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Alterations in Cardiac Structure and Function in Hypertension

Mário Santos, M.D.[†,*] and **Amil M. Shah, M.D., M.P.H.**[*]

[†] Department of Physiology and Cardiothoracic Surgery, Cardiovascular R&D Unit, Faculty of Medicine, University of Porto, Portugal.

[*]Division of Cardiovascular Medicine, Brigham and Women's Hospital.

Abstract

Hypertension is a powerful risk factor for cardiovascular mortality and morbidity, including heart failure with both preserved and reduced ejection fraction. Hypertensive heart disease (HHD) defines the complex and diverse perturbations of cardiac structure and function occurring secondary to hypertension. Left ventricular hypertrophy (LVH) is one of the most recognized features of HHD and is an established risk factor for adverse CV outcomes in hypertension. Beyond LVH, LV geometry provides additional information regarding the cardiac response to hypertension. Imaging studies from larger cohorts of hypertensive patients reveal wide variability in the prevalence of LVH and LV geometric patterns, with the prevalence of concentric LVH similar to that of eccentric LVH. Hypertension is also associated with concomitant impairments in LV diastolic and systolic function. It remains uncertain why patients develop different patterns of LVH, although demographics and clinical comorbidities appear to influence that response.

Keywords

Hypertension; Ventricular Remodeling; Echocardiography

INTRODUCTION

Hypertension is a major public health concern and one of the most important modifiable cardiovascular (CV) risk factors, responsible for up to half of all cardiovascular deaths[1]. It is also a powerful risk factor for incident heart failure (HF) with both preserved and reduced ejection fraction[2], conditions that are increasing in prevalence in parallel with the aging population.[3] Most importantly, treating hypertension can effectively prevent its associated complications, even in the elderly.[4, 5]

Hypertensive heart disease (HHD) defines the complex and diverse perturbations of cardiac structure and function occurring secondary to hypertension. It is frequently characterized by

Address for Correspondence: Amil M. Shah MD MPH, Division of Cardiovascular Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115. Fax: 617-732-5291, Tel: 617-732-5681, ashah11@partners.org.

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left ventricle hypertrophy (LVH), left atrial enlargement (LAE), and left ventricular (LV) systolic and diastolic dysfunction which are themselves potent risk factors for heart failure and atrial arrhythmias.[6] LVH, in particular, is a hallmark of HHD. [7] The pathogenesis underlying LVH is likely multifactorial.[8] In the face of abnormal loading conditions, particularly chronically elevated afterload, LVH allows for normalization of LV wall stress and preservation of LV mechanical function[9]. Despite its presumptive adaptive nature, LVH correlates with the overall CV risk of the hypertensive patient and is one of the most robust and validated prognostic markers in hypertension[10-12].

Beyond LV mass alone, assessment of LV shape, or geometry, provides additional information regarding the cardiac response to hypertension. In a seminal paper published more than fifty years ago, Linzbach described specific ventricular morphologic adaptations to different hemodynamic stimuli and their functional correlates[13]. Based on these observations, currently the most commonly used schema for classifying LV geometry relates mass (hypertrophy) with the relative wall thickness (RWT), which describes the relationship between wall thickness and cavity size (concentricity)[14]. Using these 2 features, LV geometry can be classified as concentric LVH (increased mass and increased concentricity), eccentric LVH (increased mass and normal concentricity) and concentric remodeling (normal LV mass with an increased concentricity)[15, 16].

HHD has classically been associated with concentric LVH, as increased LV wall thickness allows for normalization of LV wall stress in the face of elevated blood pressure[17]. It has been postulated that eventually, chronic increase in afterload result in LV dilatation (eccentric LVH) and reduced pump function, although several lines of preclinical and clinical evidence challenge this view of HHD progression[18-20].

There is significant heterogeneity in the cardiac phenotype in hypertension, related to disease expression in addition to variability in duration, severity, effective treatment as well as the presence of associated comorbidities. As studies with small sample sizes may fail to adequately capture the spectrum of alterations in cardiac structure and function in hypertension, in the present review we focus on larger imaging studies from epidemiology and clinical trial cohorts of hypertensive patients. We review the observed perturbations in cardiac structure and function with special emphasis on LV geometric patterns and diastolic and systolic function.

LEFT VENTRICULAR STRUCTURE

Left Ventricular Hypertrophy

The prevalence of LVH in hypertension varies according to the characteristics of the population studied. In a hypertensive population with metabolic syndrome and chronic kidney disease, Iwashima et al.[21] reported a prevalence of 71.5%, in contrast to 19.5% in a middle-aged cohort with uncomplicated hypertension.[22] This variability is also potentiated by the different criteria used in different studies to calculate LVH[23]. Currently, the formula recommended by the American Echocardiography Society[24] has gained wide acceptance, although some debate remains about the best indexation method[25]. LVH is associated with elevation in prognostically relevant cardiac biomarkers of myocardial injury (high

sensitivity troponin) and wall stress (N-terminal B-type natriuretic peptide).[26-28] Indeed, an extensive body of evidence supports the association of LVH with hypertension-related morbidity and mortality[11, 29]. Compared to hypertensive patients without LVH, Ganau et al. observed a 3-fold higher incidence of myocardial infarction or death in those with echocardiographically detected LVH[16]. Although the mechanisms linking LVH in hypertension to adverse clinical outcomes are not fully defined, LVH is a marker of the concomitant vascular disease associated with hypertension.[30, 31] In addition, the process of cardiomyocyte hypertrophy underlying chamber-level hypertrophy is paralleled by myocardial microcirculation rarefaction, interstitial fibrosis, and increased myocyte apoptosis which together appear to predispose to myocardial dysfunction, ischemia and ventricular arrhythmias[32].

Left Ventricle Geometry

There is wide variability in the prevalence of LV geometric patterns across the large epidemiology studies and clinical trials, likely related to the heterogeneity in the characteristics of the various hypertensive populations (Table 1). However, across studies, the prevalence of normal geometry was high. In only 4 epidemiologic studies was the prevalence of normal LV geometry less than 45%,[21, 33-35]and each of them had distinctive features that may explain the increased LV mass or concentricity. These included advanced age[33], untreated blood pressure that was significantly elevated[34], the presence of chronic kidney disease (CKD) or metabolic syndrome,[21] and African American ethnicity[35]. Concordant with other literature reviews[23], the prevalence of eccentric LVH was similar to, or higher than, the prevalence of concentric LVH in most of the cohorts we reviewed (Table 1). In aggregate these data emphasize the absence of a uniform LV geometric response to hypertension, likely reflecting the clinical and pathophysiological heterogeneity of hypertension. It remains uncertain why patients develop different patterns of LVH, but the duration and severity of hypertension along with demographic features, comorbidities, and genetic background are important determinants[36, 20].

Ethnicity appears to be an important modulator of the LV adaptation to hypertension. In a population-based African American cohort, Fox et al.[37] described a high prevalence of LVH, with concentric remodeling (36%) and concentric LVH (29%) more prevalent than other patterns. Concordant results are provided from other studies in black populations[35, 38]. These findings contrast with those of the Cardiovascular Health Study which, although enrolling older white hypertensive patients, found a much lower prevalence of LVH and increased concentricity [39]. In addition, Drazner et al.[40] demonstrated that the prevalence of LVH was increased in black compared to white patients even after adjustment for age, gender, body composition, blood pressure and socioeconomic status. Importantly, although these studies support an independent association between black ethnicity and higher LV mass and concentricity, ethnicity by itself only explains a small proportion of the variance in LVH[41] and environmental influences appear more relevant.

Gender also appears to influence the LV response to hypertension. Data from the Framingham Heart Study demonstrate that the LV geometric adaptation to isolated systolic hypertension differs by sex, with women more likely to develop concentric LVH and men

eccentric LVH[42]. Consistently, the effect of age and metabolic syndrome on LV structure appears to differ by gender, a more pronounced impact on LV mass and concentricity in women than men[34, 43,43]. Estrogen cannot fully explain this as the association was observed before and after menopause[43]. Differences in neurohumoral changes may be implicated in this sex-specific LV response[44-46].

Diabetes is a major CV risk factor that is increasingly prevalent and clearly associated with hypertension[47, 48]. In the HyperGEN population-based cohort, diabetes was associated with LVH and concentricity independent of age, sex, BMI, blood pressure, and antihypertensive medication[49]. Interestingly, in a hypertensive Asian cohort, Eguchi et al. observed that diabetes influenced LV geometry but not LVH independently of ambulatory BP[33]. Differences in the demographic and clinical features of the studied populations such as ethnicity, duration of hypertension and degree of insulin-resistance may explain some between-study discordance regarding the influence of diabetes on the LV structure among hypertensive patients[50-52].

Obesity is also a very prevalent comorbidity in hypertensive patients[53]. However unlike diabetes, obesity appears associated with eccentric rather than concentric LVH[54]. The increased cardiac output associated with relative hypervolemia in obesity may partially explain this impact on LV geometry. These changes are reversible, as morbidly obese patients demonstrate significant improvement of LV geometry after bariatric surgery due both to reductions in LV mass and degree of concentricity[55, 56]. As discussed in a recent meta-analysis[57], differences in demographic and clinical features, including ethnicity, severity of obesity, and coexistence of obstructive sleep apnea, along with differences in the echocardiographic criteria employed might explain some of the discordance in findings between studies on the impact of obesity on cardiac structure in hypertension.

Greater LV mass is associated with chronic kidney disease (CKD) [58, 59]. The presence of LVH correlates with the severity of glomerular filtration rate impairment and proteinuria, and is highly predictive of CV morbidity and mortality[60, 61]. CKD is associated with a concentric pattern of hypertrophy [21, 62]. One plausible mechanistic explanation of the increased prevalence of concentric geometry is the increased aortic stiffness often observed in CKD patients. The noncompliant arterial tree increases LV afterload by enhancing wave reflections toward LV, which had been linked with concentric hypertrophy in preclinical and clinical studies[63, 64]. The precise mechanisms underlying the development of LVH in CKD are still not clearly defined although several studies also point to an important role of insulin resistance, inflammation, oxidative stress, and abnormalities of calcium-phosphate homeostasis [65, 66].

LV geometry and prognosis

Several studies have evaluated the prognostic value of LV geometry beyond just the presence of LVH with mixed results. This question is particularly challenging, as LV concentricity and mass are interrelated measures. Some studies have observed incremental prognostic value of LV geometric pattern beyond that conveyed by LV mass alone[15, 67, 68]. In untreated hypertensive patients, Muiesan et al.[69] demonstrated that not only changes in LV mass but also changes in LV geometry from baseline to follow-up after initiation of

antihypertensive therapy had independent prognostic value. In a population of patients with atrial fibrillation and a high prevalence of hypertension (>70%), concentric LVH was found to be an independent prognostic marker for all-cause mortality[70]. However, several other studies failed to demonstrate additive prognostic value of LV geometry[71, 72]. Using data from the Framingham Heart Study, Krumholz et al.[73] found little prognostic value of LV geometry when adjusted to LV mass. Further studies are needed to evaluate the incremental prognostic value of characterizing LV geometry in hypertension. Using data from the Framingham cohort participants free of prevalent CV disease, Velagaleti et al. observed that eccentric LVH preferentially increased the risk of HF with reduced ejection fraction, while concentric LVH was associated with the development of HF with preserved ejection fraction[74]. Although limited by the absence of adjustment for relevant potential confounders such as coronary artery disease and valvular heart disease, these results suggest LV geometry is a determinant of subsequent functional impairment and HF phenotype.

LV geometry – limitations of the current classification

One limitation of the classification scheme for LV geometry described above is the failure to distinguish eccentric hypertrophy with or without LV dilatation. LV volume is a robust and validated prognostic marker in a wide range of CV diseases including hypertension[75]. Khouri et al.[76] and Bang et al.[77], using cardiac MRI and echocardiography respectively, classified LV geometry into 4 groups using LV volume and mass. They demonstrated differences in clinical and hemodynamic profiles between patients with eccentric LVH subclassified into either dilated or normal LV volume categories[77]. This suggests that the inclusion of LV volume, in addition to LVH and LV concentricity, may further refine the identification of relevant sub-phenotypes within hypertension, although its prognostic value has not yet been defined.

LV DIASTOLIC FUNCTION IN HYPERTENSION

There is extensive evidence demonstrating an association between hypertension and diastolic dysfunction in community-based populations[78, 79]. Similarly, the prevalence of diastolic dysfunction is high in hypertensive cohorts.[80-83] Importantly, these noninvasive measures of diastolic performance are prognostic of incident HF and CV death[78, 79, 82]. The occurrence of diastolic dysfunction appears to occur in parallel with the structural changes characterizing hypertension. The presence of LVH is associated with both concomitant impaired relaxation and elevated LV filling pressure. [80, 84, 85]. In contrast, concentric remodeling, while associated with impaired LV relaxation, does not appear to be a predictor elevated filling pressure. [86]

Left atrial size is a barometer of chronic LV filling pressure and LAE has demonstrated prognostic value in several CV diseases[87,90, 91]. In hypertension, LAE correlates with blood pressure values, LVH and other echocardiographic measures of diastolic function[88]. The overall prevalence of LAE in hypertension patients is difficult to estimate because of the diversity of echocardiographic criteria and the clinical heterogeneity of patients. Cuspidi et al. recently analyzed 15 studies that reported LAE in hypertensive patients and estimated a pooled prevalence of 32%[89]. Although few studies have assessed the prognostic value of

LAE specifically in hypertensive cohorts, LAE has been consistently and robustly associated with CV events in studies across the spectrum of CV disease[87, 90].

LV SYSTOLIC FUNCTION IN HYPERTENSION

Among asymptomatic subjects with hypertension and no overt HF, the prevalence of LV systolic dysfunction defined by an LV ejection fraction (LVEF) <50% is approximately 3.6%,[91] and identified patients at a 9-fold higher risk of developing HF [92]. However, the LV structural changes associated with hypertension can also be associated with abnormalities in LV systolic function despite preserved LVEF. For example, midwall fractional shortening (FSmw) is a measure of LV radial deformation that appears less load-dependent than LVEF. In hypertension, FSmw is reduced despite preserved LVEF and this reduction is associated with greater LVH. Importantly, reduced FSmw is also associated with worse prognosis[93, 94]. Using novel echocardiography-based myocardial deformation imaging to assess cardiac mechanics, some groups have observed impairment in LV deformation in a variable proportion of hypertensive patients[95-97]. Although the association between systolic function and LV geometry is still debatable[86, 98], the negative correlation between LVM and systolic function is quite consistent across studies[91, 95, 99]. These studies challenge the common perception of systolic abnormalities as a late change in the natural history of hypertension, although the clinical correlates and prognostic significance of these more subtle abnormalities is systolic function remain to be determined.

RV CHANGES IN HYPERTENSION

A meta-analysis of echocardiography studies of hypertensive subjects demonstrate that on average 25% have concomitant RV hypertrophy (range: 25-80%) and its severity correlates with the prevalence and magnitude of LVH[100]. Patients enrolled in these studies were unlikely to have pulmonary hypertension to explain these findings[101, 102]. Therefore, while the relationship between right and left ventricular structure is commonly framed in anatomic or hydraulic terms, these findings suggest that systemic diseases such as arterial hypertension can influence the RV through neurohumoral activation. Among the several putative pathophysiological mechanisms, increased sympathetic tone and abnormal activation of reninangiotensin-aldosterone system deserve particular attention and have been supported by several preclinical studies [103, 104]. Using echocardiography-based deformation imaging, Tadic et al.[105] observed worse RV and right atrial mechanics in hypertensive patients with inadequate BP control. In addition, these changes in the right-sided chambers correlate with aerobic exercise performance. Further studies are needed to examine the impact of treatment on RV function and to determine the prognostic value of these perturbations in RV structure and function in hypertension.

IMPACT OF ANTIHIPERTENSIVE TREATMENT ON CARDIAC STRUCTURE AND FUNCTION

Antihypertensive therapy has been associated with significant reduction in LV mass in several studies.[69, 81, 106, 107] Interestingly, the magnitude of reduction in LV mass was found to correlate only modestly with the extent of BP decline[81]. Muiesan et al.[69] also observed an

impact of antihypertensive treatment on LV geometry, with a normalization of LV geometry occurring in 9% of the 436 subjects and associated with a better prognosis. In hypertensive patients treated with losartan or atenolol, Wachtell et al.[108] reported a conversion of concentric to eccentric LVH in 34% of subjects, whereas only 3% of patients with eccentric LVH transitioned to concentric LVH.

Several groups have also noted an improvement of diastolic function in response to antihypertensive therapy[109-111]. However, two randomized clinical echocardiography sub-studies with larger sample sizes and longer duration of follow-up demonstrated no impact of antihypertensive therapy on diastolic function, despite adequate blood pressure control and significant regression of LV mass[81, 106]. This dissociation between structural and functional improvement may be related to the multifactorial pathogenesis of diastolic dysfunction. Alternatively, this dissociation could represent a preferential dependence of hypertension-induced diastolic dysfunction on the extracellular matrix composition as opposed to cardiomyocyte hypertrophy, which is the principal determinant LV mass[81].

CONCLUSIONS

Patients with hypertension demonstrate diverse patterns of perturbation in cardiac structure and function (Figure 1). The prevalence of LVH varies considerably based on population characteristics including age, race, and co-morbidites. When present, LVH identifies patients at higher risk of CV events. Although classically associated with concentric hypertrophy, eccentric LVH is also common in hypertensive cohorts. HHD is also characterized by subclinical impairment in diastolic and systolic function. The determinants of the LV structural and functional response to hypertension – and its inter-individual variability – remain unclear, although patient characteristics including age, gender, race/ethnicity, and comorbidities likely contribute. Our current understanding of the underlying cellular and molecular mechanisms have been reviewed elsewhere[32, 112, 113]. Ultimately, a better understanding of the mechanisms and prognostic significance of these different cardiac phenotypes in hypertension may help improve our ability to individualize treatment and, ultimately, further reduce the morbidity and mortality caused by hypertension.

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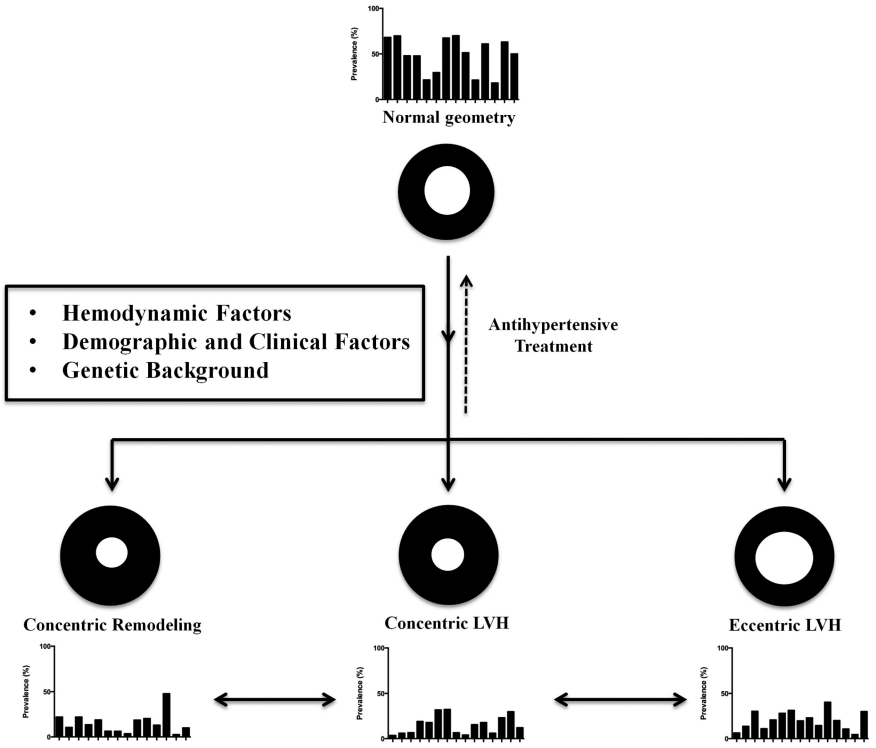

Figure 1.

Representation of different left ventricular geometric patterns and their interrelationship in hypertension. Bar graphs depict the prevalence of each LV geometric pattern in the reviewed epidemiological studies and clinical trials (Table 1; scale 0-100%). Arrows highlight the dynamic nature of cardiac structure, as illustrated by studies of the effect of antihypertensive treatment (see text for further discussion).

Table 1

Cardiac geometry patterns prevalence in hypertension epidemiological studies and clinical trials.

	Demographics				LV structure			LV geometry			
Studies	**Age, y**	**Male gender, %**	**White, %**	**BMI, Kg/m^2**	**EDD, mm**	**LVMi, g/m^2**	**LVH, %**	**Normal, %**	**Concentric Remodeling, %**	**Concentric LVH, %**	**Eccentric LVH, %**
Saba et al. * (N=966)	53±13	47.7	100	29.0±6.7	52.9±5.7	124±27	9.9	68.1	22	3.6	6.3
PAMELA Study * (N=944)	59±10	53.6	100	27.4±4.6	NA	NA	19.5	69.9	10.5	6	13.6
APROS Study † (N=1074)	48±11	53	100	26.9±4.7	NA	NA	36.9	NA	NA	6.6	30.3
Fesler et al. † (N=645)	44±13	57.1	100	25.3±3.7	NA	NA	33	48	22	19	11
Muiesan et al. ‡ (N=436)	56±8	57.1	100	26.5±3.5	NA	NA	38.6	47.9	13.5	17.9	20.7
Eguchi et al. † (N=400)	68±9	38	0 (100% Asian)	24.5±3.5	NA	NA	59.75	21.5	18.75	31.75	28
St. Petersburg Study ‡ (N=734)	51±3	35.2	100	29.0±5.0	50.1±4.3	130±32	63.7	29.6	6.4	32.4	31.3
Glorioso et al. † (N=493)	47±10	59.6	100	26.8[1.3]	49±4.1	97{25]	26.2	67.5	6.3	6.5	19.7
HyperGEN Study * (N=1384)	53±11	64	37 (AA-63%)	31.8±6.8	NA	NA	27	70	3.5	4	23
APROS-diadys Study† (N=2545)	70±4	49	100	26±2.6	NA	NA	30	51.4	18.6	15.5	14.5
Iwashima et al. † (N=1160)	63±11	53	0 (100 Asian)	24.2±3.4	NA	NA	58.3	21.4	20.4	17.9	40.3
LOLIPOP Study ‡ (N=1074)	NA	NA	100	NA	NA	NA	26	61	13	6	20
Adebayo et al. † (N=1020)	58±13	56	0 (100% Africans)	27.0±5.3	NA	NA	33.9	18.2	47.8	23.2	10.7

	Demographics				LV structure			LV geometry			
Studies	**Age, y**	**Male gender, %**	**White, %**	**BMI, Kg/m^2**	**EDD, mm**	**LVMi, g/m^2**	**LVH, %**	**Normal, %**	**Concentric Remodeling, %**	**Concentric LVH, %**	**Eccentric LVH, %**
LIFE Study [§] (N=937)	NA	82	NA	27.2±4.4	NA	NA	34.3	63.1	2.6	29.8	4.5
SEAS Subtudy[§] (N=1238)	69±11	59	NA	27.2±4.5	50.4±6.3	NA	40.2	*50*	*10*	12.1	*30*

AA, African American; EDD – end-diastolic diameter, LVMI – left ventricular mass index; LVH – left ventricular hypertrophy. Values in italics were estimated by the authors from primary data provided in the referenced manuscript.

[*] population-based cohort

[†] hospital-based cohort

[‡] Primary care practice-based cohort

[§] Clinical trial