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REVIEW

Quantitative left ventricular contractility analysis under stress: a new practical approach in follow-up of hypertensive patients

F Yalçin, H Yalçin, N Küçükler and TP Abraham
Divisions of Cardiology and Nuclear Medicine, Department of Medicine, Johns Hopkins Medical Institutions, Cardiovascular Imaging Center, Baltimore, MD, USA

Excessive sympathetic activity and stress-induced left ventricular (LV) hypercontractility have been described in hypertensive LV hypertrophy. Recent quantitative data have shown that hypertensive LV hypertrophy is associated with preserved global LV function. However, progression of uncontrolled hypertension have detrimental effects on both the ejection fraction (EF) and LV contractile response to stress. Hypertensive LV hypertrophy has some common characteristics, including preserved global LV systolic function and LV volume with heart failure with preserved EF (HFPEF), which makes it difficult to differentiate between the two conditions at rest. Studies suggest that adopting an efficient antihypertensive therapy regimen may positively effect on the LV contractile capability in patients with long-standing hypertension. Evaluation of quantitative LV contractility under stress may be beneficial to differentiate between the hypertensive LV hypertrophy and HFPEF. It may also assist in developing a more effective modality in medical management of patients with hypertensive heart disease.
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Introduction

Hypertension is a major risk factor for cardiovascular and cerebrovascular disease. Stress-induced exaggerated blood pressure response during exercise testing suggests the probability of left ventricular hypertrophy (LVH), despite the absence of diagnosed hypertension. Myocardial tissue remodelling and LVH are some of the 'end-organ damage' manifestations of hypertension specifically on the cardiac tissue.[1,2] Stress-induced exaggerated blood pressure response at exercise test may be a predictor for future incidence of clinical hypertension.[3,4] The benefits of medical treatment are well described in the management of patients with cardiovascular complications due to chronic hypertension.[5] The risk of serious cardiovascular events and death can be reduced by effective control of hypertension, which is the major casual factor of >75% of patients with heart failure (HF).[6] In addition to lowering blood pressure, blockade of the renin–angiotensin–aldosterone system may prove beneficial in slowing the progression of HF. The use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptors blockers, alone or in combination, is associated with a mortality and morbidity benefit in patients with HF.[6]

Correspondence: Dr F Yalçin, Division of Cardiology, Department of Medicine, Johns Hopkins Medical Institutions, Cardiovascular Imaging Center, 720 Rutland Avenue/Ross Research Building, Room 1044, Baltimore, MD 21205, USA.
E-mail: fyalcin1@jhmi.edu
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The role of sympathetic stimulation and LV dynamics in hypertension

Previous studies have analysed the LV function by relating endocardial fibre shortening to end-systolic stress. Findings suggest an enhanced ventricular contractility even in mild hypertension.[7,8] One study shows that LV hypercontractility exists in patients with borderline blood pressure elevations, suggesting that patients with elevated blood pressures have a greater velocity of fibre shortening in relation to end-systolic wall stress.[9] This is indicative of an enhanced inotropic state. Excessive sympathetic stimulation and LV hypercontractile state possibly are important in the clinical presentation of hypertension.[10,11] In a study conducted in

patients with findings of chest pain and normal coronary arteries, wall motion analysis has shown a LV hypercontractile response to sympathetic stimulation.[12] The same study showed that hypertension was more frequent in patients with hypercontractile response to stress compared with those without hypercontractility. Microneurography and isotope dilution studies of sympathetic activity in hypertensives have shown that increased sympathetic activity and its trophic effects on cardiac muscle are directly related to the development of LVH.[13]

The role of sympathetic stimulation in the development of LVH

Hypertension is associated with multiple end-organ involvement, including LVH. Echocardiography provides a documentation of a relatively high frequency of LVH in even mild hypertension.[14,15] It is known that LVH is the primary adaptive mechanism to compensate for increased cardiac workload produced by conditions causing volume and/or pressure overload.[16] It has been reported that increased sympathetic activity is correlated with the LV mass index, suggesting an association between sympathetic hyperactivity and myocardial mass.[17] In normal anatomy, the diameter of the LV cavity is the largest at the base and the wall stress is greater in the basal cavity compared with that of the mid-apical LV cavity.[18] It is suggested that, unlike primary cardiomyopathy, the regional hypertrophy may be secondary or contributory to the enhanced ventricular dynamics in hypertensive LVH.[19] In hypertensive patients, our observation shows that LV base is the most predominantly hypertrophied myocardial region, which possibly is related to dynamic ejection by stress-induced dynamic LV outflow tract (LVOT) obstruction.[20] Cardiac remodelling induced by hypertension may have certain regional features (Figures 1 and 2). Regional hypertrophy may be initiated on the LV base or may be begin from base and extent to mid portion.[21] Increased afterload results in a significant burden on the LV base and this leads to the development of LVOT obstruction, which is remarkable in advanced hypertensive heart disease (Figure 3).[22] Utilisation of septal alcohol ablation could be effective therapy for remarkable hypertension-mediated predominant LV base, which results in dynamic LVOT obstruction.[23]

In patients with hypertensive LVH, we have derived a regional quantitative volume index, and have described a narrowed LV basal cavity by real-time three-dimensional echocardiography.[24] In cadaveric human heart specimens, LV fibres in the mid-wall are circumferential and oriented towards the base of the septum. Therefore, the thickest LV region is at the base. By the same logic the ventricular wall decreases in width towards the apex.[25] Real-time three-dimensional echocardiography has demonstrated prominent LV base in patients with hypertension.[26] In addition to the close location of LV base to increased afterload, it is now determined that LV base has regional neurohumoral feature that may possibly have remodelling effects



Figure 1 Transthoracic echocardiographic image at end-diastole shows a regional thicker myocardium on LV base than the other regions in a hypertensive patient with regional LV remodeling.

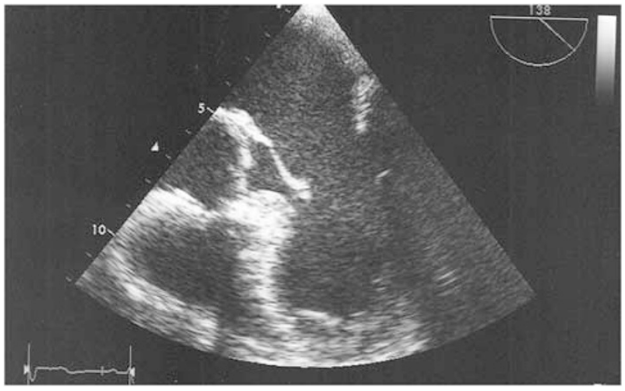


Figure 2 Transesophageal echocardiographic image shows focal predominant hypertrophy on LV base in another hypertensive patient.

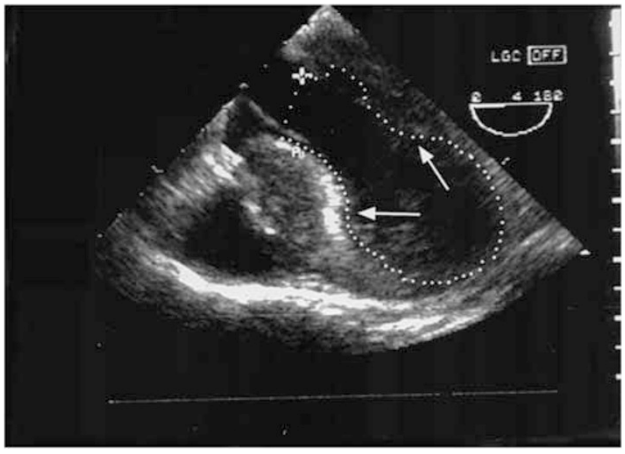


Figure 3 Remarkable hypertrophy on LV base in a patient with long-standing hypertensive heart disease.

on the LV myocardium in response to hypertensive stress. In this region, intramyocardial noradrenaline concentration was found to be greater compared with mid-apical part of LV myocardium.[27] It is well known that the sympathetic innervation of the LV becomes increasingly sparse from the base to apex.[28–30] Greater β-adrenergic receptor density and increased myocardial responsiveness to adenylate stimulation in apical myocardium compensates its sparse sympathetic innervation.[31]

Pursuant to combined analysis of tissue Doppler imaging and dobutamine stress echocardiography, we have found that predominant LV base is associated with stress-induced hypercontractility. It is also conceivable that LV basal hypercontractility may be lead to dynamic LVOT obstruction in patients with chronic hypertension.[32] In pressure overload model, early marked increase in angiotensin 2 type 1 (AT1) receptor density in the LV myocardium increases both plasma norepinephrine concentration and LV myocardial epinephrine content.[33] Nakagawa *et al*.[34] have observed that AT1 receptor antagonist therapy is effective in LVOT gradient reduction. This management modality has also resulted in a regression of myocardial hypertrophy in mild hypertensive patients with LVH. Al-Nasser *et al*.[35] have shown that β-blocker therapy has a beneficial effect on the reduction of LVOT gradient and rate–pressure product provoked by pharmacologic stress in patients with focal hypertrophy of LV base (all hypertensive but one subject). The effects were similar in patients with hypertrophic cardiomyopathy.[36]

In addition to LV regional features, hypertensive patients usually develop LV cavity obliteration (Figures 4a and b). Secknus *et al*.[37] have demonstrated that LV cavity obliteration (a consistent finding in LV hypercontractility), frequently respond to dobutamine echocardiography and this may indicate a favourable outcome. In this study, more frequent LV cavity obliteration was detected in patients with LVH compared with the control group. It was shown that stress-induced ejection fraction (EF) response is an independent predictor of mortality.[38] This was concluded based on the clinical and exercise test data and resting LV function in LVH patients (92% of whom were hypertensive). It is known that LV hypocontractility is associated with an increased risk for cardiovascular events.[39] Mid-wall mechanics may be impaired in patients with preserved global LV function. Improvement in mid-wall mechanics by effective medical therapy is associated with reduced cardiovascular events and a decreased HF incidence.[40] In hypertensive patients, scintigraphic analyses, in addition to ischaemic studies, may allow for a more accurate prognostication. In this regard, data show that increased end-systolic LV volume is associated with worse outcome in patients with hypertensive LVH.[41,42] Various types of antihypertensive drugs have been used to slow the progression of hypertensive LVH. A meta-analysis of 80 double-blinded, randomised and controlled trials has shown that AT1 receptor blockers, ACEIs and calcium antagonists are the most effective pharmaceutical options in reducing myocardial mass in hypertensive patients.[43]

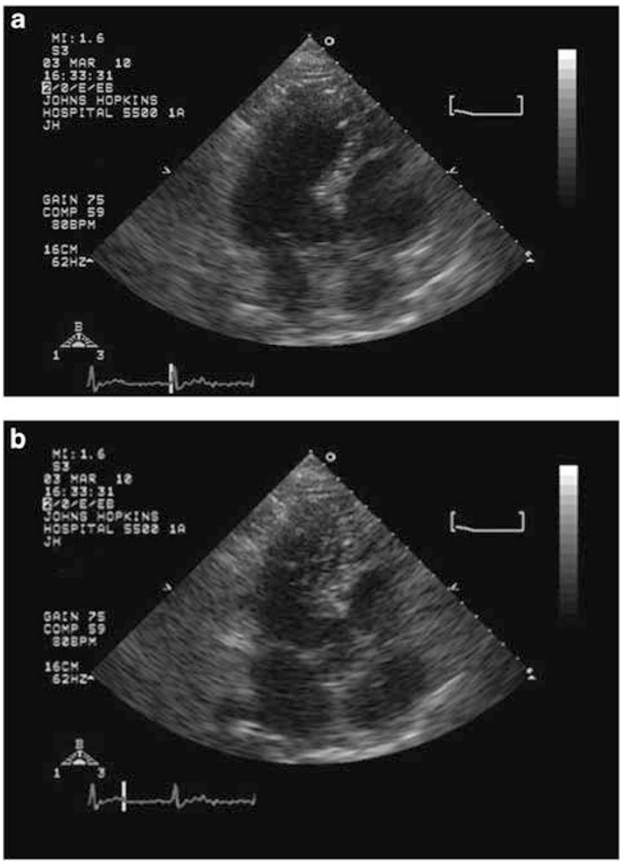


Figure 4 (**a**) End-diastolic echocardiographic image represents a regional thicker myocardium on LV base than the other regions in a hypertensive patient. (**b**) End-systolic echocardiographic image represents an end-systolic LV cavity obliteration in the same patient.

Sympathetic stimulation and dynamics in hypertension-mediated HF

Imaging studies on hypertensive patients with optimal medical management have shown that global LV function is preserved in majority of this subset of patients.[44,45] Our comparison analysis of patients with hypertensive LVH versus cardiomyopathy through real-time three-dimensional echocardiography of mitral annular circumferential and longitudinal motions, which reflect global LV function, are preserved in patients with hypertensive LVH unlike those with cardiomyopathy.[45] Cardiac tissue energy metabolism has been found to be unchanged at the LVH stage of pressure-overload model before HF development in Dahl salt-sensitive rats.[46] This preserved LV contractility and energy

metabolism at rest are consistent with findings of hypercontractile response to stress in hypertensive LVH. Preserved global systolic function was also documented by freehand three-dimensional echocardiography at rest in patients with HF with preserved EF (HFPEF).[47]

Abnormal coronary flow is detected even in early stages of hypertension, and the flow defect progressively worsens with disease progression.[48] Impaired coronary flow reserve, defined as a reduced coronary vasodilator response to stress, is associated with hypertensive LVH may be related to perivascular fibrosis.[49] In addition to impairment in microcirculation, myocardial structure is altered during the process of hypertensive heart disease and apoptosis, and fibrosis may contribute to hypertensive LV remodelling and reduced LV contractility.[50] In hypertensive patients older than 70 years of age,[51] LV contractility may be impaired at stress possibly as the result of myocardial fibrosis compared with the relatively younger groups.[32,44,45] It has been reported that AT1 receptor blocker agent used in this subset of patients may lead to a decrease in destruction of cardiomyocytes and halt the progressive fibrosis.[52,53]

HFPEF is the relatively new clinical entity, and almost half of total HF patients have a LV EF of at least 45%. Because majority of the HFPEF patients have systemic hypertension, HFPEF is usually accepted as a hypertension-mediated phenomenon with the presence of a normal or supernormal LV systolic function. Recent studies which compare hypertensive LVH patients and HFPEF patients have documented that HFPEF patients have more severe LV diastolic abnormality than that in hypertensive LVH.[54] Fibrotic tissue accumulation with a change in spatial orientation of collagen fibres may progressively decrease diastolic filling and result in impaired LV contractility.[55] Despite normal EF in patients with HFPEF, it has been emphasised that contractile abnormalities and severe diastolic dysfunction are more common in HFPEF, unlike patients with hypertensive LVH.[56]

LV volume studies have shown that the vast majority of HFPEF patients have normal end-systolic volume.[57] Preserved LV systolic function and LV volume leads to a difficulty in differentiating hypertensive LVH from hypertension-mediated HF at rest. LV hypercontractility in the earlier stage of hypertensive heart disease is detectable at rest and under stress in the outpatient setting.[7–12,32,58] Recently, it has been demonstrated by comprehensive imaging studies, that LV contractility parameters are blunted by stress in the HFPEF group.[59,60] These findings have consistently correlated with poor prognostic factors of low EF and larger volume under stress.[37,38,42]

These findings may support the argument that stress-induced contractile capability may be used in differentiating hypertensive LVH from HFPEF. Melenovsky *et al*.[54] reported that, HFPEF patients who were on an effective medical therapy had similar endocardial and mid-wall fractional shortening compared with that of hypertensive LVH. In this study, 68% of HFPEF patients were on an ACEI. This supports the hypothesis that myocardial tissue contractility may be preserved if an effective medical therapeutic regiment is developed using appropriate pharmaceutical interventions. Although comprehensive imaging studies show a preserved LV function in this group of patients, the Olmsted County study shows that HFPEF is associated with a high mortality rate similar to that of patients with reduced EF.[61] However, only 17% of the patients in this study were on an ACEI or AT1 receptor blocker therapy. This number was increased to include 51% of patients after the echocardiographic study findings were reviewed. More than 70% of patients in this study had moderate or severe LV diastolic dysfunction.

I-Preserve trial has shown that the previously mentioned medication regimen may result in a decrease in the development of LVH in HFPEF.[62] LVH was present in only 31% of the patients who were well treated. This group was largely on inhibitors of renin–angiotensin–aldosterone system as well as β-adrenergic blockage. In all, 26% of patients were on an ACEI, 15% were on spironolactone and 59% were taking a β-blocker. The prevalence of advanced LV diastolic dysfunction was lower in I-Preserve population compared with the other published HFPEF studies. The limited prevalence of LVH in I-Preserve may be a therapeutical disadvantage since it was mentioned that the severity of LVH may help clarify pathophysiology and define a target HFPEF population for future trials.[54]

Future directions

Quantitative determination of the LV contractility under stress, in addition to LV cavity analyses and EF measurements in the follow-up of hypertensive patients, may provide foresight for the future adverse consequences and allow for a strategic advantage in developing more effective medical management regimens for altering the natural course of the disease.

Conclusions

The LV hypercontractility in the earlier stage of hypertensive heart disease is detectable at rest and under stress. This finding may be obscured under stress, however, poor prognostic factors of low EF and larger end-systolic volume are reliable indicators in estimating the progression of hypertensive heart disease. These findings imply that, solely relying on the contractile parameters at rest may be insufficient in evaluating the patients with hypertensive heart disease. Also the evaluation of LV

contractility under stress may contribute to developing therapeutic regimens, which are more efficacious in managing patients with hypertensive heart disease. Furthermore, a history of effective medical therapy and a low prevalence of LVH in study subjects may possibly be the potential culprits for the therapeutic failure of AT1 receptor blockage in patients with HFPEF. Finally, despite the recent advancements in the diagnostic evaluation of myocardial contractility under stress, the currently available therapeutic strategies are not promising for effectively managing this group of cardiac patients.

Conflict of interest

The authors declare no conflict of interest.

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