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Abnormal Myocardial Acoustic Properties in Diabetic Patients and Their Correlation With the Severity of Disease

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Although patients with diabetes mellitus may be afflicted by cardiomyopathy, its prevalence and nature are controversial. Studies have shown that fibrosis alters the acoustic properties of the heart in animals and humans and that the changes are detectable by cardiac tissue characterization with ultrasound. The present study was performed to characterize myocardial acoustic properties in patients with insulin-dependent diabetes to determine whether ultrasound tissue characterization could detect changes potentially indicative of occult cardiomyopathy.

The magnitude of cyclic variation of myocardial ultrasound integrated backscatter and its phase delay with respect to the onset of the cardiac cycle in the septum and posterior wall of the left ventricle were measured in 54 patients with diabetes who had no overt cardiac disease. Conventional echocardiography documented normal ventricular systolic function in 96%. As compared with results in age-matched patients without diabetes studied previously, cyclic variation of integrated backscatter was reduced (4.6 ± 0.8 vs. 3.6 ± 1.4 dB; $p < 0.001$). In addition, delay was significantly increased (0.86 ± 0.09 vs. 0.99 ± 0.15).

The primary analysis of the data focused on differences among the diabetic patients. Reduction of cyclic variation of backscatter was greatest in patients with diabetes who had neuropathy (3.2 ± 1.0 dB; $p < 0.001$) as was the increase in delay (1.04 ± 0.16, $p < 0.001$ vs. values in patients without neuropathy). Retinopathy and nephropathy were associated with abnormal myocardial acoustic properties as well.

Thus, abnormalities that may reflect fibrosis or other occult cardiomyopathic changes in diabetic patients without overt heart disease are readily detectable by myocardial tissue characterization with ultrasound and parallel the severity of noncardiac diabetic complications.

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Diabetes mellitus has been associated not only with an increased risk of atherosclerosis, coronary artery disease and myocardial infarction (1,2), but also with impairment of ventricular performance in the absence of ischemia (3,4) or disproportionate to the extent of infarction (5,6) or cardiomegaly (7,8). Diabetic cardiomyopathy has been implicated on the basis of results in studies of laboratory animals with induced glucose intolerance (9,10). This condition is thought to be associated with altered uptake or release of calcium by the sarcoplasmic reticulum, microvascular coronary disease or increased cross-linkage of collagen in the heart. However, the frequency of occurrence, nature and severity of cardiomyopathy in patients remain controversial (11) despite the unequivocally excess morbidity and mortality in patients with cardiac disease who happen also to have diabetes (12). Furthermore, the impact of rigorous control of diabetes on retarding the evolution of myocardial dysfunction has not yet been elucidated.

This study was performed to characterize the physical properties of myocardium by ultrasound tissue characterization (13–18) in diabetic patients without overt, conventional manifestations of cardiac disease and to determine whether the presence of altered acoustic properties of myocardium correlates with the presence and severity of noncardiac, systemic complications of diabetes. We did not undertake a correlative study with endomyocardial biopsies or coronary arteriography, because the risks of these invasive procedures were not deemed to be sufficiently low to justify their performance in patients without any signs or symptoms of cardiac disease.

Methods

Patients studied. Fifty-four patients with type I diabetes were recruited from the Washington University Diabetes Registry. Patients were enrolled after signing informed consent approved by the university's Human Studies Committee. They exhibited a broad range of age, duration of diabetes and spectrum of renal, retinal and neurologic com-

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plications. Clinical evaluation included a history and physical examination for assessment of blood pressure, body mass index, symptoms or signs of peripheral or autonomic neuropathy, and atherosclerosis. Laboratory tests included fasting glucose, glycated hemoglobin (by affinity chromatography, normal value = 4.4% to 6.3%), total cholesterol, creatinine and 24-h creatinine clearance and urinary protein. Ophthalmologic examination included funduscopic photography. Patients were excluded if a history of cardiovascular disease (symptoms or documented disease) or an abnormal electrocardiogram (ECG) was obtained. Myocardial tissue characterization with ultrasound was implemented by methods developed previously in our laboratory (13,14), and results were analyzed by two investigators (J.E.P. and A.D.W.) who were unaware of any of the characteristics of the patients.

Control subjects. Although our primary focus was on data analysis within the group of patients with diabetes and intragroup comparisons, a preliminary analysis involved comparisons with historical control subjects. These included 18 persons who had been referred for echocardiography because of suspicion of mitral valve prolapse, history of atypical chest pain or evaluation of ventricular function. They were shown to be nonhypertensive and nondiabetic by history and on the basis of conventional laboratory results. They were age-matched to the diabetic patient group studied. The control subjects had been studied previously, with the same instrumentation as that employed in this study, and the acquisition of myocardial backscatter data and its analysis had been identical (19).

Cardiac Studies

Two-dimensional, M-mode and Doppler echocardiography. Before tissue characterization studies were performed, conventional two-dimensional echocardiograms were acquired (Hewlett-Packard, Sonos 500 system, 2.5 MHz transducer) with multiple standard views (long- and short-axis, apical four- and two-chamber) for assessment of cardiac chamber anatomy and systolic left ventricular global and segmental function. From the parasternal views, M-mode echocardiograms were obtained to estimate left ventricular end-diastolic and end-systolic dimensions and septal and posterior wall thickness. Left ventricular fractional shortening was calculated as an index of systolic function (20). Pulsed Doppler echocardiographic measurements of the transmitral flow velocity profile were used to evaluate diastolic function by positioning a sample volume initially in the left ventricular inlet at the tip of the mitral valve as delineated in the apical four-chamber view. Spectral analysis of the flow velocity profile was displayed at 100 mm/s with low filter settings. The peaks of the early diastolic velocity wave (E) and the late diastolic (A; atrial contribution to filling) wave were measured (in cm/s) and their ratio (E/A) was determined. Deceleration time of mitral valve flow from the time of the peak early diastolic velocity (E) to the point at which velocity extrapolated to 0 in mid-diastole was measured in ms. By positioning the sample volume partially in the left ventricular outflow tract, the aortic systolic velocity and the mitral diastolic velocity waveforms could be recorded simultaneously. Isovolumetric relaxation time was measured in ms.

Tissue characterization with ultrasound (backscatter imaging). The tissue characterization system employed was developed and validated previously in our laboratory (21–26). With it, signals arriving from each transducer element are mixed to an intermediate frequency, phase-shifted, delayed and summed with signals from all other elements. The summed analog signal is digitized with 6-bit resolution (or 64 analog-digital steps) and sent to either a standard video processing path or a special integrated processor before scan conversion. The time constant of integration is 3.2 μs, and the dynamic range of the integrated backscatter processor is approximately 30 dB. The digitized integrated backscatter signal is reconverted to analog format and displayed in real time as a two-dimensional gray scale video image with 5-bit resolution (32 gray levels/pixel).

A linked M-mode acquisition and analysis system (25,26) permitted immediate analysis of myocardial integrated backscatter data obtained from the septum and posterior wall (parasternal long-axis view). M-mode integrated backscatter signals with 6-bit resolution were displayed in real time on the video screen with 5-bit resolution. Single M-mode frames of integrated backscatter images were recorded with a simultaneous ECG signal at a sweep speed of 50 mm/s, frozen on the imager's video screen and analyzed immediately to provide a measurement of the diastolic to systolic (cyclic variation) integrated backscatter over the cardiac cycle (27). A square analysis cell encompassing approximately 100 pixels was placed in the mid-myocardial region and adjusted to fit within the boundaries of the myocardial wall at end-diastole, avoiding the epicardial and endocardial specular bright echoes. The analysis cell was then moved across the frozen myocardial M-mode backscatter image for selection of integrated backscatter values stored in the imaging system's memory and computation of spatially averaged integrated backscatter values for the entire intramyocardial region of interest. A value for integrated backscatter was computed every 10 ms, displayed instantaneously to produce a plot of cyclic variation of integrated backscatter as a function of time and recorded on 0.5 in.- (1.27 cm-) video tape.

Once the transmit power and time-gain compensation controls had been set for each subject, they were not changed during the course of data acquisition. Because the acquired data represent the relative cyclic variation in the magnitude of integrated backscatter over four to six cardiac cycles rather than the absolute level of backscatter, it was not necessary to calibrate the instrument in absolute terms as long as the values of integrated backscatter remained within the dynamic range of the system throughout the cardiac cycle as was the case for each patient.

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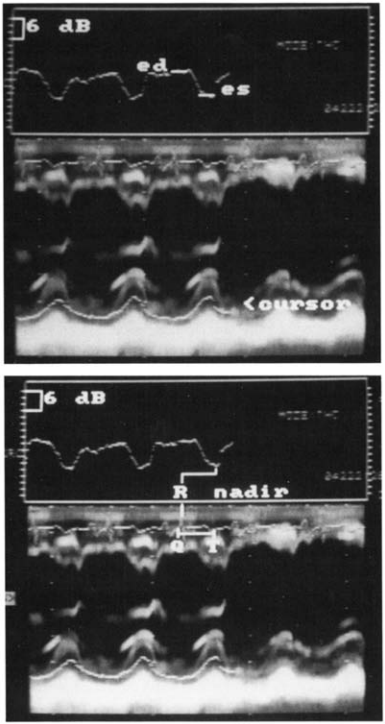

Figure 1. Top, M-mode integrated backscatter image frozen and recorded at the bedside at the time of data acquisition. The cursor was scrolled across the intramyocardial echoes (posterior wall in this example) to generate a tracing of the integrated backscatter **(upper panel)** over time with a vertical calibration of 2 dB/division. Cyclic variation (ed = end-diastole to es = end-systole) is noted. **Bottom,** The delay measurement was obtained by dividing the interval from the onset of inscription of the electrocardiographic R wave to the nadir of the integrated backscatter tracing by the QT interval, which yields a dimensionless value.

Magnitude of cyclic variation of backscatter. The magnitude of cyclic variation of integrated backscatter was calculated as the difference in backscatter at the onset of the Q wave of the ECG and the end of the T wave (end-diastole and end-systole) in decibels (Fig. 1, top). At least five measurements were averaged to yield a mean value of the magnitude of cyclic variation per region for each patient. This approach has been validated previously (19,25–27).

Delay of cyclic variation of backscatter. The delay of regional myocardial cyclic variation of integrated backscatter with respect to the onset of global electrical systole was expressed in terms of a dimensionless ratio. Delay was defined as the interval from the onset of the R wave on the ECG to the nadir of cyclic variation on the backscatter recording divided by the QT interval. It was calculated for the same sites as those used to determine the magnitude of cyclic variation of integrated backscatter as shown in Figure 1, bottom. Values exceeding unity are indicative of asynchronous regional contractile performance and have been described in patients with both temporally remote (24) and acute (25) myocardial infarction.

Statistical Analysis

M-mode, Doppler and measured integrated backscatter values were calculated off-line from the recorded video images with the use of a computer-assisted review station (Nova Microsonics). Results were tabulated and evaluated statistically with respect to results of clinical and other laboratory data in blinded fashion by one of the investigators (K.B.S.). For the purpose of analysis, patients with diabetes were grouped according to the presence or absence of peripheral neuropathy, retinopathy of any extent, nephropathy, the severity of noncardiac complications of diabetes (clinical score 0 to 8) and with respect to either poor or good control as judged from glycated hemoglobin values and duration of diabetes. The summated complication score devised values were assigned as follows: peripheral neuropathy (0 = none, 1 = clinically evident); autonomic neuropathy (0 = none, 1 = clinically evident); retinopathy (0 = none, 1 = background, 2 = proliferative), nephropathy (0 = none, 1 = <1 g/24 h proteinuria, 2 = nephrotic syndrome, 3 = serum creatinine >2 mg/dl or end-stage renal disease); hypertension (0 = none, 1 = present [blood pressure >150/90 mm Hg]). In addition to use of the overall score as described in the Results section, patients were grouped according to the presence or absence of neuropathy, retinopathy or nephropathy.

Comparison with control values. The myocardial integrated backscatter values measured in the heart of patients with diabetes with or without associated neuropathy, retinopathy or nephropathy and with specific clinical scores were compared also with values measured in the heart of age-matched control subjects among a group studied previously in our laboratory who had no cardiovascular disease or diabetes. However, the primary analysis focused on severity of changes within the diabetic patient group with respect to independent criteria of the severity of noncardiac, systemic complications.

Statistics. Data were analyzed with SAS software implemented on a SUN computer system of the Division of Biostatistics at Washington University. All continuous data

Table 1. Clinical Characteristics and Complications in 54 Patients With Diabetes

	All Diabetic Patients (n = 54)	Neuropathy		Retinopathy		Nephropathy	
		Present (n = 28)	Absent (n = 26)	Present (n = 38)	Absent (n = 16)	Present (n = 23)	Absent (n = 31)
Age (yr)	35 ± 10.5	36.9 ± 10.4	33 ± 10.5	36.5 ± 10.1	31.5 ± 10.8	34.7 ± 8	35.2 ± 12.1
Gender	26M/28F	17M/11F	9M/17F	24M/14F‖	2M/14F	12M/11F	14M/17F
History of smoking	14y/40n	10y/18n	4y/22n	11y/27n	3y/13n	6y/17n	8y/23n
HbA_1C (%)	12.2 ± 3.7	12.9 ± 4.3	11.5 ± 2.9	12.1 ± 4	12.6 ± 3.3	12.6 ± 4.6	11.9 ± 2.9
Cholesterol (mg/dl)	202 ± 51	210 ± 54	193 ± 45	202 ± 54	200 ± 43	219 ± 58*	189 ± 40
Hypertension	19y/35n	14y/14n§	5y/21n	16y/22n	3y/13n	14y/9n‖	5y/26n
Duration of diabetes (yr)	18.1 ± 8.5	21.6 ± 8†	14.3 ± 7.4	21.2 ± 7.1‡	10.6 ± 6.7	22.9 ± 6.1‡	14.4 ± 8.2

All values are mean values ± SD. *p = 0.02, †p < 0.001, ‡p < 0.0001 by analysis of variance, §p = 0.02, ‖p < 0.05 by chi-square analysis between those with and without the complication. F = female; HbA_1C = glycated hemoglobin; M = male; n = no; y = yes.

are presented as mean values ± SD. Chi-square tests were used to test the hypothesis of equal proportions. Whenever the necessary assumptions were satisfied, *t* tests were used to compare mean values in different groups. When sample standard deviations were significantly different, the Wilcoxon test was used as a nonparametric alternative to the *t* test. Analysis of covariance was employed to confirm that observed differences in backscatter variables (control subjects vs. patients with diabetes) were independent of age and the duration of diabetes and independent of the coexistence of hypertension among the diabetic patients with or without systemic complications.

Results

Clinical characteristics of the patients studied (Table 1). Gender, age, blood pressure, duration of diabetes, presence of systemic but noncardiac complications, glycated hemoglobin values and cholesterol values are shown in Table 1. All 54 patients studied had insulin-dependent diabetes; 18 were hypertensive.

Peripheral neuropathy was present in 28; mild or severe diabetic retinopathy in 38 and mild, moderate or severe nephropathy in 23 patients. Nineteen exhibited signs of autonomic nervous system dysfunction. There were no statistically significant differences in age, history of smoking or glycated hemoglobin values among patients with or without neuropathy, retinopathy or nephropathy. As expected, patients with diabetes of longer duration had a higher incidence of complications including neuropathy, retinopathy and nephropathy. Hypertension was more common in patients with nephropathy or neuropathy, but not those with retinopathy, than in patients without noncardiac complications.

Results with conventional and Doppler echocardiography (Table 2). In general, conventional echocardiographic findings did not differentiate patients with from those without noncardiac complications of diabetes. Left ventricular internal dimensions were normal in all patients studied, and left ventricular fractional shortening was normal in 96%. Dimensions did not differ in diabetic patients with or without peripheral neuropathy or retinopathy, or both. The patients with nephropathy had smaller internal dimensions than did those without nephropathy. Left ventricular septal and posterior wall thickness values were normal (<1.2 cm) in 91% and 96% of patients, respectively. Those patients with increased wall thickness were those who were found to be hypertensive.

As judged from results of Doppler studies (Table 2), none of the patients exhibited more than physiologic mitral regur-

Table 2. M-Mode and Doppler Echocardiographic Measurements in 54 Patients

	All Diabetic Patients (n = 54)	Neuropathy		Retinopathy		Nephropathy	
		Present (n = 28)	Absent (n = 26)	Present (n = 38)	Absent (n = 16)	Present (n = 23)	Absent (n = 31)
LVDD (cm)	4.6 ± 0.6	4.7 ± 0.6	4.6 ± 0.5	4.7 ± 0.6	4.5 ± 0.6	4.4 ± 0.6*	4.8 ± 0.5
LVSD (cm)	3 ± 0.5	3 ± 0.5	2.9 ± 0.5	3 ± 0.5	2.9 ± 0.3	2.9 ± 0.5	3.1 ± 0.5
FS (%)	36 ± 5.2	36.3 ± 4.7	35.8 ± 5.8	35.7 ± 4.8	36.7 ± 6.1	36.1 ± 4.6	36 ± 5.7
Septal thickness (mm)	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.1	1 ± 0.2*	0.8 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
Posterior wall thickness (mm)	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1†	0.8 ± 0.1	1 ± 0.1*	0.9 ± 0.1
E/A	1.2 ± 0.4	1.1 ± 0.3*	1.3 ± 0.3	1.1 ± 0.4*	1.4 ± 0.3	1 ± 0.3†	1.3 ± 0.4
DT (ms)	181 ± 40	189 ± 41	174 ± 35	186 ± 43	170 ± 28	182 ± 47	181 ± 34
IVR (ms)	86 ± 14	93 ± 20*	81 ± 9	90 ± 18	80 ± 9	90 ± 16	85 ± 17

All values are mean values ± SD. *0.01 < p < 0.05, †p < 0.01 comparing between those with and without the complication; DT = mitral valve deceleration time; E/A = ratio of the peak-to-the-late diastolic transmitral flow velocity; FS = left ventricular fractional shortening; IVR = isovolumetric relaxation period; LVDD = left ventricular end-diastolic dimension; LVSD = left ventricular end-systolic dimension.

Table 3. Myocardial Backscatter Measurements in 54 Patients With Diabetes and 18 Control Patients

	Control Nondiabetic Patients (n = 18)	All Diabetic Patients (n = 54)	Neuropathy		Retinopathy		Nephropathy	
			Present (n = 28)	Absent (n = 26)	Present (n = 38)	Absent (n = 16)	Present (n = 23)	Absent (n = 31)
IBs (dB)	4.6 ± 0.8	3.6 ± 1.4†	3.2 ± 1.0‡‖	4.1 ± 1.6	3.3 ± 1.3‡‖	4.4 ± 1.4	3.4 ± 1.4†	3.8 ± 1.4*
IBp (dB)	4.8 ± 0.8	4.0 ± 1.4*	3.6 ± 1.5¶‖	4.5 ± 1.1	3.9 ± 1.5†	4.4 ± 1.0	3.6 ± 1.5†	4.3 ± 1.2
Ds	0.86 ± 0.07	0.97 ± 0.19*	1.04 ± 0.21‡¶	0.89 ± 0.13	1.02 ± 0.2‡¶	0.86 ± 0.1	1.00 ± 0.17*	0.94 ± 0.2
Dp	0.86 ± 0.09	0.99 ± 0.15‡	1.04 ± 0.16‡§	0.94 ± 0.11	1.03 ± 0.16‡‖	0.91 ± 0.1	1.04 ± 0.17‡	0.96 ± 0.13*

All values are mean values ± SD. *$0.01 < p < 0.05$, †$0.001 < p < 0.01$, ‡$p < 0.001$ versus control nondiabetic patients; §$p = 0.06$, ‖$0.001 < p < 0.01$, ¶$p < 0.001$ versus absence of the complication (after adjustment for hypertension [analysis of covariance]). Dp = delay of cyclic variation in the posterior wall; Ds = delay of cyclic variation in the septum; IBp = cyclic variation of integrated backscatter in the posterior wall; IBs = cyclic variation of integrated backscatter in the septum.

gitation, and none exhibited stenosis or appreciable regurgitation at the site of any valve. The E/A ratio of mitral valve flow did correlate inversely with the clinical complications score, reflecting manifestations of diastolic dysfunction of the left ventricle ($r = -0.46$; $p < 0.001$). Patients with neuropathy or nephropathy had significantly lower E/A values than did those without these noncardiac systemic complications. The isovolumetric relaxation time in diabetic patients was higher than values reported for normal persons (28), although this index of diastolic function generally did not differ among the patients with or without noncardiac, systemic complications. Mitral valve deceleration time was normal in all patients and did not differentiate those with from those without systemic complications of diabetes. Thus, some of the Doppler indexes of diastolic function were abnormal in patients with noncardiac complications of diabetes as has been previously reported (29).

Results of tissue characterization with ultrasound (analysis of backscatter) (Table 3). When backscatter results in the entire group of diabetic patients (age 35 ± 10.5 years) were compared with values from the nondiabetic, normotensive, age-matched control subjects (10 male, 8 female) studied previously (age 37.5 ± 12.4; p = NS) who had normal ventricular dimensions (4.6 ± 0.3 and 3.1 ± 0.2 cm in diastole and systole, respectively), fractional shortening (31.7 ± 2.5%) and regional function, significant differences in cardiac acoustic properties were evident (Fig. 2). Cyclic variation of integrated backscatter in control subjects exceeded that in diabetic patients in the septum (4.6 ± 0.8 vs. 3.6 ± 1.4 dB; p = 0.001) and the posterior wall (4.8 ± 0.8 vs. 4.0 ± 1.4 dB; p = 0.02). Delay values in the two sites were lower in control subjects than in diabetic patients in the septum (0.86 ± 0.07 vs. 0.97 ± 0.19; p = 0.05) and the posterior wall (0.86 ± 0.09 vs. 0.99 ± 0.15; p = 0.001). To exclude possible confounding effects of hypertension on the data, the 35 normotensive diabetic subjects were evaluated separately; these patients still exhibited significantly prolonged delay and reduced cyclic variation values (except for cyclic variation in the posterior wall; p = 0.07). Furthermore, measurement of backscatter values differentiated groups of diabetic patients from each other strikingly (those with and those without the complications and those with low compared with high overall complication scores). Diabetic patients with peripheral neuropathy (Table 3) had significantly lower values of cyclic variation of integrated backscatter in both the septum and the posterior wall than did patients without neuropathy (Fig. 3). They also had significantly prolonged values of delay in the septum compared with values in patients without neuropathy. Diabetic patients with retinopathy had significantly lower values of cyclic variation of backscatter in the septum (Fig. 4) and greater delay values than those of patients without retinopathy. These significant differences remained after adjustment for hypertension as a covariate. However, among patients with or without nephropathy none of the acoustic variables exhibited significant differences when adjusted for hypertension.

Although differences in backscatter variables among groups with and without the systemic complications of diabetes were significant, there was some overlap, precluding the definition of precise cutoff values of backscatter with narrow confidence limits for separation of individual pa-

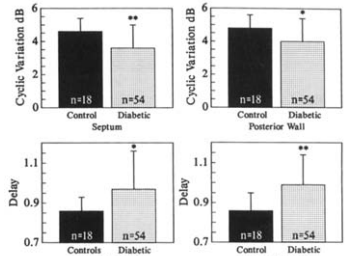

Figure 2. Comparison of backscatter variables (cyclic variation in dB, **upper panels** and delay, **lower panels**) in the septum and posterior wall in the control group (patients without diabetes studied previously) and in the group of diabetic patients evaluated in the present study. **$0.001 < p < 0.01$ versus control subjects; *$0.01 < p < 0.05$ versus control subjects; **error bars** represent SD.

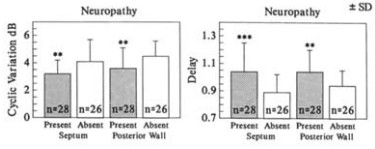

Figure 3. Comparisons of cyclic variation and delay values in each myocardial wall in patients with diabetes with (Present) and those without (Absent) neuropathy. ***$p < 0.001$ compared with values in patients without neuropathy; **$0.001 < p < 0.01$ compared with values in patients without neuropathy.

tients. Nevertheless, the observed differences in backscatter variables among patients with and without neuropathy and retinopathy were significant and independent of the presence or absence of hypertension. Overall, cyclic variation of backscatter in both the septum and the posterior wall correlated inversely ($r = -0.32$, $p = 0.01$ and $r = -0.40$, $p = 0.002$) with the clinical complications score whereas delay values correlated directly with the complications score ($r = 0.35$, $p = 0.009$ and $r = 0.41$, $p = 0.002$). Thus, altered magnitude and delay of cyclic variation of backscatter consistent with occult myopathic processes reflected by changes in acoustic properties of the heart were hallmarks of the presence of diabetes associated with severe, noncardiac complications despite the presence of normal ventricular size and function as judged from results of conventional echocardiographic analysis (Fig. 5).

Discussion

Detection of abnormal myocardial acoustic properties. Our results indicate that patients with insulin-dependent diabetes associated with noncardiac systemic complications often manifest occult changes suggestive of cardiomyopathy as well, detectable by quantitative tissue characterization of the heart with ultrasound. The abnormally low values of cyclic variation of integrated backscatter and its considerable delay are likely to reflect early cardiomyopathic changes perhaps attributable to deposition of collagen in the heart as is the case, with diabetes, in other organs (30–33). Detection of such changes may be analogous to detection and quantification of glycated hemoglobin (A1C) in that both may provide indexes of the biologic impact of the disorder integrated over time. It is of course possible that the changes we observed are related to hyperinsulinemia rather than to diabetes itself. Studies are in progress to correlate changes detectable by ultrasound backscatter interrogation of the heart with prevailing insulin levels and the severity of diabetes in noninsulin-dependent patients to clarify this issue.

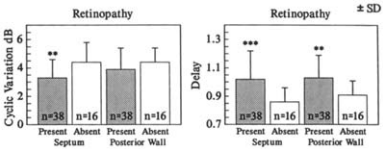

Figure 4. Comparisons of cyclic variation and delay values in each myocardial wall among patients with diabetes with (Present) and without (Absent) retinopathy. ***$p < 0.001$ compared with values in those without retinopathy; **$0.001 < p < 0.01$ compared with values in those without retinopathy.

With backscatter imaging, abnormal acoustic properties in tissue can be recognized despite preserved normal systolic function and normal left ventricular chamber dimensions. Early signs of diastolic dysfunction were suggested by some of the Doppler measurements in the diabetic patients as well, consistent with previous observations in young diabetic patients (29). However, early structural derangements such as those implied by the abnormal backscatter data in our patients have not been detected previously with noninvasive techniques or associated with the presence and severity of noncardiac complications of diabetes.

Backscatter and collagen. We (30) have previously shown that quantitative tissue characterization with ultrasound detects altered physical characteristics of myocardium in experimental animals and humans. Marked increases in absolute values of integrated backscatter are seen in zones of temporally remote infarction and correlate with increases in collagen content delineated biochemically. Similar increases have been correlated with cardiomyopathic changes secondary to doxorubicin (31). In the heart of Syrian hamsters with hereditary cardiomyopathy, backscatter values increase with the age of the afflicted animal and in association with the development of fibrosis (32). Absolute backscatter values in the human heart correlate with the collagen content of tissue (34) as judged from higher values in the right than in the left ventricle and the correspondingly higher collagen content of the right ventricular wall (35).

Cyclic variation of integrated backscatter. Measurement of cyclic variation of backscatter permits assessment of dynamic properties of the heart reflecting the physical state of the tissue (36). Cyclic variation is decreased in hypokinetic regions of temporally remote myocardial infarcts in the heart of experimental animals (22) and patients (24). Hearts with end-stage dilated cardiomyopathy exhibit widespread, markedly decreased cyclic variation of backscatter (23). These observations and those of Masuyama et al. (37), who evaluated cyclic variation as a function of age of the subject, are consistent with the view that decreased cyclic variation of backscatter may reflect the extent of deposition of collagen in the heart. Our results are consistent with the hypothesis that diabetic patients with severe disease have altered myocardial acoustic properties consistent with increased accumulation or cross-linkage of collagen in the heart detectable by tissue characterization with ultrasound and pre-

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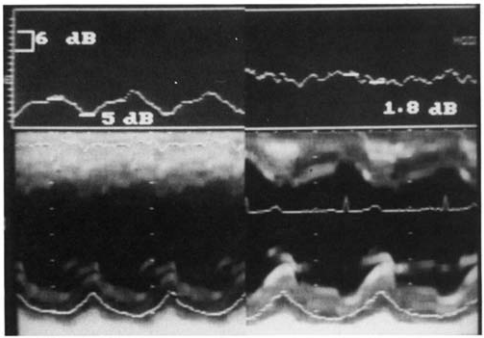

Figure 5. Comparison of a typical M-mode integrated backscatter image from a patient with diabetes with a low clinical complications score (**left panel**, posterior wall cyclic variation of 5 dB with normal delay) with that from a patient with diabetes with a high score (**right panel**, posterior wall cyclic variation of 1.8 dB with prolonged delay). Results differ despite comparable and normal segmental systolic function measured conventionally in both patients.

ceding deterioration of cardiac function detectable by conventional echocardiography.

Reduced cyclic variation of backscatter may, of course, not be tantamount to accumulation of collagen. Regions of severe hypokinesia or akinesia in the heart of patients with acute myocardial infarction may exhibit recovery of cyclic variation of backscatter after coronary recanalization with thrombolytic drugs (25). Transient reductions in cyclic variation accompany rejection of cardiac allografts (38) with recovery of cyclic variation inducible by intensive antirejection therapy. We cannot completely exclude the possibility that the diabetic patients studied could have had macrovascular or diffuse microvascular coronary disease. Our results do not imply that the abnormal myocardial acoustic properties detected in the diabetic patients occur in the absence of occult coronary disease. In fact, they could be a reflection of such occult disease and a marker of it. However, the diffuse nature of the altered acoustic properties of the heart that were detected, the lack of abnormal segmental systolic ventricular function and the lack of ECG abnormalities in the patients studied coupled with the lack of symptoms or signs of coronary artery disease lead us to a different conclusion. We believe that the abnormal myocardial backscatter indexes seen in the presence of preserved segmental and global systolic function at rest are best explained as reflecting abnormalities of a structural nature, particularly deposition of collagen. Further support for this interpretation comes from the observation that an ECG exercise stress test obtained retrospectively in the 12 patients with the most abnormal backscatter indexes was abnormal in only 1 patient and that results of echocardiographic stress tests were negative as well. One other patient with echocardiographic criteria indicative of old infarction underwent cardiac catheterization and was found to have coronary artery disease.

Collagen deposition in diabetes. Deposition of collagen is a well recognized characteristic in diverse organs in diabetic patients. Monnier et al. (33) demonstrated increased fluorescence attributable to collagen associated with severe diabetic retinopathy, stiffened arterial walls and diminished mobility of joints. Collier et al. (39) showed that skin thickness reflected collagen content and was increased in patients with type I diabetes. Dominiczak et al. (40) demonstrated increased cutaneous fluorescence attributable to collagen in such patients in relation to the duration of disease and the age of the patient.

Brownlee et al. (41) suggested that deposition of collagen in diabetic patients is a reflection of chronic hyperglycemia. They postulate that glucose combines with the amino groups of proteins to form Schiff bodies that rearrange into Amadori products eventually forming irreversible, glycosylation products. Such products can promote cross-linkage of collagen and accumulation of matrix proteins. Our results are consistent with the hypothesis that accumulation of collagen is responsible for alterations in the acoustic properties of the heart in diabetic patients with severe or prolonged disease that are, in fact, preclinical signs of occult cardiomyopathy. Direct histologic evidence of increased collagen in tissue was not acquired because myocardial biopsy (with its morbidity of ≥3.4%) was not deemed justified (42) in these patients who had no conventional signs or symptoms of cardiac disease.

Implications with respect to diabetic cardiomyopathy. Increased stiffness of myocardium occurs in the heart of animals with experimentally induced diabetes and is associated with deposition of material with histochemical characteristics of collagen (43). Our group (5) has documented increased impairment of cardiac function and more severe congestive heart failure in diabetic than in nondiabetic patients with acute myocardial infarction of comparable extent. Similar results were obtained in a large group of patients as well (44).

Delineation of cardiomyopathy in diabetic patients has

been elusive even when the left ventricular ejection fraction response to exercise is reduced. As Borow et al. (45) have shown, patients with diabetes exhibit normal contractile reserve after stimulation with dobutamine. Furthermore, both load- and heart rate-independent indexes of contractility are apparently normal. However, recent data from the Framingham study (46) with the use of two-dimensional echocardiography support the hypothesis that cardiomyopathy is present in at least some diabetic patients.

Conclusions. Our results indicate that application of ultrasound tissue characterization to the study of diabetic patients can detect occult myocardial acoustic changes suggestive of cardiomyopathy at a time when systolic ventricular performance at rest has not deteriorated and that the changes observed are present most often when the diabetes has been prolonged or severe, as judged from the presence of noncardiac complications. The results suggest that cardiac involvement can be recognized before ventricular function has become impaired and when arrest of the progression or reversal of cardiomyopathy may be possible. Thus, tissue characterization of myocardium with ultrasound based on quantitative backscatter imaging may be useful in longitudinal studies designed to assess the efficacy of therapeutic measures designed to retard or preclude adverse effects of diabetes on the heart.

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