Fibrinogen and Preclinical Echocardiographic Target Organ Damage
The Strong Heart Study

Vittorio Palmieri, Aldo Celentano, Mary J. Roman, Giovanni de Simone, Michael R. Lewis, Lyle Best, Elisa T. Lee, David C. Robbins, Barbara V. Howard, Richard B. Devereux, for the Strong Heart Study Investigators

Abstract—Relations of fibrinogen to preclinical target organ damage, such as left ventricular hypertrophy, systolic dysfunction, and increased arterial stiffness while accounting for traditional risk factors, are unknown in a population-based sample free of clinically overt coronary heart disease. Therefore, we studied clinical and echocardiographic characteristics of 2709 American Indians participating in the Strong Heart Study without symptomatic atherosclerosis. The study sample was divided into tertiles of fibrinogen (cut-points, 3.24 and 3.83 g/L). Mean age, body mass index, proportion of women, and prevalences of hypertension and diabetes increased from the first to third tertile of fibrinogen. After adjustment for covariates, systolic and pulse pressures did not significantly differ among tertiles of fibrinogen, whereas diastolic pressure was slightly lower in the third than in lower tertiles of fibrinogen. HDL cholesterol was lower and plasma creatinine and urinary albumin/creatinine ratio was higher in the third tertile of fibrinogen. Left ventricular mass index, pulse pressure/stroke index, an estimate of arterial stiffness, and cardiac index were higher and left ventricular systolic function and total peripheral resistance were lower in the third than in two lower tertiles of fibrinogen independent of major covariates. In multiple regression analyses, left ventricular mass and pulse pressure/stroke index were positively associated with, and stress-corrected midwall shortening negatively associated with fibrinogen, independent of major covariates. Participants with fibrinogen >3.83 g/L were more likely to have at least 1 preclinical cardiovascular abnormality such as left ventricular hypertrophy, elevated arterial stiffness, or systolic myocardial dysfunction independent of covariates including renal dysfunction (adjusted odds ratio, 1.38; P<0.001). Thus, in a population sample of adults without clinically overt coronary heart disease, elevated fibrinogen is an independent correlate of prognostically relevant cardiovascular target organ damage. (Hypertension. 2001;38:1068-1074.)

Key Words: fibrinogen ■ risk factors ■ cardiovascular diseases ■ hypertrophy ■ echocardiography

Elevated plasma fibrinogen has been associated with increased prevalent and incident cardiovascular events in different populations,1–7 including American Indians.8 The relation of fibrinogen to cardiovascular events is in part due to its role in the coagulation cascade and in acute vascular syndromes.9 Fibrinogen could be a marker of clinically overt atherosclerosis10,11 rather than a risk factor. Indeed, subjects with clinically overt atherosclerosis have a higher prevalence of echocardiographic target organ damage and higher levels of fibrinogen.12 An important issue is whether fibrinogen is related to cardiovascular abnormalities in subjects in whom there is no evidence of overt atherosclerotic disease, because such information might contribute to risk stratification in populations and individuals. In particular, echocardiographic abnormalities such as left ventricular (LV) hypertrophy, LV systolic dysfunction, and elevated arterial stiffness are often diagnosed in relatively asymptomatic subjects with cardiovascular risk factors13,14 and are strong independent predictors of cardiovascular events.15–18 It would be relevant to assess whether fibrinogen is related to preclinical cardiovascular abnormalities independent of other traditional risk factors because it might contribute to better understanding of the pathophysiological relation between fibrinogen and cardiovascular events.10,12,19 This is especially relevant among hypertensive subjects because hypertension is a major cardiovascular risk factor associated with target organ damage such as LV hypertrophy, LV systolic dysfunction, and ele-
vated arterial stiffness.\textsuperscript{14,15,20} Therefore, the aim of our study was to investigate the relations of fibrinogen with echocardiographically identified cardiovascular target organ damage in adults free of clinically overt coronary heart disease while accounting for major confounding factors\textsuperscript{21} such as age, gender, body size, hypertension, diabetes, and lipids.

**Methods**

**Population**

The Strong Heart Study (SHS) is a population-based survey of cardiovascular risk factors and prevalent and incident cardiovascular disease in 13 American Indian communities in Arizona, Oklahoma, and South and North Dakota,\textsuperscript{22} recruited for an initial evaluation in 1989 to 1992 (rate, 62\%).\textsuperscript{23} Characterization of participants comprised standardized anthropometric, clinical, and laboratory data including 2-hour glucose tolerance test.\textsuperscript{22,23} The second examination (1993 to 1995) included medical history, clinical examination, ECG, and laboratory assessment. The study sample comprised 2709 participants with clinical information and without overt ischemic heart disease, defined as previously described.\textsuperscript{24} Hypertension was defined by resting clinical systolic blood pressure (BP) ≥140 mm Hg and/or diastolic BP ≥90 mm Hg or use of antihypertensive medications. Diabetes was defined by World Health Organization criteria.\textsuperscript{25} Alcohol use and smoking were assessed by self-report.\textsuperscript{22} Ex-smokers and current smokers were combined into one group. Body mass index (BMI) and body surface area (BSA) were calculated by standard formulas.

**Echocardiographic Methods**

A standard echocardiographic protocol was used to obtain parasternal views with optimal orientation to maximize LV internal diameter and apical views to evaluate optimal transmural and transaortic Doppler signals.\textsuperscript{26} All echocardiograms were recorded on tape and sent to the echocardiographic reading center for central evaluation by trained readers and subsequent overreading by highly experienced physician investigators.

**Echocardiographic Measurements and Derived Variables**

After controlling for correct orientation of planes for imaging,\textsuperscript{27} LV internal dimension and wall thickness were measured at end-diastole by American Society of Echocardiography (ASE) recommendations.\textsuperscript{28} When optimal orientation of M-mode LV recordings could not be obtained, linear LV measurements were derived with the use 2-dimensional imaging by the leading-edge ASE convention.\textsuperscript{29} LV mass was estimated by an anatomically validated formula, which yields values closely related \((r=0.90)\) to necropsy LV weight.\textsuperscript{30} Methods used to estimate LV mass have shown excellent reliability \((\text{intraclass correlation coefficient}=0.93)\).\textsuperscript{31} LV mass was indexed for BSA and for height\textsuperscript{2.7} \(\text{LV} \text{concentricity was estimated by the relative wall thickness (posterior wall thickness/LV internal radius). LV volumes were derived by Teichholz’s formula from LV linear dimensions, and used to estimate LV ejection fraction (EF) by a standard formula. Stroke volume, calculated as end-diastolic minus end-systolic volumes, was divided by BSA to obtain stroke index. Cardiac output and total peripheral resistance were calculated by standard methods. Pulse pressure/stroke index, an estimate of arterial stiffness, was calculated as (systolic–diastolic BP)/stroke index \([\text{mm Hg} \times \text{mL}]/\text{mL}\).}

Circumferential end-systolic stress (cESS) and midwall fractional shortening were assessed as previously reported.\textsuperscript{33,34} cESS calculated by the described method is closely related to values calculated by substituting central blood pressure estimated using applanation tonometry for cuff blood pressure \((r=0.95)\).\textsuperscript{34} Stress-corrected midwall shortening (MWS), an estimate of myocardial contractility, was calculated as percent-predicted MWS by given cESS.\textsuperscript{34} Good reliability of LV functional measurements was previously reported \((\text{intraclass correlation coefficient}, 0.65 \text{ to } 0.71)\).\textsuperscript{31}

### Definition of Cardiovascular Abnormalities

LV hypertrophy, high arterial stiffness, and low myocardial contractility were considered prognostically significant cardiovascular abnormalities.\textsuperscript{15–18,35} LV hypertrophy, defined as LV mass index >49.2 g/m\(^2\) in men and >46.7 g/m\(^2\) in women, was present in 24% of the study population. The 95th percentile of the distribution of pulse pressure/stroke index, obtained in 256 normotensive, nondiabetic SHS participants with BMI <30 kg/m\(^2\), without LV hypertrophy, significant valvular disease, or prior myocardial infarction, was used to define high arterial stiffness (>1.88 mm Hg/mL per m\(^2\)), which identified 17% of the study population. Low myocardial contractility, defined as stress-corrected MWS <89.2%,\textsuperscript{35} was present in 10% of the study population. Of the study sample, 40% had at least 1 echocardiographic sign of cardiovascular organ target damage.

**Laboratory Data**

Participants were examined in the morning after an overnight fast of \(\geq 12\) hours. Laboratory methods have been reported in more detail elsewhere.\textsuperscript{22} Plasma fibrinogen levels were centrally determined by a modification of the Clauss method;\textsuperscript{37} the technical error of the fibrinogen determination was 12.4%.\textsuperscript{22} Plasma fibrinogen levels were centrally determined by a modification of the Clauss method;\textsuperscript{37} the technical error of the fibrinogen determination was 12.4%.\textsuperscript{22}

**Statistical Analysis**

Distribution of fibrinogen was nearly normal; therefore tertile cut-points \((3.24 \text{ g/L} \text{ and } 3.83 \text{ g/L})\) were generated to divide the study population into 3 approximately equal groups. For continuous variables, data are expressed as mean ± SD. Log-transformation of continuous variables was used when needed to satisfy distributional requirements for parametric tests. ANCOVA, followed by Sidak post hoc test, was used to assess between-group differences adjusting for age, gender, SHS center, hypertension, and diabetes. Relations of fibrinogen to LV mass, pulse pressure/stroke volume, and stress-corrected MWS adjusted for covariates were assessed with multiple linear regressions by a stepwise-forward procedure \((\text{with variables removed from the model for } P<0.1)\). The \(\chi^2\) statistic was used to test differences for categoric variables. Logistic regression models were used to derive odds ratios of being in the third tertile \((>3.83 \text{ g/L})\) with cardiovascular abnormalities by means of a stepwise-forward procedure \((\text{with variables removed from the model for } P<0.1)\). A 2-tailed value of \(P<0.05\) was considered statistically significant.

An expanded Methods section can be found in an online data supplement available at [http://www.hypertensionaha.org](http://www.hypertensionaha.org).

**Results**

**Clinical and Laboratory Findings**

After exclusion criteria, 2709 American Indian participants were included into the study and subdivided into 3 groups of approximately equal size. Age and proportions of women, hypertensive subjects, and diabetics increased from the first to third tertile of fibrinogen (Table 1). Compared with

### TABLE 1. Demographic and Clinical Characteristics of SHS Participants Stratified by Tertiles of Plasma Fibrinogen

<table>
<thead>
<tr>
<th>Variables</th>
<th>Fibrinogen</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>(\leq 3.24 \text{ g/L})</td>
<td>59±8</td>
</tr>
<tr>
<td>Women, %</td>
<td>55</td>
<td>66</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>39</td>
<td>42</td>
</tr>
<tr>
<td>Type II diabetes, %</td>
<td>37</td>
<td>51</td>
</tr>
<tr>
<td>Smokers (current), %</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Cigarettes/d, n (median)</td>
<td>11 (6)</td>
<td>12 (10)</td>
</tr>
</tbody>
</table>

\(*P<0.01.\)
participants in the lower tertiles of fibrinogen, those with the highest values were more likely to be treated with insulin (28% versus 7% to 14%, \( P<0.001 \)) or treated with antihypertensive medications (38% versus 23% to 27%, \( P<0.001 \)), and specifically with ACE inhibitors (22% versus 16% to 18%, \( P=0.008 \)) and/or diuretics (19% versus 10% to 13%, \( P<0.001 \), without differences in \( \beta \)-blocker or calcium-channel blocker use. Prevalence of smoking and number of cigarettes smoked per day did not differ among groups; however, only 7.4% of participants smoked \( \geq 1 \) pack cigarettes/d. More participants in the first tertile (38%) were moderate alcohol consumers than in the second and third tertiles of fibrinogen (33% and 29%, \( P<0.01 \) for trend). Because of the important associations of fibrinogen with older age, female gender, hypertension, and diabetes, in turn important correlates of cardiovascular abnormalities, further analyses to assess differences in clinical, laboratory, and echocardiographic characteristics among tertiles of fibrinogen were adjusted for those potential confounders and for SHS center.

After adjustment for covariates, BMI was higher in the third than first tertile of fibrinogen (Table 2). Systolic BP and pulse pressure were similar among the 3 groups, whereas diastolic BP was slightly lower in the third tertile of fibrinogen; heart rate was highest in the third tertile of fibrinogen.

Total cholesterol did not differ among tertiles of fibrinogen, whereas HDL cholesterol was higher in the first tertile than second or third tertiles of fibrinogen (Table 2). Plasma creatinine and urinary albumin/creatinine increased from the lowest to the highest tertile of fibrinogen. On average, fibrinogen levels assessed during the first SHS examination (2.58±0.58 g/L, 2.97±0.62 g/L, and 3.43±0.79 g/L in the first, second, and third tertiles of the present study) closely paralleled those during the second SHS examination.

**LV Structure and Geometry**

Adjusting for covariates, LV mass/BSA, accounting for the impact of obesity, and LV mass/height\(^2\) were both highest as the result of higher values for septal and posterior wall thicknesses in the third tertile of fibrinogen (Table 3). LV internal diameter was slightly higher in the third tertile of fibrinogen than in the first, and relative wall thickness did not differ among tertiles of fibrinogen. To further account for additional covariates of LV mass, we developed a multiple linear regression analysis, which showed that LV mass increased with increasing fibrinogen values (\( \beta=0.06, P=0.01 \)) independent of age, gender, BMI, systolic BP, hypertension, diabetes, plasma creatinine, physical activity, degree of American Indian heritage, and indicator variables for SHS centers and for antihypertensive drug classes (eg, \( \beta \)-blockers, ACE inhibitors, diuretics, and calcium channel blockers) (multiple \( R=0.56 \)).

**LV Systolic Function, Hemodynamics, and Arterial Stiffness**

After adjustment for covariates, EF was slightly lower in the third than in the first tertile of fibrinogen, whereas cESS was higher in the third than in lower tertiles of fibrinogen (Table 3). MWS and stress-corrected MWS were both higher in the first than in higher tertiles of fibrinogen. Stroke volume did not differ among tertiles of fibrinogen, whereas cardiac index was higher and total peripheral resistance was lower in the third tertile of fibrinogen (Table 3). Total peripheral resistance was still lower in the third tertile of fibrinogen (\( P<0.01 \)) after further adjustment for BMI, in addition to other covariates.

In a multiple regression analysis, fibrinogen was related to stress-corrected MWS (\( \beta=-0.07, P<0.001 \)) independent of age, gender, body size, relative wall thickness, hypertension, antihypertensive drug classes, HDL and LDL cholesterol, diabetes, degree of American Indian heritage, and SHS centers (multiple \( R=0.52, P<0.001 \)). After further consideration of plasma creatinine, the relation of fibrinogen to stress-corrected MWS remained significant (\( \beta=-0.05, P=0.03 \), with a small increase in multiple \( R \) to 0.53, suggesting that fibrinogen level is associated, at least in part, with both pathophysiological processes of renal dysfunction and reduced myocardial contractility.

Pulse pressure/stoke index was higher in the third than in the first tertile of fibrinogen (Table 3). In a multiple regression analysis, fibrinogen was mildly but significantly related

### Table 2. Comparison of Clinical and Laboratory Data Among SHS Participants Stratified by Tertiles of Plasma Fibrinogen

<table>
<thead>
<tr>
<th>Variables</th>
<th>( \leq 3.24 ) g/L</th>
<th>3.24–3.83 g/L</th>
<th>&gt;3.83 g/L</th>
<th>Post Hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, kg/m(^2)</td>
<td>30.5±5.7</td>
<td>31.2±5.7</td>
<td>31.8±5.7</td>
<td>3&gt;1,2†</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>130±16</td>
<td>129±16</td>
<td>129±16</td>
<td>( P=NS )</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>75±10</td>
<td>75±10</td>
<td>74±10</td>
<td>3&lt;1,2*</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>54±14</td>
<td>54±14</td>
<td>55±14</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>66±11</td>
<td>68±10</td>
<td>70±10</td>
<td>3&gt;1,2†</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>4.91±1.03</td>
<td>4.92±1.03</td>
<td>4.92±1.04</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.11±0.33</td>
<td>1.06±0.34</td>
<td>1.06±0.33</td>
<td>1&gt;2,3†</td>
</tr>
<tr>
<td>Plasma creatinine, µmol/L</td>
<td>82.2±71.8</td>
<td>84.9±71.6</td>
<td>97.2±72.2</td>
<td>3&gt;1,2†</td>
</tr>
<tr>
<td>Loge Ur (ALB/CR), mg/g</td>
<td>2.93±1.69</td>
<td>3.03±1.68</td>
<td>3.87±1.68</td>
<td>3&gt;1,2†</td>
</tr>
</tbody>
</table>

Loge Ur (ALB/CR) indicates log of urinary albumin/creatinine ratio.
Mean±SD and \( P \) adjusted for age, gender, SHS center, hypertension, and diabetes; \( *P<0.05; †P<0.01. \)
to pulse pressure/stroke volume, independent of covariates including age, gender, BSA, heart rate, hypertension, antihypertensive drug classes, HDL and LDL cholesterol, diabetes, degree of American Indian heritage, and SHS centers ($\beta=0.05$, $P=0.013$; multiple $R=0.56$). In a subsequent model adjusting for plasma creatinine levels in addition to the set of covariates previously described, the relation between fibrinogen and pulse pressure/stroke volume became insignificant ($P=0.125$), without a substantial change in multiple $R (0.57)$.

### Cardiovascular Organ Target Damage and Fibrinogen

Of the study population, 24% had LV hypertrophy, 17% had elevated arterial stiffness, and 10% had low myocardial contractility. In a first set of logistic models, LV hypertrophy, low myocardial contractility, and elevated arterial stiffness were considered individually (Table 4). Adjusting for significant covariates (reported in detail for each model in Table 4 including plasma creatinine), LV hypertrophy ($P=0.0048$) and elevated arterial stiffness ($P=0.0058$) were significantly more prevalent in SHS participants in the third tertile of fibrinogen (odds ratios between 1.38 and 1.45), independent of major significant covariates. The relation of elevated fibrinogen to low myocardial contractility did not reach statistical significance after accounting for covariates including relative wall thickness and plasma creatinine. Overall, 40% of the selected SHS participants had at least 1 echocardiographic abnormality (28%, 39%, and 52% in the first, second, and third tertiles of fibrinogen, respectively, $P<0.001$). Fibrinogen $>3.83$ g/L was associated with 1.51-fold increased frequency of cardiovascular target organ abnormalities ($P<0.001$), independent of covariates. This result was confirmed after further exclusion of 25 SHS participants who died of malignancy during an observational period going from the date of echocardiogram (1993 to 1995) to December 1997 in a logistic model in which the log urinary albumin/creatinine ratio replaced plasma creatinine (adjusted odds ratio for association of fibrinogen to target organ damage, 1.36; $P<0.01$).

### Discussion

In a population sample of adults free of clinically overt cardiovascular disease, we found that elevated fibrinogen was

### TABLE 3. Comparison in LV Geometry, LV Systolic Function, and Hemodynamics Among SHS Participants Stratified on the Basis of Tertiles of Fibrinogen

<table>
<thead>
<tr>
<th>Variables</th>
<th>Fibrinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\leq$3.24 g/L</td>
</tr>
<tr>
<td>LV mass/BSA, g/m²</td>
<td>81±18</td>
</tr>
<tr>
<td>LV mass/height², g/m²²</td>
<td>40.2±9.9</td>
</tr>
<tr>
<td>Interventricular septum, cm</td>
<td>0.92±0.12</td>
</tr>
<tr>
<td>Posterior wall thickness, cm</td>
<td>0.86±0.09</td>
</tr>
<tr>
<td>LV diastolic diameter, cm</td>
<td>4.9±0.5</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.35±0.06</td>
</tr>
<tr>
<td>EF, %</td>
<td>64.2±8.2</td>
</tr>
<tr>
<td>MWS, %</td>
<td>17.8±2.3</td>
</tr>
<tr>
<td>cESS, kdyne/cm²</td>
<td>149±38</td>
</tr>
<tr>
<td>Stress-corrected MWS, %</td>
<td>106.1±12.1</td>
</tr>
<tr>
<td>PP/SVi, mm Hg/ml/m²</td>
<td>1.44±0.45</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>74±14</td>
</tr>
<tr>
<td>Cardiac index, L/min per m²</td>
<td>2.47±0.60</td>
</tr>
<tr>
<td>TPR, dyne · s⁻¹ · cm⁻⁵</td>
<td>1657±390</td>
</tr>
</tbody>
</table>

PP/SVi indicates pulse pressure/stroke index; TPR, total peripheral resistance. Mean, SD, and $P$ were adjusted for covariates.

Mean±SD and $P$ adjusted for age, gender, SHS center, hypertension, and diabetes; *$P<0.05$; †$P<0.01$.

### TABLE 4. Association of Elevated Plasma Levels of Fibrinogen With Echocardiographic Abnormalities

<table>
<thead>
<tr>
<th>Echocardiographic abnormality</th>
<th>Adjusted Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVH</td>
<td>1.38*</td>
<td>1.10–1.73</td>
</tr>
<tr>
<td>Elevated arterial stiffness</td>
<td>1.45†</td>
<td>1.11–1.88</td>
</tr>
<tr>
<td>Low myocardial contractility</td>
<td>1.05‡</td>
<td>0.70–1.57</td>
</tr>
<tr>
<td>At least 1 of the above abnormalities</td>
<td>1.51§</td>
<td>1.22–1.87</td>
</tr>
</tbody>
</table>

*Odds ratio adjusted for age, gender, systolic blood pressure, hypertension, diabetes, antihypertensive drug classes, plasma creatinine levels, SHS centers, physical activity, and degree of American Indian heritage.
†Odds ratio adjusted for age, gender, hypertension, diabetes, heart rate, LDL and HDL cholesterol, antihypertensive drug classes, plasma creatinine levels, SHS center, and degree of American Indian heritage.
‡Odds ratio adjusted for age, gender, hypertension, diabetes, relative wall thickness, LDL and HDL cholesterol, antihypertensive drug classes, plasma creatinine levels, SHS centers, and degree of American Indian heritage.
§Odds ratio adjusted for age, gender, diastolic blood pressure, hypertension, hypertension medications, diabetes, relative wall thickness, heart rate, LDL and HDL cholesterol, antihypertensive drug classes, plasma creatinine levels, physical activity, SHS center, and degree of American Indian heritage.
related to cardiovascular abnormalities such as LV hypertrophy, arterial stiffening, and LV systolic dysfunction, independent of a wide range of important confounding factors including hypertension, diabetes, SHS center, obesity, lipids, and renal dysfunction. Therefore, our study may contribute to better understanding of the relation between fibrinogen and cardiovascular events by showing that fibrinogen is strongly associated with preclinical echocardiographic target organ damage. In fact, echocardiographic abnormalities are often subclinical but well known to be associated with increased cardiovascular event rates. Moreover, the independent associations between fibrinogen and echocardiographic target organ damage may contribute to the increased cardiovascular event rates associated with higher fibrinogen levels.

Fibrinogen predicts mortality and morbidity independent of traditional cardiovascular risk factors in American Indians as well as in populations with different demographic, clinical, and genetic backgrounds. Therefore, our findings may be applicable to other populations. A longitudinal study will be needed to determine the distinct relations of fibrinogen and its interaction with cardiovascular target organ damage to morbidity and mortality.

**Fibrinogen, LV Mass, and Arterial Stiffness**

SHS participants with elevated fibrinogen (>3.83 g/L) had a 1.5-fold higher probability of showing LV hypertrophy or elevated arterial stiffness independent of important significant covariates such as hypertension, diabetes, body size, treatment, and renal dysfunction. Increased wall thickness is a pathophysiological adaptation of the LV to increased systolic stress through which increased arterial stiffness contributes. Of interest, the ratio pulse pressure/stroke index—an indirect index of arterial stiffness—increased with increasing fibrinogen, suggesting increased arterial stiffness, which leads to increased LV end-systolic stress through a mechanism that may involve pulse wave reflection in the arterial tree. Arterial structure and function are related to LV geometry and to asymptomatic atherosclerosis.

**Fibrinogen and LV Systolic Dysfunction**

In the present study, elevated fibrinogen was related to lower EF and stress-corrected MWS independent of LV geometry and overt coronary heart disease, which was excluded to minimize its confounding impact. More investigation is needed to clarify the association of fibrinogen, as a marker of inflammation, with impaired myocardial function. Interestingly, although multiple regression analysis showed a significant relation between fibrinogen and stress-corrected MWS independent of plasma creatinine, in a logistic model the relation of fibrinogen to low myocardial contractility (defined as stress-corrected MWS <89.2%) became insignificant after adjustment for renal function, which was in turn related to fibrinogen. These results suggest interrelation among microvascular disease (renal and myocardial), myocardial systolic dysfunction, and fibrinogen levels. Although adjustment for plasma creatinine rendered insignificant the relation of fibrinogen to myocardial dysfunction, our analysis cannot clarify whether renal dysfunction is the explanatory factor of the relation between fibrinogen and myocardial dysfunction. Of note, relation of fibrinogen to echocardiographic abnormalities considered as pooled together was independent of plasma creatinine levels or urinary albumin/creatinine in alternative models, suggesting that renal dysfunction may only in part account for the relation between elevated fibrinogen and echocardiographic abnormalities. Moreover, we should emphasize that in our study population, the prevalence of low myocardial function was 10%, lower than the prevalence of LV hypertrophy or elevated arterial stiffness. Consequently, the analysis on low myocardial contractility had lower statistical power than those performed to assess associations between fibrinogen and LV hypertrophy or elevated arterial stiffness.

**Fibrinogen and Renal Dysfunction**

Our study showed a pathophysiologically relevant association between fibrinogen and renal dysfunction independent of important covariates including BP, age, SHS center, and diabetes. It is noteworthy that elevated fibrinogen was associated with higher urinary albumin/creatinine levels, a marker of microvascular disease. Relation of inflammation with microvascular disease has been reported, and a relation of fibrinogen to endothelial dysfunction has also been described. Therefore, elevated fibrinogen may be a marker of subclinical atherosclerosis, endothelial dysfunction, and microvascular disease with involvement of the renal and cardiac activation of the renin-angiotensin system, in turn strongly related to LV and vascular hypertrophy and fibrosis. However, although renal dysfunction appeared to contribute to the association between fibrinogen and echocardiographic abnormalities, in our subanalyses it did not completely explain the relation of fibrinogen to LV hypertrophy. Finally, because the SHS population was not systematically examined for connective tissue diseases or malignancy, possible contributions of such conditions to high fibrinogen levels cannot be assessed. However, association of elevated fibrinogen to echocardiographic preclinical abnormalities was unaffected by exclusion of 25 SHS participants who died of malignancy during a mean 3-year follow-up after the echocardiogram.

**Fibrinogen and Obesity**

BMI, a strong correlate of LV mass, increased with increasing fibrinogen levels, confirming a positive relation between overweight and fibrinogen. Fibrinogen is a determinant of whole blood viscosity, which is in turn related to obesity and increased LV mass. However, fibrinogen was associated with LV hypertrophy independent of obesity, hypertension, and diabetes.

**Conclusion**

In a population-based sample, elevated fibrinogen is associated with a high prevalence of prognostically relevant preclinical echocardiographic target organ damage independent of clinically overt cardiovascular disease and traditional cardiovascular risk factors including hypertension, diabetes, obesity, lipids, and renal function. The relations of fibrinogen to cardiovascular target organ damage may contribute to the negative prognostic impact of elevated fibrinogen levels.
Acknowledgments
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