Although hypertension is diagnosed by the clinical sign of elevated blood pressure, it takes its importance from the increased likelihood of cardiovascular morbidity and mortality events to which it predisposes. Over the past decade, noninvasive methods of assessing the structure and function of the heart and arteries have made it possible to detect pathological transformations or "preclinical disease" in the form of cardiac and vascular hypertrophy and atherosclerosis. The aggregate risk of stroke, heart attack, and other cardiovascular morbidity and mortality events to which it predisposes is reduced by antihypertensive therapy, but treatment of large numbers of patients is needed to prevent a modest number of events, and many patients suffer complications despite intervention. This suggests that the intensiveness and type of treatment given to hypertensive patients may not be well matched to their individual levels of risk and to the mechanisms that predispose to morbid events. One potential approach to resolving this problem is to use noninvasively detectable evidence of "preclinical" hypertensive disease to identify patients at especially high risk and need for intensive treatment among the large number of adults with elevated arterial pressure in the clinic. In this article, we will use the findings in individual patients to introduce specific changes in the heart and vasculature that are of known or likely prognostic relevance and to integrate them into a conceptual framework that can be used to help inform aspects of patient care and future research.

**Patient Presentations**

**Patient 1**

The first patient was a 59-year-old male engineer with a 20-year history of hypertension that had been intermittently treated before he underwent comprehensive evaluation in April 1976. His height was 1.78 m and his weight was 88.9 kg, yielding a body surface area of 2.07 m² and body mass index of 28.1 kg/m². At that time his clinic blood pressure was 142/104 mm Hg, his heart rate was 68 beats per minute, and there were grade II retinal changes. Serum creatinine was 106 mmol/L, total cholesterol was 6.23 mmol/L, and plasma renin activity was 2.4 ng/mL per hour on a salt-restricted diet.

Electrocardiogram (ECG) revealed T wave inversions in I, aVL, and V₅; the Cornell voltage combination of SV₅ + RaVL was 3.0 mV, exceeding the gender-specific partition value of 2.8 mV used to identify left ventricular (LV) hypertrophy in a man, whereas hypertrophy was not detected by Sokolow-Lyon voltage (SV₃ + RV₅ = 3.2 mV) or other conventional criteria. M-mode echocardiogram revealed interventricular septal (IVSd) and posterior wall (PWTd) thicknesses of 1.6 and 1.5 cm, respectively, and LV internal dimensions at end diastole (LVIDd) and end systole (LVIDs) of 5.3 and 3.1 cm. From these primary echocardiographic measurements, LV mass was calculated to be 216 g/m² of height, with a ratio of end-diastolic LV wall thickness and discrete atheromas noninvasively. Carotid wall thickness and lumen diameter parallel similar ventricular dimensions in normotensive and hypertensive humans, indicating the presence of integrated patterns of cardiac and vascular adaptation to hypertension. Furthermore, peripheral atherosclerosis is associated with higher ventricular mass and a more adverse 24-hour blood pressure profile. In summary, noninvasive visualization of the heart and blood vessels reveals a spectrum of patterns of anatomic and functional adaptations that are related to the pathophysiology and prognosis of hypertension. (Hypertension. 1994;23[Part 1]:802-809.)

**Key Words** • hypertension • hypertrophy • prognosis • atherosclerosis
thickness to chamber radius (termed relative wall thickness) of 0.57. Each of these values exceeded upper normal limits for independent M-mode echocardiograms of 125 g/m², 51 g/m², and 0.45, respectively. End-systolic meridional wall stress was 39×10⁶ dyne/cm², endocardial fractional shortening was 41.5% (99% of predicted normal for observed wall stress), and LV fractional shortening calculated at the midwall was 14% (76% of the value predicted for end-systolic stress).

This patient was treated with 80 mg propranolol twice daily and subsequently transferred his care to an outside physician. In August 1982, 52 months after his initial evaluation, he developed severe chest pain and manifested ECG signs of a massive myocardial infarction, to which he rapidly succumbed.

Patient 2

The second patient was an asymptomatic 50-year-old man with intermittently treated, clinically uncomplicated essential hypertension. At the time of his initial evaluation in 1986, he was 1.73 m tall, weighed 77.6 kg, and had a body surface area of 1.93 m² and body mass index of 26.1 g/m². Serum creatinine was 97 mmol/L, total cholesterol was 5.28 mmol/L, and plasma renin activity was 1.2 ng/mL per hour. On arrival at the echocardiography laboratory, his blood pressure was 180/104 mmHg, with a heart rate of 78 beats per minute. The ECG showed increased SV₃+RV₃ (3.6 mV) compatible with LV hypertrophy. The echocardiogram at that time revealed an IVSd of 1.3 cm, PWTd of 1.1 cm, LVIDd of 4.8 cm, and LVIDs of 3.4 cm. These primary echocardiographic measurements yielded a calculated LV mass of 114 g/m² and 50 g/m²—both within the normal range for an adult male—with an elevated relative wall thickness at 0.46. Fractional shortening of 29% was near the lower limit of normal.

In 1991, at age 55, the patient underwent treadmill exercise testing while off antihypertensive medication as part of a research study, which revealed less than 1 mm (0.1 mV) ST segment depression at maximal exercise (a negative response to exercise) (Fig 1), but when the ST–heart rate slope was calculated it was found to be 2.6 μV per beat per minute, in a range compatible with mild obstructive coronary artery disease (Fig 2). At restudy in April 1992, his weight had decreased to 75.2 kg, with a body surface area of 1.88 m² and body mass index of 25.2 kg/m². Blood pressure on medication in the echocardiography laboratory was 159/99 mm Hg. The follow-up two-dimensionally guided M-mode echocardiogram revealed an IVSd of 1.1 cm, PWTd of 1.0 cm, LVIDd of 4.5 cm, and LVIDs of 3.1 cm, with a fractional shortening of 31%. LV mass index fell well within the normal range at 87 g/m², and the relative wall thickness of 0.44 exceeded the upper normal limit of 0.43 for two-dimensionally guided M-mode recordings. Carotid ultrasonography, performed for the first time, revealed discrete atheromas 2.9 mm in thickness in the right carotid bulb (Fig 3) and 1.2 mm in thickness in the left carotid bulb. At present he continues to be free of cardiovascular symptoms or complications and is cur-
Detection of Preclinical Hypertensive Disease

The two patients we have briefly presented illustrate the ability to evaluate the cardiovascular system, which can now be applied to patients with hypertension. Abnormalities of cardiac and vascular structure and function can be detected by a number of different techniques, of which the most widely available and least expensive are forms of ultrasound. Two-dimensionally guided M-mode echocardiography can be used to visualize LV wall thicknesses and chamber diameter throughout the cardiac cycle (Fig 4, top). From these measurements it is possible to calculate LV muscle mass by formulas that have been anatomically validated in humans and experimental animals as small as rats. The same primary dimensions of LV wall thickness and internal dimension can be used to calculate the relative wall thickness of the chamber (wall thickness/chamber radius, a measure of the concentricity of ventricular geometry) and a variety of functional parameters, including fractional shortening of ventricular diameters at the endocardial surface or middle of the LV wall.

With incorporation of simultaneous measurements of blood pressure, it is possible to measure end-systolic stress, the most direct measure of myocardial afterload. LV mass and wall thicknesses can also be measured by anatomically validated two-dimensional echocardiographic methods.

Arterial structure and function can also be evaluated noninvasively by ultrasound in the carotid and other accessible arteries. Two-dimensional or B-mode imaging can be used to visualize discrete atherosclerotic plaques in the carotid bifurcation or other locations, as exemplified by findings in the second patient (Fig 3).

Prevalence and Prognostic Significance of Hypertensive Cardiac Hypertrophy

Although one might expect that the increased load imposed on the heart by arterial hypertension would consistently cause LV hypertrophy, this is not necessarily so. The first of our patients was one of the 48% of a large series of hypertensive patients in the initial report from Cornell who had increased LV mass for body size, and the second patient typifies the finding that LV mass is within the normal range in 60% to 85% of series studied more recently. The second patient participated in a more recent series of studies in which we demonstrated that the level of LV mass in hypertensive patients is better predicted by the level of blood pressure measured by ambulatory monitor during usual activities and by LV stroke volume than by conventional clinic blood pressures. Of interest, LV mass is best predicted by the level of systolic pressure, and relative wall thickness is best predicted by diastolic pressure. Other factors that make LV hypertrophy more...
FIG 4. Top, M-mode echocardiogram from a normal adult illustrating visualization throughout the cardiac cycle of the interventricular septum (IVST), left ventricular internal dimension (LVID), and posterior wall thickness (PWT) (from Devereux and Reichek7). Bottom, M-mode ultrasonic recording of the common carotid artery demonstrating its dynamic pulsation in response to varying intra-arterial pressure. Wall thickness and lumen diameter measurements are made at end diastole, the timing of which is identified by arrows showing lumen-intima and medial-adventitial interfaces that encompass the thickness of the carotid far wall.

likely at any given level of arterial pressure are obesity22,25 and increased dietary sodium intake.26 The first patient discussed and thousands of other individuals have provided the data necessary to show that increased LV mass is an exceptionally strong predictor of cardiovascular morbidity and mortality in patients with hypertension,27-28 members of the general population,29-30 and catheterized patients with or without obstructed large coronary arteries.31 In these studies high levels of LV mass were able to predict adverse outcomes either with the use of LV mass as a continuous variable or with partition values in the range of 116 to 125 g/m². The predictive ability of LV mass—especially for cardiovascular and all-cause mortality—was independent of and generally considerably stronger than that of blood pressure and other cardiovascular risk factors.28,30,31 Increased LV mass is equally predictive of adverse outcomes in women and men28-31 and in predominantly white27-30 or African-American31 populations. The ominous implication of LV hypertrophy in hypertensive patients is underscored by our finding that among our patients who developed angina, myocardial infarction, or other cardiovascular events during prospective follow-up, 55% of those with increased LV mass, including our first patient, but only 5% of those with normal LV mass died by the end of follow-up.28

The capacity to predict an adverse outcome is also shared by ECG manifestations of LV hypertrophy.32 However, the proportion of hypertensive patients in whom hypertrophy is identified is far lower by ECG (<5%20) than by echocardiogram (15% to 50%), and the prevalence of definite ECG LV hypertrophy may be as low as 1% in the general population.30 The sensitivity of the ECG for LV hypertrophy is particularly poor in obese or elderly individuals, who are at especially high risk for hypertension and its complications.33 As a result, echocardiography is a more efficient and, when prices are not excessive, cost-effective means of detecting LV hypertrophy than the ECG.34

Patterns of Left Ventricular Adaptation to Hypertension: Pathophysiology and Clinical Significance

Use of echocardiographic measurements to calculate relative wall thickness in addition to LV mass makes possible a more informative classification of LV geometric patterns.22,28,35 As shown in Fig 5, this approach allows patients with increased LV mass to be separated into those with concentric versus eccentric hypertrophy and patients with normal ventricular mass to be separated into those with concentric remodeling or normal ventricular geometry.

Studies from our laboratories, to which both of the present patients contributed data, have revealed that these geometric patterns are associated with distinctive pathophysiological and prognostic profiles12,22,28,35-37 (Table). Patients with concentric LV hypertrophy have substantially increased clinic and ambulatory pressures,
Pathophysiological and Prognostic Features of Patterns of Left Ventricular Geometric Adaptation to Hypertension

<table>
<thead>
<tr>
<th>Healthy Subjects</th>
<th>Normal Geometry</th>
<th>Concentric Remodeling</th>
<th>Eccentric Hypertrophy</th>
<th>Concentric Hypertrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting blood pressure</td>
<td>NI</td>
<td>↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Ambulatory blood pressure</td>
<td>NI</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Body mass index</td>
<td>NI to ↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Peripheral resistance</td>
<td>NI</td>
<td>NI to ↑</td>
<td>↑↑</td>
<td>NI to ↑</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>NI</td>
<td>NI to ↑</td>
<td>↑↑</td>
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</tr>
<tr>
<td>Plasma volume</td>
<td>NI</td>
<td>NI</td>
<td>↓</td>
<td>Nl</td>
</tr>
<tr>
<td>Afterload-adjusted fractional shortening</td>
<td>NI</td>
<td>NI</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Morbidity and mortality</td>
<td>NI</td>
<td>NI to ↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
</tbody>
</table>

NI indicates normal. Based on data in References 12, 22, 28, and 35 through 37. Differences from normal are indicated as small to large increases (↑, ↑↑, or ↑↑↑) or decreases (↓, ↓↓, or ↓↓↓).

high peripheral resistance with maintained cardiac output, and a tendency for depressed myocardial function as revealed by stress–midwall shortening relations. Hypertensive patients with eccentric hypertrophy have considerably lower ambulatory than clinic blood pressures, elevated resting cardiac output and plasma volume with relatively normal peripheral resistance, normal myocardial performance, and somewhat more spherical LV shape than normal. Patients with concentric LV remodeling have mildly elevated ambulatory and clinic blood pressures because of very high peripheral resistance despite low cardiac output, reduced plasma volume, and preserved myocardial function, whereas those with normal ventricular geometry have mildly elevated arterial pressure and peripheral resistance, with normal cardiac output and myocardial performance. Although body mass index did not differ among the subgroups defined by geometric patterns in our initial study of 165 hypertensive patients, stratification of a larger group (n=475) of hypertensive patients into those with normal or increased body weight revealed higher prevalences of concentric and eccentric ventricular hypertrophy—and reciprocally lower ones of concentric remodeling or normal LV geometry—in obese patients.

Classification of patients by their pattern of LV geometry has been shown to further enhance prediction of prognosis in patients with initially uncomplicated essential hypertension. Patients with concentric LV hypertrophy (including patient 1) had the greatest risk of death (Fig 6) as well as of nonfatal plus fatal cardiovascular events, whereas, not unexpectedly, patients with normal ventricular geometry had the lowest level of risk. Of note, the incidence of nonfatal morbid events was 0.6% per year in patients with normal ventricular geometry who did not smoke and had fasting serum glucose and cholesterol levels less than 140 and 240 mg/dL, respectively. Patients with concentric LV remodeling and eccentric ventricular hypertrophy had intermediate levels of risk for both all-cause mortality and total cardiovascular events (Fig 6). In accord with these findings, the first patient presented in this article, who had marked concentric LV hypertrophy, died of fatal myocardial infarction slightly more than 4 years after his evaluation by echocardiogram despite intervening therapy with β-adrenergic receptor blockade, whereas the second patient, who exhibited concentric LV remodeling, remains free of clinical complications 7 years after his initial evaluation despite evidence of carotid atherosclerosis and an ischemic ECG response to exercise.

Relation of Cardiac Geometry to Arterial Hypertrophy and Atherosclerosis

Arteriographic and necropsy studies revealed associations between obstructive atherosclerosis in coronary and extracoronary circulation and increased LV mass, but the highly selected nature of the populations left the generalizability of the association open to
question. Recent studies from our laboratory and others have demonstrated that positive relations exist between carotid artery wall thickness and LV wall thickness and mass and between carotid and LV internal diameters that are independent of age, gender, the level of arterial pressure, and other potentially confounding variables. Further analyses suggest that arterial hypertension may promote cardiac hypertrophy at least in part by causing an earlier return of reflected pressure waves from the peripheral circulation, thereby amplifying the hemodynamic load placed on the left ventricle in late systole. The late-systolic augmentation of central arterial pressure parallels and may be due to the increased arterial stiffness seen in hypertensive patients at their elevated levels of arterial distending pressure.

Dilation of increased carotid artery wall thickness has been shown to predict a more than twofold increase in the subsequent risk of myocardial infarction, but in the same Finnish population an even greater enhancement of risk (nearly threefold) was found in subjects with discrete carotid atheromas detected by ultrasound. In our laboratory we have found that the presence of ultrasonically detectable atheromas (eg, Fig 3) is associated with a twofold increase in the probability of LV hypertrophy and with significantly greater LV wall thicknesses (as found in patient 2) and mass after age, gender, arterial pressure, cholesterol level, smoking, and other risk factors are taken into account. Of note, subjects with discrete atheromas and increased carotid wall thickness have been found to have a more adverse 24-hour blood pressure profile, characterized especially by exaggerated blood pressure variability, which has in turn been shown to predict cardiovascular complications and development of target-organ damage in longitudinal studies.

Preclinical Cardiac and Arterial Disease and Myocardial Ischemia

The association between LV hypertrophy and arterial abnormalities may be of particular clinical importance because of their ability to promote myocardial ischemia additively by different mechanisms. Thus, myocardial ischemic responses to stress and abnormal coronary circulatory regulation, which may occur (at least in part because of enhanced basal oxygen demand and myocardial blood flow) in patients with myocardial hypertrophy and normal coronary arteries, can also be produced independently of the level of ventricular mass due to hypertrophy and altered dynamics of coronary resistance vessels.

Segmental abnormalities of myocardial perfusion can be produced by LV hypertrophy alone but are reasonably predictive of large-vessel coronary obstruction when prominent segmental defects are detected by thallium scintigraphy in older men with other coronary risk factors. Myocardial ischemic responses to exercise stress can be detected at considerably lower expense by assessing the ECG response to exercise stress, albeit without the localizing information provided by radionuclide scintigraphy.

The greatest amount of information is obtained from the exercise ECG by using methods that relate the magnitude of the putatively ischemic response (ST segment depression) to that of the imposed stimulus to myocardial ischemia (for which the increase in heart rate during exercise is a useful surrogate). Evaluation of the slope of the ST depression–heart rate increment relation in the latter stages of exercise using the linear regression–based ST segment/heart rate (ST/HR) slope method can more accurately assess the presence of coronary disease, the anatomic and functional significance of coronary obstructions, and the likelihood of future morbid events than standard ST depression criteria based on the magnitude and configuration of ST depression at end exercise. The abnormal ST/HR slope commonly present in patients with myocardial hypertrophy and subendocardial ischemia even in the absence of coronary obstruction, suggests that abnormal ST/HR slope values may be found in patients with myocardial hypertrophy and subendocardial ischemia even when large coronary artery obstruction is absent. Further studies are necessary to more clearly delineate the clinical utility of this methodology in stratifying risk and identifying anatomic and functional important coronary artery disease in patients with hypertensive cardiac adaptation.

Clinical Implications

The fundamental importance of cardiac and vascular hypertrophy and atherosclerosis in mediating the development of morbid and mortal events in humans and experimental animals with hypertension has long been well appreciated but remained inaccessible to practical evaluation. The development over the past 15 years of methods using ultrasound to evaluate cardiac and arterial structure and function has spawned a virtual tidal wave of research. Sufficient progress has been achieved that it is now possible to discern several distinct patterns of integrated cardiac and vascular adaptation to hypertension and to relate these to the pathophysiology and prognosis of this condition.

As exemplified by the patients discussed in this article, the information obtained from a noninvasive evaluation can stratify patients into groups at high or low risk of subsequent complications. This information may help guide clinical decisions concerning the institution, intensiveness, and specific choice of antihypertensive treatment under several circumstances. Examples of such situations include (1) patients with borderline or very mild established hypertension in whom the presence of normal LV geometry would indicate a high likelihood of blood pressure control by nonpharmacologic therapy, (2) patients with established hypertension with only partial blood pressure control by serial drug monotherapy in whom evidence of target-organ damage would identify a high enough level of risk to justify the cost and side effects of combinations of two or more drugs, and (3) patients with signs or symptoms suggestive of coexisting cardiac disease that would be particularly benefited by specific types of treatment (eg, angiotensin-converting enzyme inhibitors for depressed systolic function or severe mitral regurgitation, β-blockers if segmental wall motion abnormalities suggest severe coronary artery disease, or calcium-channel blockers for impaired early diastolic LV relaxation). However, for the additional cost of noninvasive testing to be justified, the tests must be done expensively at reasonable cost, and the ordering physician needs to be prepared to alter management...
decisions in a way that could be clinically beneficial, cost-saving, or both depending on the test outcome.

Acknowledgments
Supported in part by grants HL-18323 and HL-48945 from the National Heart, Lung, and Blood Institute, Bethesda, MD. We thank Virginia Burns for her assistance in the preparation of this manuscript.

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Cardiac and arterial hypertrophy and atherosclerosis in hypertension.
R B Devereux, M J Roman, A Ganau, G de Simone, P M Okin and P Kligfield

Hypertension. 1994;23:802-809
doi: 10.1161/01.HYP.23.6.802

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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