1987

Echocardiographic study of myocardial performance after exercise in type I diabetes mellitus

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Recommended Citation

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ECHOCARDIOGRAPHIC STUDY OF MYOCARDIAL PERFORMANCE AFTER EXERCISE IN TYPE I DIABETES MELLITUS

ROBERT R. ENGLANDER

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ECHOCARDIOGRAPHIC STUDY OF MYOCARDIAL PERFORMANCE AFTER EXERCISE IN TYPE I DIABETES MELLITUS

A Thesis Submitted to the Yale University
School of Medicine in Partial Fulfillment
of the Requirements for the Degree of
Doctor of Medicine

by

Robert R. Englander

1987

ABSTRACT

Echocardiographic Study of Myocardial Performance After Exercise in Children with Type I Diabetes Mellitus

Robert R. Englander

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Resting echocardiographic abnormalities have been documented in healthy type I diabetic patients. In order to evaluate the physiological relevance of this finding and to determine left ventricular responses to the stress of exercise in young diabetics, 28 normal children and 30 otherwise healthy type I diabetics had M-Mode echocardiograms of the left ventricle(LV) and aorta at rest and immediately following maximal exercise on a supine bicycle ergometer. Adequate studies were obtained in 26 controls (aged 10.7 to 17.7 years) and 25 diabetics (aged 9.2 to 18.3 years). Duration of exercise was less for diabetics ($8.5\pm.5$ vs.$7.0\pm.5$ min.,$p<.05$) (mean±SE). There were no significant differences in fractional shortening (FS) ($.34\pm.01$ vs. $.32\pm.01$), LV systolic time intervals (PEP/LVET) ($.26\pm.01$ vs. $.28\pm .01$) or velocity of circumferential fiber shortening (Vcf) ($1.17\pm.04$ vs. $1.17\pm.05$) at rest. Following exercise all these indices of LV contractility increased in both groups but FS was significantly different between controls and diabetics ($.43\pm.02$ vs. $.37\pm.02$, $p<.05$) as was Vcf ($2.20\pm.12$ vs. $1.77\pm.12$, $p=.003$). Otherwise healthy young diabetics have abnormal cardiac function which can be demonstrated by exercise testing with echocardiographic evaluation, a non-invasive technique. These abnormalities might represent an early manifestation of the diabetic cardiomyopathy seen in older patients.

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INTRODUCTION

Cardiac disease has long been considered a major cause of morbidity in the diabetic patient. The first clear epidemiological quantification of the increased risk of heart disease in diabetic patients came with the Framingham Study.[1] This longitudinal study, begun in 1949, found that diabetic males had a 2.4-fold increased risk of congestive heart failure while diabetic females had a 5-fold increased risk over their nondiabetic male and female counterparts.

Through the late 1960s, the excess risk of cardiac disease among diabetics was believed to be secondary to an accelerated atherosclerotic process. In 1972, however, Rubler et al published a post-mortem pathological study of four adult diabetics with known Kimmelstein-Wilson disease and congestive heart failure, in the absence of valvular, congenital, or hypertensive heart disease, alcoholism or significant atherosclerosis.[2] These authors proposed the term "diabetic cardiomyopathy" to account for the finding of congestive heart failure in the absence of other known heart disease in diabetic patients.

Kannel et al, in reviewing the Framingham study data, corroborated the findings of Rubler's group, when they found the increased risk of congestive heart failure to be independent of atherosclerotic disease, age, blood pressure, weight, and/or serum cholesterol.[3] These findings, of note, were confined to insulin-treated diabetics.

Since the publications of Rubler's and Kannel's groups, a myriad of research has been done in an effort to characterize this diabetic cardiomyopathy. Researchers have examined asymptomatic diabetics to isolate preclinical abnormalities in systolic and diastolic function. Methods

have included measurements of systolic time intervals, echocardiography, myocardial scintigraphy, experimental animal models, and histologic exam of extramural and intramural cardiac vessels. In this paper, I will examine the literature to date on diabetic cardiomyopathy and then present the data from research in which I was involved during the summer of 1984.

Systolic Time Interval Studies

These studies employ simultaneous ECG, phonocardiogram, and carotid pulse tracings to determine total electromechanical systole (QS_2), left ventricular ejection time (LVET), pre-ejection period (PEP), total conduction time, and isovolumic contraction time. LVET, PEP, and the ratio of PEP/LVET are particularly useful determinants of systolic function, and have the best correlation with invasive measurements of left ventricular function, such as ejection fraction.[4] An elevated PEP/LVET approximately two-fold is characteristic of congestive heart failure.[5]

Ahmed et al[5] examined 25 diabetic patients aged 20-56 years with a duration of their disease of one month to 25 years, as well as 37 age and gender matched controls. Their experimental subjects had no evidence of other systemic disease affecting the heart. They found the diabetic subjects to have an increased resting heart rate, diastolic blood pressure , and PEP, with a decreased LVET and, therefore, an increased PEP/LVET ratio. In addition their diabetic patients had increased conduction times and prolonged isovolumic contraction times compared to the controls. The investigators further evaluated the variable of treatment modality (diet alone vs. oral hypoglycemic agent vs. insulin) and found that the subgroups did not differ in their abnormal PEP/LVET ratios. They also reported no correlation between systolic time intervals and gender or age. They concluded that

patients with diabetes mellitus had an abnormality in systolic time intervals intermediate between normal controls and patients with CHF.

Zoneraich et al[6] also studied adult diabetics and confirmed the finding of increased PEP/LVET when compared to age and gender matched controls. They also found no correlation with mode of treatment, gender or age. In addition, these investigators examined the variables of duration of diabetes and control of serum glucose and found no correlation with the extent of abnormality in the ratio PEP/LVET.

Seneviratne[7] examined a group of 28 diabetics, all female, with a mean age of 46.7 years and a mean duration of diabetes of 10.9 years. He added to his study the variable of microangiopathy as evidenced by proliferative retinopathy and/or proteinuria>3 grams/24 hours. When examined by presence or absence of microangiopathy, only the former patients had increased PEP/LVET when compared to controls. He therefore postulated small vessel disease of the heart as responsible for the diabetic cardiomyopathy.

Finally, Rynkiewicz et al[8] looked at young male diabetics, aged 20-29 years , with a mean duration of their disease of only five years. They found that the abnormalities described above had already developed in their diabetic subjects (i.e. increased resting heart rate, increased diastolic blood pressure, decreased LVET, and increased PEP/LVET). In addition, they examined diastolic time intervals and found that the A_2O interval (interval between the aortic component of the second heart sound and the O-point of the apex curve) was prolonged in their diabetic patients, correlating with a prolonged relaxation time.

The systolic time interval data can thus be summarized as follows: a) diabetic patients have a prolonged PEP, a shortened LVET, and an

abnormally increased PEP/LVET ratio; b) these abnormalities are independent of age, gender, mode of treatment, control of serum glucose, or duration of disease; and c) at least one study suggests that the abnormalities in systolic time intervals correlate with the presence of microvascular disease.

Echocardiographic Studies

Echocardiographic studies of diabetic heart function first appeared in the mid 1970s and added to the literature by providing examination of left ventricular wall measurements, the cardiac chamber sizes, more precise systolic time intervals with resultant increased ability to calculate left ventricular function parameters, and a more precise measurement of diastolic function parameters. Standard techniques for echocardiographic measurements have been described in the literature.[9,10]

Zoneraich et al[6], in addition to examining systolic time intervals, examined resting echocardiograms of 40 diabetics and 20 age and gender matched controls. They found no difference between groups in left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), fraction shortening (FS), calculated stroke volume (SV), or calculated ejection fraction (EF). In six of their diabetic subjects, however, there was a significant decrease in FS, SV, and EF when compared to the controls ($p<.0001$). Unfortunately, the authors provide no other discerning variable from these six patients, nor whether statistical significance would have been reached if the six controls with the lowest FS and SV had been used as the basis of comparison.

Seneviratne[7], whose systolic time interval data is presented above, had echocardiography available to him 18 months after his original study. He was able to study four of the original 14 diabetics with microangiopathy and

20 normal controls. He found his diabetic subjects had significantly decreased FS ($p<.001$) and calculated EF ($p<.01$).

Saiki[11] examined two groups of young (age 15-29 years) insulin dependent diabetics and their age matched controls for the effects of autonomic nervous system blockade and exercise on cardiac function. In addition to the increased resting heart rate, PEP, and PEP/LVET ratio in diabetics described previously, he found that exercise alone did not show a differential response in the two groups, while exercise plus propranolol and atropine resulted in an increased EF, increased velocity of circumferential fiber shortening, and increased posterior wall excursion in the controls, without a commensurate ability in the diabetic hearts to respond appropriately to that stress. Because the diabetic subjects had responded normally to exercise alone, Saiki proprosed that they have normal *B*-receptors, but a decreased ability to respond to stress by increasing pump function without the aide of those *B*-receptors.

Sanderson et al[12] examined 23 young diabetic patients with a mean age of 31 years and a mean duration of their disease of 17 years, looking specifically at diastolic function. 16 of their experimental group had retinopathy. While their 15 control subjects all had normal diastolic intervals, they found their diabetic subjects divided into five groups: a) six patients had normal studies; b) three patients had delayed mitral valve opening without significant posterior wall movement during the delay; c) five patients in whom the mitral valve opening was delayed, the peak left ventricular lengthening rate occurred significantly later than the peak opening velocity of the mitral valve, and left ventricular filling continued during the period of mid-diastolic closure of the mitral valve; d) six patients with a prolongation of the rapid filling period; and e) three patients with

delayed mitral valve opening as well as significant outward wall movement before opening. All patients had normal left ventricular end diastolic diameter and peak lengthening rates. The authors found no correlation between the type of diastolic dysfunction and the degree of retinopathy, duration of diabetes, or quality of previous control. The authors comment:

> Echo studies in healthy people have shown that diastole is a coordinated and precisely timed process. Relaxation of the left ventricle and the consequent filling is reflected in the outward wall movement seen echocardiographically, and this movement is closely related to movement of the mitral valve, both events showing identical pattern of movement. Disturbance of the close relation between left ventricular wall movement and mitral valve movement seems to be a sensitive index of a myocardial abnormality, and abnormalities have been shown in both ischaemic heart disease and hypertrophic cardiomyopathy. (p.404)

Finally, the authors conjecture that perhaps the diastolic dysfunction seen in their diabetic patients was secondary to myocardial small vessel disease, as the majority of their patients had retinopathy; however, by their own statistical analysis, there was no correlation between degree of retinopathy and type of diastolic abnormality.

Shapiro et al[13,14,15] published a series of studies in which they examined a large number of diabetics looking specifically at correlations between systolic and diastolic function and a) duration of diabetes; b) extent of microvascular complications; and c) type of treatment. In all of these studies, they divided their diabetic population into four groups: a) diabetics without microvascular complications; b) patients with mild microvascular

complications (background retinopathy and/or mild proteinuria); c) patients with severe microvascular complications (proliferative retinopathy and/or heavy proteinuria); and d) diabetics diagnosed within the prior three years. In addition, two of the three studies examined the variable of clinical heart disease as defined by angina on exertion.

Their findings can be summarized as follows: a) diabetic patients diagnosed within the prior three years were normal in all variables; b) the remaining diabetics had a significantly decreased beat-to-beat variability, a prolongation of the isovolumic relaxation time and the time from minimal dimension to mitral valve opening, and an increased PEP/LVET ratio; c) diabetic patients with mild microvascular complications, in addition to the above findings, had increased duration of posterior wall thinning and a diminished rate of left ventricular lengthening; d) diabetics with severe microvascular complications were abnormal in all areas of diastolic function studied; e) both diabetic and non-diabetic patients with clinical heart disease had an increased left ventricular dimension change during isovolumic relaxation which was significantly different from their non-anginal counterparts ($p<0.001$); f) left ventricular dimensions were normal in all subjects without clinical heart failure; and g) left ventricular dysfunction was generally more severe in, though not limited to, insulin dependent diabetics when compared to those taking oral hypoglycemic agents.

The authors found positive correlations between: a) duration of diabetes and i) microvascular complications, ii) increased isovolumic relaxation time, iii) time from minimal dimension to mitral valve opening, and iv) loss of beat-to-beat variation; and b) microvascular complications and abnormalities in systolic time intervals.

Airaksinen et al[16], in addition to reporting the diastolic dysfunction

previously noted in other studies, found that their diabetic subjects had a significant decrease in their ECG voltage. The authors likened their finding to the findings in infiltrative cardiomyopathies (e.g. cardiac amyloidosis) as a possible explanation for the diastolic and systolic abnormalities in diabetic patients.

Gregor et al[17] looked more specifically at cardiac wall and chamber sizes in diabetic patients and controls who had had negative exercise tolerance tests. They found the diabetic subjects to have increased left ventricular posterior wall (LVPW) thickness, increased interventricular septal (IVS) thickness, increased calculated left ventricular mass, and an increased h/r ratio (LVPW/chamber radius). When the hypertensive subjects were excluded from the study, however, only the increased IVS thickness remained statistically significant. In addition these investigators found no correlation between wall abnormalities and treatment modality or duration of diabetes.

Two studies are noteworthy in their use of adolescent subjects.[18,19] Friedman et al[18] examined 33 children with IDDM of greater than one year's duration and 51 age and gender matched controls. Only one of their subjects had any evidence of microvascular disease. They found a significantly decreased FS, calculated EF and minor axis shortening in their diabetics as well as a decreased left ventricular end systolic diameter. These results together were suspected to indicate incomplete emptying of the ventricle during systole. Their results showed no correlation with age, control of diabetes or duration of disease.

Lababidi and Goldstein[19] also examined young subjects with IDDM but without microvascular complications. They looked more closely at the age factor, splitting their subjects into three age groups: 8-12, 13-15, and >15

years. They found the following: a) increased left ventricular end systolic diameter, left ventricular end diastolic diameter, right ventricular diameter, and left atrial dimension in the diabetic subjects aged 8-12 and >15; b) increased left ventricular end systolic diameter and right ventricular diameter only in the diabetics 13-15 years old; c) IVS hypertrophy in diabetics >12 years; d) decreased IVS excursion in all diabetics; and e) normal mean calculated EF in all subjects. They also note that hypertrophy of the IVS has been described in infants of diabetic mothers. The presence of echocardiographic abnormalities in this study were noted to correlate to age of subject but not to duration of disease or degree of control. The authors conclude that the findings reflect a cardiomyopathic process similar to those described in known cardiomyopathies such as with viral infections and certain drugs (e.g. alcohol and adriamycin).

Finally, one study deserves mention that has contradictory results to the echocardiographic studies outlined above. Theusen et al[20] examined 24 patients with IDDM with a mean age of 29 years and a mean duration of disease of eight years, and 24 age and gender matched controls. They found that the diabetics had a 12% <u>higher</u> FS and a statistically significant <u>increased</u> velocity of circumferential fiber shortening. The authors claim this finding is not contradictory stating that it is likely secondary to the short duration of the disease in their experimental group; however, the two studies mentioned above had younger subjects with a shorter mean duration of disease, and nonetheless showed echocardiographic abnormalities consistent with the prior literature. The present author could find no clear explanation for the increased FS and Vcf in Theusen et al's diabetic patients.

To summarize the echocardiographic literature: a) findings of abnormal systolic time intervals were confirmed; b) diastolic dysfunction as

represented by delayed time to mitral valve opening and a prolongation of the isovolumic relaxation time was found; c) diabetics had decreased responsiveness to exercise when autonomic nervous system receptors were blocked; d) some studies, though not all, found a correlation between presence of microvascular disease of the retina and/or kidneys and degree of systolic and diastolic dysfunction; e) there was generally no correlation between degree of cardiomyopathy and gender, duration of diabetes, or method of treatment; f) isolated studies found decreased ECG voltage[16] and IVS hypertrophy[17,19]; and g) one study actually showed improved myocardial contractility as measured by FS and calculated EF[20].

Scintigraphic Studies

Scintigraphic studies have added to the literature by providing more direct measurement of systolic function (through measurement of ejection fraction), diastolic function (through measurement of peak filling rate), and general quality of wall motion.

Abenovali et al[21] studied adult diabetic and control patients before and after exercise. They found that their diabetic subjects had statistically significant decreased exercise duration, decreased maximal HR, decreased maximal oxygen consumption, and increased functional aerobic impairment (functional aerobic impairment = predicted VO_{2max} minus estimated $VO_{2 max}$ divided by predicted VO_{2max} times 100). In addition, 5 of the 12 diabetic males tested had perfusion defects consistent with myocardial scars, perhaps a result of old silent infarcts. Only 1 of 11 controls had similar perfusion defects. The authors report that the perfusion defects appeared more consistent with old ischemic events than cardiomyopathy as they tended to be discreet rather than patchy. The authors concluded that the defects

were likely secondary to coronary artery disease rather than a diabetic cardiomyopathy as they had performed resting echocardiograms on their subjects which had failed to uncover dysfunctions; however, the authors fail to account for a statistically significant decreased FS in their diabetics compared to controls as all subjects were within normal limits when compared to established criteria.

Vered et al[22] studied young male diabetics (aged 21-35) and aged matched controls before and after exercise. They found that, while all of their patients had normal pre-exercise EF, post-exercise EF decreased in 5 out of 30 diabetics, was unchanged in 8 out of 30, and increased normally in 17 out of 30, while increasing normally in all control patients. The abnormal EF was not correlated with serum glucose, modality of treatment, or duration of diabetes. Three of four patients with microvascular complications also had post-exercise abnormal EF. The authors concluded that diabetic patients without known cardiac disease may demonstrate global LV dysfunction after exercise.

Pauwels et al[23] examined 14 diabetic patients aged 21-38, six of whom had proliferative retinopathy. They found their subjects to have normal EF by published data for age and gender matched normals; however, all 14 subjects had abnormal wall motion, by both cine wall motion and Fourier filtered analysis, in the septal region and/or the anterior wall. There was no correlation with blood glucose or glycosylated hemoglobin, or with presence of autonomic neuropathy.

Finally, Kahn et al[24] specifically examined diastolic function as measured by peak filling rate (PFR). They found that, while mean PFR was normal, 6 of 28 subjects had abnormal PFRs. Further, all 6 fell into the group of 15 diabetic patients who had an autonomic neuropathy by standard

measures (beat-to-beat variation), and also had decreased norepinephrine response to postural changes. They conclude that alterations in sympathetic nervous system activity are associated with abnormalities in left ventricular filling.

Although few studies have been done using scintigraphic techniques, they have indicated a tendency among diabetics to have abnormal wall motion, abnormal diastolic function as measured by PFR, and some, though not all , diabetics with abnormal systolic function as measured by EF, particularly after stressing the heart with exercise. In addition, diabetic subjects had decreased endurance for exercise and a decreased O_2 consumption in at least one study. Finally, one study found a correlation between abnormal wall motion and autonomic neuropathy.

Experimental Studies

Using animal models offers the researcher more precise access to clinical, histopathologic, and biochemical correlations in the diabetic myocardium. Write Fein and Sonnenblick[25]:

> Experimental studies can most clearly address the following questions: (1) How is the contractile element altered in diabetes? (2) Are the interstitial changes responsible for altered ventricular function? (3) Is myocardial small vessel disease the fundamental alteration in diabetes leading to cardiomyopathy? (4) Are the myocardial changes preventable or reversible with hypoglycemic therapy? (p.264).

Researchers have used streptozotocin or alloxan to induce diabetes in dogs[26,27], rats[28,29,30,31,32,33,34] and rabbits[35,36]. Both of these agents are taken up preferentially by the *B*-islet cells of the pancreas, and destroy those cells

with resultant insulin deficiency. Neither agent is known to induce alterations in cardiac muscle function.

Fein and Sonnenblick[25] provide an excellent review of the experimental research, and the reader is referred to that article. Results, however, can be summarized. Canine studies[26,27] revealed normal basal left ventricular function but, when infused with saline, diabetic dog hearts showed a higher left ventricular end diastolic pressure. Further, collagen concentrations were increased 50% in layers from the endocardial to the epicardial surfaces. The decreased compliance was not reversed by chronic insulin treatment. The researchers therefore concluded that the diabetic dogs' hearts, though seemingly normal at rest, show decreased compliance with increased preload secondary to increased myocardial deposition of collagen.

Studies of the diabetic rat have been more numerous. Early studies[28,31] showed a depressed myocardial response (i.e. decreased cardiac output) to increasing preload and afterload in the diabetic rat heart. This effect was not eliminated by adding insulin to the perfusate; however, chronic insulin treatment did reverse the abnormalities. Of note, coronary flow was not decreased during the decrease in cardiac output suggesting that ischaemia was not the underlying etiology.

Lopaschulk et al[32,33] looked specifically at the sarcoplasmic reticulum. They found a significantly decreased ATP-dependent calcium transport into the sarcoplasmic reticulum in diabetic rat hearts associated with a significant elevation of long chain acyl carnitines. Those rats they treated with insulin, however; showed no abnormality in function of the sarcoplasmic reticulum and in concentration of long chain acyl carnitines. Of note, those rats treated with carnitine, an agent which lowers the long chain acyl carnitine

concentration, continued to show depressed myocardial function, suggesting that the increased long chain acyl carnitine concentration could not be solely responsible for the defect in calcium uptake by the sarcoplasmic reticulum.

Fein et al[30,31] looked specifically at papillary muscle function in diabetic rats and found abnormal diastolic function with a slowing of relaxation and a depression of shortening velocity. They also found that these abnormalities were associated with a decreased function of actomyosin and myosin ATP-ase, with a reversal of the normal isoenzyme ratios. Bathing the papillary muscles in insulin had no effect on function, while chronic treatment with insulin led to a complete reversal of the papillary muscle dysfunction and the actomyosin and myosin ATP-ase abnormalities. The reversal of abnormalities, further, correlated with duration of treatment.

Fein et al also studied diabetic rabbit hearts[34,35]. They found that the results of their rat studies could also be applied to this second mammalian species. Diabetic rabbits showed prolongation of their relaxation phase as well as diminished shortening velocity. These changes were again reversible with chronic insulin therapy.

The experimental data can be summarized as follows: a) heart muscle in animals rendered diabetic by streptozotocin or alloxan showed decreased responsiveness to increased preload and afterload, and decreased papillary muscle diastolic function with a slowing of relaxation and a depression of shortening velocity. b) These functional abnormalities were associated with the following histologic and biochemical abnormalities: i) increased interstitial deposition of collagen (dogs only), ii) abnormal calcium ATP-ase-activated uptake of calcium into the sarcoplasmic reticulum, and iii) abnormal isoenzyme ratios in actomyosin and myosin ATP-ase. c) All

abnormalities, except for the excess deposition of collagen found in dog hearts, were reversed by chronic insulin therapy.

Invasive Studies

The present author found only one study that examined diabetic patients' hearts through angiography.[37] These authors were actually examining patients with idiopathic cardiomyopathy and found that 16 of their 73 subjects had diabetes, representing a statistically significant increase over the general population ($p<.025$). They performed angiography on the 16 patients and found a statistically significant increased left ventricular end diastolic volume and a significantly decreased EF. Of note, only one patient had an abnormal coronary angiogram with a 25% right coronary artery lesion, suggesting that ischaemia on the basis of large vessel disease was not the cause of the cardiomyopathy.

Pathological Correlations

While pathological studies are severely limited by lack of material to analyze and have only been obtained through post-mortem studies, they do offer a unique vantage point in the literature for histologic correlation to the systolic and diastolic function seen in diabetic patients.

Four of the sixteen patients studied by Hamby et al[37] (see above) died within 21 months of the original study, and three of those four were studied at autopsy. Of note, all four patients died in congestive heart failure. They found focal myocardial fibrosis and intimal proliferation of small myocardial arterioles. Electron microscopic examination further revealed focal perivascular damage with loss of contractile myocardial elements. Only one of 28 nondiabetics with cardiomyopathy showed small vessel

disease, and this patient had a diagnosis of polyarteritis nodosa.

Ledet[38] performed autopsies on 12 subjects who had suffered from IDDM, and 9 controls. He found increased perivascular connective tissue in the diabetic hearts as well as PAS positive staining of intramural coronary arteries in 9 of 12 diabetics versus only 3 of 9 controls(this finding, however, did not reach statistical significance). Of note, this author found no increase in the size of capillary walls, in direct contradistinction to microvascular findings in the diabetic retina and kidney.

Finally, Sunni et al[39], in perhaps the most definitive study to date, examined the microvasculature of patients who had had diabetes alone, hypertension alone, diabetes with hypertension, or neither diabetes nor hypertension. They found no statistically significant trends to distinguish a microvasculopathy in either the diabetic or hypertensive subjects. They further explained that the PAS positive material between strands of proliferative cells noted in prior studies was probably an artifact of vessel collapse as a result of improper fixation techniques. They conclude "with the limitations for material to analyze, which are severe...neither the diabetes nor hypertension is associated with any readily definable anatomic alteration in intramyocardial arteries that differs from or exceeds that seen with aging."(p. 381)

Thus, though few studies have been done on histological correlations with diabetic cardiomyopathy, the most definitive study to date both in number of vessels examined and in control for confounding variables, particularly hypertension, would indicate that no specific microangiopathy can be assigned to the diabetic heart. Doubt ,therefore, is shed on the hypothesis that microvascular disease forms the basis for the systolic and diastolic dysfunction seen in diabetic patients.

RATIONALE FOR THE CURRENT STUDY[40]

Echocardiograms done during or immediately following isometric or dynamic exercise have been utilized by several investigators to demonstrate abnormal cardiac function which is not apparent at rest[41,42,43,44,45,46]. In order to examine further the early myocardial involvement of otherwise healthy children and adolescents with insulin dependent diabetes, we evaluated left ventricular function by echocardiography at rest and immediately following supine bicycle exercise in a group of asymptomatic young diabetic subjects and in a group of age matched healthy controls. Our study represents the first in the literature to look at older children and adolescents with diabetes in the post-exercise state, as the other studies reported involving adolescent patients[18,19] examined their subjects at rest only. Further, our study represents the first attempt to establish standard normal values for post-exercise cardiac function in a healthy adolescent population, via our control subjects. Finally, by examining a fairly uniform group of insulin dependent child and adolescent diabetic patients, we have attempted to eliminate the variables of a) other systemic manifestations of diabetes (e.g. microvascular disease of the kidney or retina or autonomic neuropathy) and b) type of treatment.

SUBJECTS AND METHODS

30 young insulin dependent diabetic patients recruited from consecutive patients in the Michael Reese Hospital (Chicago, Illinois) diabetes clinic and 28 normal control subjects recruited from the children of friends and workers were evaluated. Subjects were accepted into the study if they had no conduction abnormalities on ECG, no ventricular dyssynergy on two-

dimensional echocardiogram other than flat septal motion, and were otherwise in good health. Diabetic subjects had no clinically apparent renal, ocular or peripheral nerve involvement based on routine physical exam, bi-monthly urinalysis, and annual ophthalmologic exam. They were clinically euthyroid by physical exam and laboratory evaluation of thyroid function performed every one to two years.

Exercise studies were performed in the Michael Reese Medical Center Clinical Research Center. Informed consent was obtained from all subjects and a parent or legal guardian (see Appendix 1). M-mode echocardiograms were derived from two-dimensional echocardiogram generated images using a commercially available instrument (ATL MK 300C). All diabetic subjects had a semiquantitative evaluation of serum blood glucose (bG Chemstrip) both before and following exercise. In addition each diabetic subject had a determination of glycohemoglobin in the day of the study as measured by GlycoAffin columns (Isolabs).

All subjects had echocardiograms done while resting in the supine position. Recordings were made at the level of the aortic valve and of the left ventricle at the level of the mitral chordae. Subjects then underwent graded exercise on a supine bicycle ergometer according to published protocol[47]. Subjects pedaled at a constant rate through stages of increasing resistance, beginning at 200 kg-m/min, to exhaustion. All subjects were encouraged to exercise to maximal voluntary effort. Immediately following exercise, the echocardiogram was repeated from the left parasternal window. All measurements were obtained within three minutes of the cessation of exercise. This time limit was based on a study by Berberich et al who recently reported that the echocardiographic changes induced by exercise persist for three minutes or longer folowing dynamic exercise[46]. All

echocardiograms were reproduced from an M-mode image frozen on the screen at the time of study. This reproduction resulted in a final sweep speed of 75 mm/sec. Technically adequate end-expiratory echocardiograms at the aortic valve and left ventricular levels were obtained for three cardiac cycles at rest and were compared to the earliest adequate post-exercise studies, which were only obtainable at end-expiration. Aortic studies had to have a clear onset of the QRS complex and clearly defined opening and closure points of the aortic valve. Left ventricular studies required clear delineation of the entire interventricular septal and left ventricular posterior wall endocardial surfaces throughout the cardiac cycle. In addition, much care was taken to analyze only cycles in which the posterior mitral valve leaflet was clearly separate from the left ventricular posterior wall and to assure that the echocardiographic beam transected the left ventricle such that the posterior wall represented left ventricle and not left atrium. This was particularly difficult in the post-exercise studies due to the very marked hyperventilation with hyperpnea.

All echocardiograms were subsequently reviewed by an echocardiographer masked to the identity of the subjects. Aortic valve echocardiograms had the onset of the QRS complex, aortic valve opening and aortic valve closure identified. Left ventricular echocardiograms had the onset of the QRS complex and the point of maximal anterior excursion of the left ventricular posterior wall (representing end-diastole and end-systole) identified. The following were calculated using a Hewlett Packard 9847A digitizer coupled to a Hewlett Packard 9845A computer: LVET, FS and Vcf. FS (end-diastolic diameter - end-systolic diameter/ end-diastolic diameter) reflects the degree of ejection of the left ventricle during systole and can be thought of as analogous to a one-dimensional ejection fraction. Vcf

(FS/LVET) takes into account the rapidity with which the ventricle contracts. Because Vcf is rate sensitive, a rate corrected Vcf was also calculated by normalizing Vcf to a heart rate of 60 beats/min. Rate corrected Vcf was calculated as end-diastolic diameter - end-systolic diameter/end-diastolic diameter X LVET X VRR interval, as described by Colan et al[48]. In addition, the left ventricular septal and posterior wall endocardial surfaces were digitized and divided by the computer into 50 equal segments. Maximal rates of left ventricular diastolic expansion and systolic contraction, indexed for maximal diastolic diameter (dD/dt diast and dD/dt syst), were calculated by the computer and are reported as diameters/sec. These measurements were also rate corrected in a similar manner to that described for Vcf. Data were evaluated by Student's t-test for paired or unpaired data in conjunction with the Bonferroni multiple comparisons procedure, the Fisher exact test, and by multiple linear regression analysis. All data are presented as mean±SE.

RESULTS

All diabetic and normal subjects met the inclusion criteria. 26 of 28 control subjects had satisfactory echocardiographic studies at rest and post-exercise. We were unable to obtain satisfactory post-exercise studies within the prescribed time limit in two instances. 25 of 30 diabetic subjects had adequate studies. Three subjects were excluded because it was felt that they did not exercise to tolerance (one developed a leg cramp). One subject had technically inadequate echocardiographic studies at rest and following exercise, and one had an inadequate post-exercise study. The data reported include only those subjects in whom adequate studies were obtained. Of the 26 controls, there were 14 males and 12 females, aged 10.7 to 17.7 years

(14.0 ± .4). Of the 25 diabetic subjects there were 13 males and 12 females, aged 10.5 to 19.2 years (14.3 ± .5) with a duration of diabetes from 0.25 to 16.7 years (6.1 ± .82). There were 16 black and 10 white controls and 16 black and 9 white diabetics.

The mean glycosylated hemoglobin of diabetic subjects was 13.5 ± 4.0% (range of 5.2 to 22.6% with a laboratory normal of 4.0-6.5%). The range of blood glucose by chemstrip was 80-400 mg/dl prior to exercise. Following exercise, blood glucose remained within the same gradation in all subjects, by the semi-quantitative chem-strip.

Insert Tables 1 A and B Here

Post-exercise left ventricular echocardiograms were obtained at a mean of 47 ± 9 seconds in the control group and 51 ± 8 seconds in the diabetic group (p=NS). Aortic valve echocardiograms were obtained at 65 ± 9 and 63 ± 7 seconds (p=NS) for the control and diabetic subjects, respectively.

Resting blood pressures were 109/62 ± 4/2 in the control group and 113/66 ± 3/2 in the diabetic group (p=NS). The resting heart rate was 71 ± 2 beats per minute in control and 74 ± 2 in diabetic subjects. Maximal heart rates were not obtained as the first echocardiograms were recorded at least several seconds following the cessation of exercise. Since heart rate continued to fall during recovery from exercise during the period that the echocardiograms were being performed, heart rates were evaluated at the time of both left ventricular and aortic studies. There was no significant difference between groups for heart rate during the left ventricular study; however, there was a difference between the control and diabetic groups at the time of the aortic study. Expressed as percent of resting heart rate, the

heart rate at the time of the left ventricular echocardiogram was 200 ± 9% in controls and 178 ± 7% in the diabetic subjects (p=NS). Heart rates at the time of the aortic echocardiogram were 194 ± 6% for controls versus 167 ± 5% for diabetics (p<.001).

Exercise duration was 8.5 ± .5 minutes for the control subjects and 7.0 ± .5 minutes for diabetic subjects (p<.05). The female control subjects had an exercise duration of 6.9 ± .4 minutes versus 5.7 ± .3 minutes in the diabetic subjects (p<.025). Although the male diabetic subjects also had less exercise duration (9.9 ± .7 versus 8.2 ± .8 minutes) this did not reach statistical significance.

Data on cardiac function are reported in Table 2. All indices of cardiac function increased following exercise in both groups (p<.01 for FS in diabetics, p<.001 for all others). FS and Vcf, similar in both groups at rest, were different following exercise. Following exercise FS and Vcf were significantly higher in the control group (p<.05 and p=.003, respectively). Rate corrected Vcf was calculated utilizing the heart rate at the time of the aortic echocardiogram. At this time the heart rates of the two groups were statistically different and correcting Vcf for heart rate therefore minimizes any difference in Vcf due to the lower heart rate in the diabetic group. Rate corrected Vcf was also similar for both groups at rest and was significantly higher in the control group following exercise. When the absolute and relative changes in rate-corrected Vcf from rest to post-exercise for each individual were evaluated, the control group again had a significantly greater increase (p<.005) for both absolute and relative increases. At rest and following exercise dD/dt diast was similar, even when rate corrected.

Within the diabetic group there was a small statistical decrease in dD/dt diast at rest correlating with duration of disease (r=.36, p<.05). This

correlation was due primarily to a decreased dD/dt diast in the male subjects with prolonged disease. There was also a correlation between Vcf at rest and duration of disease for the male group only ($r=.53$, $p<.05$). Neither of these correlations was affected by consideration of glycohemoglobin levels. Exercise duration in the diabetic group correlated inversely with glycohemoglobin levels ($r=.47$, $p<.01$) and again this was due to the male groups.

DISCUSSION

We have found abnormal post-exercise parameters of left ventricular function in otherwise healthy adolescents with type I diabetes mellitus. Our results differ from those of Saiki[11], who found no post-exercise differences except with the addition of autonomic nervous system blockers, and whose subjects were young adults rather than adolescents. Our results also differed from those of Friedman et al [18] as well as Lababidi and Goldstein[19] who showed resting abnormalities in their adolescent diabetic subjects in both diastolic and systolic function. We found no difference between our diabetic subjects and controls <u>at rest</u>. As a result, our findings do not contradict those of Shapiro et al[13,14,15] who found no altered resting cardiac function in those patients who had had diabetes for less than three years.

Our post-exercise findings, on the other hand, confirm prior studies which have utilized exercise to demonstrate abnormal cardiac function not apparent at rest[41,42,43,44,45,46]. In fact, our results suggest a noninvasive means to eliciting abnormal cardiac function in patients who might appear normal at rest.

Our abnormal post-exercise findings were limited to the systolic measurements of FS and Vcf. The latter persisted even when corrected for

heart rate. Since the aortic and left ventricular echocardiograms were not recorded simultaneously and heart rate decreased throughout the immediate post-exercise study, the values for post-exercise Vcf of necessity must be approximate. Within each group, however, post-exercise heart rates were statistically similar for both echocardiographic views (LV and aorta). Because these indices of systolic function are afterload-dependent[48], differences due to ventricular loading, for example due to subtle differences in autonomic regulation, cannot be excluded.

We only measured one parameter of diastolic function, dD/dt diastolic, which showed no significant difference between our diabetic and control patients. This finding does not necessarily contradict findings of abnormal diastolic function reported above. Possible explanations for our findings include: a) that dD/dt diast simply was not a sensitive indicator of global diastolic function, or b) that our subjects were too young to be manifesting such dysfunctions. If the latter were true, one could hypothesize that abnormalities in systolic function are first to appear in the diabetic cardiomyopathy and that these can be most easily recognized after stressing the heart, such as with dynamic exercise.

Our study did not examine the question of etiology of the diabetic cardiomyopathy. In fact, studies involving human subjects have been unable to suggest an etiology. While some studies have found a correlation between diabetic cardiomyopathy and microangiopathy of the retina or kidney[7,13,14,15,22], others, including our own, have shown development of abnormalities in heart function before development of microangiopathy of other organs[18,19,40]. In addition, the most definitive study to date involving post-mortem pathological findings has shown no definitive lesion in the diabetic cardiac microvasculature[39].

One might look to the experimental literature for possibilities of etiology, understanding the inherent danger in trying to generalize across species. Several biochemical abnormalities have been demonstrated in diabetic dog, rat, and rabbit hearts. These abnormalities could be extrapolated to some of the systolic and diastolic abnormalities found in the diabetic heart. For example, the abnormal deposition of collagen found in dog hearts[26,27] would be expected to result in decreased compliance, which might be manifested in such findings as increased LVEDP. Abnormal uptake of calcium into the sarcoplasmic reticulum found in diabetic rats[32,33] would be expected to adversely affect both contractility and relaxation of the myocardium, which might result in increased PEP with a decreased LVET or, in diastole, as decreased peak filling rate or increased time to relaxation. Abnormal actomyosin and myosin ATP-ase[30,31] should also adversely affect contractility and could be implicated in abnormalities in systolic function. Clearly, further research is needed to examine which of the biochemical abnormalities found in experimental animal models can be generalized to the human species, or, in fact, if a biochemical abnormality specific to human diabetes exists.

Perhaps most important will be further efforts to examine whether the diabetic cardiomyopathy is reversible. Once again, one must look to the experimental studies for the available evidence to date: these studies, encouragingly, have found all abnormal parameters of cardiac function reversible in the diabetic rat and rabbit with chronic insulin treatment. The excess collagen deposition found in diabetic dog hearts, on the other hand, was not found to be reversible with treatment.

Only one study, as yet unpublished, has looked at the effects of better glucose control on echocardiographic abnormalities in type I diabetes.

Edidin et al[49] examined the patients studied by Friedman et al [18] after four months of improved glycemic control (via daily telephone contact, biweekly visits, twice daily split-mixed insulin injections, and home blood glucose monitoring). They found, in addition to statistically significant decreased glycohemoglobin and serum triglyceride levels, decreased IVS thickening in 15 of the 20 subjects restudied. They did not, however, find reversals in the abnormalities in minor axis shortening, LVEF, left ventricular end systolic volume, Vcf, or left ventricular end diastolic diameter. Of note, while their subjects' glycohemoglobin levels decreased, they remained statistically elevated compared to normals. Clearly, more longitudinal data is necessary to examine the effects of better glycemic control on cardiac function in type I diabetics.

CONCLUSION

Short-term diabetes in the otherwise healthy child and adolescent can produce myocardial dysfunction that may be the harbinger of the severe cardiomyopathy sometimes seen in long-term diabetes. The tasks of the future will be in following these individuals longitudinally and trying to discriminate those at greatest risk for deterioration, as well as finding ways to prevent that deterioration. In addition, further work must be done to elucidate the etiology of the diabetic cardiomyopathy.

Finally, we have established the usefulness of post-exercise echocardiography, a non-invasive technique utilizing commonly available equipment which does not require radiation exposure, in the evaluation of potential subclinical cardiomyopathy in child and adolescent populations.

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ACKNOWLEDGEMENTS

I would like to thank Drs. Lynne Levitsky and Victor Baum for their guidance and for the opportunity to conduct clinical research with them; Dr. William Tamborlane for his sponsorship of my thesis; the Northern Illinois affiliate of the American Diabetes Association for their research fellowship; my parents, for supporting me through my academic endeavors; and, most of all, my wife for her constant support and inspiration.

TABLE 1A: DIABETIC SUBJECTS

Subject	Gender	Age	Race	Duration of Diabetes (yrs)	Glycosylated Hemoglobin (%)	Duration of Exercise (min)
1	F	17.80	B	7.50	19.4	6.30
2	F	14.40	B	3.00	19.4	5.00
3	F	15.60	B	10.00	16.7	5.20
4	F	13.80	B	6.00	11.9	5.50
5	F	13.70	B	4.00	22.6	5.50
6	F	13.60	B	10.80	13.9	3.20
7	F	12.10	W	1.70	17.8	7.30
8	F	10.70	B	3.00	11.0	4.80
9	F	10.50	W	1.00	8.4	6.00
10	F	12.50	B	3.00	14.2	5.30
11	F	15.80	W	3.00	11.4	6.50
12	F	15.75	W	9.50	9.8	7.25
13	M	18.33	B	16.70	11.6	8.50
14	M	12.00	W	8.00	10.3	5.60
15	M	15.00	B	9.00	16.4	7.00
16	M	12.10	W	8.00	13.4	7.30
17	M	13.60	B	2.30	15.1	6.00
18	M	17.40	B	4.80	12.8	7.80
19	M	12.70	W	3.00	16.7	7.30
20	M	13.00	W	8.00	10.4	7.50
21	M	16.70	W	0.25	5.2	11.70
22	M	16.10	B	6.00	14.6	6.80
23	M	17.90	B	3.20	10.7	9.50
24	M	9.20	B	7.00	9.1	15.70
25	M	17.50	B	14.00	15.1	6.20
Mean± SE		14.3± .5		6.1± .82	13.5± 4.0	7.0± .5

TABLE 1B: CONTROL SUBJECTS

Subject	Gender	Race	Age (yrs)	Duration of Exercise (mins)
1	F	W	10.80	8.00
2	F	B	11.40	5.50
3	F	B	14.30	8.70
4	F	B	16.30	6.20
5	F	B	15.20	8.60
6	F	B	13.60	6.50
7	F	B	14.30	9.00
8	F	B	14.30	6.40
9	F	W	10.70	6.00
10	F	B	15.30	6.80
11	F	B	12.80	5.00
12	F	B	13.10	6.50
13	M	W	15.70	8.00
14	M	W	15.80	11.00
15	M	W	11.90	8.90
16	M	B	17.70	15.00
17	M	B	14.20	12.50
18	M	B	16.80	12.40
19	M	W	15.00	13.30
20	M	W	14.80	7.80
21	M	B	11.70	6.00
22	M	B	13.50	9.30
23	M	B	11.90	6.20
24	M	W	17.30	10.30
25	M	W	11.80	7.10
26	M	W	14.80	10.20
Mean± SE			14.0± .4	8.5± .5

TABLE 2: CARDIAC FUNCTION DATA

Measurement	CONTROLS	DIABETICS	P*
Resting Heart Rate	71 ± 2	74 ± 2	NS
Resting Blood Pressure	109/62 ± 4/2	113/66 ± 3/2	NS
FS (rest)	.34 ± .01	.32 ± .01	NS
FS (exercise)	.43 ± .02	.37 ± .02	<.05**
Vcf (rest)	1.17 ± .04	1.17 ± .05	NS
Vcf (exercise)	2.29 ± .12	1.77 ± .12	.003
Rate-corrected Vcf (rest)	1.31 ± .05	1.37 ± .07	NS
Rate-corrected Vcf (exercise)	3.35 ± .24	2.58 ± .19	<.02
dD/dt syst (rest)	2.32 ±.08	2.37 ± .09	NS
Rate-corrected dD/dt syst (rest)	.082 ± .003	.085 ± .004	NS
dD/dt syst (exercise)	5.57 ± .43	5.08 ± .39	NS
Rate-corrected dD/dt syst (exercise)	.276 ± .025	.241 ± .021	NS
dD/dt diast (rest)	3.22 ± .14	3.16 ± .14	NS
Rate-corrected dD/dt diast (rest)	.114 ± .006	.114 ± .003	NS
dD/dt diast (exercise)	6.60 ± .70	5.26 ± .34	NS
Rate-corrected dD/dt diast (exercise)	.326 ± .038	.251 ± .019	NS

Data are presented as mean ± SE. FS = fraction shortening; vcf = velocity of circumferential fiber shortening (in circumferences/second); dD/dt syst = maximal rate of systolic minor axis shortening (in diameters/second); dD/dt diastolic = maximal rate of diastolic minor axis expansion (also in diameters/ second).

*P = probability of statistical significance in the difference between the means for the control and diabetic groups.

**FS difference loses statistical significance when corrected by multiple comparison testing.

APPENDIX 1: CONSENT FORM

Michael Reese Hospital and Medical Center
Department of Pediatrics

Title: Exercise Echocardiogram in Children with Type I Diabetes Mellitus and in Normal Children

Investigators: Lynne L. Levitsky and Victor C. Baum, M.D.

CONSENT FORM

1. Purpose

I understand that I (my child) am being asked to participate in this study because I have (my child has) insulin dependent diabetes mellitus or because I have (my child has) normal heart function. Although my (my child's) heart is probably normal, some people with diabetes have been shown to have moderately abnormal heart function in the past.

2. Subject's Statement of Consent

I hereby authorize Drs. Levitsky and Baum and their associates to perform an echocardiogram which is a sound wave test of the heart on me (my child), to exercise on a lying down bicycle, and to repeat the echocardiogram during this time.

3. Nature of the Procedures

I understand that I (my child) will be asked to have an exercise echocardiogram performed. I understand that the way this is done is that I (my child) will lie down on an examining table, and a sound wave machine which can measure the shape and function of the heart with sound waves will be used to check my heart function. I (my child) will then be asked to pedal as hard as I (my child) can on an exercise bicycle while still lying down, and the sound wave machine test

(echocardiogram) will be repeated.

4. Risks

I understand that this test is without risk, but that if I have (my child has) diabetes, it is possible I (my child) could get a low blood sugar reaction, and I understand that the doctors will give me (my child) some sugar to treat the low blood sugar reaction if this should happen. I understand that it is remotely possible that I (my child) could have a problem with my (my child's) heart from being asked to exercise, so my (my child's) heart will be monitored with an electrocardiogram, an electrical test of heart function, and that doctors and nurses will be watching during the procedure. I understand that the major risk will be that I (my child) will be very tired during the exercise.

5. Discomforts

I understand that I (my child) will be very tired following the exercise.

6. Benefits

I understand that resting echocardiogram (sound wave test) will be able to tell if my (my child's) heart function is normal. I understand that the exercise part of the echocardiogram is the experimental part, and if I have (my child has) diabetes, it may show if this is different from other children who do not have diabetes.

7. Alternative Procedures

I understand that the alternative procedures to evaluate heart function in people with diabetes include the use of radioactive substances which carry a small risk in children.

8. Injury to research subjects

I understand that in the event of physical injury resulting from the

research procedures, the hospital will provide me (my child) with free emergency care, if such care is necessary. I also understand that if I wish, the hospital will provide non-emergency medical care, but neither Dr. Levitsky, Dr. Baum, nor the hospital assumes any responsibility for such care or to provide me with financial compensation.

9. Inquiries and Withdrawal

I have been advised that Dr. Levitsky or Dr. Baum will answer any further questions that I have and that I am free to discontinue participation in the project at any time. In the event that I do not (my child does not) participate or that I withdraw (my child withdraws) from the study, I understand that I (my child) will receive conventional treatment for my (my child's) condition.

10. Guarantees

I understand that Dr. Levitsky and Dr. Baum do not make any guarentee of any benefits to be received during the course of this treatment.

11. Confidentiality

I understand that information obtained from this study will remain confidential and will be disclosed only with my permission or as required by law.

Date:____________________________Time:____________________________

If consenting party is other than patient:

WITNESS:

______________________________	____________________________________
Name of consenting party and relationship to patient. PLEASE PRINT.	Name of witness. PLEASE PRINT
______________________________	____________________________________
Signature of consenting party	Signature of witness