Interatrial dyssynchrony may contribute to heart failure symptoms in patients with preserved ejection fraction: a potential novel therapeutic target.

SHORT TITLE: Interatrial dyssynchrony in HPEF

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ABSTRACT

Purpose: Heart failure (HF) with preserved ejection fraction (HFPEF) is the most prevalent type of HF in nonhospitalized patients, but its pathophysiology remains poorly understood. The aim of our study was to assess the existence of interatrial dyssynchrony (IAD), a potentially treatable condition, in the development of HF symptoms.

Methods: Consecutive patients with new onset of shortening of breath, referred for suspected HF, were screened. In all cases, a transthoracic echocardiography, ECG, and determination of plasma BNP level were performed at initial consultation. Patients were diagnosed according to current guidelines. Patients with HF and reduced ejection fraction were excluded. Later, the time from P-wave onset on the ECG to peak negative strain (atrial contraction) was determined using speckle tracking echocardiography; the time difference between both atria (ms) was used as an index of IAD.

Results: Sixty-six patients were included. Mean age was 74 ± 8 years (74% female, 77% hypertensive). HFPEF patients (n = 32) showed an increased IAD as compared to subjects with non-HF (n = 34; interatrial time difference 72.7 ± 27 vs. 28 ± 7 ms, $P < 0.001$). IAD showed a significant correlation with BNP levels, diastolic pattern, and echocardiographic parameters indicative of elevated LV filling pressures. LA function assessed by LA strain rate was not significantly different between HPPEF patients with and without IAD > 60 ms.

Conclusions: We showed that IAD was present at initial stages of symptomatic HFPEF. It might be an important mechanism involved in the development of symptoms in HFPEF and a potential target amenable to be treated with device therapy.

KEY WORDS: heart failure with preserved ejection fraction, interatrial dyssynchrony, speckle tracking echocardiography, outpatients.

INTRODUCTION

Heart failure (HF) with preserved ejection fraction (HFPEF) represents more than 50% of all HF outpatients.[1] Despite its high prevalence, its pathophysiology continues being poorly understood,[1] and potential therapies to address this clinical syndrome are therefore scarce. Diastolic impairment was suggested as the major contributor to the pathophysiology of HFPEF, but it is not the unique one, indeed, it is also observed in HF patients with reduced ejection fraction (HFREF).[2]

Many mechanisms have been investigated on top of diastolic abnormalities as a potential underlying etiology of HFPEF, including exercise-induced ventricular dysfunction,[3,4] impaired ventricular-arterial coupling,[5] chronotropic incompetence,[6] pulmonary hypertension,[7] and even a systemic pro-inflammatory state.[8] Additionally, several authors have described mechanical ventricular abnormalities in HFPEF patients reporting changes in longitudinal [9,10] radial and torsional motion.[11] They support the hypothesis of the existence of a potential latent ventricular systolic dysfunction not diagnosed by conventional methods. More recently, though, an "atrial hypothesis" suggesting atrial dysfunction as a contributor to symptoms among HFPEF patients is gaining ground.[12] Interatrial conduction delay (interatrial block) is associated with abnormal atrial excitability, leading to electromechanical dysfunction of the left atrium (LA) and a markedly reduction of left ventricular filing.[13]

Recently, Eicher et al.[14] proposed interatrial dyssynchrony (IAD), assessed by pulse-wave Doppler study of the mitral and tricuspid inflows, as a potential mechanism in a small group of HFPEF patients that could be improved with pacing.[15] Speckle tracking strain has been also applied to evaluate LA asynchrony in previous studies[16]; accordingly, we used speckle tracking echocardiography to determine IAD.

Our objective was to study the prevalence and distribution of IAD in a group of patients with new-onset HF symptoms and preserved left ventricular (LV) ejection fraction using speckle- tracking echocardiography.

MATERIALS AND METHODS

All patients with new-onset symptoms suggestive of HF, who were referred to a 1-stop clinic for diagnosis between 2009 and 2012, were screened (n = 172). All of them provided a written informed consent at the moment of the inclusion in the study. The study complies with the Declaration of Helsinki and was approved by the local ethics committee at the hospital. Inclusion criteria were patients with recent onset of symptoms suggestive of HF and with no previous cardiologic study. Exclusion criteria were age under 18 years, comorbidity with life expectancy lower than 1 year, atrial fibrillation or flutter at the moment of the visit, reduced left ventricular ejection fraction and significant heart valve disease (severity of dysfunction more than mild).

At the initial consultation, a clinical evaluation by a cardiologist was performed together with an ECG, chest x-ray, blood tests with determination of plasma BNP, and a comprehensive transthoracic echocardiography. The final diagnosis (HFPEF, HFREF, or non-HF) was established in each patient according to the current guidelines using the modified algorithm proposed by Paulus et al.[17] As previously stated, patients with HFREF were excluded from this study. BNP plasma levels were determined using the immunoassay Chemiluminescence and autoanalyzer ADVIA Centaur BNP kit (Siemens Healthcare Diagnostics, Tarrytown, NY, USA).

Echocardiography was performed using a commercial ultrasound machine (Vivid 7;

General Electric, Milwaukee, WI, USA). Left ventricular (LV) ejection fraction and mass were determined using the biplane Simpson method and the Devereux formula, respectively. LV diastolic function was evaluated using pulsed Doppler interrogation of the mitral valve inflow (early and late mitral peak velocities [E, A], deceleration time of E and A, E/A ratio), pulmonary vein flow (systolic and diastolic waves), and tissue Doppler to determine early and late diastolic myocardial velocities at the lateral mitral annulus (E0, A0 and E/E0 ratio).

LV diastolic function was graded as normal, mild dysfunction (grade I), moderate dysfunction (grade II), and severe dysfunction (grade III) using current recommendations.[18] Systolic pulmonary arterial pressure (PAP) was estimated from the tricuspid regurgitation peak velocity. LA volumes were calculated by modified Simpson's Method from images in the four-chamber apical view. LA active volume was calculated as the difference between LA volume at the onset of the P-wave on the ECG (preatrial contraction volume) and LA minimum volume. LA passive volume was calculated as the difference between LA maximum volume and LA volume at the onset of the P-wave on the ECG (preatrial contraction volume). LA deformation was measured with a commercially available dedicated software from 2D echocardiographic images (2D strain, EchoPAC; GE Healthcare, Milwaukee, WI, USA). To measure LA function, location of the trigger was set at the P-wave on the ECG instead of the QRS and adequate tracking of the LA walls was ensured before processing the images. The frame rate was set between 60 and 80 frames. Global longitudinal LV strain rate (6 segments from the four-chamber view) was measured. Global atrial strain (the sum of the peak negative and positive atrial strain) and strain rate (atrial peak systolic strain rate [s-wave] and atrial peak strain rate after atrial contraction [a-wave]) (6 segments from the four-chamber view) were quantified.

INTERATRIAL ELECTRICAL AND MECHANICAL DYSSYNCHRONY

The presence of mechanical IAD was evaluated using speckle tracking echocardiography in an off-line analysis using commercially available software (2Dstrain, EchoPAC). Global longitudinal myocardial strain of both atria was obtained from the apical four-chamber view. The electro- mechanical delay from the P-wave onset to the peak of left and right atrium systole was estimated as the difference between the time from onset of the P-wave on the surface ECG and the time to peak negative longitudinal strain (atrial contraction) of the left (LAps) and right atria (RAps). The time difference between both atria (LAps-RAps) (ms) was used as an index of mechanical IAD (Fig. 1). Intra-LA delay was measured as the delay between the peak negative longitudinal strain of the septal and lateral LA wall.

Interatrial electrical dyssynchrony was evaluated assessing the interatrial conduction delay on the surface ECG, which was performed at 25 mm/sec speed. P-wave duration, QRS width, PR interval, and the interval between the onset of the P- to the end of the R-waves (PeR) were measured. Additionally, and according to the Spodick Criteria, interatrial conduction delay was defined as the prolongation of P by more than 120 ms in at least 1 of the 12 leads.[19]

STATISTICAL ANALISYS

Data are reported as percentages or mean values ± standard deviation. Comparison between categorical or quantitative groups was performed with chi-squared or Student's t-test, when appropriate. Pearson's correlation test was used to explore correlations between quantitative variables. A P-value lower than 0.05 (2-sided) was considered statistically significant. All the statistical analysis was performed with SPSS v.19 (IBM Corporation, Armonk, NY, USA).

RESULTS

CLINICAL CHARACTERISTICS

One hundred thirty-eight patients were screened with suitable echocardiograhic images acquisition; final diagnoses were as follows: 23.2% (n = 32) patients with HFREF, 45.7% (n = 63) with HFPEF, and 31.2% (n = 43) with non-HF. Then, HFREF patients (n = 32) and those with atrial fibrillation at the moment of the echocardiography (n = 29) were excluded according to the preestablished exclusion criteria of the study. Eleven additional patients were also excluded for significant heart valve disease. Finally, a group of 66 patients constituted this study population.

Mean age was 74 ± 8 years, and 74% were females. Final diagnosis was HFPEF in 34 patients (51.5%) and non-HF in 32 (48.5%). There were no significant differences between the 2 groups regarding age, gender, NYHA functional class, and cardiovascular risk factor profiles, except for systemic hypertension that was more prevalent in the HFPEF group. In HFPEF patients, higher BNP levels were also observed. Table I summarizes the clinical features of the study population.

INTERATRIAL DYSSYNCHRONY

Electrical IAD parameters are shown in Table II. The prevalence of an interatrial block as defined on the surface ECG and the length of the PR interval were not statistically different in both groups, despite a trend to higher prevalence of electrical interatrial dyssynchrony and longer PR intervals in the HFPEF group. Additionally, no differences existed regarding P-wave or QRS duration, either.

Table III depicts the echocardiographic characteristics of both groups of patients

including the assessment of mechanical IAD. LV ejection fraction, dimensions, and longitudinal strain rate were not significantly different in the HFPEF and non-HF groups. LV mass was significantly larger in the HFPEF group. PAP was mildly elevated in the 2 groups without significant differences between them (37.5 ± 6 vs. 33.7 ± 9 mmHg). As anticipated, we found a higher LA volume and parameters indicative of elevated LV filling pressure in the HFPEF group (higher E/e0 and E/A ratios). LA strain and strain rate ("a"—depicting atrial contraction and "s"—depicting ventricular systolic peak strain rate) were significantly decreased in HFPEF group, while RA strain and strain rate showed no statistically significant differences between groups. HFPEF patients also showed an increased interatrial time difference to peak atrial contraction as a marker of IAD as com- pared to the non-HF group (72 ± 27 vs. 28 ± 7 ms, $P < 0.001$).

Significant LV diastolic dysfunction (grade ≥ II) was present in 40.6% of the HFPEF patients and in none of the non-HF patients. Patients with HFPEF and grade II LV diastolic dysfunction had significantly higher systolic pulmonary artery pressure estimates (40.8 ± 6 vs. 34.8 ± 7 mmHg; $P = 0.040$) and more IAD as shown by longer interatrial time difference to atrial contraction (83.3 ± 26 vs. 41.4 ± 25 ms; $P < 0.001$).

RELATION BETWEEN ELEVATED FILLING PRESSURES AND INTERATRIAL DYSSYNCHRONY

IAD had a significant correlation with echocardiographic parameters of elevated LV filling pressures (E/E0 $r = 0.46$, $P < 0.001$; E/A $r = 0.41$, $P < 0.001$), LA indexed volume ($r = 0.43$, $P < 0.001$), diastolic pattern ($r = 0.53$, $P < 0.001$), and BNP levels ($r = 0.37$, $P = 0.002$).

Figure 2 shows the relationship between BNP plasma levels and IAD, representing each individual by his/her final diagnosis and LV diastolic function pattern. Patients with higher IAD showed higher BNP levels. All patients with non- HF (all with normal LV diastolic pattern

or grade I diastolic dysfunction) are depicted in a small area of the graph with BNP levels below 100 ng/mL and IAD <60 ms. Conversely, HFPEF patients are mainly depicted outside this area.

The prevalence of severe IAD, as defined by a cut-off point of 60 ms as previously described,[14] was 66% in HFPEF patients and 0% in the non- HF group. Table IV shows the clinical and echocardiographic characteristics of HFPEF patients depending of the severity of the IAD. There were no significant differences between groups in age, LA size, or arterial systolic pressure. The measurement of LA and RA strain and strain rate showed no statistically significant differences between groups despite a trend to lower LA SRs in patients with IAD >60 ms was observed. Patients with IAD >60 ms also showed higher prevalence of significant LV diastolic dysfunction with a trend toward higher levels of plasma BNP levels. Intra-LA delay showed no significant differences between groups.

DISCUSSION

Patients with new-onset symptoms of HF and a final diagnosis of HFPEF according to the Paulus criteria[17] presented more IAD than non-HF patients. A significant correlation was also found between BNP levels and the presence of IAD in the studied population.

It is well known that electromechanical abnormalities of the LA correlate with its contractile dysfunction and represent a risk factor for the development of congestive HF and atrial arrhythmias.[13,20] In our study, the surface ECG was registered at a 25 mm/sec speed, which might explain its low sensibility and specificity to assess the atrial electromechanical delay as compared to the report of Spoddick. Indeed, we found a low prevalence of interatrial block (non-HF 11.8% vs. HFPEF 18.8%; P = 0.429) with no significant

increase of P-wave duration in the 2 study groups. However, when we analyzed mechanical IAD with the use of speckle tracking echocardiography, we found a significantly high prevalence of IAD in patients with HFPEF, which is in accordance to what has been previously reported.[14] We found that patients with HFPEF presented a mean time difference to peak atrial contraction between both atria 72 ± 27 ms, which is similar to that described by Eicher et al.[14]; also, values observed in our control group and those reported by Eicher et al. in their control group were similar (27.8 ± 7 vs. 24.1 ± 12 ms). However, our population included only patients with new-onset symptoms, indicating the presence of this mechanical abnormality even in early stages of HF and suggesting a potential role in the pathogenesis and development of symptoms in patients with HFPEF.

The linear relationship between IAD and plasma BNP also suggests a correlation between higher IAD value and worse clinical status.[21] According with the cutoff point of severe IAD (≥60 ms) previously established by Eicher et al.,[14] we found a significantly worse diastolic pattern and a trend to higher BNP levels in the group of patients with more severe IAD (i.e., longer time differences between onset of contraction of both atria). Despite there was a significant correlation of IAD with LA volume, the latter was not significantly differed in the HFPEF patients with or with- out severe IAD. If we focused on LA function, it was significantly decreased in HFPEF compared to non-HF group (lower atrial strain rate), but when we compared HFPEF patients with an IAD lower and higher than 60 ms, no differences were noted in LA function (LA strain rate). These findings are important because the group of patients with severe IAD had worse classical clinical indicators of HF (BNP and LV diastolic dysfunction pattern) with similar LA size and strain rate, suggesting that IAD is an independent mechanism implicated in HFPEF beyond LV diastolic dysfunction or LA strain. On the other hand, we found patients with LV diastolic dysfunction grade I (impaired

relaxation) in non-HF and HFPEF groups, but HFPEF patients had higher BNP levels and longer interatrial time differences for reaching atrial contraction (i.e., more IAD), as compared to non-HF patients. This finding also indicates that diastolic function impairment is not the same as HFPEF. It is a complex clinical syndrome with several involved mechanisms with LV diastolic dysfunction being only one of them.

According to our findings, our hypothesis is that IAD is not only a consequence of an elevated LA filling pressure but might be also a contributor to the development of overt clinical HFPEF. A delayed atrial contraction induces loss of atrioventricular coupling, and consequently, the loss of "atrial kick" reducing atrial emptying volume and increasing atrial afterload and filling pressure. Moreover, this mechanism could be exacerbated during exercise with higher heart rates. The LA responds to higher volume and pressure overload with progressive dilatation and fibrosis,[22,23] its performance finally getting impaired when dilatation is excessive.[24]

A dual-chamber pacemaker (one lead in coronary sinus and one lead at interventricular septum) has been attempted in 6 patients with high degree of IAD and severe LV diastolic dysfunction with an improvement in exercise capacity, ventricular filling, and symptoms as well as a reduction in hospital admissions at 1 year of follow-up.[15] Therefore, pacing may be effective by interrupting a vicious circle where the alteration in the conduction of the electrical signal secondary to LA enlargement and fibrosis irreversibly deteriorate already sick atria.

LIMITATIONS

Our study had several limitations. This is an observational study with a reduced number of patients; the control group (non-HF patients) was also derived to the one-stop clinic for

suspected HF, but this diagnosis was ruled out after the consultation; therefore, they were not a pure healthy control group, and they could, indeed, have other conditions that could act as confounders.

We did not perform electrophysiological studies to the studied population. Consequently, there was no direct comparison of the IAD data obtained with speckle tracking echocardiography and the electrophysiological study. However, the reproducibility with the data of Eicher et al.[14] suggests a good concordance with the electro-physiological data and validates our measurements. Even though mechanical dyssynchrony is complex to assess by single measurements such as time to peak, we believe that its relevance is enough for the perspective of our application. The low prevalence of interatrial block and the low mean values of P-wave duration as compared to previous studies may be explained by the fact that we did not use a magnifying lens and that ECGs were registered at a 25 mm/sec, which limited the accuracy in the measurement of ECG segments. However, we believe that our observations are at least enough to generate this pathophysiologic hypothesis that should certainly be confirmed with larger prospective studies.

CONCLUSIONS

In outpatients with HF symptoms onset and HFPEF, there is an increased prevalence of IAD. Our findings suggest that IAD could be an early abnormality in HFPEF and that it could contribute to overt clinical symptoms in these patients. IAD would worsen LA filling pressure, thus worsening exercise performance in the early stage of HFPEF; later on, it would contribute to resting symptoms.

Speckle tracking echocardiography to assess IAD is a reliable and noninvasive technique that could be added to the conventional echocardiographic study of symptomatic patients

with suspected HFPEF to identify a potential target for device therapy.

CONFLICT OF INTEREST: none declared

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FIGURES:

FIGURE 1: Interatrial dyssynchrony determination using speckle tracking echocardiography. In all subjects, the time from onset of the P-wave on the ECG to peak negative strain (atrial contraction) was determined using speckle tracking from apical four-chamber views; the time difference between both atria (ms) was used as an index of IAD. IAD = interatrial dyssynchrony; RA = right atria; LA = left atria.

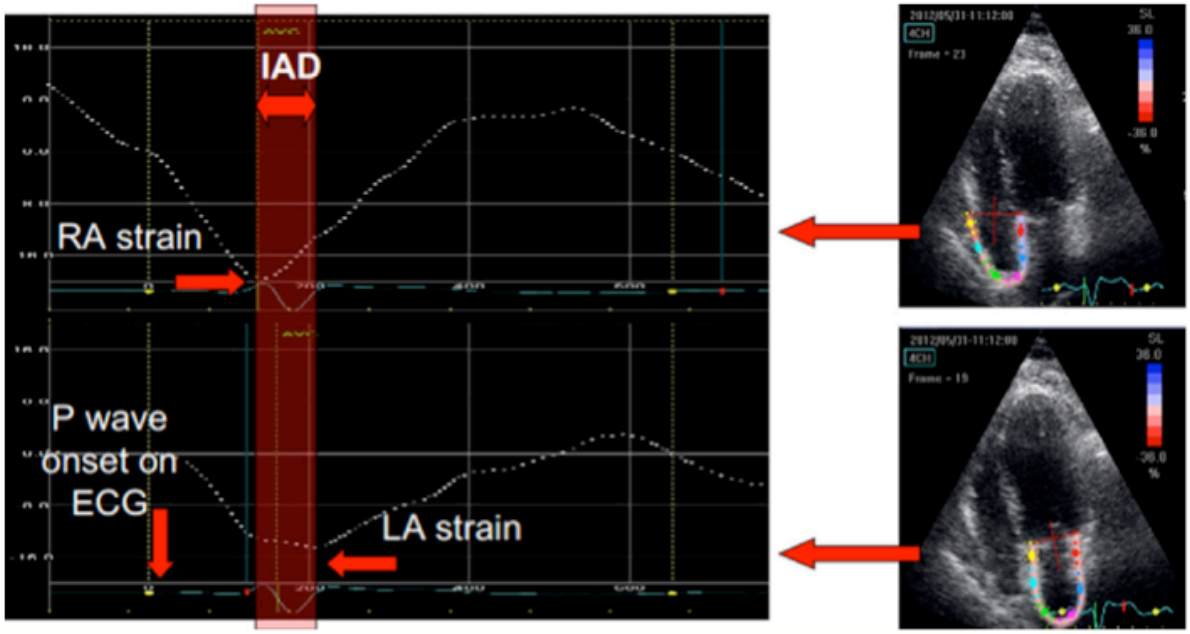
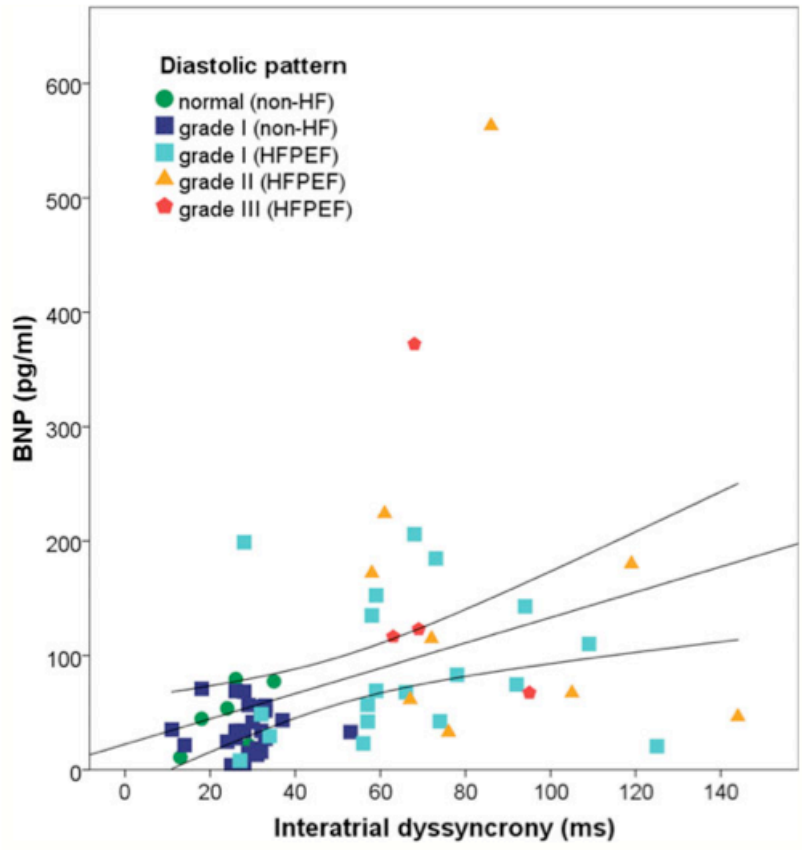


FIGURE 2. Correlation of interatrial dyssynchrony with BNP (r = 0.372; P = 0.002). Individual diastolic pattern is showed. HFPEF = heart failure preserved ejection fraction; non-HF = no heart failure.



TABLES:

TABLE 1. Clinical characteristics of diagnostic groups

	HFPEF (n=34)	**Non-HF** (n=32)	**p-value**
Age (years)	75.2 ± 8.9	72.9 ± 7.5	0.254
Male	28 % (9)	23 % (8)	0.525
BMI	30.1 ± 5.1	31.2 ± 3.6	0.329
Hypertension	93.6 % (30)	61.8 % (21)	**< 0.001**
Smokers	25 % (8)	35.3 % (12)	0.363
GFR < 60 ml/min	40.6 % (13)	23.5 % (8)	0.136
Diabetes	21.9 % (7)	17.6 % (6)	0.666
Dyslipemia	44.1 % (15)	53.1 % (17)	0.806
BNP	119.9 ± 112.0	37.4 ± 21.0	**< 0.001**
FC NYHA >II	25 % (8)	8.8 % (3)	0.078

Bold values indicate statistically significant differences. BMI: Body mass index; BNP: Brain natriuretic peptide; FC NYHA: functional class New York Heart Association.

TABLE 2. ECG intervals.

	HFPEF	Non-HF	p-value
P wave [ms]	81 ± 35	74 ± 33	0.430
PR [ms]	173 ± 26	158 ± 36	0.089
PeR [ms]	86.3 ± 31	84.5 ± 30	0.828
QRS [ms]	95 ± 24	97 ± 27	0.783
IAB (n)	18.8 % (6)	11.8 % (4)	0.429

IAB: presence of inter-atrial block; PeR : end of P to R interval; PR: PR interval; QRS: QRS interval.

TABLE 3. Echocardiographic measures.

	HFPEF (n=34)	**Non-HF** (n=32)	**p-value**
LVEF (%)	59.6 ± 5	60.6 ± 4	0.379
LVMi (g/m2)	133.2 ± 28	110.9 ± 26	**< 0.001**
LVTDD (mm)	51 ± 5.9	49 ± 5.2	0.153
LVTDVi (ml/m2)	116.9 ± 39.6	106.5 ± 29.4	0.229
LAVi (ml/m2)	58.2 ± 16	32 ± 11	**< 0.001**
LA active volume (ml)	16.9 ± 10.7	15.5 ± 9.8	0.628
LA passive volume (ml)	20.5 ± 12.2	17.4 ± 11.7	0.349
E/e'	12.3 ± 6	7.4 ± 2	**< 0.001**
E/A	1.08 ± 0.6	0.79 ± 0.25	**0.022**
Mitral E DT (ms)	233 ± 32	237 ± 45	0.810
PAPs (mmHg)	37.5 ± 6	33.7 ± 9	0.171
Degree diastolic dysfunction ≥ 2	40.6 % (13)	0	**< 0.001**
IAD (ms)	72.7 ± 27.2	27.8 ± 7.5	**< 0.001**
LV longitudinal SR (/sec)	-0.98 ± 0.27	-1.02 ± 0.3	0.582
LV global strain (%)	19.27 ± 5.17	25.26 ± 6.21	**0.001**
LA SR a-wave (/sec)	-1.14 ± 0.72	-1.92 ± 0.53	**< 0.001**
LA SR s-wave (/sec)	0.94 ± 0.32	1.42 ± 0.37	**< 0.001**
RA global strain (%)	22.50 ± 7.36	24.08 ± 9.23	0.532
RA SRa (/sec)	-1.47 ± 0.57	-1.80 ± 0.62	0.079
RA SRs (/sec)	1.18 ± 0.49	1.31 ± 0.59	0.413

Bold values indicate statistically significant differences. IAD = interatrial dysssynchrony; LA = left atrial; LAVi = left atrial indexed volume; LV = left ventricular; LVEF = left ventricular

ejection fraction; LVMi = left ventricular mass indexed to body surface area; LVTDD = left ventricular telediastolic diameter; LVTDVi = left ventricle indexed diastolic volume; PAPs = systolic pulmonary artery pressure; RA = righ atria; SRa = peak atrial strain rate; SRs = peak systolic strain rate.

TABLE 4. Comparison between patients according to the IAD (HFPEF patients).

	IAD < 60ms (n=11)	IAD ≥ 60ms (n=21)	p-value
IAD	47.73 ± 14	85.90 ± 22.99	**<0.001**
Age (years)	75.91 ± 10.29	74.86 ± 8.34	0.773
BNP	85.03 ± 66.82	138.11 ± 127.23	0.208
LAVi (ml/m2)	60.48 ± 13.93	57.02 ± 16.62	0.561
E/e'	11.16 ± 2.11	12.93 ± 6.95	0.417
E/A	0.78 ± 0.31	1.25 ± 0.70	0.048
Mitral E DT (ms)	246.64 ± 52.04	226.19 ± 71.73	0.411
PAPs (mmHg)	36.63 ± 7.73	38.18 ± 4.73	0.593
Grade diastolic dysfunction ≥ 2	9.1%	57.1%	**0.007**
NYHA > II	18.2%	28.6%	0.535
Previous use of diuretics	45.4%	47.62%	0.519
LA global strain (%)	20.00 ± 4.05	18.90 ± 5.92	0.608
LA SR a-wave (/sec)	-1.33 ± 0.69	-1.04 ± 0.73	0.348
LA SR s-wave (/sec)	1.09 ± 0.38	0.86 ± 0.26	0.079
RA global strain (%)	25.35 ± 6.70	20.67 ± 7.23	0.140
RA SRa (/sec)	-1.68 ± 0.40	-1.34 ± 0.63	0.170
RA SRs (/sec)	1.21 ± 0.36	1.16 ± 0.57	0.833
Intra-LA delay (ms)	41.25 ± 36.71	57.19 ± 35.12	0.268

Bold values indicate statistically significant differences. IAD = interatrial dysssynchrony; LA = left atrial; LAVi = left atrial indexed volume; LV = left ventricular; PAPs = systolic pulmonary artery pressure; RA = right atria; SRa = peak atrial strain rate; SRs = peak systolic strain rate.