Left Atrial Function Analysis in Patients in Sinus Rhythm, Normal Left Ventricular Function and Indeterminate Diastolic Function

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Abstract

Background In ~25% of echo studies discrepant diastolic measurements make the assessment of diastolic function indeterminate. We aimed to assess whether left atrial function may contribute to LV filling evaluation in patients with indeterminate diastolic function (IndtDFx). Methods In our retrospective echocardiography database we found 1674 consecutive patients in sinus rhythm, and EF[?]45%. Patients were divided according to the parameters mitral E', mitral E/E' ratio , left atrial maximal volume index , and pulmonary pressure. Normal diastolic function (NDFx) was defined as less than 2 abnormal parameters, definite diastolic dysfunction (DDFx) as more than 2 abnormal parameters, and IndtDFx as 2 abnormal parameters. We retrospectively and randomly selected 30 patients from each group for left atrial assessment by speckle tracking echocardiography for off line strain and volumes analysis. Results: sixty seven patients were included in strain analysis. The DDFx group (n=21) and IndtDFx (n=19) were significantly different form NDFx (27) in demographics, cardiovascular risk factors., presentation and echocardiographic parameters. Phasic LA maximal and minimal volume indexes were larger in DDFx and indtDFx groups, and overall and passive LA strains were decreased in DDFx and indtDFx groups compared with NDFx group, while active strain remained in the normal range. Phasic LA minimal volume index was found to be associated with HF symptoms. Conclusion LA phasic function suggests that IndtDFx is similar to DDFx , helping in re- classification of patients with IndtDFx as DDFx. LA minimal volume index correlated with symptoms.

Keywords

Heart failure, cardiac function, Echocardiography, Left atrial mechanics, Left ventricular diastolic dysfunction

Background

The diagnosis of Heart failure (HF) with preserved ejection fraction (HFpEF) is based on the presence of preserved left ventricle (LV) ejection fraction (EF) with evidence of advanced diastolic dysfunction in the absence of cardiac or non cardiac conditions that could cause HF symptoms [1,2,3]. However, diagnosis of diastolic dysfunction is challenging as it can only done by invasive catheterization. In the other hand , in daily practice echocardiography is the main noninvasive method used to role in the diagnosis and role out other cardiac conditions [4, 5]. Several echocardiographic parameters were suggested to define and grade diastolic function[6] . Unfortunately, these parameters are discrepant in many patients, and thus diastolic function is indeterminate [6].

Left atrial (LA) function assessment had recently undergone a renaissance, as its assessment has become easier to perform. Contemporary myocardial mechanics using echocardiographic 2D speckle tracking allows for measurement of LA left strain and volume changes throughout the cardiac cycle. It is able to measure phasic atrial volumes in the various phases of diastole (reservoir, passive, conduit and active), that directly represent LV filling. Given the close interplay between the LA and LV left, LA function analysis is actually a functional analysis of LV filling that may improve our understanding of the left ventricular diastolic physiology and prove valuable in the diagnosis of diastolic dysfunction [7, 8].

The purpose of our study to assess whether left atrial function may contribute to LV filling evaluation in patients with indeterminate diastolic function (IndtDFx).

Methods

Patients

Consecutive patients (ambulatory and hospitalized) referred to a transthoracic echocardiography study at our laboratory between 2014 and 2015 were retrospectively screened. Inclusion criteria were sinus rhythm and LVEF [?]45% at the time of screening.

Patients with [?]moderate left-sided valvular heart disease, acute coronary syndrome, chronic lung disease, pulmonary thrombo-embolic disease, and myocardial and pericardial diseases were ruled out. Subjects (n=1672) were divided into 3 groups based on the assessment of diastolic function: normal diastolic function (NDFx, n=1279); definite diastolic dysfunction (DDFx, n=237); and IndtDFx (n=156) according to the recent guidelines [6]. The parameters mitral E', mitral E/E' ratio , LA maximal volume index , and pulmonary pressure were used for the definition of each group [6]. NDFx was defined as less than 2 abnormal parameters, DDFx was defined as more than 2 abnormal parameters, and IndtDFx as 2 abnormal parameters.

We randomly selected 30 patients from each group for off-line strain and volumes analysis using speckle tracking echocardiography. Demographics , comorbidities, and HF symptoms (dyspnea, fatigue, weakness and/or reduced ability to exercise) were recorded.

Two-dimensional and Doppler Echocardiography

A standard echocardiographic study was performed using one of 3 commercially available systems (Vivid 7, E9 and I, GE Medical systems, Milwaukee, WI) for the evaluation of cardiac chambers, systolic and diastolic function and Doppler measurements were performed according to guidelines [6, 9, 10].

LV and LA functional analysis

Cardiac Mechanics Analysis

Retrospective LA and LV measurements were performed offline by a single operator who was unaware to clinical and echocardiographic data, using special software (eSie VVI, Siemens Medical System, Mountain View). An average cardiac cycle (of 2-3 cycles) was created for each representative view and the onset of R wave was used as the reference point for both LA and LV strain and volume curves.

Left Ventricle

A total of 6 views (apical 4, 3 and 2 chamber views) were analyzed to measure endocardial longitudinal strain and biplane chamber volumes as previously described [11-13] .

Left Atrium

LA functional morphometry

Using a bi-plane approach of apical 4 and 2 chamber views, the LA endocardial surface was traced manually using a point and click approach after which an endocardial tracking was automatically performed by the VVI software (figure 1). The following parameters were determined to assess phasic LA volumes and function [14]: phasic LA maximal volume (LAmax), phasic LA minimum volume (LAmin), LA total emptying volume ,Conduit volume, LA reservoir function, LA Passive ejection fraction (PEF), and LA Active ejection fraction (AEF)

LA myocardial mechanics

Stretching (strain) of the LA during LV systole was measured and determined as LA reservoir strain. Diastolic shortening from peak strain was divided in two phases – LA passive strain (shortening from peak to pre-A time, automatically identified using speckle tracking derived LA longitudinal displacement curve), and LA active strain (shortening from pre-A time to end diastole).

Statistical analysis

Categorical variables were expressed as percentages and continuous variables as means ± standard deviations. The effects of risk factors on echocardiographic parameters were evaluated using the Wilcoxon-Mann-Whitney non-parametric test. Patients with/without HF were compared using the Wilcoxon-Mann-Whitney non-parametric test for continuous variables as normal distributions could not be assured. Chi-Square analysis was used for categorical variables. Uni- and multivariable predictors of HF symptoms were assessed by logistic regression analysis. Statistical significance was defined as a p value < 0.05. Statistical analyses were performed using MedCalc Statistical Software version 15.6.1 (MedCalc Software bvba, Ostend, Belgium).

Ethical Aspects

The study was approved by our local research ethics committee.

Results

Demographic and clinical characteristics: The study groups included 27 patients with echocardiographically NDFx, 21 patients with DDFx and 19 patients with IndtDFx who met the inclusion/exclusion criteria and had strain (using speckle tracking echocardiography) analyzable echo studies. The quality of 23 studies was insufficient for strain-analysis, mostly due to low frame rates.

Clinical characteristics are demonstrated in table 1. Patients with DDFx were nearly 2 decades older compared to patients with NDFx (69±11 vs. 50±15 years, $p<0.05$, respectively). Their body mass index was higher, and they were 5 time more likely to be referred for echocardiography for the evaluation of HF symptoms. Parameters included in the metabolic syndrome (diabetes, hyperlipidemia, hypertension) were also significantly more common in patients with DDFx. Patients with IndtDFx showed the same pattern of differences as patients with DDFx compared to patients with NDFx, showing an "in-between" pattern regarding HF symptoms and diabetes mellitus. Age, body mass index, hypertension and hyperlipidemia rates among patients IndtDFx were nearly identical to patients with DDFx..

Echocardiographic findings: LV dimensions and systolic function were similar and within the normal range in the 3 groups (table 2). Left ventricular mass indexed for body surface area was abnormal and significantly larger in patients with DDFx and IndtDFx compared to NDFx (114±16, 110±25 vs. 94±16 gr/m^2, respectively, $p<0.05$ both compared to NDFx). LV global longitudinal strain was found to be reduced among DDFx patients compared to NDFx and IndtDFx patients.

As expected from the group allocation process, the parameters E', E/E' , pulmonary pressure, and LA volume index were abnormal and significantly different in the DDFx compared to NDFx group. IndtDFx demonstrated intermediate parameter abnormalities; overlapping with DDFx but significantly different regarding E/E'. The parameters E', E/E' and LA volume index in IndtDFx were significantly different compared to NDFx., Pulmonary pressure estimation followed the same pattern between groups, but the difference was statistically significant between DDFx vs. NDFx.

Left atrial phasic volumes and function

LA phasic function is demonstrated in table 3. Phasic LA volumes (LA maximal volume index and LA minimal volume index) were larger in both DDFx and IndtDFx groups. Interestingly conduit volume index {volume passing directly from the LA to LV without "filling" the LA) was not different among subgroups.

Overall (LA reservoir function), passive (LA passive EF) and active LA (LA active EF) functions were decreased in both DDFx and IndtDFx groups. LA reservoir strain and LA passive strain ("E") were reduced in both DDFx and IndtDFx groups compared to NDFx. However, LA active strain ("A") remained in the normal range. Generally LA function in patients with IndtDFx was abnormal and similar to DDFx.

Correlates of heart failure symptoms :

HF symptoms were found among 7% of patients with NDFx. Symptoms were much more common in the DDFx group (38%), and IndtDFx group (18%). Echocardiographic parameters associated with HF symptoms by univariate analysis (all cohort) were average E', average E/E', pulmonary pressure and LA volume index (parameters involved in the classification of diastolic function), and LA reservoir function, phasic LA maximal volume index, phasic LA minimal volume index. LA conduit volume index, and LA reservoir strain (parameters of LA phasic function) .

Multivariate logistic regression analysis showed that phasic LA minimal volume index remained as the only parameter significantly associated with HF. The area under the curve for LA minimal volume index to predict HF symptoms on receiver operator curve (ROC) analysis was 0.743 for LA minimal volume index [?] 8 ml/m^2 (CI=0.615- 0.846, p=0.0046) (figure 2).

Discussion

Similar to previously reported data, our study showed that nearly 12% of echocardiographic studies resulted in a classification of IndtDFx [15]. The writing committee of the latest American Society of Echocardiography endorse the reporting of LV filling status as follows: "normal, elevated or cannot be determined" especially in cases referred with symptoms of dyspnea and HF, in view of their prognostic information [6].

In this study we have demonstrated that patients with indtDFx by Doppler echocardiography criteria exhibit a similar clinical profile to patients with definite diastolic dysfunction. It was associated with established major cardiovascular disease risk factors and a two-fold relative risk of presenting HF symptoms compared to patients with normal diastolic function as assessed by echocardiography. IndtDFx may not be a benign condition and needs to be clinically defined.

All conventional classifiying parameters were responsible for the inability to determine diastolic function in the indtDFx groop, showing large variability and values overlapping with either groups. The fact that the indtDFx group exhibit similar clinical profile and intermediate parameters compared to DDFx may suggest that most of these patients were at an early stage of DDFx, with an already impaired diastolic function. Furthermore, LA phasic function analysis patients (subgroups) demonstated a similar pattern of clinical and conventional echocardiographic characterstics as our global database cohort and thus were representative of our population.

We found that LA phasic function parmaters like phasic LA minimal volume (LA geometry) and LA resevoir strain (LA function) in IndtDFX and DDFx were significantly different than in NDFx, and thus could be helpful in re- classification of IndtDFX as actual DDFx. Both parameters were probably related to the various aspects of LA remodeling following changes in relaxation and stiffening of the LV resulting in LA enlargement and reduced LA relaxation and contractility. Phasic LA minimal volume index was the only parameter that remained a significant correlates of HF symptoms by multivariate analysis. Interestingly, LA maximal volume, which is the mostly commonly measured parameter and generally associated with prognosis – was not found to be predictive of symptoms when tested along with LA strain and minimal volume. LA minimal volume was previously shown to have a better correlation with LA total ejection fraction compared to the maximal volume. We found LA maximal volume not helpful in redefining diastolic function. This is probably because the minimal volume holds both size and functional information of LA [16].. In a recent study looking at the correlation between LA function and risk of de novo HF admissions, LA function was a stronger predictor than LVEF, LV global strain, or even LA volume index, highlighting the importance of the LA in the evolution and progression of symptoms [17]. Future studies are requested to determine whether LA functional analysis may help re-defining the IndtDFx group [18] and more prospective studies are required to confirm LA minimal volume as a better predictor of outcome.

Limitations

This study cohort was retrospective and based on referral echocardiographic examination, and thus potentially prone to selection bias . Similarly, clinical data was based on referral documents, the completeness of which could not be ascertained. This also resulted in our inability to obtain heart failure functional classification and drug therapy status.

Conclusion

Patients with IndtDFx demonstrate a clinical and echocardiographic profile that closely resembles that of patients with DDfx as opposed to NDFx. LA phasic function suggests that IndtDFx is similar to DDFx , helping in re- classification of patients with IndtDFx as DDFx. LA minimal volume index (parameter of LA phasic function) correlated with HF symptoms. Further study is suggested to establish whether functional LA analysis can provide additional information over assessment of conventional measurements.

Figure legends

Figure 1. Left atrial function analysis.

Left panel shows Left atrial tracking. Right panel shows left atrial volume curve generates by speckle tracking echocardiograpy, V_{max} denotes phasic maximal volume (end systolic), V_{preA} – volume before atrial contraction, V_{min} – phasic minimal volume (end diastolic). Arrows denote emptying fractions.

Figure 2: Receiver operator curve (ROC) analysis.

The area under the curve for phasic LA minimal volume index to predict HF symptoms on ROC analysis was 0.743 for LA minimal volume index [?] 8 ml/m2 (CI=0.615- 0.846, p=0.0046).

Tables

Table 1. **Demographics, risk factors**

	NDFx, n=27	DDFx n=21	IndtDFx N=19	p-Value
Patients				
Age (years)	50±15	69±11*	68±8*	<0.001
Male (%)	10 (36)	8 (38)	9 (47)	0.723
Body mass index	26±4	30±7*	31±4*	0.003
Heart failure symptoms (%)	2 (7)	8 (38)*	3 (18)	0.021
Hypertension (%)	5 (18)	14 (67)*	9 (49)*	<0.001
Diabetes Mellitus (%)	3 (11)	10 (48)*	7 (37)	0.013
Hyperlipidemia (%)	5 (18)	8 (38)	9 (47)	0.085
Smoking (%)	3 (10)	2 (10)	2 (11)	0.991

* p<0.05 compared to normal; + p<0.05 compared to DDFx

Table 2. **Echocardiographic findings (conventional and strain)**

	NDFx, n=27	DDFx n=21	IndtDFx N=19	p-Value
Left Ventricle				
LV mass index (gr/m^2)	94±16	114±18*	110±6*	0.002
LV EF (visual, %)	64±4	63±6	63±6	0.596

	NDFx, n=27	DDFx n=21	IndtDFx N=19	p-Value
LV Global longitudinal strain (%)	-18±2	-16±3*	-19±2+	<0.001
Mitral E to A ratio	1.2±0.4	1.4±0.8	1.1±0.4	0.246
Average E' (mm/s)	10±3	6±2*	7±1*	<0.001
Average E/E'	8.8±2.1	16.4±5.8*	11.9±3.0*+	<0.001
Pulmonary pressure (mmHg)	29±6	39±9*	35±8	<0.001
LA Volume index (ml/m2)	19±6	35±12*	30±9*	<0.001

* p<0.05 compared to normal; + p<0.05 compared to DDFx

Table 3. **Left atrial function analysis**

	NDFx, n=27	DDFx n=21	IndtDFx N=19	p-Value
LA phasic function				
Maximal Volume index (ml/m^2)	25±6	36±14*	33±8	<0.001
Minimal Volume index (ml/m^2)	7±3	16±8*	11±5*+	<0.001
LA total emptying Volume index (ml/m^2)	18±3	22±5	20±8	0.455
Conduit Volume Index (ml/m^2)	15±6	17±6	16±7	0.567
LA reservoir function (LA EF%)	76±8	60±14*	64±9	<0.001
LA Passive EF (%)	45±14	29±15*	34±13*	<0.001
LA Active EF (%)	55±14	43±16*	45±12	0.010
Conduit fraction from LVSV (%)	43±9	45±11	44±16	0.802
LA reservoir strain (% stretching)	56±15	35±13*	38±11*	<0.001
LA passive strain ("E") (% shortening)	-34±4	-17±8*	-20±10*	<0.001
LA Active strain ("A") (% shortening)	-22±10	-19±12	-18±13	0.467

* p<0.05 compared to normal; + p<0.05 compared to DDFx

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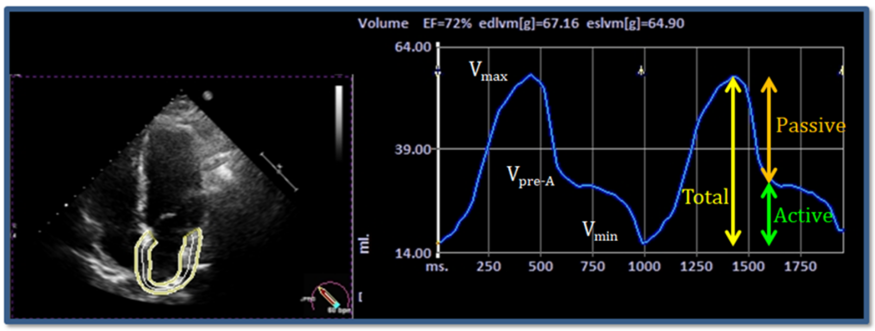

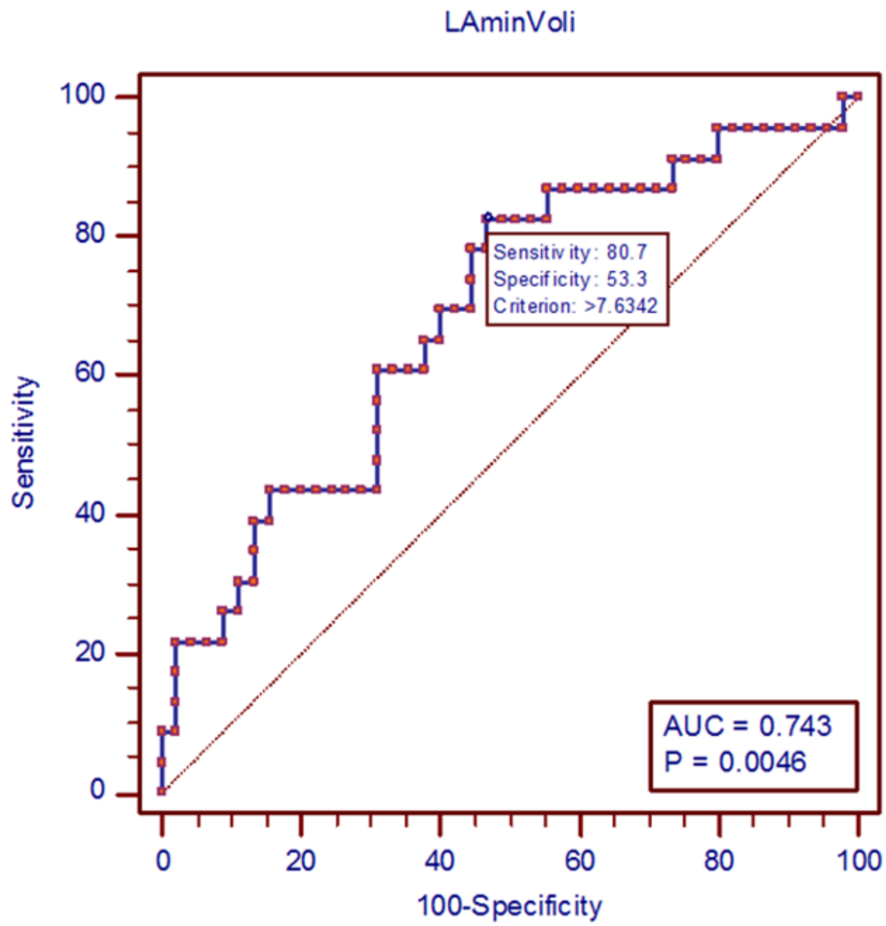
LAminVoli
Sensitivity
100-Specificity
100
80
60
40
20
0
0
20
40
60
80
100
Sensitiv ity: 80.7
Specif icity: 53.3
Criterion: >7.6342
AUC = 0.743
P = 0.0046