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 log10 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 vascular resistance 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 (15-18). 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 annular 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 ($r = 0.98$, $P < 0.001$) to necropsy measurements (20), which also showed good reproducibility ($r = 0.93$, $P < 0.001$) 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 weight (23). 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 901 participants with normal glucose tolerance (51% women) and 487 with impaired glucose tolerance (64% women) were directionally similar and were statistically significant in the larger groups, 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.
Among women, univariate correlations were found between log₁₀ 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 height², 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 log₁₀ insulin, the latter variable was weakly associated with higher LV relative wall thickness. Left atrial diameter was positively related to log₁₀ insulin. Log₁₀ insulin had a weak positive association with endocardial fractional shortening but not with measures of LV systolic midwall function. Higher log₁₀ 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 log₁₀ 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 log₁₀ 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.

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
INTRODUCTION

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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