

## Atrial contractile function and fibrosis in patients with paroxysmal atrial fibrillation in sinus rhythm

**Función contráctil auricular y fibrosis en pacientes con fibrilación auricular paroxística en ritmo sinusal**

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### Abstract

**Objectives:** The aim of the study was to investigate atrial contractile function in patients with paroxysmal atrial fibrillation (AF) in sinus rhythm using transthoracic echocardiography (EchoCG). **Methods and results:** Thirty-five patients with paroxysmal AF and arterial hypertension (mean age  $62 \pm 10$  years, 43% male) in sinus rhythm were enrolled in the study. The control group was composed of comparable patients with arterial hypertension without heart rhythm disturbances. EchoCG was performed during sinus rhythm according to an extended protocol, which included the ejection fraction (EF) of the left atrium (LA) and tissue Doppler measurements. Myocardial fibrosis was assessed quantitatively by videodensitometry in intraventricular and intraatrial (IAS) septa using an original image post-processing algorithm. We found a significant decrease in the left atrial contraction function during sinus rhythm in patients with AF when compared to controls. LA EF ( $34 \pm 14$  vs.  $54 \pm 17$ ,  $p = 0.03$ ) and A' velocity ( $0.17 \pm 0.04$  vs.  $0.22 \pm 0.04$ ,  $p = 0.008$ ) decreased while A/A' ratio ( $2.7 \pm 0.2$  vs.  $1.9 \pm 0.1$ ,  $p = 0.006$ ) increased. Peak A velocity was not affected. Videodensitometric analysis revealed a 2.3-fold increase in IAS fibrosis fraction in AF patients compared with controls ( $p = 0.01$ ). **Conclusion:** Patients with AF in sinus rhythm have markedly depressed atrial contractile function. Videodensitometry of IAS has the potential to be used as inexpensive method of atrial fibrosis assessment in patients with AF.

**Keywords:** Atrial contractile function. Atrial fibrosis. Videodensitometry.

### Resumen

**Objetivo:** El objetivo del estudio fue investigar la función contráctil auricular en pacientes con fibrilación auricular paroxística (FA) en ritmo sinusal mediante una ecocardiografía transtorácica (EchoCG). **Material y métodos:** Treinta y cinco pacientes con FA paroxística e hipertensión arterial (edad media de  $62 \pm 10$  años, el 43% varones) se inscribieron en el estudio en ritmo sinusal. El grupo de control estaba compuesto por pacientes comparables con hipertensión arterial sin alteraciones del ritmo cardíaco. Se realizó una ecocardiografía durante el ritmo sinusal, según el protocolo extendido, incluidas la fracción de eyeción (FE) de la aurícula izquierda (AI) y las mediciones Doppler tisulares. La fibrosis miocárdica se evaluó cuantitativamente mediante una videodensitometría de los septos interventricular e interauricular (IAS) utilizando un algoritmo de

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posprocesamiento de imágenes originales. **Resultados:** Encontramos una disminución significativa en la función de contracción de la aurícula izquierda durante el ritmo sinusal en pacientes con FA en comparación con el grupo de control. Cabe destacar que la FE de la AI ( $34 \pm 14$  vs.  $54 \pm 17$ ,  $p = 0.03$ ) y la velocidad A' disminuyeron ( $0.17 \pm 0.04$  vs.  $0.22 \pm 0.04$ ,  $p = 0.008$ ) mientras que la relación A/A' aumentó ( $2.7 \pm 0.2$  vs.  $1.9 \pm 0.1$ ,  $p = 0.006$ ). La velocidad pico A no se vio afectada. El análisis videodensitométrico reveló que la fracción de fibrosis IAS en pacientes con FA fue 2.3 veces mayor que en el grupo de control ( $p = 0.01$ ). **Conclusiones:** Incluso en ritmo sinusal, los pacientes con FA tienen una función contráctil auricular marcadamente deprimida. La videodensitometría de IAS tiene el potencial de utilizarse como método económico de diagnóstico de la fibrosis auricular en pacientes con FA.

**Palabras clave:** Función contráctil auricular. Fibrosis auricular. Videodensitometría.

## Introduction and aim

Atrial fibrillation (AF), the most prevalent sustained arrhythmia in the adult population<sup>1</sup>, is recognized as the most important risk factor for stroke and is linked with other thrombotic cardiovascular events. Paroxysmal AF considerably reduces life quality, not only immediately during paroxysm but also within the sinus rhythm period between attacks.

The phenomenon of the loss of atrial contractile function immediately after cardioversion ("atrial stunning") is well-known<sup>2</sup>. Work is underway to investigate the phenomenon of atrial failure as a combination of pathophysiological factors leading to deterioration in atrial functioning and a decrease in overall heart productivity<sup>3</sup>. A special place in the concept of atrial failure is occupied by the processes of atrial myocardial fibrosis and remodeling. From a clinical point of view, the issue of atrial contractile function in patients with paroxysmal AF maintaining sinus rhythm is important; however, this problem remains poorly understood. The aim of the present research was to evaluate the atrial contractile function in patients with paroxysmal AF and arterial hypertension (AH) in sinus rhythm in comparison with matched patients without supraventricular arrhythmias.

## Methods

### Patient population

The study was conducted as a single-center case-control clinical trial with consecutive enrollment of patients. Thirty-five patients with paroxysmal AF and AH (stage III WHO, very high risk) were included in AF group (15 [42.9%] were male and 20 [57.1%] were female).

Diagnosis of the paroxysmal form of AF was confirmed through analysis of electrocardiogram (ECG) records. Patients with persistent AF in anamnesis or

with poor echocardiographic (EchoCG) visualization were excluded from the study.

The control group consisted of 35 patients of comparable age and sex with AH (16 [45.7%] were male and 19 [54.3%] were female). All patients in the control group did not have any significant heart rhythm disturbances, which were confirmed by ECG analysis, Holter monitoring and clinical history. Patients in both groups received continuous antihypertensive therapy.

The mean age of patients in both groups was comparable at the time of inclusion in the study ( $62.2 \pm 10.2$  years in the AF group and  $60.7 \pm 11.2$  years in the control group). Clinical characteristics, concomitant diseases spectrum and medical therapy are shown in table 1.

AF paroxysms were characterized using the European Heart Rhythm Association (EHRA) standards. Some 14.3% of patients were EHRA class I (asymptomatic), 20% were EHRA class II, 42.9% were EHRA class III, and 22.9% were EHRA class IV (severe dyspnea and weakness).

Patients were characterized for the duration of time elapsed between an AF paroxysm and enrollment in the study. Eight (22.9%) patients had an AF paroxysm 1-3 days before enrollment, 12 (34.3%) patients 4-7 days prior, nine (25.7%) patients 1-2 weeks prior, and three (8.6%) patients 1 month prior. Patients who had AF paroxysms  $< 24$  h before EchoCG evaluation were not included in this study.

### EchoCG methods

Assessment of the left atrial contractile function was carried out using transthoracic EchoCG in sinus rhythm. The EchoCG protocol includes standard measurements for (1) the assessment of systolic and diastolic function of the left ventricle (LV); (2) the assessment of atrial contractile function by ejection fraction (EF) estimation in 2D B-mode, pulsed-wave and tissue Doppler,

**Table 1.** Concomitant pathology in patients and medications used in AF and control groups

Concomitant pathology	AF group	Control group	p-level
AH, stage III (WHO), n (%)	35 (100)	35 (100)	1
Diabetes mellitus, n (%)	6 (17.1)	5 (14.3)	0.74
History of stroke or TIA, n (%)	10 (28.6)	3 (8.6)	0.03
History of ACS/MI, n (%)	6 (17.1)	8 (22.9)	0.55
CHF, NYHA I-II functional class, n (%)	11 (31.4)	13 (37.1)	0.61
CHF, NYHA III functional class*, n (%)	3 (8.6)	2 (5.7)	0.64
Obesity, n (%)	11 (31.4)	13 (37.1)	0.61
Non-alcoholic steatohepatitis, n (%)	3 (8.6)	2 (5.7)	0.64
ACE inhibitors, n (%)	13 (37.1)	14 (40)	0.8
AT <sub>1</sub> -receptor blockers, n (%)	2 (5.7)	3 (8.6)	0.64
Spironolactone, n (%)	2 (5.7)	1 (2.9)	0.55
Dihydropyridine calcium channel blockers, n (%)	8 (22.9)	10 (28.6)	0.58
Diuretics, n (%)	5 (14.3)	4 (11.4)	0.72
Verapamil, n (%)	4 (11.4)	1 (2.9)	0.16
Beta-blockers, n (%)	12 (34.4)	10 (28.6)	0.6
Sotalol, n (%)	6 (17.1)	0	0.1
Amiodarone, n (%)	7 (20)	0	0.005
IC class antiarrhythmics, n (%)	5 (11.4)	0	0.02

AH: arterial hypertension; AF: atrial fibrillation; TIA: transient ischemic attack; ACS: acute coronary syndrome; MI: myocardial infarction; CHF: chronic heart failure; NYHA: New York Heart Association. \* All patients with NYHA III functional class had preserved LV ejection fraction (EF).

and (3) videodensitometric assessment of fraction of fibrosis in the atria and ventricles by of Image J software (NIH, USA) using the original method described below.

The following parameters were assessed using standard methods:

- Peak E velocity of transmitral diastolic flow and E/E' ratio;
- Peak S, D and Ar velocities of in pulmonary veins;
- Volumes of the left atrium (LA) in the end of the atrial systole and diastole derived from apical four-chamber position estimated by method of disks with subsequent calculation of the LA EF;

– Velocity, duration and velocity-time integral (VTI) of peak A of transmitral diastolic flow and corresponding peak A' measured by tissue Doppler on the level of the lateral site of the fibrous ring of the mitral valve.

Fibrosis fraction in the myocardium of the atria (in the intraatrial [IAS]) and LV (in the intraventricular [IVS]) was estimated in the heart diastole by the original technique described below.

EchoCG images were derived from an apical four-chamber view with clearly visible mitral valve, IAS and IVS. All images were recorded in the same mode using a Siemens Sequoia 512 with the default profile “Cardiac Difficult” (gray-scale images, harmonic frequency 3.5 MHz, convex probe) with automatic brightness adjustment.

Images were saved in the JPEG format and transferred to desktop computer for subsequent analysis using Image J 1.4 software, which is designed for the quantitative analysis of medical and biological images. Gray-scale images were converted into black and white (single bit) format with the threshold determined by the maximal entropy method. On such single bit images, the pericardium and valve leaflets were the “brightest” structures because of higher echogenicity and the maximum content of connective tissue fibers. Consequently, the fraction of fibrosis in the pericardium and mitral valve leaflets was defined as 100%. The chamber filled with blood remained “black”, therefore its videodensitometric “fibrosis fraction” was defined as 0%. IAS and IVS with different echogenicity ranged from five to 80%. We used the percent of white pixels on the black background as a reflection of the fibrosis fraction in IAS and IVS. Using Image J software, the percentage of area covered with white pixels in the basal segment of IVS and IAS was estimated and then used as fibrosis fraction in the structures.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. It was approved by the Local Ethics Committee. Informed consent was obtained from each patient.

### Statistical analysis

Statistical analysis was performed using Statistica 7.0 software (Statsoft, USA). For the comparison of variables, Mann-Whitney, Student and  $\chi^2$  tests were used based on data type and values distribution. Bivariate correlations between variables were determined by Pearson correlation coefficient. A  $p = 0.05$  or less was considered to indicate statistical significance. Data in

**Table 2.** Results of echocardiographic investigation: standard parameters

Parameter	AF group	Control group	p-level
LA volume, ml	85.5 ± 30.6	65.7 ± 17.4	0.02
LV end diastolic size, cm	4.7 ± 0.43	5.0 ± 0.58	0.21
IVS thickness, cm	1.32 ± 0.1	1.23 ± 0.1	0.07
LV posterior wall thickness, cm	1.13 ± 0.2	1.2 ± 0.2	0.22
LV EF (by Teichholz), %	78.8 ± 6.3	78.4 ± 5.4	0.54
Stroke volume, ml	85.7 ± 17.2	98.0 ± 18.4	0.35
LV EF (by Simpson), %	60.1 ± 5.3	59.4 ± 7.2	0.41
RV size, cm	2.6 ± 0.3	2.4 ± 0.3	0.9
Mitral valve insufficiency > I grade, n (%)	24 (68.6)	11 (31.4)	0.001
Tricuspid valve insufficiency > I grade, n (%)	9 (25.7)	7 (20.0)	0.56
Pulmonary artery systolic pressure, mm Hg	42 ± 3.2	35.4 ± 2.2	0.04
Pulmonary artery diastolic pressure, mm Hg	12 ± 3.1	9 ± 2.3	0.14

LA: left atrium; LV: left ventricle; IVS: intraventricular septum; EF: ejection fraction; RV: right ventricle.

tables and in the text below are provided as mean ± standard deviation (SD), prevalence of signs in groups are shown as absolute number and percentage of patients in the group.

## Results

### Comparison of EchoCG parameters for control and AF patients

Standard EchoCG parameters were assessed and compared for the AF and control groups (Table 2). The average LA volume was higher in the AF group than the control (85.5 ± 30.6 ml vs. 65.7 ± 17.4 ml, respectively, p < 0.05). This led to the assessment of LA contractile function, which is closely related to the diastolic function of ventricles (Table 3).

In patients with AF, there was a substantial decrease in LA contractile function measured by EF LA and impulse and tissue Doppler (Table 2). Notably, there was depressed LA contractile function (i.e., below 45%) in 77.1% of the patients with AF, whereas LA contractile function of all control patients was not depressed

**Table 3.** Results of echocardiographic investigation: atrial contractile function and LV diastolic function

Parameter (mean values)	AF group	Control group	p-level
Transmitral diastolic flow, pulsed wave Doppler echocardiography			
Peak E velocity, m/s	0.68 ± 0.05	0.54 ± 0.04	0.04
Isovolumic relaxation time, ms	167 ± 36.5	154 ± 18.2	0.11
Peak A velocity, m/s	0.4 ± 0.1	0.51 ± 0.1	0.08
Tissue Doppler echocardiography of lateral and medial portion of mitral valve fibrous ring			
Peak Sm velocity (lateral), m/s	0.14 ± 0.1	0.16 ± 0.1	0.25
Peak E' velocity (lateral), m/s	0.12 ± 0.01	0.14 ± 0.01	0.33
Peak E' velocity (medial), m/s	0.09 ± 0.01	0.11 ± 0.01	0.31
Peak A' peak velocity (lateral), m/s	0.17 ± 0.04	0.22 ± 0.04	0.008
VTI A' (lateral), cm	2 ± 0.2	4 ± 0.3	0.02
Peak A' duration (lateral), ms	83 ± 28	140 ± 46	< 0.001
Estimated ratios			
E/E' relation (lateral)	6.5 ± 1.4	6.0 ± 1.1	0.27
E/E' ratio (medial)	8.4 ± 2.3	7.3 ± 2.0	0.2
E/A ratio	1.9 ± 0.2	1.6 ± 0.1	0.03
E'/A' ratio (lateral)	0.9 ± 0.1	0.5 ± 0.1	0.004
A/A' ratio	2.7 ± 0.2	1.9 ± 0.1	0.006
LA contractile function measured in B-mode			
LA volume in atrial systole, ml	57.3 ± 15.6	30.0 ± 17.1	0.03
LA volume in atrial diastole, ml	85.5 ± 30.6	65.7 ± 17.4	0.04
LA EF, %	34 ± 14	54 ± 17	0.03

AF: atrial fibrillation; LA: left atrium; EF: ejection fraction.

(p < 0.01). The mean LA EF was significantly higher in the control group than the AF group (54 ± 17% vs. 34 ± 14%, respectively, p = 0.03; Table 3).

To further quantify the LA contractile function, we used EchoCG techniques to assess A-wave functions, such as transmitral diastolic flow peak A velocity, which have been associated as a marker of LA contractile function. Here, we found that peak A velocity was slightly, albeit insignificantly, lower in AF patients than in controls (0.4 ± 0.1 m/s vs. 0.51 ± 0.1 m/s, respectively;

**Table 3**). More notable was the change in lateral peak A' velocity, which was measured by tissue Doppler and reflects the movement of the atrial wall during systole. Lateral peak A' velocity was significantly lower in AF patients ( $0.17 \pm 0.04$  m/s) than the control group ( $0.22 \pm 0.04$  m/s) (**Table 2**). Peak A' duration and VTI were also substantially lower in the AF group than the control group ( $83 \pm 28$  ms vs.  $140 \pm 46$  ms,  $p < 0.001$ ; and  $2 \pm 0.2$  cm vs.  $4 \pm 0.3$  cm,  $p = 0.02$ , respectively; **Table 3**).

Correlation analysis detected a statistically significant negative correlation between LA volume and LA EF ( $r = -0.39$ ;  $p = 0.03$ ) and peak A' velocity ( $r = -0.47$ ;  $p = 0.02$ ). This suggests that LA contractile function depression is associated with LA dilation.

### **LA contractile function in subgroups of AF patients without the expressed dilatation LA**

To further assess the contribution of LA dilation, we examined a subgroup of AF patients without dilated LA (i.e., an LA volume of  $< 55$  ml,  $n = 7$ ). It showed that the degree of LA contractile function in patients without LA dilation was comparable to that in patients with LA dilatation. Mean A' peak velocity in this subgroup was  $0.16 \pm 0.02$  m/s.

#### **Relationship of Sinus Rhythm Period Duration with Degree of LA Contractile Function Depression.**

Most of the patients included in the study had a recent AF paroxysm during the past 2 weeks until hospitalization. Correlation analysis showed no statistically significant relation between LA contractile function decrease (measured by EF LA and Doppler indicators) and duration of stay in sinus rhythm.

### **Assessment of LA Function in Patients with LV Diastolic Dysfunction**

Diastolic dysfunction was diagnosed in 33 (94.2%) patients in the AF group and 31 (88.6%) patients in the control group. The severity of diastolic dysfunction was comparable between groups (**Table 4**). There was a statistically significant increase of E/A in the AF patients compared to the control patients ( $1.9 \pm 0.2$  vs.  $1.6 \pm 0.1$ ,  $p = 0.03$ ; **Table 4**). This can likely be explained as a result of peak A reduction caused by a decrease in the LA contractile function, rather than deterioration of the LV diastolic function.

To reduce the influence of the increased LV end diastolic pressure on Doppler LA contractile function

**Table 4.** Results developed from EchoCG: integral assessment of the LV diastolic function

Parameter (mean values)	AF group	Control group	p-level
Diastolic dysfunction (overall), n (%)	33 (94.2)	31 (88.6)	0.39
Impaired LV relaxation, n (%)	18 (51.4)	19 (54.3)	0.81
Pseudo-normalization, n (%)	8 (22.9)	7 (20.0)	0.77
Reversible LV restriction, n (%)	4 (11.4)	3 (8.6)	0.69
Irreversible LV restriction, n (%)	3 (8.6)	2 (5.7)	0.64

AF: atrial fibrillation; LV: left ventricle.

markers, this work conducted the first analysis of the A/A' parameter. It was suggested that this parameter more accurately reflects a decrease in the contractile function of the atria. In the AF group, a remarkable increase in the A/A' was shown ( $2.7 \pm 0.2$  vs.  $1.9 \pm 0.1$  in the control group,  $p = 0.006$ ).

### **Videodensitometric assessment of diffuse fibrosis fraction in IAS and IVS**

Patients who underwent myocardial infarction were excluded from the fibrosis analysis, since they could have large foci of fibrosis due to the previous infarction. There were no statistically significant differences in fibrosis fraction in IVS ( $21.4 \pm 15.3\%$  in the AF group vs.  $23.7 \pm 17.5\%$  in the control group,  $p = 0.39$ ). At the same time, in the AF group there was a remarkable 2.3-fold increase in fibrosis fraction in IAS ( $32.7 \pm 15.6\%$  vs.  $13.9 \pm 8.4\%$  in the control group,  $p = 0.01$ ). The mean IAS/IVS fibrosis fraction ratio (FFR) was 1.5 in the AF group and 0.6 in the control group. IAS/IVS FFR  $> 1$  was diagnosed in 29 (82.8%) patients with AF and only in 4 (11.4%) patients without AF ( $p < 0.001$ ). Fibrosis fraction in AF patients positively correlated with AF anamnesis ( $r = 0.36$ ;  $p = 0.042$ ), AH anamnesis in years ( $r = 0.41$ ;  $p = 0.04$ ) and systolic arterial pressure ( $r = 0.32$ ;  $p = 0.045$ ).

### **Discussion**

Fibrosis, dilatation, and spherical remodeling of the atria are significant factors in the development of a whole spectrum of cardiovascular manifestations, including stroke, ischemia, heart failure, arrhythmias, and other conditions. Bisbal et al. describe the complex and

multifaceted vicious circle of atrial failure, while giving a key role to the methods of atrial imaging, including the assessment of fibrosis and the characteristics of blood flow<sup>3</sup>. When the LA reaches a critical size (4.3 × 4.4 × 4.7 cm) the chance of successful sinus rhythm restoration sharply decreases<sup>4</sup>.

Imaging of myocardial fibrosis can be performed by various methods from standard ECG to magnetic resonance imaging (MRI) with late gadolinium enhancement and pathological examination. EchoCG methods for visualizing atrial myocardial fibrosis are of practical interest.

Lacalzada-Almeida et al. used speckle tracking EchoCG (STE) to assess signs of atrial myocardial fibrosis<sup>5</sup>. Their study showed for the 1<sup>st</sup> time that using this method of deformity imaging, it is possible to determine the decrease in LA strain as one of the indicators of atrial fibrosis in patients with intra-atrial block<sup>6</sup>. On further observation of patients, the authors also noted that this indicator can serve as a predictor of AF and stroke<sup>7</sup>.

The Doppler scan of transmural diastolic flow is frequently used for the characterization of atrial contractile function. A decrease in transmural diastolic flow peak A velocity has been shown in patients with AF, including those who have just undergone cardioversion<sup>8</sup>. However, peak A velocity is not a suitable single marker of atrial contractility in the presence of LV diastolic dysfunction because LV diastolic dysfunction significantly affects the transmural flow pattern. Peak A velocity reflects the pressure gradient between the atrium and ventricle during atrial systole but does not show the true force of the atrial contraction. This disparity further explains the low accuracy of peak A velocity as an indicator of atrial contractile function<sup>8</sup>. In cases of concurrent reduced contractile function of the LA and mild diastolic LV dysfunction, peak A velocity may remain unchanged. This may explain why we found no statistically significant differences in peak A velocity between the studied groups.

In practical settings, the assessment of diastolic function in patients with paroxysmal AF even in sinus rhythm represents a difficult task. The patients present with a relative increase of peak E (as expected with a decrease in "atrial" peak A velocity) and a relative increase of peak E' (accompanying a parallel decrease in peak A'). However, an increase of velocities of peaks A and A' which is usually treated as a deterioration of diastolic function (with growth of pressure in the LA without decompensation) in AF patients might really reflect the improvement of the LA contractile function.

Tissue Doppler parameters reflect a "true" speed of the movement of the walls of the heart in systole and diastole. Peak E' represents a tissue Doppler parameter most frequently used in clinical practice and subsequent calculation of the E/E' ratio give clinicians extremely valuable information about the degree of diastolic dysfunction.

Tissue Doppler peak A' velocity can be used as reliable marker of atrial contractile function<sup>9</sup>. Peak A' velocity measurement at the level of the fibrous ring of the mitral valve reflects a reduction of LA contractile force, while measurement of this peak at the level of the fibrous ring of the tricuspid valve corresponds with the right atrium systolic function<sup>10</sup>.

In the present study, we found a substantial reduction of peak A' velocity in patients with AF, which reflects a significant decrease in atrial contractile function. It should be noted that in the studies that investigated the recovery of atrial function following cardioversion; there was even more considerable LA contractile function depression<sup>9</sup>.

In addition to peak A' velocity, we analyzed A' duration, A' VTI and the A/A' ratio. In AF patients, we found a statistically significant two-fold decrease of A' VTI, a 1.7-fold decrease of peak A' duration and a 1.4-fold decrease of the A/A' ratio that might reflect an extent of atrial contractile function decline. We suggest that use of these additional parameters, rather than simply assessing peak A velocity, may help to improve the accuracy of assessment in patients with AF in sinus rhythm and LV diastolic dysfunction.

Previous works have shown a dramatic decline in atrial contractile function immediately after cardioversion<sup>11</sup>. This led us to the hypothesis that extent of atrial contractile function decrease will be negatively correlated with the sinus rhythm period. However, we found no such correlation in our research. This can be explained in three ways. First, most patients were enrolled into the current research at a similar time period after a recent AF paroxysm (which occurred in last 1-2 weeks). Second, some patients might have had more recent asymptomatic AF paroxysms. Third, we include no patients directly after cardioversion (< 24 h) because the 'stunned' atria phenomenon is expected<sup>2</sup>.

We showed for the 1<sup>st</sup> time that videodensitometric analysis of IAS fibrosis fraction was increased 2.3-fold in AF patients when compared to control patients. Previously, the degree of atrial fibrosis assessment was limited because of the difficulty of differentiation of atrial tissue from the nearby structures. This complexity can be overcome using our novel technique. On their own,

the videodensitometric data can be biased; however, errors due to threshold adjustment may be corrected using IAS/IVS FFR derived from a single apical four-chamber image.

Our results showing a decrease in the left atrial contractility in patients with AF in sinus rhythm align with the concept of atrial failure. Myocardial fibrosis leads to a decrease in the contractility of the LA and its subsequent dilatation. This process does not exist autonomously in the atria, but captures the whole heart, as evidenced by our associations with LV diastolic dysfunction. Thus, our study confirms the complex organization of pathophysiological processes of atrial failure and its manifestations described in the review of Bisbal et al.<sup>3</sup>.

It has been shown by MRI assessment that patients with extensive fibrosis in the atrial myocardium had a higher recurrence rate of AF following catheter ablation<sup>12</sup>. Our proposed videodensitometric analysis is an inexpensive and accurate method that has the potential to serve as an alternative to MRI or STE in the measurement of atrial fibrosis in AF.

### **Study limitations**

One of the limitations of the study was the small sample size due to participant characteristics and the need for rapid evaluation of the new ultrasound-based videodensitometry of atrial fibrosis. We use this technique without direct validation by comparison with cardiac MRI or biopsy because of the limited access to those methods. A second limitation was that 23% of patients had AF episodes in the 1-3 days preceding the echo measurements. This circumstance could lead to an even greater decrease in the contractile function of the atria. Regarding the well-known phenomenon of residual mechanical dysfunction after electrical or pharmacological cardioversion, the reduction in LA systolic function may have a temporal effect.

### **Conclusion**

Patients with the paroxysmal form of AF with recent AF paroxysm (within 1 month) have a significant decrease in atrial contractile function irrespective of length of stay in sinus rhythm. AF patients have a 2.3-fold increase in IAS fibrosis fraction assessed by videodensitometry compared with controls. Extended EchoCG evaluation of atrial contractile function measurement beyond simple peak A velocity assessment and

videodensitometric analysis may improve the quality of treatment of patients with AF in the near future.

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### **Conflicts of interests**

The authors declare that they have no conflicts of interest.

### **Ethical disclosures**

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

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