Associations of Insulin Levels With Left Ventricular Structure and Function in American Indians

The Strong Heart Study

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We evaluated the association of insulin and echocardiographic left ventricular (LV) measurements in 1,388 (45% men) nondiabetic American Indian participants in the Strong Heart Study (SHS). Significant (all $P < 0.05$) relations were found in men and women between $\log_{10}$ fasting insulin and LV mass ($r = 0.24$ and 0.26), left atrial diameter ($r = 0.25$ and 0.28), posterior wall thickness ($r = 0.20$ and 0.26), septal thickness ($r = 0.19$ and 0.24), LV diameter ($r = 0.17$ and 0.16), and cardiac output ($r = 0.20$ and 0.24) and in women relative wall thickness ($r = 0.11$) and peripheral resistance ($r = -0.17$). In regression analyses, adjusting for BMI, age, height, and systolic pressure, fasting insulin was independently correlated with cardiac output in men and relative wall thickness and septal thickness in women (all $P < 0.05$). The 97th percentiles of fasting insulin (25 μU/ml for men, and 23 μU/ml for women) in 163 apparently normal (BMI <26; blood pressure <140/90; and absence of diabetes, valvular disease, LV wall motion abnormality, or antihypertensive treatment) SHS participants were used to separate normal from elevated fasting insulin levels. Adjusting for age, BMI, and height, men with elevated insulin levels had larger LV diameters (5.41 vs. 5.16 cm; $P = 0.05$), higher cardiac output (5.5 vs. 4.9 l/min; $P < 0.001$), and lower peripheral resistance (1,487 vs. 1,666; $P = 0.01$), paralleling results of regression analyses. Positive relations between insulin and heart size in nondiabetic adults are largely due to associations with body size; after adjustments for covariates, fasting insulin levels are related to greater LV size and cardiac output in men and more concentric LV geometry in women. *Diabetes* 51: 1543–1547, 2002

Insulin has been shown in human and animal experiments to have cardiovascular effects, including increased sympathetic stimulation (1,2), reduced peripheral vascular resistance (1,2), and increased renal sodium retention under some (3) but not other (4) circumstances. Left ventricular (LV) mass and geometry have been shown to predict cardiovascular events and death independent of conventional risk factors in a wide variety of populations (5). However, the LV effects of insulin have been only rarely studied in large populations of nondiabetic individuals (6).

Accordingly, the present study was undertaken to assess relations of plasma insulin levels with various parameters of LV structure and function in individuals without diabetes among American Indians who participated in the Strong Heart Study (SHS) (7–9). This population includes tribes with an exceptionally high prevalence of diabetes but moderate rates of coronary heart disease and others in Oklahoma and North/South Dakota with high rates of diabetes and moderate to high rates of coronary heart disease (10,11). The specific objectives of the study were *1*) to determine whether higher insulin levels are associated with greater LV hypertrophy and worse LV function in a population-based sample of middle-aged to elderly adults and *2*) to determine whether observed relations with insulin are independent of BMI (known to be associated with both insulin level and LV mass) and other potential confounders (blood pressure, sex, and age) that may be correlated with both variables.

RESEARCH DESIGN AND METHODS

Subjects. The SHS is a population-based survey of cardiovascular risk factors and cardiovascular disease in American Indians. As previously described (7–9), members aged 45–74 years of three American Indian communities in Arizona, seven tribes in Southwestern Oklahoma, and three tribes in South and North Dakota were recruited from all eligible individuals (overall participation rate 62%) for an initial examination in 1989–1992. Extensive characterization of subjects included standardized measurement of seated brachial blood pressure; aspects of body habitus including BMI, waist/hip ratio, and percentage of body fat by bioelectric impedance; fasting glucose, insulin, lipid, and lipoprotein concentration; and 2-h glucose tolerance test and glycosylated hemoglobin levels. Diabetes was diagnosed by World Health Organization (WHO) criteria (12) if fasting blood glucose was ≥140 mg/dl, glucose level after a 2-h challenge was ≥200 mg/dl, or subjects received hypoglycemic medication. For the present study, subjects with diabetes were excluded.

Insulin measurements used antibody 1012, WHO-traceable (1988) insulin standards, and supplies purchased from Linco Research (St. Louis, MO). The

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LV, left ventricular; SHS, Strong Heart Study; WHO, World Health Organization.

interassay and intra-assay coefficients of variation of the insulin assay at mid-range were 8.5 and 2.2%, respectively.

The second SHS examination began in August 1993 to assess changes over time in cohort members of body habitus, blood pressure, and most other baseline measures. In addition, echocardiograms were performed in 3,501 (97%) of the 3,630 phase II participants.

Echocardiographic methods. Imaging and Doppler echocardiography was performed as previously described (13–15). A standardized protocol was followed under which the parasternal and apical acoustic windows were used to visualize the LV internal diameter and wall thicknesses, assess LV wall motion, and search for mitral and aortic regurgitation.

Echocardiographic measurements. Correct orientation of planes for imaging and Doppler recordings was verified as previously described (16). LV internal dimension and septal and posterior wall thicknesses were measured at end-diastole and end-systole by American Society of Echocardiography recommendations (17,18) on up to three cardiac cycles. The aortic anular diameter was measured in the long-axis view that maximized this dimension (13), and the Doppler flow velocity profile was used to calculate stroke volume by an invasively validated method (19).

Calculation of derived variables. End-diastolic LV dimensions were used to calculate LV mass by a formula shown to yield values closely related ($r = 0.90$, $P < 0.001$) to necropsy measurements (20), which also showed good reproducibility ($\rho = 0.93$, $P < 0.001$) between separate echocardiograms in 183 hypertensive patients (21). LV mass was primarily indexed for the power of the allometric (or growth) relationship between height and LV mass (height$^{2.7}$), as has been shown to detect expected deviations from normal in populations with BMI in the ranges 25–30, 30–40, and ≥40 kg/m^2 (22) and also for body surface area (21). Relative wall thickness was calculated as posterior wall thickness/internal radius; systolic fractional shortening in percentage of the ventricle's internal dimension and end-systolic wall stress were calculated by standard methods (16).

Measures of myocardial performance. Myocardial contractile efficiency was examined by relating LV systolic shortening to end-systolic stress (23). Primary reliance was placed on the relation of midwall fractional shortening to midwall circumferential end-systolic stress measured at the LV minor axis as previously described (23,24). Midwall fractional shortening was calculated taking into account the epicardial migration of the midwall. For evaluating LV performance taking circumferential end-systolic stress into account, midwall fractional shortening was expressed as a percentage of the value predicted from circumferential end-systolic stress using an equation derived in previously studied normal subjects (23), termed stress-corrected midwall fractional shortening (25).

Statistical analyses. SPSS (SPSS, Chicago, IL) software was used for data management and statistical analyses. Data are expressed as mean ± SD. Because the distribution of fasting plasma insulin was right skewed, it was log transformed before application of parametric statistical methods. Preliminary analyses examined the associations of $\log_{10}$ insulin and LV mass with potential confounders, including age, sex, BMI, height, and systolic blood pressure. Univariate relations of $\log_{10}$ insulin with measures of LV structure or function as dependent variables were assessed by Pearson correlations, followed by multiple linear regression analyses with the identified confounders as additional independent variables. A stepwise procedure was used with P to enter <0.05 and to remove <0.10. Statistical analyses were first performed separately in the 901 participants with normal glucose tolerance (51% women) and the 487 with impaired glucose tolerance (64% women); because results in both groups were directionally similar and were statistically significant in the larger subgroup with normal glucose tolerance for the same comparisons as in the entire population, data from the combined groups are presented.

RESULTS

Participant characteristics. Of the 3,501 participants in the second SHS examination who underwent echocardiography, glucose tolerance testing, plasma insulin evaluation, and clinical examination, 1,388 (45% men) were free of diabetes and had other data needed for the present report. A large proportion of the population was obese with a mean BMI of 30 ± 6 kg/m^2. Other clinical characteristics of the study group are shown in Table 1.

Identification of confounders. Among nondiabetic participants in the second SHS examination, preliminary analyses examined the associations of $\log_{10}$ insulin and LV mass with potential confounders, including age, sex, BMI, height, and systolic blood pressure. In univariate analyses, LV mass was significantly related among women and men to older age, greater height, higher BMI, and higher systolic pressure (Tables 2 and 3). Regression analysis revealed that each of these variables plus male sex had highly significant statistically independent associations with LV mass. In univariate analyses, log insulin was significantly associated with age, height, BMI, and systolic pressure among men and with BMI and systolic pressure among women (Tables 4 and 5). In regression analysis, female sex, height, BMI, and systolic pressure—but not age—were independently associated with higher log fasting plasma insulin levels. On the basis of the finding of significant relations of age, height, BMI, and systolic blood pressure with both LV mass and the log plasma insulin level in one or both sexes, these variables were considered as confounders in multivariate analyses of the relations between insulin levels and LV mass as well as other measures of LV geometry, function, and systemic hemodynamics.

Relations of $\log_{10}$ insulin with LV mass and other structural and functional parameters. Among men (Table 6), univariate correlations were found between $\log_{10}$ insulin and LV mass and its component parts, LV wall thicknesses, and chamber diameter. This association was preserved by indexation of LV mass for height$^{2.7}$, but it was eliminated by indexation of LV mass for body surface area, a variable strongly determined by body weight. Because of parallel increases in LV wall thicknesses and diameter, there was no association of $\log_{10}$ insulin with LV relative wall thickness. Left atrial diameter was positively related to $\log_{10}$ insulin, whereas no associations were observed between $\log_{10}$ insulin and measures of LV systolic chamber or midwall function. Higher $\log_{10}$ insulin was positively related to higher cardiac output but not cardiac output indexed for body surface area or total peripheral resistance.

TABLE 1
Clinical characteristics of the study population

	Mean ± SD	Range
Age (years)	59 ± 8	47–80
Women (%)	55	—
Height (cm)	166 ± 9	142–189
Weight (kg)	83 ± 17	35–181
Body surface area (m^2)	1.90 ± 0.21	1.26–2.72
Systolic blood pressure (mmHg)	126 ± 19	80–218
Diastolic blood pressure (mmHg)	74 ± 10	43–127
Heart rate (bpm)	66 ± 11	44–158
Insulin (μU/ml)	16 ± 15	2–241
HbA_{1c} (%)	5 ± 1	1.8–12.0

TABLE 2
Univariate analysis of LV mass in study participants

	Women		Men	
	Correlation coefficient	P	Correlation coefficient	P
Age (years)	0.10	0.006	0.004	NS
Height (cm)	0.11	0.002	0.21	<0.001
BMI (kg/m)	0.44	<0.001	0.36	<0.001
Systolic blood pressure (mmHg)	0.29	<0.001	0.21	<0.001

TABLE 3
Linear regression analysis of LV mass in study participants

	B	SE	β	*t*	*P*
Age (years)	0.452	0.113	0.096	4.000	<0.001
Male sex	14.185	2.700	0.189	5.253	<0.001
Height (cm)	1.227	0.148	0.300	8.270	<0.001
BMI (kg/m)	2.389	0.154	0.364	15.533	<0.001
Systolic blood pressure (mmHg)	0.359	0.047	0.179	7.610	<0.001

TABLE 5
Linear regression analysis of log insulin in study participants

	B	SE	β	*t*	*P*
Age (years)	0.003	0.002	0.004	0.169	NS
Female sex	0.102	0.051	0.070	1.991	0.047
Height (cm)	0.007	0.003	0.089	2.505	0.012
BMI (kg/m)	0.071	0.003	0.571	25.194	<0.001
Systolic blood pressure (mmHg)	0.002	0.001	0.054	2.343	0.019

Among women, univariate correlations were found between $\log_{10}$ insulin and LV mass and its component parts, LV wall thicknesses, and chamber diameter (Table 6). This association was preserved by indexation of LV mass for height$^{2.7}$, but it was eliminated by indexation of LV mass for body surface area, a variable strongly determined by body weight. Because of stronger relations of LV wall thicknesses than LV diameter with $\log_{10}$ insulin, the latter variable was weakly associated with higher LV relative wall thickness. Left atrial diameter was positively related to $\log_{10}$ insulin. Log_{10} insulin had a weak positive association with endocardial fractional shortening but not with measures of LV systolic midwall function. Higher $\log_{10}$ insulin was positively related to higher cardiac output but not to cardiac output indexed for body surface area or total peripheral resistance.

Multiple linear regression analysis in women identified septal thickness and LV relative wall thicknesses but not the primary outcome measure of LV mass as being significantly related to $\log_{10}$ insulin after adjusting for age, BMI, height, and systolic pressure (all $P < 0.05$). In men, LV structural parameters were not independently related to insulin level in similar multiple linear regression analyses, whereas cardiac output and peripheral resistance retained an independent positive relation with $\log_{10}$ insulin.

DISCUSSION

That as much as half of the interindividual variability in LV mass remains unexplained after standard demographic and hemodynamic factors are taken into account (14) has stimulated investigation of potential cardiac effects of a variety of hormones and growth factors. A number of previous studies have evaluated relations between LV findings and fasting or postchallenge plasma insulin levels, with variably positive or negative results (6,26–41). One potential explanation for cardiac effects of insulin, hormonal stimulation of sodium retention, seems to occur under some but not other circumstances (2–4). The present study documents univariate associations between insulin levels and several measures of LV structure, thereby confirming previous positive reports, and also demonstrates that these univariate relations are markedly weakened or even completely attenuated in multivariate analyses, controlling for the strong confounding effects of obesity and the lesser ones of age and arterial pressure.

TABLE 4
Univariate analysis of log insulin in study participants

	Women		Men	
	Correlation coefficient	*P*	Correlation coefficient	*P*
Age (years)	−0.023	NS	−0.099	0.013
Height (cm)	0.025	NS	0.091	0.023
BMI (kg/m)	0.542	<0.001	0.639	<0.001
Systolic blood pressure (mmHg)	0.148	<0.001	0.117	0.003

An important result of the present study is that associations between fasting plasma insulin levels and LV variables seem to differ by sex. Multivariate analysis revealed that higher insulin levels were associated, independent of covariates, with higher cardiac output in nondiabetic men and with higher LV wall thicknesses in women. Limited precedent for sex differences in cardiac effects of insulin is provided by a report from the Tecumseh Blood Pressure Study (6) in which insulin was positively related to LV hypertrophy in men but not women. Whether this represents a direct interaction between sex and trophic effects of insulin on the heart or, alternatively, whether this sex difference might be a nonspecific phenomenon paralleling the greater tendency of women than men to develop concentric LV geometry in response to pressure overload (42) is uncertain. Of note, other features of the insulin resistance syndrome were similar in both sexes, including ~20% higher BMI and 20% lower HDL cholesterol levels in individuals with relatively high insulin levels.

A potential limitation of the present study is assessment of insulin levels in the fasting state but not in response to glucose loading. Several studies have found positive associations between postload insulin levels or areas under the postload insulin curve and LV structural variables (28,31–33,37,41), whereas several others have not (30,34,39). The lack of postload insulin measurements in SHS participants makes it impossible to determine whether there might have been stronger relations between LV variables and insulin responses to glucose loading than those observed with fasting insulin. However, one reason for stronger relations of postload than fasting insulin levels to other biologic variables in some studies—use of assays with poor sensitivity at low levels—does not apply to the SHS, which measured insulin by a sensitive radioimmunoassay. Another potential limitation of the present study is its use of fasting insulin rather than a more sensitive measure of insulin action; unfortunately, it was not feasible to perform direct assessments of insulin sensitivity in addition to a multifaceted examination that required at least 3 h of participant time.

A strength of the present study is the relatively large number of nondiabetic individuals from a population-based sample who were evaluated. Most previous studies have assessed relatively small groups of individuals (n = 26–120) from selected clinical samples (25,27,29,30,32–34,36,37,40,41). With one exception (6), most of the previous population-based studies of insulin-LV relations have

TABLE 6
Correlation of cardiovascular parameters with $\log_{10}$ (insulin) in men and women

	Men			Women		
	Univariate analysis		Linear regression*	Univariate analysis		Linear regression*
	R	*P*	(*P*)	R	*P*	(*P*)
Interventricular septum (cm)	0.185	<0.001	NS	0.241	<0.001	0.040
LV internal diameter (cm)	0.169	<0.001	NS	0.163	<0.001	NS
Posterior wall thickness (cm)	0.195	<0.001	NS	0.256	<0.001	(0.070)
LV mass (g)	0.244	<0.001	NS	0.255	<0.001	NS
LV mass/body surface area (g/m^2)	0.019	NS	NS	0.060	NS	NS
LV mass/height$^{2.7}$ (g/m)	0.206	<0.001	NS	.231	<0.001	NS
Relative wall thickness	0.032	NS	NS	0.110	0.003	0.010
Left atrial diameter	0.254	<0.001	NS	0.279	<0.001	NS
Fractional shortening (%)	0.001	NS	NS	0.068	0.011	NS
Midwall shortening (%)	−0.009	NS	NS	−0.03	NS	NS
Stress-corrected midwall shortening	0.041	NS	NS	0.024	NS	NS
Cardiac output (l/min)	0.197	<0.001	0.022	0.244	<0.001	NS
Cardiac index ($l \cdot min \cdot m^{-2}$)	−0.029	NS	NS	0.068	0.082	NS
Total peripheral resistance ($mmHg \cdot l \cdot min^{-1}$)	−0.073	(0.075)	NS	−0.169	<0.001	NS

R, univariate Pearson correlation coefficient. *Multiple linear regression analysis included age, BMI, height, and systolic blood pressure.

also involved smaller populations (from 62 to 351) (27,29,33,36) than in the present study. An additional strength of the present study is the ability to measure adipose body mass and percentage of body fat by bioelectric impedance (43). However, substitution of the latter variables for BMI did not alter the results of the study; therefore, findings using the more easily measured BMI are presented.

In conclusion, strong univariate associations between fasting plasma insulin levels and abnormalities of LV structure, function, and systemic hemodynamics are attenuated but not completely eliminated when the effects of overweight and other covariates are taken into account. The mechanisms of the observed associations are uncertain but may include enhancement by insulin of increased distal tubular sodium reabsorption (3,44), with resultant increases in hemodynamic volume and pressure loads and possible direct myocardial trophic effects of insulin (45). One potential stimulus to increased LV wall thicknesses, elevated arterial stiffness, has been identified in women and men with type 2 diabetes in the SHS (15) but was not detected by the pulse pressure/stroke volume ratio in nondiabetic participants with elevated insulin levels in the present study. Additional research is needed to determine the generalizability of the present results to other population-based samples and to elucidate the mechanisms involved.

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REFERENCES

1. Liang C, Doherty JU, Faillace R, Maekawa K, Arnold S, Gavras H, Hood WB Jr: Insulin infusion in conscious dogs: effects on systemic and coronary hemodynamics, regional blood flows, and plasma catecholamines. *J Clin Invest* 69:1321–1336, 1982
2. Anderson EA, Hoffman RP, Balon TW, Sinkey CA, Mark AL: Hyperinsulinemia produces both sympathetic neural activation and vasodilation in normal humans. *J Clin Invest* 87:2246–2252, 1991
3. DeFronzo RA, Cooke CR, Andres R, Faloona GR, Davis PJ: The effect of insulin on renal handling of sodium, potassium, calcium, and phosphate in man. *J Clin Invest* 55:845–855, 1975
4. Friedberg CE, van Buren M, Bijlsma JA, Koomans HA: Insulin increases sodium reabsorption in diluting segment in humans: evidence for indirect mediation through hypokalemia. *Kidney Int* 40:251–256, 1991
5. Vakili BA, Okin PM, Devereux RB: Prognostic significance of left ventricular hypertrophy. *Am Heart J* 141:334–341, 2001
6. Marcus R, Krause L, Weder AB, Dominguez-Meja A, Schork NJ, Julius S: Sex-specific determinants of increased left ventricular mass in the Tecumseh Blood Pressure Study. *Circulation* 90:928–936, 1994
7. Lee ET, Welty TK, Fabsitz R, Cowan LD, Le NA, Oopik AJ, Cucchiara AJ, Savage PJ, Howard BV: The Strong Heart Study—a study of cardiovascular disease in American Indians: design and methods. *Am J Epidemiol* 132:1141–1155, 1990
8. Howard BV, Welty TK, Fabsitz RR, Cowan LD, Oopik AJ, Le NA, Yeh J, Savage PJ, Lee ET: Risk factors for coronary heart disease in diabetic and non-diabetic Native Americans. *Diabetes* 41 (Suppl. 2):4–11, 1992
9. Welty TK, Lee ET, Yeh JL, Cowan LD, Go O, Fabsitz RR, Le NA, Oopik AJ, Robbins DC, Howard BV: Cardiovascular disease risk factors among American Indians: the Strong Heart Study. *Am J Epidemiol* 142:269–287, 1995
10. Lee ET, Cowan LD, Welty TK, Sievers M, Howard WJ, Oopik AJ, Wang W, Yeh JL, Devereux RB, Rhoades ER, Fabsitz RR, Go O, Howard BV: All-cause mortality and cardiovascular disease mortality in three American Indian populations, aged 45–74 years, 1984–1988: the Strong Heart Study. *Am J Epidemiol* 147:995–1008, 1998
11. Howard BV, Lee ET, Cowan LD, Devereux RB, Galloway MJ, Go OT, Howard WJ, Rhoades ER, Robbins DC, Sievers ML, Welty TK: The rising tide of cardiovascular disease in American Indians: the Strong Heart Study. *Circulation* 99:2389–2395, 1999
12. WHO Expert Committee on Diabetes Mellitus: Second report. Geneva: World Health Organization: 1980 (Technical Report Series 646)
13. Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Wood EA, Howard BV, Welty TK, Lee ET, Fabsitz RR: Relations of Doppler stroke distance and aortic anular diameter to left ventricular stroke volume in normotensive and hypertensive American Indians: the Strong Heart Study. *Am J Hypertens* 10:619–628, 1997
14. Devereux RB, Roman MJ, de Simone G, O'Grady MJ, Paranicas M, Yeh J-L, Fabsitz RR, Howard BV: Relations of left ventricular mass to demographic

and hemodynamic variables in American Indians: the Strong Heart Study. *Circulation* 96:1416–1423, 1997
15. Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Lee ET, Welty TK, Fabsitz RR, Robbins D, Rhoades ER, Howard BV: Impact of diabetes on cardiac structure and function: the Strong Heart Study. *Circulation* 101:2271–2276, 2000
16. Devereux RB, Roman MJ: Evaluation of cardiac and vascular structure by echocardiography and other noninvasive techniques. In *Hypertension: Pathophysiology*, *Diagnosis*, *Treatment*. 2nd ed. Laragh JH, Brenner BM, Eds. New York, Raven Press, 1995, p. 1969–1985
17. Sahn DJ, De Maria A, Kisslo J, Weyman A: The Committee on M-mode Standardization of the American Society of Echocardiography: recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 58:1072–1083, 1978
18. Schiller NB, Shah PM, Crawford M, De Maria A, Devereux RB, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I, Silverman NH, Tajik A: American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms: recommendations for quantitation of the left ventricle by two-dimensional echocardiography. *J Am Soc Echocardiogr* 2:358–367, 1989
19. Dubin J, Wallerson DC, Cody RJ, Devereux RB: Comparative accuracy of Doppler echocardiographic methods for clinical stroke volume determinations. *Am Heart J* 120:116–123, 1990
20. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N: Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 57:450–458, 1986
21. Palmieri V, Dahlöf B, DeQuattro V, Sharpe E, Bella JN, de Simone G, Paranicas M, Fishman D, Devereux RB: Reliability of echocardiographic assessment of left ventricular structure and function: the PRESERVE Study. *J Am Coll Cardiol* 34:1625–1632, 1999
22. Palmieri V, de Simone G, Arnett DK, Bella JN, Kitzman DW, Oberman A, Hopkins PN, Province MA, Devereux RB: Relation of various degrees of body mass index in patients with systemic hypertension to left ventricular mass, cardiac output and peripheral resistance (The Hypertension Genetic Epidemiology Network Study). *Am J Cardiol* 88:1163–1168, 2001
23. de Simone G, Devereux RB, Roman MJ, Ganau A, Saba PS, Alderman MH, Laragh JH: Assessment of left ventricular function by the mid-wall fractional shortening-end-systolic stress relation in human hypertension. *J Am Coll Cardiol* 23:1444–1451, 1994
24. Shimizu G, Hirota Y, Kita Y, Kawamura K, Saito T, Gaasch WH: Left ventricular midwall mechanics in systemic arterial hypertension: myocardial function is depressed in pressure-overload hypertrophy. *Circulation* 83:1676–1684, 1991
25. Devereux RB, de Simone G, Pickering TG, Schwartz JE, Roman MJ: Relation of left ventricular midwall function to cardiovascular risk factors and arterial structure and function. *Hypertension* 31:929–936, 1998
26. Hartford M, Wikstrand J, Wallentin I, Ljungman S, Wilhelmsen L, Berglund G: Left ventricular mass in middle-aged men: relationship to blood pressure, sympathetic nervous activity, hormonal and metabolic factors. *Clin Exp Hypertens* 5:1429–1451, 1983
27. Sharp SD, Williams RR: Fasting insulin and left ventricular mass in hypertensives and normotensive controls. *Cardiology* 81:207–212, 1992
28. Sasson Z, Rasooly Y, Bhesania T, Rasooly I: Insulin resistance is an important determinant of left ventricular mass in the obese. *Circulation* 88:1431–1436, 1993
29. Lind L, Andersson PE, Andren B, Hanni A, Lithell HO: Left ventricular hypertrophy in hypertension is associated with the insulin resistance metabolic syndrome. *J Hypertens* 13:433–438, 1995
30. Costa CH, Batista MC, Moise VA, Kohlmann NB, Ribeiro AB, Zanella MT: Serum insulin levels, 24-hour blood pressure profile, and left ventricular mass in nonobese hypertensive patients. *Hypertension* 26:1085–1088, 1995
31. Ohya Y, Abe I, Fujii K, Ohmori S, Onaka U, Kobayashi K, Fujishima M: Hyperinsulinemia and left ventricular geometry in a work-site population in Japan. *Hypertension* 27:729–734, 1996
32. Paolisso G, Galderisi M, Tagliamont MR, de Divitiis M, Galzerano D, Petrocelli A, Gualdiero P, de Divitiis O, Varricchio M: Myocardial wall thickness and left ventricular geometry in hypertensives: relation with insulin. *Am J Hypertens* 10:1250–1256, 1997
33. Vetta F, Cicconetti P, Ronzoni S, Rizzo V, Palleschi L, Canarile G, Lupattelli MR, Migliori M, Morelli S, Marigliano V: Hyperinsulinaemia, regional adipose tissue distribution and left ventricular mass in normotensive, elderly, obese subjects. *Eur Heart J* 19:326–331, 1998
34. Jelenc M, Zemva A, Marn-Pernat A, Zemva Z: Are insulin metabolism and night-time blood pressure related to left ventricular hypertrophy? *Int J Cardiol* 63:261–265, 1998
35. Gutin B, Treiber F, Owens S, Mensah GA: Relations of body composition to left ventricular geometry and function in children. *J Pediatr* 132:1023–1027, 1998
36. Phillips RA, Krakoff LR, Dunaif A, Finegood DT, Gorlin R, Shimabukuro S: Relation among left ventricular mass, insulin resistance, and blood pressure in nonobese subjects. *J Clin Endocrinol Metab* 83:4284–4288, 1998
37. Scuteri A, Di Bernardo MG, De Propris AM, Marigliano V: Insulin effects on the left ventricle in older hypertensive subjects. *J Am Geriatr Soc* 47:727–729, 1999
38. Urbina EM, Gidding SS, Bao W, Elkasabany A, Berenson GS: Association of fasting blood sugar level, insulin level, and obesity with left ventricular mass in healthy children and adolescents: the Bogalusa Heart Study. *Am Heart J* 138:122–127, 1999
39. Rheeder P, Stolk RP, Mosterd A, Pols HA, Hofman A, Grobbee DE: Insulin resistance syndrome and left ventricular mass in an elderly population (The Rotterdam Study). *Am J Cardiol* 84: 233–236, 1999, A9
40. Watanabe K, Sekiya M, Tsuruoka T, Funada J, Kameoka H: Effect of insulin resistance on left ventricular hypertrophy and dysfunction in essential hypertension. *J Hypertens* 17:1153–1160, 1999
41. Verdecchia P, Reboldi G, Schillaci G, Borgioni C, Ciucci A, Telera MP, Santeusanio F, Porcellati C, Brunetti P: Circulating insulin and insulin growth factor-1 are independent determinants of left ventricular mass and geometry in essential hypertension. *Circulation* 100:1802–1807, 1999
42. Aurigemma GP, Silver KH, McLaughlin M, Mauser J, Gaasch WH: Impact of chamber geometry and gender on left ventricular systolic function in patients >60 years of age with aortic stenosis. *Am J Cardiol* 74:794–798, 1994
43. Bella JN, Devereux RB, Roman MJ, O'Grady MJ, Welty TK, Lee ET, Fabsitz RR, Howard BV: Relations of left ventricular mass to fat-free and adipose body mass: the Strong Heart Study. *Circulation* 98:2538–2544, 1998
44. Endre T, Mattiasson I, Berglund G, Hulthen UL: Insulin and renal sodium retention in hypertension-prone men. *Hypertension* 23:313–319, 1994
45. Holmang A, Yoshida N, Jennische E, Waldenstrom A, Bjorntorp P: The effects of hyperinsulinaemia on myocardial mass, blood pressure regulation and central haemodynamics in rats. *Eur J Clin Invest* 26:973–978, 1996