Circulation Reports
Circ Rep 2019; 1: 8–16
doi:10.1253/circrep.CR-18-0017

REVIEW

Heart Failure With Preserved Ejection Fraction
— Time for a Paradigm Shift Beyond Diastolic Function —

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At present, heart failure with preserved ejection fraction (HFpEF) is a commonly accepted condition in HF patients. In contrast to HF with reduced EF (HFrEF), HFpEF is strongly associated with aging, and vascular, metabolic, neurohormonal, and systemic inflammatory comorbidities. Two major hypotheses explain the pathophysiology of HFpEF (stages C,D in the American College of Cardiology Foundation/American Heart Association HF staging system): (1) impaired active relaxation and increased passive stiffness of the left ventricular (LV) myocardium during diastole (left atrial [LA]-LV coupling); and (2) LV and arterial stiffening during systole (LV-arterial coupling). Cardiac structural and functional abnormalities can be evaluated using non-invasive measures, such as 2-D, flow velocity Doppler, and tissue Doppler echocardiography, to estimate LV filling pressure and afterload mismatch. The clinical application of 2-D speckle-tracking echocardiography (2D-STE) is feasible for earlier diagnosis of functional abnormalities of the LA, LV, and elastic arteries in asymptomatic patients with cardiovascular risk factors (stages A,B). The goal of this review is to highlight the role of 2D-STE to detect impairment of LA-LV-arterial coupling beyond diastolic function earlier, because it may provide important information on the pathophysiology and prevention of HFpEF.

Key Words: 2-D speckle-tracking echocardiography; HFpEF; LA-LV-arterial coupling

Previous heart failure (HF) research was directed primarily toward HF with reduced ejection fraction (HFrEF). In recent community-based epidemiological studies, however, approximately one-half of patients with HF had normal left ventricular (LV) systolic function,[1,2] called HF with preserved ejection fraction (HFpEF).[3]

Patients with HFpEF are generally characterized by aging with underlying traditional cardiovascular risk factors, including hypertension, diabetes, dyslipidemia, obesity, and smoking.[1–4] Recent studies have emphasized that systemic tissue oxidation and inflammation induce myocardial fibrosis, pulmonary and renal dysfunction, and vascular pathology that can contribute to HFpEF (**Table**).[5–7] Also, the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guideline for management of HF lists 4 stages based on evidence of cardiac structural and functional abnormalities and symptoms: asymptomatic HF, stages A,B; and symptomatic HF, stages C,D.[8] Therefore, early detection of left atrial (LA), LV, and elastic arterial dysfunction on 2-D speckle-tracking echocardiography (2D-STE) may help to elucidate the progressive changes that occur before asymptomatic (stages A,B) patients develop overt symptoms of HFpEF (stages C,D).

The objective of this review was to underline the role of 2D-STE to detect impairment of LA-LV-arterial coupling beyond diastolic function earlier in asymptomatic patients with cardiovascular risk factors, given that it is pivotal in delaying HF development.

Definition of HFpEF

LVEF is the most commonly used measure of systolic pump function, but not contractility, in clinical practice.[9] This index has been used to divide HF into categories of HFpEF (EF ≥50%), HF with mid-range EF (HFmrEF; 40%≤EF<50%), and HFrEF (EF <40%),[8] although there is a continuum of abnormal LV function from preserved EF to reduced EF. It remains controversial, however, whether HFpEF and HFrEF are overlapping or distinct phenotypes within the HF spectrum,[10,11] and whether LV systolic function is normal in HFpEF.[12]

The LV myocardium consists of longitudinal fibers in the subendocardial and subepicardial layers, and circumferential fibers in the mid-wall layer.[13] HFrEF usually develops when there are transmural abnormalities in all 3 layers, caused by conditions such as acute myocardial infarction, dilated cardiomyopathy, myocarditis, or the effects of toxins (e.g., alcohol or chemotherapy).[11] HFpEF

Received November 22, 2018; accepted November 22, 2018; J-STAGE Advance Publication released online December 14, 2018
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ISSN-2434-0790

Table. Potential Factors for Progression to Symptomatic HFpEF
Abnormal LA-LV coupling
Hypertrophic cardiomyopathy, cardiac amyloidosis, sarcoidosis, Fabry disease, endomyocardial fibrosis, hemochromatosis, radiation-, and chemotherapy-induced cardiotoxicity, mitochondrial myopathy
Abnormal LV-arterial coupling
Hypertension
Abnormal LA-LV-arterial coupling
Aging, gender, traditional cardiovascular risk factors (hypertension, diabetes, dyslipidemia, obesity, smoking), metabolic syndrome
Valvular heart disease
Mitral stenosis, mitral regurgitation, aortic stenosis, aortic regurgitation
Ventricular interaction (RV overload)
Pulmonary hypertension, pulmonary thromboembolism, tricuspid regurgitation, arrhythmogenic RV cardiomyopathy, atrial septal defect
Fluid overload
Anemia, beriberi heart, obesity, renal dysfunction, hyperthyroidism, sepsis, arteriovenous fistula
Rhythm disorder
Atrial fibrillation, tachycardia, left bundle branch block, chronotropic incompetence
Extracardiac factors
Constrictive pericarditis, effusive-constrictive pericarditis, aortic aneurysm, mediastinal tumor, pulmonary disease, renal dysfunction, sarcopenia (skeletal muscle dysfunction), sleep-disordered breathing

HFpEF, heart failure with preserved ejection fraction; LA, left atrial; LV, left ventricular; RV, right ventricular.

patients, however, are older, more likely to have traditional cardiovascular risk factors, and less likely to have coronary artery disease.[10,11] Although the level of radial thickening during systole in the subendocardial layer is approximately 2-fold greater than that in the subepicardial layer,[14] the subendocardial layer is most vulnerable to the effects of aging and other cardiovascular risk factors. Therefore, abnormal LV function is first evident in the subendocardium, and subsequently extends to the mid-wall (i.e., not transmural) in patients with HFpEF and HFmrEF. This indicates that HFpEF and HFmrEF should be defined as "HF with preserved subepicardial myocardial function" rather than "HF with preserved EF", and that EF (40–60%) is dependent on the extension from subendocardial to mid-wall myocardial lesions.

HFpEF represents a broad cohort of patients with a range of comorbid conditions,[7] even after removing the specific causes of this syndrome, such as primary cardiomyopathy, pericardial disease, valvular heart disease, and ventricular interaction (**Table**). Also, recent paradigms of the pathophysiology of HFpEF have laid stress on the importance of additional factors, including extracardiac comorbidities.[7] Hence, EF provides no definitive information on the underlying mechanism responsible for the difference between HFpEF and HFrEF.[9]

LA-LV-Arterial Coupling

Pathophysiology

The main symptoms in HF that are independent of EF, include dyspnea due to an elevation in LV filling pressure (LA-LV coupling), and fatigue due to impaired cardiac output reserve (LV-arterial coupling).

The previous understanding of HFpEF using invasive hemodynamic techniques is based on diastolic dysfunction alone (i.e., abnormalities in both myocardial active relaxation and passive stiffness),[1,2] leading to the elevation of LV end-diastolic pressure (LVEDP), LA pressure, and pulmonary venous pressure. This condition (impaired LA-LV coupling) is frequently observed in hypertrophic cardiomyopathy and restrictive cardiomyopathy, which are not associated with an intrinsic increase in afterload.

In contrast, hypertension is one of the most powerful contributors to HFpEF.[2,4] Stiffening of the elastic arteries is a common finding in elderly individuals, and is more severe in patients with various cardiovascular risk factors, particularly hypertension.[15] Therefore, LV-arterial coupling is a central determinant of cardiovascular performance and cardiac energetics in asymptomatic hypertensive (stages A,B) patients and patients with HFpEF (stages C,D).[4,16]

Recently, it has become widely recognized that HFpEF involves additional cardiovascular alterations beyond diastolic dysfunction, such as subtle systolic dysfunction in the longitudinal direction,[17,18] impaired LV-arterial coupling,[4,16,19] inappropriate peripheral arterial-venous oxygen difference,[7,20] and atrial fibrillation.[21] Accordingly, assessment of LA-LV-elastic arterial interaction may allow HFpEF to be extracted into a distinct diagnosis based on the underlying pathophysiology.

LV Mechanics In general, systolic and diastolic transformations in the LV myocardium are produced by 3 determinant factors: myocardial deformation along the myofiber direction (i.e., longitudinal and circumferential fibers); arrangement of sheets that transverse the myofibers; and helical myofiber orientation of the subendocardial and subepicardial layers, which is responsible for torsion and untwisting.[22] It is interesting that the level of radial thickening during systole in the subendocardial layer is approximately 2-fold greater than that in the subepicardial layer,[14] and that myocardial ischemia and/or fibrosis generally spreads from the subendocardium to the subepicardium.[17,23]

Subendocardial fiber shortening first begins during the isovolumic contraction phase in the presence of subepicardial fiber stretching.[13,24,25] Subsequently, both subendocardial and subepicardial fiber shortening spreads from the apex toward the base, with circumferential fiber shortening during the ejection phase. Subendocardial and subepicardial fiber shortening causes torsion along the longitudinal direction. In contrast, relaxation begins in the apical

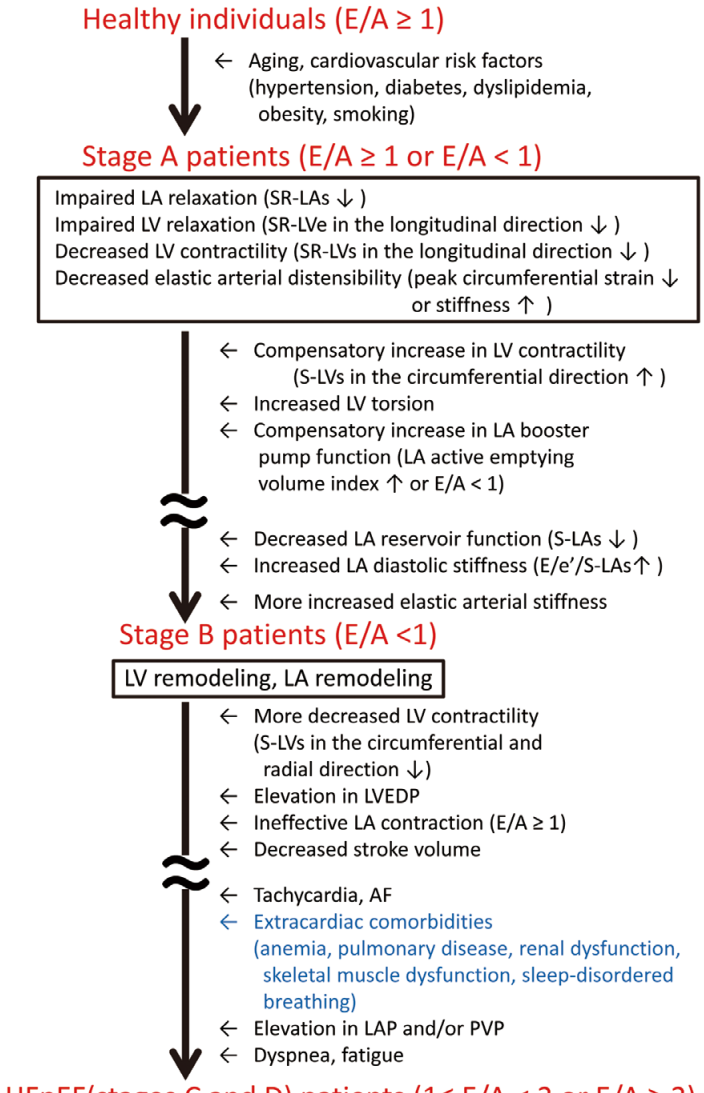

Figure 1. Progressive changes in inappropriate left atrial (LA)-left ventricular (LV)-arterial coupling as a pathway from healthy stage to heart failure with preserved ejection fraction (HFpEF). AF, atrial fibrillation; E/A, ratio of peak early diastolic to atrial systolic velocity of transmitral flow; E/e', ratio of peak early diastolic transmitral flow to mitral annular motion velocity; LAP, LA pressure; LVEDP, left ventricular end-diastolic pressure; PVP, pulmonary venous pressure; S-LAs, peak LA strain during ventricular systole; S-LVs, peak LV strain during ejection phase; SR-LAs, peak LA strain rate during ventricular systole; SR-LVe, peak LV strain rate during isovolumic diastole; SR-LVs, peak LV strain rate during isovolumic systole.

subendocardial fibers just before the isovolumic relaxation phase, although subepicardial fiber shortening at the base begins after aortic valve closure, and continues during early diastolic filling. The relaxation sequence between subendocardial and subepicardial fibers creates the energy required for early diastolic suction.

LV torsion and untwisting play important roles in LV ejection and filling, respectively.[26,27] The mechanisms of increased LV torsion in asymptomatic (stages A,B) patients include systolic longitudinal deformation related to subendocardial myocardial fibrosis compared with subepicardial layer, and/or LV concentric hypertrophy-related differences in torque between the subendocardial and subepicardial layers.[28,29]

LA Mechanics The principal role of the LA is to regulate LV filling through the interaction of atrial reservoir, conduit, and booster pump function.[30] In healthy individuals with normal transmitral flow (TMF) velocity pattern (E/A ≥1), the relative contribution of LA reservoir, conduit, and booster pump function to LV filling is approximately 40%, 35%, and 25%, respectively. With impaired LV relaxation (E/A <1; stage A), the relative contribution of LA reservoir and booster pump function increases (Frank-Starling mechanism), and conduit function decreases. Subsequently, LA reservoir function is gradually disturbed despite the augmented LA contraction, resulting in an enlargement of the LA in stage B. Furthermore, as LV filling pressure progressively elevates with advancing diastolic dysfunction (pseudonormal or restrictive [E/A >1] TMF velocity pattern; stages C,D), the LA serves predominantly as a conduit.

LA reservoir function is governed by active LA myocardial relaxation, passive LA filling, and LA diastolic stiffness. These parameters are influenced by LA myocardial fibrosis,[31,32] LV diastolic and systolic function,[31–34] elastic arterial stiffness,[32,34] and LA contraction (Frank-Starling mechanism).[35]

Elastic Arterial Mechanics Multiple mechanisms have been suggested to explain age-dependent vascular stiffening, such as alterations in endothelial function, structural

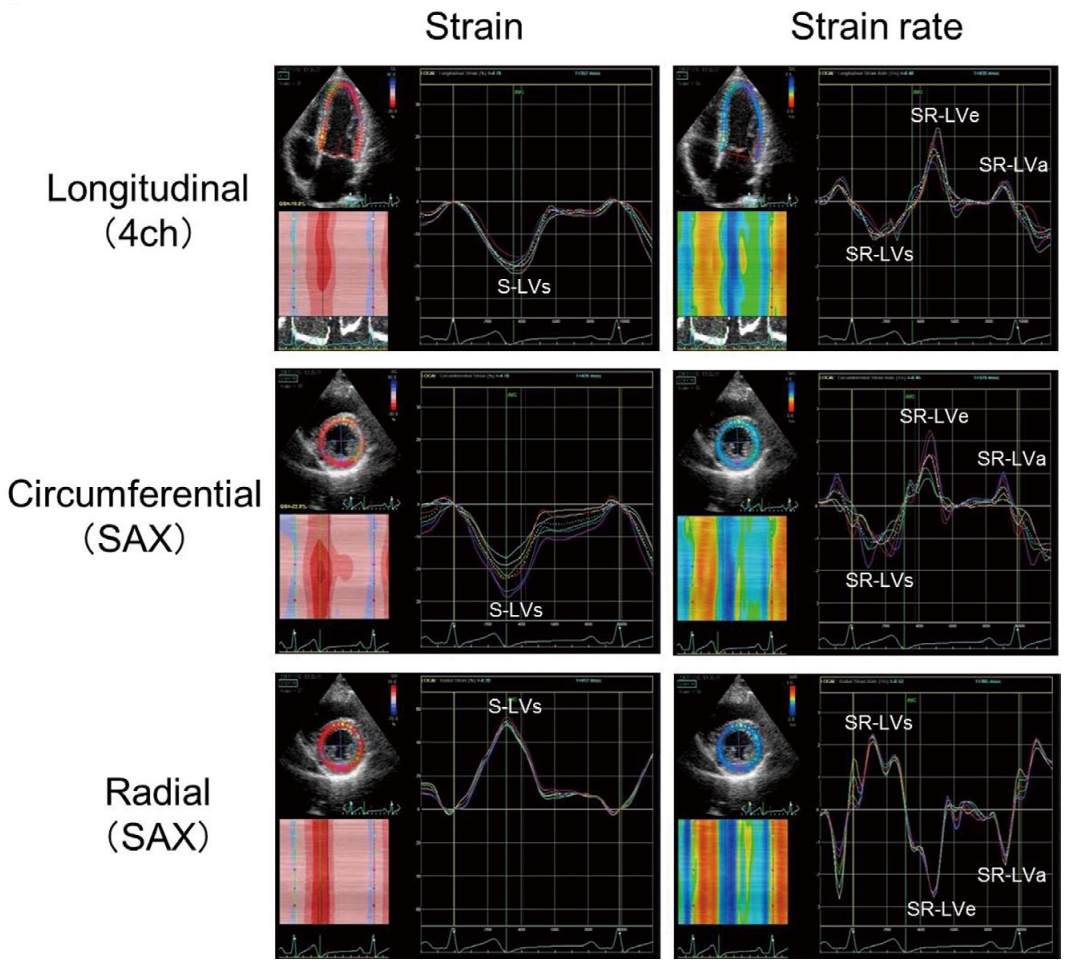

Figure 2. Left ventricular (LV) (**Left**) strain and (**Right**) strain rate curves obtained from 2-D speckle-tracking echocardiography in a healthy individual (25 years old). 4ch, 4-chamber view; S-LVs, peak LV strain during ejection phase; SAX, short-axis view; SR-LVa, peak LV strain rate during atrial systole; SR-LVe, peak LV strain rate during isovolumic diastole; SR-LVs, peak LV strain rate during isovolumic systole.

protein composition, collagen cross-linking, geometric changes, and neurohormonal signaling.[36] The media of elastic arteries consists of elastic and collagen fibers and vascular smooth muscle cells, and the principal structural change with aging is medial degeneration, which leads to progressive stiffening of the elastic arteries.

O'Rourke and Hashimoto reported that arterial aging occurs beyond the age of 30 years old.[37] They suggested that arterial stiffening can occur in the absence of atherosis. Elastic arterial stiffness increases to a far greater extent than peripheral arterial stiffness with advancing age and cardiovascular risk factors.[15,16,37] Therefore, central aortic distensibility is a strong and independent predictor of exercise capacity in patients with HFpEF.[16,38]

Diagnostic Technology

In the diagnosis of HFpEF (**Figure 1**), the recent development of 2D-STE allows a detailed assessment of LV myocardial deformation in the longitudinal, circumferential, and radial directions (**Figure 2**);[39] LV torsion and untwisting;[26,27] and deformation of the LA myocardium (**Figure 3**)[40] and elastic arterial walls (**Figure 4**).[15] This technique should enable detection of subtle dysfunction in the LA, LV, and elastic arteries.

LV Mechanics

It has been established using 2D-STE that LV myocardial contraction during isovolumic systole, which is measured as the peak early systolic strain rate (SR-LVs), is first impaired in the longitudinal direction in asymptomatic patients with cardiovascular risk factors (stage A).[41] Furthermore, there are concomitant increases in circumferential fiber shortening during the ejection phase, which is measured as the peak systolic strain (S-LVs),[41] and in torsion along the longitudinal direction,[28,29] maintaining peak radial systolic strain (EF ≥60%). Early dysfunction in stage A is also characterized by impaired LV myocardial relaxation during isovolumic relaxation, which is measured as the peak early diastolic strain rate (SR-LVe), in the longitudinal direction,[41] maintaining LV filling (E/A ≥1 or E/A <1).

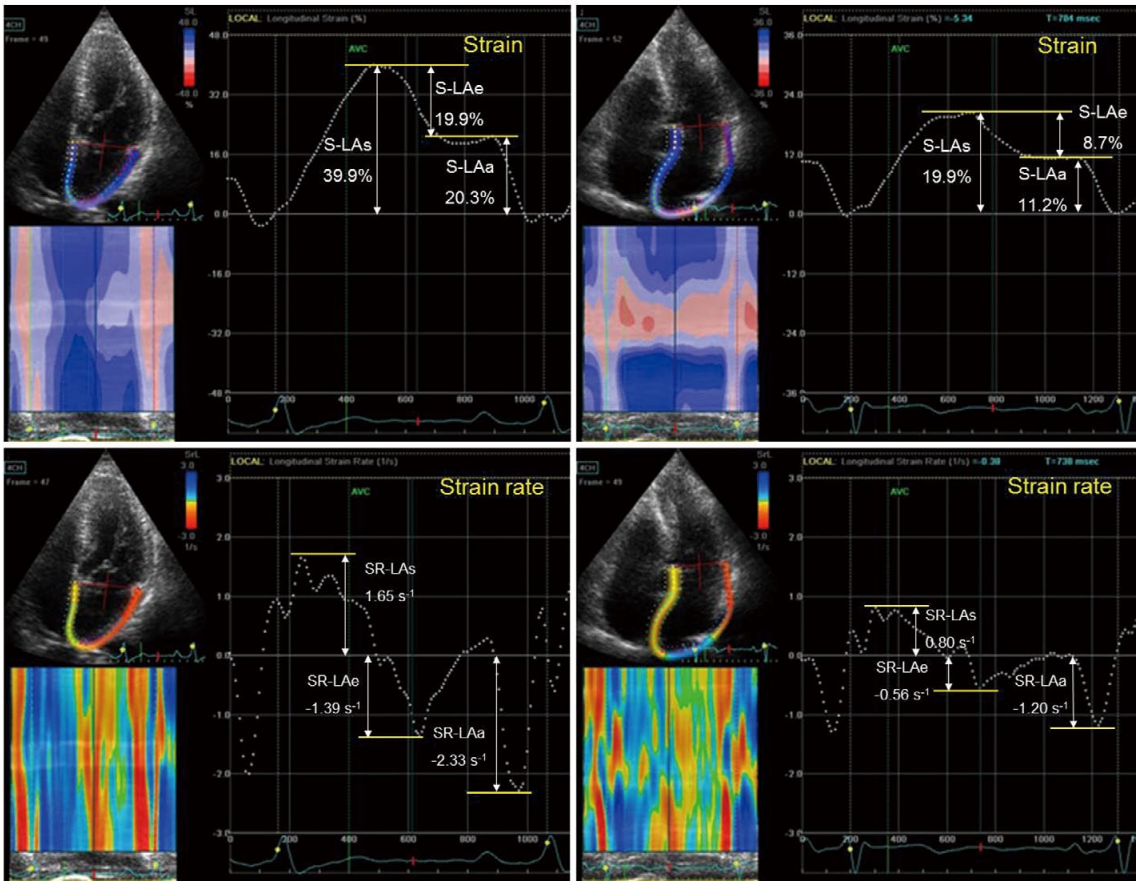

Figure 3. Left atrial (LA; **Top**) strain and (**Bottom**) strain rate curves obtained from 2-D speckle-tracking echocardiography in (**Left**) a healthy individual (22 years old) and (**Right**) an asymptomatic stage B patient (60 years old) with cardiovascular risk factors. LA reservoir function (S-LAs and SR-LAs) is significantly lower in the (**Right**) asymptomatic stage B patient (19.9% and 0.80 s^{-1}, respectively) compared with the healthy individual (39.9% and 1.65 s^{-1}, respectively). S-LAa, peak LA strain during atrial systole; S-LAe, peak LA strain during early ventricular diastole; S-LAs, peak LA strain during ventricular systole; SR-LAa, peak LA strain rate during atrial systole; SR-LAe, peak LA strain rate during early ventricular diastole; SR-LAs, peak LA strain rate during ventricular systole. (Reproduced with permission from Oishi Y, et al.[34])

Previous studies using traditional echocardiographic, radionuclide, and hemodynamic techniques have claimed that "diastolic dysfunction precedes systolic dysfunction" in asymptomatic patients with cardiovascular risk factors and in the ischemic cascade proposed by Nesto and Kowalchuk.[42] When some impairment occurs during systole, it should be reflected in diastole, given that there is tight coupling between systolic and diastolic function.[43] Therefore, it is difficult to separate both abnormalities from either a mechanical or energetics standpoint. Indeed, early diastolic LV function is dependent on not only active relaxation, but also the release of stored potential energy during systole and early diastolic lengthening by elevated LA pressure.[44] 2D-STE, however, has shown that "subtle diastolic dysfunction starts at the same time as subtle systolic dysfunction" in asymptomatic patients (stage A).[41]

Subsequently, a gradual decline in circumferential fiber shortening in addition to decreased longitudinal shortening results in more deterioration of radial systolic strain (50%≤EF<60%), with LV filling maintained by a compensatory increase in LA contraction (E/A <1) in asymptomatic patients with cardiac remodeling (stage B).[45,46] This may be explained by the fact that, on cardiovascular magnetic resonance imaging, the electrocardiogram strain pattern is a specific marker of both the subendocardial and mid-wall myocardial fibrosis in patients with LV hypertrophy.[47] Further decreases in radial systolic strain (40%≤EF<50%) and impaired LV filling and increased LV diastolic stiffness (E/A >1) may lead to HFpEF (stages C,D).[48,49]

LA Mechanics

The LA myocardium consists of 2 layers, predominantly arranged with inner longitudinal and superficial circumferential fibers.[50] Therefore, the peak LA strain rate during ventricular systole (SR-LAs) measured on 2D-STE mainly reflects LA subendocardial relaxation in the longitudinal direction, and its impairment is possibly associated with the same fibrotic process that affects the LV subendocardial fibers in the longitudinal direction.[32,51] SR-LAs is reduced according to physiological aging in healthy individuals,[52]

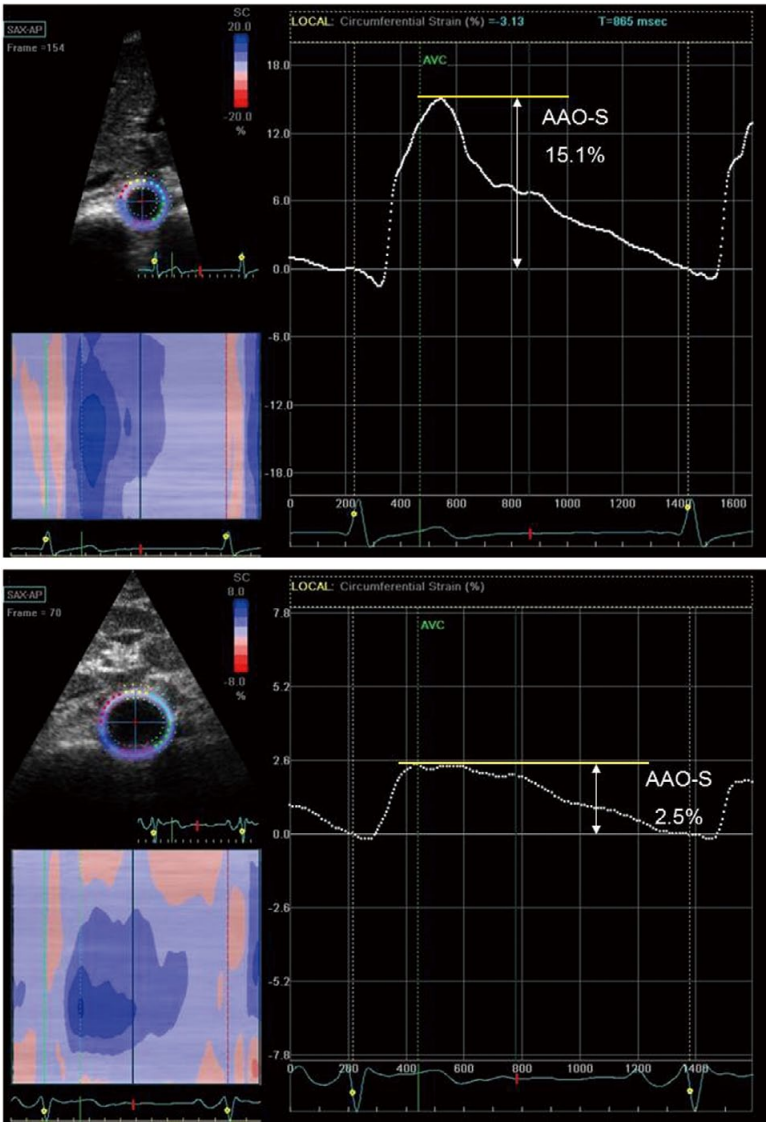

Figure 4. Representative abdominal aortic peak circumferential strain (AAO-S) patterns obtained from 2-D speckle-tracking echocardiography in (**Top**) a healthy individual (20 years old) and (**Bottom**) an asymptomatic stage B patient (65 years old) with cardiovascular risk factors. The AAO-S is markedly lower in the patient (2.5%) compared with the healthy subject (15.1%).

and deteriorates before the development of LA and LV remodeling in patients with hypertension or diabetes (stage A).[53] Subsequently, LA filling, which is measured as the peak LA strain during ventricular systole (S-LAs), is disturbed by LV longitudinal systolic dysfunction and increased LA diastolic stiffness (E/e'/S-LAs)[54] due to subendocardial fibrosis of the LA myocardium in patients with or without elevated LVEDP (from stage A to stage B; **Figure 3**).[33,55,56] LA myocardial fibrosis is inversely correlated with SR-LAs and S-LAs, as has been shown on delayed-enhanced magnetic resonance imaging.[57]

Elastic Arterial Mechanics

Several non-invasive methods, such as pulsed wave velocity and augmentation index, are currently used to assess vascular stiffness. Recently, speckle tracking of the elastic arteries (abdominal aorta and carotid artery) has been reported to be a feasible and reproducible method for measuring circumferential strain, suggesting that 2D-STE may allow a more direct assessment of elastic arterial stiffnesses (**Figure 4**).[15] The peak circumferential strain of the abdominal aorta or carotid arterial wall is measured during systole at end-expiration with breath-holding, and stiffness is defined as ln(systolic blood pressure [SBP]/diastolic blood pressure [DBP])/peak arterial systolic strain.

Stiffening of the elastic arteries on 2D-STE increases with age in clinically healthy individuals, and is accelerated in asymptomatic patients with cardiovascular risk factors, particularly hypertension, increasing dramatically after the fifth decade of life (stages A,B; **Figure 4**).[15] The best markers of subclinical arterial aging are peak circumferential systolic strain in younger individuals (<50 years old), and stiffness in older patients (≥50 years old).[15]

The arterial wave reflection returns during early diastole in younger healthy individuals with compliant elastic arteries. With aortic stiffening, however, pulse-wave velocity increases, and reflected pressure waves return more rapidly, arriving in the central aorta during late systole.[4,16] As a result, there is an increase in late systolic load that prolongs the systolic time interval, resulting in a delayed onset of LV

relaxation.[43] Furthermore, decreased distensibility of the elastic arteries increases SBP and decreases DBP. These changes lead to LV concentric hypertrophy and impairment of myocardial blood flow because of decreased coronary perfusion pressure, resulting in decreased blood supply to the subendocardial myocardium (impaired LV contraction and relaxation in the longitudinal direction during the isovolumic phase).[41,58]

Clinical Implications

Recent studies have advocated that the pathophysiology of HFpEF is primarily attributed to systemic inflammation and coronary microvascular endothelial dysfunction (cardiac endothelium-myocardium interaction) through metabolic risk factors.[5–7] Furthermore, systemic inflammation (which also contributes to HFrEF) involves extracardiac comorbidities, such as anemia, obesity, pulmonary arterial hypertension, and skeletal muscle and renal dysfunction.[20,59–62]

Early detection of impaired LA-LV-arterial interaction on 2D-STE is expected to be a manifestation of subclinical cardiovascular disease by virtue of the associations with cardiovascular risk factors and with an increased risk of HFpEF.[32,34] Generally, the concept of uncomplicated cardiovascular risk factors is not practical in the clinical setting, particularly in elderly individuals, due to the rare occurrence of this phenotype. Many studies have demonstrated that inappropriate increases in the number of cardiovascular risk factors, particularly the combination of aging, hypertension, and obesity, seem to cause aggravation in LA-LV-arterial interaction, providing a potential prediction for the future development of HFpEF and HFmrEF ($40\% \leq EF < 60\%$).[4,61,62] These functional abnormalities are the earliest signals for the progression to HFpEF and, therefore, may have major implications for the future of public health due to the aging of the general population.

In asymptomatic patients in stage A, LA myocardial relaxation in the longitudinal direction (SR-LAs), LV myocardial contraction and relaxation in the longitudinal direction (SR-LVs and SR-LVe, respectively), and elastic arterial distensibility are first and simultaneously impaired.[15,32,41,53] Also, an increase in elastic arterial stiffness is associated with alterations in not only LV diastolic function (particularly, active relaxation [SR-LVe] in the longitudinal direction) rather than systolic function, but also in LA reservoir function (particularly, active relaxation [SR-LAs]) rather than passive filling.[32] EF (≥60%), however, is maintained by compensatory increases in circumferential systolic function and torsion.[28,29,41] This may be explained by abnormally depressed subendocardial LA and LV function in the longitudinal direction resulting from endothelial dysfunction and ischemia and/or fibrosis, and by elastic arterial stiffening resulting from endothelial dysfunction and medial degeneration, due to aging and metabolic factors.[15,17,52,53,63] Even if global LV systolic and diastolic function are maintained (EF ≥60% and E/A ≥1 or <1), there is a subtle deterioration of LA, LV, and elastic arterial function in stage A. Also, aortic stiffening is a primary determinant of "early" LV afterload.

With structural and functional abnormalities (stage B), radial thickening ($50\% \leq EF < 60\%$) gradually falls due to a decline in circumferential shortening,[45,46] resulting from LV concentric hypertrophy mediated by increased aortic stiffness. Also, higher aortic stiffness is associated with impaired LV relaxation (SR-LVe) in the longitudinal direction and increased LA diastolic stiffness (E/e'/S-LAs),[34] suggesting that LA diastolic stiffness is already increased, even when LV filling pressure is only slightly elevated. Increased LA active emptying in stage A (E/A <1) leads to augmentation of LA reservoir function using the Frank-Starling mechanism,[35,55] and an increasing LA diastolic stiffness prevents further compensatory augmentation of LA active emptying. Subsequently, enlargement of the LA occurs when the LA stroke volume has to increase beyond that of the Frank-Starling mechanism in stage B.

At the present time, the management of HFpEF has created a "therapeutic dilemma" for many clinicians.[7] The recent development of 2D-STE has facilitated the early detection of abnormal LA-LV-arterial coupling,[15,32,34,41] indicating that effective medication use in the early stages (stages A,B) directly improves LA and LV myocardial structure and function, and vascular stiffness.[29,64–67] Improvement of abnormal LA-LV-arterial coupling and clinical outcome, however, may be limited by irreversible myocardial and arterial wall alterations, which are related to the severity and duration of disease.[55] Therefore, earlier intervention with angiotensin II receptor blockers (ARBs), selective peroxisome proliferator-activated receptor-γ agonists,[29,64,66] and/or statins with pleiotropic effects[65,67] may have a beneficial impact on LA and LV myocardial function and vascular stiffness. In addition, these drugs may prevent progressive changes in impaired LA-LV-arterial coupling that can cause asymptomatic patients with cardiovascular risk factors to develop HFpEF.

Conclusions

Evaluation of the relationships between LA, LV, and elastic arterial function is essential to better characterize the pathophysiology of HFpEF, rather than that of only LA-LV or LV-arterial interaction. 2D-STE is considered a sensitive tool for early detection of abnormal LA-LV-elastic arterial coupling, and for identifying therapeutic interventions with ARBs and statins to delay the progression to overt HF in asymptomatic patients. Overall, a new concept, LA-LV-arterial coupling beyond diastolic function, may provide important information on the pathophysiology and prevention of HFpEF.

Acknowledgment

We acknowledge Kathryn Brock, BA, for her work in editing this article.

Disclosures

The authors declare no conflicts of interest.

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