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Geometric Changes Allow Normal Ejection Fraction Despite Depressed Myocardial Shortening in Hypertensive Left Ventricular Hypertrophy

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Objectives. **This study of hypertensive left ventricular hypertrophy 1) assessed myocardial shortening in both the circumferential and long-axis planes, and 2) investigated the relation between geometry and systolic function.**

Background. **In hypertensive left ventricular hypertrophy, whole-heart studies have suggested normal systolic function on the basis of ejection fraction–systolic stress relations. By contrast, isolated muscle data show that contractility is depressed. It occurred to us that this discrepancy could be related to geometric factors (relative wall thickness).**

Methods. **We studied 43 patients with hypertensive left ventricular hypertrophy and normal ejection fraction (mean ± SD 69 ± 13%) and 50 clinically normal subjects. By echocardiography, percent myocardial shortening was measured in two orthogonal planes; circumferential shortening was measured at the endocardium and at the midwall, and long-axis shortening was derived from mitral annular motion (apical four-chamber view). Circumferential shortening was related to end-systolic circumferential stress and long-axis shortening to meridional stress.**

Results. **Endocardial circumferential shortening was higher than normal (42 ± 10% vs. 37 ± 5%, $p < 0.01$) and midwall circumferential shortening lower than normal in the left ventricular hypertrophy group (18 ± 3% vs. 21 ± 3%, $p < 0.01$). Differences between endocardial and midwall circumferential shortening are directly related to differences in relative wall thickness. Long-axis shortening was also depressed in the left ventricular hypertrophy group (18 ± 6% in the left ventricular hypertrophy group, 21 ± 5% in control subjects, $p < 0.05$). Midwall circumferential shortening and end-systolic circumferential stress relations in the normal group showed the expected inverse relation; those for ~33% of the left ventricular hypertrophy group were >2 SD of normal relations, indicating depressed myocardial function. There was no significant relation between long-axis shortening and meridional stress, indicating that factors other than afterload influence shortening in this plane.**

Conclusions. **High relative wall thickness allows preserved ejection fraction and normal circumferential shortening at the endocardium despite depressed myocardial shortening in two orthogonal planes.**

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It has been a matter of some controversy whether the myocardium preserves normal systolic function in pressure overload hypertrophy. Such controversy results in part from the fact that most whole-heart studies incorporate endocardial measurements (e.g., ejection fraction) that reflect left ventricular chamber function (1–10), whereas most experimental studies utilize myocardial or myofibril function (11–13). Because left ventricular chamber function depends in part on left ventricular geometry, it occurred to us that a concentric geometry (with high relative wall thickness) might contribute to a normal ejection fraction despite some depression of myocardial shortening at the midwall (14,15). If this were the case, the whole-heart studies would be consonant with experimental studies. We therefore studied myocardial shortening and stress–shortening relations in hypertensive patients with a normal ejection fraction and normal circumferential shortening at the endocardium. Endocardial shortening variables were used as indexes of left ventricular chamber function, and midwall circumferential stress–shortening relations were used to assess myocardial function. In addition, shortening in the long-axis plane was measured and related to meridional stress. Thus, stress–shortening relations in two orthogonal planes were used to test the hypothesis that myocardial shortening is depressed in patients with hypertensive left ventricular hypertrophy and a normal ejection fraction.

Methods

Study patients. The study included 43 patients (mean [±SD] age 58 ± 17 years, range 19 to 84) undergoing echocardiography at the University of Massachusetts Medical Center from December 1, 1991, to December 31, 1993, who

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were found to have evidence of concentric left ventricular hypertrophy (16,17). No patient had clinical evidence of ischemic heart disease, significant valvular regurgitation or left ventricular outflow tract obstruction. All patients fulfilled Framingham criteria for left ventricular hypertrophy; these criteria were left ventricular mass index ≥131 g/m^2 in men and ≥100 g/m^2 in women (18). Fifty subjects (mean age 42 ± 16, range 18 to 74) who underwent echocardiography within the same time period and whose studies were interpreted as normal served as control subjects.

Echocardiographic measurements. M-mode, two-dimensional and Doppler echocardiography were performed by experienced ultrasonographers using commercially available equipment (Hewlett-Packard series 77020a). Two-dimensionally guided M-mode recordings were obtained from the parasternal window, and strip chart recordings were made at 50-mm/s paper speed. Septal and posterior wall thicknesses were measured at end-diastole; left ventricular minor axis dimensions were measured at end-diastole ($LVID_d$) and end-systole ($LVID_s$). Measurements were made in triplicate by a single investigator (K.H.S.) according to American Society of Echocardiography standards (19). Left ventricular ejection fraction was calculated by the method of Teichholz et al. (20). Left ventricular mass was calculated from M-mode measurements using the formula of Troy et al. (21), as modified by Devereux et al. (22); mass was indexed to body surface area. Diastolic relative wall thickness was calculated as 2 $Th_p/LVID_d$ (23), where Th_p = end-diastolic posterior wall thickness.

Calculations. Circumferential shortening at the endocardium was calculated as $100 \times (LVID_d - LVID_s/LVID_d)$. Midwall fractional shortening was calculated using a two-shell cylindrical model, the details of which have been described previously (24,25). This method is a refinement of the conventional midwall method and provides data that reflect shortening of a theoretic circumferential midwall fiber or ring of myocardium. It assumes a constant left ventricular mass throughout the cardiac cycle and does not require the assumption that inner and outer wall thickening fractions are equal (24,25). Circumferential shortening (both endocardial and midwall) was related to circumferential end-systolic wall stress (σ_c), which was calculated as follows:

$$\sigma_c = P \cdot a^2[1 + (b^2/r^2)]/(b^2 - a^2),$$

where P = end-systolic pressure; a = internal (endocardial) radius; b = external (epicardial) radius; and r = midwall radius (26). Arterial pressure was measured using cuff sphygmomanometry; end-systolic pressure was determined by the method described by Rozich et al. (27).

An assessment of longitudinal shortening of the left ventricle was made using previously described M-mode methods (28). With two-dimensional echocardiographic guidance from the apical window, the transducer was oriented to maximize apical endocardial to mitral annular distance. M-mode tracings were made with the cursor directed through the lateral aspects of the mitral annulus; recordings of at least three cardiac cycles were made on strip chart paper at 50-mm/s paper speed. Mitral annular descent was measured from the M-mode tracings as the maximal excursion of the line of greatest echogenicity. Mitral annular descent measurements were performed by investigators who were unaware of minor axis dimensions and circumferential shortening indexes. Long-axis shortening (LAS [%]) was calculated as follows:

$$LAS = 100 \cdot MAD/D,$$

where MAD = mitral annular descent (cm); and D = diastolic distance from apex to mitral annulus.

As with the circumferential stress–shortening analysis, we assessed stress–shortening relations in the long-axis plane. Meridional stress (σ_m) was calculated as follows:

$$\sigma_m = \frac{P \cdot LVID_s}{4 \cdot Th_{es}[1 + (LVID_s/Th_{es})]},$$

where P = end-systolic pressure; $LVID_s$ = left ventricular end-systolic dimension; and Th_{es} = posterior wall thickness measured at end-systole (4).

Statistics. Data are expressed as mean value ± SD. Comparisons between continuous variables were performed using a two-tailed unpaired Student *t* test. Dichotomous variables were compared using contingency table and chi-square analysis; $p < 0.05$ was considered statistically significant. The coefficient of determination (r) was used to assess the simple regression analysis between stress and shortening at the endocardium and midwall. The 95% confidence intervals (CIs) for shortening values for control subjects were also computed and displayed on the regression plot (29).

Table 1. Echocardiographic Data (mean ± SD)

	Patients With LVH (n = 43)	Control Subjects (n = 50)
$LVID_d$ (cm)	4.6 ± 0.7*	4.9 ± 0.6
$LVID_s$ (cm)	2.7 ± 0.7*	3.0 ± 0.4
Th_s (cm)	1.4 ± 0.3*	0.9 ± 0.2
Th_p (cm)	1.3 ± 0.3*	0.9 ± 0.1
EF (%)	69 ± 13*	63 ± 11
LVMI (g/m^2)	154 ± 48*	83 ± 20
RWT	0.62 ± 0.15*	0.36 ± 0.1

*$p < 0.01$ compared with control subjects. EF = ejection fraction; LVH = left ventricular hypertrophy; $LVID_d$ ($LVID_s$) = left ventricular end-diastolic (end-systolic) dimension; LVMI = LV mass indexed to body surface area; RWT = relative wall thickness; Th_p (Th_s) = diastolic posterior (septal) wall thickness.

Results

The mean values for echocardiographic measurements and for stress and shortening are shown in Tables 1 and 2. By definition, left ventricular mass index and relative wall thickness were increased in the left ventricular hypertrophy group (Table 1); left ventricular chamber dimensions were significantly smaller in patients with left ventricular hypertrophy than in control subjects, and septal and posterior wall thickness values were increased in the left ventricular hypertrophy group. Ejection fraction was significantly higher in the patients

Table 2. Wall Stress and Shortening in Study Patients (mean ± SD)

	Patients With LVH (n = 43)	Control Subjects (n = 50)
Meridional stress (g/cm^2)	31 ± 14*	46 ± 15
Circumferential stress (g/cm^2)	62 ± 27*	100 ± 27
FS_{endo} (%)	42 ± 10*	37 ± 5
FS_{mw} (%)	18 ± 3*	21 ± 2
Long-axis shortening (%)	18 ± 6†	21 ± 5

*p < 0.01, †p < 0.05 compared with control subjects. FS_{endo} (FS_{mw}) = circumferential shortening at endocardium (midwall); LVH = left ventricular hypertrophy.

with left ventricular hypertrophy than in the control group. Stress and shortening data are shown in Table 2. End-systolic stress in both the meridional and circumferential planes was significantly lower in left ventricular hypertrophy patients than in control subjects. In patients with left ventricular hypertrophy, endocardial circumferential shortening was increased, whereas shortening variables at the midwall and along the long axis were decreased, compared with that in control subjects. Thus, indexes of chamber function (ejection fraction and endocardial circumferential shortening) tend to be higher than normal in the left ventricular hypertrophy group; by contrast, shortening is depressed at the midwall and along the long axis.

Stress–shortening relations. A plot of circumferential stress versus endocardial shortening is shown in Figure 1. The regression line and 95% CIs are shown for the 50 normal subjects. The stress–shortening relation of virtually all patients with left ventricular hypertrophy falls within the 95% CI of this relation in normal subjects; this analysis does not detect a difference in contractile function between the two groups. A plot of circumferential stress versus midwall shortening is shown in Figure 2; as with the endocardial analysis, the regression line was derived from the normal subjects. In distinct contrast to the data shown in Figure 1, the stress–shortening relation for ~33% of patients with left ventricular hypertrophy falls below the 95% CI for this relation in normal subjects, indicating that myocardial function is depressed in patients with concentric left ventricular hypertrophy despite an ejection fraction at the high end of the normal range and a normal endocardial circumferential shortening. However, when patients whose stress-shortening relation falls below the 95% CI were compared with the rest of the cohort with left ventricular hypertrophy, there was no significant difference with regard to either ejection fraction (72 ± 13% for those within vs. 67 ± 13% for those below the 95% CI, p = NS) or endocardial circumferential shortening (44 ± 11% for those within vs. 41 ± 8% for those below the 95% CI, p = NS).

Long-axis shortening is plotted against meridional stress in Figure 3. The mean value of long-axis shortening in patients with left ventricular hypertrophy is lower than that in normal subjects (Table 2), but as shown in Figure 3, there is considerable overlap between patients with left ventricular hypertrophy and control subjects. Moreover, the inverse relation be-

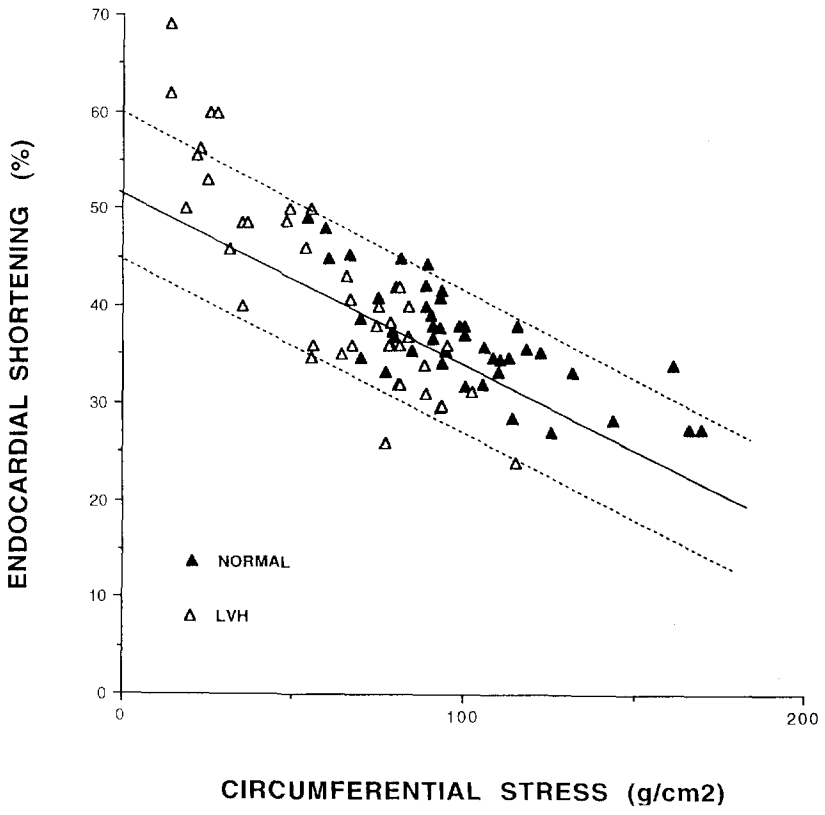

Figure 1. Relation between circumferential shortening at the endocardium plotted against end-systolic circumferential stress. Regression line **(solid line)** and 95% confidence intervals **(dashed lines)** are shown for the 50 normal subjects. As can be seen, data from virtually all patients with left ventricular hypertrophy (LVH) fall within the confidence limits of this relation, indicating that this analysis does not detect a difference in contractile function between normal patients and those with left ventricular hypertrophy.

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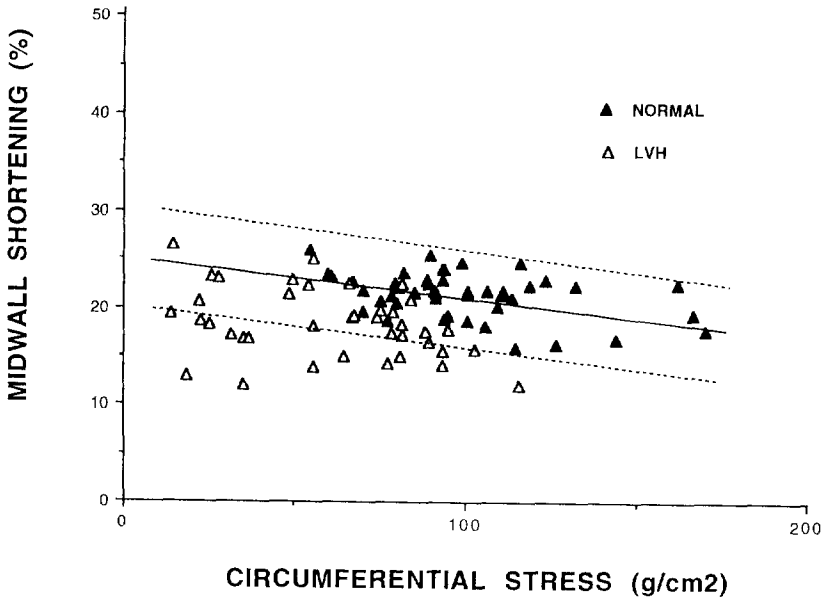

Figure 2. Midwall shortening plotted against circumferential stress. Regression line **(solid line)** and 95% confidence intervals (CIs) **(dashed lines)** are derived from data from normal subjects. In contrast to the analysis in Figure 1, data from ~33% of patients with left ventricular hypertrophy fall outside the confidence limits obtained in normal subjects, indicating that contractile function is depressed in patients with concentric left ventricular hypertrophy (LVH) and normal ejection fraction. However, when patients with data below 95% CIs were compared with the rest of the left ventricular hypertrophy cohort, there were no significant differences with regard to either ejection fraction (72 ± 13% for those within vs. 67 ± 13% for those below 95% CIs, p = NS) or endocardial circumferential shortening (44 ± 11% for those within vs. 41 ± 8% for those below 95% CIs, p = NS).

tween stress and shortening seen at the endocardium and midwall is not observed in the long-axis plane.

Influence of left ventricular geometry on chamber function. In order to assess the influence of left ventricular geometry on chamber function, we plotted endocardial versus midwall circumferential shortening at three different levels of relative wall thickness (Fig. 4): 1) normal subjects (<0.45); 2) moderate concentric hypertrophy (relative wall thickness between 0.45 and 0.60); and 3) marked concentric hypertrophy (relative wall thickness >0.6). The regression equation relating endocardial (FS_{endo}) to midwall circumferential shortening (FS_{mw}) for normal subjects was $FS_{endo} = 1.8\ FS_{mw} - 1$, r = 0.83; that for patients with relative wall thickness 0.45 to 0.59 was $FS_{endo} = 2.5\ FS_{mw} - 7.9$, r = 0.82; and that for patients with relative wall thickness >0.6 was $FS_{endo} = 2.3\ FS_{mw} + 6.4$, r = 0.78. Figure 4 demonstrates that endocardial shortening ex-

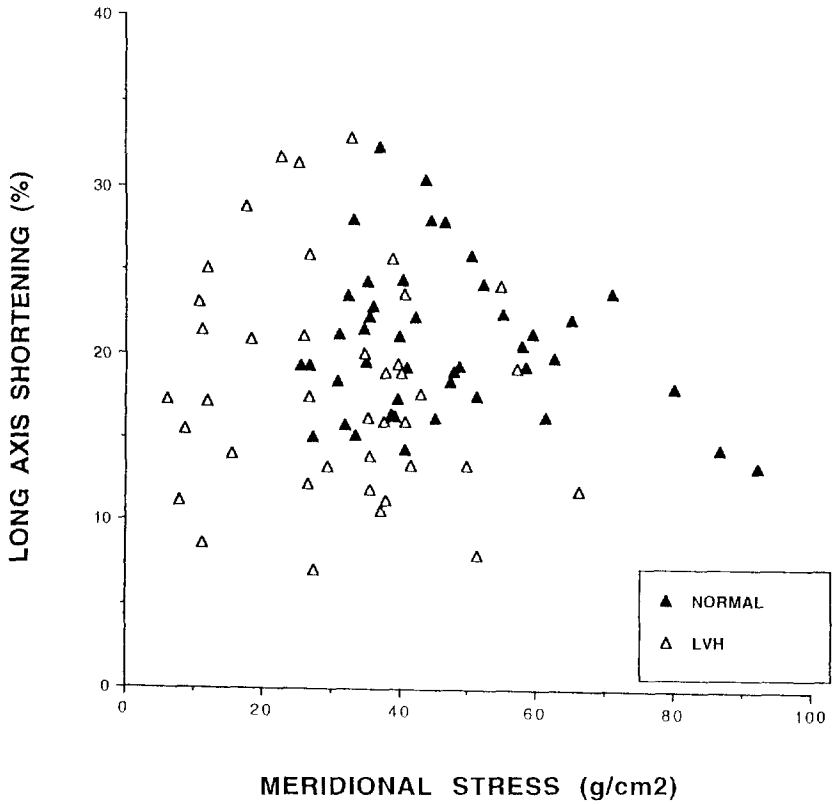

Figure 3. Long-axis shortening plotted against meridional stress. As in Figures 1 and 2, the shortening and stress vectors are in the same direction. Although the mean value of long-axis shortening in patients with left ventricular hypertrophy (LVH) is lower than that in normal subjects, there is considerable overlap between patients and control subjects. Moreover, the inverse relation between stress and shortening seen at the endocardium and midwall is not observed, which suggests that long-axis shortening is influenced by factors other than afterload.

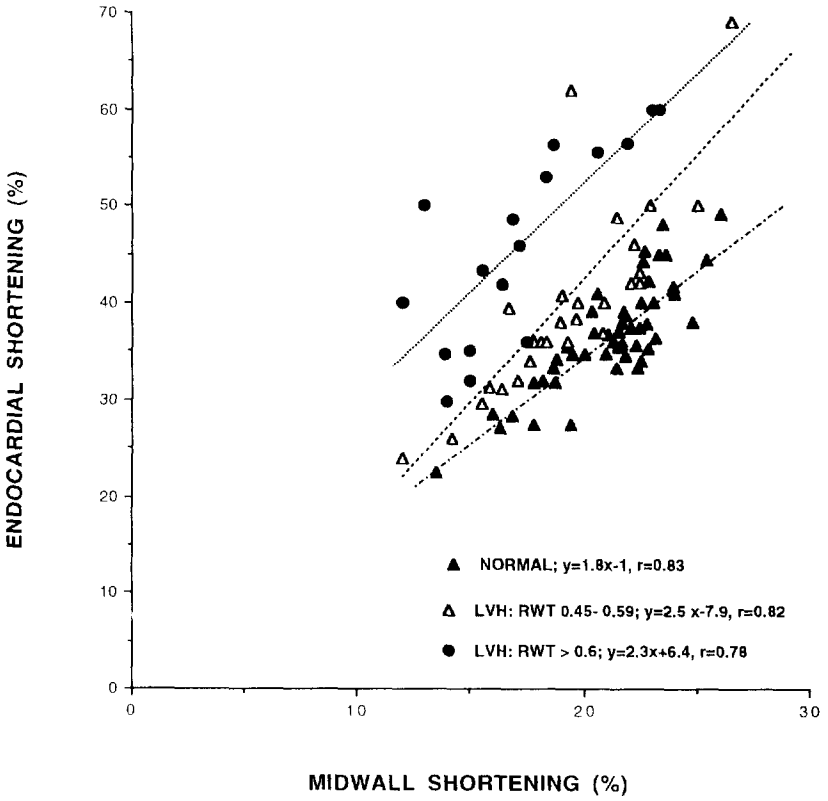

Figure 4. Relation between endocardial and midwall shortening for different levels of relative wall thickness (RWT). Over a wide range of midwall fiber shortening, endocardial shortening exceeds that seen at the midwall, and the difference between endocardial and midwall function is related to relative wall thickness. Even at levels of midwall shortening considered to be subnormal, increases in relative wall thickness are associated with preserved, if not exaggerated, endocardial shortening. **Dotted lines** = regression line for left ventricular hypertrophy (LVH) (relative wall thickness >0.6); **dashed lines** = regression line for left ventricular hypertrophy (relative wall thickness 0.45 to 0.59); **dashed-dotted lines** = regression line for normal subjects.

ceeds that seen at the midwall, and the difference (Δ) between endocardial and midwall shortening is directly related to relative wall thickness (RWT); the regression equation relating these two variables was $\Delta = 31 \cdot RWT + 3.1$ ($r = 0.69$, $p = 0.0001$).

Discussion

The principal result of the present study in patients with hypertensive left ventricular hypertrophy is that indexes of left ventricular chamber function (ejection fraction and circumferential shortening at the endocardium) may be normal or increased in the presence of depressed midwall and long-axis shortening. The mean values for both circumferential and meridional systolic stress were lower than those of normal controls; thus, this depression in myocardial shortening, present in more than one anatomic plane, is not caused by afterload excess (Fig. 1 and 2). Although many human and experimental studies have been designed to investigate myocardial function in pressure overload hypertrophy (1–3,5–8,24,25,30–35), few have simultaneously measured shortening in both the minor axis (circumferential) and long-axis (longitudinal) planes (14). Such an approach is desirable because of the theoretic concern that reduced shortening in one plane could be offset by an increase in shortening in another plane; this could occur if there were nonuniform function or alterations in fiber orientation. However, depressed shortening in both the circumferential and longitudinal planes indicates that this is not the case. Thus, our findings indicate a generalized myocardial shortening abnormality that is not apparent when the ejection fraction or endocardial length transients are used.

Depressed midwall shortening. As in previous studies (15,24–26,30), we used a midwall shortening analysis rather than conventional endocardial shortening to assess myocardial function. There are several reasons to warrant this approach. At the equator of the left ventricle, circumferentially oriented myocardial fibers predominate at the midwall (36,37). Thus, the use of midwall fractional shortening is anatomically appropriate in that shortening is measured in the same direction as the myocardial fiber orientation. A second reason to use midwall circumferential shortening variables is the logical consideration that stress and shortening vectors should be oriented in the same direction. In this regard, our circumferential stress–shortening relations are appropriate. It should be recognized that the calculation of circumferential shortening at the endocardium provides a shortening or strain variable that is at right angles to the subendocardial myofibrils. Fibers in the subendocardium are longitudinally directed; thus, calculation of circumferential shortening at the endocardium represents "cross-fiber shortening" that cannot be caused by shortening of subendocardial fibers per se.

The midwall shortening method used in this study is a simple refinement of the conventional midwall method that is known to overestimate shortening or lengthening parameters (24,25). The method takes into account nonuniform wall thickening and predicts the relative transmural position of a theoretic midwall fiber (or circumferential ring of myocardium) throughout the cardiac cycle (24,25). By assuming a

constant left ventricular mass throughout the cardiac cycle, a cylindrical model predicts that the inner half of the left ventricular wall is responsible for ~67% of the total wall thickening (24); this consideration is consistent with experimental data that indicate that the inner half contributes slightly more than 67% of total thickening. Thus, use of the cylindrical model probably results in a small overestimate of true myocardial shortening. However, the shortening results are similar when an ellipsoidal geometry is used (30).

Experimental studies of pressure overload hypertrophy consistently indicate depressed myocardial contractility (10,38). By contrast, most studies that use the whole heart support the notion that the functional state of hypertrophied hearts remains normal until a late stage of exhaustion and decompensation, at which time the ejection fraction and other functional indexes are abnormal. Our current data and some previously published work (14,15,24,25,30) indicate that when left ventricular midwall stress–shortening data are used, myocardial contractile function in hypertensive pressure overload hypertrophy can be depressed in the presence of a normal ejection fraction. For example, work published by Takahashi et al. (6) indicates normal end-systolic stress and normal circumferential shortening at the endocardium; however, application of our midwall analysis to the data of Takahashi et al. demonstrates that shortening at the midwall is lower than normal (16 ± 0.1% vs. 22 ± 0.1%, $p < 0.05$). It appears, therefore, that myocardial function may be depressed, whereas ejection fraction or endocardial stress–shortening relations indicate normal function, and that the overestimation of function in most clinical studies is related to the use of endocardial measurements that are more reflective of left ventricular chamber function than myocardial function.

Depressed long-axis shortening. Anatomic studies indicate that longitudinally oriented myocardial fibers are located in the subepicardial and subendocardial layers of the left ventricular wall and that these fibers show a continuous variation in fiber angle across the wall. There are experimental data indicating that measurements taken within 18.5° of the fiber axis can be used to represent fiber shortening (39). This finding supports the notion that a substantial portion of the left ventricular mass serves to produce long-axis shortening. It should be recognized that long-axis shortening occurs as a result of complex interactions between layers as well as geometric and loading factors. Because ventricular pump function or ejection fraction depends on a coordinated function of all layers, including a torsion or twisting motion (40), it is an oversimplification to assume that long-axis shortening represents only shortening of longitudinally oriented myocardial fibers. Despite these potential limitations, we used echocardiographic measures of systolic mitral annular motion (normalized for diastolic length) as a surrogate for long-axis shortening and an index of longitudinal myocardial shortening (41–44).

As was the case with circumferential shortening at the midwall, our measures of long-axis shortening were found to be significantly lower than normal in hypertensive patients with left ventricular hypertrophy. Although echocardiographic techniques have been used to investigate absolute changes in long-axis dimension in cardiomyopathy and in left ventricular hypertrophy, fractional shortening of the long axis of the left ventricle has not usually been reported (28,42). Our results, however, are consistent with theoretic considerations (45) as well as those recently reported by Palmon and co-workers (14) utilizing magnetic resonance imaging (MRI) tagging. These investigators reported estimates of long-axis shortening, measured at the free wall, of 20 ± 7% in normal subjects versus 17 ± 9% in patients with left ventricular hypertrophy. We observed similar differences in longitudinal shortening (21 ± 5% vs. 18 ± 6%, $p < 0.05$). However, our technique, in contrast to MRI tagging, does not permit measurement of longitudinal shortening at various transmural sites (14). Dumesnil et al. (45) estimated long-axis shortening from contrast angiograms in 11 subjects with aortic stenosis and also found that this variable was reduced in patients with pressure overload hypertrophy (13% vs. 18% in normal subjects). Thus, a variety of methods indicate that long-axis shortening is depressed in concentric left ventricular hypertrophy.

The mechanism or mechanisms underlying the observed shortening abnormality cannot be determined from the available data. However, it does appear that the reduction in myocardial shortening observed in our patients may not be caused by excessive afterload (Fig. 2). In fact, the average values for systolic wall stress in the hypertensive patients are less than normal. This is most likely because of a small subgroup of patients with excessive or inappropriate hypertrophy (15). If patients with high relative wall thickness (>0.7) are excluded, the average stresses fall within the normal range. It would seem, therefore, that wall thickness increases so as to normalize systolic stress in most patients with hypertensive heart disease (46).

Long-axis shortening is not closely related to meridional stress, which suggests that factors other than afterload have a significant influence on myocardial shortening in the apex-to-base direction. Perhaps the functional components of the mitral subvalvular apparatus or geometric factors (45) are responsible for such results. However, the average shortening in both the longitudinal and circumferential directions is similar and abnormal in both. Thus, although reduced fractional shortening may be characteristic of pressure overload hypertrophy, it is unknown whether long-term changes in fiber length or depressed inotropic state are responsible. There is reason to believe that some hypertrophic hearts operate at subnormal lengths (47) and that this might contribute to the observed subnormal shortening.

Geometry and myocardial and chamber function. Our results lend insight into the pathophysiology of altered left ventricular chamber and myocardial function in hypertensive left ventricular hypertrophy. One interpretation of our results is that the development of concentric geometry (increased relative wall thickness) allows preserved chamber function despite abnormal myocardial function. To test this hypothesis, we plotted endocardial versus midwall circumferential shortening at three different levels of relative wall thickness: normal

(<0.45), moderate concentric hypertrophy (relative wall thickness between 0.45 and 0.59) and marked concentric hypertrophy (relative wall thickness >0.6) (Fig. 4). This analysis demonstrates that over a wide range of midwall shortening, endocardial shortening exceeds that seen at the midwall, and the difference is directly related to relative wall thickness. Even at levels of midwall shortening considered subnormal, marked increases in relative wall thickness allow for preserved, if not exaggerated, endocardial shortening; this finding suggests that concentric geometry in patients with pressure overload hypertrophy is indeed an adaptive process. These considerations underscore the impact of ventricular geometry on endocardial shortening, and they suggest that an analysis of midwall indexes is particularly critical when left ventricular mass and geometry are changing. Such analysis could be especially important in the weeks to months after aortic valve replacement for aortic stenosis (30,45) or with regression of left ventricular hypertrophy during treatment of hypertensive patients.

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