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Should Echocardiography Be Performed to Assess Effects of Antihypertensive Therapy? Test–Retest Reliability of Echocardiography for Measurement of Left Ventricular Mass and Function

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Objectives. **The purpose of this study was to determine the test–retest stability of echocardiography for the measurement of left ventricular mass and function in patients with hypertension.**

Background. **Determination of changes in left ventricular mass may be impaired by study variability. The amount by which variables of mass and left ventricular function must change in an individual patient to exceed temporal variability has not been determined in a multicenter trial.**

Methods. **Ninety-six patients with hypertension had two-dimensional targeted, M-mode Doppler echocardiography repeated at 6 ± 8 days by the same technician utilizing the same machine. Left ventricular mass and variables of systolic and diastolic function were measured. Test–retest reliability and the width of the 95% confidence intervals of variable change, as well as the contributions of age, study quality and body size to measurement reliability, were determined.**

Results. **Despite excellent reliability (intraclass coefficient of correlation 0.86), the 95% confidence interval width of a single replicate measurement of left ventricular mass was 59 g, exceeding usual decreases in mass during treatment. Study quality, which was dependent on age and weight, influenced test reliability. Although the confidence interval width for ejection fraction was narrow (5 U), those for peak early (E) and late (A) diastolic velocities were wide, resulting in a confidence interval width for the E/A ratio of 1.5.**

Conclusions. **The temporal variability, particularly in obese or elderly patients, or both, of echocardiography for measurement of left ventricular mass precludes its use to measure changes in mass of the magnitude likely to occur with therapy. Measurement stability is affected by study quality, and age and body weight both influence study quality. Although ejection fraction shows little temporal variability, the large width of the confidence interval of the Doppler E/A ratio impairs its use to serially measure diastolic function.**

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In clinical trials, echocardiography has demonstrated the efficacy of antihypertensive drugs and nondrug therapy in reducing left ventricular mass (1–5), an important predictor of morbidity and mortality (6–10). Additionally, improvements in Doppler indexes of left ventricular filling occur (11–13) because left ventricular mass decreases after antihypertensive therapy. Left ventricular mass, even below partition values selected to define left ventricular hypertrophy, has been associated with cardiovascular risk independent of the magnitude of blood pressure elevation. Moreover, drugs equally effective in reduction of blood pressure may differ in their ability to reduce left ventricular mass (5,14) or to correct left ventricular hypertrophy. Hence, measurement of left ventricular mass and diastolic left ventricular function utilizing echocardiography may be of value in the clinical monitoring of antihypertensive drug therapy in patients with hypertension.

Estimation of left ventricular mass either from two-dimensional cross-sectional images (15–18) or from two-dimensional targeted M-mode (19–21) "ice-pick" views of the heart requires certain geometric assumptions and arithmetic manipulation of primary echocardiographic measurements. Nonetheless, these assumptions have in general been appropriate in most clinical studies of hypertension, and echocardiographic techniques for measurement of left ventricular mass have been well validated by autopsy studies (17,19).

However, the acquisition of echocardiograms is heavily operator interactive, requiring manual direction of the ultrasound sector through the heart. Minor variation in acquisition technique may result in image planes that are not consistent with the geometric assumptions of left ventricular mass measurement or that produce images where obscure echocardiographic boundaries make measurement of left ventricular structures difficult. Hence, it is uncertain whether the value of echocardiography in showing clinical trial effects can be extrap-

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olated to monitoring the effects of antihypertensive therapy on left ventricular mass in individual patients. Additionally, Doppler indexes of diastolic left ventricular function are sensitive to alterations in heart rate, loading conditions and autonomic tone (22–24) as well as minor differences in placement of the Doppler sample volume (25).

Therefore, we performed a simple replication reliability study within the context of a multicenter hypertension drug trial to determine the test–retest reliability of two-dimensional targeted M-mode echocardiography for the measurement of left ventricular mass, wall thickness and cavity size. In addition, we determined the test–retest reliability of commonly used Doppler indexes of diastolic function. The magnitude of change in measured variables necessary to exceed measurement and physiologic variability was determined and compared with changes in structural and functional variables reported in clinical trials of antihypertensive therapy utilizing echocardiography.

Methods

Patients. Ninety-six patients (mean age [±SD] 55 ± 8 years, range 24 to 78; 25 women, 71 men) with mild to moderate hypertension (diastolic blood pressure 95 to 110 mm Hg) recruited at 11 participating medical centers for a trial of the effects of drug therapy on left ventricular mass were the subjects for this study. Patients were excluded from participation if at the local site the screening echocardiogram was considered to be of insufficient technical quality for the measurement of left ventricular mass or left ventricular inflow velocity on Doppler. Echocardiography was performed 6 weeks after withdrawal of previous drug therapy and was repeated 6 ± 8 days after the initial examination by the same technician utilizing the same ultrasonograph as that used in the initial echocardiogram. Of the 96 patients, 74 had echocardiograms at both visits that were considered by the central echocardiography reading laboratory to be interpretable for left ventricular mass measurement; 78 had study pairs that were suitable for measurement of ejection fraction; and 88 had study pairs suitable for assessment of diastolic velocity on Doppler.

Echocardiography. *Training.* Before the acquisition of study echocardiograms, a 2-day training meeting for participating technician echocardiographers was conducted at the central echocardiography reading laboratory. During this meeting, technical and physiologic principles of echocardiography pertinent to quantitative applications of echocardiography in hypertension studies were reviewed. Additionally, the technician echocardiographers performed echocardiography in selected subjects under the direction of the central laboratory training staff to emphasize those aspects of echocardiogram acquisition pertinent to the quantitative requirements of the study. All sonographers had at least 3 years of previous clinical experience.

Acquisition. After 6 to 12 weeks of withdrawal of previous antihypertensive therapy, two-dimensional targeted M-mode echocardiography was performed with the patient in the partial left lateral decubitus position. The M-mode cursor was directed through the center of the two-dimensional parasternal short-axis image at or just distal to the tips of the mitral valve leaflets. Particular care was taken to achieve image planes orthogonal to the left ventricular anatomic long axis and to optimize definition of endocardial and epicardial interfaces. To ensure maximal recording of gray scale and sufficient M-mode image size, continuous strip chart recording on paper of derived M-mode was performed.

Mitral inflow was sampled by placing the Doppler pulsed-wave sample volume at the level of the mitral annulus with optimal adjustment of gain and filtration to achieve the acoustically purest frequency and narrowest spectral envelope obtainable. Recording was made on paper strip chart recording at 50 mm/s.

Interpretation. After comparability with the real-time two-dimensional echocardiographic parasternal images on videotape was determined, M-mode paper strip chart recordings were analyzed utilizing a commercially available off-line analysis system (Microsonics Datavue II) coupled to a digitizing tablet with a spatial resolution of 0.001 in. (0.0025 cm).

Echocardiograms were encoded according to adequacy for measurement of the components of left ventricular mass as quality grade 1 if the study was minimally acceptable for measurement of left ventricular mass (i.e., nonoblique circular [eccentricity index <1.2] cross-sectional image in the parasternal short axis with placement of the M-mode cursor through the center of the left ventricle), as well as at least 5 mm of identifiable end-diastolic endocardial surfaces of the septum and posterior wall for ≥3 beats that need not be contiguous. Grade 2 echocardiograms met the previous criteria as well as allowing identification of echocardiographic interfaces for complete noncontiguous cycles. Grade 3 echocardiograms allowed identification of echocardiographic interfaces for multiple series of at least three contiguous cycles. Grade 4 echocardiograms met the previous criteria and were considered optimal or near optimal for measurement. To minimize reader variability, all studies were interpreted by a single reader (S.L.). In addition, the echocardiograms of 30 randomly selected patients were interpreted in blinded manner by a second reader (J.S.G.) to determine whether temporal variability in left ventricular mass measurement was similar for two readers.

Measurement of ventricular septum, left ventricular cavity, posterior wall and left atrium were performed according to American Society of Echocardiography criteria (26). Left ventricular mass was calculated as described elsewhere (21). Left ventricular end-diastolic (EDV) and end-systolic (ESV) volumes were calculated as the cube function of the corresponding cavity dimensions (21). Ejection fraction was calculated as (EDV − ESV)/EDV × 100 and expressed as dimensionless units. The peak velocity (E) of early diastolic filling was taken at the maximal excursion of the leading edge of the mitral time–velocity integral, and late diastolic peak filling rate (A) was determined from the maximal excursion of the time–

Table 1. Study Data

	Study 1 (mean ± SD)	Study 2 (mean ± SD)	Average Absolute Difference (±SD)	Percent Error (mean ± SD)	95% Confidence Interval Width	Linear Correlation	Intraclass Coefficient of Correlation	SEE	No. of Pts
LVDD (mm)	50.5 ± 5.0	50.5 ± 4.9	2.0 ± 1.8	3.9 ± 3.8	3.4	0.85 (0.81–0.90)	0.87	2.6	74
LVDS (mm)	30.4 ± 5.0	30.8 ± 5.1	3.1 ± 3.4	10.4 ± 13.7	4.9	0.76 (0.64–0.84)	0.76	3.3	75
LVPW (mm)	12.2 ± 2.0	12.1 ± 1.8	0.8 ± 0.9	6.7 ± 7.4	1.7	0.80 (0.70–0.87)	0.79	1.9	74
VS (mm)	12.6 ± 2.1	12.5 ± 2.0	0.7 ± 0.8	5.5 ± 6.6	1.3	0.88 (0.82–0.92)	0.90	1.0	74
LA (mm)	41.8 ± 5.3	42.2 ± 5.4	2.7 ± 2.9	6.4 ± 6.8	5.5	0.72 (0.61–0.81)	0.72	3.6	90
LVDV (ml)	131.9 ± 39.4	133.1 ± 40.5	15.2 ± 14.7	11.7 ± 1.2	29.2	0.86 (0.79–0.91)	0.86	20.2	81
LVSV (ml)	30.6 ± 15.6	32.0 ± 15.9	8.8 ± 8.9	2.9 ± 7.7	16.01	0.73 (0.60–0.82)	0.73	10.7	75
LVMI (g/m^2)	141 ± 34	139 ± 31	14.9 ± 12.8	11.1 ± 10.0	27.2	0.82 (0.73–0.89)	0.82	19.6	74
LVM (g)	323 ± 82	320 ± 77	27.1 ± 27.1	11.4 ± 13.1	59.0	0.86 (0.78–0.91)	0.86	42.6	74
EF units	77.2 ± 7.8	77.4 ± 7.7	2.4 ± 2.3	3.2 ± 3.1	4.5	0.91 (0.86–0.94)	0.91	3.3	78
FS units	39.9 ± 7.0	39.0 ± 7.0	6.2 ± 7.1	15.4 ± 15.2	9.0	0.53 (0.35–0.68)	0.53	6.0	75
E vel (cm/s)	53.1 ± 15.9	53.7 ± 14.3	9.4 ± 8.7	5.5 ± 0.0	17.9	0.64 (0.50–0.75)	0.64	12.3	88
A vel (cm/s)	59.1 ± 15.1	60.0 ± 15.3	9.6 ± 8.1	16.2 ± 12.7	17.4	0.65 (0.51–0.76)	0.65	11.5	89
E/A ratio	1.06 ± 1.11	0.94 ± 0.31	0.29 ± 1.1	20.1 ± 22.8	1.5	0.26 (0.05–0.44)	0.12	1.09	89

A vel (E vel) = Doppler peak late (early) diastolic velocity; EF = left ventricular ejection fraction; FS = left ventricular fractional shortening; LA = left atrial dimension on M-mode echocardiography; LVDD (LVDS) = left ventricular dimension at end-diastole (end-systole); LVDV (LVSV) = left ventricular end-diastolic (end-systolic) volume; LVM = left ventricular mass; LVMI = left ventricular mass indexed to body surface area; LVPW = left ventricular posterior wall thickness; Pts = patients; VS = ventricular septal thickness in diastole.

velocity integral with atrial contraction. The average of 3 beats was used for all measurements.

Intraobserver errors of 8.2%, 6.9% and 2.3% for septum, posterior wall and left ventricular diastolic dimension had previously been established for the reader from 35 studies of hypertensive patients read 1 to 2 weeks apart. Intraobserver errors for septum, posterior wall and left ventricular diastolic dimension determined from 56 echocardiograms from the current study, reread in blinded manner 18 to 24 months from the initial reading, were 9.1%, 8.9% and 2.6%, respectively, similar to interobserver errors (comparison with reader J.S.G.) of 9.1%, 8.7% and 3.1%, respectively. For E and A peak diastolic velocities, the intraobserver errors were 8.7% and 7.9%, respectively. The Pearson coefficient for intraobserver correlation of left ventricular mass was 0.82, diastolic dimension 0.80, posterior wall 0.84, septal wall 0.83, E velocity 0.76, A velocity 0.86 and E/A ratio 0.79. There were no differences in observer error between echocardiograms of study quality grades 1 to 2 versus grades 3 to 4.

Statistical methods. The measurements and computed values analyzed are shown in Table 1. Correspondence of replicate measurements and calculated values were determined by calculation of the Pearson coefficient of correlation.

Two statistical measures of reliability (27) for the sample population were used: the standard error of the measurement and the intraclass coefficient of correlation. Using a standard analysis of variance for a nested sample, the standard error of the measurement (SE) was computed (27), from which we derived the width of the 95% confidence interval for the true value of a measured or computed variable for a single subject, (i.e., 95% CI = ± 1.96 SE/$\sqrt{N}$, where N = the number of replicate measurements).

The intraclass coefficient of correlation (rho) was calculated as rho = $S_t^2/(S_t^2 + S_e^2)$, where S_e^2 = within-subject mean square and is a measure of the variance within subjects; S_t^2 = (BMS − WMS)/K_0, where BMS = between-subject mean square, WMS = within-subject mean square, and K_0 = number of replicate measurements, which in this case equals 2. Measurements that are highly reproducible for any given degree of intersubject variability will have values of the intraclass coefficient of correlation approaching +1. In an arbitrary classification scheme, intraclass coefficients in the range 0 to 0.20 = slight reliability, 0.21 to 0.40 = fair reliability, 0.41 to 0.80 = moderate reliability, and 0.81 to 1.00 = almost perfect reliability (28). The percent error was determined as the absolute average difference between measurements divided by the mean value of the measurements times 100.

The independent contribution of age, echocardiographic study quality and body size (height and weight) to measurement variability was determined by stepwise multivariate regression analysis, where interstudy measurement difference was used as the dependent variable. Additionally, the relation of study quality to age, height and weight was determined by stepwise multivariable regression analysis.

The statistical computer package SAS, versions 5 and 6, was used to generate the statistical analyses (29). All statistical tests were two-tailed, and $p \leq 0.05$ was used to identify statistically significant results. For multivariate regression analyses, a significance level of 0.15 was required for entry into the model.

Results

Average values, absolute differences, percent error, widths of 95% confidence intervals of measurement change, linear

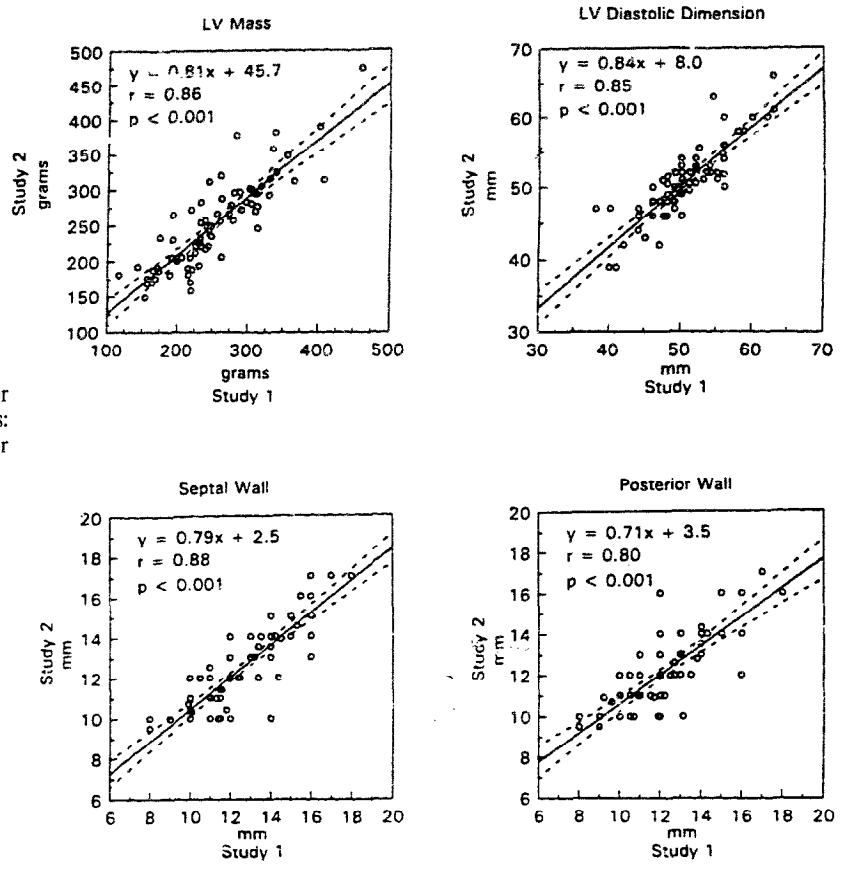


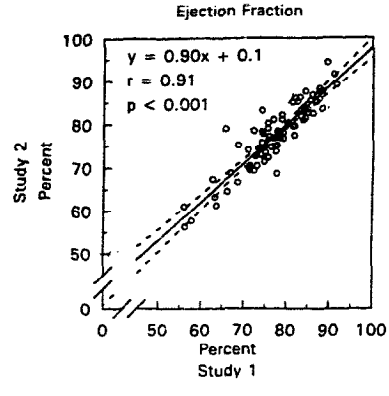
Figure 1. Test-retest comparison of values for left ventricular (LV) mass and its components: diastolic dimension, septal wall and posterior wall thickness.

and intraclass correlations are presented in Table 1. Computed average left ventricular mass and its measured components did not differ between studies (Table 1), and the Pearson coefficient of correlation ($r = 0.86$, $p < 0.001$) for left ventricular mass measurements (Fig. 1) repeated at 6 ± 8 days after the initial study was not worse than that for interobserver ($r = 0.73$) or intraobserver ($r = 0.82$) variability. Intraclass coefficient of correlation for left ventricular mass was 0.86, within the range of "almost perfect reliability." The S_e for left ventricular mass was 30.2 g; hence, the width of the 95% confidence interval for a single replicate measurement of left ventricular mass was 59.0 g (1.96 S_e). Of the components of left ventricular mass measurement, test-retest Pearson correlations (Fig. 1) were highest for septal thickness ($r = 0.88$) and left ventricular diastolic cavity dimension ($r = 0.85$) but relatively modest ($r = 0.80$) for posterior wall thickness. For the components of left ventricular mass measurement, the intraclass coefficients of correlation of 0.88 and 0.90 for left ventricular diastolic dimension and ventricular septum, respectively, were also within the range of "almost perfect reliability." The intraclass coefficient of correlation of 0.79 for posterior wall was within the range of "moderate reliability."

Of the 30 randomly selected patients in whom serial echocardiograms were reread by a second observer, 29 had study pairs that were interpretable for left ventricular mass measurement. The intraclass coefficient of correlation was 0.90, and the width of the 95% confidence interval of 55.0 g was similar to the value of 59.0 g obtained from the larger cohort interpreted by the index reader. From intraobserver comparisons of readings performed at wider time intervals, the 95% confidence width of 68.2 g was not less than that of temporal variability (59.0 g).

Left ventricular function measurements. Ejection fraction was highly correlated (Table 1, Fig. 2) on test-retest comparison. Intraclass coefficient of correlation (0.91) was within the

Figure 2. Comparison of ejection fraction measured in same subjects over 6 ± 8 days.



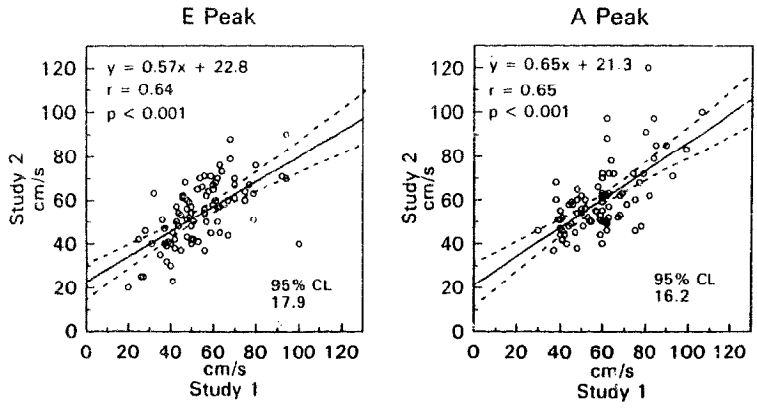


Figure 3. Test–retest comparison of values for early diastolic (E Peak) and late diastolic (A Peak) Doppler filling velocities.

range of "almost perfect reliability," and the 95% confidence interval of change had a width of 4.5 U. However, linear and intraclass correlations of replicate determinations of E velocity and A velocity were poor (Table 1, Fig. 3) with wide confidence intervals for these measurements, particularly for the calculated E/A ratio. In contrast to left ventricular mass, the width of the 95% confidence interval (0.32) determined for intraobserver variability was substantially less than that (1.5) for temporal variability.

Effects of study site, quality and age. There were no intercenter differences (analysis of variance, p = NS) in percent error of any echocardiographic measurement or in coded echocardiographic quality (average 2.9 ± 1.1). However, echocardiograms with quality grades 1 to 2 had greater left ventricular mass error (18 ± 11%) than did grade 3 to 4 studies (12 ± 9%, p = 0.04). Moreover, the average study quality of 2.5 ± 1.5 for patients ≥60 years old (average 67 ± 5, n = 26) was worse than study quality score (3.3 ± 0.9, p = 0.007) for patients ≤45 years old (average 41 ± 3, n = 25).

For patients ≥60 years old, the width of the confidence interval for left ventricular mass was increased to 62.8 g, and the intraclass coefficient of correlation was decreased to 0.82. In contrast, for patients ≤45 years old the width of the confidence interval for left ventricular mass was 46.6 g, and the intraclass coefficient of correlation was 0.91.

On stepwise multivariate regression analysis, the magnitude of difference in left ventricular mass between sequential studies was affected independently by study quality (p = 0.096, F = 2.85), and height (p = 0.117, F = 2.52)—age and weight did not meet the 0.15 significance level for entry into the model. Analysis of determinants of the magnitude of change in the components of left ventricular mass measurement showed that variation of left ventricular diastolic dimension was independently predicted by study quality (p = 0.040, F = 4.37) and age (p = 0.057, F = 3.75); height and weight did not meet criteria for entry into the model. For interstudy difference of left ventricular posterior wall and ventricular septum thickness, no variable met the 0.15 significance level for entry into the model. In turn, multiple regression analysis of the determinants of study quality showed that age (p = 0.043, F = 4.22) and weight (p = 0.098, F = 2.81) were both independently predictive; height did not meet the 0.15 significance level for entry into the model.

Discussion

Despite obtaining intraclass correlation within the range considered to represent excellent reliability, the width of the 95% confidence interval for left ventricular mass change of 59.0 g exceeds average decreases in left ventricular mass noted in echocardiographic studies of left ventricular mass regression with antihypertensive drugs. Because the width of the 95% confidence interval for left ventricular mass determined from temporal variability is no less than that for intraobserver variability, physiologic variation and differences in echocardiographic acquisition technique are likely secondary in importance to reader variability.

Additionally, despite the importance of diastolic dysfunction in the functional status of patients with hypertension, the reproducibility of peak early and late diastolic filling velocities was even worse than that of structural left ventricular measurements with echocardiography. In contrast to left ventricular mass, physiologic or technical acquisition variability are of greater importance than reader variability, because the width of the 95% confidence limits of the E/A ratio are much less for intraobserver than temporal variability.

In a meta-analysis of 109 published left ventricular mass regression studies comprising 2,357 patients (5), the average absolute reductions in left ventricular mass ranged from −21 g with diuretics (95% confidence interval [CI] −6 to −49 g) to −45 g with angiotensin-converting enzyme inhibitors (95% CI −23 to −66 g). Hence, in individual patients, the variability of echocardiography for the measurement of left ventricular mass would make it difficult to detect changes that could be expected during antihypertensive therapy.

Moreover, relatively poor study quality, even in echocardiograms that were considered to be readable, adversely affected the test–retest reliability for measurement of left ventricular mass, and age as well as weight were important determinants of poor study quality. Hence, in elderly or obese, or both, patients, and in other patients with echocardiograms considered techni-

cally suboptimal but still interpretable, the ability to detect treatment differences is even less.

Multicenter trials offer the advantage of larger numbers of patients and the possibility of more generalizable findings than might be obtained in single-center studies of smaller numbers. However, it has been suggested (30) that homogeneity of echocardiography may be virtually impossible to obtain in multicenter studies, thus increasing the technical limitations of echocardiography in the measurement of left ventricular mass. In contrast, the present study shows that uniformity of study quality can be achieved in multicenter trials. Nonetheless, we documented that study quality is an important determinant of temporal variability in left ventricular mass measurement.

Previous studies. The reproducibility of echocardiography for measurement of left ventricular mass has been studied utilizing a variety of study designs and statistical methods (16,31–35). Although important information has been generated on interobserver and intraobserver variability, beat-by-beat variability and on the temporal (test–retest) variability in normal subjects, the value by which left ventricular mass must change to exceed methodologic variability on sequential examination in hypertensive patients within a multicenter study has not been reported. On serial M-mode and two-dimensional echocardiographic evaluation in eight normal subjects (16), the mean difference for left ventricular mass over three serial examinations was 18.5 ± 13 g, in contrast to 25 ± 23 g over two examinations in the present study. In another study (36) the standard deviation of repeat measurements of left ventricular mass in a single center study of normal subjects was 30 g, which would approximate 95% confidence intervals of 60 g for a single normal subject.

In contrast to previous work, the present study evaluated patients with hypertension, many of whom had left ventricular hypertrophy. Moreover, patients were studied at multiple sites and were of varying echogenicity.

Two-dimensional echocardiography may be more reproducible than M-mode for measuring left ventricular mass in normal subjects (16,34) and in patients with a distorted left ventricular contour (15). However, it has not been demonstrated that two-dimensional echocardiography is superior to two-dimensional targeted M-mode echocardiography in the measurement of left ventricular mass in hypertension patients of varying echogenicity and in multiple centers where differences in equipment and personnel may affect study quality. Difficulties in contouring the endocardium in still-frame images, obtaining "true" long-axis measurements and in defining the epicardial border of the left ventricular free wall pose substantial difficulties to the use of two-dimensional echocardiography for left ventricular mass measurement, particularly in patients who are not optimally echogenic. Hence, in one large multicenter study the feasibility and reliability of two-dimensional measurement of left ventricular mass was substantially less than that of two-dimensional targeted M-mode echocardiography (Gardin J, personal communication, January 1994). It remains to be proved that the test–retest reliability of two-dimensional echocardiography would be sufficient in clinical practice to permit its utilization to monitor left ventricular mass in individual patients.

Limitations of the present study. The study design differed from some aspects of clinical practice in that technicians performing the studies were specifically trained and monitored by a central laboratory in those facets of echocardiographic technique specific to acquisition of studies adequate for left ventricular mass determination. Moreover, to minimize technical variability, the same technician, echo machine and reader were used for the initial and repeat examinations. However, these features might be expected to decrease temporal variability. Hence, in clinical practice the 95% confidence interval of left ventricular mass might be even greater than 59 g.

Advantages of the present study. The present study was designed to detect the variability of the complete "system" for left ventricular mass measurement by echocardiography, in which its components (i.e., patient, ultrasonograph, technician, image analysis unit, reader) were held constant during repeat testing over an interval in which true change in left ventricular mass was improbable. Several features of this study are consistent with clinical practice in that hypertension patients with a wide range of echo image quality, body weight and age were evaluated, rather than echogenic normal volunteers in whom smaller left ventricular mass and the likelihood of better image quality could result in underestimation of absolute variability of left ventricular mass.

Clinical implications. Although left ventricular hypertrophy is an important pathophysiologic manifestation of hypertension, the cost of obtaining even yearly echocardiograms to monitor the effects of antihypertensive therapy would be enormous. The reported prevalence of left ventricular hypertrophy in patients with hypertension varies from 7% to 45% based on patient selection. Moreover, elevated left ventricular mass may confer risk even at values lower than the partition value selected to define left ventricular hypertrophy (8,9).

Assuming an average cost for echocardiography of $500, obtaining an annual echocardiogram in ~50 million Americans with hypertension to measure left ventricular mass and follow up the effects of pharmacologic or nondrug therapy would translate to >$25 billion in annual costs. Even restricting echocardiography to an assumed 20% of patients with left ventricular hypertrophy would cost >$5 billion yearly. Moreover, because left ventricular mass would have to decrease by >59 g, an amount generally greater than the decrease observed with antihypertensive therapy, two-dimensional targeted M-mode echocardiography would not be capable of detecting regression, or the lack thereof, of left ventricular hypertrophy.

Although problematic for the evaluation of a small cohort, particularly in clinical practice where n = 1, echocardiography is still a useful technique in appropriately powered research studies. The width of a population confidence interval decreases proportionately with the inverse of the square root of the sample size. Hence, although the confidence interval for change in left ventricular mass for a single patient is 59 g, in 50 patients it would be $59\ g/\sqrt{50}$ or 8.4 g.

Other techniques for measurement of left ventricular mass. Studies of left ventricular mass utilizing magnetic resonance imaging (37–39) have shown that it has promise in substantially lowering the confidence limits of left ventricular mass measurement. Additionally, three-dimensional echocardiographic reconstruction may also provide comparable improvement (40). Hence, even though these may be more expensive at present than two-dimensional targeted M-mode echocardiography, their greater reproducibility may make them suitable for research studies where the greater cost could be offset by the savings from recruiting and studying fewer patients.

Whether any technique should be used to monitor left ventricular mass as part of the clinical management of hypertension will depend not just on its accuracy but also on whether selection of a therapy based on reduction of left ventricular mass confers benefit over that achieved by effects on blood pressure and clinical factors such as carbohydrate tolerance or lipid metabolism.

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