Original Paper

Regression of Left Ventricular Hypertrophy in Diabetic Nephropathy: Loss of Parasympathetic Function Predicts Response to Treatment

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Both left ventricular (LV) hypertrophy and decreased autonomic function are predictors of adverse cardiac events. Patients with diabetic nephropathy have an excess cardiovascular risk. The authors determined heart rate variability from 24-hour ambulatory electrocardiographic recordings and measures of LV mass with systolic and diastolic function from echocardiograms. Patients with diabetic nephropathy (n=16) were seen weekly for insulin and hypertension management. Glycohemoglobin decreased from 9.5±0.4% to 8.3±0.4% (p=0.01), and advanced glycated end products decreased from 12.1±2.2 to 7.4±1.2 units (p=0.03). Mean arterial pressure and body weight did not change. Serum creatinine increased (1.8±0.1 mg/dL to 2.0±0.2 mg/dL; p=0.03). The authors used a panel of markers of baseline heart rate variation to assess autonomic function. When covariance of the heart rate interval results were evaluated, the group below the median was found to have a significant decrease in LV mass, from 230 g to 184 g (p=0.013); the group above the median had an increase (182 g to 193 g; p=0.5329). Baseline covariance of the heart rate interval predicted 12-month changes in LV mass in 13 of 16 patients (predictive accuracy, 81%). Improvement in measures of heart rate variation correlated with a decrease in LV mass. Parallel improvement of LV mass and autonomic function suggests a common mechanism, allowing for prediction of LV mass improvement through analysis of baseline heart rate variation. (J Clin Hypertens. 2006;8:330–335) ©2006 Le Jacq Ltd.

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Increases in left ventricular (LV) mass and decreases in LV function have individually been associated with excess cardiovascular morbidity and mortality in both acute[1,2] and chronic studies.[3,4] Increases in LV mass have been postulated to be due to trophic and hemodynamic stresses. Loss of parasympathetic function as a result of long-term diabetes mellitus may be a major factor in excess cardiac mortality. In this prospective study, we postulated that LV remodeling and parasympathetic improvement could both be attained by aggressive treatment of hypertension and hyperglycemia. We suspected that these changes over 12 months would be closely correlated with each other. If these concepts are correct, it would be reasonable to expect that baseline tests might be useful in predicting subsequent changes.

METHODS

Patients were prospectively and consecutively enrolled as part of a multicenter study involving seven institutions in the United States. Inclusion criteria included a run-in period to assure optimal (<140/90 mm Hg) blood pressure (BP) control before the initiation of the study, and were as follows: 1) onset of insulin dependence before the age of 35; 2) albuminuria of >0.1 g/d or proteinuria of >0.3 g/d on two separate 24-hour urine collections; 3) creatinine clearance of >30 cc/min; and 4) absence of pregnancy or acute or chronic illness that would render testing uninterpretable (e.g., drug dependence, recent myocardial infarction, or stroke). Enrollment in this study required an evaluation of several weeks to collect the required urine samples and confirm the level of control of diabetes and BP.

All patients were treated with at least four daily doses of insulin. Oral hypoglycemic agents were not used in this study (average daily dose of insulin was 45 U at entry and 42 U at 12 months). Management of hypertension was commenced preferentially with angiotensin-converting enzyme (ACE) blocking agents, if tolerated. No patients were treated with angiotensin receptor blockers. Given the importance of BP control in diabetic patients with renal disease, medication regimens were regulated with the help of quarterly ambulatory BP monitoring. We attempted to avoid the use of any drug that was, at the time, known to exert major effects on the autonomic nervous system that would interfere with either the patient's sensation of hypoglycemic reactions or with the testing of cardiac autonomic function. Patients underwent 24-hour ambulatory BP measurements (model 90207, Spacelabs Medical, Issaquah, WA). Glycohemoglobin A_{1c} was measured at baseline and 12 months (high-pressure liquid chromatography, Nichols Institute, Van Nuys, CA).

Three-channel, 24-hour electrocardiographic recordings were obtained at baseline and 12 months. The studies were analyzed on a commercially available scanner (Zymed Medical Instruments, model 1610, Camarillo, CA). After a normal QRS was chosen, computer-assisted rate and arrhythmia analyses were performed with a cardiologist and technician overreading and editing. Excessive noise and artifact were noted and ectopy was quantified. After technician analysis and physician review, the results were downloaded into a computer and analyzed using software developed by Zymed. The program produced a panel of measurements of the RR interval and various derivations of the RR interval (Table I).

Table I. Panel of Measurements of the RR Interval and Various Derivations of the RR Interval

Time domain intervals
Average heart rate
Average RR interval (NN)
SD of the RR intervals over a 24-hour period (SDNN)
SD of all 5-minute mean RR intervals (SDANN)
Average SD of all 5-minute RR intervals (ASDNN)
Percentage of RR intervals with >50 ms variation (pNN50)
Square root of mean squared differences of successive RR intervals (RMSSD)
Covariance of the RR intervals (CVNN)
Frequency domain indices
Total power spectrum (0–0.4 Hz)
High-frequency power (HF, 0.015–0.4 Hz)
Low-frequency power (LF, 0.04–0.15 Hz)
Very-low-frequency power (VLF, 0.003–0.04 Hz)
Ultra-low-frequency power (ULF, ≤0.003 Hz)

Echocardiography was performed to assess the structure and function of the heart using standard echocardiographic views and measurements at baseline and 12 months (Hewlett Packard, model 2500 or 5500, Andover, MA).

Frequency data were tested for significance using Fisher's exact test since expected frequencies were less than five. For quantitative variables, unpaired *t* tests were used to test for significance between the means of various classification variables (gender, normal/abnormal stratification of cardiac autonomic function). The paired *t* test was used for changes in variables over time. Interrelationships among the variables were tested for significance using Pearson's product moment correlations. All data are expressed as frequencies or means with SEM as a measure of dispersion. An α level of 0.05 was considered statistically significant. All analyses were carried out using SAS software (SAS Institute, Cary, NC).

RESULTS

Sixteen insulin-dependent, juvenile-onset diabetics between the ages of 21 and 65 years (mean age, 42.4 years; range, 33–64 years) were enrolled in this study (Table II). Better control of glycemia was achieved, while renal function diminished and mild anemia worsened. Table III demonstrates the evaluation of LV structure and function at baseline and 12 months for the 16 patients. There was no significant change over time in BP, LV mass, septal thickness, or parameters of systolic or diastolic function for the total group.

Table II. Demographic Data for 16 Patients (10 Males) Aged 33–64 Years, at Baseline and 12 Months

Parameter (Mean ± SEM)	Baseline	12 Months	*P* Value
Glycohemoglobin A_{1c} (%)	9.5±0.4	8.3±0.4	0.01
Advanced glycated end products (units)	12.1±2.2	7.4±1.2	0.03
Serum creatinine (mg/dL)	1.8±0.1	2.0±0.2	0.03
Creatinine clearance (mL/min)	55±3	50±5.0	0.20
Hemoglobin (g/dL)	13.5±0.4	12.2±0.4	0.01
Hematocrit (%)	39.5±1.4	36.6±1.3	0.01
Systolic blood pressure (mm Hg)	140±3	141±2	0.64
Diastolic blood pressure (mm Hg)	81±2	81±1	0.93
Mean arterial pressure (mm Hg)	100±2	101±2	0.60
Weight (kg)	72.8±2.5	72.8±2.9	1.00

Table III. Left Ventricular Structure and Function at Baseline and 12 Months

Parameter (Mean ± SEM)	Baseline	12 Months	*P* Value
Left ventricular mass (g)	206.1±13.8	187.5±14.7	0.11
Left ventricular septum (mm)	10.25±0.36	9.63±0.42	0.08
Fractional shortening (%)	38.8±1.4	38.8±1.5	0.97
Ejection fraction (%)	60±2	60±2	1.00
Left ventricular compliance (ratio)	1.19±0.07	1.22±0.08	0.56

Heart rate variability was significantly depressed in the time and frequency domains (Table IV) at baseline and 12 months. There were no significant changes in time and frequency domain measures of autonomic function over 12 months with the exception of the very low frequency measure (p=0.03).

Baseline autonomic function test results above vs. below the median were used to define two groups: 1) the group with a baseline heart rate variability (CVNN) result above the median demonstrated an increase in LV mass from 182 g to 193 g (p=0.5329); 2) the group with a CVNN result below the median demonstrated a reduction in LV mass from 230 g to 184 g (p=0.0013). Thus, the group with greater cardiac autonomic impairment at baseline had a significantly larger LV mass, a reduction in LV mass (p=0.005), and an increase in ejection fraction (p=0.009) over 12 months. Baseline BP (140/81 mm Hg; mean arterial pressure [MAP], 100 mm Hg) did not change at 12 months. This comparison of baseline CVNN levels (above vs. below the median) identified 13 of 16 study subjects with respect to changes in LV mass over 12 months (sensitivity, 77%; specificity, 86%; positive predictive value, 88%; negative predictive value, 75%; predictive accuracy, 81%). The relationships of baseline CVNN results to changes in LV septal thickness, compliance, fractional shortening, or ejection fraction were not statistically significant. Square root of mean squared differences of successive RR intervals results above the median were associated with an improvement in diastolic compliance (p=0.0298): E/A 1.19 to 1.26 vs. 1.19 to 1.16 for the group below the median (p=0.6648). There was a correlation in the total group among baseline low frequency, SD of the RR intervals, and the observed change in LV mass over time (r=+0.52; p=0.04; –0.53, 0.04 respectively).

Table V sets forth the comparison of baseline autonomic data (above vs. below the median) to changes in cardiac structure and function over 1 year. Table VI lists significant negative correlations between changes in time and frequency variables vs. changes in LV mass over 12 months.

DISCUSSION

We have previously noted that LV mass improved with glycemic control over time[5] and have also described improvement in autonomic function with metabolic control.[6] In a large cohort of hypertensive patients, inappropriate LV hypertrophy was demonstrated to be an independent predictor of risk for morbidity and mortality.[7] We hypothesized that unopposed sympathetic tone in diabetic patients with increased LV mass would exacerbate diastolic dysfunction.[8] We postulated that downregulating sympathetic stimulation by pressor and glycemia control would result in a greater impact in hearts that had sustained the greatest impairment of baseline parasympathetic function.

The present study had a two-fold purpose: 1) to determine whether the most abnormal autonomic baseline function would predict the greatest susceptibility to LV remodeling (reduction of LV hypertrophy) from glycemic and hypertensive control; and 2) to determine whether there is a correlation between therapeutic LV remodeling and improvement in autonomic function over time of therapy.

With respect to the value of baseline autonomic function to predict LV remodeling, we found that

Table IV. Autonomic Function at Baseline and 12 Months

Parameter (Mean ± SEM)	Normal	Baseline	12 Months	*P* Value
Time domain variables (ms)				
Average RR interval	667–1000	711.3±16.3	723.3±19.1	0.18
SD of the average RR interval over a 24-h period	141±39	81.1±5.9	79.3±4.9	0.90
SD of all 5-min mean RR intervals	127±35	75.6±5.9	72.9±4.4	0.79
Average SD of all 5-min RR intervals		27.1±2.5	26.9±2.3	0.80
% of RR intervals with >50 ms variation		0.64±0.26	1.11±0.80	0.53
√ of mean squared differences of successive RR intervals	27±12	9.9±1.3	11.2±1.6	0.41
Covariance of the RR intervals		11.4±0.8	10.9±0.6	0.61
Frequency domain variables (Hz)				
High frequency (HF)	975±203	59.6±25.7	36.1±7.3	0.37
Low frequency (LF)	1170±416	180.3±60	119.3±29	0.14
LF/HF ratio	1.5–2.0	3.77±0.43	3.37±0.44	0.25
Very LF		715.0±166.4	411.2±72.3	0.03
Ultra LF		7186±1624	5654±830	0.30

Table V. Comparison of Baseline Autonomic Data (Above vs. Below the Median) to Changes (Δ) in Cardiac Structure and Function Over 1 Year (*t* Test)

Autonomic Test	Δ LVM	Δ LV Septum	Δ Fractional Shortening	Δ Ejection Fraction	Δ Diastolic Compliance
SDNN	0.09	1.00	0.94	0.24	0.94
SDANN	0.09	1.00	0.94	0.24	0.94
pNN50	0.99	0.93	0.72	0.55	0.12
RMSSD	0.95	0.83	0.49	1.00	0.05
CVNN	0.005	1.00	0.41	0.009	0.84
LF	0.37	0.27	0.62	1.00	0.72
HF	0.40	0.13	0.88	0.56	0.87

LVM=left ventricular (LV) mass; SDNN=SD of the RR intervals over a 24-hour period; SDANN=SD of all 5-min mean RR intervals; ASDNN=average SD of all 5-min RR intervals; pNN50=% of RR intervals with >50 ms variation; RMSSD=√ of mean squared differences of successive RR intervals; CVNN=covariance of the RR intervals; LF=low frequency; HF=high frequency

CVNN (covariance: the percent the SD is of the average RR interval) was useful in that patients with low covariance responded to treatment by reduction of LV hypertrophy with a high predictive accuracy. Thus, the group with greater cardiac autonomic impairment at baseline had a significantly larger LV mass, a reduction in LV mass (p=0.005), and an increase in ejection fraction (p=0.009) over 12 months. There were no significant differences between the groups with high as opposed to low covariance with respect to gender; age; or baseline or change in weight, serum creatinine, MAP, insulin requirement, glycohemoglobin, or advanced glycated end product. Baseline BP (140/81 mm Hg; MAP, 100 mm Hg) did not change at 12 months.

With respect to the relationship between changes in both autonomic function and LV mass over time, the present prospective study demonstrates that improvement in parasympathetic function correlates significantly with improvement in increased LV mass, a finding suggested by prior cross sectional studies[9–16] that span the spectrum of renal function from normal to dialysis dependency. This statistical correlation between improvement in autonomic function and remodeling of ventricular architecture suggests common mechanisms.

Our target BP of <140/90 mm Hg is similar to that of a large prospective study of 1590 diabetic patients with nephropathy.[17] In that study, angiotensin receptor blockade, usually with a diuretic, was used to achieve a BP <135/85 mm Hg (MAP, 102 mm Hg), demonstrating that patients with BP <120/85 mm Hg (MAP, 97 mm Hg) had a statistically significant increased incidence of myocardial morbidity and mortality. In our study, the achieved MAP was 100 mm Hg at baseline, and 101 mm Hg at 12 months. Patients with no change in BP had a similar change in LV mass to patients with a change in BP. Thus, the BP differences did not account for changes in cardiac morphology or function.

Our study group achieved an average glycohemoglobin of 8.3% at 12 months. In a study of type 1 diabetic patients followed for 18 years, the group that achieved a glycohemoglobin level

Table VI. Correlation Between Change in Autonomic Function or Clinical Data With Respect to Change in Left Ventricular Mass Over 12 Months (N=16)

	R Value	*P* Value
Autonomic tests (heart rate variations)		
SD of the RR intervals over a 24-hour period	–0.53	0.04
SD of all 5-min mean RR intervals	–0.53	0.04
% of RR intervals with >50 ms variation	–0.57	0.02
Covariance of the RR intervals	–0.59	0.02
√ of mean squared differences of successive RR intervals	–0.47	0.08
Low frequency	–0.59	0.02
High frequency	–0.63	0.01
Clinical and laboratory data		
Weight	0.34	0.23
Mean arterial pressure	–0.35	0.19
Glycohemoglobin A_{1c}	0.24	0.37
Advanced glycated end products	–0.59	0.07
Insulin dose	0.18	0.54
Serum creatinine	0.73	0.80

<8.4% had significantly less evidence of diminished heart rate variation than the group that had a glycohemoglobin level >8.4%.[18] Animal models of uncontrolled diabetes demonstrate high catecholamine levels, down-regulation of cardiac adrenoreceptors, and diastolic dysfunction. These pathologic mechanisms have been reversed by the use of insulin[19] or angiotensin-converting enzyme inhibition[20] or blockade of formation of advanced glycated end products.[20] Our results in both genders of type 1 diabetic patients confirm a relationship between altered parasympathetic function and diminished diastolic compliance previously noted in type 2 diabetic men.[21]

The most common explanations for the cardiac dysfunction found in diabetic patients with renal insufficiency include concomitant coronary artery disease, fluid overload, uremia, and hypertension. Hyperglycemia, in addition to its hemodynamic effects, increases catecholamine levels and down-regulates cardiac adrenoreceptors, leading to ventricular diastolic dysfunction. Although cardiac remodeling is most often considered hemodynamically mediated, the similar hemodynamic profiles in our groups suggest metabolic sources, or a reset of autonomic receptors or cardiomyocyte responsiveness to growth factors. It is reasonable to assume that unopposed sympathetic stimulation would have resulted in greater LV mass (and decreased LV compliance). Reduction of the sympathetic tone would, in such cases, be more likely to therapeutically modulate hypertrophy (and diastolic function). It is not clear whether pharmacologic blockade of the adrenergic receptor can achieve the same LV remodeling as down-regulation of sympathetic tone achieved through metabolic improvement.

Mechanisms for cardiac dysfunction in uncontrolled diabetes have been studied in animal models. Ventricular size enlarges with the accumulation of collagen bound to advanced glycated end products, a pathologic process that can be prevented by the administration of insulin or aminoguanidine, which inhibit the formation of advanced glycated end products. ACE inhibitors also prevent the accumulation of advanced glycated end products in ventricular tissue.[20–22] A similar observation demonstrated inhibition of cardiac adrenoreceptors 1 and 2 plus stimulation of receptor 3, culminating in a negatively inotropic response to uncontrolled glycemia. These adrenoreceptor changes were reversed by insulin replacement.[21] Experimental animals demonstrating cardiac accumulation of collagen have been shown to have altered myocardial pressure–volume curves that correct to normal by inhibition of the production of angiotensin II or advanced glycated end products.[20,22] The enzyme responsible for energy production in diastole was shown to be impeded by advanced glycated end products and restored by insulin administration.[23]

We demonstrate herein that diabetic patients with nephropathy and severe cardiac autonomic dysfunction may, through a common mechanism, have parallel improvement in both LV mass and autonomic function through intensive therapy, which improved sympathetic tone by restoring glycemic control.

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