Left Atrial Systolic and Diastolic Dysfunction in Heart Failure with Normal Left Ventricular Ejection Fraction

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Background: The authors hypothesized that in patients with heart failure with normal left ventricular (LV) ejection fraction (HFNEF), the same fibrotic processes that affect the subendocardial layer of the left ventricle could also alter the subendocardial fibers of the left atrium. Consequently, these fibrotic alterations, together with chronically elevated LV filling pressures, would lead to both systolic and diastolic subendocardial dysfunction of the left atrium (i.e., impaired left atrial [LA] longitudinal systolic and diastolic function) in patients with HFNEF.

Methods: Patients with HFNEF and a control group consisting of asymptomatic patients with LV diastolic dysfunction (LVDD) matched by age, gender, and LV ejection fraction were studied using two-dimensional speckle-tracking echocardiography.

Results: A total of 420 patients were included (119 with HFNEF and 301 with asymptomatic LVDD). LA longitudinal systolic (LA late diastolic strain rate) and diastolic (LA systolic strain and strain rate) function was significantly more impaired in patients with HFNEF (LA late diastolic strain rate, $-1.17 \pm 0.63\ s^{-1}$; LA systolic strain, $19.9 \pm 7.3\%$; LA systolic strain rate, $1.17 \pm 0.46\ s^{-1}$) compared with those with asymptomatic LVDD ($-1.80 \pm 0.70\ s^{-1}$, $30.8 \pm 11.4\%$, and $1.67 \pm 0.59\ s^{-1}$, respectively) (all P values $< .0001$). On multiple regression analysis, LV global longitudinal systolic strain and diastolic strain rate were the most important independent predictors of LA longitudinal systolic and diastolic function, in contrast to noninvasive LV filling pressures (i.e., mitral E/e′ average septal-lateral ratio), which were modestly related to LA longitudinal systolic and diastolic function. Furthermore, in patients with HFNEF, the subendocardial function of both the left atrium and the left ventricle was significantly impaired in high proportions. In that regard, in patients with HFNEF, the rate of LA longitudinal systolic and diastolic dysfunction was 65.5% and 28.5%, whereas the prevalence of LV longitudinal systolic and diastolic dysfunction was 81.5% and 58%, respectively. In addition, patients with both systolic and diastolic longitudinal dysfunction of the left atrium presented worse NYHA functional class as compared with those with normal LA longitudinal function.

Conclusions: In patients with HFNEF, LA subendocardial systolic and diastolic dysfunction is common and possibly associated with the same fibrotic processes that affect the subendocardial fibers of the left ventricle and to a lesser extent with elevated LV filling pressures. Furthermore, these findings suggest that LA longitudinal systolic and diastolic dysfunction could be related to reduced functional capacity during effort in patients with HFNEF. (J Am Soc Echocardiogr 2011;24:651-62.)

Keywords: Left atrium, Systole, Diastole, Echocardiography, Heart failure

Heart failure (HF) with normal left ventricular (LV) ejection fraction (HFNEF) is a highly prevalent pathology,[1] with a significant increase of prevalence in patients aged ≥85 years.[1] Unlike systolic HF, HFNEF is characterized by normal LV systolic function, often evaluated using the biplane Simpson's method.[2] However, with the development of new echocardiographic technologies (two-dimensional speckle tracking), recent studies have shown that despite having normal LV ejection fraction (LVEF), patients with HFNEF have significantly lower values of LV longitudinal systolic function both at rest[3-5] and during submaximal exercise[4] than healthy subjects, suggesting that in these patients, LV subendocardial systolic function is not preserved.[3-5] Nevertheless, despite these recent studies,[3-5] the role of left atrial (LA) subendocardial systolic and diastolic function (i.e., the longitudinal systolic and diastolic function of the left atrium) in the pathophysiology of HFNEF remains poorly understood.

HFNEF is a known cause of elevated LV filling pressures.[2] An increase in LA afterload through the development of elevated LV filling pressures secondary to severe LV diastolic dysfunction (LVDD) has long been considered the main underlying mechanism of LA dysfunction.[6,7] However, several and recent studies suggest that the degree of elevated LV filling pressures may not fully explain LA failure and that LA myocardial fibrosis may play a role in the systolic and diastolic dysfunction of the left atrium.[8-11] It is well known that LV interstitial fibrosis as a consequence of comorbid conditions, such as type 2

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Abbreviations

CAD = Coronary artery disease

DTI = Doppler tissue imaging

HF = Heart failure

HFNEF = Heart failure with normal left ventricular ejection fraction

LA = Left atrial

LA-SR = Left atrial longitudinal systolic strain rate

LA-SRa = Left atrial longitudinal late-diastolic strain rate

LA-Strain = Left atrial longitudinal systolic strain

LV = Left ventricular

LVDD = Left ventricular diastolic dysfunction

LVEF = Left ventricular ejection fraction

LV-SRe = Left ventricular global longitudinal early diastolic strain rate

LV-Strain = Left ventricular global longitudinal systolic strain

NSTEMI = Non–ST-segment elevation myocardial infarction

NYHA = New York Heart Association

PCWP = Pulmonary capillary wedge pressure

SRe = Left ventricular longitudinal early diastolic strain rate

STEMI = ST-segment elevation myocardial infarction

diabetes, obesity, hypertension, and previous history of coronary artery disease (CAD), affects primarily the subendocardial systolic and diastolic function of the left ventricle (i.e., LV longitudinal systolic and diastolic function).[12-20] In that regard, we hypothesized that in patients with HFNEF as a result of elevated prevalence of comorbidities (i.e., type 2 diabetes, obesity, hypertension, and history of CAD), the same fibrotic processes that affect the subendocardial layer of the left ventricle could also alter the subendocardial fibers of the left atrium. Consequently, these fibrotic alterations and to a lesser extent elevated LV filling pressures would lead to both systolic and diastolic longitudinal dysfunction of the left atrium in patients with HFNEF. With the aim of validating our hypothesis and elucidating the pathophysiologic mechanisms of HFNEF, we analyzed LA longitudinal systolic and diastolic function using two-dimensional speckle-tracking echocardiography in patients with HFNEF and in a control group consisting of asymptomatic patients with LVDD matched by age, gender, and LVEF.

METHODS

Study Population

We enrolled consecutive patients aged ≥18 years with signs or symptoms of HF with LVEF > 50% by transthoracic echocardiography (according to the diagnostic criteria of the consensus of experts in HFNEF[2] and in LV diastolic function[21] of the European Society of Echocardiography and the American Society of Echocardiography) and a control group consisting of asymptomatic patients with LVDD without history of HFNEF (in accordance with the diagnostic criteria of the European Society of Echocardiography and the American Society of Echocardiography; i.e., septal e′ mitral annular peak velocity < 8 cm/s, lateral e′ mitral annular peak velocity < 10 cm/s, or maximal LA volume index ≥ 34 mL/m^2).[21] These two groups were matched by age, gender, and LVEF (matching 1:2; i.e., two control subjects for each patient with HFNEF). Three conditions were necessary for the diagnosis of HFNEF: (1) presence of signs or symptoms of congestive HF (dyspnea [New York Heart Association (NYHA) class ≥ II], pulmonary rales, pulmonary edema, bilateral lower extremity edema, hepatomegaly, or fatigue), (2) presence of normal LV systolic function (LVEF > 50% by Simpson's method), and (3) evidence of LVDD (septal e′ mitral annular peak velocity < 8 cm/s, lateral e′ mitral annular peak velocity < 10 cm/s, or maximal LA volume index ≥ 34 mL/m^2).[2,21] We included consecutive inpatients and outpatients admitted to the Department of Cardiology (Campus Virchow-Klinikum) of Charité University Hospital (Berlin, Germany) from April 1, 2009, to April 1, 2010. The Charité institutional review board approved this research project, and informed consent was obtained from all subjects.

The selection of exclusion criteria in this study was based on the consensus of experts in HFNEF[2] and in LV diastolic function.[21] In that regard, to avoid reversible causes of myocardial dysfunction, patients with active CAD were excluded from this study (i.e., patients with unstable angina or non–ST-segment elevation myocardial infarction [NSTEMI] without revascularization or with revascularization in the past 72 hours, patients with ST-segment elevation myocardial infarction [STEMI] in the past 30 days, subjects awaiting coronary artery bypass grafting or within 90 days postoperatively, subjects with chronic stable angina, and patients with evidence of myocardial ischemia assessed by stress echocardiography). Moreover, with the purpose of excluding causes of dyspnea or myocardial dysfunction other than HFNEF, patients with pulmonary arterial hypertension (causes other than isolated LVDD or HFNEF), severe pulmonary disease (defined as pulmonary pathology with supplemental oxygen requirement), severe kidney disease (glomerular filtration rate < 30 mL/min/1.72 m^2 for ≥3 months, history of renal transplantation, or severe acute renal failure with dialysis requirement), severe chronic liver disease or history of liver transplantation, congenital heart disease, pericardial disease (moderate or severe pericardial effusion [echo-free space in diastole ≥ 10mm] or constrictive pericarditis), cardiomyopathy, and valvular heart disease (defined as mild, moderate, or severe mitral or aortic stenosis, moderate or severe nonfunctional mitral or tricuspid regurgitation, severe functional mitral or tricuspid regurgitation, and moderate or severe aortic regurgitation)[22] were excluded from this study. In addition, to avoid underestimations of myocardial and mitral annular measurements, patients with valvular heart surgery, mitral annular calcification (≥5 mm), cardiac pacing or cardiac resynchronization therapy, and poor two-dimensional quality in ≥1 LV or LA myocardial segment (for analysis by two-dimensional and speckle-tracking echocardiography in the apical four-chamber, two-chamber, and long-axis views) were excluded from this study. Furthermore, to avoid an underestimation of LA systolic function by LA myocardial stunning, patients with atrial arrhythmias in the past 8 weeks or at the time of inclusion in the study were also excluded.

Two-Dimensional and Speckle-Tracking Echocardiography

LV Measurements. All patients were examined at rest in the left lateral decubitus position using a Vivid 7 ultrasound system (GE Vingmed Ultrasound AS, Horten, Norway). The echocardiographic measurements and analyses were performed by experienced echocardiographers blinded to each other's results. LV diameters, LV volumes, LV mass and grading of LV hypertrophy, LVEF (Simpson's method), LA volumes and remodeling (maximal LA volume index ≥ 34 mL/m^2), LV filling pressures, and LV diastolic function were assessed as recommended by the American Society of Echocardiography.[21,23] LV filling pressures were noninvasively assessed by the mitral E/e′ average septal-lateral ratio (i.e., the ratio of early diastolic mitral inflow peak velocity by pulsed-wave Doppler to e′ mitral annular [average septal-lateral] peak velocity using spectral Doppler tissue imaging [DTI]).[21]

The analyses on two-dimensional speckle-tracking echocardiography (using EchoPAC version 6.1 workstation; GE Vingmed Ultrasound AS) were performed offline and blinded to the clinical characteristics of the patients. The measurements of LV longitudinal systolic strain and LV longitudinal early diastolic strain rate (SRe) were performed in the apical four-chamber, two-chamber, and long-axis views.[3,18,24] The average values of peak longitudinal systolic strain and peak longitudinal early-diastolic SRe, obtained of all segments of the left ventricle, were denominated as LV global longitudinal systolic strain (LV-Strain) and LV global longitudinal early-diastolic SRe (LV-SRe), respectively.[3,18,24] All echocardiographic measurements and analyses were performed in sinus rhythm and were the average of three consecutive cycles.

LA Measurements. In patients in sinus rhythm, quantitative assessments of the systolic and diastolic function of the left atrium were obtained. The volumetric parameters of LA systolic function were calculated as follows[25,26]: LA total emptying fraction = (LA total emptying volume/maximal LA volume in ventricular systole just before mitral valve opening) × 100, and LA active emptying fraction = (LA active emptying volume/LA volume at the onset of the P wave on electrocardiography) × 100. LA total and active emptying fractions were derived in the apical four-chamber and two-chamber views using two-dimensional (Simpson's method) echocardiography. LA total emptying volume was calculated as = (maximal LA volume in ventricular systole just before mitral valve opening − minimal LA volume after mitral valve closure), and LA active emptying volume derived as = (LA volume at the onset of the P wave on electrocardiography − minimal LA volume after mitral valve closure). Furthermore, LA longitudinal systolic and diastolic function was analyzed (offline and blinded to the clinical characteristics of the patients) in the apical four-chamber and two-chamber views using two-dimensional speckle-tracking echocardiography (using EchoPAC version 6.1 workstation; GE Vingmed Ultrasound AS).[27] LA longitudinal systolic strain (LA-Strain) and LA longitudinal systolic strain rate (LA-SR) (parameters of the longitudinal relaxation or diastolic function of the left atrium) were derived as the average values of peak systolic strain and strain rate of all LA segments obtained in the four-chamber and two-chamber views during LV systole.[27] LA longitudinal late-diastolic strain rate (LA-SRa) (a parameter of the longitudinal contraction or systolic function of the left atrium) was calculated as the average value of peak late diastolic strain rate of all LA segments obtained in the four-chamber and two-chamber views during LV late-diastole or atrial contraction.[27] Furthermore, quantitative pulsed spectral DTI to assess LA systolic function was also performed (i.e., septal and/or lateral late diastolic [a′] mitral annular peak velocity on DTI).[28] All echocardiographic measurements and analyses were the average of three consecutive cycles.

Echocardiographic Criteria

The criteria of LA and LV systolic and diastolic dysfunction were based on previously validated studies (i.e., values below the 95% confidence interval of healthy subjects).[3,18,25,29] In that regard, LV and LA dysfunction was defined as follows: LV longitudinal systolic dysfunction = LV global longitudinal systolic strain $> -16\%$,[3,18] LV longitudinal diastolic dysfunction = LV global longitudinal early-diastolic SRe $< 0.80\ s^{-1}$,[18] LA longitudinal systolic dysfunction = LA-SRa $> -1.32\ s^{-1}$,[29] LA longitudinal diastolic dysfunction = LA-SR $< 0.82\ s^{-1}$,[29] and LA systolic dysfunction (by Simpson's method) = LA total emptying fraction $< 50\%$ or LA active emptying fraction $< 35\%$.[25,29]

Statistical Analysis

Continuous data are presented as mean ± SD and dichotomous data as percentages. Differences in continuous variables between groups (comparisons of two groups) were assessed using unpaired Student's t tests only, because all data were normally distributed (the Kolmogorov-Smirnov test was used to test for normal distribution). Categorical variables were compared using χ^2 tests and Fisher exact tests as appropriate. Comparisons between three or more groups were assessed using one-way analysis of variance. The relationships between continuous variables were analyzed using simple linear regression analysis. Selections of independent variables for the prediction of LA longitudinal systolic and diastolic function were performed using forward stepwise multivariate analysis. With the purpose of determining the intraobserver and interobserver variability of LA measurements, we analyzed the mean absolute differences and interclass correlation coefficients of LA longitudinal systolic and diastolic function in 22 randomly selected patients. All statistical analyses were performed using SAS version 9 (SAS Institute Inc., Cary, NC). Differences were considered statistically significant at $P < .05$.

RESULTS

Patient Characteristics and LV Echocardiographic Measurements

A total of 654 patients met the eligibility criteria during the study period (218 with HFNEF and 436 with asymptomatic LVDD). However, 89 patients (17 with HFNEF and 72 with asymptomatic LVDD) could not be enrolled, because of poor two-dimensional quality in one or more LA and LV segments for analysis by speckle-tracking echocardiography and Simpson's method ($n = 24$), severe kidney disease ($n = 12$), cardiac pacing ($n = 8$), severe chronic liver disease ($n = 8$), NSTEMI in the past 72 hours ($n = 7$), STEMI in the past 30 days ($n = 15$), coronary artery bypass grafting in the past 90 days ($n = 4$), evidence of myocardial ischemia assessed by stress echocardiography ($n = 5$), mild aortic stenosis ($n = 4$), mild mitral stenosis ($n = 1$), and moderate pericardial effusion ($n = 1$). Moreover, to avoid an underestimation of LA systolic function by LA myocardial stunning, patients with atrial arrhythmias in the past 8 weeks or at the time of inclusion in the study were also excluded (82 with HFNEF and 63 with asymptomatic LVDD). Thus, 420 patients were ultimately studied and analyzed (119 with HFNEF and 301 with asymptomatic LVDD). Clinical and echocardiographic characteristics of these patients are summarized in Table 1. The comorbidities in patients with HFNEF and those with asymptomatic LVDD were characterized by the presence of type 2 diabetes, hypertension, obesity, and previous history of CAD (92% NSTEMI and 8% STEMI in patients with HFNEF and 95% NSTEMI and 5% STEMI in those with asymptomatic LVDD; Table 1). Furthermore, we found that patients with HFNEF presented significantly more impaired LV global longitudinal systolic strain and early-diastolic SRe than those with asymptomatic LVDD (Table 1). Nevertheless, there were no significant differences in LVEF or LV end-diastolic volume index between patients with HFNEF and those with asymptomatic LVDD, and moderate or severe functional mitral regurgitation was absent in both groups.

LA Systolic and Diastolic Function in Patients with HFNEF

The analyses of LA function showed that patients with HFNEF had significantly more impaired LA systolic and diastolic function compared to those with asymptomatic LVDD (Tables 2 and 3, Figures 1and 2). Moreover, we found that patients in NYHA functional

Table 1 Clinical characteristics and LV echocardiographic measurements

Variable	HFNEF (n = 119)	Asymptomatic LVDD (n = 301)	P
Clinical characteristics			
Age (y)	70 ± 10	69 ± 9	.151
Women	44%	39%	.398
Body mass index (kg/m^2)	29 ± 5	27 ± 4	.0019
Hemoglobin (g/dL)	13.3 ± 1.6	13.4 ± 1.6	.282
eGFR (mL/min/1.73 m^2)	67.6 ± 22.6	75.9 ± 21	.0006
Hypertension	100%	82%	<.0001
Type 2 diabetes	34.5%	22%	.0023
Obesity	35%	11%	<.0001
History of CAD	62%	33%	<.0001
Systolic blood pressure (mm Hg)	140 ± 22	133 ± 20	.016
Diastolic blood pressure (mm Hg)	80 ± 11	79 ± 12	.202
LV conventional measurements			
LVEF (%)	59 ± 7	61 ± 6	.078
LVEDVI (mL/m^2)	45 ± 13	42 ± 11	.088
LV mass index (g/m^2)	122 ± 30	105 ± 23	<.0001
Septal e′ mitral annular peak velocity (cm/s)	4.6 ± 1.4	6 ± 1.4	<.0001
Lateral e′ mitral annular peak velocity (cm/s)	6.4 ± 1.4	8 ± 1.6	<.0001
Mitral E/e′ (average septal-lateral) ratio	17.1 ± 5.9	10.6 ± 3.9	<.0001
LV measurements by speckle-tracking			
LV global longitudinal systolic strain (%)	−14.09 ± 3.31	−19.01 ± 2.63	<.0001
LV longitudinal systolic dysfunction (LV-Strain > −16%)	81.5%	15.5%	<.0001
LV global longitudinal early-diastolic SRe (s^{-1})	0.82 ± 0.26	1.03 ± 0.31	<.0001
LV longitudinal diastolic dysfunction (LV-SRe < 0.80 s^{-1})	58%	22%	<.0001

Data are expressed as mean ± SD or as percentages.
eGFR, Estimated glomerular filtration rate (Modification of Diet in Renal Disease formula); *LVEDVI*, LV end-diastolic volume index.

Table 2 LA two-dimensional and Doppler measurements

Variable	HFNEF (n = 119)	Asymptomatic LVDD (n = 301)	P
LA volumes			
LA Vol_{max} (mL)	64.8 ± 24	45 ± 16	<.0001
LA Vol_{min} (mL)	27.8 ± 18.3	15.3 ± 9.5	<.0001
LA Vol_p (mL)	48.8 ± 21.1	33.5 ± 12.9	<.0001
LA total emptying volume (mL)	37 ± 11	29.7 ± 9.5	.0006
LA active emptying volume (mL)	21 ± 7.5	18.2 ± 6.4	.0885
LA Doppler parameters			
A mitral inflow peak velocity (cm/s)	65.5 ± 26.8	76.6 ± 19.8	<.0001
Septal a′ mitral annular peak velocity (cm/s)	6.8 ± 2.3	9.1 ± 2	<.0001
Lateral a′ mitral annular peak velocity (cm/s)	8.3 ± 2.9	10.6 ± 2.4	<.0001
Septal-lateral a′ mitral annular peak velocity (cm/s)	7.5 ± 2.4	9.8 ± 2	<.0001
LA remodeling			
LA Vol_{max} index (mL/m^2)	32.5 ± 13	23.5 ± 8	<.0001
LA Vol_{max} index ≥ 34 mL/m^2	78%	19.6%	<.0001
LA systolic function			
LA total emptying fraction (%)	57 ± 14.7	66 ± 10.6	<.0001
LA active emptying fraction (%)	43 ± 16.2	54.3 ± 13	<.0001
LA systolic dysfunction			
LA total emptying fraction < 50%	31%	5.6%	<.0001
LA active emptying fraction < 35%	26%	9.3%	<.0001

Data are expressed as mean ± SD or as percentages.
LA Vol_{max}, Maximal LA volume in ventricular systole just before mitral valve opening; *LA Vol_{min}*, minimal LA volume after mitral valve closure; *LA Vol_p*, LA volume at the onset of the P wave on electrocardiography.

classes II, III, and IV had significantly lower values of LA longitudinal systolic and diastolic function than patients in NYHA functional class I (Table 4). Furthermore, on multiple regression analysis, we found that LV global longitudinal systolic strain and early-diastolic SRe were the most important independent predictors of LA longitudinal systolic and diastolic function (Table 5, Figure 3), in contrast to noninvasive

Table 3 LA measurements by two-dimensional speckle-tracking echocardiography

Variable	HFNEF (n = 119)	Asymptomatic LVDD (n = 301)	P
LA longitudinal diastolic function			
LA-Strain (%)	19.9 ± 7.3	30.8 ± 11.4	<.0001
LA-SR (s^{-1})	1.17 ± 0.46	1.67 ± 0.59	<.0001
LA longitudinal systolic function			
LA-SRa (s^{-1})	−1.17 ± 0.63	−1.80 ± 0.70	<.0001
LA longitudinal diastolic dysfunction			
LA-SR < 0.82 s^{-1}	28.5%	1.3%	<.0001
LA longitudinal systolic dysfunction			
LA-SRa > −1.32 s^{-1}	65.5%	30%	<.0001

Data are expressed as mean ± SD or as percentages.

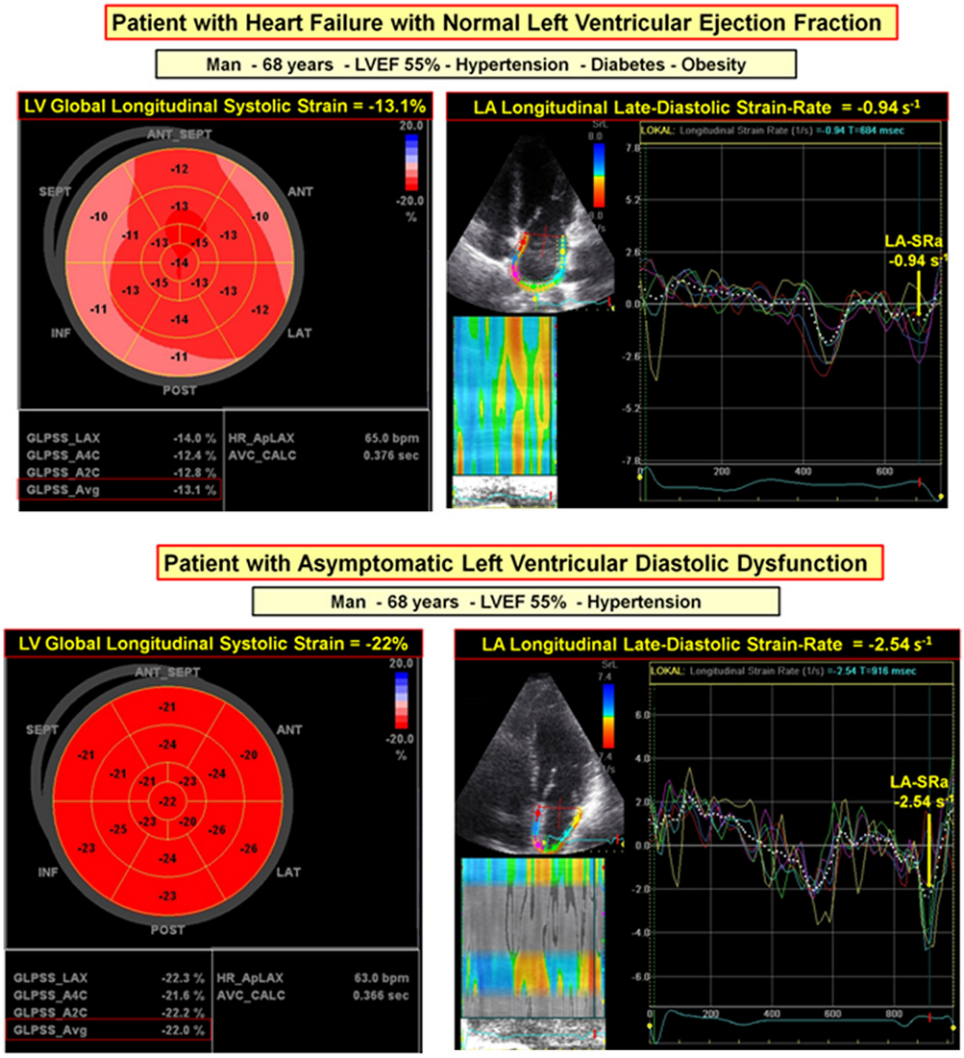

Figure 1 LA systolic dysfunction in HFNEF. Example showing marked LA longitudinal systolic dysfunction (i.e., LA-SRa >−1.32 s^{-1}) as well as LV longitudinal systolic dysfunction (i.e., LV global longitudinal systolic strain >-16%) in a patient with HFNEF compared with a patient with asymptomatic LVDD.

LV filling pressures (i.e., mitral E/e′ average septal-lateral ratio), which were modestly related to LA longitudinal systolic and diastolic function.

In patients with HFNEF, the subendocardial function of both the left atrium and the left ventricle was significantly impaired in high proportions. In that regard, in patients with HFNEF, the rate of LA longitudinal systolic and diastolic dysfunction was 65.5% and 28.5%, whereas the prevalence of LV longitudinal systolic and diastolic dysfunction was 81.5% and 58%, respectively (Tables 1 and 3). In addition, in subgroups analyses, we found that patients with LA

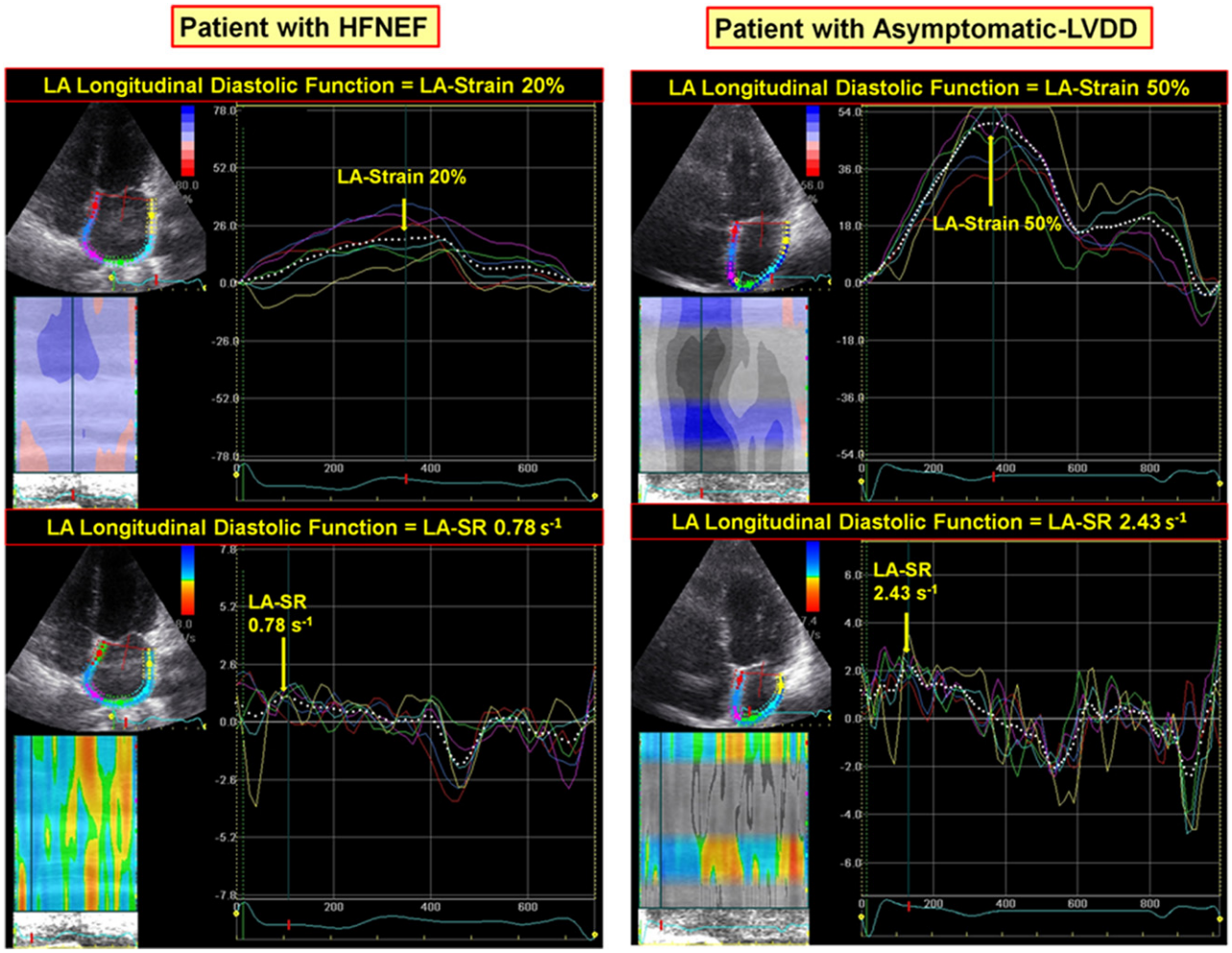

Figure 2 LA diastolic dysfunction in HFNEF. Example showing in the same patients as in Figure 1 significantly more impaired LA longitudinal diastolic dysfunction (i.e., LA-SR and LA-Strain) in HFNEF as compared to asymptomatic LVDD.

longitudinal systolic and diastolic dysfunction presented worse NYHA functional class and more impaired LV longitudinal systolic and diastolic function compared with patients with preserved LA longitudinal function (Table 6). Furthermore, patients with both systolic and diastolic longitudinal dysfunction of the left atrium had higher values of pulmonary arterial systolic pressure and pulmonary capillary wedge pressure (PCWP) compared with patients with normal LA longitudinal function (Table 6).

Reproducibility

The intraobserver variability (mean absolute difference: LA-Strain, 0.36 ± 0.44%; LA-SR, 0.07 ± 0.13 s^{-1}; LA-SRa, −0.08 ± 0.14 s^{-1}; interclass correlation coefficient: LA-Strain, 0.990; LA-SR, 0.987; LA-SRa, 0.985) and interobserver variability (mean absolute difference: LA-Strain, 0.43 ± 0.47%; LA-SR, 0.07 ± 0.13 s^{-1}; LA-SRa, −0.09 ± 0.16 s^{-1}; intraclass correlation coefficient: LA-Strain, 0.990; LA-SR, 0.988; LA-SRa, 0.983) of LA measurements were not of statistical or clinical significance.

DISCUSSION

In the present study, we performed a comprehensive assessment of the systolic and diastolic function of the left atrium and the left ventricle in patients with HFNEF and in a control group consisting of patients with asymptomatic LVDD. Using two-dimensional speckle-tracking echocardiography at rest, we have demonstrated that patients with HFNEF have severely impaired systolic and diastolic functions of the subendocardial fibers of both the left ventricle and the left atrium (i.e., impaired LV and LA longitudinal systolic and diastolic function). Other interesting findings of our study were that patients with both systolic and diastolic longitudinal dysfunction of the left atrium were characterized by presenting worse NYHA functional class.

Comorbidities and LV Subendocardial Systolic and Diastolic Dysfunction in Patients with HFNEF

As in other studies,[1,3-5] patients with HFNEF in the present study had high rates of comorbid conditions such as type 2 diabetes, obesity, hypertension, and history of CAD. Several studies have demonstrated that these comorbid disorders are characterized by producing LV interstitial fibrosis through diverse mechanisms.[15,30-37] In patients with type 2 diabetes and obesity, the fibrotic processes of the left ventricle have been mainly related to metabolic, inflammatory, and hormonal changes (i.e., insulin resistance and hyperinsulinemia), resulting in decreased glucose utilization, increased free fatty acid utilization, and subsequent perivascular fibrosis and increased collagen deposition in the left ventricle.[30,31] The pathogenesis of LV interstitial fibrosis in

Table 4 LA systolic and diastolic function according to NYHA functional class

Variable	NYHA functional class				*P* (ANOVA)
	I (*n* = 301)	II (*n* = 85)	III (*n* = 21)	IV (*n* = 13)	
LA systolic function					
LA total emptying fraction (%)	66 ± 10.6	59.1 ± 14.3*	53.8 ± 15.4†	50.7 ± 14.4‡	<.0001
LA active emptying fraction (%)	54.3 ± 13	45.7 ± 15.7*	38.5 ± 16.4†	36.1 ± 16.9‡	<.0001
LA-SRa (s^{-1})	−1.80 ± 0.70	−1.13 ± 0.59*	−1.40 ± 0.82†	−0.88 ± 0.14‡	<.0001
LA diastolic function					
LA-Strain (%)	30.8 ± 11.4	19.6 ± 7.1*	22.1 ± 8.6†	17.0 ± 1.17‡	<.0001
LA-SR (s^{-1})	1.67 ± 0.59	1.15 ± 0.44*	1.33 ± 0.57†	0.83 ± 0.07‡	<.0001

Data are expressed as mean ± SD.
ANOVA, Analysis of variance.
*P < .05, NYHA class II versus class I.
†P < .05, NYHA class III versus class I.
‡P < .05, NYHA class IV vs class I.

Table 5 Predictors of LA longitudinal systolic and diastolic function in all patients

Variable	LA late diastolic strain rate		LA systolic strain rate		LA systolic strain	
	R	*P*	R	*P*	R	*P*
LV global longitudinal systolic strain	.41	<.0001*	.44	<.0001†	.52	<.0001‡
LV global longitudinal early-diastolic SRe	.30	<.0001*	.41	<.0001†	.43	<.0001‡
Mitral E/e′ (average septal-lateral) ratio	.27	.0002	.32	<.0001	.30	<.0001
E mitral inflow peak velocity	.29	<.0001	.25	.0002	.19	.0054
Septal-lateral e′ mitral annular peak velocity	.10	.1155	.16	.0488	.23	.0014
LV mass index	.27	<.0001	.22	.0004	.21	.0009
LV relative wall thickness	.05	.3605	.01	.8379	.10	.2158
Midwall fractional shortening	.25	<.0001	.24	.0001	.21	.0008
Body mass index	.20	.0108	.17	.0458	.22	.0002
Pulse pressure	.04	.6473	.12	.1369	.10	.2160
Systolic blood pressure	.03	.7341	.01	.8998	.06	.4596
Diastolic blood pressure	.07	.175	.17	.0458	.05	.5276
Age	.02	.7403	.08	.2265	.16	.0116

*Independent predictor of LA late diastolic strain rate by multivariate analysis. The variables with significant correlations with LA late-diastolic strain rate by univariate analysis were included in the multiple regression model.
†Independent predictor of LA systolic strain rate by multivariate analysis. The variables with significant correlations with LA systolic strain rate by univariate analysis were included in the multiple regression model.
‡Independent predictor of LA systolic strain by multivariate analysis. The variables with significant correlations with LA systolic strain by univariate analysis were included in the multiple regression model.

patients with hypertension has been associated with microvascular abnormalities,[32,33] LV hypertrophy,[32,33] and changes in the renin-angiotensin-aldosterone system.[34-37] Myocardial alterations as a result of a history of CAD in patients with HFNEF are generally not transmural and include subendocardial fibrotic alterations secondary to myocardial necrosis due to a previous acute coronary syndrome (92% NSTEMI and 8% STEMI in our cohort of patients with HFNEF). Interestingly, in these comorbidities, most of the above-mentioned fibrotic changes affect primarily the subendocardial layer of the left ventricle, with subsequent LV longitudinal systolic and diastolic dysfunction.[12-20] Accordingly, in the presence of high rates of these comorbid disorders, the degree of alteration of the subendocardial fibers of the left ventricle would be elevated. In this regard, in the present study, we found in patients with HFNEF (characterized by a high prevalence of comorbid conditions) impaired parameters of LV subendocardial function and consequently elevated rates of LV longitudinal systolic and diastolic dysfunction.

LA Systolic and Diastolic Function in Patients with HFNEF

We observed that patients with HFNEF had significantly more impaired LA systolic and diastolic function compared with those with asymptomatic LVDD. These findings are similar to previous reports in systolic HF, which have also shown more reduced LA function in these patients compared with asymptomatic control subjects.[7,38,39] An increase in LA afterload through the development of elevated LV filling pressures secondary to severe LVDD has long been considered the main underlying mechanism of LA dysfunction.[6,7,40] However, several and recent findings suggest that the degree of elevated LV filling pressures may not fully explain LA failure and that LA myocardial fibrosis may play a role in the systolic and diastolic dysfunction of the left atrium.[8-11] In this respect, in our study, noninvasive LV filling pressures were modestly associated with LA systolic and diastolic function. According to these findings, previous reports have also demonstrated a modest association between LV filling pressures and LA function.[11,41] Kuppahally *et al.*[11] recently showed in a cohort of

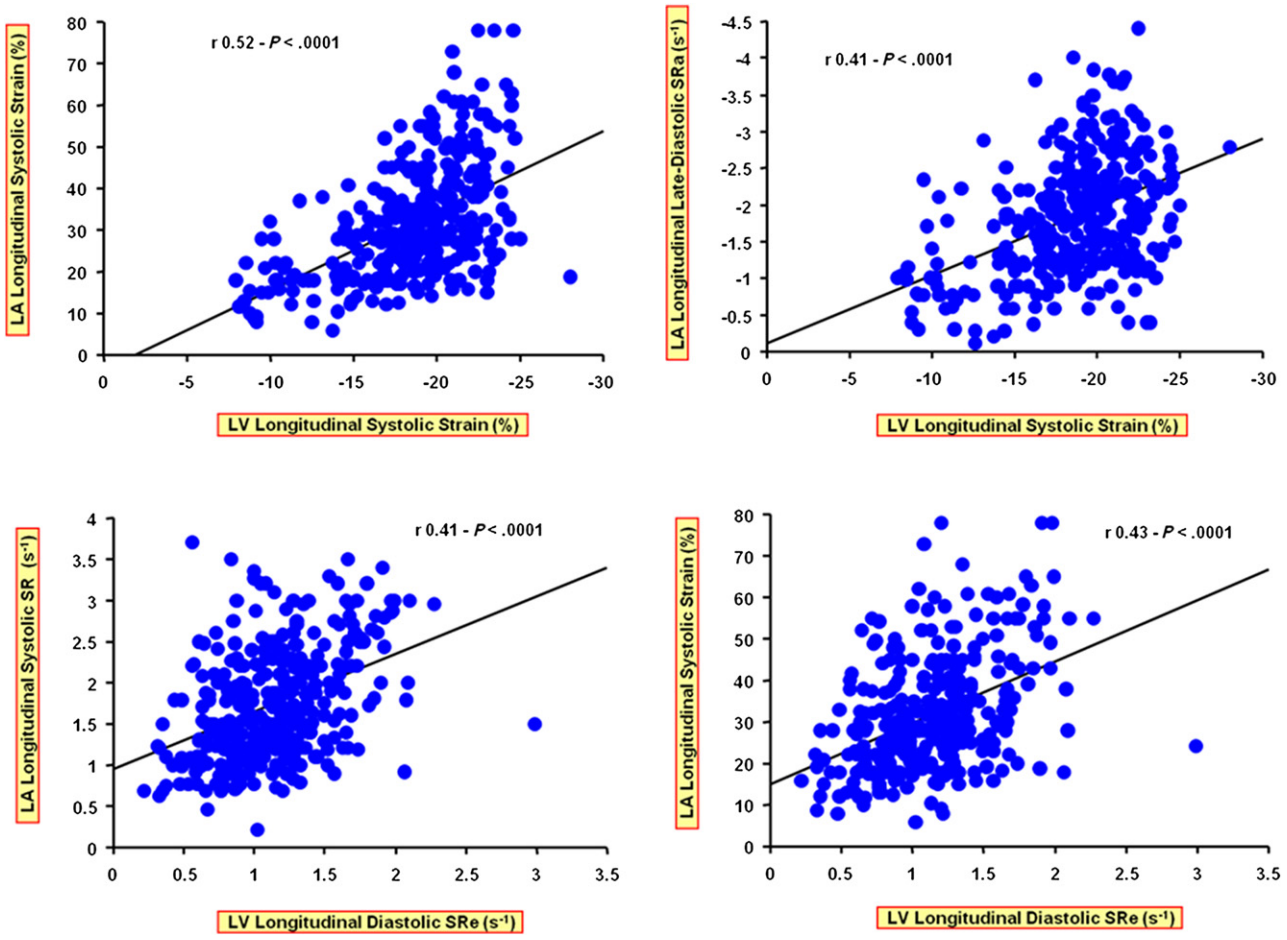

Figure 3 Regression plot showing a significant relationship between LA longitudinal systolic (LA-SRa) and diastolic (LA-Strain and LA-SR) function with LV global longitudinal systolic and diastolic function.

patients with hypertension, diabetes, and CAD that LV filling pressures (i.e., mitral E/e′ ratio) do not predict LA diastolic function (measured by LA-Strain). In addition, Tan *et al.*[41] reported in patients with HFNEF a modest relationship ($r = -0.31$) of noninvasive LV filling pressures with the systolic function of the left atrium at rest (measured by late-diastolic DTI velocity at the mitral annulus). Hence, our findings and the aforementioned reports[11,41] suggest that in patients with HFNEF, LA systolic and diastolic dysfunction is moderately related to increased LV filling pressures and that other pathophysiologic processes could also contribute to these dysfunctions.

New Insights in LA Systolic and Diastolic Dysfunction in Patients with HFNEF

The myoarchitecture of the left atrium is complex, with fibers predominantly arranged in two layers, the subendocardial layer (frequently composed of longitudinal fibers) and the subepicardial layer (mostly composed of circumferential fibers).[42] In patients with HFNEF, the same fibrotic changes that affect the subendocardial fibers of the left ventricle secondary to comorbidities such as hypertension,[16] type 2 diabetes,[18,30] obesity,[17,31] and history of CAD[15] could also affect the subendocardial layer of the left atrium (i.e., LA longitudinal systolic and diastolic function). These pathophysiologic postulates in patients with HFNEF are consistent with our findings and those of previous studies.[14-18,40,43-47] Kang *et al.*[16] and D'Andrea *et al.*[43] demonstrated that in patients with hypertension (even with normal LVEF), LV and LA longitudinal systolic and diastolic function is significantly impaired.[16,43] Furthermore, several studies have also shown that obese patients and subjects with history of CAD have significant alterations of longitudinal systolic and diastolic function of both the left ventricle and the left atrium.[15,17,40,44,45] In patients with type 2 diabetes with LVEF > 50%, abnormalities of the subendocardial fibers of the left atrium and the left ventricle (i.e., impaired LA and LV longitudinal systolic and diastolic function) have also been reported.[14,18,46] Therefore, one might expect that in a setting of high prevalence of these comorbidities, such as HFNEF, the degree of impairment of the subendocardial fibers of the left atrium and the left ventricle would be relevant. In that regard, in our study, characterized by patients with HFNEF with high rates of comorbid conditions, we found that 28.5% and 65.5% of these patients had diastolic and systolic longitudinal dysfunction of the left atrium (i.e., LA subendocardial dysfunction), whereas 58% and 81.5% of these patients also had diastolic and systolic longitudinal dysfunction of the left ventricle (i.e., LV subendocardial dysfunction), respectively. In addition, we found that patients with LA longitudinal systolic and diastolic dysfunction had higher values of PCWP and worse NYHA functional class. Thus, these results demonstrate that in patients with HFNEF, LA subendocardial systolic and diastolic dysfunction is common and possibly associated with the same fibrotic processes that affect the subendocardial layer of the left ventricle as a consequence of comorbid conditions such as hypertension, type 2 diabetes, obesity,

Table 6 Characteristics of patients with LA longitudinal systolic and diastolic dysfunction

Variable	LA systolic dysfunction* (n = 168)	LA normal systolic function† (n = 252)	P	LA diastolic dysfunction‡ (n = 38)	LA normal diastolic function§ (n = 382)	P
NYHA functional class	1.54 ± 0.69	1.19 ± 0.48	<.0001	1.95 ± 0.62	1.27 ± 0.56	<.0001
$PCWP_{echo}$ (mm Hg)‖	17.3 ± 6.1	12.7 ± 4.7	.0022	20.5 ± 6.4	14.3 ± 5.4	.0018
$PASP_{echo}$ (mm Hg)	39.8 ± 10.2	35.2 ± 5.6	.0002	43.0 ± 12.7	36.4 ± 7.2	.0012
$PASP_{echo}$ > 41 mm Hg	42.8%	17.8%	.0033	60.5%	24.6%	.0016
LV longitudinal diastolic SRe (s^{-1})	0.92 ± 0.33	1.05 ± 0.33	.0023	0.75 ± 0.28	1.03 ± 0.33	<.0001
LV longitudinal systolic strain (%)	−16.0 ± 4.2	−18.9 ± 3.0	<.0001	−13.1 ± 3.8	−18.2 ± 3.5	<.0001

Data are expressed as mean ± SD or as percentages. The peak velocity of the tricuspid regurgitation jet by continuous-wave Doppler together with right atrial pressure (using the modified Bernoulli equation and with values fixed of RAP at 10 mm Hg) were used to derive pulmonary arterial systolic pressure ($PASP_{echo}$).
*LA systolic dysfunction = LA-SRa > -1.32 s^{-1}.
†LA normal systolic function = LA-SRa ≤ -1.32 s^{-1}.
‡LA diastolic dysfunction = LA-SR < 0.82 s^{-1}.
§LA normal diastolic function = LA-SR ≥ 0.82 s^{-1}.
‖$PCWP_{echo}$ (estimated PCWP, Nagueh's method) = (mitral E/e′ lateral × 1.3) + 2.

and history of CAD. Furthermore, our findings suggest that LA longitudinal systolic and diastolic dysfunction could contribute to reduced functional capacity during effort in patients with HFNEF.

Potential Mechanisms of LA Dysfunction Related to Reduced Functional Capacity in Patients with HFNEF

In patients with HFNEF, diverse pathophysiologic mechanisms such as abnormalities of LV myocardial stiffness and relaxation,[48,49] increased arterial stiffness,[50] reduced systolic and diastolic mitral annular motion,[4] and diminished LV suction[4] have been associated with reduced functional capacity during effort. Additionally, in our study, we have reported that patients with LA longitudinal systolic and diastolic dysfunction presented worse NYHA functional class as compared with patients with normal LA longitudinal function. On the basis of our findings, we consider that the role of LA dysfunction in the symptomatology of HFNEF may include an additional new pathophysiologic model in this disease, characterized by "failure" and "stiffness" of the left atrium.

In a noncompliant left atrium or "stiff LA syndrome," the reduction in the compliance, reservoir, or diastolic function of the left atrium occurs independently from mitral valve disease or LV dysfunction.[51-53] Thus, these LA alterations result in a profound impairment of LA filling with consequent stasis in pulmonary venous flow.[51-53] Consequently, patients with this disorder invariably develop pulmonary venous hypertension, increase of PCWP, and subsequent pulmonary congestion and dyspnea.[51,53] Interestingly, severe fibrosis and calcification of the left atrium are pathognomonic autopsy findings in these patients.[51-53] In this regard, Kuppahally *et al.*[11] recently studied a group of patients with diverse comorbid conditions, such as hypertension, diabetes, and CAD, by delayed enhancement magnetic resonance imaging and two-dimensional speckle-tracking echocardiography and found an inverse relationship between LA longitudinal diastolic function (LA-Strain) and the percentage of fibrosis in the LA wall. Furthermore, Kurt *et al.*[54] demonstrated in a group of 66 patients (20 with HFNEF, 19 with asymptomatic LVDD, and 27 healthy subjects) that patients with HFNEF had significantly lower values of LA-Strain (measured by strain Doppler) compared with patients with asymptomatic LVDD and healthy subjects. The present study confirms and extends these data in patients with HFNEF by showing that LA diastolic dysfunction is associated to impaired functional capacity and higher PCWP. Hence, we consider that the pathophysiologic alterations of "stiff LA syndrome" secondary to fibrotic processes as a result of comorbid conditions, such as hypertension, type 2 diabetes, obesity, and history of CAD, could also occur in the setting of HFNEF.

On the other hand, other complex pathophysiologic mechanisms could also contribute to LA systolic and diastolic dysfunction in patients with HFNEF. In an initial asymptomatic stage, LV longitudinal diastolic and systolic dysfunction (even with normal LVEF), due to fibrotic abnormalities caused by comorbidities such as hypertension,[16] diabetes,[18,30] obesity,[17,31] and CAD,[15] can lead to elevated LV filling pressures (i.e., increased LA afterload).[55] Consequently, these alterations produce a compensatory mechanism of the left atrium characterized by LA dilatation that contributes to enhanced LA emptying volume by activation of the Frank-Starling mechanism, which is partially responsible for the maintenance of stroke volume in patients with asymptomatic LV dysfunction.[6,7,26,39,53,56,57] However, in a subsequent stage, chronic increases in LA afterload in addition to possible LA fibrotic changes by comorbid conditions may produce an alteration of the compliance, reservoir function, and pump performance of the left atrium (i.e., "LA failure").[26,39,53,56-59] We hypothesize that these reductions in LA systolic and diastolic function could eventually contribute to the development of HF symptoms in previously asymptomatic patients with chronic LV longitudinal diastolic and systolic dysfunction and preserved LVEF. Moreover, once in the context of HFNEF, the severe remodeling of the left atrium[53] and the persistence of uncontrolled comorbidities would induce more fibrosis of the left atrium, leading thereby to more severe LA dysfunction, regardless of increased LV filling pressures. These pathophysiologic postulates in the setting of HFNEF are consistent with our findings. In that regard, in our cohort of HFNEF, with high rates of comorbid conditions, we found that patients with HFNEF presented a significant alteration of the diastolic and systolic longitudinal function of the left atrium, which was modestly related to LV filling pressures. In addition, we showed that patients with both systolic and diastolic longitudinal dysfunction of the left atrium were characterized by presenting higher PCWP and worse NYHA functional class.

Clinical Perspectives

Isolated LVDD (i.e., abnormalities of LV myocardial stiffness and relaxation with normal LVEF) has long been considered the main

underlying mechanism of HFNEF.[48,49] On the basis of this pathophysiologic evidence, several clinical trials have been conducted to restore LV diastolic function in patients with HFNEF and thereby improve the prognosis of these patients.[60-62] However, none of these treatments has been shown to decrease mortality in patients with HFNEF.[60-62] For this reason, new pathophysiologic paradigms should arise with the goal of discovering novel therapeutic targets in this disease.

Recent studies have shown that fibrotic changes of the left atrium can be reversed with antifibrotic therapies such as spironolactone, with a consequent improvement of the remodeling and function of the left atrium.[63,64] In the current study using measurements at rest with two-dimensional speckle-tracking echocardiography, we have demonstrated that patients with HFNEF presented both systolic and diastolic LA dysfunction with subsequent reduced functional capacity during effort. Hence, we consider that in patients with HFNEF, treatments destined to improve LA systolic and diastolic function could be of great importance in the treatment of this complex disease for which, so far, no effective therapies exist.

Limitations

Our study had several limitations. Our analyses of the left atrium were limited because we did not compare our findings with the obtained using three-dimensional echocardiography. Nevertheless, previous studies using two-dimensional echocardiography have shown similar accuracy to three-dimensional measurements of the left atrium.[39,65] Moreover, in the present study, we did not perform an analysis of the variables under study using exercise echocardiography, which recently has shown an interesting role in HFNEF.[4,41] Another study limitation was the lack of invasive hemodynamic data. Cardiac catheterization provides more accurate information about LV filling pressures than echocardiographic measurements.[21] Nonetheless, several studies have demonstrated the high sensitivity, specificity, and accuracy of the mitral E/e′ ratio to determine LV filling pressures.[66-69] In this regard, this noninvasive estimation of LV filling pressures is currently recommended by the consensus of experts or guidelines in LV diastolic function of the American Society of Echocardiography.[21] Furthermore, in our study, we did not analyze healthy subjects. Because it is very difficult to find healthy people aged > 65 years, we were not able to match the age of normal subjects with patients with HFNEF. For this reason, we decided to exclude this group of subjects from our analysis to avoid error bias. It is also worth noting that our cohort of HFNEF was characterized principally by patients in NYHA functional class II. Therefore, future studies with larger numbers of patients in NYHA functional class III and IV are needed to validate the findings of our study. On the other hand, it is important to point out that in this work, we did not perform a prospective evaluation of each variable under study. Hence, in patients with HFNEF, the cutoff values used in our study for the definitions of LA and LV longitudinal systolic and diastolic dysfunction should be prospectively evaluated to determine its prognostic significance (mortality from HF and/or rehospitalization for HFNEF).

CONCLUSIONS

In patients with HFNEF, the subendocardial systolic and diastolic dysfunction of the left atrium (i.e., LA longitudinal systolic and diastolic dysfunction) is common and possibly associated with the same fibrotic processes that affect the subendocardial layer of the left ventricle as a consequence of comorbid conditions such as hypertension, type 2 diabetes, obesity, and history of CAD. Furthermore, our findings suggest that LA longitudinal systolic and diastolic dysfunction may be important factors that contribute to reduced functional capacity during effort in patients with HFNEF. Thus, in this study we have highlighted that HFNEF is characterized by diastolic and systolic subendocardial dysfunction of both the left atrium and the left ventricle as a consequence of several pathologic disorders. Therefore, strict control of comorbidities as well as the restoration of the subendocardial systolic and diastolic abnormalities of both the left atrium and the left ventricle could be of great importance in the treatment of patients with HFNEF.

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REFERENCES

1. Kitzman DW, Gardin JM, Gottdiener JS, Arnold A, Boineau R, Aurigemma G, et al. Importance of heart failure with preserved systolic function in patients ≥65years of age. Am J Cardiol 2001;87:413-9.
2. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007;28:2539-50.
3. Wang J, Khoury DS, Yue Y, Torre-Amione G, Nagueh SF. Preserved left ventricular twist and circumferential deformation, but depressed longitudinal and radial deformation in patients with diastolic heart failure. Eur Heart J 2008;29:1283-9.
4. Tan YT, Wenzelburger F, Lee E, Heatlie G, Leyva F, Patel K, et al. The patho-physiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist and longitudinal motion. J Am Coll Cardiol 2009;54:36-46.
5. Liu YW, Tsai WC, Su CT, Lin CC, Chen JH. Evidence of left ventricular systolic dysfunction detected by automated function imaging in patients with heart failure and preserved left ventricular ejection fraction. J Card Fail 2009;15:782-9.
6. Prioli A, Marino P, Lanzoni L, Zardini P. Increasing degrees of left ventricular filling impairment modulate left atrial function in humans. Am J Cardiol 1998;82:756-61.
7. Ito T, Suwa M, Kobashi A, Yagi H, Hirota Y, Kawamura K. Reversible left atrial dysfunction possibly due to afterload mismatch in patients with left ventricular dysfunction. J Am Soc Echocardiogr 1998;11:274-9.
8. Ohtani K, Yutani C, Nagata S, Koretsune Y, Hori M, Kamada T. High prevalence of atrial fibrosis in patients with dilated cardiomyopathy. J Am Coll Cardiol 1995;25:1162-9.
9. Masugata H, Mizushige K, Senda S, Lu X, Kinoshita A, Sakamoto H, et al. Evaluation of left atrial wall elasticity using acoustic microscopy. Angiology 1999;50:583-90.
10. Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. Circulation 1999;100:87-95.
11. Kuppahally SS, Akoum N, Burgon NS, Badger TJ, Kholmovski EG, Vijayakumar S, et al. Left atrial strain and strain rate in patients with paroxysmal and persistent atrial fibrillation. Relationship to left atrial structural remodeling detected by delayed-enhancement MRI. Circ Cardiovasc Imaging 2010;3:231-9.
12. Marcos-Alberca P, García-Fernández MA, Ledesma MJ, Malpica N, Santos A, Moreno M, et al. Intramyocardial analysis of regional systolic and diastolic function in ischemic heart disease with Doppler tissue

imaging: role of the different myocardial layers. J Am Soc Echocardiogr 2002;15:99-108.
13. Martinez DA, Guhl DJ, Stanley WC, Vailas AC. Extracellular matrix maturation in the left ventricle of normal and diabetic swine. Diabetes Res Clin Pract 2003;59:1-9.
14. Fang ZY, Leano R, Marwick TH. Relationship between longitudinal and radial contractility in subclinical diabetic heart disease. Clin Sci (Lond) 2004;106:53-60.
15. Chan J, Hanekom L, Wong C, Leano R, Cho GY, Marwick TH. Differentiation of subendocardial and transmural infarction using two-dimensional strain rate imaging to assess short-axis and long-axis myocardial function. J Am Coll Cardiol 2006;48:2026-33.
16. Kang SJ, Lim HS, Choi BJ, Choi SY, Hwang GS, Yoon MH, et al. Longitudinal strain and torsion assessed by two-dimensional speckle tracking correlate with the serum level of tissue inhibitor of matrix metalloproteinase-1, a marker of myocardial fibrosis, in patients with hypertension. J Am Soc Echocardiogr 2008;21:907-11.
17. Kosmala W, Wong C, Kuliczkowska J, Leano R, Przewlocka-Kosmala M, Marwick TH. Use of body weight and insulin resistance to select obese patients for echocardiographic assessment of subclinical left ventricular dysfunction. Am J Cardiol 2008;101:1334-40.
18. Ng AC, Delgado V, Bertini M, van der Meer RW, Rijzewijk LJ, Shanks M, et al. Findings from left ventricular strain and strain rate imaging in asymptomatic patients with type 2 diabetes mellitus. Am J Cardiol 2009;104:1398-401.
19. Stanton T, Marwick TH. Assessment of subendocardial structure and function. J Am Coll Cardiol Img 2010;3:867-75.
20. Geyer H, Caracciolo G, Abe H, Wilansky S, Carerj S, Gentile F, et al. Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications. J Am Soc Echocardiogr 2010; 23:351-69.
21. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009;22:107-33.
22. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr., Faxon DP, Freed MD, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice. J Am Coll Cardiol 2008;52. e1-142.
23. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification. J Am Soc Echocardiogr 2005;18:1440-63.
24. Wang J, Khoury DS, Thohan V, Torre-Amione G, Nagueh SF. Global diastolic strain rate for the assessment of left ventricular relaxation and filling pressures. Circulation 2007;115:1376-83.
25. Triposkiadis F, Tentolouris K, Androulakis A, Trikas A, Toutouzas K, Kyriakidis M, et al. Left atrial mechanical function in the healthy elderly: new insights from a combined assessment of changes in atrial volume and transmitral flow velocity. J Am Soc Echocardiogr 1995;8:801-9.
26. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, et al. Left atrial size: physiologic determinants and clinical applications. J Am Coll Cardiol 2006;47:2357-63.
27. Vianna-Pinton R, Moreno CA, Baxter CM, Lee KS, Tsang TS, Appleton CP. Two-dimensional speckle-tracking echocardiography of the left atrium: feasibility and regional contraction and relaxation differences in normal subjects. J Am Soc Echocardiogr 2009;22:299-305.
28. Khankirawatana B, Khankirawatana S, Peterson B, Mahrous H, Porter TR. Peak atrial systolic mitral annular velocity by Doppler tissue reliably predicts left atrial systolic function. J Am Soc Echocardiogr 2004;17:353-60.
29. Saraiva RM, Demirkol S, Buakhamsri A, Greenberg N, Popović ZB, Thomas JD, et al. Left atrial strain measured by two-dimensional speckle tracking represents a new tool to evaluate left atrial function. J Am Soc Echocardiogr 2010;23:172-80.
30. Marwick TH. Diabetic heart disease. Heart 2006;92:296-300.
31. Horwich TB, Fonarow GC. Glucose, obesity, metabolic syndrome, and diabetes relevance to incidence of heart failure. J Am Coll Cardiol 2010;55: 283-93.
32. Hittinger L, Shannon RP, Bishop SP, Gelpi RJ, Vatner SF. Subendomyocardial exhaustion of blood flow reserve and increased fibrosis in conscious dogs with heart failure. Circ Res 1989;65:971-80.
33. Lips DJ, deWindt LJ, van Kraaij DJ, Doevendans PA. Molecular determinants of myocardial hypertrophy and failure: alternative pathways for beneficial and maladaptive hypertrophy. Eur Heart J 2003;24:883-96.
34. Brilla CG, Matsubara LS, Weber KT. Antifibrotic effect of spironolactone in preventing myocardial fibrosis in systemic arterial hypertension. Am J Cardiol 1993;71:A12-6.
35. Brilla CG, Funck RC, Rupp H. Lisinopril-mediated regression of myocardial fibrosis in patients with hypertensive heart disease. Circulation 2000;102:1388-93.
36. Díez J, Querejeta R, López B, González A, Larman M, Martínez Ubago JL. Losartan-dependent regression of myocardial fibrosis is associated with reduction of left ventricular chamber stiffness in hypertensive patients. Circulation 2002;105:2512-7.
37. Zhong J, Basu R, Guo D, Chow FL, Byrns S, Schuster M, et al. Angiotensin-converting enzyme 2 suppresses pathological hypertrophy, myocardial fibrosis, and cardiac dysfunction. Circulation 2010;122:717-28.
38. Gottdiener JS, Kitzman DW, Aurigemma GP, Arnold AM, Manolio TA. Left atrial volume, geometry, and function in systolic and diastolic heart failure of persons ≥ 65 years of age (the Cardiovascular Health Study). Am J Cardiol 2006;97:83-9.
39. Tsai CT, Hung CL, Hou CJ, Hung TC, Yeh HI, Tsai CH. Real-time three-dimensional echocardiography in the evaluation of left atrial structure and function in normal, aging, hypertensive and heart failure patients: new insights into left atrial adaptation and remodeling. Int J Gerontol 2009;3:53-65.
40. Yu CM, Lin H, Kum LC, Lam WF, Fung WH, Sanderson JE. Evidence of atrial mechanical dysfunction by acoustic quantification in abnormal relaxation and restrictive filling patterns of diastolic dysfunction in patients with coronary artery disease. Eur J Echocardiogr 2003;4:272-8.
41. Tan YT, Wenzelburger F, Lee E, Nightingale P, Heatlie G, Leyva F, et al. Reduced left atrial function on exercise in patients with heart failure and normal ejection fraction. Heart 2010;96:1017-23.
42. Ho SY, Sanchez-Quintana D, Cabrera JA, Anderson RH. Anatomy of the left atrium: Implications for radiofrequency ablation of atrial fibrillation. J Cardiovasc Electrophysiol 1999;10:1525-33.
43. D'Andrea A, De Corato G, Scarafile R, Romano S, Reigler L, Mita C, et al. Left atrial myocardial function in either physiological or pathological left ventricular hypertrophy: a two dimensional speckle strain study. Br J Sports Med 2008;42:696-702.
44. Di Salvo G, Pacileo G, Del Giudice EM, Natale F, Limongelli G, Verrengia M, et al. Atrial myocardial deformation properties in obese non-hypertensive children. J Am Soc Echocardiogr 2008;21:151-6.
45. Boyd AC, Ng AC, Tran DT, Chia EM, French JK, Leung DY, et al. Left atrial enlargement and phasic function in patients following non-ST elevation myocardial infarction. J Am Soc Echocardiogr 2010;23:1251-8.
46. Muranaka A, Yuda S, Tsuchihashi K, Hashimoto A, Nakata T, Miura T, et al. Quantitative assessment of left ventricular and left atrial functions by strain rate imaging in diabetic patients with and without hypertension. Echocardiography 2009;26:262-71.
47. Guan Z, Zhang D, Huang R, Zhang F, Wang Q, Guo S. Association of left atrial myocardial function with left ventricular diastolic dysfunction in subjects with preserved systolic function: a strain rate imaging study. Clin Cardiol 2010;33:643-9.
48. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure: abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med 2004;350:1953-9.
49. Westermann D, Kasner M, Steendijk P, Spillmann F, Riad A, Weitmann K, et al. Role of left ventricular stiffness in heart failure with normal ejection fraction. Circulation 2008;117:2051-60.
50. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. Circulation 2003;107:714-20.

51. Mehta S, Charbonneau F, Fitchett DH, Marpole DG, Patton R, Sniderman AD. The clinical consequences of a stiff left atrium. Am Heart J 1991;122:1184-91.
52. Fitchett DH. Time varying loading of the pulmonary circulation: a model to describe hemodynamic observations in the stiff left atrial syndrome. Can J Cardiol 1995;11:23-9.
53. Pagel PS, Kehl F, Gare M, Hettrick DA, Kersten JR, Warltier DC. Mechanical function of the left atrium: new insights based on analysis of pressure-volume relations and Doppler echocardiography. Anesthesiology 2003; 98:975-94.
54. Kurt M, Wang J, Torre-Amione G, Nagueh SF. Left atrial function in diastolic heart failure. Circ Cardiovasc Imaging 2009;2:10-5.
55. Dokainish H, Sengupta R, Pillai M, Bobek J, Lakkis N. Assessment of left ventricular systolic function using echocardiography in patients with preserved ejection fraction and elevated diastolic pressures. Am J Cardiol 2008;101:1766-71.
56. Stefanadis C, Dernellis J, Toutouzas P. A clinical appraisal of left atrial function. Eur Heart J 2001;22:22-36.
57. Leung DY, Boyd A, Ng AA, Chi C, Thomas L. Echocardiographic evaluation of left atrial size and function: current understanding, pathophysiologic correlates, and prognostic implications. Am Heart J 2008;156: 1056-64.
58. Wakami K, Ohte N, Asada K, Fukuta H, Goto T, Mukai S, et al. Correlation between left ventricular end-diastolic pressure and peak left atrial wall strain during left ventricular systole. J Am Soc Echocardiogr 2009;22:847-51.
59. Teo SG, Yang H, Chai P, Yeo TC. Impact of left ventricular diastolic dysfunction on left atrial volume and function: a volumetric analysis. Eur J Echocardiogr 2010;11:38-43.
60. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: The CHARM-Preserved Trial. Lancet 2003;362:777-81.
61. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006;27:2338-45.
62. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359:2456-67.
63. Milliez P, Deangelis N, Rucker-Martin C, Leenhardt A, Vicaut E, Robidel E, et al. Spironolactone reduces fibrosis of dilated atria during heart failure in rats with myocardial infarction. Eur Heart J 2005;26:2193-9.
64. Yang SS, Han W, Zhou HY, Dong G, Wang BC, Huo H, et al. Effects of spironolactone on electrical and structural remodeling of atrium in congestive heart failure dogs. Chin Med J (Engl) 2008;121:38-42.
65. Anwar AM, Soliman OI, Geleijnse ML, Nemes A, Vletter WB, ten Cate FJ. Assessment of left atrial volume and function by real-time three-dimensional echocardiography. Int J Cardiol 2008;123:155-61.
66. Rivas-Gotz C, Manolios M, Thohan V, Nagueh SF. Impact of left ventricular ejection fraction on estimation of left ventricular filling pressures using tissue Doppler and flow propagation velocity. Am J Cardiol 2003;91: 780-4.
67. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a non-invasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997;30:1527-33.
68. Nagueh SF, Mikati I, Kopelen HA, Middleton KJ, Quinones MA, Zoghbi WA. Doppler estimation of left ventricular filling pressure in sinus tachycardia. A new application of tissue Doppler imaging. Circulation 1998;98:1644-50.
69. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. Circulation 2000;102: 1788-94.