

Review

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Review

Challenges in Echocardiography for the Diagnosis and Prognosis of Non-Ischemic Hypertensive Heart Disease

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Abstract: It has been well established that hypertension is considered as a predominant risk factor for the development of cardiovascular diseases. Despite the link between hypertension and cardiovascular diseases, hypertension may directly affect the cardiac function leading in heart failure, mostly with preserved ejection fraction (HFpEF). There are echocardiographic findings indicating hypertensive heart disease (HHD) defined as altered cardiac morphology (left ventricular concentric hypertrophy, left atrium dilatation) and function (systolic or diastolic dysfunction) in patients with persistent hypertension irrespective of cardiac pathologies to which it contributes, such as coronary artery disease and kidney function impairment. In addition to classical echocardiographic parameters, novel indices, like speckle tracking of the left ventricle and left atrium, 3D volume evaluation, myocardial work in echocardiography may provide more accurate and reproducible diagnostic and prognostic data in patients with hypertension. However, their use is still underappreciated. An early detection and prompt therapy of HHD will greatly improve the prognosis. Hence, in the present review, we shed light on the role of echocardiography in the contemporary diagnostic and prognostic approach of HHD.

Keywords: hypertensive heart disease; echocardiography; prognosis; speckle tracking

Introduction

Hypertension (HTN) is a very common disease worldwide and a strong risk factor for cardiovascular diseases and a plethora of conditions, including atrial fibrillation (AF), perioperative ischemia, coronary artery disease (CAD), rehospitalization, kidney disease, valvular diseases, acute aortic syndromes (like aortic dissection, intramural hematoma, or aortic ulcer) [1]. Although the cutoff criteria for hypertension vary between the American and European guidelines, there is substantial similarity in most recommendations for the management of hypertension and its complications [2–4]. Among hypertension-derived complications, hypertensive heart disease (HHD) has been widely recognised and refers to disturbed cardiac structure and function, affecting the left ventricle (LV), left atrium (LA), and coronary arteries as a result of prolonged exposition to high blood pressure (BP) [5]. Nevertheless, there is no universal consensus on the definition of HHD and therefore, HHD diagnosis is based on the clinical history, and the imaging modalities, like echocardiography and functional or anatomical tests for ischemia, to identify all the possible changes in the myocardium and coronary arteries.

From the pathophysiological perspective, the unmanaged high BP induces high afterload and high LV filling pressures leading to structural changes such as left ventricular hypertrophy (LVH) and fibrosis, and LA enlargement [6]. Besides this, HHD relates to systolic and diastolic LV dysfunction or a combination of them. HTN stands out as a primary risk factor for heart failure (HF)

development. Recent evidence suggests the co-existence of HTN in 76% of newly diagnosed HF cases [7], and individuals with HTN have an almost twofold higher lifetime risk of HF development compared to those with normal BP [8]. HTN stands out as the predominant and highly impactful morbidity in heart failure with preserved ejection fraction (HFpEF), with a prevalence of 80% in the Get with the Guidelines (GWTG) initiative. The most formidable challenge in the diagnosis and management of HFpEF, lies within its high incidence, affecting high percentage of individuals [9,10]. Moreover, numerous epidemiological studies have unveiled the link between HTN and coronary artery disease (CAD), a significant HF risk factor³. Individuals with HHD face an elevated risk of developing CAD affecting both large and small arteries (microvascular disease). Notably, the INTERHEART study demonstrated that 25% of the population-attributable risk for a myocardial infarction can be attributed to HTN [11].

Despite the interplay between HTN and CAD, one of the most frequent challenges in clinical practice is to diagnose HHD in patients without underlying CAD. Echocardiography is a easily performed, cheap, repeatable and accessible modality to estimate the cardiac structure and function [12]. During the working-up diagnosis of HHD, several classic echocardiographic indices (e.g. LVH) have been proposed. Besides this, novel echocardiographic parameters (e.g. speckle tracking) may be useful to identify cardiac changes due to HHD at an early stage. A prompt therapy may inhibit cardiac remodeling and attenuate cardiovascular risk [13].

The purpose of this paper is to provide an overview of the classic and novel echocardiographic findings and their role in the diagnosis and prognosis HHD without CAD. An objective knowledge of the potentiality and challenges of this imaging modality might promptly detect HHD, prevent its progression to HF or even reverse the HF.

Pathophysiology

Chronic arterial HTN trigger pathological processes, leading to structural and functional disturbances in the myocardium, like hypertrophy, fibrosis, and ischemia [14,15]. Chronic or sustained arterial HTN, leads to pressure overload of the left cardiac cavities, induce change in gene expression and confers simultaneous hypertrophy of the myocyte and changes in the extracellular matrix. Structurally, the LV walls become thicker, with or without simultaneous increase in absolute myocardial mass, as a compensatory mechanism to pressure overload. Depending on whether there is LV dilation, four patterns of hypertrophy are distinguished: eccentric non-dilated, eccentric dilated, concentric non-dilated, and concentric dilated [16]. Non-hemodynamic factors, such as the renin-angiotensin-aldosterone system, demographic factors (gender and ethnicity), obesity, and genetics, play a significant role in myocardial thickening. It is worth noting that it is not fully understood why patients with HHD develop a specific LVH pattern.

Another integral element of HHD is the myocardial fibrosis [17], either interstitial (reactive, diffuse) or replacement (reparative). Myocardial reactive fibrosis involves the accumulation of fibrous connective tissue in the interstitial and perivascular spaces without a significant loss of myocardial cells. Replacement fibrosis, on the other hand, consists of scar tissue formed due to the loss of myocardial cells and their replacement by connective tissue following myocardial infarction or myocardial death from other causes [18]. It is still unclear whether those two types of myocardial fibrosis represent distinct processes, as they may occur simultaneously [6]. Hemodynamic factors, such as chronic pressure overload causing myocardial stress or injury, lead to increased collagen production (type I, type III) in the myocardium as a reparative mechanism. Non-hemodynamic factors, such as the renin-angiotensin-aldosterone system, also play a significant role in myocardial fibrosis [6].

HHD eventually may progress towards HF, where the initial myocardial hypertrophy and fibrosis result in myocardium stiffening and systolic and diastolic LV dysfunction. Eccentric hypertrophy is more likely to lead to HF with reduced ejection fraction (HF_rEF), while concentric hypertrophy may lead to HF with preserved ejection fraction (HF_pEF). Additionally, changes in the LA morphology begin in the early stages of HHD despite the normal LV [18]. In particular, microstructural changes precede macroscopic alterations (LA dilatation), resulting in a functionally

impaired atrium despite its normal size. LA remodeling in HHD is once again the result of both hemodynamic factors (increased afterload) and non-hemodynamic factors (neurohormonal activation) [19]. The increased LV afterload leads to elevated filling pressures within the left atrium, consequently increasing its wall tension. As an adaptation, LA may reshape affecting first its contractility. Non-hemodynamic factors, such as the activation of renin-angiotensin-aldosterone system, the release of natriuretic peptides, and endothelin-1, also play a significant role. Those factors trigger inflammatory cells accumulation, leading to fibrosis and further remodeling of the LA. Additionally, there is an increase in sympathetic nervous system activation due to neurohormonal activation. In the context of HHD, the involvement of norepinephrine plays a pivotal role in the pathophysiological cascade. The sequence begins with increased sympathetic nerve activity, particularly in young hypertensive individuals, leading to elevated heart rate, cardiac output, renal vascular resistance, and blood pressure. Norepinephrine, along with other humoral factors like angiotensin II, contributes to a hemodynamic profile that induces adaptive changes in cardiac structure, ultimately culminating in hypertensive left ventricular (LV) hypertrophy. The significance of norepinephrine becomes apparent as its high levels or interactions with humoral factors potentiate structural changes in the heart [20].

Despite the acknowledged importance of norepinephrine in the development of LV hypertrophy, there exists a notable discrepancy in the effects of antiadrenergic drugs on regression. While α 1-adrenergic blockers, such as doxazosin, demonstrate favorable effects on reversing LV hypertrophy, the clinical consequences may be not always beneficial with reducing LA mass, as evidenced by an increased risk of HF incidence during treatment [21].

AF is frequently observed not only in patients with dilated LA, but also when atrial fibrosis is present. Speckle tracking and cardiac magnetic resonance have clarified this point [22]. It is worth mentioning that several mechanisms have been proposed to explain how systemic HTN leads to remodeling of the right ventricle (RV), and fewer have been proposed for the right atrium (RA). However, the whole process is not yet fully understood. The same pathophysiological steps present in the left cavities are involved in the right cavities as well: hypertrophy of myocardial cells, fibrosis, and alterations in the composition of the extracellular matrix. The RV myocardium becomes thicker, dilated, accompanied by RA dysfunction [22]. Finally, persistent HTN leads to arteriosclerosis of the vessels in circulation, as well as microvascular rarefaction. The co-existence of hypertrophic myocardium and arterial stiffness increases the LV afterload and precipitates the LV remodeling affecting the overall systolic and diastolic function of the heart.

Classical Echocardiographic Indices

Echocardiography plays a pivotal role in identifying structural changes in individuals with HTN, leading to the development of HHD. Table 1 summarizes the challenges and the prognostic value of proposed parameters.

Table 1. Classical and novel echocardiographic indices of hypertensive heart disease.

Variable	Indices	Challenges	Prognostic value
LVH	IVSd \geq 12mm, RWT \geq 0.42, LVMI \geq 95g/m ² (female) and \geq 115g/m ² (male), LVEDD \geq 5.3cm (female) and \geq 5.8 cm (male)	<ul style="list-style-type: none"> • Moderator band • Different sites for measurements • Wall thickness at the papillary muscles • BSA or height indexing 	<ul style="list-style-type: none"> ↑↑↑IVS ↑↑LVMI ↑LVH pattern
	LV systolic function	LVEF (either PLAX or Simpson's biplane) FS	<ul style="list-style-type: none"> • Regional WMA • Geometrical assumptions • Foreshortened views • Endocardial delineation
LA	LA dimension (PLAX or PSAX) LAVI LAVmin	<ul style="list-style-type: none"> • Suboptimal views • Angled views • Poor endocardial definition • Foreshortening 	<ul style="list-style-type: none"> ↑LA dimension ↑LAVI ↑LAVmin

Diastolic dysfunction	MV inflow pattern. E/A ratio, septal E' <7cm/s, lateral E' <10cm/s, average E/e' ≥14 pulmonary venous flow pattern	<ul style="list-style-type: none"> • Proper alignment of the ultrasound beam • Limited mitral annulus movement • Pulmonary vein flow infrequently obtainable 	<ul style="list-style-type: none"> ↑↑↑E/A>2 ↑↑E/E' ratio ↑pulmonary ↑venous S/D ratio
RV systolic function	TAPSE, S', RVEF, FAC, PASP	<ul style="list-style-type: none"> • variations in load and angle • longitudinal function of the basal RV free wall • absent tricuspid regurgitation <ul style="list-style-type: none"> • RV load • assumptions and meticulous manual tracings of the RV endocardial edge • calculation of trans-tricuspid pressure gradient, significantly attenuated in severe TR 	<ul style="list-style-type: none"> ↑↑TAPSE ↑↑RVEF ↑↑PASP
Diastolic stress echo	E/e' >15 and TRVmax>3.4m/s	<ul style="list-style-type: none"> • TR detection • Validation for HFpEF diagnosis 	↑↑↑ HFpEF
Speckle tracking LV	GLS Myocardial work index	GLS is load-dependent Unknown cut-off values of myocardial work index	↑GLS
Speckle tracking LA	LASr, and contraction strain	Optimal views of all LA walls	LASr (?)

LASr, left atrium strain reservoir; LAVmin, minimal left atrial volume; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MV, mitral valve; PASP, pulmonary artery systolic pressure; PLAX, parasternal long-axis; PSAX, parasternal short-axis; RV, right ventricle; RVEF, right ventricular ejection fraction; RWT, relative wall thickness; S', systolic velocity of the tissue doppler of the tricuspid valve; TAPSE, tricuspid annular plane systolic excursion; TRVmax, tricuspid regurgitant maximum velocity; WMA, wall motion abnormalities.

Left Ventricular Hypertrophy

LVH is a common manifestation of HDD and defined as LV thickening (≥ 12 mm) or increased LV mass [23]. LVH has been long used as a risk factor of individuals without known cardiovascular disease. Hence, its detection stratifies the cardiovascular risk of patients with and without HDD and has considerable impact on patient's management and prognosis. Both LV thickening and increased LV mass rely on linear measurements of LV dimensions on 2-dimensional (2D) images, while LV mass calculation uses geometric assumptions regarding the LV shape [24]. The echocardiography image quality is of paramount importance for measurements. Moreover, there is a high intra-observer and inter-observer variability even with the high image resolution 2D echocardiography. The presence of moderator band, different sites for dimension measurements in parasternal long-axis (PLAX) and parasternal short-axis (PSAX) views and the miscalculation of wall thickness at the papillary muscles origin may attenuate the reliability of measurements. Thus, the 2D echocardiographic assessment of LV mass has significant drawbacks and tends to overestimate LV mass in comparison to cardiac magnetic resonance (CMR) imaging [25]. This is the case when image quality is suboptimal. The recent advances in 3D echocardiography may compensate the abovementioned limitations, with less overestimation of LV mass than CMR [26]. However, an optimal 2D image quality is a prerequisite for valid 3D echocardiography, while it is difficult to detect changes in LV mass along time. Therefore, a technically perfect echocardiographic examination from an experienced operator is deemed necessary.

Three main patterns of LVH have been first described: (a) concentric hypertrophy, (b) eccentric hypertrophy, and (c) concentric remodeling⁶. The first two, concentric and eccentric LVH, are the two main patterns of LVH. That classification is based on three parameters with their cut-off values: 1) the relative wall thickness ($RWT \geq 0.42$), 2) the left ventricular mass index [$LVMI \geq 95$ g/m² (female) and ≥ 115 g/m² (male)], 3) end-diastolic diameter [$LVEDD \geq 5.3$ cm (female) and ≥ 5.8 cm (male)] in hypertensive individuals, enhancing clinical understanding, and guiding appropriate interventions.

By adding the end-diastolic volume refines the classification of LVH in four distinct patterns: eccentric non-dilated, eccentric dilated, concentric non-dilated, and concentric dilated hypertrophy (Figure 1)

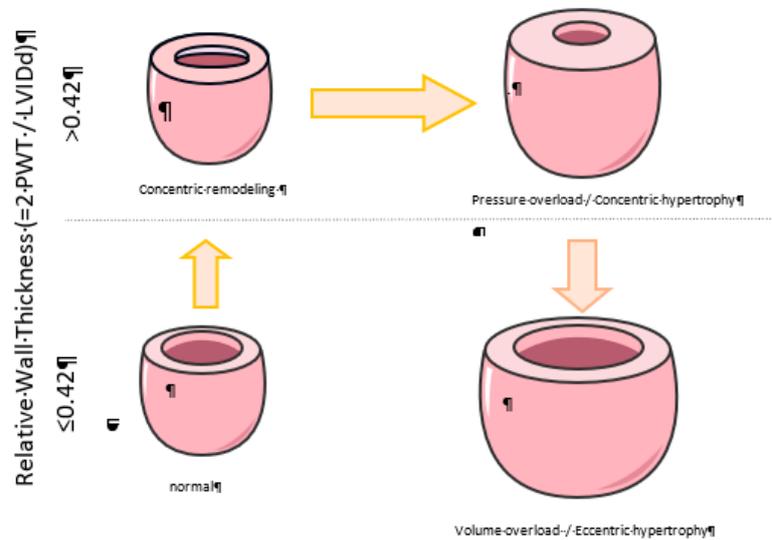


Figure 1. Common patterns of left ventricular hypertrophy in hypertensive heart disease.

Since LV mass relates to body size, indexing values to body surface area (BSA) has been used in population-based studies for reference values. The LV mass indexed by BSA underestimates the prevalence of LVH in obese patients [27]. An alternative to traditional BSA indexing is using height alone for adjusting cardiac parameter measurements, particularly relevant in HHD assessments. This method aims to provide a more nuanced evaluation by considering an individual's height as the sole determinant, addressing variations in body size not fully captured by BSA. Height indexing enhances precision in evaluating cardiac structure and function, providing a more individualized assessment of dimensions. Utilizing height as a reference in obese patients acknowledges the significance of differentiating between overall body size and its composition. This approach enhances the ability to gain a more accurate understanding of cardiac health within this specific population [28,29]. The cutoff values, based on height alone, for left ventricular mass index are established at equal to or greater than 45 g/m^{2.7} in females and equal to or greater than 49 g/m^{2.7} in males.

The prognostic value of LVH is unambiguous. The pattern of increased LV mass has an added value to LVH in general and hypertensive population [30,31]. Since 1990s, it has been demonstrated that LVH is a strong factor for cardiovascular mortality [32]. 10 years follow-up of hypertensive patients have outlined the prognostic power of LVH and ventricular arrhythmias [33]. An indexed LV mass has better prognostic ability and may be preferred instead of absolute values of LVH. However, it is subject of debate to use either BSA or height for LV mass indexing. Another proof of the prognostic impact of LVH derives from studies using anti-hypertensive medications. The targeted LVH regression has been accompanied with cardiovascular benefits [34].

Left Ventricular Systolic Function

The conventional assessment of left ventricular systolic function relies on metrics like LV ejection fraction (LVEF) and endocardial fractional shortening (FS). However, their application, primarily at the endocardial surface, sparks concern about their relevance in the context of LVH. It becomes apparent that these measurements may tend to overstate LV systolic function. This phenomenon can be ascribed to cross-fiber shortening, where myocardial fibers not only shorten along their direction but also perpendicular to it [35]. This unique dual direction shortening allows the LV wall to contract in multiple dimensions, resulting in considerable thickening despite reduced shortening in specific myocardial segments, particularly evident in hypertrophic left ventricles. Interestingly, the impact of cross-fiber shortening diminishes in the myocardial midwall [36].

A rising embraced metric is to enter stress-corrected midwall fractional shortening. This can provide a more nuanced reflection of systolic function, particularly beneficial in cases of LVH. Unlike left ventricular endocardial FS, this parameter paints a more accurate picture [37]. The LV systolic function assessment may face challenges, especially in patients with inadequate quality of acoustic windows, like obese individuals or those with chronic obstructive pulmonary disease. Unfortunately, overweight or obesity are common predisposition factors of HHD, preventing the echocardiographic early diagnosis. Moreover, regional wall motion abnormalities is another obstacle faced in systolic function variation. Measurements taken from specific views of the left ventricle (parasternal axis) do not align overall ventricular function. Instead of them, Simpson biplane technique is the most reliable, but it is still based on geometrical assumptions and faces important limitations. In particular, its accuracy is compromised with off-axis or foreshortened imaging planes. In the latter case, an obscured true apex may introduce potential errors, especially when wMA are present (e.g. apical infarcts) [38]. All echocardiographic methods rely on good acoustic windows for clear delineation of the blood/endocardial border, vital for accurate measurement/tracing. Large studies have reported the failure of the modified Simpson method to determine LVEF in a significant proportion of participants (31–38%) due to poor image quality, blurred visualization of endocardial borders leading to potential inaccuracies. The alternative administration of contrast agents has proven effective in improving LVEF determination in patients with challenging acoustic windows [39].

Additionally, in terms of accuracy, studies have consistently shown that echocardiography tends to underestimate the LVEF when compared to the more advanced imaging capabilities of CMR [40]. A reduced LVEF, or even a low normal LVEF has been long associated with poor prognosis in HHD, which outlines the necessity to get accurate measurements and intensive therapy. In the context of HFrEF, the prognosis is reduced proportionally to the degree of LV systolic impairment [41].

Left Atrium Dilatation

In the context of HHD, LA enlargement signifies an early and prevalent structural change. Interestingly, the specific geometric pattern of the LVH does not affect the size of the LA in the initial stages of essential hypertension, whether expressed in terms of diameter or volume. What emerges as a critical determinant of LA enlargement, independent of potential confounding factors, is the left ventricular mass index (LVMI) [42]. The greatest anterior-posterior dimension at the level of the aortic root of LA has long been discussed as an unambiguous index of LA enlargement. To quantify LA volume, methods such as area-length or modified Simpson's are employed, typically normalized for BSA and presented as mL/m² (left atrial volume index - LAVI). The normal range of LAVI extends up to 34 mL/m².

A notable challenge in evaluating the LA stems from the potential inaccuracies in echocardiographic measurements. LA anterior-posterior diameter can be obtained from the PLAX or PSAX views and it is highly dependent on perpendicularity of axis. Suboptimal views, angled views or bad visualization of the posterior wall may lead to miscalculation of LA dimension. The assessment of LAVI necessitates the employment of two orthogonal echocardiographic views (apical 4 chamber and apical 2 chamber view). To refine the LA length, align it perpendicular to the midpoint between the mitral annular plane and the midpoint of the LA superior wall. When appropriately captured, the LA length should exhibit minimal variation, ideally not exceeding 5 mm, between the 4-chamber and 2-chamber views [43]. Ensuring the avoidance of foreshortening in the long axis of the LA is critical for maintaining precision in the evaluation process [44]. Accurate assessment of the LA requires calculating the maximum LA area and ensure optimal evaluation of all LA walls. It is equally imperative to carefully navigate around the confluence of pulmonary veins and the left atrial appendage during this process which may influence the final measurements [45].

Comparative studies between Transthoracic echocardiography (TTE) and CMR have consistently demonstrated the underestimation of both LA and RA volumes in TTE. The disparity, statistically significant in mean values, was not attributed to interobserver differences, clinical events, or image quality. These findings are in agreement with previous studies, revealing CMR's tendency to overestimate atrial volumes. Discrepancies between imaging modalities may stem from poor

endocardial definition and foreshortening in echocardiography, particularly evident in standard apical views, impacting the lateral atrial walls. Less accurate delineation of pulmonary veins and appendices may be the case of echocardiography, as highlighted by area discrepancies being more frequent than length discrepancies [46].

Notably, the LAVI has been related to mortality risk, regardless of the left ventricular geometry, in a substantial cohort of patients exhibiting preserved LV systolic function [47,48]. LA enlargement has been considered as a bad prognostic factor in patients with HHD and HFrEF [49]. On the other hand, it may be a consequence of HFpEF which interplays with AF occurrence and other comorbidities [50]. Recent studies indicate that measuring minimal left atrial volume (LAVmin) at LV end-diastole, when the left atrium is directly exposed to LV end-diastolic pressure, may offer a closer correlation to LV filling pressure and clinical outcomes compared to maximal left atrial volume (LAVmax) [51,52].

This suggests that LAVmin could be a more effective marker for LA structural remodeling. It's noteworthy that while the prognostic value of LAVmax in patients with HFpEF is contentious, there is limited data on the prognostic value of LAVmin in HFpEF patients, necessitating further research [53–56]. The adaptation to BSA leads to the calculation of the LAVmin index (LAVImin), whose power to predict HF hospitalization appears to be notably stronger for individuals without a history of AF compared to those with AF, especially when juxtaposed with LAVI_{max}⁵⁸.

Diastolic Dysfunction

Mitral inflow measurements play a crucial role in assessing diastolic function. Parameters such as, E and A velocity, their ratio (E/A), the deceleration time of E velocity, and the isovolumic relaxation time provide valuable insights. Notably, in hypertensive individuals, a normal in-treatment transmitral flow pattern serves as an indicator of a lower risk for HF, irrespective of BP levels. Although the implementation of antihypertensive therapy in patients with LVH improves mitral inflow patterns, this has not been correlated with a reduction in cardiovascular morbidity and mortality [57]. On the other hand, high E/A ratio has been associated with grade III diastolic dysfunction indicating high LV filling pressures and poor prognosis, especially when HF has been already developed [58,59].

The main limitation of echocardiography in diastolic dysfunction assessment is the clustering of numerous parameters and the inaccuracy in blood flow calculation. The proper alignment of the ultrasound beam is pivotal, given that Doppler tends to significantly underestimate flow velocities when the angle of interrogation exceeds 30°. To counteract the impact of transducer angulation, it is imperative to align the Doppler sample as parallel as possible with blood flow, ensuring optimal waveform morphology and maximal diastolic flow velocities. Color flow echocardiography may guide the alignment of sample volume parallel to flow [60]. The placement of pulsed-Doppler sample at the tips of the mitral leaflets (4 chamber view) is a prerequisite for the estimation of the left atrioventricular gradient, which may be miscalculated if it is placed at the mitral valve annulus level. Using the lowest filter setting is advised to capture the full velocity profile [61].

The pulsed Tissue Doppler-derived E' velocity of the mitral annulus is an essential component in the evaluation of cardiac diastolic function. A decline in septal (<7cm/s) and lateral e' (<10cm/s) and the increased average ratio (E/e' ≥14) signal compromised LV relaxation, albeit with certain limitations, like limited mitral annulus movement, calcification, or prosthetic valves (aortic or mitral). It is worth emphasizing the predictive capability of the E/E' ratio for primary cardiac events in a hypertensive population without established cardiac disease [62]. The additional assessment of late (atrial) diastolic velocity (A'), may be influenced by LA function and LV end-diastolic pressure, but its diagnostic and prognostic values have not been established.

The evaluation of pulmonary venous flow pattern, when obtainable, has been implicated as an independent diagnostic criterion and a valid predictor of CVD events in essential hypertension. A high S/D ratio per se is independently associated with an increased cardiovascular disease risk in hypertensive patients [63]. Furthermore, the concomitant high pulmonary venous systolic-to-diastolic wave ratio (S/D, normal values: male < 1.51, female < 1.66) and a low E/A ratio exerts

predictive value in HHD⁶⁵. In TTE S, D flow data are usually acquired from the orifice of the right upper pulmonary vein in the apical 4-chamber view. Color flow Doppler should be employed to accurately place the sample volume 1 to 2 cm into the pulmonary vein, acknowledging that the far-field nature of the structure may limit the quality of the recording [64]. Overall, the echocardiographic assessment of diastolic function has several limitations, including dependence on number of Doppler measurements, potential interobserver variability and acoustic window challenges in hypertensive population. In contrast, CMR has the advantage of precise volumetric measurements, tissue velocity mapping, independent of acoustic window quality [65].

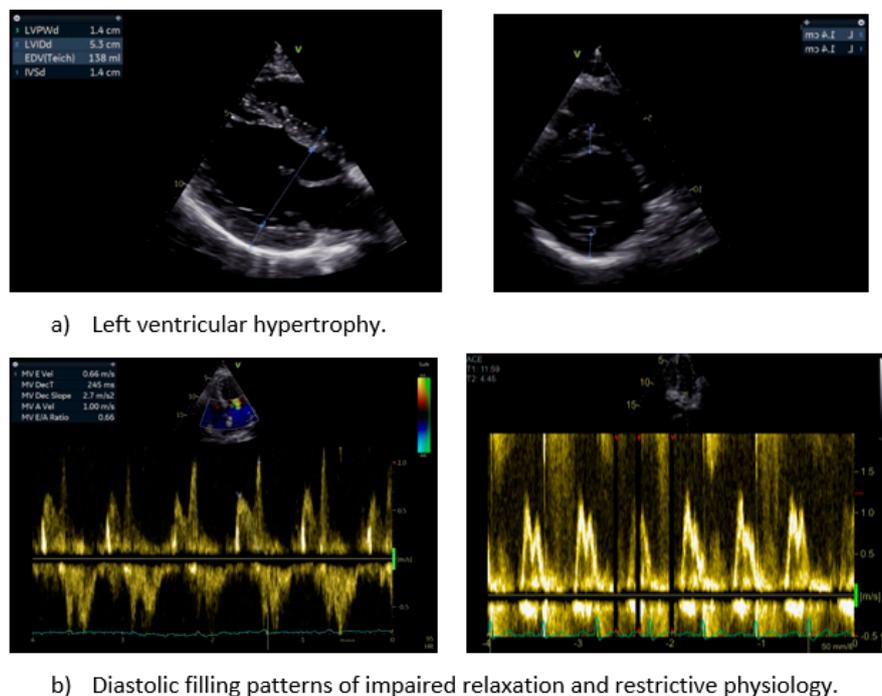


Figure 2. Classical echocardiographic indices of hypertensive heart disease.

RV Systolic Function

RV systolic dysfunction is not only a recognized marker of adverse prognosis in HF but is also linked to poor prognosis in HHD [66]. All the following parameters have been associated with negative prognosis in the whole spectrum of cardiac diseases. On the other hand, RV measurements are usually influenced by volume load or are based on geometrical assumptions which attenuate the accuracy of RV systolic function estimation.

Echocardiographic evaluation of the RV systolic function in HHD involves a comprehensive assessment of various parameters of the right cavities: tricuspid annular plane systolic excursion (TAPSE), systolic velocity of the tissue doppler of the tricuspid valve (TV) annulus, right ventricular ejection fraction (RVEF), Fractional Area Change (FAC), pulmonary artery systolic pressure (PASP), size of RV ventricle, right ventricular systolic pressure (RVSP). A comprehensive echocardiographic assessment and early detection of right cavities dysfunction may contribute to risk stratification and tailored clinical management of individuals with HHD [67].

The TAPSE method stands out for its simplicity and reproducibility, but it's susceptible to variations in load and angle. This technique involves measuring edge-to-edge the excursion of tricuspid annulus during systole with a swift sweep speed of ≤ 100 mm/s. In cases of severe tricuspid regurgitation, TAPSE may exhibit pseudo-normalization due to volume overloading [68]. In parallel, the tissue Doppler RV systolic wave velocity may assist to assess the longitudinal function of the basal RV free wall, lacking a comprehensive evaluation of global RV function. Similar to TAPSE, it's also angle- and load-dependent, requiring precise alignment of the ultrasound beam with the lateral TV annulus, essentially capturing only the longitudinal function of the RV base [69].

The assessment of RV size and systolic function through conventional echocardiography should be conducted in all patients with HHD, considering RV loading conditions. It is crucial to employ a multi-parametric approach and utilize various echocardiographic views to ensure accurate evaluation, especially when there is a discrepancy between different echocardiographic parameters [70]. This comprehensive approach enhances the precision and reliability of the interpretation of findings related to RV size and function.

HFpEF is acknowledged as a contributor to pulmonary hypertension (PH) [71]. The estimation of PH relies on the detection of the tricuspid regurgitant jet, to calculate the RA-RV gradient and leads to the calculation of the right ventricle systolic pressure (RVSP) through the simplified Bernoulli equation [72]. However, if tricuspid regurgitation is absent, as is occasionally encountered, the assessment of RVSP becomes challenging through conventional echocardiography. It's crucial to acknowledge that RVSP estimation is subject to assumptions, such as the absence of right ventricular outflow tract obstruction and accurate assessment of right atrial pressure [73]. The co-existence of RV systolic dysfunction and PH leads to underestimation of RVSP due to 2 important limitations: the arbitrary set of RA pressure (RAP) levels and the calculation of trans-tricuspid pressure gradient which is usually severely attenuated in severe TR. Despite the great advantage of echocardiography to easily estimate the RVSP in a non-invasive way, this remains an indirect measurement of pulmonary pressures providing a likelihood of PH and not a firm diagnosis. A detailed assessment often necessitates additional testing, particularly right heart catheterization, to provide more accurate and comprehensive insights into pulmonary hemodynamics [74].

Calculation of the RVEF and FAC is based on assumptions as well and demands meticulous manual tracings of the RV endocardial edge at both end-systole and end-diastole, and it should include papillary muscles, trabeculations, and the moderator band [75]. 3D echocardiography has emerged as a solution to the inherent limitations of 2D echocardiography. It surpasses these constraints in RVEF calculation, and it is considered the gold standard for global RV function evaluation. Notably, the 3D calculation of RVEF closely aligns to CMR relative measurements. It's crucial to know that accurate 3D echocardiography is strongly dependent on high-quality imaging, invariable heart rates, specialized and expensive software, and demands substantial time and expertise [76].

Stress Echocardiography

The interplay between HF with preserved Ejection Fraction (HFpEF) and HHD is complex. Both are characterized by exertional dyspnea and effort intolerance due to elevated LV filling pressure [77]. HFpEF may be not clinically apparent, posing challenges to diagnosis based solely on symptoms and standard evaluations. Diastolic dysfunction is the first manifestation of this pathological process, discernible in early, mild arterial hypertension even before the development of LVH. HFpEF is not uncommon among patients with HHD, but surprisingly hypertensive medications do not considerably alleviate symptoms or alter prognosis. Up to now the diagnosis of HFpEF is challenging and most recently diastolic stress echocardiography (DSTE) has been proposed in cases where diastolic dysfunction at rest is mild (grade I) [78]. On top of the resting echocardiography parameters and natriuretic peptides levels, an abnormal response during exercise test is defined as $E/e' > 15$ and an increase in $TRV_{max} > 3.4$ m/s. According to the consensus statement, DSTE may be useful to confirm or reject HFpEF diagnosis in patients at intermediate risk. However, recent questions have arisen about the reliability and technical feasibility of using this parameter during physical activity [79]. The differentiation of dyspnea among elderly requires a non-invasive test for HFpEF diagnosis, as patients without exercise-related diastolic dysfunction may not benefit from specific treatments [80]. Despite DSTE's potential, the absence of diagnostic and prognostic validation, the limited expertise capacity and the required equipment restrict its widespread use [81].

A cardiopulmonary exercise test (CPET) evaluates the cardiopulmonary system by observing how the cardiovascular and respiratory systems respond to the energy demands of muscle contraction during physical exercise. The choice of exercise modalities, such as a bicycle ergometer

or treadmill, and specific protocols is personalized based on factors such as the patient's fitness level, health, weight, age, under the guidance of the requesting physician [82].

The combined exercise stress echocardiography (ESE) and cardiopulmonary exercise test (CPET) constitute a diagnostic approach aiming to unmask HFpEF in patients with hypertension. It's noteworthy that physical exercise has the capacity to stress cardiopulmonary homeostasis and reveal pathological hemodynamic changes that may not be apparent at rest. In addition to the aforementioned changes during DSTE, lower peak values of oxygen consumption (VO_2) and end-tidal carbon dioxide ($P_{et}CO_2$), along with a higher ventilatory equivalent for carbon dioxide (VE/VCO_2) slope, are independent predictors of masked HFpEF [83,84]. This comprehensive diagnostic approach enables timely intervention and personalized management strategies [85,86]. Notably, CPET-ESE has recently demonstrated additional predictive value in patients with subclinical HF compared to the two techniques used separately [87]. Among its limitations, CPET-ESE is a more time-intensive and expensive procedure, requiring specialized equipment and personnel. Careful patient selection is critical, guided by clinical judgment. Therefore, hypertensive individuals exhibiting symptoms and signs indicative of HFpEF, should initially undergo a comprehensive evaluation that encompasses standard rest echocardiography and the measurement of natriuretic peptides and then if it is medically deemed necessary further exercise testing [88]. Overall, the diagnosis of HFpEF in the context of HHD may require multimodality imaging approach to unmask symptoms and detect hemodynamic changes during exertion associated with elevated LV filling pressures [89].

Novel Echocardiographic Indices

Speckle Tracking of Left Ventricle

Myocardial strain and its sensitive index of myocardial deformation, global longitudinal strain (GLS), provides a widely accepted, accurate, repeatable evaluation of LV systolic function [90]. The sub-endocardial layer of LV supports predominantly the longitudinal mechanics, whereas the mid-wall and sub-epicardium contribute mostly to the circumferential, rotational, and twisting motions. HTN is well-known that severely suppresses the LV myocardial shortening in the longitudinal direction, than in the circumferential direction [91]. Impaired myocardial deformation has been long associated with HHD [92]. Moreover, speckle tracking has the potential to differentiate various types of LVH diseases [93]. The adverse structural cardiac remodelling in HHD involves the expansion of cardiomyocytes and accumulation of fibrosis in the extracellular matrix. Speckle tracking in echocardiography has the advantage of detecting a decline in myocardial strain in patients with HHD and normal LVEF before apparent structural changes, unravelling subtle impairment of systolic function [94]. A recent meta-analysis of 6 studies reported the clinical value of GLS to detect subclinical cardiac damage in patients with masked hypertension [95]. However, the myocardial strain is load dependent. Hence, an increase in afterload may lead to a decreased GLS, thereby attenuating the accuracy of research results [96]. A compensatory modality using myocardial strain with a limited influence of blood pressure on its results is myocardial work index [97]. This is a non-invasive index, based on the speckle tracking technique, to assess myocardial deformation incorporating the left ventricular pressure. Growing evidence supports the potentiality of myocardial work index to assist the diagnostic algorithm of HHD [98,99]. A growing number of studies suggests that speckle tracking performs better than LVEF, since it may uncover subtle LV systolic dysfunction in hypertensive patients, before LVEF starts declining [100].

In addition to the diagnostic value, the contribution of GLS to prognosis has been proved in a wide a spectrum of cardiomyopathies, however its application in risk stratification of patients with HHD has not been validated [101]. Future studies will assess the efficacy of speckle tracking to predict cardiac organ damage and determine the anti-hypertensive regimen [102]. The introduction of 3D-speckle tracking echocardiography may further increase the sensitivity of echocardiography to detect regional alterations of longitudinal strain and area strain. With optimal echocardiographic views, the

3D speckle tracking may assist to better quantify the degree of myocardial damage [103]. It is a promising technique which requires further investigation.

Speckle Tracking of Left Atrium

Most recently, researchers have hypothesized the LA dysfunction before structural changes become evident, like LA dilatation [104]. All three phases of LA function (reservoir, conduit and booster pump) functions have been found significantly impaired in HTN patients than healthy controls [105]. Classical (E/E' , LA size) and novel indices (reservoir strain (LASr), conduit strain, and contraction strain) of LA myocardial deformation have been associated with HTN [106]. Notably, LA reservoir and booster pump strain seem to correlate with GLS in hypertensive patients. Changes in LA deformation are more sensitive than other indices, since acute blood pressure lowering in patients with hypertensive urgency improves promptly LA strain [107]. Unambiguously, alterations in LA mechanics come up early in the course of HHD development [108]. Up to now, the evidence of the diagnostic power and to a lesser extent of the prognostic value of LA strain in HHD is not robust [109]. More studies are required to verify the cut-off values of LA strain. In all cases, speckle tracking implementation has a prerequisite of good quality views of LA in order to achieve accurate and repeatable measurements (Figure 3).

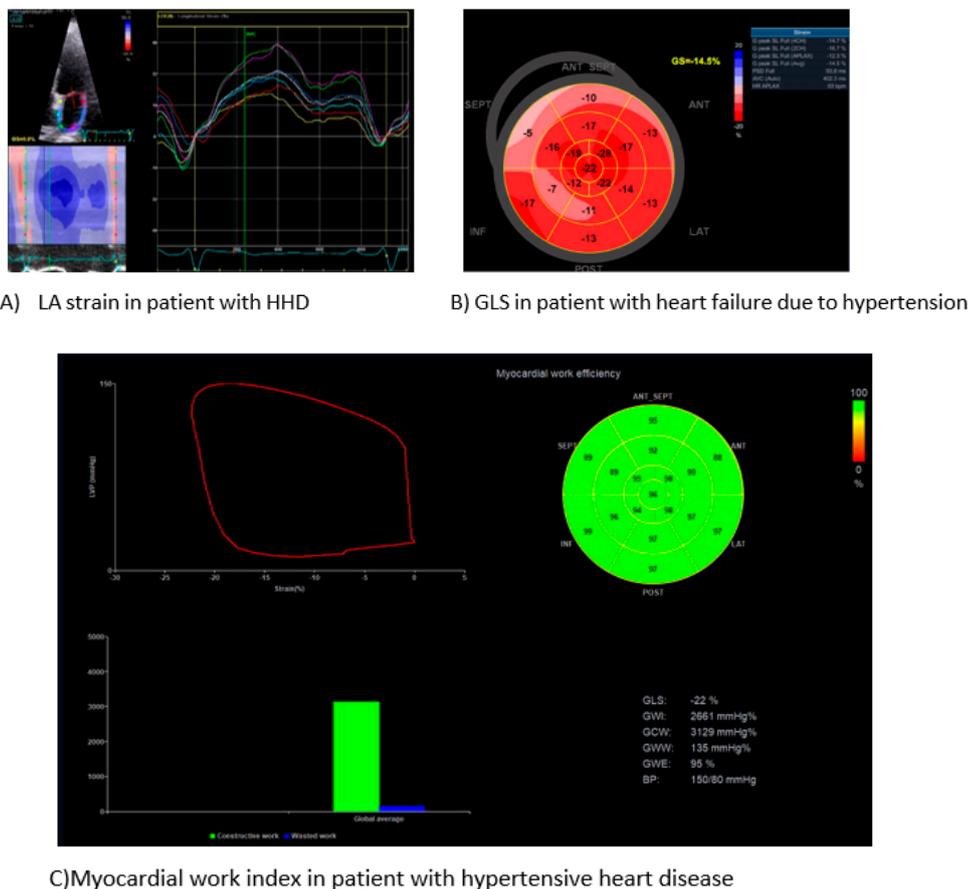


Figure 3. Representative images of speckle tracking in patients with hypertensive heart disease.

Recently, both TTE and CMR, stand as indispensable tools for cardiac evaluation, each presenting distinctive advantages. Echocardiography, with its real-time imaging capabilities and widespread accessibility, emerges as a dynamic and cost-effective option, capable of assessing valve function and chamber dimensions. Its bedside utility and portability enhance its versatility in various clinical scenarios. Conversely, CMR, renowned for superior spatial resolution and tissue characterization, offers unparalleled insights into cardiac anatomy and function. Despite the higher costs and specialized requirements associated with CMR, its ability to provide detailed information

about myocardial tissue texture and views of high imaging quality make it a valuable complement to echocardiography. The selection between these modalities hinges on clinical nuances, specific diagnostic needs, and available resources, often prompting a synergistic integration for a comprehensive cardiac assessment. The technological advances in echocardiography open new roads in its clinical application and future research will clarify its diagnostic and prognostic power.

Conclusions

HHD as a consequence of high-pressure overload on the heart has been increasingly recognized comprising an emerging cardiac disease. It presumably consists of a clinical entity with unfavourable prognosis beyond CAD or kidney function impairment. Echocardiography is a first-line modality for HHD diagnosis clustering a number of parameters of cardiac morphology and function in patients with persistent hypertension. The absence of a single, gold-standard diagnostic parameter has compromised all estimations about the incidence, evolution and prognosis of HHD. The addition of novel indices, like speckle tracking of the left ventricle and left atrium, 3D volume evaluation, myocardial work to classical echocardiographic parameters, may provide more accurate and reproducible diagnostic and prognostic data in those patients. Till now, their use is still underappreciated, but they have the potential to objectively define the HHD and estimate its prognosis.

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