

## STATE-OF-THE-ART PAPERS

# The Hypertensive Heart

## An Integrated Understanding Informed by Imaging

Subha V. Raman, MD, MSEE

*Columbus, Ohio*

Clinical sequelae of hypertension include heart failure, arrhythmias, and ischemic events, especially myocardial infarction and stroke. Recognizing the hypertensive heart has diagnostic as well as prognostic implications. Current imaging techniques offer noninvasive approaches to detecting myocardial fibrosis, ischemia, hypertrophy, and disordered metabolism that form the substrate for hypertensive heart disease. In addition, recognition of aortopathy and atrial myopathy as contributors to myocardial disease warrant incorporation of aortic and atrial functional measurements into a comprehensive understanding of the hypertensive heart. (J Am Coll Cardiol 2010;55:91-6) © 2010 by the American College of Cardiology Foundation

Investigators of hypertensive heart disease (HHD) have traditionally studied elements of its pathophysiology from distinct perspectives—hypertrophy, hemodynamic models, genetic influences, and neurohormonal pathways, to name a few. One is reminded of the allegory of the blind men who walk into a forest and encounter an elephant, an animal unknown to them. Each unseeing man tries to understand what stands before him by exploring what is closest—the man feeling the stout leg labels it a tree, and another brushes by the tail and thinks it is a rope. Ultimately, none “see” the elephant for what it is without composing these disparate perspectives into one. Such an aggregation of viewpoints is similarly required to better diagnose and treat HHD.

The ongoing need for coherence in comprehension is evident when one finds that hypertensive patients’ risk of heart failure has changed little since its recognition by large population-based studies over the past decades (1). Also apparent is the link between HHD and atrial fibrillation, whose likelihood increases by 40% to 50% in the presence of hypertension (2). Ventricular arrhythmias occur more frequently in hypertensive patients (3), with QT dispersion increasing directly with left ventricular (LV) mass (4). Increased susceptibility to ischemic heart disease rounds out the cardiovascular sequelae of HHD, with a 6-fold higher risk of myocardial infarction in hypertensive patients than in normotensive individuals (1).

### Structural Remodeling

Cardiomyocyte hypertrophy is but one of many structural alterations in HHD (5). Fibroblasts undergo hyperplasia and conversion to myofibroblasts, along with hypertrophy of vascular smooth muscle cells. Noncellular elements central to myocardial remodeling in HHD include expansion of interstitial and perivascular collagen that make up the extracellular matrix. Changes in intramyocardial capillary density and arteriolar thickening compound ischemia in the hearts of patients with hypertension. These remodeling events are orchestrated via effects of biomechanical stress on the extracellular matrix that, in turn, signals stretch-activated ion channels leading to intracellular transmission of signals to the nucleus, up-regulating hypertrophic gene expression. Similar transduction occurs from cytokine signaling via intracellular calcium handling to myocardial transformation (6).

Is there a benefit to myocardial hypertrophy? In the short-term, increasing wall thickness in proportion to increased pressure helps to normalize myocardial stress; hemodynamic studies have shown that the pressure-overloaded LV has reduced wall stress when compared with the volume-overloaded ventricle (7). However, long-term outcomes clearly worsen with progressive hypertrophy, with increasing LV mass index translating to commensurate increases in adverse cardiovascular events and all-cause mortality (8). Conversely, regression of hypertrophy by either electrocardiographic measures or echocardiography confers lower rates of cardiovascular death, myocardial infarction, stroke, and all-cause mortality (9–11).

This underscores the need to measure LV mass with care, as it informs not only diagnosis but also prognosis in HHD. Reliance on the electrocardiogram alone has limitations in both sensitivity and specificity of voltage-based criteria, an

From the Departments of Internal Medicine and Biomedical Informatics, The Ohio State University, Columbus, Ohio. Dr. Raman receives funding from a National Heart, Lung, and Blood Institute grant (#HL095563) and from Siemens Medical Solutions.

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**Abbreviations and Acronyms**

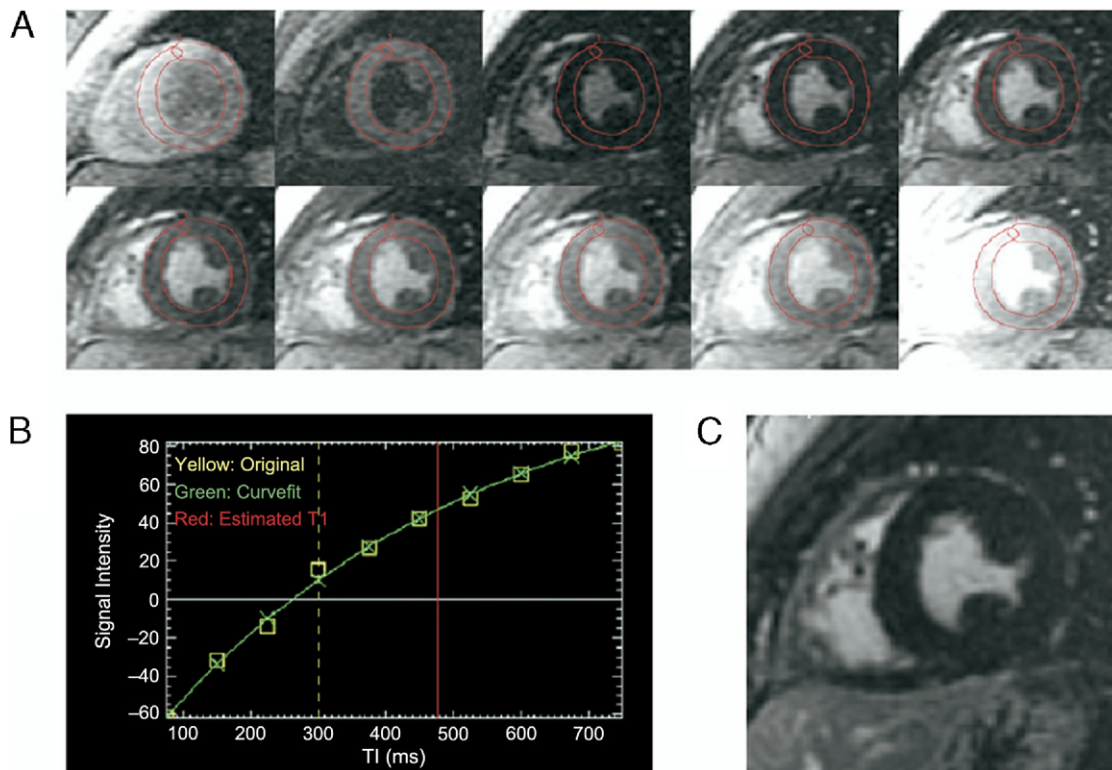
- CMR** = cardiac magnetic resonance
- HHD** = hypertensive heart disease
- LGE** = late gadolinium enhancement
- LV** = left ventricle/ventricular
- <sup>31</sup>P-MRS** = phosphorus magnetic resonance spectroscopy

understanding made possible with the advent of cardiac imaging (12). Particularly prone to error is the diagnosis of LV hypertrophy in young male patients using conventional electrocardiographic criteria (13). Echocardiography performs well in detection of concentric hypertrophy given an adequate acoustic window; asymmetric and milder forms of hypertrophy may benefit from alternate imaging approaches. Reproducibility of LV mass measurement using cardiac

magnetic resonance (CMR) is well-established (14), making it the standard when evaluating newer techniques such as 3-dimensional echocardiography (15). Cardiac computed tomography also allows precise measurement of LV mass (16,17), requiring less radiation exposure with progressive technological advances. High reproducibility is relevant to clinical practice as it affords the following: 1) cost-effective sample size design in clinical trials of therapeutics targeting LV hypertrophy; 2) quantitative investigation of rare diseases; and 3) precise detection of serial changes in individual patients.

**Myocardial Fibrosis**

A common end point of many cellular and noncellular pathologic processes in HHD is myocardial fibrosis. Fibrosis quantification in endomyocardial samples obtained via transjugular biopsy showed significantly greater collagen volume fraction in patients with hypertension than in normotensive controls (18). Various imaging techniques have emerged to quantify myocardial fibrosis noninvasively. Echocardiography with integrated backscatter show good correlation with collagen volume fraction, recognizing that slightly less than half of patients may have suitable backscatter signal for analysis (19). A more robust approach for visualization of myocardial fibrosis is late gadolinium enhancement (LGE)-CMR. This technique shows enhancement in regions of fibrosis with appropriate T<sub>1</sub>-weighted techniques 10 to 15 min after intravenous administration of gadolinium-based contrast because of: 1) expanded extravascular volume in fibrotic myocardium that is occupied by this extracellular contrast agent; and 2) impaired efflux of gadolinium-based contrast due to vascular changes in fibrotic myocardium. A recent European study showed that approximately one-half of patients with LV hypertrophy due to arterial hypertension manifested patchy enhancement



**Figure 1** Magnetic Resonance T<sub>1</sub> Mapping for Myocardial Fibrosis Quantification

(A) Images obtained at multiple inversion times show recovery of myocardial signal after initial inversion. (B) Plot of myocardial signal intensity versus inversion time (TI) shows an exponential recovery curve from which myocardial T<sub>1</sub> can be calculated. (C) Conventional late post-gadolinium image shows minimal grossly apparent hyperenhancement, underscoring the need for more quantitative approaches. Reproduced, with permission, from Iles et al. (23).

on LGE imaging (20); this pattern is clearly distinguishable from the subendocardial enhancement of infarcted myocardium. Our group has shown that severity of diastolic dysfunction increases with extent of fibrosis by LGE (21). This suggests a potential noninvasive metric for trials of novel agents to treat heart failure with preserved ejection fraction, an all too common outcome in hypertensive patients with diastolic dysfunction.

In other populations with cardiomyopathy, myocardial enhancement by LGE-CMR has been shown to identify substrate for ventricular arrhythmias and sudden cardiac death (22,23). Similar prospective studies in patients with hypertrophy due to hypertension are needed before ascribing arrhythmia risk to the patchy enhancement seen in HHD.

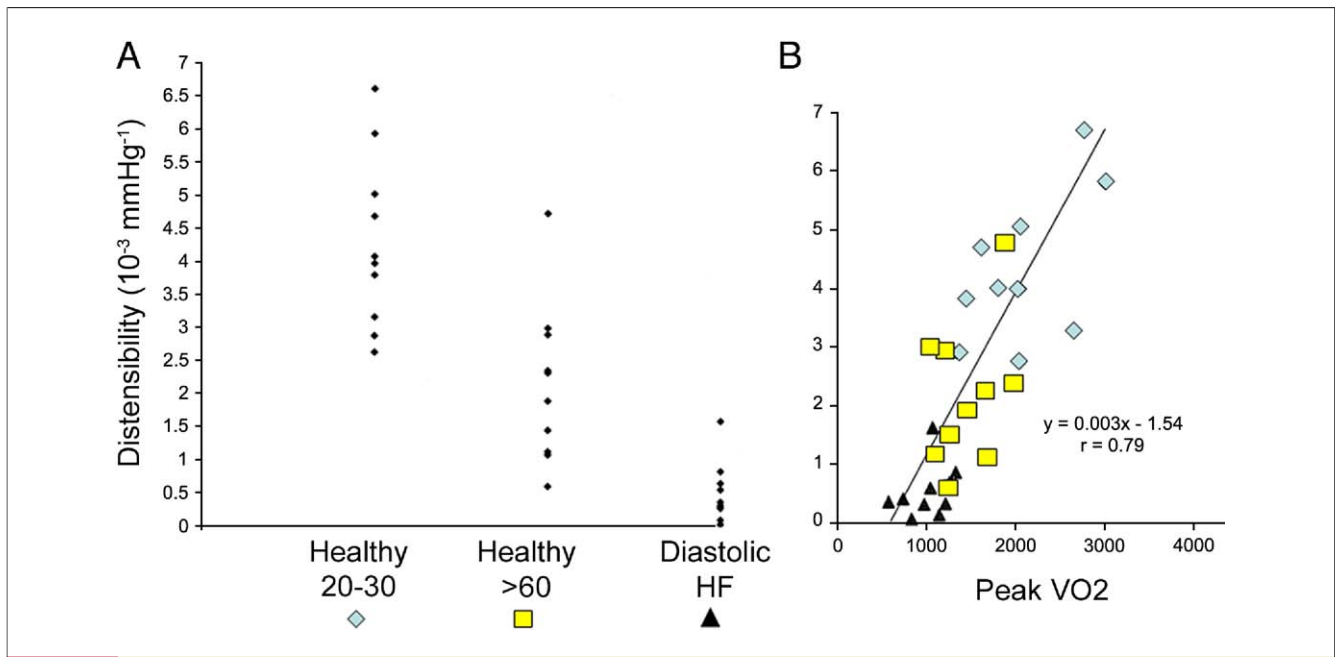
Visibly enhanced myocardial regions by LGE-CMR may be absent in HHD even in the presence of diffuse interstitial fibrosis. This has prompted the development of  $T_1$  mapping. This technique may be applied to the entire myocardium allowing quantification of differences in  $T_1$  relaxation, an intrinsic property of spins or protons in fibrotic versus normal myocardium. These differences are further exaggerated after gadolinium administration, which showed good correlation with collagen volume fraction in a small study of post-orthotopic heart transplant patients (Fig. 1) (24). Brilla et al. (25) used endomyocardial biopsy in patients with hypertension and diastolic dysfunction to show that treatment with an angiotensin-converting enzyme inhibitor produced measurable reduction in collagen volume fraction

and improved diastolic function, neither of which were achieved with diuretic therapy despite similar improvement in blood pressure control. One could envision similar studies using  $T_1$  mapping as an end point in future therapeutic trials targeting fibrosis in HHD, eliminating the need for serial invasive myocardial sampling.

### Vascular and Other Changes in Hypertensive Myocardial Disease

Microvascular disease and endothelial dysfunction are apparent in hypertensive heart disease. A study of African-American men with hypertension showed progressive impairment of flow-mediated vasodilation as LV mass increased (26), consistent with the previously described ultrastructural remodeling of myocardial microvessels. Looking directly at myocardial perfusion with vasodilator stress CMR, Pilsz et al. (27) showed increased frequency of hypertension in patients with chest pain, angiographically normal coronary arteries, and subendocardial ischemia on perfusion imaging. Of course, hypertensive patients may also have myocardial ischemia due to epicardial coronary stenosis that can be detected noninvasively using stress perfusion scintigraphy (28) or coronary computed tomography (29).

At the macrovascular level, increased arterial stiffness often seen in long-standing hypertension accelerates aortic pulse wave velocity (30). This, in turn, results in earlier return of the wave reflected at the iliac bifurcation in systole,



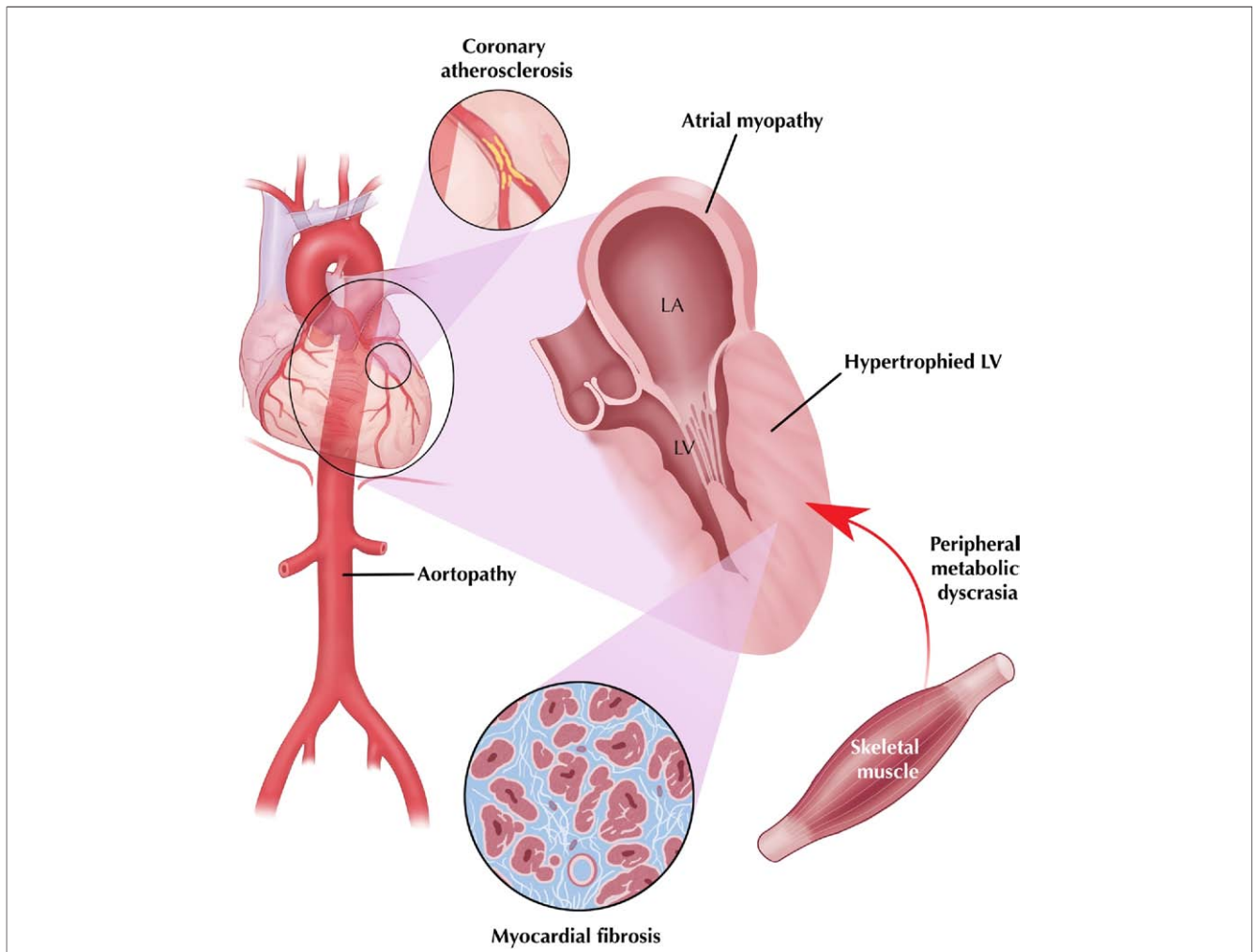
**Figure 2** Aortic Distensibility and Diastolic HF

(A) Aortic distensibility obtained with cine cardiac magnetic resonance imaging as one proceeds from healthy young to healthy old individuals; distensibility is most reduced in diastolic heart failure patients. (B) Peak oxygen consumption declines with age and is lowest in patients with diastolic heart failure. Adapted and reproduced, with permission, from Hundley et al. (32). HF = heart failure;  $Vo_2$  = oxygen consumption.

increasing LV afterload and central pulse pressure. The concomitant fall in central diastolic blood pressure decreases coronary perfusion, further contributing to myocardial ischemia. The pulse wave velocity measurement, either with CMR velocity-encoded imaging or multistation arterial tonometry, provides an assessment of aortic function. Ahimastos et al. (31) applied the latter in showing that angiotensin-converting enzyme inhibition affected its benefit on aortic remodeling via lowering of aortic pulse wave velocity, further mediated by changes in matrix metalloproteinases and transforming growth factor-beta that are known to degrade aortic integrity (31). Aortic distensibility, albeit a load-dependent measure of aortic function, can be readily quantified using high temporal resolution cine CMR techniques. With this approach, Hundley et al. (32) showed a progressive decline in aortic distensibility with age that was lower still in patients with diastolic heart failure. These aortic changes paralleled reduction in peak oxygen con-

sumption, an important metric of functional capacity that further illuminates how the aorta contributes to clinical sequelae of hypertension (Fig. 2).

Several other mechanisms warrant consideration in completing our current understanding of hypertension and the heart. Altered myocardial energy use in HHD has been studied by Lamb et al. (33) using phosphorus magnetic resonance spectroscopy ( $^{31}\text{P}$ -MRS) during pharmacologic stress. Because of the critical role of adenosine triphosphate and creatine cycling in supplying myocytes with the energy needed for normal function, changes in the ratio of phosphocreatine to adenosine triphosphate that can be measured noninvasively with  $^{31}\text{P}$ -MRS allow noninvasive quantification of myocardial metabolism. With prolonged dobutamine and atropine infusion to allow sufficient time to collect the  $^{31}\text{P}$ -MRS signal, patients with hypertension had measurably lower phosphocreatine to adenosine triphosphate ratios during stress compared with healthy controls, indicating



**Figure 3** The Many Aspects of Hypertensive Heart Disease

Hypertensive heart disease involves disparate elements, ranging from aortopathy to myocardial remodeling and even peripheral energy utilization that interact to produce sequelae such as heart failure, arrhythmias, and ischemic events. Figure illustration by Rob Flewell. LA = left atrium; LV = left ventricle.



impaired myocardial energetics. Recognizing the systemic vasculature's role in energy use and blood flow may require consideration of not only myocardium but also skeletal muscle in HHD, facilitated by imaging techniques such as  $^{31}\text{P}$ -MRS (34) and positron emission tomography with 15-oxygen labeled water (35).

Finally, no discussion of hypertensive heart disease would be complete without appreciating the role of the left atrium. As witness to chronically elevated LV filling pressures, left atrial enlargement is a reliable marker of diastolic dysfunction in the absence of mitral valve disease. The correlation between left atrial volume and brain natriuretic peptide levels further underscores its role as sentinel in heart failure with preserved ejection fraction (36). Beyond passive expansion, Kurt et al. (37) have recently shown that changes in active left atrial strain by tissue Doppler may distinguish between asymptomatic patients with diastolic dysfunction and those with diastolic heart failure, something not feasible with traditional echo-Doppler measures such as E/E' ratio. Thus, left atrial myopathy warrants inclusion in our coalescent understanding of hypertensive heart disease.

### Future Directions

Increasing recognition of genetic factors that produce variable therapeutic response among patients with hypertension (38,39) should motivate better understanding of the structural and functional differences that mediate this heterogeneity. Imaging attuned to the multiple aspects of HHD (Fig. 3), by quantifying the degree to which specific elements predict variability in disease development and progression, can provide specific phenotypic evidence to guide development of novel therapeutics.

### Conclusions

The clinical burden of HHD is great, as is the opportunity to develop new treatment options for patients with heart failure with preserved ejection function that so often results from unchecked hypertension. Innovation will require investigations that consider hypertrophy, fibrosis, ischemia, altered metabolism, aortopathy, and atrial myopathy as interconnected mechanisms along the HHD spectrum. Contemporary noninvasive imaging facilitates such an understanding, and warrants incorporation into pre-clinical research and therapeutic trials to improve the lives of patients with HHD.

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**Reprint requests and correspondence:** Dr. Subha V. Raman, The Ohio State University, Internal Medicine, 473 West 12th Avenue, Suite 200, Columbus, Ohio 43210. E-mail: raman.1@osu.edu.

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**Key Words:** hypertension ■ left ventricular hypertrophy ■ diastolic heart failure ■ imaging ■ hypertensive heart disease ■ pathophysiology.