Hypertension remains a major public health problem associated with considerable morbidity and mortality. Hypertensive heart disease is a constellation of abnormalities that includes left ventricular hypertrophy (LVH), systolic and diastolic dysfunction, and their clinical manifestations including arrhythmias and symptomatic heart failure. The classic paradigm of hypertensive heart disease is that the left ventricular (LV) wall thickens in response to elevated blood pressure as a compensatory mechanism to minimize wall stress. Subsequently, after a series of poorly characterized events (“transition to failure”), the left ventricle dilates, and the LV ejection fraction (EF) declines (defined herein as “dilated cardiac failure”).\(^1\) The purpose of this review is to focus on the key steps in the progression of hypertensive heart disease (Figure 1), highlighting recent advances as well as some unresolved controversies.

From Hypertension to LVH

What is LVH?

Although an increase in cardiomyocyte size has been offered to be the sine qua non of LVH,\(^3\) in the epidemiological or clinical setting, it is not feasible to document this abnormality. Rather, in those settings, LVH is defined as an increase in LV mass. Criteria to define LVH require using a somewhat arbitrary threshold to dichotomize a trait that appears to have a continuous threshold to dichotomize a trait that appears to have a continuous

There is widespread agreement that LVH is an important intermediate phenotype in the progression of hypertensive heart disease\(^1\) and is associated with adverse outcomes.\(^6\) Although LVH can antedate the development of hypertension,\(^7\) the progression from hypertension to concentric LVH (pathway 1, Figure 1) is an important step on the pathway toward heart failure and will be the focus of this section. Pathological changes present in patients with hypertensive LVH include an increase in the size of the cardiomyocyte, alterations in the extracellular matrix\(^8,9\) with accumulation of fibrosis, and abnormalities of the intramyocardial coronary vasculature, including medial hypertrophy and perivascular fibrosis.\(^10\) The mechanisms responsible for progression to hypertrophy include not only a response to the mechanical stress from elevated blood pressure but also the influences of neurohormones,\(^11\) growth factors, and cytokines.\(^12\) Nevertheless, a recent clinical trial demonstrated that tighter control of systolic blood pressure (target of <130 mm Hg versus <140 mm Hg) was associated with a reduction in the development of LVH on ECG,\(^13\) emphasizing the importance of the pressure load itself.

What Explains the Variability in the Development and Pattern of LVH?

There is considerable interindividual variability in the increase of LV mass in response to hypertension. For example, blacks compared with whites have increased LV mass\(^14,15\) as well as more severe diastolic dysfunction.\(^16\) In large, well-characterized cohort studies, multivariable models adjusted for known risk factors, including systolic blood pressure, explained only 50% of the variability of LV mass as assessed by echocardiography\(^17\) and 60% to 68% by cardiac magnetic resonance imaging.\(^18,19\) These data suggest the presence of other unmeasured risk factors. Because there is strong evidence for heritability of LV mass, including observations from studies of the general population,\(^19\) sibling studies,\(^20\) and recent longitudinal twin studies,\(^21\) considerable interest exists in identifying putative genetic risk factors that modulate LV mass. These efforts have progressed from candidate gene association studies\(^22\) to genome-wide expression analyses with the use of microarray data\(^23\) and genome-wide association studies\(^24\) but remain in their relatively early stages and have not yet yielded results that have translated into the clinical arena. It seems likely that multiple variants, each with modest effect size, will be involved in modulating complex traits,\(^25\) including LV mass.

LV Geometry

LV mass can increase from either wall thickening or chamber dilation. Wall thickening occurs more commonly in response to pressure overload, and chamber dilation occurs more commonly in response to volume overload.\(^1\) In an attempt to categorize these 2 patterns of response, the ratio of the LV wall thickness to diastolic diameter (“relative wall thickness”) is measured by echocardiography (Figure 2).\(^26\) When the relative wall thickness is increased (eg, >0.42,\(^2\) although age-variable cutoffs may be necessary\(^29\)), LVH is classified as concentric; when the relative wall thickness is not increased, LVH is classified as eccentric. A third pattern, termed eccentric remodeling, occurs when relative wall thickness, but not LV mass, is increased. Echocardiographic studies

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Hypertension progresses to concentric (thick-walled) LVH (cLVH; pathway 1). The direct pathway from hypertension to dilated cardiac failure (increased LV volume with reduced LVEF) can occur without (pathway 2) or with (pathway 3) an interval myocardial infarction (MI). Concentric hypertrophy progresses to dilated cardiac failure (transition to failure) most commonly via an interval myocardial infarction (pathway 4). Recent data suggest that it is not common for concentric hypertrophy to progress to dilated cardiac failure without interval myocardial infarction (pathway 5). Patients with concentric LVH can develop symptomatic heart failure with a preserved LVEF (pathway 6), and patients with dilated cardiac failure can develop symptomatic heart failure with reduced LVEF (pathway 7). The influences of other important modulators of the progression of hypertensive heart disease, including obesity, diabetes mellitus, age, environmental exposures, and genetic factors, are not shown to simplify the diagram. A thicker arrow depicts a more common pathway compared with a thinner arrow.

Adapted from Drazner. Copyright 2005 ©, the American Heart Association.

Table 1. Factors Influencing LV Geometry in Hypertensive Patients

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Hypertension progresses to concentric hypertension (cLVH).</td>
</tr>
<tr>
<td>2</td>
<td>No MI with chronic hypertension.</td>
</tr>
<tr>
<td>3</td>
<td>No MI with chronic hypertension and interval myocardial infarction.</td>
</tr>
<tr>
<td>4</td>
<td>MI with chronic hypertension, diabetes, obesity, and/or valvular heart disease.</td>
</tr>
<tr>
<td>5</td>
<td>MI with chronic hypertension, diabetes, obesity, and/or valvular heart disease and interval MI.</td>
</tr>
<tr>
<td>6</td>
<td>MI with chronic hypertension, diabetes, obesity, and/or valvular heart disease and interval MI.</td>
</tr>
<tr>
<td>7</td>
<td>MI with chronic hypertension, diabetes, obesity, and/or valvular heart disease and interval MI.</td>
</tr>
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**Figure 2.** Classification of LV geometry based on LV mass and relative wall thickness (the ratio of LV wall thickness to diastolic dimension).28 Depicted schematically are cross sections of the left ventricle. The striped area represents LV wall thickness, and the area of the inner circle represents LV volume. Adapted from Sehgal and Drazner26 (copyright © 2007, Elsevier) and Khouri et al.27 (copyright © 2010, the American Heart Association).
Variation in neurohormonal activation in hypertension is another putative factor influencing the development of either concentric or eccentric hypertrophy. Differences in plasma renin activity are widespread in hypertensive subjects, and some investigators equate high- versus low-renin states with concentric versus eccentric hypertrophy, respectively. Patients with eccentric hypertrophy have been shown to have low plasma renin activity. Other neurohormones, including angiotensin II and aldosterone, have also been associated with LV geometry in small cross-sectional studies. However, the Framingham Offspring Study recently reported that an increased aldosterone-to-renin ratio was associated with both concentric and eccentric hypertrophy in multivariable models. Their sample was by far the largest to date (n = 2119), and these data question whether variability in the renin-angiotensin-aldosterone axis will be a key factor in the predilection to develop increased LV wall thickness versus ventricular dilation in hypertension.

Alterations in the extracellular matrix are suspected to be critical mediators in the development of LV chamber dilation. In a study of hypertensive subjects with heart failure in which coronary artery disease was excluded by angiography, endomyocardial biopsy of the right ventricular septum was performed in 16 subjects with dilated cardiac failure and 23 with a preserved LVEF. Those with dilated cardiac failure had a lower amount of collagen surrounding the cardiomyocytes, a higher amount of perivascular and scar-related collagen, and a higher ratio of matrix metalloproteinase-1 to tissue inhibitor of matrix metalloproteinase-1, highlighting the importance of alterations of the extracellular matrix in leading to LV dilation.

As with LV mass (see above), there likely will be genetic influences discovered that affect the pattern of the hypertrophic response (wall thickening or dilation). In a canine model of aortic constriction, dogs that had a higher baseline indexed LV mass and lower systolic wall stress before placement of the aortic band had a larger increase in LV mass and preservation of cardiac function compared with dogs with baseline lower LV mass and higher systolic wall stress. Similarly, approximately one half of rats who underwent suprarenal aortic banding remodeled concentrically and one half eccentrically at 20 weeks. These data suggest that intrinsic factors, possibly genetic, that are operative before exposure to injury can modulate the hypertrophic response. This hypothesis is supported by the murine model of transverse aortic constriction, in which the background mouse strain influenced whether concentric or eccentric hypertrophy developed.

Potential molecular pathways affecting the ability of the ventricle to tolerate pressure overload have been delineated. In total, these data suggest that genetic factors may influence the response to pressure overload and, specifically, whether concentric or eccentric hypertrophy develops.

**Regression of LV Mass**

The pathway from hypertension to concentric LVH is not unidirectional. With pharmacological control of blood pressure, LV mass decreases and is associated with reduced risk of clinical events including cardiovascular death, myocardial infarction, and stroke. However, whether a strategy tailored to reduction of LV mass provides additional clinical benefit compared with blood pressure controlled to conventional targets is uncertain.

**From LVH to Dilated Cardiac Failure and to Clinical Heart Failure**

The classic paradigm of the cardiac structural and functional changes in hypertensive heart disease is that hypertension leads to concentric hypertrophy (pathway 1, Figure 1), which then (transition to failure) is followed by dilated cardiac failure (pathways 4 and 5, Figure 1), commonly referred to as a “burned-out” left ventricle. This transition to failure was described in principle by Meerson and colleagues 50 years ago on the basis of a series of experiments that imposed aortic constriction in rabbits and dogs and continues to be an accepted paradigm today. However, recent data have challenged the “classic” tenets of this paradigm (Table 2).

**Challenges to the Classic Paradigm of Hypertensive Heart Disease**

**Classic Tenet 1: Concentric LVH Is Necessary to Avoid Dilated Cardiac Failure**

In the 1970s, the concept that LVH, manifest as increased wall thickness, was compensatory in pressure overload to reduce wall stress, thereby allowing preservation of LVEF, was supported by animal models of ascending aortic constriction and studies of patients with aortic stenosis. However, this compensatory, and thus beneficial, aspect of LVH was not consistent with epidemiological data that showed that LVH was associated with adverse clinical outcomes. Furthermore, animal models of aortic constriction have now demonstrated that prevention of LVH does not lead to dilated cardiac failure in the setting of pressure overload. Specifically, blockade of calcineurin either pharmacologically with cyclosporine or via transgenic overexpression of myocyte-enriched calcineurin-interacting protein-1 (an endogenous inhibitor of calcineurin) attenuated the increase in LV mass after aortic banding but did not lead to ventricular dilation or decline in fractional shortening. Similarly, inhibition of concentric hypertrophy in 2 other transgenic mouse models (1 in which Gq-mediated signaling was inhibited and 1 in which the dopamine β-hydroxylase gene was disrupted, blocking production of endogenous norepinephrine and epinephrine) was not associated with ventricular dilation or reduced fractional shortening despite elevated wall stress. These data from animal studies suggest that inhibition of concentric LVH is a potential therapeutic target in pressure-
overload states such as hypertension, a hypothesis that awaits testing in humans.

**Classic Tenet 2: Concentric LVH Is a Common Precursor to Dilated Cardiac Failure in the Absence of Myocardial Infarction**

Several lines of evidence support the concept that concentric LVH commonly precedes dilated cardiac failure in patients with hypertension. First, the findings of Meerson have been duplicated in numerous animal models, including the spontaneously hypertensive rat and transgenic models of pathological hypertrophy including calcineurin overexpression. Second, hypertension is a major risk factor for the development of clinical heart failure. Third, progression from concentric LVH to dilated cardiac failure has been demonstrated in humans with aortic stenosis and hypertrophic cardiomyopathy. Fourth, LVH overestimates cardiac contractility in the setting of concentric hypertrophy. Indeed, more sophisticated measures assessing LV midwall shortening and peak systolic midwall circumferential strain document abnormalities in systolic function in patients with concentric LVH despite a normal LVEF, suggesting that the process of developing dilated cardiac failure has begun.

However, there are important caveats when one considers the aforementioned data. It is not known how well the natural history in animal models or patients with aortic stenosis or hypertrophic cardiomyopathy faithfully recapitulates that of human hypertensive disease. Although hypertension is associated with the development of clinical heart failure, the percentage that is associated with a reduced or preserved LVEF is uncertain. Finally, although concentric LVH is associated with subtle abnormalities in systolic function, it is not known whether such patients subsequently develop ventricular dilation.

Another important consideration is the role of myocardial infarction in the progression from hypertension to dilated cardiac failure (pathways 3 and 4, Figure 1). LVH is associated with incident coronary heart disease, including myocardial infarction. Although the mechanisms linking LVH and myocardial infarction remain obscure, LVH has been associated with subclinical atherosclerosis as assessed by coronary artery calcium as well as inflammation. Moreover, in a study in which serial cardiac catheterizations were performed, plaque rupture was more common among patients with LVH. A hypertensive patient with (pathway 4) or without (pathway 3) concentric LVH who sustains a large myocardial infarction will be at risk for developing dilated cardiac failure. The key unresolved question is whether concentric hypertrophy is a common precursor to dilated cardiac failure in the absence of interval myocardial infarction in hypertensive patients (pathway 5).

Over the last 5 years, several studies have provided data to address this question. In a retrospective study of 159 subjects (77% black; mean age, 56 years) who had concentric LVH, a normal LVEF, and a follow-up echocardiogram performed for clinical indications at least 1 year after the baseline echocardiogram, only 18% developed a reduced LVEF after a median follow-up of 4 years. Furthermore, this transition occurred after an interval myocardial infarction in 41% of patients. In 3042 participants of the Cardiovascular Health Study with a normal LVEF, 8.7% developed a low LVEF after 5 years of follow-up. Although increased LV mass was an independent risk factor for that transition, it was eccentric but not concentric hypertrophy that was associated with this outcome. In total, these data suggest that concentric hypertrophy does not commonly progress to dilated cardiac failure after 5 to 7 years of follow-up in the absence of interval myocardial infarction (ie, pathway 5 is not common). Large prospective studies with serial assessment of ventricular structure and function over 5 to 10 years or longer are necessary.

**Classic Tenet 3: In the Absence of Myocardial Infarction, Hypertension Does Not Lead Directly to Dilated Cardiac Failure Without Antecedent Concentric Hypertrophy**

The classic paradigm of the progression of hypertensive heart disease is that hypertension does not lead to dilated cardiac failure unless there is interval myocardial infarction or a preceding phase of concentric hypertrophy (which would be contrary to the conclusions of the animal studies discussed above in the section about classic tenet 1) or a defect in the ability to develop LV wall thickening to determine whether patients who progress along this pathway have a defect in the ability to develop LV wall thickening (which would be contrary to the conclusions of the animal studies discussed above in the section about classic tenet 1) or rather a predisposition to develop LV dilation perhaps due to an underlying abnormality in the extracellular matrix.

Overall, further work is needed to determine how frequently hypertensive patients progress directly to LV dilation (pathway 2) or concentric LVH (pathway 1). Because the transition between the 2 appears uncommon in the absence of interval injury (pathway 5), identifying factors that predispose patients to develop either LV dilation or wall thickening will have implications for predicting the risk of subsequently developing heart failure with a reduced or preserved LVEF, respectively.

**From LVH to Clinical Heart Failure**

It is now well recognized that clinical heart failure can occur either in the setting of reduced LVEF (pathway 7, Figure 1) or preserved LVEF (pathway 6). The progression of asymptomatic LV dysfunction to clinical heart failure (pathway 7)
has been reviewed recently. Thus, this review will focus on the progression from concentric LVH to symptomatic heart failure with a normal LVEF (pathway 6, Figure 1).

One factor that appears to be associated with the development of heart failure in those with LVH and a normal LVEF is a progressive change in the extracellular matrix. In an elderly canine model of hypertension, exogenous mineralocorticoid (deoxycorticosterone acetate) administration was associated with progressive cardiac fibrosis and increased LV stiffness, suggesting that mineralocorticoid receptor activation may be important in this progression. Others have demonstrated a shift in serum levels of matrix metalloproteinases and tissue inhibitor of matrix metalloproteinases with progression in the continuum of hypertensive heart disease.

Higher tissue inhibitor of matrix metalloproteinase-1 levels, which are associated with increased collagen accumulation, were observed in patients with LVH and clinical heart failure compared with patients with hypertension and LVH but no clinical heart failure. In a study of 85 hypertensive patients, serum levels of matrix metalloproteinase-2 and -9 and amino peptide of procollagen type 3 were independent predictors of identifying those with heart failure with a preserved LVEF, and matrix metalloproteinase-2 had a better diagnostic utility than B-type natriuretic peptide for this purpose. Together, these studies suggest that progressive changes in the extracellular matrix may be responsible for the transition from LVH to symptomatic heart failure with a preserved LVEF.

Another key component in the development of clinical heart failure with a preserved LVEF appears to be elevation in LV filling pressures. Data from implantable hemodynamic monitors demonstrate that such filling pressures appear elevated in both the chronically compensated and acutely decompensated state of heart failure with preserved LVEF. Consistent with this hypothesis are echocardiographic data that demonstrate an enlarged left atrium in patients with heart failure and preserved LVEF as well as elevated pulmonary artery pressures, which are themselves correlated with LV filling pressures.

Conclusion

Hypertensive heart disease encompasses a broad spectrum including asymptomatic LVH (either a concentric or an eccentric pattern) and clinical heart failure (with either a preserved or a reduced LVEF). There is considerable interindividual variability in the progression from hypertension to LVH in both the magnitude of the increase in LV mass and its geometric pattern (ventricular dilation or wall thickening). Some of these differences are likely attributable to differences in the pressure load (which may not be discernable by office measurements of blood pressure), concomitant medical conditions, and the underlying neurohormonal milieu. However, these differences in LV geometry also suggest the likelihood of operative genetic influences that are only beginning to be uncovered. The classic paradigm of the progression from hypertension to concentric hypertrophy and then dilated cardiac failure has been established in animal models, but recent data have challenged several of its components. First, in animal models of pressure overload, concentric hypertrophy, which normalizes wall stress, is not obligatory to prevent dilated cardiac failure, raising the possibility that targeted therapy of the hypertrophic pathway may be a potential means to prevent hypertensive heart disease. Second, the progression from concentric hypertrophy to dilated cardiac failure in the absence of interval myocardial infarction may not be a common pathway. Third, patients with hypertension may progress directly to dilated cardiac failure in the absence of myocardial infarction or antecedent concentric hypertrophy. The frequency of this occurrence and its triggers remain to be defined but are important to uncover in order to determine why some hypertensive subjects develop LV dilation and others concentric LVH. Finally, the mechanisms for the progression from asymptomatic concentric LVH to clinical heart failure with a preserved LVEF are just now being unraveled. Presently, this transition appears to be associated with progressive adverse remodeling of the extracellular matrix and increase in LV filling pressures. Further advances in our understanding of the risk factors for progression along each of these pathways will undoubtedly help to accomplish the goal of reducing the burden of heart failure.

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**Key Words:** heart failure, hypertension, hypertrophy, remodeling
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