Recommendations Concerning Use of Echocardiography in Hypertension and General Population Research

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SUMMARY Use of echocardiography to quantify left ventricular structure and function requires standardization of recording conditions and techniques, accurate machine calibration, and definition of requirements for measurable images. Measurement of left ventricular muscle mass should use M-mode, two-dimensional, or three-dimensional echocardiographic methods that have been anatomically validated to maximize accuracy and comparability of results among studies. Body size and sex influence ventricular muscle mass sufficiently to be taken into account for clinical and research purposes, while age and physical activity are of less certain importance. Echocardiographic studies have clarified the prevalence of left ventricular hypertrophy in hypertensive patients and the effect of blood pressure during normal activity on left ventricular muscle mass, and they have provided data suggesting that left ventricular hypertrophy is a major cardiac risk factor in hypertensive and general populations. Further research is needed to obtain definitive results in these areas, to track the hitherto elusive transition from functionally compensated cardiac hypertrophy to congestive heart failure, and to determine the degree and selectivity of beneficial cardiac effects of antihypertensive treatment. Three-dimensional echocardiographic reconstruction and Doppler measurement of intracardiac blood flow and systemic hemodynamics are likely to extend the usefulness of echocardiography for hypertension and general population research.

Key Words • echocardiography • epidemiology • hypertension • left ventricular hypertrophy

DURING the past decade considerable progress in elucidating the role of the heart in human hypertension has been achieved with quantitative echocardiographic methods of studying left ventricular (LV) structure and function.1-5 The present workshop brought together researchers in hypertension, cardiology, and epidemiology to review critically the present status of echocardiographic methods in hypertension and general population research. Manuscripts in this supplement to Hypertension provide new research findings and review the current status of echocardiographic methods of evaluating left ventricular hypertrophy (LVH) and function. This concluding paper summarizes recommendations developed by the workshop participants concerning use of echocardiography in hypertension and general population research.

Echocardiographic Technique

Use of echocardiography for quantitative measurements requires optimization of echocardiographic image quality, establishment of technical requirements for measurability of echocardiograms, and attention to factors enhancing reproducibility (Table 1). Since delineation of the heart from the parasternal window is improved in most patients by use of the left decubitus position, this procedure should be adopted uniformly. Wedges of firm foam rubber made to rotate patients by specified amounts (e.g., 30 degrees, 45 degrees, etc.) are useful, and use of the same wedge in each patient during serial studies facilitates replication of recording conditions. Removing a semicircular cutout from the side of the mattress, as described by Schiller,6 improves access to the cardiac apex for two-dimensional (2D) and Doppler echocardiography. With patients in the left decubitus position, performance of the study by the sonographer’s left hand while the echocardiograph is adjusted with the right hand provides the best combination of acoustic access and patient comfort.

Quantitative echocardiography depends for its accuracy on correct calibration of the examining equipment. Tissue phantoms are available from several sources (e.g., American Institute of Ultrasound in Medicine, Bethesda, MD, USA; RMI, Madison, WI, USA) that permit calibration in both vertical and horizontal axes and have finely spaced wires for calculation of axial and lateral resolution. The importance of objective calibration of each machine at installation and at regular intervals thereafter is indicated by Schiller’s observation6 that differences of appreciable degree in measurement accuracy exist between brands of echocardiographic equipment, and our finding that errors can develop over time in the accuracy of one (videotape or stripchart) method of recording but not the other.

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Table 1. Recommendations Regarding Echocardiographic Technique for Measurement of Left Ventricular Muscle Mass

| Instrument calibration, Calibrate against phantom at installation and at regular intervals thereafter. |
| Echocardiographic performance: Standardize and record decubitus position. Record images in held expiration. |
| Location of imaging planes: Independent M-mode: Below mitral leaflet tips on long-axis sweep, maximum dimension on transverse scan. 2D guided M-mode: From short-axis view with correct angulation of short-axis plane defined in long-axis view. 2D echo: Define correct orientation of short-axis and apical views by use of 90-degree orthogonal planes. |
| Recognition of measurable images: M-mode: Dominant lines with correct motion representing interfaces for at least 5 mm (0.10 second). 2D echo: Visualization of complete interface in motion with persistence in stop-frame mode. Enhancement of reproducibility: Use three or more cardiac cycles. Record imaging window location and patient's position. Independent readings by two to three investigators. |

Orientation of Imaging Planes

Performance of echocardiography for quantitative research requires meticulous orientation of imaging planes. Identification of the correct view for LV measurements—at or just below the tips of the mitral leaflets—is best achieved for independent (i.e., non-2D guided) M-mode studies by use of base-to-apex and transverse scanning techniques. Finding that the distance is similar from chest surface to the interventricular septum and to the anterior wall of the aorta helps to confirm correct transducer location, while abrupt posterior motion of the interventricular septum during systole indicates that too low a window has been chosen. While 2D guidance of the M-mode beam is theoretically optimal, this has not been shown to improve the accuracy or reproducibility of LV measurements. This disappointing result may be due to the tendency to begin 2D parastomal imaging from the window that permits most complete visualization of the left ventricle in long-axis view, which is likely to be a relatively low window, particularly when a 2D transducer with a large contact area is used.

Proper orientation of 2D imaging planes requires attention to their correct placement in the orthogonal plane. For example, the interspace used for the parasternal long-axis view needs to be selected so that the short-axis view obtained by rotating the transducer 90 degrees would be perpendicular to the interventricular septum and posterior LV wall at the level of the papillary muscle tips. Similarly, the LV apex should be centered at the top of the fan in both two- and four-chamber apical views to ensure correct positioning of the full long-axis length. Development of transducers that permit rotation of the imaging plane while keeping the transducer housing stationary represents a theoretically optimal system with cine-loop capability, in which a single transducer 90 degrees would be perpendicular to the interventricular septum can often be recognized by their moving closer to adjacent septal interfaces in systole and away from them in diastole, contrary to the physiologic pattern of interfaces representing contracting and relaxing muscle.

Enhancing Reproducibility of Measurements

Several aspects of echocardiographic technique, in addition to those outlined above, enhance reproducibility. These include recording images during held expiration on each study, making measurements on three or more cardiac cycles, and recording details of the examination, including the degree of patient inclination and the chest wall location of the window used for each view. Independent readings by two or three investigators appear to enhance reproducibility significantly for relatively small-scale studies, while inclusion of the entire population, made possible by use of a single experienced reader, is preferable in large-scale studies.

Measuring Left Ventricular Muscle Mass

An optimal method for measurement of LV muscle mass should be accurate, safe, easily repeatable, inexpensive, and applicable to all patients. Methods have been developed that use M-mode echocardiographic data to fulfill all these conditions (Table 1). Three-dimensional (3D) echocardiographic reconstruction promises to be even more accurate but is currently too complex for routine application. The most important feature of these methods is that each has been validated by comparison with necropsy findings to give anatomically correct estimates of LV muscle mass. Therefore, all provide roughly interchangeable results; in contrast, other methods either introduce random scatter into the results or cause systematic overestimation or underestimation of LV mass.

M-Mode Echocardiography

The first method of LV mass determination to be validated, the Penn method,7 was developed empirically by examination of alternative methods of measuring LV dimensions in combination with different geometric models. The thickness of endocardial interfaces is excluded from wall thickness measurements and included in chamber dimensions by the Penn convention (Figure 1).

The more recent recommendations of the American Society of Echocardiography20 to make all measurements from leading edge to leading edge (see Figure 1) have been widely adopted, but their use in the standard cube function formula results in systematic overestimation of necropsy LV mass.15,21 Recent publication of a formula for correction of this error,19 however, makes it possible to use American Society of Echocardiography measurements for accurate determination of LV muscle mass. LV mass measurement by M-mode echocardiography has reasonably good accuracy, with standard deviations between completely blind ed echocardiographic measurements and necropsy LV mass of 25-30 g under research conditions.2,12 and approximately 40 g under more arduous clinical circumstances1; variability between unpaired readings of repeat studies on the same patient is also approximately 25 g.12 M-mode measurements for accurate determination of LV muscle mass. LV mass measurement by M-mode echocardiography has reasonably good accuracy, with standard deviations between completely blind ed echocardiographic measurements and necropsy LV mass of 25-30 g under research conditions.2,12 and approximately 40 g under more arduous clinical circumstances1; variability between unpaired readings of repeat studies on the same patient is also approximately 25 g.12 M-mode
Anatomically validated methods of measuring LV mass

M-mode
- Penn convention\(^7\)\(^{15,15}\)
- American Society of Echocardiography with regression correction\(^15\)\(^{,22}\)

2D
- Area-Length\(^8\)\(^{,26}\)
- Prolate ellipsoid\(^6\)\(^,17\)

Standardization of LV muscle mass
- Factors to take into account: body surface area, sex, age
- Upper normal limits of LV mass index
  - Penn\(^6\)\(^,45\)
    - Men, 134 g/m\(^2\); women, 110 g/m\(^2\)
    - Men, 131 g/m\(^2\); women, 100 g/m\(^2\)
  - Truncated ellipsoid 2D\(^24\)
    - Men, 110 g/m\(^2\); women, 90 g/m\(^2\)

Validated methods of LV functional assessment\(^29\)\(^{-31}\)

- Fractional shortening\(^29\) = \(\frac{LVIDd - LVIDs}{LVIDd}\)
- \(Vcf31\) = \(\frac{\text{Fractional shortening}}{\text{Left ventricular ejection time}}\)
- \(\text{End-systolic stress}\(^{30}31\) = \(0.334 \times LVIDs \times SBP\)
  - \(\text{PWTs} \times \left(1 + \frac{\text{PWTs}}{LVIDs}\right)\)
  - \(1.35 \times LVIDs \times \text{end-SBP}\)
  - \(4 \times \text{PWTs} \left(1 + \frac{\text{PWTs}}{LVIDs}\right)\)

2D = two-dimensional; LV = left ventricular; LVIDd = end-diastolic LV internal dimension, LVIDs = end-systolic LVID; Vcf = velocity of circumferential fiber shortening; SBP = systolic blood pressure; PWTs = end-systolic posterior wall thickness.

determination of LV mass is not possible in 10 to 20% of unselected patients,\(^23\)\(^,24\) and overestimation of LV mass occurs in the presence of LV aneurysm or other causes of distorted chamber geometry.\(^6\)\(^,16\)\(^,25\) The established accuracy and variability of M-mode measurements as well as the roughly predictable percentage of patients in whom LV images are adequate for quantitation\(^23\) need to be taken into account in study design and calculation of sample size.

Two-Dimensional Echocardiography

Anatomically validated methods of LV mass determination use either a short-axis area–long-axis length method\(^16\)\(^,16\) or a truncated ellipsoid model.\(^17\) The measurements and formulas needed to measure LV muscle mass by these methods are illustrated in the contributions by Reichek\(^26\) and Schiller\(^6\) in this supplement. These methods improve accuracy of measurements in patients with distorted ventricular geometry\(^16\)\(^,25\) and may increase the percentage of patients in whom LV mass may be measured.\(^27\) The recent publication of LV mass values in a moderate number of clinically normal subjects provides tentative normal limits to use for recognition of LVH by 2D echocardiography.\(^28\) Whether 2D echocardiography is more accurate than M-mode echocardiography for measuring the mass of symmetric ventricles, such as occur in patients with hypertension, has not been established.\(^22\)\(^,26\) Research is needed to answer these questions and to establish the reproducibility of 2D measurements as well as their sensitivity and specificity for detection of LVH and dysfunction in hypertension. Standardization of methods for 2D echocardiographic measurement among laboratories is also needed before quantitative use of this technique can reach its full potential.

Related Functional Measurements

Validated methods for assessing the functional impact of LVH include measurement of systolic fractional shortening of the LV minor axis\(^29\) and end-systolic meridional wall stress.\(^30\)\(^,31\) Inferences about the contractile state of the LV myocardium can be made from the relationship between fractional...
shortening and end-systolic stress. Whether 2D echocardiographic methods of assessing LV fractional shortening and wall stresses in multiple planes provide incremental information about cardiac mechanics in patients with hypertension beyond that obtained from simpler M-mode methods needs to be established.

Standardization of Measurements
Several factors influence LV muscle mass to a sufficient degree to be worth taking into account for research and clinical purposes. Most important to these are body size and sex. Body size may be taken into account by indexing LV mass by weight or body surface area, but the latter approach appears slightly preferable. Even after indexation for body size, LV mass remains substantially higher in men than in women, making it essential to use sex-specific partition values for detection of LVH. Increasing subject age has been reported to influence LV mass in some, but not other studies of adult populations. Although the effect of age appears to be less important than sex on body size, it may be appropriate to use age-stratified norms for some purposes, particularly studies of young adult women. In the pediatric age range, body size again seems to be most important in defining normal limits of LV anatomic measurements, but further information is needed concerning possible independent effects of age or sexual maturation.

Even after the most important known factors are taken into account, LV mass varies widely even among apparently normal subjects. Further research is needed to determine whether additional factors contribute to this variability, including blood pressure during normal activity, physical conditioning due to occupational or recreational exercise, or genetic factors.

Hypertensive Cardiac Hypertrophy
Echocardiographic studies in Framingham have shown elevated blood pressure to be associated with both concentric and eccentric patterns of hypertrophy. Other studies have revealed the prevalence of increased LV muscle mass to differ markedly among hypertensive patient populations, ranging from just under 20% in employed patients with uncomplicated systemic hypertension to more than 80% in hospitalized patients with moderate to severe hypertension — mostly corresponding to Stage 2 of the World Health Organization classification. Wall thicknesses and other LV measurements are generally less sensitive than calculated LV muscle mass in detecting hypertensive cardiac hypertrophy. Although the severity of hypertensive cardiovascular disease appears to be the most important cause of this variation, further research is needed to clarify the role of other factors, including the age, sex, and race of patients.

Available studies suggest that M-mode echocardiography using sex-specific upper normal limits for LV mass index is threefold to as much as eightfold more sensitive than standard electrocardiographic criteria for detection of hypertensive LVH. Preliminary calculations suggest that this greater sensitivity makes echocardiography the more cost-effective of these two methods, but more data are needed before this conclusion is definitively established. It may be possible to reduce the full direct and indirect costs of quantitative M-mode echocardiography — including equipment purchase and maintenance, space, study performance, and measurement and analysis of data by qualified investigators — to less than $100 per subject, but data are needed on this point as well. Echocardiographic studies have revealed a clear linear relationship between the severity of LVH and the prevalence of the so-called strain pattern of electrocardiographic repolarization abnormality, whereas such a relationship is not clearly seen with LVH criteria in which QRS voltage abnormalities must be present. Since it is most important to detect severe degrees of LVH, consideration should be given to the use of the strain pattern of repolarization abnormalities as a sign of LVH without requiring that other electrocardiographic findings be present.

Hypertrophy and Blood Pressure
In contrast to early studies, recent reports have found only weak relationships between casual blood pressure level and indices of LVH. Although LV mass has been more closely related to blood pressure measured at home, during normal activity, and during exercise, the correlation coefficients have generally been 0.60 or lower, suggesting that only 35% or less of variability in LV mass can be explained by blood pressures. Such a modest impact may be due in part to suggested differences in blood pressure-mass relations in patients with and without LVH. Clarification of other environmental and genetic factors that influence LV muscle mass may reveal closer relationships between blood pressure and the heart. Conversely, ambulatory monitoring of blood pressure for hours or more may be necessary to obtain representative and reproducible readings (F. Halberg, personal communication) and to take into account the patterns of blood pressure variation.

Another explanation for the wide range of cardiac findings in patients who have similar blood pressures may be that hypertrophy is directly stimulated by some but not by other biochemical mediators of hypertension. Preliminary evidence suggests that catecholamines but not the renin-angiotensin system may act in this way. Further research is needed to test the potentially important catecholamine hypothesis of hypertensive cardiac hypertrophy.

Clinical Implications
A major reason for widespread interest in the use of echocardiographic methods in patients with hypertension has been the expectation that they would be more useful than previously available techniques for predicting the risk of complications and for studying the progression and regression of hypertensive cardiac involvement.

Predictive Value of Echocardiography
Preliminary reports from Framingham and Cornell indicate that increased echocardiographic LV mass, measured by anatomically validated M-mode methods, is a strong predictor of cardiovascular morbid events during prospective follow-up, independent of conventional risk factors. This has been established both in a clinical population of male patients with initially uncomplicated essential hypertension at Cornell and in the meticulously studied Framingham general population sample. These findings have potentially important implications for research and clinical practice because the presence of either LVH or low normal LV mass in persons with borderline or mild established hypertension might identify polar groups that would receive substantial or conversely negligible benefit from antihypertensive treatment. Furthermore, clinical trials of the efficacy of alternative antihypertensive therapies in patients with LVH would provide a high enough incidence of expected morbid events to permit detection of significant differences between the beneficial effects of different agents. Further research is needed to establish the degree to which the presence or absence of LVH segregates hypertensive patient groups at high and low risk of subsequent morbid events and to determine whether this segregation is similar in all hypertensive subgroups or differs between subsets defined by age, sex, race, blood pressure level, or biochemical mechanisms of hypertension.
Hypertensive Hypertrophy and Dysfunction

Although echocardiography is ideally suited to track the evolution of hypertensive cardiac involvement, only limited longitudinal data are yet available on development of LVH in patients with untreated borderline or mild systemic hypertension.57,58 No study has followed objective measurements of LV function prospectively from the state of normal or supennormal resting function usually found in hypertensive patients to the development of congestive heart failure, despite the great importance of defining the mechanisms by which hypertension leads to heart failure. Studies of the natural history of cardiac findings in patients with borderline hypertension and in these with mild essential hypertension who decline treatment as well as the unnatural history of the heart in treated hypertensive patients are also needed to develop means of identifying patients who will develop progressive cardiac involvement.

Regression of Hypertrophy and Dysfunction

Numerous echocardiographic studies of regression of hypertensive LVH in response to antihypertensive treatment have been performed.59,60 Studies have shown a reduction in LV mass when blood pressure is lowered substantially by most classes of antihypertensive drugs, including diuretics in a highly selected group of patients.61 Whether different types of drugs cause more or less regression of LVH for a given degree of antihypertensive effect remains controversial, whether systematic data exist as to whether pretreatment patient or cardiac characteristics affect the induced regression of hypertrophy. Similarly, it is unknown whether regression of hypertensive cardiac hypertrophy benefits either intrinsic myocardial state or the clinical course of patients.

Research to answer these questions needs to take into account several aspects of echocardiographic methods emphasized in this supplement. Patient position and other pertinent details of technique62 need to be reproduced precisely in serial studies. Tracings on all patients should be coded and read blindly in random order so that clues to treatment status that would be obtained by paired reading of studies on individual patients (e.g., heart rate changes induced by β-blockers or verapamil) cannot bias results. Population size should be based on prior considerations, with equality of numbers in age strata is important to study design. Initial studies suggest that the greater sensitivity of echocardiography than electrocardiography for detection of LVH,43,44 makes it the more cost-effective method; the information provided by echocardiography about myocardial and valvular function as well as the size of other heart chambers is an additional bonus.

Available data suggest that echocardiographic measurement of cardiac structure and function in selected longitudinally followed population cohorts will provide important information about the evolution and natural history of a variety of forms of heart disease. Most important will be elucidation of the promising role of LVH as a strong predictor of cardiovascular morbidity and mortality.55,56 Clinical67-69 and necropsy59 data suggest that LVH is likely to be a risk factor for subsequent development of a wide spectrum of cardiovascular disease, including clinically recognizable coronary disease events, heart failure, vascular disease of cerebral and systemic circulations, and renal failure. As suggested by Schoenberger,70 development or regression of echocardiographic LVH may serve as a useful intermediate endpoint in selected studies. Based on these considerations, echocardiography should be seriously considered for studies of unselected populations as well as large clinical trials in hypertensive patients.

New Echocardiographic Techniques

Three promising methodologies fall into this category: 3D cardiac reconstruction, Doppler assessment of intracardiac blood flow velocities and hemodynamics, and measurement of LV diastolic function.

Three-Dimensional Echocardiographic Reconstruction

Several research groups have developed computer-assisted methods of utilizing 2D echocardiographic images in multiple planes to reconstruct LV geometry in three dimensions and measure volumes accurately by comparison with a variety of reference standards.70-72 McCaughhey et al.73 have recently presented preliminary evidence that LV muscle mass can be measured accurately by one such technique. All these methods are extremely complex and time-consuming, precluding their present use in large-scale studies, but refinements are anticipated. The standard deviation of the correlation between echocardiographic and necropsy LV mass estimates may be reduced to perhaps 10-15 g18 from 25-30 g with anatomically validated M-mode and 2D methods.72

Doppler Echocardiography

Rapid progress has been made in recent years in perfecting technology for Doppler echocardiography and developing methods for its clinical application. Several methods combining Doppler and imaging echocardiography show potential for precisely measuring cardiac output and other hemodynamic parameters.77,78 Research is needed to verify the ability of Dop-
ler methods to assess hemodynamics precisely and repeatedly in unselected subjects under more natural conditions than prevail during invasive studies. Properly validated Doppler methods could help solve many unsettled controversies in the hemodynamics of hypertension.

Doppler echocardiography is already suitable for assessment of other aspects of cardiac performance in hypertension. In this issue Gardin et al. provide initial information about intracardiac blood flow velocity in systole and diastole in patients with hypertension. The important effects of age noted by Gardin et al. in both hypertensive and normotensive subjects emphasize the need to standardize Doppler measurements for age, sex, and other relevant variables or to include fully matched normal control subjects in order to allow use of this technology in hypertension research.

Assessment of Diastolic Function

Echocardiographic methods of assessing LV diastolic function have documented abnormalities in patients with LVH of various causes as well as coronary artery disease. Recent studies utilizing radionuclide-based methods have revealed a high prevalence of diastolic function abnormalities in patients with systemic hypertension. These appear to be a manifestation of pathologic LVH because similar degrees of physiologic LVH due to aortic valve disease have been associated with normal LV diastolic function. As emphasized by Smith and colleagues, diastolic dysfunction may be an even more sensitive marker than LVH of hypertensive cardiac involvement. Further research is needed to test this hypothesis and to determine whether detection of diastolic LV dysfunction has the same value for prediction of subsequent cardiovascular morbidity as recognition of LVH.

Clinical Implications

The above recommendations with regard to echocardiographic technique and use of validated methods of measuring LV mass and function should be applied to clinical use of echocardiography in patients with hypertension. Routine performance of echocardiography in all patients with hypertension is not recommended at present in view of the substantial cost involved. If preliminary data about the value of echocardiography to predict cardiovascular morbidity in patients with mild (Stage I) hypertension are borne out in further studies, however, it may be less expensive to identify low risk patients by this technique than to subject them to long-term treatment with a risk of side effects. At present, selection of hypertensive patients for echocardiographic examination remains a matter of clinical judgment. A particularly high yield of information may be expected in patients with evidence of cardiac abnormality (due to hypertension or coexistent heart diseases) by chest roentgenogram, electrocardiogram, or auscultation and in patients in whom blood pressure measurements and clinical estimation of the severity of hypertensive cardiovascular disease are discordant.

Acknowledgments

We thank Daniel D. Savage, M.D., Ph.D. for his critical reading of this manuscript and Miss Virginia Burns for her assistance in its preparation.

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Hypertension. 1987;9:II97
doi: 10.1161/01.HYP.9.2_Pt_2.II97

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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