Left Ventricular Midwall Mechanics in Systemic Arterial Hypertension

Myocardial Function is Depressed in Pressure-Overload Hypertrophy

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Background. **Left ventricular (LV) midwall geometry has been described conventionally as the sum of the chamber radius and half of the wall thickness; this convention is based on the assumption of uniform transmural thickening during systole. However, theoretical considerations and experimental data indicate that the inner half (inner shell) of the LV wall thickens more than the outer half (outer shell). Thus, an end-diastolic circumferential midwall fiber exhibits a relative migration toward the epicardium during systole. As a result, the conventional method provides an overestimate of the extent of the midwall fiber shortening.**

Methods and Results. **We developed an ellipsoidal model with a concentric two-shell geometry (nonuniform thickening) to assess midwall fiber length transients throughout the cardiac cycle. This modified midwall method was used in the analysis of LV cineangiograms from 15 patients with systemic arterial hypertension and 14 normal subjects. Study groups were classified according to LV mass index (LVMI): 14 normal subjects (group I), eight hypertensive patients with a normal LVMI (group II), and seven hypertensive patients with an increased LVMI (group III). There were no significant differences in LV end-diastolic pressure or volume among the three groups; the ejection fraction was slightly greater in group II (70±5%) than in groups I (65±8%) and III (66±4%), but this trend did not achieve statistical significance. Values for endocardial and conventional midwall fractional shortening (FS) were also similar in the three groups. By contrast, FS by the concentric two-shell geometry (modified midwall method) in group III (16±2%) was significantly less than that seen in groups I and II (21±4% and 21±5%, respectively; both $p<0.05$). This difference achieves greater importance when it is recognized that mean systolic circumferential stress was lower in group III (151±22 g/cm^2) than in groups I and II (244±37 g/cm^2 and 213±38 g/cm^2, respectively; both $p<0.01$). The midwall stress–shortening coordinates in six of the seven group III patients were outside the 95% confidence limits for the normal (group I) subjects. Thus, despite a normal ejection fraction, systolic function is subnormal in hypertensive patients with LV hypertrophy.**

Conclusions. **Chamber dynamics provide an overestimate of myocardial function, especially when LV wall thickness is increased. This is due to a relatively greater contribution of inner shell thickening in pressure-overload hypertrophy. (*Circulation* 1991;83:1676–1684)**

Left ventricular (LV) function is generally assessed by measuring the extent and velocity of fiber shortening (i.e., ejection fraction and velocity of circumferential fiber shortening) and relating these parameters to systolic wall stress; thus, the stress–shortening relation is used to characterize LV function. Although LV midwall mechanics have been considered in the assessment of fiber shortening and wall stress, most investigators have assumed a uniform transmural wall thickening and simply add half of the wall thickness to the chamber radius for a definition of LV midwall dimension.[1–5] Such assumptions are unwarranted, especially when normal and hypertrophic hearts are compared.

Theoretical considerations and experimental data indicate that circumferential midwall fibers (midwall at end-diastole) exhibit a relative migration toward

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Some of these data were presented at the 61st Annual Scientific Sessions of the American Heart Association in Washington, DC, in 1988.

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Received July 21, 1989; revision accepted January 8, 1991.

TABLE 1. Study Population and Basic Hemodynamic Data

Group	*n*	Age (yr)	HR (sec^{-1})	LVsp (mm Hg)	LVedp (mm Hg)	EDVI (ml/m^2)	ESVI (ml/m^2)	EF (%)	LVMI (g/m^2)	σ_{ed} (g/cm^2)	σ_m (g/cm^2)	σ_p (g/cm^2)
I	14	43±12	68±16	133±13	13±5	82±15	28±7	65±8	90±19	52±19	245±37	384±61
II	8	59±6*	64±14	164±27*	13±3	72±16	21±6	70±5	93±12	41±12	213±38	305±67*
III	7	50±6	71±15	161±33†	16±5	67±19	23±8	66±4	134±9*‡	30±9*	151±22*‡	222±26*‡

HR, heart rate; LVsp, left ventricular systolic pressure; LVedp, left ventricular end-diastolic pressure; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; EF, ejection fraction; LVMI, left ventricular mass index; σ_{ed}, left ventricular end-diastolic stress; σ_m, left ventricular mean systolic stress; σ_p, left ventricular peak systolic stress. Data are mean±standard deviation.

*†$p<0.01$ and 0.05, respectively, different from group I.

‡$p<0.01$ different from group II.

the epicardium during systole.[6–10] Thus, the conventional concept of midwall geometry has underestimated the systolic midwall dimension and overestimated midwall fiber shortening. Shimizu and associates[8,10] previously developed a modified midwall method that does not assume uniform transmural wall thickening; they used this method to assess differences between chamber filling and midwall fiber lengthening rates in patients with LV hypertrophy. Endocardial fiber shortening and modified midwall fiber shortening have likewise been assessed and compared in dogs with pressure-overload hypertrophy.[11] Although this midwall model has the advantage of simplicity (i.e., cylindrical geometry and echocardiographic data), angiographic methods provide a more appropriate ellipsoidal geometry.[12] We therefore used the angiographic method to assess endocardial and midwall fiber shortening in patients with essential hypertension.

It has been a matter of controversy whether the myocardium preserves normal systolic function in pressure-overload hypertrophy. The majority of basic studies of muscle mechanics indicate a depressed inotropic state,[13–16] while most experimental and clinical studies employing the whole ventricle indicate that the functional state of the hypertrophied heart remains normal.[17–23] Other studies indicate exaggerated endocardial motion in some hypertrophic hearts.[11,24–26] These differences are due in part to the fact that whole heart studies use endocardial measurements that reflect the chamber mechanics, not myocardial mechanics.[8] The purposes of this study are to develop a concentric two-shell ellipsoidal model of the left ventricle and to assess endocardial and midwall fiber shortening in patients with essential hypertension; thus, LV chamber and myocardial function could be compared in patients with and without LV hypertrophy.

Methods

Study Population

The LV cineangiograms from 29 patients who underwent diagnostic catheterization for chest pain were selected for this study (Table 1). Fourteen subjects (10 men and four women) without evidence of heart disease served as controls (group I). Fifteen patients had a history of essential hypertension with elevated arterial pressure (exceeding 160/90 mm Hg). No patient had cineangiographic evidence of coronary artery disease; patients with previous symptoms of congestive heart failure were excluded from this study. The patients with hypertension were divided into two groups according to their LV mass index (LVMI, see below). The eight patients in group II (four men and four women) had a normal LVMI (within mean±2 SD of that in group I). The seven patients in group III (six men and one woman) had an increased LVMI (greater than mean±2 SD of that in group I).

Cardiac Catheterization

The details of our catheterization methods have been described elsewhere.[27] All medications were withdrawn 24 hours before the catheterization. LV pressures were measured with a tip-manometer angiocatheter after electrical calibration and zero shift adjustment with the fluid-filled system. LV cineangiograms (60 frames/sec) were obtained in a 30° right anterior oblique projection (10 ml of 80% iothalamate sodium per second). On a frame-by-frame basis an area (A) and a long radius (L), where L is one half the long axis of the ventricular silhouette, were measured. The short radius (D), where D is one half of the short diameter, and LV volume were calculated with the area–length method by the formulas $D=A/\pi\times L$ and LV volume$=4\pi D^2L/3$. End-diastolic wall thickness was measured at the mid-anterior position on the LV cineangiogram. LV mass was calculated as $4\pi[(D+h)^2(L+h)-D^2L]/3$, where h is an end-diastolic wall thickness and D and L are defined above.[28] LV mass was corrected by body surface area (BSA) as LVMI=LV mass/BSA. LV pressures were digitized with a graphic tablet and microcomputer. Pressure–volume curves were then constructed from the cineangiographic data and the simultaneous record of LV pressure. End-diastole was defined by the electrocardiographic QRS complex, and end-systole was defined by the inflection point between ejection and isovolumic relaxation periods on the pressure–volume diagram.

Pressure–Volume Synchronization

The LV volume was determined over one cardiac cycle (from the onset of one QRS complex to the onset of the next QRS complex); LV volume was also measured from five cine frames before and five

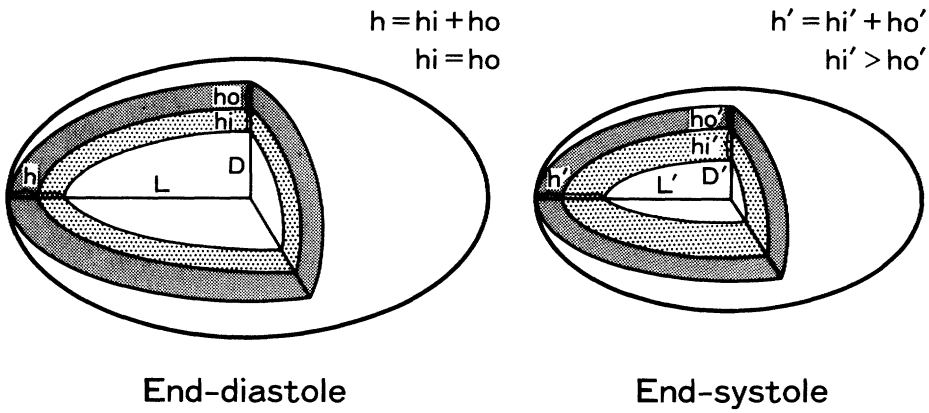

FIGURE 1. *Two-shell geometry of left ventricle illustrating ellipsoidal left ventricular model. Thicknesses of concentric shells at end-diastole are equal. At end-systole, thickness of inner shell is greater than that of outer shell. This indicates that the "end-diastolic" midwall fiber migrates in an epicardial direction in systole (see Appendix). L, long radius; D, short radius.*

cine frames after this cardiac cycle. LV pressure was measured with a digitizing tablet and microcomputer system during the same period. A cinepulse system (Cardoskop-U, Siemens-Elema, AB, Solna, Sweden) was used to synchronize the pressure and volume coordinates. End-diastole was defined as the onset of the QRS complex, and a pressure–volume loop was constructed for a single cardiac cycle. Accurate synchronization of the pressure and volume coordinates was confirmed by constructing a series of pressure–volume loops from cine frames that were adjacent to the frame initially identified as end-diastole; five frames immediately before and five frames after the end-diastolic frame were used. By matching a single end-diastolic pressure coordinate with each of the 11 volumes, we constructed 11 pressure–volume loops. This series of loops was examined visually, and the most physiologic loop (that with the most vertical isovolumic contraction and relaxation segments) was selected for analysis; an adjustment of one to three frames was necessary to achieve this.

Model and Calculations

The left ventricle was represented by an ellipsoidal model with uniform wall thickness. The LV wall is divided into an inner and an outer shell, thus defining a concentric two-shell geometry (Figure 1). The volume of each shell is assumed to be constant throughout the cardiac cycle, and instantaneous wall thickness and midwall fiber position are calculated (see Appendix).

Ejection fraction was calculated using a standard formula. Three methods were used to calculate circumferential fractional shortening (as a percentage) at the equator of the ellipsoid: endocardial fractional shortening (eFS), standard midwall fractional shortening using the conventional assumption of uniform wall thickening (sFS), and a modified midwall fiber fractional shortening using the nonuniform wall thickening model (mFS). LV midwall circumferential stresses (as grams per square centimeter) were calculated as $\sigma = p(B/h)(1 - h/2B - B^2/2A^2)$, where p is LV pressure, h is wall thickness, and A and B are the LV long and short radii to the midwall fiber position ($A = L + h_i$ and $B = D + h_i$ at end-diastole and $A = L' + h_i'$ and $B' = D' + h_i'$ for any instant in a cardiac cycle according to the Appendix); these stress calculations incorporate the nonuniform wall thickening concept.[11,29] Peak systolic stress (σ_p) was defined as the maximum instantaneous stress; mean systolic stress (σ_m) was calculated as the arithmetic mean of the time course of stresses from end-diastole to end-systole.

Data are presented as mean±SD. One-way analysis of variance and Duncan's method were used as appropriate, and differences were considered significant if the probability value was less than 0.05.

Results

Hemodynamic and angiographic characteristics of the three groups are summarized in Table 1. LV systolic pressure was significantly elevated in groups II and III, but there were no significant differences in end-diastolic pressure among the three groups. LV volumes and the ejection fraction were likewise similar in the three groups. By study design, LVMI in group III was significantly greater than that in the other two groups. LV end-diastolic stress was decreased in group III. Systolic wall stresses in the hypertensive patients (groups II and III) were lower than those in the control group.

The LV geometry and fractional shortening data are shown in Table 2. The three groups exhibited similar systolic and diastolic chamber dimensions, but wall thickness was significantly greater in group III than in the other two groups. The end-systolic midwall radius (i.e., chamber radius plus the inner shell thickness) was consistently greater when results from the modified midwall method were compared with those from the conventional method. This difference was directly related to LV end-diastolic wall thickness and LVMI (Figure 2); the difference was significantly greater in group III than in the normal control group ($p<0.01$). Therefore, when nonuniform wall thickening is considered, a circumferential midwall fiber (midwall at end-diastole) exhibits relative migration toward the epicardium throughout systole. As a result, this circumferential fiber is no longer at the midpoint of the LV wall at end-systole

TABLE 2. Left Ventricular Geometry and Fractional Shortening Data

Group	D_d (cm)	D_s (cm)	WT_{ed} (cm)	WT_{es} (cm)	mWT_{es} (cm)	ΔmWT_{es} (mm)	eFS (%)	sFS (%)	mFS (%)
I	5.4±0.5	3.5±0.5	0.9±0.1	1.3±0.2	0.7±0.1	0.7±0.2	35±7	23±5	21±4
II	5.0±0.5	3.1±0.4	0.9±0.2	1.4±0.2	0.8±0.1	0.9±0.2	38±5	24±5	21±5
III	5.0±0.5	3.2±0.5	1.3±0.2*†	1.8±0.2*†	1.0±0.1*†	1.0±0.3*	35±3	20±2	16±2‡§

D_d, end-diastolic short axis; D_s, end-systolic short axis; WT_{ed}, end-diastolic wall thickness; WT_{es}, end-systolic wall thickness; mWT_{es}, end-systolic midwall fiber position relative to endocardium by concentric two-shell geometry; ΔmWT_{es}, systolic shift of midwall fiber from standard midwall position; eFS, endocardial fractional shortening; sFS, midwall fractional shortening by standard midwall concept; mFS, modified midwall fractional shortening by nonuniform wall thickening models. Data are mean±standard deviation.

*‡$p<0.01$ and 0.05, respectively, different from group I.

†§$p<0.01$ and 0.05, respectively, different from group II.

(the thickness of the inner shell exceeds that of the outer shell at end-systole).

The LV afterload–shortening relations of all patients are shown in Figures 3 and 4. In this analysis, σ_m is plotted against mean systolic shortening (i.e., ejection fraction and eFS and mFS). A linear regression line represents the afterload–shortening relation for group I. While σ_m in group III was significantly less ($p<0.01$) than that in group I, the differences in eFS did not achieve statistical significance (Table 2). These data suggest abnormal ventricular function in the group III patients (low afterload without an appropriate increase in shortening). However, most group III coordinates lie within the 95% confidence limits for the normal control group. By contrast, when mFS was used (Figure 4), the evidence for depressed function was overwhelming; here, σ_m and mFS in group III were both lower than those in the other two groups (both $p<0.05$). Moreover, six of the seven group III coordinates were outside the 95% confidence limits for the group I data. This analysis supports the hypothesis that endocardial length transients provide an overestimate of myocardial function; this error is directly related to the thickness of the LV wall.

There were no significant relations between the ejection fraction or eFS and LVMI. There was, however, an indirect relation between mFS and LVMI; despite a preserved ejection fraction, hypertrophic hearts exhibit depressed midwall fiber shortening (Figure 5). Depressed fractional shortening is not seen when endocardial fiber length transients are assessed.

Discussion

Assessments of myocardial function in LV pressure-overload hypertrophy are based on theory derived from experience with isolated myocardial mechanics. Thus, the force–length–velocity relation provides a basis for evaluating the inotropic state and function of

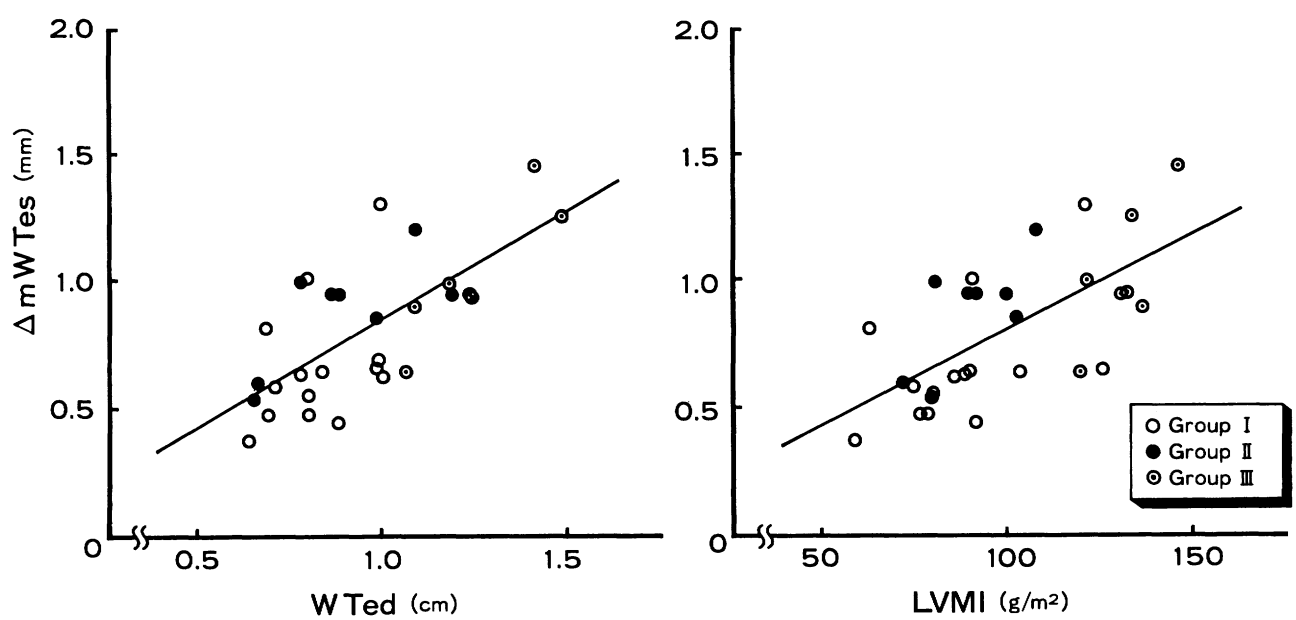

FIGURE 2. *Effect of left ventricular hypertrophy on relative difference in location of conventional and modified midwall fibers at end-systole ($\Delta mWTes$).* Left: *There is a direct relation between this difference and end-diastolic wall thickness (WTed). (Y=0.85X, r=0.69, p<0.01).* Right: *There is also a direct relation between this difference and left ventricular mass index (LVMI) (Y=0.008X+0.046, r=0.65, p<0.01). These data indicate that extent of midwall fiber migration is directly related to degree of hypertrophy. See text for details.*

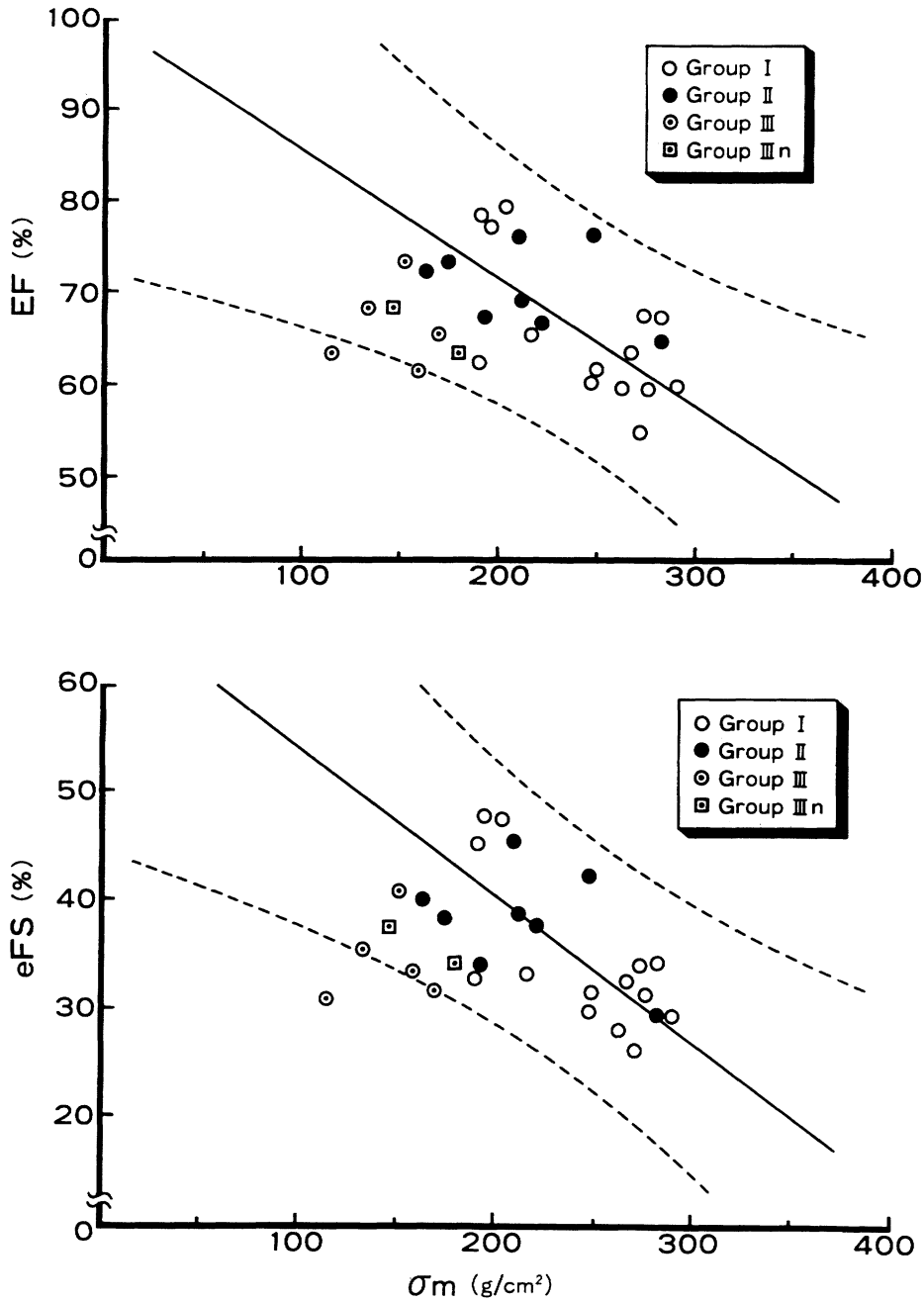

FIGURE 3. *Stress–endocardial shortening relations. Mean systolic stress (σm) is plotted against ejection fraction (EF)* (upper panel) *and endocardial fractional shortening (eFS)* (lower panel). *Regression lines with 95% confidence limits are indicated for the group I data (*$Y=-0.14X+99.87$, $r=-0.67$, $p<0.01$ *in upper panel;* $Y=-0.14X+68.11$, $r=-0.71$, $p<0.01$ *in lower panel). Group II and III coordinates lie largely within 95% confidence limits for group I data. Group IIIn, individuals in group III with normal end-diastolic stress (within SD of group I mean shown in Table 1). See text for details.*

hypertrophic hearts. While it has not been possible to measure absolute fiber length in the intact heart, fractional changes in length (ejection fraction or fractional shortening of a dimension) have been widely applied in studies of hypertrophic hearts. Such measurements are appropriately normalized (they are indexes of fiber strain), and they allow comparisons among hearts of different sizes.[30] When related to afterload (systolic wall stress), fiber shortening has been used to evaluate systolic function in a wide variety of clinical and experimental studies.[2–5,11,19,27] This approach relies heavily on two assumptions. First, it is assumed that variations or differences in resting length (fiber stretch) do not substantially influence the force–shortening relation. This, of course, is not true during acute or short-term hemodynamic interventions. Under chronic steady-state conditions, however, the situation is much more complex; it is not known whether chronic alterations in preload (end-diastolic stress) reflect differences in end-diastolic fiber or sarcomere length (see below). Second, the use of a force–shortening analysis requires that the force vector and the fiber length changes be oriented in the same direction. Thus, circumferential stress should be used in conjunction with measurements of circumferential fiber shortening. Since circumferential fibers predominate in the midwall of the left ventricle,[31–34] such an analysis

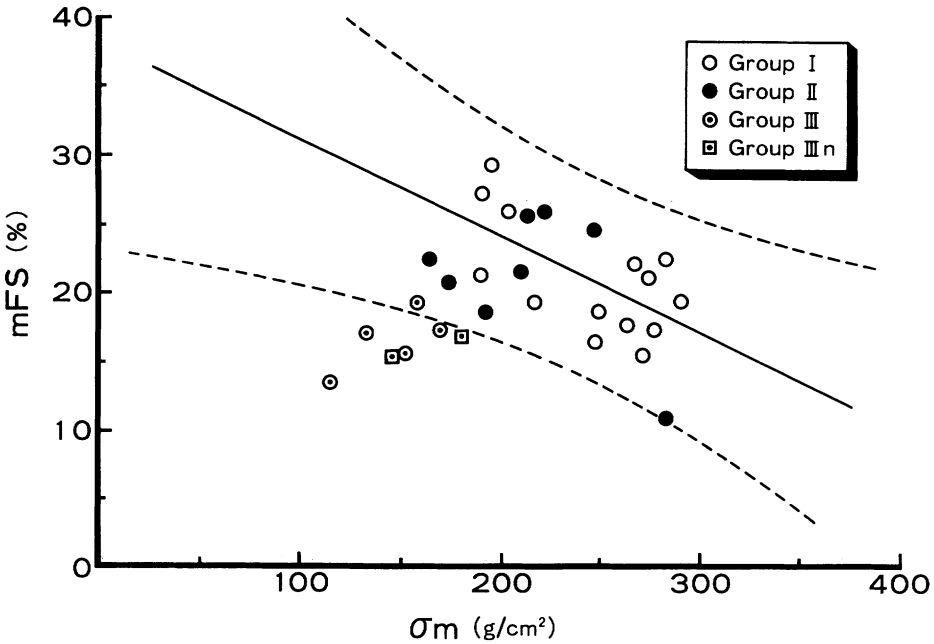

FIGURE 4. *Stress–midwall shortening relations. Mean systolic stress (σm) is plotted against midwall fractional shortening (mFS). As in Figure 3, regression line was derived from best fit to group I data (Y=−0.07X+38.31, r=−0.63, p<0.05). Six of seven group III patients lie outside 95% confidence limits of group I data. Group IIIn, individuals in group III with normal end-diastolic stress (within SD of group I mean shown in Table 1). See text for details.*

should incorporate midwall stress–shortening measurements.

In an attempt to refine the conventional midwall stress–shortening method, Shimizu and associates[8,10] developed a modified midwall model that predicts the relative transmural position of a theoretical midwall fiber throughout the cardiac cycle. They recognized that "subendocardial shortening" exceeds shortening in the subepicardium and that subendocardial fibers thicken more than those in the subepicardium. When they used the modified midwall analysis in studies of normal and hypertrophic hearts and compared the conventional and modified midwall results, these investigators found that conventional midwall methods overestimate myocardial fiber length transients. Our current studies refine further the modified midwall method; this refinement is possible because angiographic data provide a more appropriate (ellipsoidal) geometry and an accurate measurement of the long axis. Our endocardial results shown in Figure 3 indicate a tendency toward abnormal systolic function in the group III patients (low afterload without the expected increase in shortening). However, most group III coordinates do not lie outside the 95% confidence limits for the group I data. When the modified midwall shortening parameter was used (Figure 4), the evidence for depressed function is compelling; here, stress and shortening are significantly lower than those seen in the other two groups, and six of the seven coordinates lie outside the 95% confidence limits for the group I data. It appears, therefore, that depressed myocardial function can be masked if endocardial shortening parameters are analyzed. These results highlight the importance of assessing fiber shortening relative to fiber load, and they support the hypothesis that a midwall analysis is necessary when wall thickness varies.

Although our analysis confirms a reduced midwall fiber shortening in LV hypertrophy, it does not identify the mechanism underlying such reduced function. The mathematical considerations of Mirsky and associates[5] indicate that end-diastolic stress should be considered in the analysis of stress–shortening data, and it is possible that the modest reduction in preload (end-diastolic stress) that we observed in group III might be responsible at least in part for the reduced midwall shortening in this group. Preload, however, does not necessarily mirror fiber or sarcomere length. In chronic steady-state conditions, length is influenced by preload (the force acting to stretch the fiber) and by the factors resisting stretch (i.e., stiffness); thus, end-diastolic stress is an imperfect index of fiber length. Despite this, the present analysis and the work of others[35] suggest that some hypertrophic hearts may operate at low or marginal fiber lengths and that this might contribute to reduced shortening. These uncertainties do not, however, affect our conclusion that a midwall analysis should be used when fiber shortening is assessed in normal and hypertrophic hearts.

Recognizing the limitations of endocardial shortening parameters, it would appear that some previously published data should be reinterpreted. Experimental and clinical studies of ventricular function in pressure-overload hypertrophy indicate a wide spectrum of changes in function.[4,11,17–26,36–39] If our modified midwall method were applied in these studies, the results would likely indicate lower fiber shortening than that reported; hyperkinetic ventricles might be associated with normal midwall shortening, and a normal ejection fraction might indicate depressed midwall function. Thus, the conclusions from these

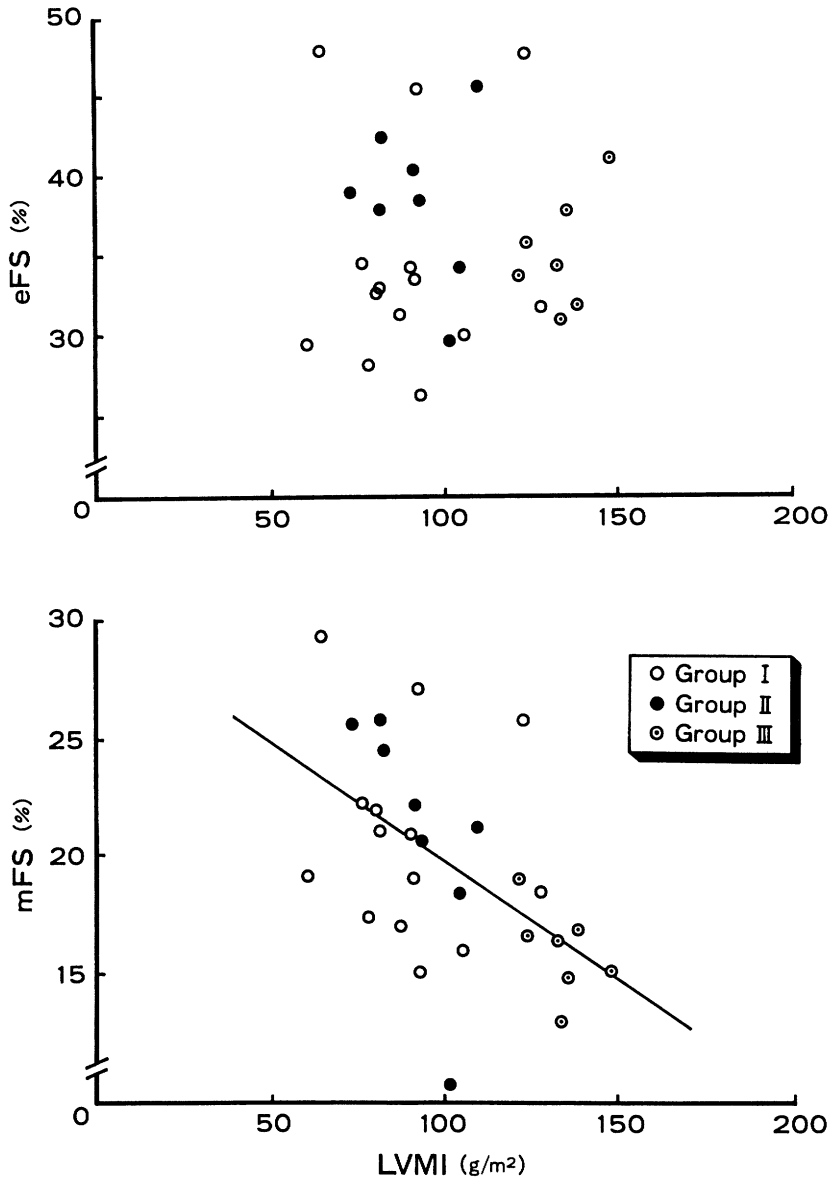

FIGURE 5. *Relations between left ventricular mass and fractional shortening. Left ventricular mass index (LVMI) is plotted against endocardial fractional shortening (eFS)* (upper panel) *and midwall fractional shortening (mFS) according to concept of concentric two-shell geometry* (lower panel). *There is significant relation between LVMI and mFS* ($Y = -0.098X + 29.77$, $r = -0.54$, $p < 0.01$).

studies would be quite different if the midwall method were used. The modified midwall analysis has, in addition, a theoretical advantage over the endocardial method; that is, the normal values for midwall shortening are in close agreement with our understanding of sarcomere shortening data. Assuming that sarcomeres shorten from an end-diastolic length of 2.1–2.2 μm to an end-systolic length of 1.7–1.8 μm, normal sarcomere shortening exceeds 13%.[40] Our clinical data indicate that the lower limit of normal midwall fiber shortening is 16%; similar results have been observed in hypertrophic dog hearts.[11] Except under intense inotropic stimulation, normal sarcomere shortening does not reach 25–30%, as was seen in some of our patients. Despite this, the modified midwall results appear to be in much closer agreement with known sarcomere shortening data than are the endocardial or even the conventional midwall results. Recognizing the complex three-dimensional geometric changes that contribute to ejection,[41] the relatively simple analysis of circumferential midwall stress–shortening is a methodological refinement that should be used in the assessment of myocardial function in normal and hypertrophic hearts.

Appendix

The left ventricle is represented by an ellipsoidal model (Figure 1) with wall volume (i.e., muscle mass) represented by the equation

$$\text{LV wall volume} = 4\pi[(D+h)^2(L+h) - D^2L]/3 \quad (1)$$

where L is the long radius, D is the short radius, and h is the wall thickness at end-diastole. Assuming an incompressible and homogeneous myocardium with

constant specific gravity, LV wall volume (which is therefore constant throughout the cardiac cycle) can be represented at any instant in the cycle by the equation

$$\text{LV wall volume} = 4\pi[(D' + h')^2 \times (L' + h') - D'^2 L']/3 \quad (2)$$

where L', D', and h' are the dimensions at a specific time during the cardiac cycle. Total wall volume at end-diastole (Equation 1) equals the wall volume at any instant during the cycle (Equation 2):

$$4\pi[(D+h)^2(L+h) - D^2L]/3 = 4\pi[(D' + h')^2 \times (L' + h') - D'^2 L']/3 \quad (3)$$

Since D, L, h, D', and L' are known parameters, one can calculate wall thickness h' at any instant during the cycle by solving the third order polynomial.

The LV wall is divided into inner and outer shells; at end-diastole the thickness of the inner shell (h_i) is equal to the thickness of the outer shell (h_o). At end-diastole, $h_i + h_o = h$. Since the volume of each shell remains constant throughout the cardiac cycle, the midwall radii can be represented at any instant during the cycle by $L' + h_i'$ and $D' + h_i'$. The parameter h_i' represents the distance of the midwall fiber from the endocardium. Likewise, the volume of the inner shell at end-diastole equals the volume of the inner shell at any instant during the cycle:

$$4\pi[(D+h_i)^2(L+h_i) - D^2L]/3 = 4\pi[(D' + h_i')^2 \times (L' + h_i') - D'^2 L']/3 \quad (4)$$

Thus, the "true" location of the original (end-diastole) midpoint of the LV wall can be determined at any instant during the cardiac cycle.

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KEY WORDS • essential hypertension • left ventricular function • left ventricular hypertrophy • myocardial function