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Predictors of Atrial Fibrillation in Middle-Aged Patients without Overt Heart Disease: Strain Echocardiography Study

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Abstract

Aim: The aim of the study was to establish echocardiographic predictors of AF in middle-aged patients without overt heart disease.

Methods: Prospective consecutive patients with AF (n= 936), who had been admitted for sinus rhythm restoration in our hospital for the period January 2016- December 2018, were screened for participation in the study. A total of 70 patients met the inclusion criteria: stable sinus rhythm, age between 40-60 years, no overt heart disease. They were separated in two groups: new onset AF (n=33) and Paroxysmal AF (n=37); 30 healthy subjects were enrolled in the control group. All patients underwent 2DE assessment with volumetric and speckle tracking analyses.

Results: There were significant differences between all groups in LA structural and functional echocardiographic indices as follows: LA indexed volumes; LA total, passive and active emptying fractions; LA reservoir; conduit and contractile strain and strain rate; LA expansion and stiffness index. Also there were significant differences between all groups in LV mass, LV global longitudinal strain and E/Em ratio from transmitral flow and TDI of medial mitral annulus.

Conclusion: In middle- aged patients without overt heart disease LA reservoir and contractile strain can have additive value to LA volume index in the prediction of AF.

Keywords: AF; LA Reservoir Strain; LA Contractile Strain; STE

Abbreviations: AF: Atrial Fibrillation; EF: Ejection Fraction; GLS: Global Longitudinal Strain; LA: Left Atrium; LAVI: Left Atrial Volume Index; LATEF: Left Atrial Total Emptying Fraction; LAPEF: Left Atrial Passive Emptying Fraction; LAAEF: Left Atrial Active Emptying Fraction; LASR: Left Atrial Reservoir Strain; LASCD: Left Atrial Conduit Strain; LASCT: Left Atrial Contractile Strain; LV: Left Ventricle; ICC: Intra class Correlation Coefficient; PAF: Paroxysmal Atrial Fibrillation; PLASRR: Strain Rate During Reservoir Phase; PLASRCD: Strain Rate During Conduit Phase; PLASRCT: Strain Rate During Contraction Phase; STE: Speckle Tracking Echocardiography; TDI: Tissue Doppler Imaging; 2DE: Two Dimensional Echocardiography; 3DE: Three Dimensional Echocardiography.

Introduction

Atrial fibrillation is the most sustained arrhythmia and is associated with significant morbidity, mortality and impaired quality of life [1]. Echocardiography plays significant role in the diagnosis, therapeutic implications, and prognosis and risk stratification of patients with AF. Conventional echocardiographic indices such as EF, LA size and LA volume index has proven prognostic value in AF patients but they reflect advanced process in cardiac structural and functional remodeling [2,3]. It has also been recognized that AF occurs in individuals with structurally normal heart and without overt heart disease [2]. Early changes in LA can be detected using volumetric and speckle-tracking (STE) analysis using two- dimensional echocardiography. These advanced methodologies are feasible and reproducible for early detection of structural and functional changes in LA [3,4]. In this study we aimed to explore different changes in LA phasic function of middle- aged patients with AF and to evaluate the clinical and prognostic significance of disturbed LA functions.

Study Population

Prospective consecutive patients with AF (n=936), who had been admitted for sinus rhythm restoration in our hospital for the period January 2016- December 2018 were screened for participation in the study; figure 1. AF was defined and classified according to current guidelines [1]. A total of 70 patients met the inclusion criteria: stable sinus rhythm, age between 40-60 years, without over heart disease. The exclusion criteria were: age >60 years, coronary heart disease, valve disease, congenital heart disease, any other arrhythmia, cardiomyopathy, left ventricular systolic dysfunction (ejection fraction <50%), pericarditis, myocarditis, heart failure, chronic obstructive pulmonary disease, bronchial asthma, pneumonia, diabetes mellitus, thyroid disease, pacemaker implantation, cardiopulmonary or other surgery as a reason for AF, sleep apnea, anemia, neoplastic disease, alcohol or substantial abuse, chronic kidney disease, chirrhosis hepatis, history of ablation procedure, and poor image quality (Figure 1).

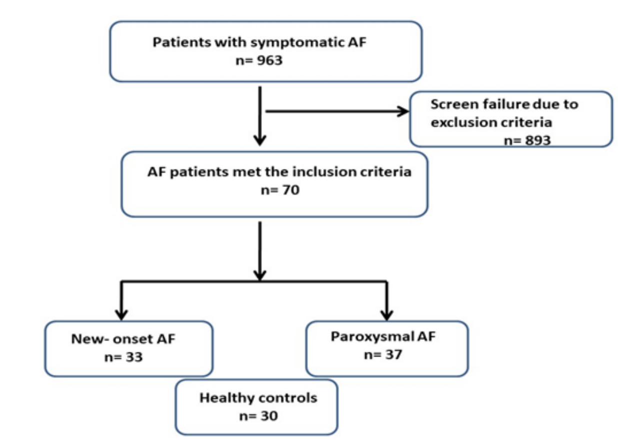

Figure 1: Study flow chart. AF, atrial fibrillation.

The control group was selected among healthy individuals who attended our hospital for routine health checkup(s). In this group of subjects all of the results from clinical examination, lab tests, electrocardiographic findings and conventional echocardiography were normal. Thus, 30 subjects were enrolled in the control group. None of the controls had a history of AF or any other cardiovascular or systemic diseases. The study was approved by our ethics committee and informed consent was obtained from all patients before participation.

Echocardiography

The transthoracicechocardiographic examination was performed using the ultrasound machine Philips EPIQ7, by one operator. Patients were examined in the left lateral position. All measurements were averaged over three consecutive heart cycles with a frame rate >50 Hz for all acquired views. Conventional echocardiographic parameters of LV structure and function were obtained according to current guidelines [4,5]. LA volumes were calculated from the apical four and two chamber views of the LA using the biplane method of the discs [6]. Maximal LA volume (LAmax) occurs at ventricular end-systole just before the opening mitral valve; while minimum LA volume (LAmin) occurs at end diastole, just before closure of mitral valve. Pre- atrial volume (LApre-A) is at beginning of P- wave on an ECG. All volumes were indexed to body surface area. Left atrial phasic function was assessed by volumetric method: Total emptying fraction: LATEF %= LAmax - LAmin /LAmax x 100; Passive emptying fraction: LAPEF%= LAmax - LApre-A /LAmax x 100; Active emptying fraction: LAAEF%= LApre-A- LAmin / LApre-A x 100; LA expansion index= LAmax - LAmin / LAmin x 100.

STE Analysis

LV longitudinal strain was assessed according to current recommendations and a peak GLS in the range of −20% is expected in a healthy person [4] - Figure 2.

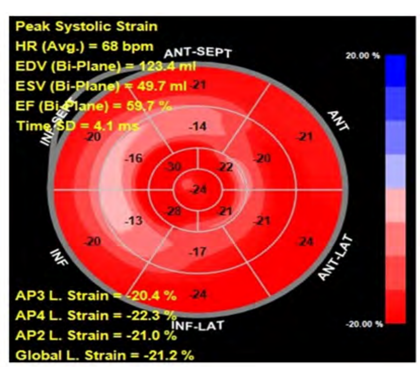

Figure 2: Bull eye’s plot.

LV GLS of middle-aged patient with PAF

LA strain analysis was performed according to current recommendations of The European Association of Cardiovascular Imaging (EACVI)/American Society of Echocardiography (ASE)/Industry Task Force [4]. LA strain components were measured using a non-foreshortened apical four-chamber view of the LA. All measurements were calculated offline using Phillips QLAB 10.3 software. As a cyclic process, LA deformation was subdivided into 3 phases: reservoir, conduit and contraction phase.

These phases can be characterized with three measurements in a LA strain curve- Figure 3:

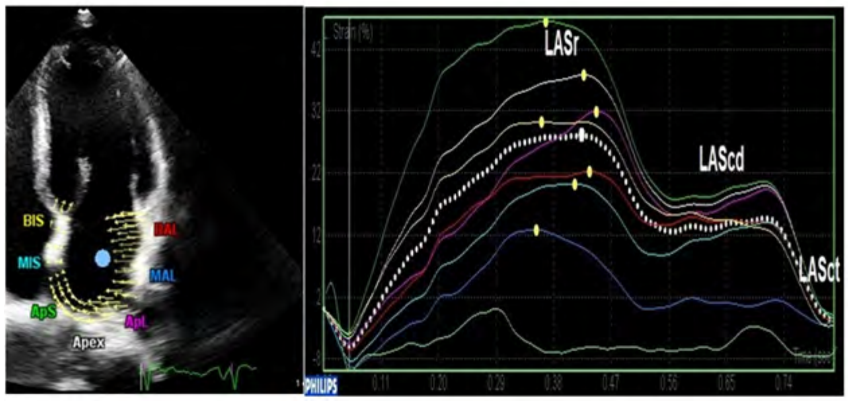

Figure 3: Measurement of left atrial strain components in middle-aged patient with PAF.

Reservoir phase: LASr % - strain during reservoir phase, measured as the difference of the strain value at mitral valve opening minus ventricular end-diastole (positive value).
Conduit phase: LAS cd % - strain during conduit phase, measured as the difference of the strain value at the onset of atrial contraction minus mitral valve opening (negative value).
Contraction phase: LAS ct % - strain during contraction phase as the difference of the strain value at ventricular end-diastole minus onset of atrial contraction (negative value).
LA stiffness index was calculated by: E/Em/ LASr. LA dispersion was defined as the SD of time to peak positive strain (SD-TPS) from the 12 LA segments [2].

Statistical Analysis

Using SPSS version 23.0, data from the patients and controls were collected and subjected to statistical analysis. Descriptive statistics are given in the mean ± standard deviation form. Categorical variable comparisons used chi-square testing and are given as % . Dispersion analysis (ANOVA) with Bonferroni was used for the analysis of the differences between the independent measurements of the groups. Relationships between variables were assessed by Pearson's and Spearman correlation coefficient. The best independent predictors of AF were identified by linear stepwise regression analysis. The level of significance was 95%. Hence, a P-value less than 0.05 were considered a significant result, and that less than 0.001 was considered a highly significant result. To assess intra observer variability and reproducibility, a second measurement of the same echocardiographic loops over time in 20 randomly chosen subjects was performed and Bland- Altman plots were designed. To test reproducibility, the intra class correlation coefficient (ICC) for single measures was used, with a value of 1 representing a perfect correlation.

Results

A total cohort comprises 100 patients with 33 Patients with new onset AF (51,9 ± 8,55 years; 66,7% male) , 37 patients with Paroxysmal AF (54,95 ± 6,49 years; 59,5% male) and 30 healthy subjects (51,43 ± 6,10 years, 16,7 % male) . Baseline clinical characteristics are shown in Table 1. There were significant differences in baseline cardiovascular risk factors between AF group and healthy controls. Patients with AF had Hypertension and obesity and a slightly higher incidence of metabolic syndrome compared to the control group. There were no differences in smoking status between groups. Patients with AF had a slower heart rate and higher systolic and diastolic BP as compared to controls. All patients with AF were on anticoagulant and b-blocker therapy and only 19% were on antiarrhythmic therapy. All hypertensive patients had with optimal BP values- Table 1.

Clinical characteristics	New onset AF N=33	Paroxysmal AF N=37	Healthy controls N=30	P – value
Age	51,9 ± 8,55	54,95±6,49	51,43±6,10	0,269
Male, %	66,7^	59,5^	16,7	0,001
Hypertension, %	72,7^	75,7^	0	0,001
Overweight, %	48,5^	40,5^	23,3	0,01
Obesity, %	51,5^	59,5^	0	0,001
Metabolic syndrome, %	24,2^	21,6^	0	0,016
Hyperlipidemia, %	15,2^	32,4^	6,7	0,022
Smoking, %	36,4	29,7	26,7	0,692
Heart rate, beats/min	71,09±9,44	68,08±7,92^	74,13±8,79	0,021
Systolic blood pressure, mmHg	129,75±6,44^	129,62±6,83^	118,73±10,28	0,001
Diastolic blood pressure, mmHg	80,57±5,01^	79,72 ± 5,66^	74,73±6,94	0,001

Table 1: Clinical characteristics.
Values are mean ± SD, n (%). Between group comparisons: * p<0.05 vs new onset AF; ^ p<0.05 vs healthy.
Table Abbreviation: AF: Atrial Fibrillation

The echocardiographic parameters indicated normal LV systolic and diastolic function- Table 2.

Patients with Paroxysmal AF had a concentric remodeling of LV. There were significant differences between AF and control groups in LV mass; however, all parameters were within normal range. All three groups had a normal EF, but there were differences in GLS in the AF groups. Also, there were differences in some TDI- derived diastolic parameters: early diastolic mitral annulus motion (Em) and E/Em ratio between AF groups and controls.

Parameter	New onset AF N=33	Paroxysmal AF N=37	Healthy controls N=30	P- value
LV mass, gr/m2	76,96 ± 9,66^	79,38 ± 9,44^	66,03 ± 8,01	0,001
RWT	0,41 ± 0,01	0,42 ± 0,02^	0,4 ± 0,01	0,013
EF Simpson method , %	59,99 ± 1,91	60,29 ± 2,26	61,07 ± 1,83	0,098
GLS, %	-20,77 ± 0,93^	-20,78 ± 0,94^	-21,86 ± 1,15	0,001
E, cm/s	75,35 ± 19,7	78,78 ± 18,26	78,35 ± 16,13	0,702
A, cm/s	65,27 ± 15,93	65,47 ± 14,62	61,76 ± 14,93	0,551
DT, ms	187,63 ± 43,34	188,19 ± 40,2	167,2 ± 35,00	0,063
TDI				
Sm, cm/s	8,08 ± 1,03	8,07 ± 1,15	8,6 ± 1,05	0,092
Em, cm/s	8,45 ± 1,4^	8,34 ± 1,6^	10,36 ± 1,92	0,001
Am, cm/s	9,24 ± 1,84	9,00 ± 2,27	9,73 ± 1,93	0,346
E/Em ratio	8,86 ± 1,87^	9,08 ± 3,38^	7,13 ± 0,89	0,001
Sl, cm/s	10,15 ± 0,99	10,08 ± 1,5	10,83 ± 1,85	0,081
El, cm/s	12,05 ± 3,01	11,7 ± 1,72	13,05 ± 2,47	0,073
Al, cm/s	9,46 ± 2,57	9,00 ± 3,32	9,19 ± 2,57	0,792
E/El ratio	6,56 ± 2,19	6,84 ± 1,79	6,12 ± 1,22	0,258

Table 2: Structural and functional LV echo indices.
Values are mean ± SD. Between group comparisons: * p<0.05 vs new onset AF; ^ p<0.05 vs healthy
Table Abbreviation: AF: atrial fibrillation; LV mass: left ventricular mass; RWT: relative wall thickness; EF: ejection fraction; GLS: global longitudinal strain; E: early diatolic filling of transmitral flow; A: late diastolic filling of transmitral flow; DT: deceleration time; TDI: Tissue Dopller imaging; Sm: systolic myocardial wave of medial annulus; Em: early myocardial diatolic wave of medial annulus; Am: myocardial diastolic late wave of medial annulus; Sl: systolic myocardial wave of lateral annulus; El: early myocardial diastolic wave of lateral annulus; Al: myocardial diastolic wave of lateral annulus.

In contrast to LV echocardiographic parameters, LA structural and functional indices demonstrated significant differences between AF groups and controls- Table 3. Left atrial indexed volumes in AF groups were dilated in comparison to healthy controls. Left atrial phasic function assessed by volumetric analysis was impaired in these groups with significant reduced LATEF, LAPEF and LAAEF. Left atrial strain analysis also demonstrated reduced parameters in the AF groups. Furthermore, patients with Paroxysmal AF had significant reduced LATEF, LA expansion index, LA reservoir strain and a higher LA dispersion.

Parameter	New onset of AF N=33	Paroxysmal AF N=37	Healthy controls N=30	P- value
LAVi, ml/m2	29,88 ± 10,56^	33,16 ± 13,89^	21,02 ± 6,73	0,001
LA minimal volume, ml/m2	11,37 ± 6,76^	14,38 ± 8,72^	5,78 ± 2,81	0,001
LA pre- A volume, ml/m2	19,54 ± 8,17^	21,95 ± 10,12^	11,26 ± 3,13	0,001
LATEF, %	64,76 ± 10,71^	57,61 ± 13,61*^	71,68 ± 7,65	0,001
LAPEF, %	36,42 ± 9,27^	33,25 ± 9,95^	45,03 ± 8,62	0,001
LAAEF, %	45,10 ± 13,95^	38,46 ± 13,05^	49,93 ± 14,81	0,004
LA expansion index	2,15 ± 1,33	1,69 ±0,96^	2,80 ± 1,11	0,001
LASr, %	35,34 ± 7,83^	30,38 ± 7,59^*	44,12 ± 8,33	0,001
LAScd, %	-18,56 ± 6,60^	-16,40 ± 5,24^	-24,98 ± 6,22	0,001
LASct,%	-14,02 ± 6,29^	-14,40 ± 6,74^	-18,81 ± 7,10	0,009
LA stiffness index	0,30 ± 0,13^	0,37 ± 0,22^	0,16 ± 0,04	0,001
LA dispersion, ms	47,35 ± 41,36	79,99 ± 66,57^*	35,31 ± 37,55	0,002

Table 3: Structural and functional indices of LA.
Values are mean ±SD. between group comparisons: * $p<0.05$ vs new onset AF; ^ $p<0.05$ vs healthy
Table Abbreviation: AF- atrial fibrillation, LAVi- left atrial volume index, LATEF- lefta atrial total emptying fraction, LAPEF- left atrial passive emptying fraction, LAAEF- left atrial active emptying fraction, LA- left atrial, LASr- lefta atrial reservoir strain, LAScd- lefta atrial conduit strain, LASct- left atrial contractile strain.

Multivariable linear regression analysis demonstrated that the best predictive model of AF included: LAVi (B= 0,012, p= 0, 05, 95%CI 0,000- 0,023), LASr (B= -0,055, p= 0,0001, 95%CI -0,071- -0,039), LASct (B= 0,041, p= 0,001, 95%CI 0,016- 0,066) are independent predictors of AF with 43% prediction within this model (adjusted R).

Repeatability and Reproducibility

To assess intraobserver variability and reproducibility, a second measurement of the same echocardiographic loops over time in 20 randomly chosen subjects was performed and Bland- Altman plots were designed- Figure 4.

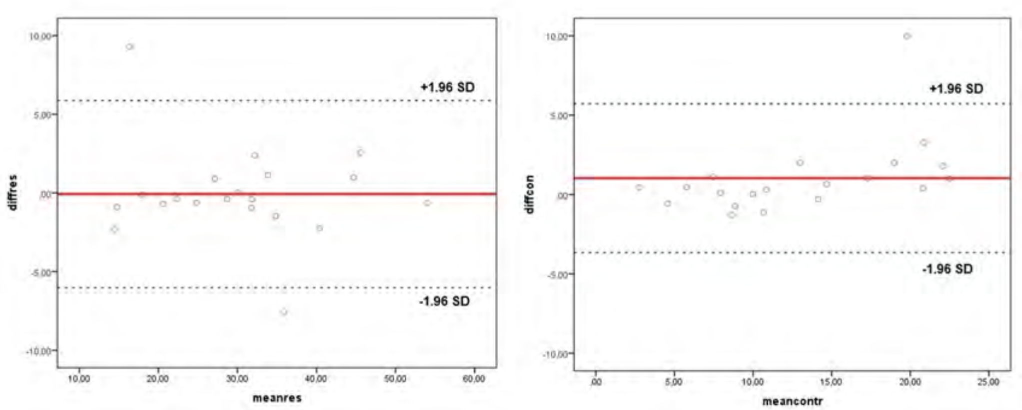

Figure 4A: Bland-Altman analysis for intra-observer variability of LASr.
(Upper limit=SD* 1.96+means=5.88252; mean=0.07; lower limit= mea-SD* 1.96=6.02252)
Figure 4B: Bland-Altman analysis for intra-observer variability of LASct.
(Upper limit=SD*1.96+means=5.71536; mean=1.029; lower limit=mean-SD*1.96=3.65736)

The solid line represents bias and dotted lines represent 95% limits of agreement. The bias was assessed by the mean of 20 differences of two measurements and the 95% confidence interval was calculated as ±1.96 SDs from the mean. Overall, small differences were observed for all LASr and LASct measurements because most of the differences were within the range of 95% limits of agreement, which suggests good repeatability and reproducibility in LASr and LASct. High ICC between 2 measurements showed good agreement between different measures- LASr (ICC 0,996; p<0,001; 95, 0% CI 0,989-0,998) and LASct (ICC 0,958; p<0,001; 95CI 0,889-0,984).

Discussion

The main findings of our study are as follows: there were subclinical alteration in LV longitudinal function, assessed by STE in middle–aged patients with AF with normal conventional 2DE; early LA structural and functional abnormalities were found by volumetric and STE analysis in AF groups; out of many investigated LA and LV echocardiographic variables, parameters of LA mechanics as well as LAVi were independent predictors of AF in middle-aged patients with normal standard echocardiography. Previously it was demonstrated that atrial fibrosis is a hallmark of structural remodeling [7]. Moreover, atrial remodeling and fibrosis play important roles in the initiation, maintenance and progression of AF [8]. Recently, there is evidence for a correlation between LA strain (assessed by STE) and LA fibrosis, as detected by MRI [7] or hystopathological specimen [9]. Two-dimensional speckle-tracking echocardiography is the most widely used advanced methodology for early detection of changes in cardiac mechanics in patients with structurally normal hearts.

Our study included middle-aged patients with AF who had normal conventional echocardiography. Previously, these groups of patients had been classified as patients with lone AF, but current AF guidelines didn't recommend using this historical descriptor [1]. Because of increasing knowledge about the pathophysiology of AF, in every patient a cause of arrhythmia is present. In the present study, the most prevalent risk factor for AF is arterial hypertension, following by obesity, which has well-known morbidities that cause heart chamber remodeling [1]. Conventional echocardiography of the study group demonstrated significant differences in the LV mass index in patients with AF. Here we have to point out that all parameters of LV geometry are within normal limits. Moreover, patients with PAF had concentric remodeling, probably the consequence of underlying disease. Previously it has been described that a hemodynamic model is responsible for left chamber remodeling in hypertension and obesity [10,11].

All investigated groups had normal systolic and diastolic LV functions as inclusion criteria. Even that patients with AF had normal EF, reduced LV longitudinal function assessed by GLS in AF groups was found. Similar results were reported by Kuo in patients with the new onset AF and a normal EF [12]. Consistency of results was reported by Hirose in the same population with normal EF [13]. STE is a more sensitive method for early detection of LV functional alterations. Also there were significant differences in the AF groups in comparison to controls in E/Em. Similar results were demonstrated by Caputo [14]. Left atrial volume index (LAVi) has been established as a surrogate marker for chronically elevated left ventricular (LV) filling pressure and has been incorporated into the recommendations for the echocardiographic assessment of diastolic function [15]. Moreover, it is a powerful predictor of atrial fibrillation (AF) in different pathologies [16-19]. The Copenhagen City Heart Study demonstrated that LA functional measures (minimal and maximal LA volumes) and LA emptying fraction predicted AF in the general population. When the analysis was restricted to individuals without hypertension and non-dilated LA (LAVmax <34 ml/m2), these measures indicated an increased risk of AF [20]. However, there is limited data for additional echocardiographic predictors of AF in specific populations, such as middle- aged patients with normal conventional echocardiography. Few 2D echocardiographic studies have reported early changes in LA structure and function in this special population, using volumetric analysis and STE. Tenekecioglu et al. investigated LA volumes and LA function (volumetric analysis) in middle--aged hypertensive subjects with AF. They demonstrated significant differences in LA volumes in an AF group as compared to a hypertensive group. Furthermore, patients with hypertension and AF had a significant reduced LATEF [21]. Recently, Schaaf, et al. [22] investigated LA anatomy and function by 2DE and 3DE in AF patients without overt heart disease. Anatomical remodeling was assessed using indexed maximal, minimal, and pre-atrial contraction volumes, whereas functional remodeling was assessed by volume and strain methods. They demonstrated that anatomical and functional LA remodeling was independent and strongly associated with PAF [22]. These results in similar groups of patients are confirmed by our study. There were significant differences in LA indexed volumes- minimal, maximal and pre-atrial in AF groups in comparison to healthy controls. These alterations may be attributed by the Frank- Starling's law, stating that increased atrial volumes, which lead to increased atrial dilation, resulting in increased atrial strength, a compensatory mechanism for maintaining atrial phasic function [23]. But there have been significant differences between AF groups and controls in LATEF, LAPEF and LAAEF, probably reflecting early alterations in LA phasic function. Furthermore, patients with PAF had an additional reduction in LATEF in comparison to the new-onset in AF groups.

Disturbed LA phasic function in AF patients assessed by volumetric analysis has been reported in several studies. Our finding is consistent with Abhayaratna who pointed out that patients with incident of AF had significant reduced LATEF [24]. Other findings, similar to our results, have been reported by Hirose et al., who demonstrated that patients with the new onset AF had a larger LA volume and reduced LAAEF [25]. Recent studies demonstrated that LA strain can detect an impairment in LA function without LA enlargement, which has an incremental predictive value for AF over LA enlargement in a variety of cardiac conditions [26,27]. In our study, LA strain and strain rate parameters were reduced in AF groups in comparison to controls. Furthermore, patients with PAF had a significant reduced LASr in comparison to new onset an AF group. LA stiffness index was higher in AF groups. Our results are consistent with Yeonyee who demonstrated that patients with PAF had dilated LA, reduced LASr and higher a LA stiffness index [28]. In the same population Shang reported that patients with PAF had reduced LASr and LASct without any differences in LA volumes in comparison to controls [29]. Similar results were reported by Zhu in a hypertensive and AF population. Patients with lone AF had reduced LASr and LA mechanical dyssynchrony [30]. Our study confirms that patients with PAF had LA dyssynchrony. Importantly, LA dispersion can detect LA functional impairment and asynchrony in patients without LA enlargement [29,31]. In the present study, the average LAVI in the patients with AF was within the normal range.

Previously multiple factors have been shown to be predictors of AF in the general population (LA size, LAVi, EF etc.), but they reflect an advanced process in cardiac anatomical and functional remodeling. In our study, early changes in LA were detected using volumetric and STE analysis of two-dimensional echocardiography. Recently, Donal, et al. [32] had highlighted that atrial anatomy and functions are keys and should not be forgotten by imagers, because there are key pathophysiological, prognostic and therapeutic values in analyzing the LA. He pointed out that atrial volumes are important and atrial deformation during the reservoir and probably also during the active booster pump function have to be considered in dealing with patients in AF [32]. Our study confirmed that LAVi (B= 0,012, p= 0, 05, 95%CI 0,000-0,023), LASr (B= -0,055, p= 0, 0001, 95%CI -0,071- -0,039), and LASct (B= 0,041, p= 0,001, 95%CI 0,016- 0,066) are independent predictors of AF with 43% prediction in using this model (adjusted R).

Study Limitations

There are several limitations of the present study. This study includes the small sample size from a single institution. The reason for this is strict exclusion criteria. But on the other side, the exclusion criteria made the group more homogeneous and the analysis of results limits the influence of confounding factors. The control group enrolled in our study consisted of healthy individuals who came to our hospital for regular health check-ups. They are without history of cardiovascular disease, normal body weight and with normal findings on clinical examination and echocardiography. Another limitation is that STE is operator-dependent and dedicated software for LA strain analysis has not yet been released. In this study we used the software for LV analysis to study LA strain.

Conclusion

In middle- aged patients without overt heart disease LA reservoir and contractile strain can have additive value to LAVi in the prediction of AF. These finding emphasize that LA volumes along with LA mechanics have to be considered in dealing with patients in AF. Further research should be undertaken for defining cut-off values for LA dysfunction in larger study populations.

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