

Impact of Diabetes on Cardiac Structure and Function

The Strong Heart Study

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Background—Whether diabetes mellitus (DM) adversely affects left ventricular (LV) structure and function independently of increases in body mass index (BMI) and blood pressure is controversial.

Methods and Results—Echocardiography was used in the Strong Heart Study, a study of cardiovascular disease in American Indians, to compare LV measurements between 1810 participants with DM and 944 with normal glucose tolerance. Participants with DM were older (mean age, 60 versus 59 years), had higher BMI (32.4 versus 28.9 kg/m²) and systolic blood pressure (133 versus 124 mm Hg), and were more likely to be female, to be on antihypertensive treatment, and to live in Arizona (all $P < 0.001$). In analyses adjusted for covariates, women and men with DM had higher LV mass and wall thicknesses and lower LV fractional shortening, midwall shortening, and stress-corrected midwall shortening (all $P < 0.002$). Pulse pressure/stroke volume, a measure of arterial stiffness, was higher in participants with DM ($P < 0.001$ independent of confounders).

Conclusions—Non-insulin-dependent DM has independent adverse cardiac effects, including increased LV mass and wall thicknesses, reduced LV systolic chamber and myocardial function, and increased arterial stiffness. These findings identify adverse cardiovascular effects of DM, independent of associated increases in BMI and arterial pressure, that may contribute to cardiovascular events in diabetic individuals. (*Circulation*. 2000;101:2271-2276.)

Key Words: diabetes mellitus ■ echocardiography ■ hypertrophy ■ ventricles

Reports from Framingham and from other studies have established diabetes mellitus (DM) as a strong risk factor for cardiovascular morbidity and mortality,¹⁻³ especially in women.⁴ In addition, several studies suggest that DM has direct adverse effects on the heart, independent of obstructive coronary artery disease.^{5,6} Specifically, the Framingham Heart Study identified an association between DM and increased left ventricular (LV) wall thickness and mass that appeared to be independent of conventional risk factors in women but not in men.⁷ In another study,⁸ associations between DM and abnormal LV structure and function appeared to be independent of arterial blood pressure (BP). These observations may be important in view of the strong relation between LV hypertrophy and adverse cardiovascular outcomes that has been documented in many populations.⁹⁻¹¹ Also, most data on cardiovascular effects of DM have been derived from predominately white populations, despite the fact that DM is more prevalent in other ethnic groups, including American Indians.^{12,13}

Accordingly, the present study was undertaken to assess LV structure and function in individuals with and without

DM among American Indians participating in the Strong Heart Study (SHS).¹⁴⁻¹⁶ This population includes tribes with various prevalence rates of both DM and coronary heart disease. The specific objectives were to determine whether (1) non-insulin-dependent DM is associated with LV hypertrophy and dysfunction in a population-based sample of middle-aged to elderly adults, (2) observed associations are independent of major correlates of LV hypertrophy (body size, BP, sex, and age), and (3) DM is associated with more severe LV abnormalities in women than in men.

Methods

The SHS is a population-based survey of cardiovascular risk factors and prevalent and incident cardiovascular disease in 13 American Indian tribal communities in Arizona, Oklahoma, and South and North Dakota. As previously described,¹⁵⁻¹⁷ members 45 to 74 years of age in 3 tribes in central Arizona, 7 in southwestern Oklahoma, and 3 in South and North Dakota were recruited from tribal members living on reservations or (in Oklahoma) in a defined geographic area (overall participation rate=62%) for a first examination in 1989 to 1992. Standardized measurements of seated brachial BP; aspects of body habitus, including body mass index, waist-to-hip ratio, and

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percent body fat by bioelectric impedance; and fasting and 2-hour postload glucose and glycosylated hemoglobin levels were obtained. DM was diagnosed by World Health Organization criteria¹⁷ if fasting glucose was >140 mg/dL, 2-hour postchallenge glucose was >200 mg/dL, or participants were receiving hypoglycemic medication; normal glucose tolerance was identified by fasting sugar levels <140 mg/dL and 2-hour postchallenge glucose <200 mg/dL. Individuals with impaired glucose tolerance were not considered in the present study to maximize the contrast between groups.

The second SHS examination was conducted in 1993 to 1995 to assess change over time in body habitus, BP, and other baseline measures and to add echocardiography. A total of 3630 surviving SHS enrollees participated in the second examination, an 89% return rate. Echocardiograms were performed in 3501 participants (97%), with the remainder missed because of delay in initiating echocardiography in 2 field centers.

Echocardiographic Methods

Imaging and Doppler echocardiograms were performed with previously described methods.^{18,19} Studies were performed by use of a standardized protocol and phased-array echocardiographs with M-mode, 2-dimensional, and pulsed, continuous-wave, and color-flow Doppler capabilities. Participants were examined with the head of the examining table elevated about 30° in a partial decubitus position. Recordings were made entirely on videotape.

Echocardiographic Measurements

Correct orientation of planes for imaging and Doppler recordings was verified as previously described.^{18,19} Measurements were made with a computerized review station equipped with digitizing tablet and monitor screen overlay for calibration and measurement performance. LV internal dimension and interventricular septal and posterior wall thicknesses were measured at end diastole and end systole by American Society of Echocardiography (ASE) recommendations.²⁰ When optimal orientation of the M-mode line could not be obtained, correctly oriented leading-edge linear dimension measurements were made from 2-dimensional images by ASE recommendations.²¹ Aortic annular diameter was measured as previously described.^{18,22} Doppler transaortic flow was assessed by identifying the projection in which peak flow velocity was maximal and, after calibration, tracing the black-white interface outlining the Doppler flow envelope.²³ Heart rate was measured simultaneously.

Calculation of Derived Variables

End-diastolic LV dimensions were used to calculate LV mass by an anatomically validated formula.²⁴ Relative wall thickness and systolic fractional shortening of the LV internal dimension and end-systolic stress (ESS) were calculated by standard methods.^{19,25} Aortic annular cross-sectional area was calculated as $\pi \times (\text{diameter}/2)^2$. Doppler stroke volume was calculated as annular cross-sectional area times the time-velocity integral.²³ Arterial stiffness was estimated by the ratio of pulse pressure to stroke volume.²⁶

Measures of Myocardial Performance

The primary approach to assess myocardial contractile efficiency was examination of LV systolic shortening in relation to ESS.²⁷ Because the traditional practice of relating endocardial shortening to mean ESS across the LV wall yields misleading results in individuals with concentric geometry,²⁵ primary reliance was placed on the relation of LV midwall shortening to midwall circumferential ESS at the LV minor axis; these variables were calculated as previously described.^{25,27,28} To evaluate LV performance taking circumferential ESS into account, observed midwall shortening was expressed as a percent of the value predicted from circumferential ESS with an equation derived from apparently normal adults.²⁵ This variable is called stress-corrected midwall shortening.²⁹

Statistical Analyses

Data, expressed as mean±SD, were analyzed by use of SPSS software. Differences between the DM and non-DM groups were

TABLE 1. Characteristics of Diabetic and Nondiabetic SHS Participants

	DM Patients (n=1810)	Glucose-Tolerant Subjects (n=944)	P
Age, y	60.2±7.8	58.9±7.8	<0.0001
Women, n (%)	1227 (68)	478 (51)	<0.0001
Arizona residents, n (%)	825 (46)	150 (16)	<0.0001
Height, cm	163.1±8.5	166.6±9.1	<0.0001
Weight, kg	86.2±18.8	80.3±16.9	<0.0001
Body mass index, kg/m ²	32.4±6.5	28.9±5.6	<0.0001
Fat-free mass, g	52.9±11.4	53.1±11.5	NS
Systolic BP, mm Hg	133±21	124±18	<0.0001
Diastolic BP, mm Hg	75±10	74±10	0.002

Values are mean±SD where appropriate.

assessed by independent Student's *t* test and by ANOVA with consideration of appropriate covariates. Independent associations of DM with measures of LV structure or function were assessed by multiple linear regression with an enter procedure. Because of differences between SHS participants in Arizona, Oklahoma, and North and South Dakota for several clinical variables identified from the first examination¹⁶ and confirmed in the second examination for prevalence of DM (see below) and other variables (data not shown), indicator variables comparing Arizona and Oklahoma participants with those in North and South Dakota were entered as covariates. In addition to primary multivariate analyses in which DM and sex were considered main effects, supplemental multivariate analyses also considered a variable representing female sex-by-DM interaction, constructed as the product of indicator variables for DM (normal glucose tolerance=0, DM=1) and sex (male=0 and female=1). Because of the large number of variables analyzed, *P*<0.01 was considered significant.

Results

Characteristics of Participants

Of SHS participants who underwent echocardiography, 3261 (93%) also had glucose tolerance and clinical information needed to document DM or normal glucose tolerance; 1810 (52%) had DM, and 944 (27%) had normal glucose tolerance. Compared with participants with normal glucose tolerance, diabetic participants were older; were more likely to be female, to reside in Arizona, and to be on antihypertensive treatment; and had higher body mass indexes and systolic BPs (Table 1). Because of the strong association of DM with female sex, primary comparisons of cardiac findings between diabetic and glucose-tolerant participants were performed separately by sex; other variables that differed between DM and non-DM groups were considered covariates.

Findings in Diabetic and Nondiabetic Women

The 1227 diabetic women had higher body mass indexes and systolic BPs and were more likely to live in Arizona and be receiving antihypertensive medication than the 478 with normal glucose tolerance.

LV and Hemodynamic Characteristics

Mean interventricular septal and posterior LV wall thicknesses were greater in diabetic women, with no difference between groups in LV chamber size (Table 2); therefore, relative wall thickness was greater in diabetic individuals. In

TABLE 2. LV and Hemodynamic Characteristics of Diabetic and Nondiabetic Women

	DM Patients (n=1227)	Glucose-Tolerant Subjects (n=478)	P
IVS, cm	0.95±0.13	0.87±0.11	<0.0001
LVID, cm	4.85±0.48	4.81±0.42	NS
PWT, cm	0.87±0.10	0.82±0.09	<0.0001
LV mass, g	155±40	138±32	<0.0001
LV mass/BSA, g/m ²	85±21	78±16	<0.0001
LV mass/height, g/m ^{2.7}	44.6±11.5	39.2±9.6	<0.0001
LV mass/fat-free mass, g/kg	3.3±0.8	3.1±0.7	<0.001
Relative wall thickness	0.36±0.05	0.34±0.04	<0.0001
Fractional shortening, %	35±6	36±5	0.008
Midwall shortening, %	17.3±2.5	18.4±2.1	<0.0001
Stress-corrected midwall shortening, % predicted	103±13	108±11	<0.0001
Cardiac index, L · min ⁻¹ · m ⁻²	2.56±0.57	2.47±0.56	0.01
Peripheral resistance, dyne · s ⁻¹ · cm ⁻⁵	1716±495	1790±461	0.004
Pulse pressure/stroke volume, mm Hg/mL	0.92±0.41	0.81±0.29	<0.0001

IVS indicates interventricular septal thickness; LVID, LV internal dimension; PWT, posterior wall thickness; and BSA, body surface area. Values are mean±SD.

parallel, LV mass in absolute terms or indexed for measures of body size was 9% to 14% greater in diabetic than glucose-tolerant women. Mean endocardial fractional shortening was slightly lower in diabetic women; both midwall shortening and stress-corrected midwall shortening were statistically lower in those with DM. Cardiac index was similar in the 2 groups, whereas peripheral resistance was slightly lower in diabetic women. Mean pulse pressure/stroke volume, an indirect measure of arterial stiffness, was ≈12% higher in diabetic women.

Findings in Diabetic and Nondiabetic Men

The 583 diabetic men were older, had substantially higher body mass indexes and systolic BP, had slightly higher diastolic BP, and were more likely to be Arizona residents

and to be on antihypertensive medication than the 466 glucose-tolerant men.

LV and Hemodynamic Characteristics

Similar to findings in women, diabetic men had greater mean LV wall thicknesses than nondiabetic men, with no difference in LV chamber size (Table 3). LV mass in absolute terms or indexed for measures of body size was higher, by 6% to 12%, in diabetic men. In parallel with results in women, LV endocardial and midwall shortening and stress-corrected midwall shortening were all lower in diabetic men, with no between-group difference in cardiac index or peripheral resistance. Similar to results in women, pulse pressure/stroke volume was ≈13% higher in diabetic than glucose-tolerant men.

TABLE 3. LV and Hemodynamic Characteristics of Diabetic and Nondiabetic Men

	DM Patients (n=583)	Glucose-Tolerant Subjects (n=466)	P
IVS	0.98±0.14	0.92±0.10	<0.0001
LVID	5.22±0.55	5.19±0.48	NS
PWT	0.90±0.10	0.86±0.08	<0.0001
LV mass, g	183±44	167±35	<0.0001
LV mass/BSA, g/m ²	89±22	84±17	0.001
LV mass/height, g/m ^{2.7}	42.4±11.0	37.7±8.1	<0.0001
LV mass/fat-free mass, g/kg	2.85±0.70	2.76±0.59	NS
Relative wall thickness	0.35±0.05	0.33±0.04	<0.0001
Fractional shortening, %	32±7	33±6	0.001
Midwall shortening, %	16.2±2.9	17.3±2.3	<0.0001
Stress-corrected midwall shortening, % predicted	99±15	104±13	<0.0001
Cardiac index, L · min ⁻¹ · m ⁻²	2.49±0.60	2.43±0.58	NS
Total peripheral resistance, dyne · s ⁻¹ · cm ⁻⁵	1622±418	1666±512	NS
Pulse pressure/stroke volume, mm Hg/mL	0.77±0.30	0.68±0.27	<0.0001

Abbreviations as in Table 2. Values are mean±SD.

TABLE 4. Multivariate Correlates of LV and Hemodynamic Variables

	Diabetes	Age	Male Sex	Height	Body Mass Index	Systolic BP	Hypertension Rx	Arizona vs North and South Dakota	Oklahoma vs North and South Dakota	<i>R</i>
IVS	<0.001	<0.001	0.003	0.001	<0.001	<0.001	0.004	0.001	NS	0.42
LVID	NS	NS	<0.001	<0.001	<0.001	<0.001	<0.001	<-0.001	<-0.001	0.50
PWT	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.004	<0.001	NS	0.44
LV mass	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<-0.001	<-0.001	0.53
LV mass/BSA	<0.001	<0.001	<0.001	<-0.001	-0.003	<0.001	<0.001	<-0.001	<-0.001	0.39
LV mass/height ^{2.7}	<0.001	<0.001	<0.001	<-0.001	<0.001	<0.001	<0.001	<-0.001	<-0.001	0.53
LV mass/fat-free mass	0.005	<0.001	<0.001	-0.006	<-0.001	<0.001	0.001	NS	<-0.001	0.45
Relative wall thickness	<0.001	0.001	NS	-0.005	-0.003	<0.001	NS	<0.001	<0.001	0.36
Fractional shortening	-0.002	NS	<-0.001	-0.001	NS	NS	-0.001	0.003	0.002	0.29
Midwall shortening	<-0.001	<-0.001	<-0.001	NS	NS	<-0.001	<-0.001	NS	NS	0.33
Stress-corrected midwall shortening	<-0.001	<-0.001	<-0.001	NS	<0.001	0.002	<-0.001	<-0.001	NS	0.28
Cardiac output	<0.001	NS	0.007	<0.001	<0.001	<0.001	NS	<-0.001	NS	0.41
Total peripheral resistance	<-0.001	NS	NS	<-0.001	<-0.001	<0.001	NS	<0.001	<0.001	0.35
Pulse pressure/stroke volume	0.001	<0.001	<-0.001	<-0.001	<-0.001	<0.001	NS	NS	NS	0.58

Rx indicates treatment; other abbreviations as in Table 2.

Results of Multivariate Analyses

Multiple linear regression models were first developed separately in women and men for each dependent variable listed in Table 4 with consideration of age, height, body mass index, systolic BP, use of antihypertensive medication, and region of residence as covariates, in addition to the primary independent variable representing DM or normal glucose tolerance. Because results of analyses in the 2 sexes were virtually identical, subsequent multiple linear regressions combined both sexes, with the addition of an indicator variable for sexes. As shown in Table 4, DM was independently associated with greater absolute and relative LV wall thicknesses (but not larger chamber size) and with higher absolute and indexed LV mass independent of all confounders. Older age and higher systolic BP also had independent positive associations with LV wall thicknesses and mass, whereas associations of the latter with height, body mass index, antihypertensive medication, and North or South Dakota residence were less consistent.

DM, as well as male sex and antihypertensive medication use, also had strong, statistically independent associations with lower LV endocardial shortening, midwall shortening, and stress-corrected midwall shortening. DM had independent associations with higher cardiac output, lower peripheral resistance, and especially higher pulse pressure/stroke volume, an index of increased arterial stiffness. Alternative analyses in which stroke volume/pulse pressure replaced systolic BP confirmed independent associations of DM with measures of LV structure and function. Additional regression analyses showed no associations between the sex-by-DM interaction and measures of LV structure or function ($P=0.07$ to 0.89).

Discussion

The present study represents the first comprehensive comparison of LV structure and function and measures of systemic hemodynamics between diabetic and glucose-tolerant members of a large adult population. It confirms and extends some previous findings and reveals additional, hitherto unappreciated cardiovascular abnormalities associated with DM. In addition, the nature of the study population of American Indian participants in the SHS, a population in which DM is highly prevalent and almost invariably non-insulin dependent, makes the present study findings potentially relevant to the large and increasing number of adults in other ethnic groups affected by non-insulin-dependent DM.

Diabetes and LV Structure

One previous report from Framingham identified associations of DM with higher LV wall thickness and mass in women but not in men. The present report confirms and extends this observation by demonstrating associations of LV absolute and relative wall thicknesses, as well as LV mass in absolute terms and indexed for measures of body size with DM in both men and women. The differences in LV structure between diabetic and glucose-tolerant individuals seen in univariate analyses remained statistically significant (generally $P<0.001$) in multivariate analyses that took relevant confounders into account.

Of greatest potential clinical relevance, the prognostically validated measures of LV mass indexed for body surface area or (height)^{2.7} were greater by 6% to 9% and by 12% to 14%, respectively, in diabetic compared with glucose-tolerant women and men. Future research will be needed to determine whether and to what extent the abnormalities of LV structure

that we have identified in diabetic individuals contribute to their excess risk of cardiovascular events.

Diabetes and LV Function

A notable and hitherto unreported finding in the present study is that both LV chamber and myocardial function are significantly lower in diabetic than in glucose-tolerant women and men. This finding is particularly notable in view of the greater absolute and relative LV wall thicknesses in diabetic compared with nondiabetic participants, which would be expected to yield increased LV chamber function if myocardial function were normal and to keep it normal if myocardial function were mildly decreased.^{25,30} Precedent for our findings is provided by a report from Framingham⁹ in which LV fractional shortening was reduced in men but not women with DM. In keeping with these observations, stress-corrected LV midwall shortening was $\approx 5\%$ lower in diabetic adults. Results of a previous study in hypertensive adults³¹ suggest that lower values of this contractility index are likely to predict a higher rate of cardiovascular events. Future research is needed to determine the prognostic significance of noninvasively detected myocardial dysfunction in diabetic adults.

Systemic Hemodynamics in Diabetic and Nondiabetic Subjects

No consistent, independent associations between DM and classic hemodynamic measures of cardiac output and peripheral resistance were detected in our analyses. In contrast, a clear and consistent result of the present study is that stiffness of the systemic arterial tree, estimated by the ratio of pulse pressure to stroke volume, is higher in diabetic than in nondiabetic women and men. The $\approx 12\%$ increase in this parameter in diabetic SHS participants is slightly greater than the between-group differences in measures of LV structure and function. This result is in keeping with the widely accepted concept that DM has adverse effects on large arteries and the microcirculation. Although pulse pressure/stroke volume is an index that can be measured noninvasively by simple methods,²⁶ it is important to emphasize that most of this difference between groups is attributable to pulse pressure being higher by a mean of 7 mm Hg in diabetic individuals. Of note, an association between DM and elevated arterial stiffness has been detected previously.³² One possible mechanism of this association, which might also be relevant to LV abnormalities, is the nonenzymatic production of irreversible advanced glycosylated end products that has been observed in arteries of diabetics.³³ Although increased pulse pressure/stroke volume did not appear to mediate the association between DM and LV abnormalities, preliminary data obtained through applanation tonometry³⁴ in a subset of the present population an average of ≈ 3 years later revealed alterations in the central arterial pressure waveform, including an earlier peak of the reflected wave (by a mean of 8 ms) and a higher ratio of peak to diastolic pressure (by a mean of 3%) in diabetic than glucose-tolerant individuals (both $P < 0.05$). Further research with concurrent arterial pressure waveform and echocardiographic measurements is needed to elucidate the role of altered arterial dynamics in DM-associated cardiac abnormalities.

Impact of Sex on the Cardiovascular Effects of Diabetes

Contrary to one of our hypotheses, there were no appreciable differences between women and men in the magnitude of DM-associated abnormalities of LV structure or function or of arterial stiffness. Thus, absolute and indexed LV mass values were higher in diabetic than glucose-tolerant participants by 9% to 14% among women and by 6% to 12% among men. Similarly, stress-corrected midwall shortening was 5% lower and the ratio of pulse pressure to stroke volume was $\approx 12\%$ higher in diabetic women and men. The consistent lack of any discernible sex difference across a variety of measures of cardiovascular structure and function strongly suggests that the greater impact of DM on coronary heart disease risk in women than in men is not mediated via a differential effect on these measures of preclinical cardiovascular disease. An alternative mechanism, previously reported from the SHS,⁴ is that conventional risk factors are proportionally more abnormal in women than men with DM.

Study Limitations

The present study assessed stroke volume and myocardial performance by noninvasive methods that necessarily involve approximations. Nevertheless, compared with invasive reference standards, Doppler echocardiography has been shown to determine stroke volume and cardiac output accurately.²³ Similarly, the noninvasive stress-shortening measures we used to provide approximate estimates of myocardial contractile efficiency have been used in invasive studies.^{27,28}

Another characteristic of the present study, its performance in an American Indian population, may constitute a strength. The high prevalence of DM in this population (compared with rates of 2% in women and 4% in men in Framingham⁹), the rarity of insulin-dependent DM in American Indians, and careful ascertainment of glucose tolerance status in the SHS are advantages of the present study. The ability to assess relations of DM to cardiac structure and function and to systemic hemodynamics in a population with an exceptional prevalence of DM illustrates the portability and robustness of imaging and Doppler echocardiography. Further research is needed to determine the applicability of present findings to populations with different ethnicity and lower prevalences of DM.

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