Original Paper

Left Ventricular Mass Reduction in Type 1 Diabetic Patients With Nephropathy

Larry A. Weinrauch, MD;[1,3,4] Andrew Burger, MD;[1,2] Ray E. Gleason, PhD;[1]
Annette T. Lee, PhD;[5] John A. D'Elia, MD[1,2,3]

Left ventricular hypertrophy regression was postulated more likely to occur in diabetic patients when renal function was preserved. Seventeen type 1 diabetic patients followed for 12 months while receiving protocol-driven glycemic and blood pressure control had baseline and 12-month echocardiography. Despite identical treatment resulting in similar blood pressures, patients with better renal function (below the group mean, serum creatinine ≤1.7 mg/dL) demonstrated reduction in left ventricular mass and septal thickness as well as increase in left ventricular fractional fiber shortening not observed in those with worse renal function (above the group mean, serum creatinine >1.7 mg/dL). This latter group also did not experience the improvement in glycemic control observed in those with better renal function. Regression of left ventricular mass and functional improvement can be accomplished with improved glycemic control. In the presence of renal dysfunction, however, efforts to control glycemia and cardiac work are suboptimal. Aggressive glycemic and blood pressure targets to reduce cardiovascular morbidity in this high-risk population should be studied. (J Clin Hypertens. 2005;7:159–164) ©2005 *Le Jacq Ltd.*

From the Harvard Medical School, Boston, MA;[1] Beth Israel Deaconess Medical Center, Boston, MA;[2] Joslin Diabetes Center, Boston MA;[3] Mount Auburn Hospital, Cambridge, MA;[4] North Shore University Hospital, Manhasset, NY[5]
Address for correspondence:
Larry A. Weinrauch, MD, 521 Mount Auburn Street, Watertown, MA 02472
E-mail: lweinrauch@hms.harvard.edu
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Left ventricular (LV) diastolic dysfunction and left ventricular hypertrophy (LVH) increase in prevalence with the duration of diabetes mellitus and hypertension. Type 1 diabetic patients show a high prevalence of LV diastolic dysfunction and LVH once albuminuria is noted.[1] Those individuals who respond to antihypertensive therapy by regression of hypertrophy and improvement of diastolic function can be expected to have a lower incidence of cardiovascular events compared with matched patients who develop LVH or whose LVH does not respond to therapy.[2] Reduction of LV mass and improvement in diastolic function have been observed over 12 months of intensive control of glycemia and blood pressure (BP) in patients with type 1 diabetes mellitus with proteinuria. The purpose of this study is to determine whether these improvements are dependent upon either level of renal function at the onset of treatment or stability of renal function over time.

PATIENTS AND METHODS

Seventeen patients (12 men, 5 women) between the ages of 21 and 65 years (mean age 41±2 years), enrolled as part of a cooperative study designed to determine whether aggressive glycemic control slowed progression of renal dysfunction in diabetic nephropathy.[3] All patients had insulin-dependent diabetes with onset before age 35; albuminuria >0.1 g/d and/or proteinuria >0.3 g/d on two separate 24-hour urine collections; creatinine clearance (CrCl) of >30 mL/min; and were without pregnancy, acute or other chronic illness (e.g., drug dependence, active liver disease, recent myocardial infarction, or stroke). All received a daily regimen of four subcutaneous injections of insulin. One half received weekly infusions of IV insulin.[4] BP was assessed clinically and by quarterly ambulatory 24-hour BP

monitoring (SpaceLabs Medical, Redmond, WA). During ambulatory monitoring, BP was recorded every 20 minutes during the day (8 a.m. to 10 p.m.) and every 30 minutes at night (10 p.m. to 8 a.m.). BP control was achieved preferentially with initial angiotensin-converting enzyme inhibition unless otherwise contraindicated, with a goal of achieving a maximum systolic BP of <140 mm Hg and diastolic BP of 90 mm Hg.

Doppler echocardiography (Hewlett Packard, model 2500 or 5500, Andover, MA) was performed on entrance into the study and at 1 year. Images were obtained in the parasternal long-axis, short-axis, apical four-chamber and apical two-chamber views. An experienced reader, shielded with regard to the patient's clinical data and sequence of studies, obtained all measurements directly from the two-dimensional images. LV internal diameters were measured in the parasternal long-axis view at the level of the papillary muscles at end diastole and end systole. Septal and posterior wall thickness were determined in the same view at end diastole. The LV long axis was measured in the apical four- and two-chamber views, with the longer of the two measurements used to calculate the LV mass by the area-length method. Fractional shortening was calculated as the difference between end diastolic and end systolic diameter divided by the end diastolic diameter and multiplied by 100. Pulse-wave Doppler echocardiography of the LV mitral inflow was obtained in the apical four-chamber view with the sample volume positioned at the tips of the mitral valve leaflets. Peak early inflow, deceleration time of the early inflow velocity, and peak atrial inflow were determined. Plasma levels of advanced glycated end products (AGE) were measured at baseline and 1 year by enzyme-linked immunosorbent assay using polyclonal antibodies to AGE-modified proteins.[4–7] Quantitative data were tested for significance using unpaired *t* tests for significance between the means of different groups. Paired *t* tests were employed to test for significance between the means of the same groups at different time intervals. All data were expressed as means with standard error as a measure of dispersion. An $\alpha \leq 0.05$ was considered significant. All statistical analyses were carried out using SAS software (SAS Institute, Cary, NC).

RESULTS

Laboratory parameters for the entire group of patients at baseline and 12 months are depicted in Table I. The 17 patients demonstrated significant decrease in hemoglobin (Hgb), hematocrit (Hct), glycohemoglobin (HbA_{1c}) and AGE products, while the serum creatinine (SCr) rose significantly.

LV Mass

Regression of LV mass of ≥20 g was noted in 10 of the 17 patients in this study. This group of patients had a mean decrease in mass of 46±7 g (221±14 g vs. 175±17 g, p=0.0001). The group of seven patients who did not meet criteria for decreased LV mass had a mean increase of 20±12 g (186±24 g vs. 205±23 g, p=0.1586; difference between groups p=0.0002).

The two groups defined by changes in LV mass were different with respect to baseline and 12-month SCr level, as well as change in CrCl over 12 months. The 10 patients with a decrease in LV mass maintained mean CrCl at 63 mL/min. The seven patients without a decrease in LV mass decreased CrCl from 54 mL/min to 40 mL/min (p=0.0305). CrCl between these groups was not different at baseline, but was significantly different at 12 months (p=0.0436). Mean arterial pressures (MAPs) were different at baseline (94 vs. 107 mm Hg, p=0.0045), but were similar in the two groups at the end of the study (98 mm Hg vs. 103 mm Hg, p=0.2458) after 12 months of weekly visits. Thus, the changes in LV mass appeared to be independent of changes in BP.

LV mass was similar in men and women at baseline, and was significantly smaller at 12 months in women than men (p=0.0239). These two groups also differed with respect to change in AGE (p=0.0083), but not HbA_{1c} over 12 months.

LV Septal Thickness

Of the 17 patients, eight were observed to have decreased septal thickness ≥1 mm over the course of 12 months (10.4±0.3 mm vs. 8.6±0.4 mm, p=0.0002). The remaining nine patients showed a small, but significant increase over 12 months (10.1±0.6 mm vs. 10.7±0.5 mm, p=0.0133); difference-between-group change over 12 months (–1.75±0.25 mm vs. 0.56±0.18 mm, p=0.0001). The two groups differed with respect to baseline (1.4±0.01 mg/dL vs. 2.0±0.2 mg/dL, p=0.0321) and 12-month mean levels of SCr (1.5±0.1 mg/dL vs. 2.3±0.3 mg/dL, p=0.0315). There were no statistically significant differences in mean levels of CrCl between the two groups at either entry or 12 months. These two groups also differed with respect to change in HbA_{1c} (p=0.0463), but not in AGE or MAP. BP at baseline and 12 months were similar in the two groups.

LV Diastolic Function

Of the 17 patients, 10 showed an increase in the ratio of early to late diastolic filling (E/A ratio) (reflecting improved diastolic compliance), over 1 year (1.3±0.2 vs. 1.5±0.2, p=0.0002). A decrease in E/A ratio was noted in seven patients (1.2±0.1 vs.

Table I. Data on 17 Patients at Baseline and 12 Months

	Baseline	12 Months	*P* Value
Glycohemoglobin A_{1c} (%)	9.41±0.39	8.23±0.37	0.0067
AGE (n=12) (IU)	11.79±2.04	7.39±1.33	0.0244
Serum creatinine (mg/dL)	1.73±0.14	1.93±0.18	0.0308
Creatinine clearance (mg/min)	58.76±4.70	54.44±6.20	0.2503
Hemoglobin (g/dL)	13.6±0.4	12.4±0.4	0.0002
Hematocrit (%)	39.8±1.3	37.0±1.2	0.0008
Weight (kg)	73.2±2.34	73.4±2.8	0.8255
Mean arterial pressure (mm Hg)	99.29±2.38	100.18±1.93	0.6178
Systolic BP (mm Hg)	138±3	140±2	0.4465
Diastolic BP (mm Hg)	80±2	82±1	0.5484
D/NMAP (n=15)	1.01±0.02	1.05±0.02	0.1743
LV mass (g)	206.65±13.00	187.76±13.81	0.0864
LV septal thickness (mm)	10.24±0.34	9.70±0.40	0.1199
E/A ratio	1.26±0.10	1.31±0.12	0.4004
Fractional shortening (%)	38.65±1.33	39.66±1.66	0.6017
Ejection fraction (%)	60.29±2.03	60.29±2.03	1.0000

AGE=advanced glycated end products; BP=blood pressure; D/NMAP=diastolic/nonsignificant mean arterial pressure; LV=left ventricular; E/A=early-to-late diastolic filling

Table II. Relationship of Changes Observed Over 12 Months to Baseline Renal Function

	Creatinine ≤1.7 mg/dL (n=10)			Creatinine >1.7 mg/dL (n=7)		
	Baseline	12 Months	*P* Value	Baseline	12 Months	*P* Value
Glycohemoglobin A_{1c} (%)	9.5±0.6	7.6±0.4	0.0027	9.3±0.6	9.2±0.6	0.7423
AGE (n=7,5) (IU)	11.3±2.1	6.8±1.9	0.1660	15.4±5.0	8.2±1.9	0.1118
Serum creatinine (mg/dL)	1.4±0.1	1.5±0.1	0.1506	2.2±0.2	2.6±0.3	0.1015
Creatinine clearance (mg/min)	69±5.6	68±7.1	0.9157	44±4.2	35±5.4	0.0317
Hemoglobin (g/dL)	14.4±0.5	13.4±0.5	0.0173	12.5±0.6	11.0±0.5	0.0077
Hematocrit (%)	42.0±1.7	39.5±1.5	0.0273	36.7±1.5	33.3±1.3	0.0195
Weight (kg)	75±1.5	75±3	0.9584	71±5.	72±6	0.4113
Mean arterial pressure (mm Hg)	97±3.6	99±3.1	0.5907	102±2.4	102±1.7	0.9119
Systolic BP (mm Hg)	136±5	137±3	0.6885	142±2	144±4	0.4295
Diastolic BP (mm Hg)	79±3	82±2	0.3252	82±2	81±2	0.2683
D/NMAP (n=8,7)	1.03±0.03	1.07±0.02	0.2607	0.99±0.03	1.02±0.04	0.5046
LV mass (g)	196±7	171±8	0.0259	222±30	212±31	0.6565
LV septal thickness (mm)	10.5±0.3	9.2±0.5	0.0063	9.9±0.7	10.4±0.6	0.0300
E/A ratio	1.3±0.1	1.4±0.2	0.0983	1.2±0.1	1.2±0.2	0.6914
Fractional shortening (%)	38±2	43±2	0.0984	39±2	36±2	0.2277
Ejection fraction (%)	62±1	62±1	0.7263	58±5	57±5	0.6036

AGE=advanced glycated end products; BP=blood pressure; D/NMAP=diastolic/nonsignificant mean arterial pressure; LV=left ventricular; E/A=early-to-late diastolic filling

1.1±0.1, p=0.0182; difference between group change over 12 months, p=0.0001). Patients with improved diastolic compliance were not significantly different from those without improved diastolic compliance with respect to changes over 12 months in MAP, HbA_{1c} or AGE, SCr, CrCl, ejection fraction, fractional fiber shortening, LV mass, or septal thickness. The group of patients who did not improve LV compliance had significantly higher MAP at the end of the study (106±2 mm Hg vs. 96±2 mm Hg, p=0.0098) despite significant improvement in HbA_{1c} (9.0±0.4% vs. 7.6±0.5%, p=0.0035). There was a significant negative correlation between SCr and E/A change over 12 months (r=–0.4942, p=0.0437).

LV Systolic Function

Neither the mean ejection fraction nor the mean fractional shortening in our 17-patient study

changed over the year of follow-up. Of the 17 patients, fractional fiber shortening improved in six (36±1% vs. 45±2%; p=0.0042) and did not improve in 11 (40±2% vs. 37±2%, p=0.0251), difference between group change over 12 months (p=0.0001). The group defined by improved fractional shortening had a significantly lower SCr at baseline and 12 months than the group that did not demonstrate improvement (1.4±0.1 mg/dL vs. 1.9±0.2 mg/dL, p=0.0473; 1.4±0.2 mg/dL vs. 2.2±0.2 mg/dL, p=0.0404). However, there were no significant differences in mean change of SCr or CrCl over 12 months. There were also no significant differences between these groups with respect to change in BP, HbA_{1c} or AGE, LV mass, or septal thickness. There was a positive correlation between change in fractional shortening and change in AGE (r=0.5874, p=0.0446).

Renal Function

When patients were divided by baseline mean or median level of SCr (≤1.7 mg/dL, n=10 vs. >1.7 mg/dL, n=7), Table II, the group of patients with better renal function had a significant mean decrease in LV mass (196±7 g vs. 171±8 g, p=0.0259) and septal thickness (10.5±0.3 mm vs. 9.2±0.5 mm, p=0.0063; difference between group change over 12 months, p=0.0013). When we looked at patients defined by changes in LV mass and the group defined by SCr, we found that these were not necessarily the same individuals. Three of 10 individuals with baseline SCr ≤1.7 mg/dL did not achieve a 20 g decrease in LV mass at 12 months; two did decrease LV mass by 13 g and 2 g, respectively, and one increased. Two of 10 individuals with SCr ≤1.7 mg/dL did not achieve a decrease in septal thickness; one remained unchanged and one increased.

The group with better renal function demonstrated improved mean fractional shortening over 12 months when compared with the group with lesser renal function (p=0.0433). The group with better kidney function achieved a significant decrease in mean HbA_{1c} over 12 months; the group with lesser kidney function did not. Although mean baseline HbA_{1c} was similar in both groups of patients, the groups differed at 12 months (p=0.0340) and with respect to change over 12 months (p=0.0153). For the two groups defined by SCr above and below 1.7 mg/dL, there were no significant differences in BP (Table II) or antihypertensive medication use (including angiotensin-converting enzyme inhibition).

BP Control

When patients were divided by MAP control at 12 months (Table III), eight patients attained MAP ≤100 mm Hg and nine had MAP >100 mm Hg (94±2 mm Hg, vs. 106±2 mm Hg, p=0.0002). There were no significant differences between these groups with regard to change in LV mass or septal thickness. The group with lower attained MAP did have significant improvement in diastolic compliance not seen in the group with higher MAP.

Gender

When patients were divided by gender, men (n=12) demonstrated normal diastolic compliance, but abnormal compliance was recorded for five women at baseline and 12 months. There was significant improvement in HbA_{1c} and AGE for men, but not for the small group of women. The trends for rise in creatinine in men and fall in CrCl for women approached significance (p<0.06). Hgb and Hct decreased in both genders.

Anemia

Patients divided into groups defined by baseline Hgb or Hct above or below the median (Hgb, 15.0±0.5 g/dL vs. 12.4±0.4 g/dL; Hct, 44±1.5 g/dL vs. 36.0±0.9%) demonstrated no difference between groups with respect to changes over 12 months in any measure of BP (MAP, systolic, diastolic), or LV mass, septal thickness, diastolic compliance, or fractional shortening.

DISCUSSION

While it is well known that control of glycemia is associated with a decrease in microvascular complications of diabetes, recognition that glycemic control affects cardiac mass and autonomic function is less well appreciated. [3–5] We recently demonstrated evidence for significant LV mass and septal thickness regression in those patients (63%) whose HbA_{1c} improved vs. those (37%) without improvement.[6] Improvement in glycemic control has also been associated with significantly better ambulatory electrocardiographic measures of cardiac autonomic function.[7,8] Better cardiac autonomic function has also been associated with decreased progression of renal dysfunction.[9]

Deterioration of cardiac and renal function occurs over time, and often simultaneously, in long-term diabetes. Thus indices of cardiac autonomic neuropathy are associated with glycemic stability and level of renal dysfunction with instability.[10] In the current study, we postulate that renal dysfunction will have an impact on LV mass, septal thickness, systolic function, and diastolic compliance as intensive diabetes control is applied over 12 months.

Table III. Relationship of Changes Observed Over 12 Months to Attained Mean Arterial Pressure Control (MAP ≤100 vs. >100)

	MAP ≤100 mm Hg (n=8)			MAP >100 mm Hg (n=9)		
	Baseline	12 Months	*P* Value	Baseline	12 Months	*P* Value
Glycohemoglobin A_{1c} (%)	9.9±0.6	8.4±0.7	0.0811	9.0±0.5	8.0±0.4	0.0384
AGE (n=7,5) (IU)	7.7±1.2	6.3±1.8	0.4043	15.6±3.2	8.1±1.5	0.0366
Serum creatinine (mg/dL)	1.5±0.2	1.5±0.2	0.8088	1.9±0.2	2.3±0.3	0.0156
Creatinine clearance (mg/min)	66±7	68±9	0.5073	53±6	42±7	0.0757
Hemoglobin (g/dL)	13.9±0.6	13.2±0.6	0.0790	13.4±0.6	11.7±0.6	0.0008
Hematocrit (%)	40.8±1.8	39.2±1.5	0.1480	38.9±1.9	35.0±1.7	0.0018
Weight (kg)	75.2±3.8	74.6±4.5	0.6048	71.4±2.9	72.4±3.7	0.6015
Mean arterial pressure (mm Hg)	93±3	94±2	0.6578	105±2	106±0.02	0.7955
Systolic BP (mm Hg)	129±4	133±2	0.2311	146 ± 3	146±3	0.9464
Diastolic BP (mm Hg)	75±2	79±2	0.1588	86±2	84±1	0.3620
D/NMAP (n=8,7)	0.98±0.04	1.03±0.05	0.5413	1.02±0.03	1.06±0.02	0.2190
LV mass (g)	205±11	188±18	0.3435	208±24	188±21	0.1681
LV septal thickness (mm)	10.6±0.4	9.8±0.6	0.1108	9.9±0.5	9.7±0.5	0.6224
E/A ratio	1.32±0.19	1.52±0.19	0.0252	1.20±0.10	1.12±0.11	0.2414
Fractional shortening (%)	39±2	42±2	0.1888	39±2	37±2	0.5717
Ejection fraction (%)	61.2±1.2	61.9±1.3	0.7318	59.4±3.8	58.9±3.7	0.5943

AGE=advanced glycated end products; BP=blood pressure; D/NMAP=diastolic/nonsignificant mean arterial pressure; LV=left ventricular; E/A=early-to-late diastolic filling

Our total study group had significant improvement in glycemic control (Table I). When the study patients were subdivided according to baseline SCr, the group defined by better renal function demonstrated a significant reduction in LV mass and septal thickness associated with a significant fall in HbA_{1c}. The group defined by SCr >1.7 mg/dL had neither improvement in HbA_{1c} nor reduction in LV mass over 12 months. Moreover, septal thickness in this latter group increased significantly. With respect to fractional shortening, the group with SCr below the mean showed improvement, but the group with SCr above 1.7 mg/dL showed a decrease.

In our study, we observed that despite weekly visits for 1 year, motivated patients with similar education and treatment did not achieve that level of glycemic control associated with cardiac remodeling when SCr exceeded the group mean (>1.7 mg/dL). Thus, when renal function has begun to deteriorate, more effective technology to control glycemia will be required to achieve cardiac remodeling. BPs were not significantly different at 12 months for groups demonstrating significant differences in LV mass or septal thickness, suggesting that in our study changes in LV remodeling were not dependent upon changes in BP.

A recent meta-analysis[2] of 1064 patients concluded that aggressive treatment of high BP reduces the risk of vascular complications with associated reduction of LV mass in patients with normal renal function. There are no published longitudinal studies reporting follow-up Doppler echocardiography in type 1 diabetic patients with early nephropathy. We defined two groups based on 24-hour MAP > or ≤100 mm Hg attained at the end of the study (Table III). The group defined by lower MAP had better, more stable renal function, and improved diastolic compliance over 12 months. The group defined by higher MAP had impaired diastolic compliance that did not improve. The groups were similar with respect to LV mass and septal thickness. Our small study demonstrates that when groups have similar BPs over 1 year, the ability to control blood glucose and reduce LV mass is impaired as renal function declines. We do not know whether improved glycemic control would potentiate antihypertensive therapy in the renal dysfunction group. Thus, interdependent metabolic and vascular factors which contribute to the excess morbidity and mortality observed at every level of renal dysfunction, may yet be susceptible to earlier and more aggressive intervention.[11]

Recent studies demonstrate that improving glycemic control blunts the progression of type 1 diabetic microvascular end-organ damage, e.g., retinopathy and nephropathy.[3,5] To date, few studies demonstrate an effect of glycemic control on macrovascular end points. Based on our observations, it appears that the present concept of aggressive glycemic/BP control adequate to regress LVH and slow renal deterioration needs to be revised. For the type 1 diabetic patient whose nephropathy

has advanced such that SCr is >1.7 mg/dL, options for improving treatment include:

- Lowering target BP to below 120 mm Hg systolic, and 90 mm Hg MAP, preferentially utilizing angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers with kaliuretic diuretics; aldosterone-blocking agents with mineralocorticoid replacement may be utilized in the case of hyperkalemia.
- Considering the use of physiologic algorithms for insulin dosing or insulin pump therapy before the onset of azotemia.

Clinicians will recognize certain difficulties in treating the type 1 diabetic patient with increased SCr:

- Low renin/low aldosterone hypertension makes it difficult to use potassium-sparing diuretics like spironolactone unless mineralocorticoid is replaced with fludrocortisone.
- Diabetic cardiomyopathy often remains undiagnosed until stress is superimposed. There is a definite risk that congestive heart failure will develop with the use of thiazolidinediones, despite escalating doses of diuretics. At present, experience with thiazolidinediones for relative insulin resistance in type 1 diabetes is lacking.
- Increased insulin sensitivity may result in symptomatic hypoglycemia. As renal function deteriorates, accumulation of rapid-acting insulin may become a risk for seizure.
- The potential side effects of the present generation of immunosuppressive agents likely limit the utility of either isolated pancreatic or islet cell transplant at this time.

CONCLUSION

Decrease in LV mass may be accomplished by improvements in BP control in type 1 diabetic patients with proteinuria and normal SCr. Decrease in LV mass may also be accomplished by improvements in glycemic control in type 1 diabetic patients whose SCr remains equal to or below the group mean (1.7 mg/dL). With respect to the present observations, it seems clear that the presence of renal dysfunction impedes appropriate glycemic control. LV form and function did not improve in the group with a SCr greater than the group mean (1.7 mg/dL). Further studies confirming these findings may lead to more effective BP and glycemic control targets before the onset of azotemia and after its recognition.

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