

Relation of Left Ventricular Hypertrophy to Inflammation and Albuminuria in Adults With Type 2 Diabetes

The Strong Heart Study

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OBJECTIVE — To evaluate in adults with type 2 diabetes the extent to which the relation of left ventricular hypertrophy (LVH) to markers of systemic inflammation (fibrinogen and high-sensitivity C-reactive protein [hsCRP]) are affected by microangiopathy.

RESEARCH DESIGN AND METHODS — We selected adults with type 2 diabetes using American Diabetes Association criteria from a population-based cohort, excluding those with medical history or electrocardiographic evidence of coronary heart disease or dialysis-dependent renal failure. LVH was assessed by echocardiogram.

RESULTS — Of the 1,299 eligible participants, 384 (29.6%) had LVH, which was associated with higher BMI, hsCRP, fibrinogen, and albuminuria in univariate analyses. After controlling for significant confounders, fibrinogen and albuminuria were higher in the presence of LVH (both $P < 0.01$), whereas hsCRP was not ($P = 0.2$), mostly because of the confounding effect of BMI. Adjustment for albuminuria abolished the relation of LVH to higher fibrinogen ($P = 0.2$). However, fibrinogen was significantly higher in participants with LVH among those without pathologic levels of albuminuria (<30 mg/g creatinuria), but not independent of BMI. Although hsCRP and fibrinogen were moderately correlated, fibrinogen, but not CRP, showed a significant relation with albuminuria.

CONCLUSIONS — In adults with type 2 diabetes, echocardiographic LVH is associated with susceptibility to atherothrombosis and increased albuminuria, which is a marker of microangiopathy and endothelial dysfunction that appears in turn to be a relevant pathogenetic link between LVH and inflammation. However, in the absence of significant microalbuminuria, elevated BMI is a relevant pathogenetic factor in the relation of LVH to increased levels of markers of inflammation, potentially preceding development of significant albuminuria. In the presence of microangiopathy, we found that the atherothrombotic risk profile associated with LVH was independent of BMI and possibly reflected the association of LVH with a higher degree of endothelial dysfunction.

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Abbreviations: CRP, C-reactive protein; DBP, diastolic blood pressure; ECG, electrocardiogram; hsCRP, high-sensitivity C-reactive protein; LV, left ventricular; LVH, left ventricular hypertrophy; sBP, systolic blood pressure.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Type 2 diabetes is associated with accelerated atherosclerosis and increased cardiovascular event rates (1,2). The association between diabetes and adverse cardiovascular outcome may be partially explained by the strong independent association of type 2 diabetes with cardiovascular target organ damage, such as left ventricular hypertrophy (LVH) (3–6), a well-known predictor of cardiovascular events independent of coronary artery disease (7). However, the pathophysiologic mechanisms underlying the evolution from target organ damage to cardiovascular events are unclear.

We recently reported an independent association of LVH with an elevated fibrinogen level (8). Inflammation, and in particular elevated fibrinogen, is associated with the development of atherosclerosis (9) and consequent vascular events (10). LVH is associated with atherosclerosis (11) and albuminuria (12). In addition, albuminuria reflects in part the atherosclerotic burden (13) and level of renal failure (14). Albuminuria is also a marker of microangiopathy and endothelial dysfunction and is associated with low-grade inflammation (15) in the absence of overt renal failure. Therefore, understanding the pathophysiologic links among LVH, markers of endothelial damage/dysfunction, atherothrombosis, and inflammation is clinically and prognostically relevant. The present study was undertaken in a population-based sample of adults with type 2 diabetes to evaluate 1) the relation of LVH to fibrinogen and high-sensitivity C-reactive protein (hsCRP) as markers of inflammation and susceptibility to atherothrombosis and albuminuria, and 2) whether albuminuria, as a manifestation of concomitant microangiopathy and endothelial dysfunction, affects the relation of LVH with markers of inflammation.

RESEARCH DESIGN AND METHODS

Population

The Strong Heart Study is a population-based survey of the prevalence and incidence of cardiovascular risk factors and events in 13 American Indian communities from Arizona, Oklahoma, and South and North Dakota (the Gila River and Salt River Pima/Maricopa and Akchin Pima/Papago in Arizona, the Seven Tribes of Southwestern Oklahoma [Apache, Caddo, Comanche, DE, Fort Sill Apache, Kiowa, and Wichita], and the Oglala and Cheyenne River Sioux and Spirit Lake Community in South and North Dakota) (16,17). The study had an overall recruitment rate of 62% for an initial evaluation from 1989 to 1992. The return rate for those alive at the second exam (1993–1995) was 89%, 97% of whom (3,501 participants) underwent echocardiography (18).

Hypertension was defined by systolic blood pressure (sBP) ≥ 140 mmHg and/or diastolic blood pressure (dBP) ≥ 90 mmHg or use of antihypertensive medication. Diabetes was defined by fasting plasma glucose levels ≥ 126 mg/dl or by specific treatment (19). Alcohol use, smoking history, and number of cigarettes smoked/day were assessed by self-report (17). Of the study population, 31% had never smoked, 39% were former smokers, and 30% currently smoked. BMI was calculated by the standard formula. Participants with clinically overt coronary artery disease, defined by previously reported criteria (20), were excluded from the present study. Assessment of prevalent coronary heart disease at the second study exam used information from the first and second exams and from systematic Strong Heart Study morbidity and mortality surveillance with data from medical record reviews and electrocardiogram (ECG) diagnosis of myocardial infarction (21). The present study evaluated 1,299 Strong Heart Study participants with type 2 diabetes who were free of clinically diagnosed cardiovascular disease, ECG signs of previous myocardial infarction (2), and dialysis-dependent renal failure.

Echocardiographic methods

The echocardiographic methods used have been previously described (18). A standard protocol was used to obtain

parasternal views with optimal orientation to maximize left ventricular (LV) internal diameters. This method has been shown to allow reliable estimation of LV structure and function (22). All echocardiograms were recorded on tapes and centrally read by highly experienced readers.

Echocardiographic measurements

Measurements of LV internal dimensions and wall thicknesses were obtained from two-dimensionally guided M-mode tracings or parasternal long-axis 2-D images according to the American Society of Echocardiography recommendations (23,24). Wall motion abnormalities were visually assessed in parasternal long and short axes and in apical views (4).

Derived echocardiographic variables

LV mass was estimated by an anatomically validated formula that yields values closely related ($r = 0.90$) to necropsy LV weight (25) and is indexed for height^{2.7} ($\text{g}/\text{m}^{2.7}$). Stroke volume was derived from LV linear measurements by the standard method (26). LV hypertrophy was defined as LV mass index >49.2 $\text{g}/\text{m}^{2.7}$ in men and >46.7 $\text{g}/\text{m}^{2.7}$ in women.

Laboratory data

Participants were examined in the morning after an overnight fast ≥ 12 h. Laboratory methods have been reported in detail elsewhere (17). Blood was collected and EDTA plasma was prepared and frozen. After being stored at -80°C , samples were thawed and assayed for fibrinogen in large batches to minimize analytic variability. Plasma fibrinogen levels were determined by a modification of the Clauss method, which assesses fibrinogen based on the speed of clot formation under standardized conditions. We modified the method to use semi-automated instrumentation (Stago ST-4; American Bio-Products, Parsippany, NJ) and, by recalcification, to use the EDTA plasma available in this study (27). Within batches, the coefficient of variation (CV) was $\leq 5\%$; across the whole cohort, it was 12.4% (17). hsCRP was measured using an enzyme-linked immunosorbent assay developed in-house using purified CRP and anti-CRP antibodies from CalBio-Chem (La Jolla, CA) (28). This assay has been used extensively in epidemiological studies (29) and in the validation of the commercially available assay for hsCRP

(30). The coefficient of variation (CV) is $\sim 8\%$. Albuminuria was measured on a single spot urine sample and was expressed in relation to grams of urinary creatinine (mg/g) (17). Microalbuminuria was defined as urinary albumin/creatinine ≥ 30 mg/g but <300 mg/g, and macroalbuminuria was defined as urinary albumin/creatinine ≥ 300 mg/g.

Statistical analysis

Continuous variables are expressed as means \pm SD. Log transformation of continuous variables was used when needed to satisfy distributional requirements for parametric tests. The *t* test for continuous variables and Fisher's exact test for discrete variables were used to compare differences among subjects with or without LVH. Subsequently, ANCOVA was used to test between-group differences, accounting for covariates. Pearson's correlation was used to assess bivariate relations, and partial correlation was used to test the relation, adjusting for covariates. Multiple regression analysis was used to assess the relation of albuminuria, hsCRP, and fibrinogen to LV mass index, adjusting for covariates and using a stepwise model (variables removed for $P \geq 0.1$). Two-tailed $P < 0.05$ was considered statistically significant.

RESULTS — In our study sample of 1,299 adults with type 2 diabetes without symptoms or ECG-confirmed signs of coronary heart disease, 384 (29.6%) had LVH and 915 (70.4%) had LV mass in the normal range (Table 1). Participants with LVH were slightly older; had higher BMI, sBP and pulse pressure, and urinary albumin/creatinine and plasma creatinine levels; and were more frequently female, hypertensive, and being treated for hypertension. However, both groups had similar dBP, lipid concentrations, and HbA_{1c}; both groups also had a similar proportion of subjects on lipid-lowering agents (2.8 vs. 2.6% for LVH and normal LV mass, respectively; NS) and duration of diabetes (12 vs. 11 years for LVH and normal LV mass, respectively; $P = 0.08$). Wall motion abnormalities were more prevalent in the those with than those without LVH (14 vs. 5%; $P < 0.001$). Fibrinogen, hsCRP, and urinary albumin/creatinine levels were higher in subjects with LVH. Some joint effects of LVH and hypertension on levels of markers of inflammation emerged from a two-way

Table 1—General characteristics of the study population

	LVH	Normal LV mass	P
n	384	915	—
Age (years)	61 ± 8	59 ± 7	<0.001
BMI (kg/m ²)	34.8 ± 6.8	31.4 ± 5.8	<0.001
Female (%)	83	64	<0.001
Arterial hypertension (%)	68	48	<0.001
Hypertensives on treatment (%)	50	34	<0.001
Clinic sBP (mmHg)	139 ± 22	130 ± 19	<0.001
Clinic dBP (mmHg)	76 ± 10	75 ± 10	NS
Clinic pulse pressure (mmHg)	64 ± 20	54 ± 16	<0.001
Ankle/arm blood pressure ratio	1.12 ± 0.18	1.14 ± 0.16	NS
Plasma creatinine (mg/dl)	1.06 ± 0.75	0.92 ± 0.46	<0.001
HDL cholesterol (mg/dl)	39 ± 11	39 ± 12	NS
LDL cholesterol (mg/dl)	119 ± 34	116 ± 34	NS
Triglycerides (mg/dl)	184 ± 145	182 ± 131	NS
Fibrinogen (mg/dl)	413 ± 100	374 ± 98	<0.001
hsCRP (mg/l)	9.9 ± 14.2	6.8 ± 8.4	<0.01*
Urinary albumin/creatinine (mg/g)	1,337 ± 2,727	480 ± 1,505	<0.001*
HbA _{1c} (%)	8.5 ± 2.3	8.7 ± 2.4	NS

Data are n, %, or means ± SD. *After log-transformation of the dependent variable.

ANCOVA, in which we found a stepwise trend toward increase in fibrinogen (without LVH and without hypertension: 377 mg/dl; without LVH and with hypertension: 385 mg/dl; with LVH and without hypertension: 401 mg/dl; with LVH and with hypertension: 405 mg/dl; *P* = 0.09 for interaction, adjusted for covariates) and urinary albumin/creatinine (without LVH and without hypertension: 450 mg/g; without LVH and with hypertension: 674 mg/g; with LVH and without hypertension: 784 mg/g; with LVH and with hypertension: 1,453 mg/g; *P* < 0.05 for interaction, adjusted for covariates). In addition, hsCRP was higher with LVH, with no significant impact of history of hypertension (without LVH and without hypertension: 7.3 mg/l; without LVH and with hypertension: 7.6 mg/l; with LVH and without hypertension: 10.0 mg/l; with LVH and with hypertension: 8.8 mg/l; NS for interaction, adjusted for covariates).

In the whole study sample, in a multivariate ANCOVA adjusting for potential confounders (age, sex, smoking status, BMI, sBP, history of hypertension, HbA_{1c}, plasma creatinine and lipids, use of major anti-hypertensive and lipid-lowering drug classes, and echocardiographic wall motion abnormalities), fibrinogen and urinary albumin/creatinine were significantly higher with LVH, whereas the difference in hsCRP did not attain statistical

significance (Table 2) because of the confounding effect of BMI. When BMI was excluded as a covariate, hsCRP was significantly higher in participants with LVH (9.7 vs. 7.2 mg/l; *P* < 0.005).

In subgroup analyses, we subdivided the study population into subjects with and without significant albuminuria, and explored the association of LVH with fibrinogen and hsCRP and the influence of BMI on these associations (Table 3). Among subjects with urinary albumin/creatinine <30 mg/g, after adjusting for all covariates but BMI, those with LVH had higher fibrinogen, hsCRP, and BMI than those without LVH, whereas plasma creatinine and urinary albumin/creatinine were similar between the two groups. However, in this subgroup, adding BMI to the set of covariates abolished the differences in hsCRP (7.9 vs. 7.2 mg/l) and fibrinogen levels (364 vs. 357 mg/dl) between participants with and without

LVH (both *P* > 0.1). In subanalyses of participants with significant albuminuria, after adjusting for standard covariates except BMI (Table 3), LVH was associated with higher fibrinogen, hsCRP, urinary albumin/creatinine, and BMI, independent of covariates. In this subgroup, further adjustment for BMI diminished the between-group differences in hsCRP (9.7 vs. 7.8 mg/l; *P* = 0.08), but not in fibrinogen (424 vs. 398 mg/dl; *P* < 0.05) and urinary albumin/creatinine (2,482 vs. 2,385 mg/g; both *P* < 0.05).

In a subsequent multivariate model in the whole study sample, as summarized in Table 4, albuminuria was used as a covariate in addition to the standard set of covariates. The ANCOVA showed that adjusting for albuminuria significantly diminished differences in fibrinogen and hsCRP between participants with versus those without LVH (Table 4).

In univariate analysis, the LV mass index had stronger correlations with fibrinogen (*r* = 0.22, *P* < 0.001) and log_e-albumin/creatinine (*r* = 0.24, *P* < 0.001) than with log₁₀-hsCRP (*r* = 0.11, *P* < 0.01). In multivariate analysis adjusting for covariates (age, sex, BMI, Doppler stroke volume, hypertension, LDL and HDL cholesterol, HbA_{1c}, smoking habit, micro- and macroalbuminuria, plasma creatinine levels, wall motion abnormalities, antihypertensive drug classes, and use of lipid-lowering agents), the LV mass index was not significantly related to fibrinogen or log-hsCRP.

In our study population, fibrinogen and log-hsCRP were moderately correlated (*r* = 0.48, *P* < 0.001); adjustment for covariates (albuminuria, age, sex, sBP, hypertension, BMI, HbA_{1c}, lipids, plasma creatinine, wall motion abnormalities, smoking status, and anti-hypertensive drug classes and lipid-lowering agents) did not significantly weaken the relation between fibrinogen and log-hsCRP (partial *r* = 0.43, *P* < 0.001). However, al-

Table 2—Left ventricular hypertrophy, markers of inflammation, and albuminuria in study population

	LVH	Normal LV mass	Adjusted P
Fibrinogen (mg/dl)	402 ± 92	381 ± 91	<0.001
hsCRP (mg/l)	9.2 ± 12.0	7.5 ± 11.0	NS (0.335)
Urinary albumin/creatinine (mg/g)	1,126 ± 1,710	613 ± 1,630	<0.001

Data are adjusted means ± SD; variables tested after log-transformation. *P* adjusted for age, sex, smoking status, BMI, sBP, history of hypertension, HbA_{1c}, plasma creatinine and lipids levels, use of major antihypertensive drug classes and lipid-lowering agents, and wall motion abnormalities by ANCOVA.

Table 3—Relation of left ventricular hypertrophy to markers of inflammation, accounting for the absence or presence of albuminuria

	No albuminuria		Albuminuria	
	LVH	Normal LV mass	LVH	Normal LV mass
n	120	435	264	480
BMI (kg/m ²)	36.0 ± 6.6	31.8 ± 6.6*	34.4 ± 6.6	31.0 ± 6.4†
Fibrinogen (mg/dl)	372 ± 80	355 ± 79*	424 ± 103	398 ± 100†
hsCRP (mg/l)	8.6 ± 7.9	7.0 ± 8.1	10.3 ± 14.3	7.4 ± 13.2†
Urinary albumin/creatinine (mg/g)	12.9 ± 11	12.7 ± 12	1,645 ± 2,265	1,093 ± 2,190†

Data are adjusted means ± SD; variables tested after log-transformation. Standard covariates used were age, sex, smoking status, sBP, history of hypertension, HbA_{1c}, plasma creatinine and lipids levels, use of major antihypertensive drug classes and lipid-lowering agents, and wall motion abnormalities. **P* < 0.05 vs. LVH in the group without albuminuria; †*P* < 0.05 vs. LVH in the group with albuminuria.

though fibrinogen was moderately and independently related to log-urinary albumin/creatinine (partial *r* = 0.20, *P* < 0.001, independent of covariates), log-hsCRP was not significantly related to log-urinary albumin/creatinine (partial *r* = -0.11, *P* = 0.07).

CONCLUSIONS— We hypothesized that in subjects with type 2 diabetes, LVH would be associated with elevated markers of systemic inflammation and susceptibility to atherothrombosis (CRP and fibrinogen levels) independently of clinically overt cardiovascular disease and traditional cardiovascular risk factors. We further explored the extent to which the relation of LVH to albuminuria, a marker of microangiopathy and endothelial dysfunction, impacted the association of LVH with markers of inflammation. In 1,299 adults with type 2 diabetes, we found that those with LVH had higher levels of fibrinogen, hsCRP, and urinary albumin/creatinine than those without LVH, independent of cardiovascular risk factors and plasma creatinine levels. Fibrinogen and hsCRP were independently and significantly higher in participants with LVH among those without pathologic albuminuria, suggesting that the relation of

LVH to low-grade inflammation may precede development of clinically relevant albuminuria; in addition, in this subgroup, we showed that higher BMI was a crucial pathogenetic factor in the relation between LVH and fibrinogen and hsCRP. Therefore, our data support the concept that in type 2 diabetes, elevation of markers of inflammation with higher BMI may precede development of significant albuminuria (15), emphasizing the role of obesity in such a pathophysiologic context. In fact, we should emphasize that BMI is a strong determinant of LVH (31) and that adipose tissue is a recognized site of cytokine production, in particular interleukin-6 and tumor necrosis factor- α , therefore influencing hsCRP as well as fibrinogen levels. Diet-induced reduction of BMI, in fact, is associated with reduced cytokine levels (32). Obesity is also associated with insulin resistance, which is in turn associated with markers of inflammation (33) and pro-thrombotic risk (14,34,35).

In view of the well-known role of fibrinogen as a pro-thrombotic factor and marker of endothelial dysfunction, and the recently revealed impact of elevated hsCRP on endothelial cell functions and atherothrombotic mechanisms (36), our

Table 4—Impact of albuminuria on relation of left ventricular hypertrophy to markers of inflammation in the overall study population

	LVH	Normal LV mass	Adjusted <i>P</i>
Fibrinogen (mg/dl)	394 ± 86	383 ± 81	0.05
hsCRP (mg/l)	9.1 ± 11.8	7.5 ± 11.2	NS (0.5)

Data are adjusted means ± SD; variables tested after log-transformation. *P* adjusted for albuminuria, age, sex, smoking status, BMI, sBP, history of hypertension, HbA_{1c}, plasma creatinine and lipids levels, use of major antihypertensive drug classes and lipid-lowering agents, and wall motion abnormalities.

study results suggest mechanisms by which type 2 diabetic subjects with LVH are at greater risk for atherothrombotic events than those without LVH, even in the absence of microangiopathy.

Another fascinating hypothesis is that LVH may interact with endothelial dysfunction, cytokines, insulin resistance, and hemodynamics to increase markers of inflammation and albuminuria. Experimental evidence suggests that stretched myocardium is a site of cytokine production (37). In addition, there is evidence in humans that LV hemodynamic overload is associated with increased circulating tumor necrosis factor- α , which is proportional to the severity of heart failure (38). Recently, it has been shown that hsCRP upregulates angiotensin-I receptor in vascular smooth muscle cells (39). It is well known that the renin-angiotensin system has a central pathophysiologic role in the development of LVH and atherosclerosis. These observations and our findings may be relevant in explaining the high prevalence of cardiovascular events in adults with type 2 diabetes.

One interesting finding was that in the presence of albuminuria, a manifestation of microangiopathy, LVH was associated with higher fibrinogen, hsCRP, and albuminuria independent of cardiovascular risk factors, including BMI, subclinical coronary heart disease, and plasma creatinine level. This finding suggests that the pathogenetic role of obesity in the relation of LVH to hsCRP and fibrinogen diminishes when vascular damage is overt. The impact of albuminuria, a marker of microangiopathy and vascular damage as well as renal dysfunction, was further clarified by ANCOVA in the whole study sample, when controlling for albuminuria obscured the relation of LVH to higher fibrinogen. This finding was in part expected because of the moderately strong relation between fibrinogen and albuminuria in our study sample. Contrariwise, we did not find a significant association between hsCRP and albuminuria, as in another ethnically different population of diabetic adults (40).

Study limitations

Because of the nature of the present study, we could not demonstrate mechanisms by which LVH is related to albuminuria and inflammation, or provide explanations for the precise pathophysiologic process underlying albuminuria, inflam-

mation, and LVH. Moreover, although we excluded participants with symptoms or ECG signs of coronary heart disease, and further controlled for echocardiographic wall motion abnormalities, we could not completely exclude silent coronary atherosclerosis in our study sample.

In adults with type 2 diabetes without clinically overt cardiovascular disease or dialysis-dependent renal failure, LVH is associated with elevated levels of fibrinogen and hsCRP, and therefore with increased atherothrombotic risk. However, LVH was also associated with greater albuminuria, a marker of microangiopathy, vascular damage, and endothelial dysfunction. In fact, microangiopathy and endothelial dysfunction appear to be a relevant pathogenetic mechanism in the association of LVH with high atherothrombotic risk. In addition, increased BMI appears to be a relevant factor associated with both LVH and increased levels of fibrinogen and hsCRP, preceding the development of overt microangiopathy.

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