

Cardiac Remodeling, Adaptations and Associated Myocardial Mechanics in Hypertensive Heart Diseases

Yau-Huei Lai,^{1,2} Chi-In Lo,^{1,2} Yih-Jer Wu,^{1,2,3} Chung-Lieh Hung^{1,2,4,5} and Hung-I Yeh^{1,2,3}

Hypertension is the leading cause of heart failure and cardiovascular comorbidities in developed countries. Left ventricular structural/functional alterations such as concentric remodeling or hypertrophy have been extensively studied in hypertensive heart diseases. Furthermore, it is also well-recognized that diastolic function actually deteriorates in hypertensive subjects prior to overt heart failure.

Novel imaging modality techniques such as myocardial deformation have allowed for early detection of regional/global myocardial contractile dysfunction. Myocardial deformation, which can be quantified by measuring the systolic strain and strain rate in three different directions (longitudinal, circumferential and radial), has facilitated new insights into the understanding of cardiac systolic mechanics in subjects with early stage myocardial damage.

Previous studies had shown that longitudinal function remains the most sensitive parameter in identifying hypertension-related myocardial dysfunction, particularly for those patients who had developed LV hypertrophy. Instead, preserved or enhanced short-axis function, when presented as circumferential or radial strains, may remain relatively preserved or enhanced in order to compensate for longitudinal functional decline. In this manner, global cardiac pumping in terms of ejection fraction may remain relatively unchanged.

The early recognition of subclinical systolic dysfunction and associated mechanical compensation in the context of hypertension is crucial, which potentially helps to identify a disease stage that is still responsive to therapeutic intervention.

Key Words: Concentric remodeling • Hypertension • Myocardial mechanics • Strain • Subclinical systolic dysfunction

INTRODUCTION

Hypertension is one of the most commonly encountered patient problems in daily clinical practice. As a leading cause of adverse cardiovascular events in developed societies, the underlying mechanisms, pathophysiology and clinical consequences of hypertension are increasingly becoming more widely recognized.¹⁻³ Hypertensive heart disease, especially when accompanied by aging, is associated with numerous adverse cardiac structural/functional remodeling, repercussions that extend to the cellular level, including abnormal myocyte growth and collagen fiber deposition, leading

Received: December 13, 2012 Accepted: December 26, 2012

¹Division of Cardiology, Department of Internal Medicine, Mackay Memorial Hospital; ²Department of Medicine, Mackay Medical College, and Mackay Medicine Nursing and Management College, Taipei; ³Mackay Medical College, New Taipei City; ⁴The Institute of Health Policy and Management, College of Public Health, National Taiwan University, Taipei; ⁵Department of Health Industry Management, Kainan University, Taoyuan, Taiwan.

Address correspondence and reprint requests to: Dr. Chung-Lieh Hung, Division of Cardiology, Department of Internal Medicine, Mackay Memorial Hospital, No. 92, Chung-Shan North Road, 2nd Section, Taipei, Taiwan. Tel: 886-2-2531-9260; Fax: 886-2-2543-3535 ext. 2459; E-mail: hungcl.md@gmail.com

to myocardial fibrosis, cardiomyopathy and eventually the development of heart failure (HF).^{4,5}

Diastolic dysfunction characterized by ventricular filling abnormalities, including decreased diastolic distensibility and impaired relaxation, is thought to represent an early and important pathophysiological intermediate step between hypertension and HF.⁶ Nearly half of all patients with hypertension encounter evidence of diastolic dysfunction,⁷ which actually represents an attractive target for disease prevention because the high prevalence of hypertension may translate to a greater population-attributable risk.⁸ However, the exact mechanism of the transition from asymptomatic diastolic dysfunction to diastolic heart failure remains unclear.

The deleterious factors for impaired cardiac function in subjects with hypertension are multi-factorial, such as apoptosis of cardiomyocytes, adaptive ventricular remodeling, increased mechanical stress with subsequent ventricular hypertrophy, phenotype alterations of cardiomyocytes, interstitial and perivascular fibrosis, endothelial dysfunction, microvascular insufficiency, disturbances in intracellular calcium turnover, and neurohormonal factors.^{3,9-12} Identifying subclinical systolic dysfunction among hypertensive subjects might be helpful in targeting these patients for preventive treatment delivery.

Currently suggested phenotypic classification of HF is based on normal or reduced left ventricular (LV) ejection fraction (EF). However, it has long been debated whether systolic function is really "normal" in HF with preserved EF (HFpEF),¹³ owing to the possibility that deteriorated myocardial function may happen earlier; thus, it may be of substantial clinical benefit to look further into more complex and sophisticated mechanics than a conventional estimate such as EF.¹⁴ Furthermore, preserved global LV systolic function in a resting state does not necessarily guarantee the normal response of LV to patient exercise.¹⁵

ETIOLOGY

The presence of objective evidence indicating obvious diastolic dysfunction (e.g., elevated diastolic filling pressures or decreased mitral annulus diastolic relax-

ation velocities) or diminished cardiac output had been used to support the clinical diagnosis of abnormal myocardial function.¹⁶ Patients with HF and reduced EF (HFrEF) typically exhibit progressive LV chamber dilation, eccentric remodeling, and systolic impairment in terms of reduced EF. Specific therapies focusing on the reversal of these structural and functional alterations may reduce morbidity and mortality in these patients.¹⁷ By contrast, the pathophysiology underlying the development of HFpEF among hypertensives remains only partially understood.¹⁸ Recent large clinical trials have indicated that the presence of concentric remodeling/LV hypertrophy, left atrial (LA) enlargement, and diastolic dysfunction are the most common features of HFpEF.¹⁹

Concentric ventricular remodeling or overt hypertrophy occurs most commonly in hypertension and is more likely to be associated with normal or even reduced LV end-diastolic volume (LVEDV) accompanied by increased ventricular stiffness and limited distensibility.²⁰ On the other hand, eccentric hypertrophy was defined by similarly increased LV mass though larger LV diameter and LVEDV.²¹ The development of LV hypertrophy is actually a combined consequence of chronic pressure or volume overload. To compensate for chronic pressure overload in hypertensive subjects, LV wall thickness gradually increases in order to normalize wall stress, leading to concentric LV remodeling and hypertrophy.²⁰ Activation of several biological processes including various hormones, growth factors and cytokines also contribute to protein genesis by promoting muscle cell growth, leading to structural alterations and remodeling.²² It is thus believed that in untreated hypertension, progression from LV hypertrophy to HF is accompanied by serial events/processes such as ischemia, myocytes apoptosis or fibrosis, and eventually systolic dysfunction.²³

Strain and strain rate for assessment of cardiac function

Advances in ultrasound technology such as tissue Doppler imaging (TDI) and strain or strain rate imaging, either by Doppler tissue method²⁴ or two-dimensional (2D) speckle-tracking, has appreciably broadened our understanding of cardiac mechanics and has been shown to identify early stage myocardial dysfunction

secondary to hypertension.^{25,26} The use of TDI to measure regional myocardial velocity as part of diastolic functional assessment integration is less prone to load changes, and is mainly limited by its angle dependency, tethering effects and translational artifacts.²⁷⁻²⁹ Instead, strain imaging may provide less angle-dependent evaluation of regional and global LV function and further help to identify altered myocardial systolic mechanics at an early stage.³⁰

Strain as a linear measure of tissue deformation can be expressed as a percentage of the length changes during systole between two separate points in the myocardium from its original status.³¹ Strain rate is the derivative of strain, which represents the rate of deformation changes over a period of time. As mentioned before, speckle-tracking echocardiography has been successfully applied to the measurement of myocardial strain and strain rate.

The infrastructure of myocardium is actually composed of circumferential fibers in the mid-wall layer, with longitudinal- with oblique-oriented muscle fibers lining the endocardial and epicardial layers.³² The spatial orientation of these muscle fibers changes continuously from right-handed helix in subendocardium to left-handed helix in subepicardium.³³ Hence, cardiac systole is accomplished by a series of complicated myocardial contractions in a coordinated fashion leading to effective pumping from the LV with minimal individual sarcomere shortening.³⁴ From a practical view point, strain can be classified into three different spatial components: longitudinal, circumferential, and radial (Figure 1).³¹ Myocardial deformation can thus be evaluated by assessing systolic strain and strain rate, though somewhat diverse in the reference values from different vendors and related algorithms, within a limited region, in a specific myocardial segment or as a global measure (Figure 2). These advanced techniques allow objective quantification of cardiac motion and deformation irrespective of echo beam direction, thus providing a detailed understanding of cardiac mechanics from all aspects, and further help to explore the full spectrum of a specific myocardial disorder not limited to the ventricle.³⁵⁻³⁷

By examining the prior use of various techniques, earlier publications have shown that normal longitudinal strain can vary from 16% to 19%.^{38,39} Different image modalities have generated variable results regarding the

uniformity of strain from base to apex. This regional variation might be related to angle-limitations caused by curvatures in the myocardial architecture. Therefore, segmental cutoff values might be more appropriate than a single normal cutoff value.

Effects of hypertensive heart remodeling on myocardial strain

Among the three layers of myocardium, longitudinal subendocardial fibers are most susceptible to adverse effects of ischemia, hypoperfusion and age-related interstitial fibrosis.³³ Therefore, longitudinal dysfunction may serve as an early marker by accomplishing global longitudinal strain measurement at an early stage of myocardial damage⁴⁰ before overt development of chamber-level failure, such as reduced EF.⁴¹ Instead, the mid-wall layer is less affected by these pathological insults as early as the longitudinal function, so strain analysis based on myocardial short-axis function may remain relatively preserved at this stage.

Indeed, previous studies comparing three-directional strain parameters from echocardiography studies had consistently shown that longitudinal function de-

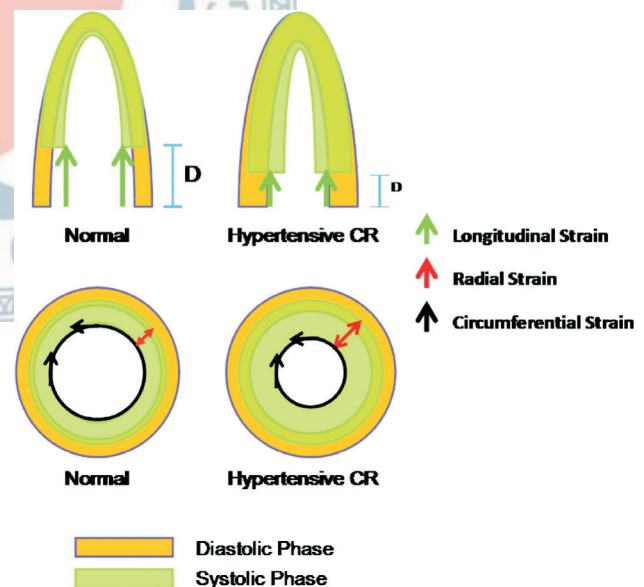


Figure 1. The commonly proposed or suggested three different spatial components of myocardial motion and related deformations as illustrated. The green arrow indicates longitudinal deformation with red and black arrows indicated radial and circumferential deformations, respectively. The differential longitudinal displacement (D) and corresponding short-axis function/motion in normal and hypertensive concentric remodeling (CR) subjects are demonstrated.

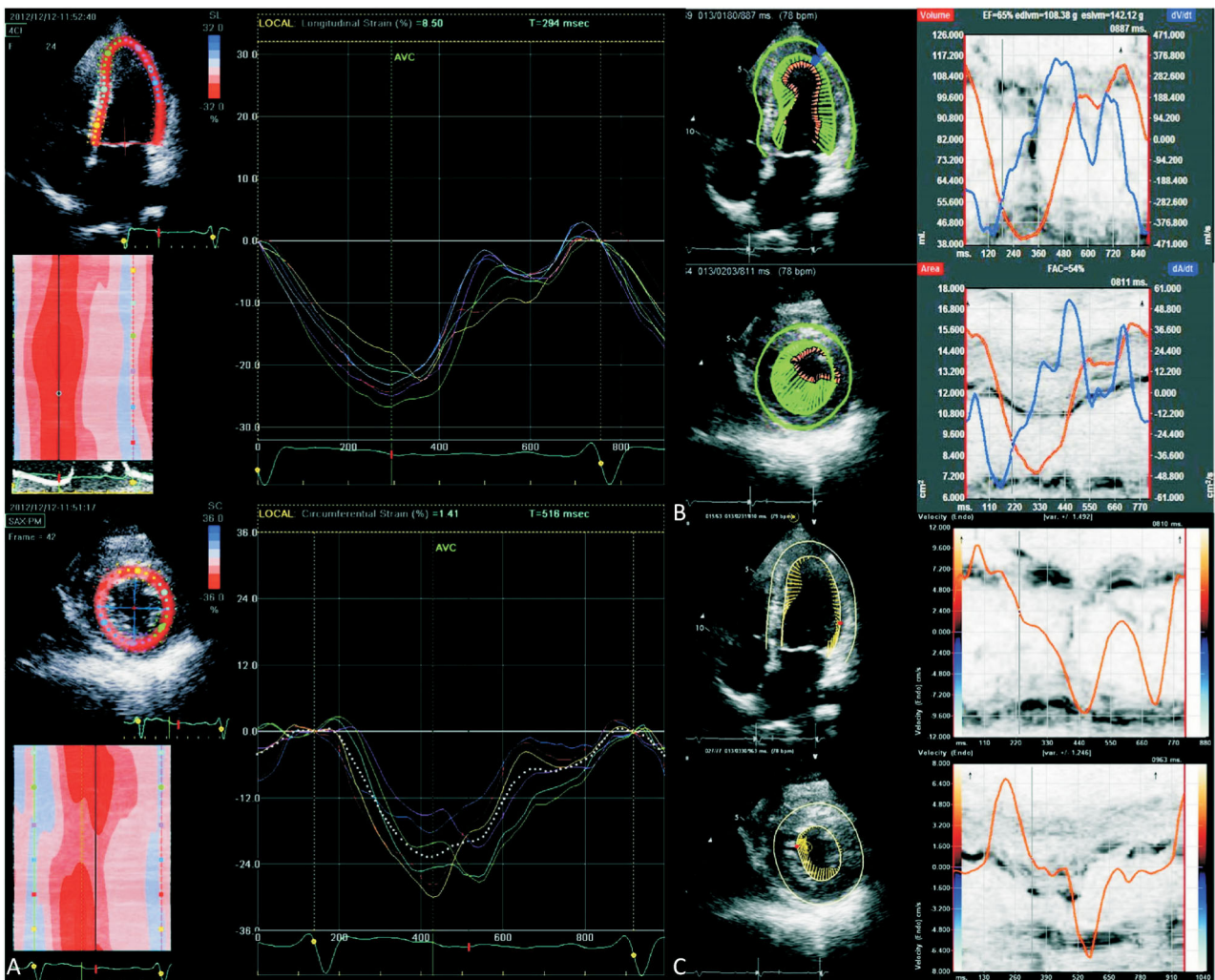


Figure 2. Myocardial longitudinal (upper panel in each demonstration) and short-axis (radial or circumferential displayed as lower panel in each demonstration) deformations are shown. Common encountered commercialized companies/software such as iE33 (QLab, Philips Medical Systems) (data not shown), GE Vingmed (A: GE Vingmed Ultrasound AS, Horten, Norway), TomTec (B: TomTec, Cardiac 2D Performance Analysis, Tomtec Imaging Systems) or Velocity Vector Imaging (C: Siemens Medical Solutions, Mountain View, CA, USA) and strain or related volume-velocity curve analysis in the same subjects are shown. The amplitude and direction from speckle-tracking analysis (B & C) represents the amplitude and direction of ongoing regional myocardial motions.

clines first with hypertension, in particular for those who had developed LV hypertrophy.^{42,43} Impaired longitudinal shortening is also observed in hypertensive remodeling without overt LV hypertrophy or clinical HF development while in short-axis function, especially for circumferential or radial mechanics, may remain preserved or even enhanced to maintain ventricular function (Table 1).⁴¹⁻⁴⁴ In addition, increased matrix metalloproteinase-1 (MMP-1) turnover, a biomarker of myocardial fibrosis, correlated well with decreased longitudinal strain in hypertension and hypertrophic cardio-

myopathy.⁴⁵ These findings again supported the concept that longitudinal contractile function as a sensitive marker is prone to early pathological changes of the myocardium, while radial and circumferential strain may be more resistant to such early myocardial alterations.⁴⁶

In diastolic dysfunction, delayed relaxation can translate into increased end-diastolic pressure and limited ventricular filling, which may exacerbate hypertensive stress responses. Though it has been observed that both longitudinal and radial strains were decreased in diastolic heart failure,^{47,48} longitudinal functional de-

Table 1. Speckle-tracking based analysis of different myocardial strain/deformations in studies relating to hypertension or hypertensive-remodeling

Modalities analyzed (Vendors)	Clinical settings	Longitudinal strain	Circumferential strain	Radial strain
Chen et al. (VVI) ⁵⁷	LVH	Decreased	Decreased	-
Narayanan et al. (EchoPac) ^{46*}	HTN & LVH	Decreased [†]	Preserved	Preserved
Galderisi et al. (EchoPac) ⁵⁰	HTN	Decreased	Preserved	Preserved
Kouzu et al. (EchoPac) ⁴³	HTN/LVH	Preserved/Decreased	Preserved/Preserved	Increased or Preserved/Preserved
Imbalzano et al. (EchoPac) ⁵⁸	HTN/LVH	Decreased/Decreased	Preserved/Increased	Preserved/Decreased
Kang et al. (EchoPac) ⁴⁵	HTN	Decreased	Preserved	Preserved

* Both longitudinal and circumferential strain correlated with LV mass; [†] Regional function. HTN, hypertension; LVH, left ventricular hypertrophy.

Table 2. Comparisons and changes of diastolic function and three-direction myocardial deformations in normal subjects with subjects with preserved (HFpEF) or reduced (HFrEF) ejection fraction heart failure

Clinical scenarios	Global EF	Diastolic filling pressures	Longitudinal mechanics	Circumferential mechanics	Radial mechanics
Normal	Normal	Normal	Normal	Normal	Normal
HFpEF	Preserved or minimally impaired	Elevated	Markedly impaired	Preserved	Preserved or minimally impaired
HFrEF	Markedly impaired	Elevated	Markedly impaired	Markedly impaired	Markedly impaired

Data summarized from literature in previous publications.^{40,59}

cline may occur with concurrent diastolic dysfunction early in hypertensive subjects⁴⁹ when short-axis function including radial or circumferential function remain unchanged.⁵⁰ Subsequent impairment in short-axis contractile functional reserve may act as a contributing factor to the transition from subclinical myocardial dysfunction to heart failure development.

The exact mechanisms underlying the maintenance of ventricular short-axis function in the context of early stages of hypertension were believed to come from the cross-fiber shortening phenomenon from hypertension-related ventricular remodeling and increased systolic wall thickening,⁵¹ partially due to multiplied myofiber units and extensive extra-cellular matrix deposition.^{52,53}

However, such compensation of short-axis function under clinical scenarios of hypertensive heart diseases does not happen without limits. It has been observed that both longitudinal and short-axis based strain measures may actually decrease in heart failure subjects even at a stage when LV EF does not decrease.^{54,55} Since deteriorated longitudinal function already exists in the early stages of hypertensive heart disease, subsequent loss of short-axis reserve may theoretically contribute to the transition from hypertension to heart failure (Table 2).^{40,53,56}

CONCLUSION

Hypertension and heart failure are closely related. Recent advances in noninvasive cardiovascular imaging modalities have contributed new insights into the understanding of underlying cardiac mechanics, and further provided accurate and objective measures on global/regional contractile function. The early detection of subclinical systolic dysfunction by deformation imaging may also help in identifying hypertensive subjects at risk for subsequent adverse events, and in selecting individuals for preventive treatment delivery.

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