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Review Article

Ultimate phases of hypertensive heart disease and stressed heart morphology by conventional and novel cardiac imaging

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Abstract: Early recognition of hypertensive heart disease is needed to prevent macrovascular and microvascular damage. Hypertension (HTN) is a risk factor for coronary artery disease, and plays a prominent role in the development of adverse left ventricular (LV) remodeling and heart failure. Here, we review new knowledge on effects of HTN on cardiac geometry and function, obtained from multimodality cardiac imaging, including echocardiography, positron emission tomography and magnetic resonance imaging. Early recognition of changes in LV geometry and function induced by HTN could identify patients at risk for end-organ damage, who could be targeted for close monitoring and intensive therapy. Basal septal hypertrophy as the early imaging biomarker at the adaptive phase may be a specific aspect not only in hypertensive heart but stress-related conditions and called stressed heart morphology.

Keywords: Hypertension, basal septal hypertrophy, adaptive phase, stressed heart morphology, echocardiography

Introduction

Chronic pressure overload caused by hypertension induces increase in LV wall thickness to normalize wall stress. In the early stage, increase in relative wall thickness before development of hypertrophy (LVH) is associated with preservation of left ventricular (LV) function. Over time, pressure-overload leads to concentric remodeling of the LV, which reduces wall stress and preserves pump function despite abnormalities in cardiac mechanics [1]. In the setting of uncontrolled HTN, progressive increase in wall thickness occurs, which manifests as LVH on cardiac imaging. Concomitantly, HTN lead to macrovascular and microvascular disease, which contribute to the development of heart failure [2, 3]. Chronic pressure-overload leads to increase in wall stress and increase in LV myocardial mass which is associated with adverse cardiovascular (CV) events and all-cause mortality [4]. However, effective medication can reduce LVH and CV death, myocardial infarction, stroke [5, 6].

Echocardiography

Echocardiography have provided great contribution to diagnose and follow-up of cardiac patients with development of treatment modalities since the basic ultrasound principals have been used practically and effectively. Unique diagnostic contribution of echocardiography in cardiology have continuously increased by the technic developments including blood flow and tissue Doppler, speckle tracking, strain imaging and real-time 3 dimensional echocardiography (RT3DE) which are being used widespreadly [7, 8].

Focal hypertrophy may be an early finding in LV geometric remodelling in hypertensive patients. It was shown that septal base is thicker than mid apical part in mild and moderate HTN [9]. Histologic features of septal base was found different from hypertrophic cardiomyopathy. On an autopsy performed in a patient, the hypertrophy was identified, although results of microscopic examination showed no fibre disarray as seen in primary cardiomyopathy [10]. We previously observed a decreased LV basal cavity volume possibly due to basal hypertrophic segment in patients with hypertensive LVH using RT3DE [11].

It was suggested that differently from primary cardiomyopathy the focal hypertrophy may be

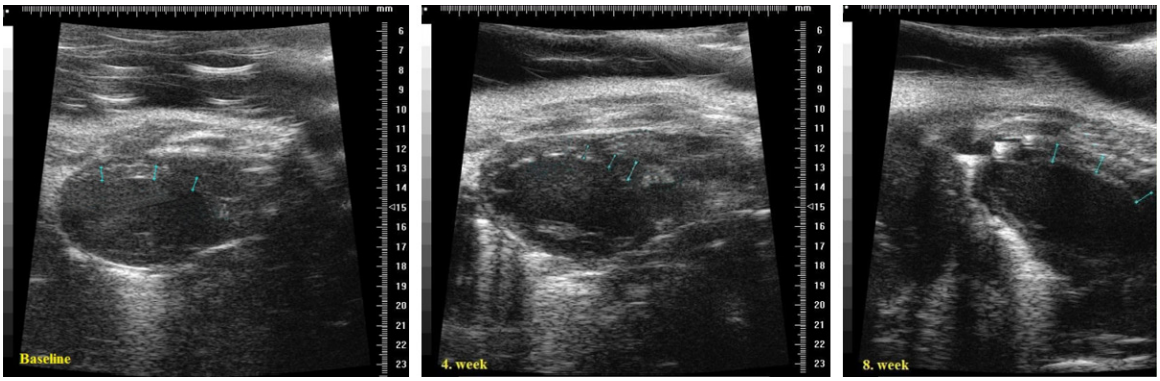

Figure 1. Cardiac images of a mice using 3rd generation microscopic ultrasound show normal cardiac geometry, relatively prominent LV septal base at 4 week after stress induction due to pressure-overload (TAC: transverse aortic construction) and global remodeling at 8 week, respectively.

secondary or contributory to the enhanced ventricular dynamics [12]. In earlier stage of hypertensive disease than LVH, we previously detected stress-induced increased LV outflow tract gradients in hypertensives with basal septal hypertrophy (BSH) [13]. Beta-blocker therapy may be beneficial for dynamic LV outflow tract obstruction in hypertensive BSH [14]. To resolve obstruction caused by striking hypertensive BSH, even alcohol septal ablation was used successfully [15]. In hypertensive BSH, we quantitatively detected the stress-induced hypercontractility on focal hypertrophied septal base by tissue Doppler imaging combined with dobutamine stress [16]. Therefore, it is usually accepted that hypercontractility is detected in HTN earlier than LVH and tissue dysfunction [17].

Similar to our documented findings in BSH [16, 18], stress-induced hypercontractility is also usual finding in patients with global hypertrophy and it may result in a diagnostic dilemma for coronary artery disease [19]. It was demonstrated using microneurography and isotope dilution methodology that increased sympathetic activity is directly related to the development of hypertensive LVH [20]. Stress-induced hypercontractility may be a reflection of preserved LV function in hypertensive LVH [21]. In fact, we observed that complex mitral annulus geometry and dynamics which reflect systolic function are preserved in patients with hypertensive patients with global hypertrophy by RT3DE [22].

Furthermore, we mentioned the importance of precise LV contractility evaluation and quantitative volume determination by cardiac imaging in HTN [23]. It was suggested that hypercontractility with LV cavity obliteration may be associated with a good prognosis [24]. Hypercontractility of LV base also was described in stress-induced cardiomyopathy [25]. Since this region is more predominant and hypercontractile in both HTN and acute stress cardiomyopathy, we have suggested that stressed heart morphology (SHM) related to predominant LV base may be a conjunctive point of determination in clinical conditions with acute or chronic stress exposure due to increased afterload [18, 26, 27]. This variety of stress-related conditions could be together with the different etiologic components including emotional, functional due to increased vascular tonus and mechanic blockage due to stenotic valve diseases as discussed in the SHM section of the current review.

3rd generation microscopic ultrasonography

Hypertensive LVH may have regional heterogeneity. Early determination of hypertensive heart disease using biomarkers could be valuable to start early antihypertensive medication which could prevent adverse disease consequences [28-31]. We documented that BSH (**Figure 1**) is an early imaging marker of hypertrophy using 3rd generation microscopic ultrasonography in an animal model [31]. The LV septal base may be the first affected region since LV cavity diameter is greatest at the base, resulting in greater wall stress, when compared to the mid and apical regions [32]. Furthermore, studies have demonstrated greater sympathetic innervation of the LV base compared to the apex. The LV

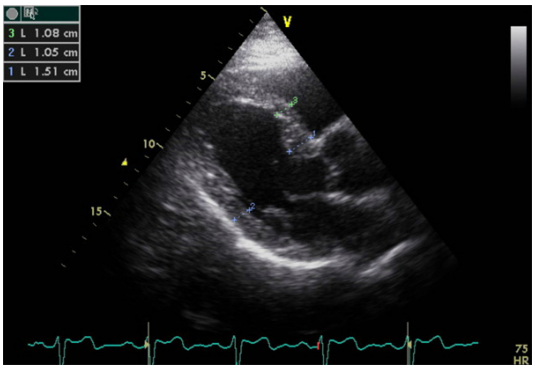

Figure 2. Parasternal long-axis echocardiography shows a predominant regional LV septal base during end-diastole in a hypertensive patient with basal septal hypertrophy.

base (**Figure 2**) also has greater tissue content of noradrenaline which could be related to the myocardial dynamics [33, 34]. Early septal involvement in turn could result in greater degree of tissue dysfunction in the basal septum compared to LV free wall in advance hypertensive disease [35].

Therefore, any delay in effective treatment may lead to a progression in LV remodeling. Notably, hypertensive remodeling in patients treated with antihypertensives is associated with increased likelihood of adverse CV events independent of age, gender, blood pressure lowering treatment modality, and in-treatment LV mass index [36]. RT3DE reconstruction data can provide a global geometric assessment in the hypertensive disease process. We and others have previously documented regional LV geometric heterogeneity and diminished LV basal cavity volume which is a consistent finding with predominant LV septal base in secondary LVH using RT3DE [11, 37].

Early documentation of the remodeling in HTN has gained more importance, because this is a reflection of early cardiac end-organ change, which could identify patients needing intense BP monitoring and treatment [38-43]. It was reported that marked elevations of BP during exercise, even in the absence of resting HTN is associated with increased LV mass [38]. We suggested that exercise HTN (greater BP than 210 mmHg in men, 190 mmHg in women) [38], may be common in otherwise healthy, young adults, can be of clinical importance [39]. It should be considered as a cause of what could otherwise be considered to be physiologic LV remodeling detected by cardiac magnetic resonance (CMR) [40]. Blood pressure trends during exercise may have prognostic information even in healthy subjects and identify individuals at risk for target organ damage, including LVH, in patients without HTN diagnosis [41, 42]. These individuals who would not be classified as hypertensive by conventional standards could undergo additional evaluation, include sleep study to rule out sleep apnea, lifestyle modifications (e.g. weight loss) to prevent development of overt HTN, as well as cardiac imaging and renal function testing to detect the presence of target organ damage [43].

Stress such as exercise, which increases blood pressure can be informative in clinical practice [23, 43]. In the early stage of hypertensive heart disease, we and the others reported that HTN-mediated early focal hypertrophy could be a part of clinical spectrum in hypertensive heart disease [9, 10, 13, 14, 16]. Regional LV functional analysis can be detectable quantitatively using novel cardiac imaging including tissue Doppler, strain and combined stress test and tissue Doppler imaging [9, 13, 16, 18, 21, 23, 26]. Furthermore, determination of exercise HTN in patients with undiagnosed HTN [42] or incidentally detected BSH [13, 16] could be important for early recognition of subclinical target organ damage.

Stressed heart morphology

Early LV remodeling detected by CMR due to exercise hypertension are being more evaluated in healthy individuals including endurance athletes [39, 40, 44-46]. Stress test with BP monitoring may be recommended especially for the individuals who look healthy and have SHM (predominant septal base with/without hypercontractility at peak stress) to eliminate exercise HTN [45]. Beyond increased arteriolar tonus in hypertension as functional and acute stress cardiomyopathy as emotional etiology, we recently have described SHM in patients with aortic stenosis as mechanic etiology [46] and discussed the special sensitivity of septal base to the variety of stress stimuli [16-18, 25-27, 35, 39, 40, 45, 46].

LV compensatory hyperfunction in patients with chest pain without any coronary artery disease was more common in patients with hyper-

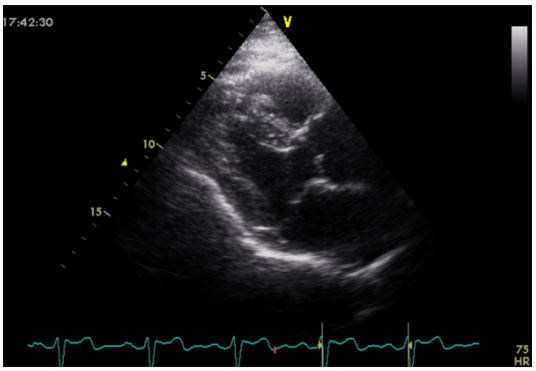

Figure 3. Remarkable protrudition of septal basal tissue into the LV outflow tract during end-systole in the same patient of **Figure 2**.

tension in wall motion analysis [47]. In mild HTN, endocardial fiber shortening as LV functional parameter to end-systolic stress was shown to be associated with enhanced ventricular contractility [48]. LV hyperfunction in higher ambulatory blood pressure was found along with a greater velocity of fiber shortening in relation to end-systolic wall stress [17]. Stress-induced LV hyperfunction could be an early component of LV remodeling even in borderline HTN [49]. However, segmental detection of LV remodeling progression geometric and functionally in humans could be challenging.

In fact, we detected a tissue velocity increment at early remodeling with BSH in small animals with pressure-overload which was consistent with the findings in humans (**Figure 3**) and a sharp transition from compensatory hyperfunction to tissue dysfunction by 3rd generation microscopic ultrasonography [31, 50]. In this animal validation study, we noted imaging aspects of this transition from compensatory LV hyperfunction with development of BSH and increased gradients to maladaptive global remodeling with low gradients during the adaptive and maladaptive phases of LV remodeling under hemodynamic stress.

Radionuclide myocardial perfusion imaging

Increased O_2 uptake with exercise HTN in normotensive individuals at rest was determined by first-pass radionuclide angiography about three decades ago [51]. In that study, LV hyperfunction plotted consistent findings with the wall motion analyses in patients with HTN. LV hyperfunction under stress induction could be detected in patients with dyspnea and considered to be related to diastolic dysfunction in radionuclide myocardial perfusion imaging [52]. However, any study neglecting existence of exercise HTN could not plot such a conclusion in patients with LV hyperfunction under stress [53].

Fibrosis and magnetic resonance imaging

Regional tissue Doppler evaluation can contribute to detect segmental dysfunction [54] or segmental wall motion abnormality which is reported to be a sign of adverse outcome in patients with HTN [36]. Hypertensive patients without global remodeling was found to have lower myocardial extracellular volume than that in patients with hypertensive LVH who have blunted myocardial strain on CMR [55]. Microcirculation and myocardial structure are altered with progression of hypertensive heart disease, apoptosis and fibrosis lead to reduced LV contractility [56]. Because fibrosis-mediated abnormalities in hypertensive heart disease course are important, development of fibrosis in hypertensive LV remodeling was pointed out as the therapeutical target [57, 58]. The older hypertensive patients with a mean age of 70 are associated with the blunted response of myocardial tissue to stress induction [59].

It was demonstrated that a significant degree of improvement in midwall or endocardial wall fractional shortening can be achieved by aggressive antihypertensive treatment leading to a reduction of observed CV events and the incidence of heart failure [60]. Although effective antihypertensive treatment is essential to improve LV function and better outcome, fibrosis markers related to aging process are associated with multiple adverse cardiac outcomes including myocardial infarction, heart failure, and death are significantly elevated [61, 62].

Conclusion

Basal septal hypertrophy with LV hyperfunction under stress both in animal model and humans is detectable by novel quantitative cardiac imaging methods and represents the early adaptive phase of LV remodeling prior to maladaptation. Novel geometric and functional imaging findings in the adaptive phase of hypertensive heart may be a conjunctive point of determination in stress-mediated cardiac conditions and called SHM.

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Disclosure of conflict of interest

None.

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