Fig. 3. The ratio of pre-ejection period to ejection time (PEP/ET) in each group.

![Fig. 4](image-url)  
Fig. 4. Correlation of PEP/ET ratio and mean fasting blood sugar levels during one year before examination in diabetics.

![Fig. 5](image-url)  
Fig. 5. PEP/ET ratio before and after controls of diabetes.  
*decreased more than 50 mg/dl in fasting blood sugar levels during observation period.
Left Ventricular Function in Diabetics

Changes in systolic time intervals with diabetic control have been investigated in 23 of the 37 inadequately controlled diabetics at 6 to 12 months after first recordings. A tendency toward normalization of PEP/ET ratio was often observed in the patients who showed a decrease of more than 50 mg/dl in fasting blood sugar levels during observation period. Two patients who showed an increase of PEP/ET value in spite of improvement of diabetic control have proliferative retinopathy and persistent proteinuria. All of subjects with no marked improvement in diabetic control during this period showed no change or an increase of PEP/ET value (Fig. 5).

Forty-three of the original 70 diabetics were available for echocardiographic study but recordings from only 35 patients were accepted as being technically good. Isovolumic relaxation time in diabetics was longer (80 ± 14 msec.) than in normal controls (59 ± 11 msec, P < 0.005).

PEP/ET ratios were significantly correlated with isovolumic relaxation time in diabetics (Fig. 6).

DISCUSSION

Recently the term diabetic cardiomyopathy has appeared in medical literature. Rubler et al. reported four patients with diabetic glomerulosclerosis who presented with cardiomegaly and congestive heart failure of unknown cause. If diabetic cardiomyopathy is a distinct condition it may pass through a preclinical phase when left ventricular function is impaired and this phase could be detected by using sensitive non-invasive method.

An abnormally raised PEP/ET ratio is a sensitive index of impaired left ventricular function and correlates well with the ejection fraction derived from invasive method. Ahmed et al. reported in adult-onset diabetics without clinically evident cardiovascular abnormalities, PEP/ET ratio was modestly but significantly elevated above normal control values. In this study remarkably high values of PEP/ET were found in patients with significant microangiopathy. These results may suggest that impaired left ventricular function was associated with microangiopathy. Shapiro et al., using systolic time interval method and echocardiography, reported a close relation between clinical microvascular complications and abnormalities of left ventricular function in diabetics without clinical heart disease.

The concept of diabetic microangiopathy in the myocardium is not new. Ledet found concentric rings of periodic-acid Schiff-positive material in the smallest intramural coronary arteries of diabetics in a necropsy series. Pearce et al. showed small-vessel disease by ventricular septal biopsy in diabetic patients with heart failure. Hamby noted high incidence of diabetes among patients with primary cardiomyopathy and found small vessel disease in necropsy cases. Although these studies postulated that myocardial disease was secondary to microangiopathy, none could exclude the direct effects of the abnormal myocardial metabolism.

In this study even in diabetic patients without microangiopathy PEP/ET ratio was significantly higher compared with findings in the normal controls. Regan has described that the failure to find demonstrable obstructive lesion of intra-
mural vessels in postmortem study in diabetics suggest that small vessel lesion may have little or no relation to cardiac abnormality. He suggests that change in cardiac function may be related to observed muscle composition in the form of interstitial glycoprotein, collagen, triglyceride and cholesterol accumulation. These abnormalities would be expected to increase left ventricular stiffness and produce the slow relaxation. In this study isovolumic relaxation time was prolonged in diabetics and was significantly correlated with PEP/ET ratio. This finding may support that cardiac dysfunction in diabetics is resulted from the stiffness of the myocardium. However, a clear relationship between isovolumic relaxation time and stiffness of the myocardium is yet to be confirmed.

In this study mean fasting blood sugar levels during one year before examination were significantly correlated with PEP/ET ratio. And most of diabetics with increase PEP/ET ratio of higher than 0.4 were not under proper care with regard to diabetic control. Furthermore, it is interesting that a tendency toward normalization of PEP/ET ratio was often observed with improvement in diabetic control during six to twelve months among the inadequately controlled diabetics. Therefore, factors other than pathological findings responsible for the cardiac dysfunction in diabetics must be considered, these include disturbance of the energy metabolism in the myocardium and/or effect on contractile protein by abnormal carbohydrate metabolism.

In the present study the abnormalities of left ventricular function are shown in diabetics without clinically evident heart disease using established non-invasive method. Although left ventricular function is subclinically impaired in most diabetics, it seems likely that there are exceptionally few who would eventually develop overt cardiac failure in the absence of hypertension or coronary heart disease. However impaired left ventricular function may explain the high immediate mortality and the high incidence of cardiogenic shock and congestive heart failure after myocardial infarction in diabetics. Our results suggest that abnormalities of left ventricular function in diabetics may be related to not only severity of microangiopathy but also the state of diabetic control. The maintenance of adequate control of diabetes seems to play an important role in the improvement of the left ventricular function and prevention of congestive heart failure in patients with diabetes mellitus.

REFERENCES