Relation of Left Ventricular Midwall Function to Cardiovascular Risk Factors and Arterial Structure and Function

Richard B. Devereux, Giovanni de Simone, Thomas G. Pickering, Joseph E. Schwartz, Mary J. Roman

Abstract—Left ventricular (LV) midwall shortening (MWS) is subnormal in relation to LV circumferential end-systolic stress (ESS) (ESS-corrected MWS) in many hypertensive patients with normal LV chamber function and predicts subsequent morbidity and mortality. However, little is known of the relations of LV midwall function to demographic and metabolic variables or to arterial geometry. Asymptomatic, unmedicated normotensive (n=366) or hypertensive (n=282) adults were assessed with echocardiography and carotid ultrasound. In normal adults, lower LV MWS and ESS-corrected MWS, an index of LV contractility, were related independently to high total peripheral resistance, high heart rate, and male gender (all \( P<.00001 \)), lower serum HDL cholesterol (\( P=.001 \)) and diastolic pressure (\( P=.003 \)), and for ESS-corrected MWS only, arterial relative wall thickness (RWT, \( P=.03 \)). Among hypertensive patients, lower values for both midwall function indices were associated independently with higher peripheral resistance (\( P<.00001 \)), heart rate (\( P<.00005 \)), body mass index (\( P<.01 \)), and arterial RWT (\( P=.04 \)), as well as male gender (\( P<.0002 \)). In the entire population, lower LV MWS was independently related to higher peripheral resistance, heart rate (both \( P<.00001 \)), body mass index (\( P=.0006 \)) and arterial RWT (\( P=.009 \)); male gender (\( P<.00001 \)); and lower age (\( P=.004 \)), diastolic pressure (\( P=.042 \)), and systolic carotid artery expansion (\( P=.032 \)). Lower ESS-corrected MWS in the entire population was independently associated with higher peripheral resistance and heart rate (both \( P<.00001 \)), body mass index (\( P=.0006 \)), arterial RWT (\( P=.004 \)); male gender; and lower diastolic pressure (both \( P<.00001 \)), age (\( P<.00005 \)), arterial expansion in systole (\( P=.006 \)), and serum HDL cholesterol levels (\( P=.04 \)). Among a subset (n=60), ESS-corrected MWS was positively related to apolipoprotein A1 (\( P=.004 \)) and negatively to hemoglobin A1c (\( P<.01 \)). Thus, higher LV midwall function is associated with female gender and more favorable profiles of hemodynamics, metabolic pattern, and arterial structure and function. (Hypertension. 1998;31:929-936.)

Key Words: ultrasonography ■ cholesterol ■ contractility ■ echocardiography ■ gender ■ vascular resistance

Left ventricular systolic chamber function plays a central role in determining the prognosis of patients with known coronary artery obstruction and other forms of symptomatic heart disease. However, despite the role of hypertension as a major cardiovascular risk factor, LV systolic chamber function in asymptomatic hypertensive patients is almost always normal or even supranormal and has not been found to predict prognosis.

In parallel with these clinical observations, a separate line of investigation has suggested that in patients with abnormal LV geometry, as commonly occurs in hypertensive patients, assessment of LV ejection fraction or fractional shortening at the endocardial surface may not accurately reflect the contractile behavior of myocardial fibers across the LV wall. Shifting to assessment of LV midwall fiber shortening in relation to midwall ESS as a measure of myocardial afterload has identified low midwall LV performance in about one sixth of hypertensive adults in a population-based study.

Low LV MWS in asymptomatic hypertensive patients has been shown to predict subsequent morbidity and mortality—largely due to coronary and cerebral arterial disease—indipendently of age, arterial pressure, or LV mass. Therefore, while LV chamber function provides prognostic information in patients with symptomatic coronary heart disease, reduced LV MWS may be both detectable at an early stage of disease evolution in asymptomatic individuals and able to characterize the severity of contractile abnormalities. For this reason, it is important to understand the relation of LV midwall mechanics to established risk factors and to arterial abnormalities in relatively unselected normotensive and hypertensive adults.

Accordingly, the present study was undertaken to examine the relation of LV midwall function to age, gender, body habitus, and other demographic variables; to determine whether LV midwall function is related to levels of lipids and glucose and other measures of metabolism; and to assess the
Selected Abbreviations and Acronyms
BP = blood pressure
ESS = end-systolic stress
LV = left ventricular
MWS = midwall shortening
RWT = relative wall thickness

Relation of LV midwall function to arterial geometry, function, and evidence of atherosclerosis.

Methods

Study Population
Unmedicated normotensive and hypertensive adults were recruited through worksite-based screening of employed adults (n=360) and through evaluation of patients (n=188) and clinically normal volunteers (n=100) undergoing diagnostic assessment at The New York Hospital–Cornell Medical Center, as previously described.12–14 Subjects were excluded if clinical evaluation or echocardiography revealed evidence of coronary, valvular, or primary myocardial heart disease.

BP was determined by arm cuff and mercury manometer before and at the time of echocardiography using the first and fifth phases of the Korotkoff sounds. Echocardiographic pressures were measured by a skilled research technician with the patient semirecumbent at the end of echocardiography, after approximately 30 minutes of rest in a dimly lit room. Height and weight were measured and used to calculate body surface area (square meters) and body mass index (kilogram/meter²) by standard formulas.

Fasting blood specimens were obtained in all subjects to determine levels of plasma glucose and serum total and HDL cholesterol, triglyceride, and creatinine. In a subset of subjects, specimens were obtained to determine levels of apolipoproteins A1 and B, hemoglobin A1c, and insulin.

Echocardiographic Methods
Two-dimensionally targeted M-mode echocardiograms were recorded on strip chart paper with the subject in a partial left decubitus position. M-mode recordings were performed with the ultrasound beam at or just below the tips of mitral valve leaflets. Strip chart tracings were consecutively coded and interpreted in a blinded manner. Septal and posterior wall thickness and LV chamber dimensions were measured according to the American Society of Echocardiography and Penn conventions.15,16 If the M-mode cursor could not be properly aligned along the LV minor axis, as was the case in approximately 7% of subjects, linear measurements of LV wall thicknesses and internal dimension were made from two-dimensional long-axis recordings according to the recommendations of the American Society of Echocardiography (ASE).17 Standard methods were used to calculate LV mass by Penn or if necessary ASE two-dimensional methods (in 91% and 9% of subjects, respectively), RWT, and endocardial fractional shortening.18,19,20 A close correlation (r=.967, mean difference=0.4 g, SD=10.2 g) between LV mass measurements by the two methods was observed in 196 subjects studied in our laboratory. End-diastolic and end-systolic LV volumes, as well as stroke volume, were estimated using the Teichholz correction of the cube formula,20 which has been shown to be accurate in patients with symmetrically contracting ventricles.21–23 These measurements were used to calculate cardiac output and peripheral resistance. Subjects were considered to have normal LV geometry if RWT was <0.42 and LV mass/body surface area was <118 g/m² in men and <108 g/m² in women;24 for this study, individuals with concentric or eccentric LV hypertrophy or concentric LV remodeling were categorized as having abnormal LV geometry.

LV fractional MWS was calculated taking into account the epicardial migration of the midwall during systole, using a model similar to that commonly used to calculate LV mass. Similar to the ellipsoidal model used by Shimizu et al10 to determine the physiological position of the midwall fibers during systole independent of the thickening of internal longitudinal fibers, a constant ratio of the volume of its inner and outer halves during the cardiac cycle was assumed. Thus,

\[
(1) \quad \text{MWS} = \frac{(\text{LVIDd} - \text{LVIDs})^3 - \text{LVIDn}^3}{\text{SBP} \cdot \text{PIWTd}^2}\]

where LVID is ventricular internal dimension, d is end-diastole, H is combined septal and posterior wall thickness, and n is any moment during the cardiac cycle. Analogously, the inner LV wall shell volume at end-systole can be calculated as follows:

\[
(2) \quad \text{MWS} = \frac{(\text{LVIDd} - \text{LVIDs})^3 - \text{LVIDn}^3}{\text{SBP} \cdot \text{PIWTd}^2}\]

where s is systole. From Equation 2, the systolic thickness of the inner shell can be calculated, allowing computation of MWS as follows:

\[
(3) \quad \text{MWS} = \frac{(\text{LVIDd} - \text{LVIDs})^3 - \text{LVIDn}^3}{\text{SBP} \cdot \text{PIWTd}^2}\]

Computation of LV mass and MWS allowed the calculation of end-systolic stress (ESS) and the assessment of LV geometry if RWT was

\[
\text{ESS} = \frac{\text{MWS} \cdot \text{SBP}}{\text{PIWTd}^2}
\]

where ESS is expressed as a percentage of LV systolic thickness, and MWS is expressed as a percentage of LV mass.

Arterial Evaluation
As previously reported,14,27 imaging of both carotid arteries was performed in all subjects using commercially available ultrasonographs equipped with 7.5-MHz imaging transducers. The carotid bulb and proximal external and internal carotid arteries were imaged in multiple projections to maximize detection of irregularities in vessel walls. Carotid atherosclerosis was defined as the presence of a discrete plaque at least 50% thicker than the surrounding wall in any carotid segment28; diffuse carotid wall thickening was recognized when wall thickness exceeded 1.0 mm.29

Two-dimensionally guided M-mode tracings of the distal common carotid artery were recorded on 0.5-in videotape, as previously described.14,27 The videotape was subsequently reviewed, and suitable frames for measurement of M-mode images were obtained in real time using a frame grabber (Imaging Technology, Inc) interfaced with a high-resolution (640×480 pixel) video monitor and stored on diskettes. The axial resolution of the M-mode system is 0.2 mm.

Carotid measurements, performed on stored images using a mouse-driven computer program after calibration for depth, included end-diastolic (minimal diameter) wall thickness, defined as the combined thickness of the apparent intimal-medial layers of the far
The ultrasound measurement of carotid wall thickness has been validated using gross and histopathologic reference standards. In our laboratory, reproducibility of carotid wall thickness measurements is high for both intraobserver (r = .98; SEE, 0.04 mm) and interobserver (r = .97; SEE, 0.05 mm) variabilities. Carotid dimensions were used to calculate diastolic RWT, cross-sectional area, and arterial strain calculated as the percentage of systolic increase in the carotid lumen diameter.

Statistical Analysis

Data are expressed as mean±SD. Differences between two groups were tested by unpaired Student or Welch’s approximate t tests for continuous variables and χ² statistics or Fisher’s exact tests for proportions. The relationships of MWS and stress-corrected MWS to continuous variables were assessed by least-squares linear regression analyses (with forced entry). Variables that were significantly related to these dependent variables in univariate analyses and did not exhibit excessive multicollinearity with each other were considered as potential independent variables in multiple linear regression analyses (with forced entry). To ensure that observed associations were not artifacts of the known confounding variables in Table 3 plus smoking history, lower LV MWS was associated with older age, cigarette smoking, and arterial hypertension or concentric remodeling, but these findings were not associated with age >50 years, former or current smoking, or the presence of discrete atherosclerotic plaques or diffuse carotid wall thickening. Ventricular RWT was higher in men than in women but differed from MWS in being statistically associated with older age, cigarette smoking, and arterial plaque. Relations between continuous variables and LV midwall function are shown in Table 2. MWS and stress-corrected MWS both had negative relations to total peripheral resistance, diastolic BP, heart rate, and arterial RWT and positive relations to the percent systolic carotid artery expansion. Among metabolic parameters, only HDL level was significantly related to both measures of LV midwall function. LV RWT was positively related to most measures of hemodynamic load and metabolic abnormality and was negatively related to percent systolic expansion of the carotid artery.

Results

Subject Characteristics

A total of 366 normotensive adults (mean±SD age, 47±12 years) with no evidence of cardiovascular disease met inclusion criteria; 71% were white, 18% were African-American or Afro-Caribbean, 6% were Hispanic, 3% Asian, and 1% American Indian; 39% were women; and 44% were former or current smokers. The 282 unmedicated (never treated or off treatment for 3 weeks to 6 years) hypertensive adults with no clinical evidence of cardiovascular disease had a mean age of 55±12 years (P<.001 versus normotensive subjects). Sixty-six percent of patients were white, 28% were black, 4% were Hispanic, and 1% each were Asian and American Indian; 37% were women; and 47% were former or present smokers.

Compared with normotensive subjects, the hypertensive patients exhibited higher LV mass (175±47 versus 146±38 g, P<.00001), RWT (0.37±0.06 versus 0.34±0.05, P<.001), meridional ESS (73±21 versus 61±14 kdyne/cm², P<.0001), and midwall circumferential ESS (149±37 versus 124±24 kdyne/cm², P<.0001). A weak trend toward higher endocardial shortening in hypertensive patients (0.38±0.06 versus 0.37±0.05) did not attain statistical significance, whereas the hypertensive patients had significantly lower LV MWS (17.8±2.3% versus 18.5±2.1%, P<.005); stress-corrected LV MWS was virtually identical in the two groups (107±12% versus 105±13%). Hypertensive patients also had higher levels than normotensive subjects of carotid wall thickness (0.83±0.20 versus 0.72±0.17 mm, P<.00001), lumen diameter (5.8±0.8 versus 5.4±0.6 mm, P<.00001), cross-sectional area (17.3±5.6 versus 13.4±4.5 mm², P<.00001), and RWT (0.29±0.07 versus 0.27±0.06, P=.001).

Correlates of LV Midwall Function in Normotensive Adults

As seen in Table 1, LV MWS and stress-corrected MWS were statistically lower in men than women and, most notably, in the subset of subjects who had either LV hypertrophy or concentric remodeling, but these findings were not associated with age >50 years, former or current smoking, or the presence of discrete atherosclerotic plaques or diffuse carotid wall thickening. Ventricular RWT was higher in men than in women but differed from MWS in being statistically associated with older age, cigarette smoking, and arterial plaque.

Multivariate Analyses

For normotensive subjects, in analyses that considered the variables in Table 3 plus smoking history, lower LV MWS was independently associated with higher total peripheral...
resistance, heart rate, and body mass index; older age; male gender; and lower diastolic BP and HDL levels. Smoking history approached but did not attain statistical significance. In a supplemental analysis, LV RWT added significantly ($P<.0001$) to a model with a higher multiple $R (0.73)$ that retained all of the same variables except for body mass index ($P<.065$). Stress-corrected MWS was independently related to most of the same variables, with the addition of arterial RWT. Age, cigarette smoking, and carotid artery expansion in systole all just failed to enter the model ($P=.06$ to .07). In a supplemental analysis, LV RWT entered significantly ($P<.0001$) as did age ($P<.0001$), resulting in a higher multiple $R (0.79)$, while body mass index ($P=.072$) and arterial RWT ($P=.205$) became insignificant. The $R^2$ values from these analyses suggest that somewhat less than half of the variability of LV midwall function in healthy normotensive adults is associated with noncardiac variables and that additional consideration of LV RWT adds about 10% to this proportion.

### Correlates of LV Midwall Function in Hypertensive Patients

As seen in Table 4, similar to findings in normotensive subjects, LV MWS, either in absolute terms or as a percentage of predicted, was statistically lower in men than women and in the subgroup with abnormal LV geometry. Neither age $>50$ years, smoking status, nor presence of arterial hypertrophy or of atherosclerotic plaques was related to LV MWS. Ventricular RWT showed a different pattern of associations, with no difference between women and men but significant positive associations with older age ($P=.003$), arterial hypertrophy ($P=.008$), and atherosclerotic plaque ($P=.007$). Relations between continuous variables and LV midwall function are shown in Table 5. Negative relations were seen between both measures of LV midwall function and peripheral resistance, body mass index, diastolic (but not systolic) BP, and plasma glucose level, with inconsistent findings concerning heart rate and carotid artery systolic expansion. LV RWT had weak positive relations to systolic BP, peripheral resistance, heart rate, and arterial RWT.

### Multivariate Analyses

In analyses that considered the same independent variables as for normotensive subjects plus plasma glucose level, lower
LV MWS was independently associated with male gender and higher total peripheral resistance, heart rate, body mass index, and arterial RWT, with a trend toward higher diastolic BP (Table 6). Inclusion of LV RWT added it (P < .0001) and age (P < .0001) and eliminated arterial RWT, while raising the R value slightly (to 0.68). Lower stress-corrected MWS was independently related to male gender and higher peripheral resistance, heart rate, body mass index, and arterial RWT and, weakly, to younger age. Inclusion of LV RWT added it and strengthened the effect of age (both P < .0001) but eliminated arterial RWT as a significant predictor of stress-corrected MWS, raising R to 0.75.

**Correlates of LV Midwall Function in the Entire Population**

In the entire population of normotensive and hypertensive adults, women had higher values than men for both MWS and stress-corrected MWS (18.8 ± 2.2% versus 17.9 ± 2.2% and 109 ± 12% versus 105 ± 12%, both P < .001), as did individuals with normal as opposed to abnormal LV geometry (18.7 ± 2.0% versus 16.4 ± 2.0% and 109 ± 11% versus 96 ± 11%, respectively; both P < .0005). Examination of linear relations confirmed strong inverse relations of both midwall LV function measures to total peripheral resistance; weaker ones with arterial RWT, heart rate, and glucose level; and positive relations between LV midwall function measures and systolic carotid artery expansion and HDL level.

**Multivariate Analyses**

In the entire population, lower MWS was independently predicted by male gender; higher peripheral resistance, heart rate, and body mass index; younger age; and weakly by lower diastolic BP and carotid artery systolic expansion (Table 7, upper panel). Inclusion of LV RWT caused it to enter the model (P < .00005) and retained the previous variables, raising the multiple R to 0.69. Lower stress-corrected MWS was independently associated with male gender; higher peripheral resistance, heart rate, body mass index, and arterial RWT; lower diastolic BP; younger age; lower arterial expansion; and lower HDL levels (Table 7, lower panel). Inclusion of LV

**TABLE 4. LV Midwall Function in Hypertensive Adults in Relation to Demographic and Cardiovascular Attributes**

<table>
<thead>
<tr>
<th>Variable</th>
<th>MWS, %</th>
<th>Stress-Corrected MWS, % Predicted</th>
<th>RWT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women/men</td>
<td>18.4 ± 2.2/17.5 ± 2.3 (&lt;.001)</td>
<td>109 ± 13/106 ± 13 (&lt;.001)</td>
<td>.37 ± .06/.37 ± .05 (NS)</td>
</tr>
<tr>
<td>Age &lt;50/≥50 y</td>
<td>17.5 ± 2.3/18.0 ± 2.3 (NS)</td>
<td>103 ± 13/106 ± 13 (NS)</td>
<td>.36 ± .05/.38 ± .06 (.003)</td>
</tr>
<tr>
<td>Never/former or current smoker</td>
<td>17.8 ± 2.5/17.8 ± 2.1 (NS)</td>
<td>106 ± 12/105 ± 14 (NS)</td>
<td>.37 ± .05/.37 ± .05 (NS)</td>
</tr>
<tr>
<td>Plaque/no plaque</td>
<td>17.5 ± 2.4/17.9 ± 2.3 (NS)</td>
<td>104 ± 14/106 ± 13 (NS)</td>
<td>.39 ± .06/.37 ± .05 (.007)</td>
</tr>
<tr>
<td>Arterial hypertrophy/no hypertrophy</td>
<td>17.5 ± 2.2/17.9 ± 2.3 (NS)</td>
<td>104 ± 13/106 ± 13 (NS)</td>
<td>.40 ± .06/.37 ± .05 (.008)</td>
</tr>
<tr>
<td>Normal/abnormal LV geometry</td>
<td>18.6 ± 2.1/16.3 ± 2.0 (&lt;.00005)</td>
<td>110 ± 11/96 ± 12 (&lt;.00005)</td>
<td></td>
</tr>
</tbody>
</table>

Probability values are shown in parentheses.

**TABLE 5. Correlates of LV Midwall Function in Hypertensive Adults**

<table>
<thead>
<tr>
<th>Variable</th>
<th>MWS, %</th>
<th>Stress-Corrected MWS, % Predicted</th>
<th>RWT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic BP</td>
<td>−0.26 (&lt;.0001)</td>
<td>−0.17 (.004)</td>
<td>(NS)</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>(NS)</td>
<td>(NS)</td>
<td>0.16 (.006)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>−0.20 (.001)</td>
<td>−0.21 (&lt;.001)</td>
<td>(NS)</td>
</tr>
<tr>
<td>Heart rate</td>
<td>(NS)</td>
<td>−0.15 (.03)</td>
<td>0.12 (.04)</td>
</tr>
<tr>
<td>Carotid diameter</td>
<td>(NS)</td>
<td>(NS)</td>
<td>(NS)</td>
</tr>
<tr>
<td>Arterial RWT</td>
<td>(NS)</td>
<td>(NS)</td>
<td>0.16 (.009)</td>
</tr>
<tr>
<td>Carotid systolic expansion</td>
<td>0.13 (.03)</td>
<td>(NS)</td>
<td>(NS)</td>
</tr>
<tr>
<td>Peripheral resistance</td>
<td>−0.30 (&lt;.00005)</td>
<td>−0.28 (.0003)</td>
<td>0.28 (&lt;.001)</td>
</tr>
<tr>
<td>Glucose</td>
<td>−0.13 (.05)</td>
<td>−0.14 (.03)</td>
<td>(NS)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>(NS)</td>
<td>(NS)</td>
<td>(NS)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>(NS)</td>
<td>(NS)</td>
<td>(NS)</td>
</tr>
<tr>
<td>HDL</td>
<td>(NS)</td>
<td>(NS)</td>
<td>(NS)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>(NS)</td>
<td>(NS)</td>
<td>(NS)</td>
</tr>
</tbody>
</table>

Probability values are shown in parentheses.
RWT added it to the model (P<.0005), while eliminating arterial RWT (P=.066) and HDL cholesterol (P=.106), and raised the multiple R to 0.75. The multiple R values derived from these analyses suggest that about 40% of the observed variability of LV MWS is predicted by noncardiac variables, with an additional 10% to 15% of its variability associated with LV RWT.

### Apolipoproteins, Glucose Metabolism, and LV Midwall Function

Determinations of serum apolipoproteins A1 and B, of glycosylated hemoglobin, and of plasma insulin levels were performed in 60 subjects. This subset was similar in age (58±15 years) and arterial pressure (150±11/88±10mm Hg) to the entire population but was more likely to be female (56%). In these subjects, apolipoprotein A1 levels were positively related to LV MWS (r=.33, P=.009) and stress-corrected MWS (r=.39, P=.003), whereas no relation existed with apolipoprotein B levels. Inverse relations of LV MWS and stress-corrected MWS existed with hemoglobin A1c (r=-.32 and -.27, both P<.01) but not plasma insulin levels.

### Discussion

This study provides evidence that a number of established cardiovascular risk factors and markers of target organ damage are associated, in a cross-sectional survey of asymptomatic normotensive or hypertensive adults, with lower performance of LV midwall fibers, whereas protective factors such as female gender and higher HDL cholesterol levels are positively associated with LV midwall function.

### Relation of Myocardial Function to Hemodynamic Parameters

The strong inverse relation between total peripheral resistance and LV midwall function is in apparent contrast with the lack of relationship noted in previous studies between peripheral resistance and endocardial measures of LV ejection-phase performance.31 In part this may be explained by the fact that high peripheral resistance is associated with concentric LV remodeling or hypertrophy,32 geometric adaptations that preserve endocardial shortening despite decreases in MWS.40,31 A previous analysis of hypertensive patients subgrouped by LV geometric pattern revealed that LV MWS was lowest in the groups with the highest peripheral resistances,10 compatible with our present results in a separate population. However, the present study goes beyond previous reports by demonstrating that the negative associations of MWS and stress-corrected MWS with peripheral resistance are statistically independent of the geometric factor of LV RWT.

The strong relationship seen between higher heart rate and lower LV midwall function that was evident after control for potential confounders in multivariate analyses (Tables 3, 6, and 7) has not been previously recognized. However, some precedent for this result is provided by the known ability of tachycardia to produce depressed LV function, the association between heart rate slowing by β-adrenoreceptor blockade and improvement of LV function in some therapeutic trials, and the association of higher heart rate with adverse outcomes in patients with coronary artery disease. Conversely,
abbreviation of diastole at higher heart rates may reduce LV filling and the preload placed on LV midwall fibers, contributing to the association between smaller LV end-diastolic dimension and lower MWS that we observed in a previous experimental study. However, invasive studies with simultaneous LV dimension and end-diastolic pressure measurement will be needed to determine the impact of end-diastolic wall stress, a direct measure of LV preload, on MWS.

In univariate analyses, diastolic BP was inversely related to LV midwall function (Tables 2 and 5); after control for other variables in multivariate analyses, diastolic BP was positively related to LV MWS in normotensive subjects and in the entire (predominately normotensive) population but was negatively related to it among hypertensive patients. Whether this reflects a beneficial effect of higher diastolic BP in the upper part of the normal range, but not at hypertensive levels, on myocardial perfusion and consequently on myocardial function can only be resolved by an invasive study, such as that in which Polese et al documented impaired myocardial flow autoregulation in hypertensive patients with LV hypertrophy.

Impact of Gender and Body Build

In all of our analyses, female gender was associated with higher MWS and stress-corrected MWS. A gender difference in LV chamber function has been previously reported in clinical and epidemiological studies and has also been observed in conditions of altered LV load at rest. In the present study, higher LV chamber function in women parallels similarly higher stress-corrected MWS. Because LV chamber size is smaller in women than in men and a significant difference in LV end-diastolic pressure is unlikely in this setting, the difference between women and men in LV midwall function that we observed is unlikely to be due to a gender difference in preload. Therefore, the gender difference in LV ejection-phase performance may be related to increased resting inotropic state in women. Of note, the gender difference in resting LV function disappears during exercise, in both apparently normal and diseased subjects, suggesting that women may use part of their maximal contractile reserve at rest. In univariate analyses, body mass index had weak or insignificant relations to LV midwall function, similar to findings in a previous study of normotensive and hypertensive adults. However, in multivariate analyses that controlled for other confounders, independent negative relations were observed between body mass index and both measures of LV midwall function. Although this association has not been previously reported, it is not surprising in view of the known relationship between obesity and an adverse cardiovascular prognosis.

Intersection of Cardiac and Arterial Structure and Function

The present study provides the first evidence that myocardial contractile function is related to the structure and function of the capacitance arteries. In univariate analyses in our normotensive subjects and our entire population, LV MWS and stress-corrected MWS were inversely related to carotid RWT and positively related to the percentage of systolic expansion of the carotid artery; among hypertensive patients, carotid artery systolic expansion was positively related to LV MWS but not stress-corrected LV MWS. In multivariate analyses in the entire population, positive relations of carotid artery systolic expansion and negative ones of arterial RWT with both LV MWS and stress-corrected LV MWS were observed independently of all confounding variables that were considered in the present study (Table 7). Supplemental multivariate analyses that also considered LV RWT raised the multiple R values by as much as 0.10 with little effect on the predictive power of most variables but eliminated independent associations of arterial RWT with LV midwall function.

Clinical Implications

Findings in the present study indicate that lower values of prognostically validated measures of LV MWS are associated with higher peripheral resistance, heart rate, and arterial wall thickness; male gender; and lower systolic arterial expansion and lower levels of HDL cholesterol. In a subset of the subjects, higher levels of apolipoproteins A1 and lower levels of hemoglobin A1c were also associated with better LV contraction, independent of arterial wall thickness or plaques. Although cross-sectional analyses cannot identify causality, the better LV contraction that we find to be associated with a more favorable metabolic profile may reflect direct myocardial benefits of its well-known cardioprotective effects. Taken together with previous studies in which subnormal LV midwall function was shown to be common and to predict an adverse prognosis in asymptomatic hypertensive patients, the present data suggest that an adverse cardiovascular risk profile is associated with subtle decreases in LV contractile efficiency in the early phases of cardiovascular disease in asymptomatic adults that are not revealed by conventional measures of LV cavity function. However, it remains for future studies to determine whether such small differences in MWS as those observed between women and men are associated with significant differences in clinical outcome.

Acknowledgments

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