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LEFT ATRIAL LONGITUDINAL STRAIN EVALUATED BY 2D SPECKLE TRACKING ECHOCARDIOGRAPHY CAN IDENTIFY PATIENTS WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION

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Abstract

The aim of the paper *is to investigate the utility of left atrial longitudinal strain (LALS) in the diagnosis of heart failure with preserved ejection fraction (HFpEF) when left ventricular diastolic function is indeterminable and the assessment of natriuretic peptides is not routinely performed.*

Method. *The study included 180 patients with signs and symptoms suggestive of non-acute heart failure, examined clinically and echocardiographically, both conventionally and via speckle tracking method.*

Results. *33 patients had a normal echocardiographic examination. Diastolic dysfunction (DD) was present in 116 patients of whom 32 patients had grade I, 66 patients grade II, 18 patients grade III DD. Diastolic function could not be determined in 31 patients. The mean value of LALS and NTproBNP in patients with normal echocardiography was significantly different from the group with DD for both variables ($p<0.001$). LALS was inversely correlated with the grade of DD ($r=-0.83$, $p<0.001$). The cut-off value of LALS for predicting DD was 25%. Applying this value in patients with indeterminate diastolic function we identified 21 patients with HFpEF ($p<0.001$).*

Conclusions. *LALS can help in the diagnosis of HFpEF when other echocardiographic criteria are irrelevant and NTproBNP is not routinely performed. LALS was correlated with the presence and severity of DD with a cut-off value of 25%.*

Key words*: left atrial longitudinal strain, echocardiography.*

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Rezumat

Scopul lucrării *este de a investiga utilitatea strain-ului atrial stâng longitudinal (SASL) în diagnosticul insuficienței cardiace cu fracție de ejecție păstrată (ICFEP) atunci când funcția diastolică a ventriculului stâng este nedeterminabilă și evaluarea peptidelor natriuretice nu se efectuează de rutină.*

Metodă. *Studiul a inclus 180 de pacienți cu semne și simptome sugestive pentru insuficiență cardiacă non acută, examinați clinic și ecocardiografic convențional și prin metoda speckle tracking.*

Rezultate. *Un număr de 33 de pacienți au prezentat examen ecocardiografic normal. Disfuncție diastolică (DD) au prezentat 116 pacienți, dintre care 32 pacienți aveau grad I, 66 pacienți grad II, 18 pacienți grad III. Funcția diastolică nu a putut fi determinată la 31 de pacienți. Valoarea medie a SASL și NTproBNP la pacienții cu ecocardiografie normală a fost semnificativ diferită de cea a grupului cu DD pentru ambele variabile (p <0,001). SASL a fost invers corelat cu gradul DD (r =-0,83, p<0,001). Valoarea cut-off a SASL pentru predicția DD a fost 25%. Aplicând această valoare pacienților cu funcție diastolică nedeterminată am identificat 21 pacienți cu ICFEP (p<0,001).*

Concluzii. *SALS poate contribui la diagnosticul ICFEP atunci când alte criterii ecocardiografice sunt nerelevante și NTproBNP nu se efectuează de rutină. SASL s-a corelat cu prezența și severitatea DD cu o valoare cut-off de 25%.*

Cuvinte cheie*: strain atrial stâng longitudinal, ecocardiografie.*

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is an entity defined by characteristic signs and symptoms, ejection fraction (EF) ≥ 50%, increased values of natriuretic peptides, the presence of structural changes of the heart (left ventricular hypertrophy and/or left atrial enlargement) and/or left ventricular diastolic dysfunction[1]. The diagnosis of HFpEF is more difficult than the diagnosis of heart failure with reduced ejection fraction (HFrEF) (EF< 40%) due to the fact that the clinical presentation is non-specific, natriuretic peptides can also be influenced by other conditions, the key parameter for the diagnosis - i.e. the ejection fraction - is normal, the structural anomalies of the heart can lack at standard echocardiographic examination, and left ventricular diastolic function assessed via echochardiography according to ASE/EACVI[2]recommendations can be indeterminable (Figure 1 and 2).

Assessment of atrial deformation parameters is a promising method for atrial mechanics analysis.

The speckle tracking method of echocardiographic assessment allows the quantification of myocardial deformation via 2D and/or 3D exploration. The advantage is represented by the fact that it is independent of the exploration angle, unlike the Doppler method, it is less influenced by reverberations, side lobe phenomenon or dropout[3].

In contrast with left ventricular global longitudinal strain, atrial strain is not validated in the present, and the indexed volume of the left atrium is the main parameter for the assessment of atrial remodelling and for cardiac prognosis.

The purpose of our study is to investigate the utility of left atrial longitudinal strain in the diagnosis of HFpEF when left ventricular diastolic function is indeterminable and the assessment of natriuretic peptides is not routinely performed.

METHOD

The study included patients with signs and symptoms suggestive of heart failure: dyspnea on moderate/intense exertion, fatigability, lower limb edemas. Patients were examined clinically and echocardiographically. Patients with acute coronary syndromes, severe valvulopathies, cardiomyopathies, severe arrhythmias, class IV symptoms and/or ejection fraction < 50% were excluded.

Standard 2D echocardiography

Left ventricular systolic and diastolic function was assessed via 2D echocardiography and Doppler examination.

The echocardiographic examination was performed with a Philipps Epiq 7G echograph, 4-2 MHz probe. The atrial and ventricular sizes were measured, also the ejection fraction via the Simpson method, the indexes of diastolic dysfunction according to recommendations[2].

The atrial volume was indexed to the body surface area. By pulsed Doppler examination with placing of the sample at tip of the mitral valves, the E wave and the A wave were determined in proto-diastole and tele-diastole, respectively. Tricuspid regurgitation was assessed via continuous Doppler examination with the sample placed parallel with the direction of the jet. The section offering the peak regurgitation velocity was chosen. The cases where tricuspid regurgitation could not be interrogated correctly (difficult echographic image) were noted.

Tissue Doppler examination

The assessment of the left ventricular longitudinal function was performed by placing the exploration sample at the level of the mitral annulus, septally and laterally. The septal and lateral proto-diastolic waves were measured (septal E^{l} and lateral E^{l}). For each examination the average of the E^{l} wave was calculated (septal E^{l} + lateral E^{l}/2). Also the values of average E/E^{l} was calculated.

2D speckle tracking echocardiography

The atrial reservoir function was assessed by 2D speckle tracking method via the analysis of peak atrial longitudinal strain, using the R wave as a reference and the model with 15 segments analysed in apical 4, 2 and 3 chamber view, excluding the anteroseptal segments corresponding to the aortic wall (Figure 3). The tracking was adjusted manually. The framerate was adjusted between 60-80 frames/second. The analysis was performed offline by the physician who performed the echocardiographies. In absence of a dedicated program we have adapted the software of the calculation of the ventricular global longitudinal strain for the determination of the atrial strain, after establishing the atrial fiducial points. The zero line was adapted to the atrial curves. Tracing of the atrial endocardium was performed automatically, with manual correction when the automatic tracing was incorrect. Peak atrial longitudinal strain was measured at the end of the reservoir phase (Figure 3), using the R wave as a reference, and was calculated automatically by averaging the values obtained in all segments.

Determination of NTproBNP was performed by the electrochemiluminescence immunoassay (ECLIA) method[2]. The cut-off value for heart failure was 125 pg/mL[(1)].

Statistic analysis

The obtained data were expressed as mean values ± standard deviations. The value $p<0.05$ was considered as statistically significant. The relationship between the continuous variables was calculated using the Pearson's correlation coefficient. The comparison between the means of two groups with continuous variables was performed using the Student's t-test, and for the categorical variables using χ^2 and between the means of several groups using the ANOVA analysis.

RESULTS

Characteristics of the study population

180 patients were selected, 94 females, mean age 65±11 years. 33 patients (18.3%) had a normal echocardiographic examination; 116 patients (64.4%) had diastolic dysfunction,

and 31 patients (17.2%) had indeterminate diastolic function. Demographic data did not differ significantly regarding age, female/male ratio, and body mass index (Table 1). In the group with patients with altered echocardiographic examination, the incidence of diabetes mellitus, hypertension, ischemic coronary artery disease, and history of atrial fibrillation was significantly higher compared to the group with normal echocardiographic examination ($p<0.001$). Patients with diastolic dysfunction and indeterminate diastolic function had an ejection fraction significantly lower compared to those with normal echocardiographic examination ($p<0.05$).

Diastolic dysfunction

The diagnosis of diastolic dysfunction was established according to the ASE / EACVI criteria[2](Figure 1). Subsequently, patients with DD were divided according to the algorithm showed in Figure 2 in three subgroups: grade I - 32 patients (27.5%), grade II - 66 patients (56.8%), and grade III - 18 patients (15.5%), respectively (Table 2). Diastolic dysfunction and/or its grade could not be determined in 31 patients (17.2%) for the following reasons: 21 cases - presence of two criteria out of four criteria of diastolic dysfunction (18 cases with criteria 2 and 4, and 3 cases with criteria 3 and 4 present, see Figure 1). In 10 cases, only three criteria of diastolic dysfunction could be analysed due to inadequate echocardiographical image (in 7 cases the tricuspid regurgitation could not be interrogated correctly, and in three cases the correct alignment for tissue Doppler could not be obtained).

Results of the determination of NTproBNP

The mean value of NTproBNP was significantly different in the group of patients with diastolic dysfunction compared to the group with normal echocardiographic examination (332±54 pg/mL vs 117±4.7 pg/mL ($p<0.05$)**.** The mean values of NTproBNP corresponding to subgroups with grade I, II and III of diastolic dysfunction (Table 2) were 224±5.1 pg/mL, 311±8.9 pg/mL, and 526±3.8 pg/mL, respectively, and differed with a statistic significance ($p<0.001$). The mean value of NTproBNP in the subgroup of patients with indeterminate diastolic function was 267±6.8 pg/mL.

Peak atrial strain

The average of the peak atrial strain was calculated in patients with normal echocardiographic examination, in patients with diastolic dysfunction, and separately for each subgroup of diastolic dysfunction, and in those with indeterminate diastolic function. The values are shown in Table 2. There is a statistically significant difference between the peak atrial strain in patients with normal echocardiographic examination vs those with diastolic dysfunction (38.4±3.2 % vs 24.9±9.3% ($p<0.001$). We noticed the same statistically significant difference also in the analysis by groups of diastolic dysfunction (grade I, grade II, and grade III vs normal examination, respectively: 31.2±3.4% ($p<0.05$), 25.9±4.7% ($p<0.001$), and 18.9±3.1% ($p<0.001$). The group of patients with indeterminate diastolic function had the mean value of peak atrial strain (PAS) of 28.7±8.1%.

Relationship of the peak atrial strain with the grade of diastolic dysfunction and the value of NTproBNP

The mean value of the peak atrial strain in the group of healthy patients was 38.4±3.2%, and the mean value of NTproBNP in the same

group was 117±4.7 pg/mL. The group of patients with diastolic dysfunction had a mean value of LALS and NTproBNP of 24.9±9.3% and 332±54 pg/mL, respectively. Patients with indeterminable diastolic function had values of LALS and NTproBNP of 28.7±8.1% and 267 pg/mL, respectively. The mean value of LALS corresponding to diastolic dysfunction of grade I, II and II was significantly lower compared to that determined in patients with normal echocardiographic examination, respectively: 31.2±3.4% (p <0.05), 25.9±4.7% (p<0.001), and 18.9±3.1% (p<0.001), and mean values of NTproBNP statistically significant higher, respectively: 224±5.1 pg/mL (p<0.05), 311±8.9 pg/mL (p<0,05), and 526±3.8 pg/ml (p<0.001). LALS was correlated with a statistical significance with the grade of diastolic dysfunction (r=-0.83, p<0.001). According to the obtained data, we chose the cut-off value for PAS of 25%. Applying this value in the group with indeterminate diastolic function, we identified 21 patients with decreased values of PAS and NTproBNP statistically significantly higher compared to those with PAS > 25%, 356 pg/mL vs 132 pg/mL, respectively (p<0.001).

DISCUSSIONS

The study that we presented demonstrates the role played by the analysis of myocardial left atrial longitudinal deformation in the diagnosis of heart failure with preserved ejection fraction. The analysed data show that left atrial longitudinal strain was significantly decreased in patients with diastolic dysfunction compared to those with normal echocardiographic examination. We demonstrated that there is a statistically significant relationship between the grade of diastolic dysfunction and the values of LALS, specifically: the more severe is the diastolic dysfunction, the more decreased is LALS, respectively: 31% corresponding to grade I, 25% corresponding to grade II, and 18% corresponding to grade III of diastolic dysfunction.

The mean values of NTproBNP were significantly increased in patients with diastolic dysfunction grade III compared to those with dysfunction grade II and grade I, respectively. Although the value of NTproBNP represents a major diagnostic criterion for heart failure, not all hospital and ambulatory laboratories determine this parameter on a routine basis. Our study shows that a value below 25% of the left atrial longitudinal strain selects patients with the highest probability to have heart failure even when diastolic dysfunction is not certain. In the performed analysis, patients with indeterminate diastolic function and atrial strain <25% had values of NTproBNP with a diagnostic significance for heart failure. The mean value

	Altered echocardiography n=147 p	Normal echocardiography n=33	*p* value
Age (years)	65±11	63±8	0.243
Female/male	76/71	18/15	0.717
BMI (kg/m^2)	52	7	0.583
Diabetes mellitus	118	27	0.001
Hypertension	74	4	0.001
Coronary artery disease	63	7	0.001
History of atrial fibrillation	11	1	0.001
NTproBNP (pg/mL)	332±54	117±4.7	0.001
Ejection fraction	54±8%	62±6%	0.05
Peak atrial strain	25±9%	38±3%	0.001

Table 1. *Patient characteristics in relationship with the echocardiographic examination: normal or altered (left ventricular hypertrophy, left atrial enlargement, left ventricular diastolic dysfunction)*

	Normal examination n=33 p	DD grade I n=32 p	DD grade II n=66 p	DD grade III n=18 p	Indeterminable DD n=31 p
E wave (cm/s)	68±10.2	59±8.3	57±7.8	97±9.8	53±7.1
E/A ratio	1.2±0.4	0.7±0.2	0.7±0.8	2.2±1.6	0.8±0.3
Septal e' (cm/s)	10.8±3.6	9.3±4.2	7.5±3.2	4.7±3.8	7.3±3.1
Lateral e' (cm/s)	13.1±4.1	11.7±3.8	8.9±3.6	6.2±4.1	9.2±3.2
Mean E/e	5.8±4.3	6.7±3.7	11.9±4.3	16.3±3.8	12.3±3.6
Tricuspid regurgitation	1.2±2.1	2.1±1.7	2.6±2.1	3.2±2.2	2.4±2.8

Table 2. *Echocardiographical characteristics and mean values of NTproBNP in study lots*

of atrial strain in the group of patients in which HFpEF was excluded was significantly higher compared to patients with altered diastolic function (34% vs 25%). Recent populational studies[4-10] demonstrated the importance of the assessment of the morphology and function of the left atrium in various cardiovascular diseases, including heart failure.

The main role of the left atrium is to modulate the ventricular filling pressure and to improve the pump performance of the left ventricle. We can distinguish three phases in the atrial cycle: the reservoir phase for venous return during the ventricular systole, the conduct phase during ventricular proto-diastole, and the pump phase in ventricular tele-diastole. The three phases contribute with 40%, 35%, and 25%, respectively, to the stroke volume in healthy subjects[4,14,15]. Both left ventricular systolic dysfunction - even a subtle one - and diastolic dysfunction, particularly when it is accompanied by increased intraventricular pressures, are reflected in the reservoir function of the left atrium[18].

The study of Cameli *et al.* demonstrated via cardiac catheterisation the correlation between atrial longitudinal strain and filling pressure of the left ventricle in patients with decreased EF[3]. Another prospective study, which followed 312 patients for a mean duration of 3 years, showed that there is a significant association between LALS and the prognosis, regardless of age, cardiovascular risk factors, severity of diastolic dysfunction, ejection fraction, history of myocardial infarction or valvular disease[10].

The same study demonstrated that the predictive value of LALS is more important that the indexed left atrial volume, suggesting that analysis of atrial dysfunction is more sensitive than morphological parameters[10]. It was demonstrated that untreated hypertensive patients can have changes of atrial deformation even in the absence of diastolic dysfunction consistent with subclinical myocardial atrial dysfunction[11]. The same association is also present in diabetic patients with HFpEF independently of other cardiovascular risk factors[12].

Studies that assessed atrial function in HFpEF showed that the same factors that determine the fibrosis of ventricular subendocardial myocardial fibres also produce fibrosis of atrial myocardium and atrial remodelling that leads to the occurrence of atrial dysfunction[20-24]. Mondillo *et al*. [23]showed that atrial deformation is impaired in patients with hypertension and/or diabetes mellitus who had a normal left atrium at the echocardiographical examination, suggesting that the alteration of atrial strain precedes the atrial changes diagnosed via standard examination. The

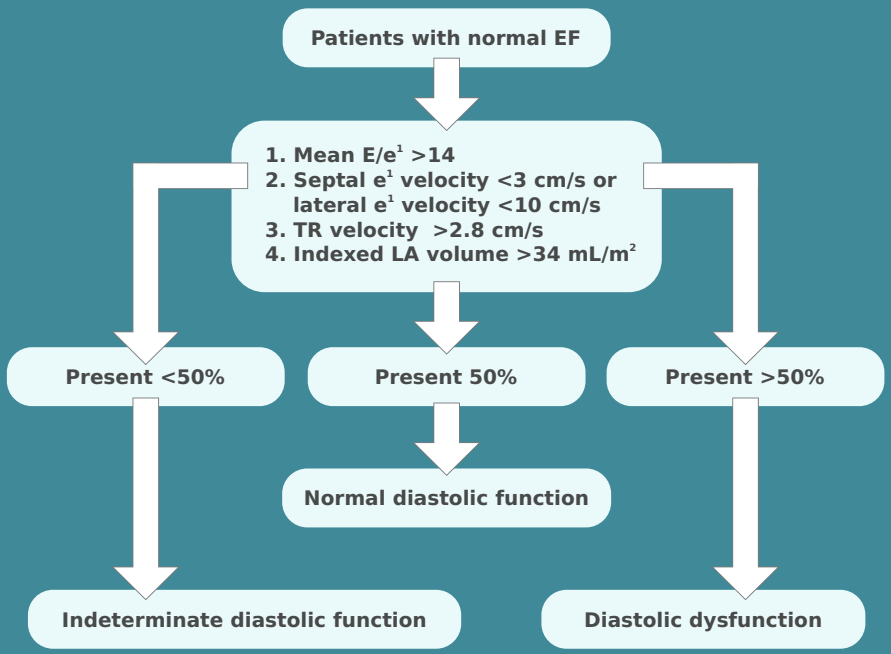

Figure 1. *Algorithm for the diagnosis of or left ventricular diastolic dysfunction in subjects with normal left ventricular ejection fraction (LVEF)*

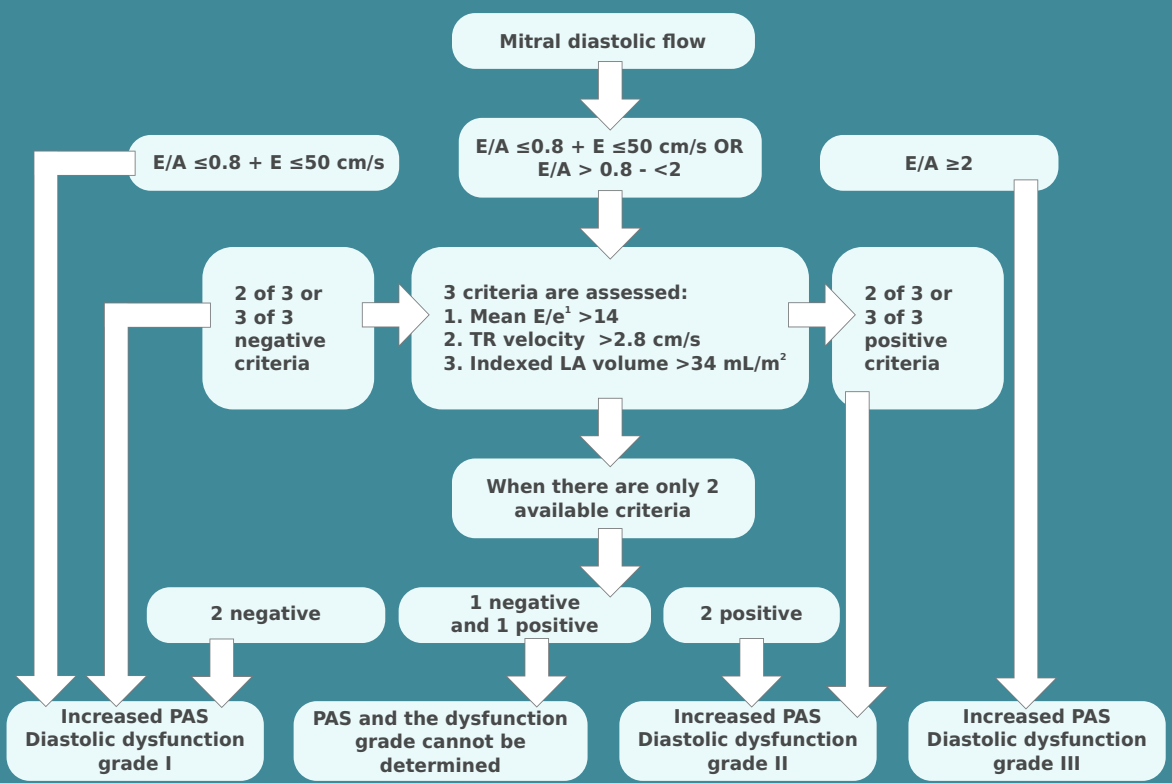

Figure 2. *Algorithm for the estimation of the left ventricular filling pressures and grading of the left ventricular diastolic dysfunction in patients with decreased LVEF and in those with myocardial disease and normal LVEF after consideration of clinical data and other 2D data*

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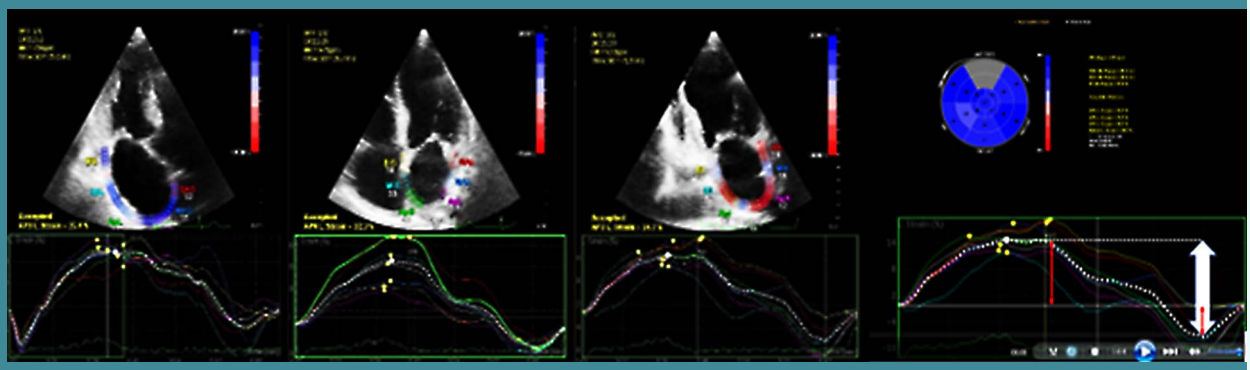

Figure 3. *Assessment via 2D speckle tracking echocardiography (STE) of the atrial global longitudinal strain with reference point indicated by the R wave, using the model with 15 segments analysed in apical 3, 4, and 2 chamber view, excluding the anteroseptal segments corresponding to the ascending aorta (image on the left). The image on the right represents the bull's eye graph of the atrial global strain. The segments corresponding to the aortic wall were excluded (top). Below the global strain curves for each segment are represented; the dotted white line is the mean value of the 15 segments. The thick arrow represents the strain in the reservoir phase. The thin red line superposed to the white one represents the strain in the pump phase of the atrium, and the long red arrow represents the strain in the conduct phase.*

reduction of the atrial strain was also associated with the risk of occurrence and/or recurrence of atrial fibrillation, its role in predicting the risk of stroke being additive to the CHADS2 score[4].

The study of Kuppahaly[19]demonstrated via MRI - speckle tracking comparative analysis the role of atrial fibrosis in functional and structural atrial remodelling. The study of Leong *et al*.[9]showed that the atrial strain in the reservoir phase is independently associated with the risk of cryptogenic stroke. Taking into consideration the many published evidence regarding clinical implications of the assessment of ventricular and atrial myocardial deformation, in 2011 Mor-Avi *et al*[14].published the first ASE/EAE Consensus Statement on Methodology and Indications of Quantitative Evaluation of Cardiac Mechanics. In the document the two evaluation methods are discussed: using as reference point the R wave, more adequate

for the analysis of the reservoir function, and the method which uses as reference point the P wave, more adequate for the analysis of the atrial pump function (Figure 1).

Both methods were equally recommended for the model with two views (apical 4 chamber and apical 2 chamber), and also for the model with 3 views (apical 4, 3, and 2 chamber).

Recently in 2018 Badano *et al*. [16] published a document EACVI/ASE/Industry Task Force regarding the standardization of left atrial deformation using two dimensional speckle tracking echocardiography. The apical 4 chamber view is recommended; the other two views are optional. It is considered that the ECG trigger is just a surrogate for end-diastole, respectively ventricular end-systole, and it is recommended that the measurements of the 3 phases of the atrial cycle to be performed effectively on the strain curve, corresponding to the end-diastolic peak for the reservoir phase, end-systolic for the pump phase, and calculated as difference for the conduct phase (Figure 1). Regarding the reference value for atrial stain, for the moment there is no consensus; this can be explained on one hand by the existence of several software packages for calculation, corresponding to the companies that manufacture the echocardiograph, and on the other hand by the different analysis methods chosen, and also the relatively low size of the study population.

A meta-analysis published in 2017 by Pathan *et al*. [15] reviewed 40 studies (2542 healthy subjects) and demonstrated the following reference values: 38-41% for the reservoir function, 21-25 % for the conduct function, and 16-19% for the pump function. An atrial strain below 20% proved to be an independent parameter of cardiovascular prognosis[10].

In our paper we assessed the reservoir function using the R wave as trigger and analysing the segments obtained in 3 views. The values of atrial longitudinal strain were consistent with the published ones[15,25]. We demonstrated the relationship between the severity of the diastolic dysfunction and the values of atrial strain in patients with preserved ejection fraction assessed for the suspicion of heart failure.

We extrapolated the obtained data to patients with indeterminate diastolic function and we showed that patients with atrial longitudinal strain (ALS) <25% have significantly increased values of NTproBNP compared to those with ALS >25%, thus suggesting that the atrial strain in the reservoir phase can represent an indirect parameter for the diagnosis of diastolic dysfunction associated to heart failure with preserved ejection fraction.

Limits

Measuring of atrial strain was not performed with a dedicated program, but using the software for the analysis of the left ventricular global longitudinal strain, using the R wave as a reference.

We did not have a reference lot of healthy subjects. The analysed lot was heterogeneous from the point of view of the treatment (the majority were on a treatment adequate for the underlying cardiac disease, but there were also patients who were assessed prior to administration of medication).

The number of patients corresponding to the analysed subgroups was relatively low. The cut-off value of 25% was chosen following the relationship with the grade of severity of the diastolic dysfunction and the value of NTproBNP, and not following the statistical analysis.

CONCLUSIONS

Left atrial longitudinal strain is an easy-to-measure parameter which can help the diagnosis of left ventricular diastolic dysfunction and the assessment of its severity. In patients suspected of heart failure with preserved ejection fraction, values of ALS below 25% suggest the diagnosis and select those in whom the determination of NTproBNP is necessary, when it is not performed on a routine basis. Finally, we consider that the routine determination of the atrial longitudinal strain significantly contributes to risk stratification and refining the therapy of patients with heart diseases.

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