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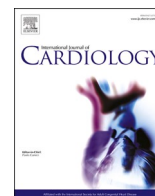
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Association between comorbidities and left and right atrial dysfunction in patients with paroxysmal atrial fibrillation: Analysis of AF-RISK

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ABSTRACT

Background: To identify the association between comorbidities and left atrial (LA) and right atrial (RA) function in patients with paroxysmal atrial fibrillation (AF).

Methods: This is a cross-sectional study. Speckle-tracking echocardiography was performed in 344 patients with paroxysmal AF at baseline, and available in 298 patients after 1-year follow-up. The number of comorbidities (hypertension, diabetes mellitus, coronary artery disease, body mass index > 25 kg/m², age > 65 years, moderate to severe mitral valve regurgitation and kidney dysfunction (estimated glomerular filtration rate < 60 ml/min/1.73 m²)) was determined and the association with atrial strain was tested.

Results: Mean age of the patients was 58 (SD 12) years and 137 patients were women (40%). Patients with a higher number of comorbidities had larger LA volumes (*p* for trend < 0.001), and had a decrease in all strain phases from the LA and RA, except for the RA contraction phase (*p* for trend 0.47). A higher number of comorbidities was associated with LA reservoir and conduit strain decrease independently of LA volume (*p* < 0.001, *p* < 0.001 respectively). Patients with 1–2 comorbidities, but not patients with 3 or more comorbidities, showed a further progression of impaired LA and RA function in almost all atrial strain phases at 14 [13–17] months follow-up.

Conclusions: In patients with paroxysmal AF, individual and combined comorbidities are related to lower LA and RA strain. In patients with few comorbidities, impairment in atrial function progresses during one year of follow-up. Whether comorbidity management prevents or reverses decrease in atrial function warrants further study.

1. Introduction

Atrial fibrillation (AF) is a progressive disease, which is mainly determined by structural atrial remodelling processes, called atrial cardiomyopathy [1], due to long-term exposure to concomitant

cardiovascular risk factors and AF itself. One component of the arrhythmogenic atrial substrate is left atrial (LA) dilatation, which is common in patients with AF and has been shown to predict AF occurrence and cardiovascular events [2]. In addition to LA dilatation, also LA function is a predictor of stroke risk and cardiovascular outcomes in

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¹ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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patients with AF [3,4].

Functional impairment of atrial deformation properties represents an important component of the progressive atrial remodelling and AF substrate [5]. During ventricular systole, LA strain (LAS) reflects LA expansibility and stiffness [6]. Deformation in the LA reservoir (LASr) strain phase has been related to recurrence rates of AF after catheter ablation [3] and increased propensity for first episode of AF or atrial flutter, independent of LA volume, left ventricular (LV) function, and clinical risk factors [7]. Despite the clear correlation between impaired reservoir deformation and AF, determinants of all phases from both the left and, specially, the right atria (RA) in patients with paroxysmal AF are unclear [8].

In this sub-study of the prospective, observational, multicenter “The identification of a risk profile to guide atrial fibrillation therapy (AF-RISK)” study [9], we aimed to accomplish the following two objectives: 1.) to identify the underlying comorbidities associated with reservoir, conduit and contractile phases of both atria, and 2.) to assess strain change after one year follow-up based on underlying comorbidities in patients with paroxysmal AF.

2. Methods

2.1. Study design

This is an ancillary sub-study of “The identification of a risk profile to guide atrial fibrillation therapy (AF-RISK)” study. AF-RISK was a multicenter, prospective study to assess AF progression rate, clinical, echocardiographic factors, and blood biomarkers associated with AF progression in patients with a short history of AF, and the association of AF progression with cardiovascular morbidity and mortality. Details are outlined elsewhere [9]. AF-RISK was performed in The Netherlands (University Medical Centre Groningen and the Maastricht University Medical Centre +). The study was performed in concordance with the Declaration of Helsinki, was approved by the institutional review boards, and was registered on [ClinicalTrials.gov](https://clinicaltrials.gov) (identifier NCT01510197). All patients gave written informed consent.

2.2. Study population

Patients with a short history of paroxysmal AF were consecutively and prospectively enrolled for AF-RISK between March 2009 and April 2016 in the University Medical Center Groningen (UMCG) and the Maastricht University Medical Center (MUMC+), the Netherlands. Inclusion criteria for paroxysmal AF were time since diagnosis < 2 years, or < 3 years in case of ≤ 2 AF episodes of ≤ 48 h per month terminating spontaneously. General exclusion criteria were a history of heart failure > 3 years; a history of severe valvular disease; acute coronary syndrome (ACS) within the previous month; AF classified as post-operative; or a contra-indication for oral anticoagulation. All patients received treatment focused on rhythm control according to the AF guidelines [10]. This treatment initially included causal treatment of underlying (heart) disease, adequate rate control therapy and initiation of antiarrhythmic drugs (AAD) in case of (frequent) symptomatic AF recurrences. At inclusion, patients’ demographics and clinical characteristics were collected. Standard physical examination was performed. Additional examination at baseline consisted of ECG, blood sampling, 24-h Holter-monitoring, and exercise test.

For this sub-study, 344 patients with available transthoracic echocardiography (TTE) during sinus rhythm at baseline were studied. TTE during sinus rhythm at approximately 1-year follow-up was available in 298 patients, of which 225 LA strain (LAS) and 159 RA strain (RAS) analyses were available to assess progression (**Supplementary Fig. 1**).

2.3. Transthoracic echocardiography

Standard TTE was performed according to the recommendations of

the European Association of Cardiovascular Imaging (EACVI), using commercially available ultrasound systems with phased array transducers (Vivid 5, Vivid 7 or Vivid E9, Vivid E95 scanner, GE Vingmed Ultrasound AS, Horten, Norway). Images were acquired in left lateral decubitus position and recorded as ECG-gated digital loops and stored for offline analysis. Because the objective of the main study did not include investigating speckle-tracking echocardiography (STE), image acquisition was not specifically optimized for this purpose (mean frame rate 51 (SD 8) Hz). Atrial and ventricular dimensions, and valvular function were measured according to the EACVI guidelines [11]. Systolic left ventricular ejection fraction (LVEF) was measured using the Simpson biplane method of discs.

2.4. Speckle-tracking echocardiography

All echocardiography recordings were anonymized and transferred to a core-lab facility for further offline analysis. Longitudinal strain assessment of the LA, RA and LV was performed during one corresponding cardiac cycle in sinus rhythm. Strain analysis was conducted offline by one experienced observer blinded to clinical data, using dedicated vendor-specific software (EchoPAC, GE Healthcare). Strain analysis was performed during sinus rhythm. LV global longitudinal strain (GLS) was analyzed in the apical two-, three- and four-chamber views using the 18-segment model. LAS and RAS were assessed in apical four-chamber view only. The regions of interest were manually outlined by marking the endocardial and epicardial borders in the LV end-systolic frame. End-systole was automatically defined by the software. The software automatically tracks myocardial speckle patterns frame-by-frame during one cardiac cycle (RR-interval). Suboptimal tracking, considered by either visual or automated assessment, was manually adjusted by redrawing the region of interest. If suboptimal tracking persisted despite multiple attempts, the concerning region of interest was eliminated from analysis. For all available strain analysis, the raw data were stored. An example of the LAS analysis is shown in **Supplementary Fig. 2**.

LAS was determined during reservoir phase (LASr) and during active contraction phase (LASct). LAS during conduit phase (LAScd) was calculated from LASr minus LASct. RAS was determined in a similar fashion for reservoir phase (RASr), contraction phase (RASct) and conduit phase (RAScd). For the left ventricle, we measured GLS defined as peak negative strain. GLS was measured in the average curve combining all segmental curves, if ≥ 12 available. If less than 12 segmental strain curves were available, GLS was not thought to be representative and was therefore excluded. All strain parameters were defined conform to the EACVI consensus document [12].

2.5. Covariate definitions

Total AF history was defined as time from first documented AF episode till inclusion. Hypertension was defined as a systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg, or by the use of antihypertensive drugs. Diabetes mellitus was defined as history of diabetes or use of anti-diabetic drugs. Clinical presentation of heart failure was defined as left ventricular ejection fraction (LVEF) $\leq 45\%$ at baseline or LVEF > 45% with symptoms associated with heart failure (New York Heart Association functional class II or III) or previous hospitalization for heart failure. Kidney dysfunction was defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m². The eGFR was calculated using modification of diet in renal disease formula: $175 \times (\text{serum creatinine} \times 0.0113)^{-1.154} \times \text{age}^{-0.203} \times 0.742$ if female). The ratio of weight to height squared (kg/m²) was used for calculation of body mass index (BMI).

The number of comorbidities is defined as the sum of the presence of the following comorbidities, awarded each a point: hypertension, coronary artery disease, age > 65 years, diabetes mellitus, BMI > 25 kg/m², moderate to severe mitral valve regurgitation, or kidney dysfunction.

Values of left atrial volume indexed (LAVI) ≥ 34 ml/m² were considered abnormal. Values of right atrial volume indexed (RAVI) ≥ 30 ml/m² were considered abnormal.

2.6. Statistical analysis

Continuous variables with normal distribution are expressed as mean and standard deviation (SD), otherwise as median with interquartile range (IQR). Categorical variables are presented as observed number with percentage. Continuous variables were compared using independent Student's *t*-test or the Mann-Whitney *U* test, as appropriate. To assess the trend of strain measures over the number of comorbidities, one-way ANOVA was used. For categorical variables Chi-square or Fisher's exact test were used to evaluate differences. Univariate and multivariate logistic regression were performed to establish association between comorbidities echocardiographic parameters. Paired *t*-test was used to assess changes of strain measures during approximately 1-year follow-up. A two-tailed value of *p* < 0.05 was considered statistically significant. Software R was used to perform analysis.

3. Results

Mean age of the population was 58 (SD 12) years and 137 patients were women (40%). The median history of AF at baseline was 5 [2–18] months, 182 patients had heart failure (52%; 2% heart failure with reduced LVEF) and 272 had hypertension (79%) (Table 1).

3.1. Individual and combined comorbidities and atrial strain

In total, echocardiographic studies were available in 344 patients with paroxysmal AF. Strain analysis by STE was feasible in the LA in 309 (90%) patients, in the RA in 253 (74%) patients and in the LV in 321 (93%) patients. The echocardiographic baseline characteristics are presented in Table 1.

Assessing the relation between individual comorbidities and atrial strain, BMI > 25 kg/m² was associated with lower strain in both atria throughout all phases. Age > 65 years and diabetes were associated with lower strain values of both atria, except for RASct (Supplementary Table 1).

Patient characteristics were evaluated by the combined number of comorbidities as 0, 1, 2 and 3 or more (Table 1). Patients with more

Table 1

Clinical and echocardiographic baseline characteristics presented for total population and stratified according to number of comorbidities.

	Total population (n = 344)	Number of comorbidities				p
		0 (n = 27)	1 (n = 87)	2 (n = 131)	≥ 3 (n = 99)	
Clinical characteristics						
Age, years	58 (SD 12)	46 (SD 13)	53 (SD 12)	57 (SD 10)	67 (SD 8)	<0.001
Women, n (%)	137(40)	11(41)	34(39)	41(31)	51(52)	0.022
History of AF, months (range)	5(2–18)	3(2–12)	5(2–19)	6(2–19)	6(2–18)	0.573
Follow up time, months	13.9 (SD 2.0)	15.0 (SD 3.3)	13.9 (SD 1.9)	13.7 (SD 1.8)	13.9 (SD 1.7)	0.032
Heart failure, n (%)	182 (53)	9 (33)	44 (51)	75 (57)	54 (55)	0.142
HFpEF, n (%)	174 (51)	9 (33)	44 (51)	70 (53)	51 (52)	0.299
HFrEF, n (%)	8 (2)	0 (0)	0 (0)	5 (4)	3 (3)	0.239
Hypertension, n (%)	272 (79)	0 (0)	47 (54)	127 (97)	98 (99)	<0.001
Diabetes, n (%)	29 (8)	0 (0)	2 (2)	1 (1)	26 (26)	<0.001
Coronary artery disease, n (%)	18 (5)	0 (0)	1 (1)	0 (0)	17 (17)	<0.001
Peripheral artery disease, n (%)	8 (2)	0 (0)	0 (0)	3 (2)	5 (5)	0.114
TIA or stroke, n (%)	18 (5)	0 (0)	3 (3)	9 (7)	6 (6)	0.408
BMI, (kg/m ²)	27.6 (SD 5.0)	22.6 (SD 1.7)	25.7 (SD 4.6)	28.5 (SD 5.0)	29.5 (SD 4.3)	<0.001
Overweight, n (%)	223 (65)	0 (0)	31 (36)	102 (78)	90 (91)	<0.001
Kidney dysfunction, n (%)	35 (10.2)	0 (0.0)	0 (0.0)	5 (3.8)	30 (30.3)	<0.001
Mitral valve regurgitation, n (%)	3 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.0)	0.058
EHRA Score, n (%)						0.301
I	94(27)	6(22)	28(32)	28(21)	32(32)	
II	203(59)	18(67)	44(51)	86(65)	54(55)	
III	47(14)	3(11)	15(17)	17(13)	13(13)	
CHA ₂ DS ₂ -VASc score ^a	1.5 (SD 1.4)	0.4 (SD 0.5)	0.8 (SD 0.8)	1.3 (SD 1.1)	2.9 (SD 1.3)	<0.001
Echocardiography						
LAVI, mL/m ²	32 (SD 9)	25 (SD 9)	30 (SD 8)	33 (SD 10)	34 (SD 9)	<0.001
RAVI, mL/m ²	35 (SD 12)	33 (SD 9)	34 (SD 12)	36 (SD 13)	35 (SD 11)	0.507
LV ejection fraction, %	57 (SD 4)	58 (SD 2)	58 (SD 2)	57 (SD 4)	57 (SD 4)	0.027
LV mass index, g/m ²	81 (SD 18)	70 (SD 19)	77 (SD 15)	84 (SD 20)	83 (SD 17)	0.001
e'	10 (SD 2.8)	14 (SD 3.6)	11 (SD 2.6)	10 (SD 2.4)	8 (SD 1.9)	<0.001
E/A ratio, (range)	1.1(0.9–1.4)	1.3(1.1–1.6)	1.1(1.0–1.4)	1.0(0.9–1.3)	1.0(0.8–1.2)	0.001
E/e', (range)	6.9(5.8–8.8)	5.5(4.7–6.1)	6.6(5.4–7.9)	6.8(5.8–8.1)	8.5(6.7–10.3)	<0.001
Speckle-tracking echocardiography						
LA strain, %						
Reservoir	34.0 (SD 12.6)	46.2 (SD 10.3)	39.0 (SD 10.9)	33.0 (SD 10.6)	27.2 (SD 10.5)	<0.001
Conduit	18.2 (SD 9.2)	27.9 (SD 9.6)	21.9 (SD 9.7)	15.3 (SD 8.1)	13.5 (SD 6.3)	<0.001
Contraction	15.7 (SD 7.2)	18.3 (SD 7.5)	17.1 (SD 6.7)	15.8 (SD 7.5)	13.6 (SD 6.7)	0.004
RA strain, %						
Reservoir	44.5 (SD 14.0)	53.7 (SD 12.5)	46.2 (SD 13.0)	44.4 (SD 14.4)	39.7 (SD 13.4)	<0.001
Conduit	25.0 (SD 10.4)	32.3 (SD 9.6)	26.5 (SD 10.3)	24.6 (SD 10.2)	21.2 (SD 9.3)	<0.001
Contraction	19.6 (SD 8.2)	21.5 (SD 8.3)	19.7 (SD 8.2)	19.7 (SD 8.2)	18.5 (SD 8.2)	0.470
GLS, %	−19.3 (SD 2.9)	−20.2 (SD 1.9)	−20.1 (SD 2.5)	−19.8 (SD 3.1)	−18.6 (SD 2.9)	0.002

AF = atrial fibrillation; EHRA = European Heart Rhythm Association symptom classification; LAVI = left atrial volume indexed; RAVI = right atrial volume indexed.

^a The CHA₂DS₂-VASc score assesses thromboembolic risk. C, congestive heart failure/LV dysfunction; H, hypertension; A₂, age ≥ 75 years; D, diabetes mellitus; S₂, stroke/transient ischaemic attack/systemic embolism; V, vascular disease; A, age 65–74 years; Sc, sex category (female sex).

comorbidities had higher LAVI (p for trend <0.001) and had lower LAS and RAS, except for the RASct (p for trend 0.47). Strain decreased proportionally to the number of comorbidities, predominantly in reservoir and conduit phases of both atria (Table 1 and Fig. 1). After adjusting for atrial volumes, a higher number of comorbidities was most strongly associated with a decrease in LAScd among all strain parameters, (OR per 1% LAScd decrease 0.92, 95%CI:0.88–0.96) (Supplementary Table 2).

3.2. Atrial dilation and atrial function

All LAS parameters were correlated with LAVI, and all RAS parameters were correlated with RAVI (Supplementary Table 3). However, patients with lower LASr had more comorbidities irrespective of LAVI (LAVI < 34 ml/m², 1.9 (SD 1.0) vs 1.3 (SD 1.0), $p = 0.002$; LAVI ≥ 34 ml/m², 2.4 (SD 1.2) vs 1.3 (SD 1.0), $p = 0.007$). The same was observed in patients with lower LAScd (Table 2). Patients with lower RASr had more comorbidities irrespective of RAVI (Table 2).

3.3. Progression of atrial strain impairment

At follow-up LAS was available in 225 patients and RAS in 159 patients (Supplementary Fig. 1). Patients with 1 to 2 comorbidities showed a further decrease in LAS and RAS in almost all phases at 14 [13–17] months follow-up. Conversely, patients with 3 or more comorbidities had less or no further progressive impairment of LA and RA function within one year follow-up (Table 3).

4. Discussion

Our study shows that the presence of individual and combined comorbidities is associated with a decrease in atrial function measured by STE in patients with paroxysmal AF. Importantly, these findings were independent of indexed atrial volumes, suggesting that LAS and RAS assessed by STE may be early markers of the atrial remodelling process as a result of concomitant comorbidities even before the atria start to dilate. Furthermore, follow-up data showed that impairment in atrial function progresses after one year in patients with few comorbidities.

4.1. Atrial cardiomyopathy

Exposure to comorbidities has been shown to contribute to a progressive atrial remodelling process, which is considered to be an interplay of structural, electrical and functional alterations of the atria [4]. Structural remodelling is characterized by atrial dilatation, cardiomyocyte hypertrophy and increased extracellular matrix formation, which influences electrical remodelling by increasing local conduction disturbances and maintenance of AF [11,13]. LAVI is well-embedded in the routine echocardiographic examination as a surrogate for structural atrial remodelling [14] and has been shown to be associated with adverse cardiovascular outcomes in various cardiac diseases. However, functional atrial remodelling is gaining more interest as atrial strain analysis using STE, which is a feasible and reproducible technique [15].

In this study, we demonstrated that atrial dysfunction is associated with atrial dilatation and both parameters are correlated with the cardiovascular risk profile, underlining the interplay of structural and functional alterations within the atrial remodelling. However, within patients with normal sized atria, reservoir and conduit strain were able to further differentiate between the number of comorbidities. These findings suggest that functional deterioration in patients with normal sized atria may represent an early alteration in the remodelling process due to concomitant comorbidities, before the atria start to dilate.

4.2. Cardiovascular risk profile

In this study we focused on functional atrial remodelling within the

concept of atrial cardiomyopathy. Atrial function comprises the reservoir, conduit and contractile phase, all together contributing to ventricular filling and function. In the current literature, there is no consensus about the best atrial strain parameter for clinical use. Although atrial function and ventricular performance are interdependent, the interaction differs throughout the atrial phases and this may influence the usability of the individual parameters for different purposes [16]. Until now, LASr is the best studied parameter in patients with declined atrial function, incidence of AF and outcomes [6,7]. Even less is known about RAS, although RA function has previously been introduced as an important early marker for cardiac impairment, especially in pressure or volume overload of the right ventricle, including heart failure, coronary artery disease and AF itself [8].

We demonstrated that all three LA and RA phasic strain functions are affected by the presence of both individual and combined comorbidities. Increased BMI is associated with deteriorating function throughout the entire LA and RA cycle. Additionally, history of diabetes and increasing age are determinants associated with deteriorating function throughout almost the entire LA and RA cycle, except for RASct. On the other hand, presence of coronary artery disease and kidney dysfunction share common associations with decreased LASr and LAScd. The greater influence of comorbidities on LAS reservoir and conduit function may be explained by the more prominent influence of cardiac loading conditions and LV performance, whereas LA contractile function is determined by intrinsic atrial function [17]. LA contractile function has potential to compensate for early LA conduit failure, which could explain the lack of association of decreased strain during the contractile phase with the number of comorbidities in this population with a relatively short AF history [17,18].

Recently, normal reference values were demonstrated for LA strain based on measurements in healthy subjects [19]. Interestingly, the mean LA strain values observed in the subgroup of patients with paroxysmal AF without any comorbidities or with one comorbidity in our cohort correspond with the normal reference values for LA strain observed in healthy subjects suggesting that the cardiovascular risk profile is an important factor in the development of atrial dysfunction and maybe even atrial cardiomyopathy. Normal values from RA strain in patients without comorbidities were consistent with a previous study [20], however, these values were obtained using 3D techniques.

4.3. Progression of atrial dysfunction

In patients with paroxysmal AF with a low number of comorbidities, our results show that atrial function progressively decreases after 1-year follow-up. This observation supports the concept, that AF itself contributes to its own perpetuation (“AF begets AF”), particularly if no other comorbidities and preexisting remodelling processes are present [21]. In contrast, in patients with a higher number of comorbidities, atrial function did not further decline or to a lesser extent, within one year of follow-up, suggesting that patients with a higher number of comorbidities already show a preexisting significant atrial remodelling at baseline. Theoretically, early treatment of concomitant comorbidities with a proactive approach may be required as an important component of the early management of patients paroxysmal AF [22]. Additionally, patients with paroxysmal AF with few obvious comorbidities may profit from early rhythm control to prevent the early progression in atrial function impairment observed in this study [14].

4.4. Clinical implications

Atrial strain is an emerging topic within world-wide research setting. Atrial strain has been shown prognostic value in both patients with AF [23] and the general population, predicting cardiovascular mortality, morbidity, and for example development of dementia [24,25]. In this observational study we focused on the determinants of atrial strain and showed an association of atrial strain with individual and combined

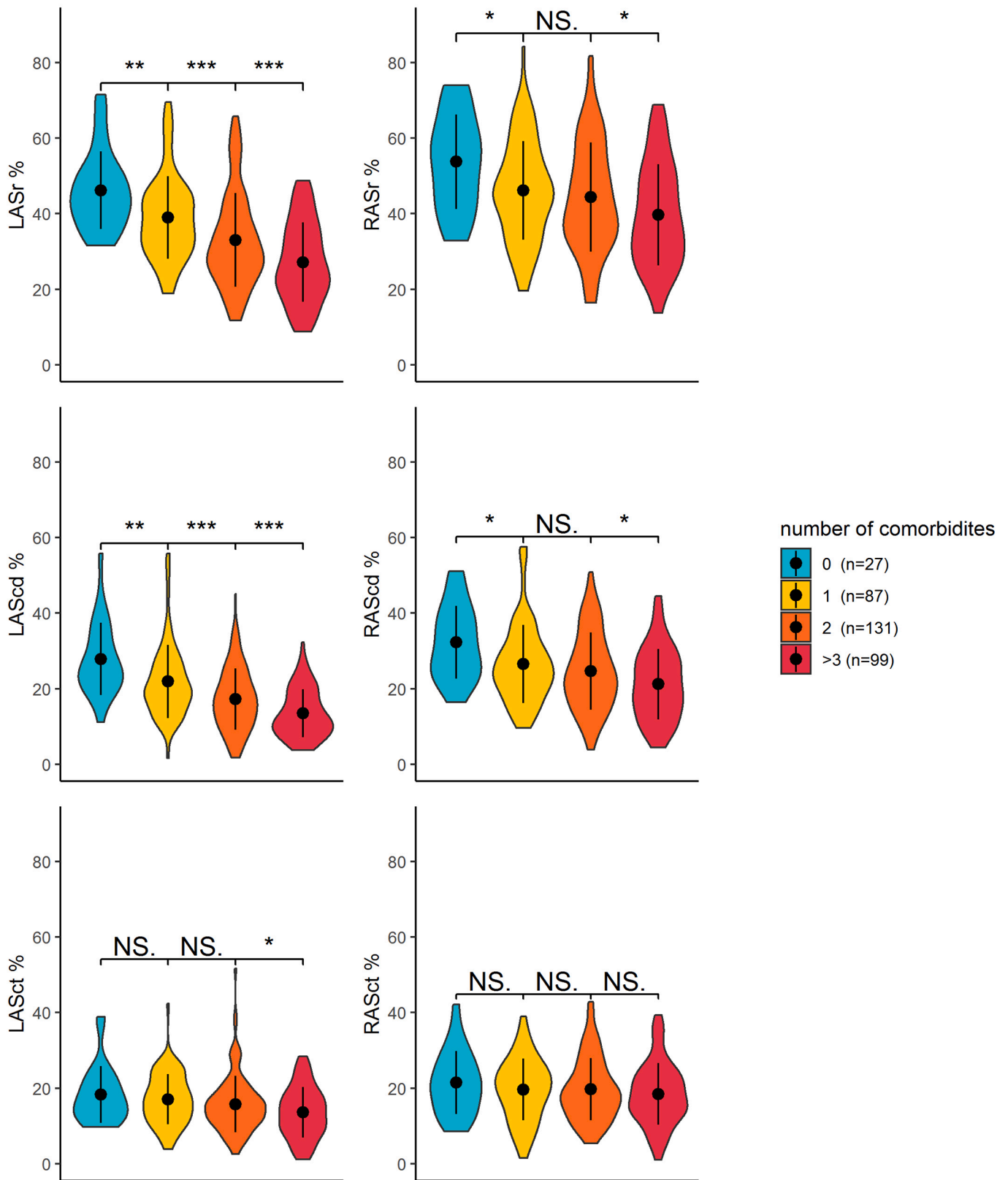


Fig. 1. Left and right atrial strain parameters grouped by the number of comorbidities.

Number of comorbidities was determined by awarding a point to each of the following, hypertension, heart failure, age > 65 years, diabetes mellitus, coronary artery disease, BMI > 25 kg/m², moderate to severe mitral valve regurgitation and kidney dysfunction (eGFR < 60 ml/min/1.73m²). Y-axis expresses percentage of deformation measure by 2D speckle-tracking echocardiography. Point within the graph expresses mean and lines determine standard deviation. LASr = left atrial reservoir strain; LAScd = left atrial conduit strain; LASct = left atrial contraction strain; RASr = right atrial reservoir strain; RAScd = right atrial conduit strain; RASct = right atrial contraction strain. NS = not significant, *p < 0.05, **p < 0.01, ***p < 0.001.

Table 2
Comorbidities compared by LAVI for strain parameters of both atria. LAS and RAS cut-off values were determined based on the median in this population.

		Normal LAVI (<34 ml/m ²)			Dilation LAVI (>34 ml/m ²)		
		LA reservoir strain					
		<33.1	>33.1	<i>p</i>	<33.1	>33.1	<i>p</i>
		(<i>n</i> = 65)	(<i>n</i> = 106)		(<i>n</i> = 72)	(<i>n</i> = 37)	
Comorbidities		2.1 (SD 1.0)	1.5 (SD 1.0)	<0.001	2.7 (SD 1.2)	1.7 (SD 1.0)	<0.001
		LA conduit strain					
		<17.7	>17.7	<i>p</i>	<17.7	>17.7	<i>p</i>
		(<i>n</i> = 71)	(<i>n</i> = 100)		(<i>n</i> = 68)	(<i>n</i> = 41)	
Comorbidities		2.8 (SD 0.9)	1.4 (SD 1.0)	<0.001	2.8 (SD 1.2)	1.7 (SD 0.9)	<0.001
		LA contraction strain					
		<15.1	>15.1	<i>p</i>	<15.1	>15.1	<i>p</i>
		(<i>n</i> = 67)	(<i>n</i> = 104)		(<i>n</i> = 73)	(<i>n</i> = 36)	
Comorbidities		1.8 (SD 1.2)	1.7 (SD 0.9)	0.720	2.5 (SD 1.2)	2.1 (SD 1.2)	0.132
		Normal RAVI (<30 ml/m ²)			Normal RAVI (>30 ml/m ²)		
		RA reservoir strain					
		<44.5	>44.5	<i>p</i>	<44.5	>44.5	<i>p</i>
		(<i>n</i> = 40)	(<i>n</i> = 50)		(<i>n</i> = 80)	(<i>n</i> = 72)	
Comorbidities		2.3 (SD 1.3)	1.7 (SD 1.3)	0.031	2.1 (SD 1.2)	1.6 (SD 1.0)	0.015
		RA conduit strain					
		<24.0	>24.0	<i>p</i>	<24.0	>24.0	<i>p</i>
		(<i>n</i> = 41)	(<i>n</i> = 49)		(<i>n</i> = 78)	(<i>n</i> = 74)	
Comorbidities		2.2 (SD 1.3)	1.7 (SD 1.3)	0.097	2.1 (SD 1.2)	1.6 (SD 1.0)	0.003
		RA contraction strain					
		<19.2	>19.2	<i>p</i>	<19.2	>19.2	<i>p</i>
		(<i>n</i> = 39)	(<i>n</i> = 51)		(<i>n</i> = 83)	(<i>n</i> = 69)	
Comorbidities		2.2 (SD 1.2)	1.8 (SD 1.4)	0.137	2.0 (SD 1.8)	1.7 (SD 1.0)	0.147

LA = left atrium; LAVI = left atrial volume indexed; RA = right atrium; RAVI = right atrial volume indexed. Comorbidities were calculated by awarding a point to each of the following comorbidities, hypertension, age > 65 years, diabetes, coronary artery disease, body mass index > 25 kg/m², kidney dysfunction (eGFR < 60 ml/min/1.73m²), and moderate or severe mitral valve regurgitation.

comorbidities, irrespective of atrial dilatation. As determination of atrial strain provides additional information about the stage of atrial remodelling in patients with paroxysmal AF beyond atrial volume index, this technique may have potential to be incorporated in routine echocardiographic assessment. Impaired atrial function should trigger a structured assessment of comorbidities and may represent an interesting measure to guide future risk factor and comorbidity management programs in AF patients. Whether atrial function improves and patients benefit from combined risk factor modification programs or early rhythm control interventions warrants further research.

4.5. Limitations

In this study, we focused solely on patients with paroxysmal AF, therefore we cannot translate these results directly to patients with an increased number of comorbidities in absence of AF nor in patients with advanced AF stage. AF is a heterogeneous disease and unidentified phenotypes may dilute specific differences among patients. The number of comorbidities is based on previous studies, other combination of comorbidities could possibly lead to other results. Because there is no long-term follow-up available at this moment, we are not able to study the changes of LA and RA function over time, nor clinical progression or outcome. Due to the observational nature of AF-RISK, we cannot

Table 3
Changes in atrial strain parameters after 1-year follow-up by number of comorbidities.

		n	Baseline	Follow-up 1-year	MD	<i>p</i>
0 Comorbidities						
LA	reservoir	20	46.2 (SD 10.3)	39.3 (SD 16.4)	6.32	0.146
	conduit		27.9 (SD 9.6)	27.0 (SD 14.3)	1.23	0.696
	contraction		18.3 (SD 7.5)	12.3 (SD 5.4)	5.09	0.003
RA	reservoir	18	53.7 (SD 12.5)	41.5 (SD 14.9)	10.01	0.024
	conduit		32.3 (SD 9.6)	25.6 (SD 10.7)	5.69	0.070
	contraction		21.5 (SD 8.3)	15.9 (SD 6.9)	4.32	0.058
1 Comorbidities						
LA	reservoir	62	39.0 (SD 10.9)	34.9 (SD 10.7)	4.28	0.008
	conduit		21.9 (SD 9.7)	19.7 (SD 7.6)	2.25	0.041
	contraction		17.1 (SD 6.7)	15.2 (SD 7.4)	2.04	0.036
RA	reservoir	52	46.2 (SD 13.0)	43.4 (SD 13.5)	4.60	0.027
	conduit		26.5 (SD 10.3)	26.0 (SD 9.9)	0.85	0.599
	contraction		19.7 (SD 8.2)	17.5 (SD 7.5)	3.74	0.003
2 Comorbidities						
LA	reservoir	88	33.0 (SD 10.6)	31.4 (SD 10.9)	2.44	0.112
	conduit		15.3 (SD 8.1)	16.2 (SD 7.7)	1.44	0.142
	contraction		15.8 (SD 7.5)	15.1 (SD 6.4)	0.99	0.223
RA	reservoir	54	44.4 (SD 14.4)	37.5 (SD 12.0)	7.70	<0.001
	conduit		24.6 (SD 10.2)	21.6 (SD 9.6)	3.79	0.005
	contraction		19.7 (SD 8.2)	16.0 (SD 6.0)	3.91	<0.001
3 or more Comorbidities						
LA	reservoir	55	27.2 (SD 10.5)	26.5 (SD 8.4)	2.58	0.107
	conduit		13.5 (SD 6.3)	13.7 (SD 6.4)	0.38	0.713
	contraction		13.6 (SD 6.7)	12.8 (SD 5.1)	2.20	0.023
RA	reservoir	35	39.7 (SD 13.4)	38.2 (SD 12.9)	3.21	0.256
	conduit		21.2 (SD 9.3)	18.1 (SD 7.8)	3.52	0.016
	contraction		18.5 (SD 8.2)	20.1 (SD 8.6)	-0.31	0.870

Comorbidities were calculated by awarding a point to each of the following comorbidities, hypertension, heart failure, age > 65 years, diabetes mellitus, coronary artery disease, BMI > 25 kg/m², moderate to severe mitral valve regurgitation and kidney dysfunction (eGFR < 60 ml/min/1.73m²). LA = left atrium; MD = mean difference; RA = right atrium.

determine causal effects.

5. Conclusions

In patients with paroxysmal AF, individual and combined comorbidities are related to lower LA and RA strain. In patients with no or few comorbidities, impairment in atrial function progresses during one year of follow-up. Whether comorbidity management and early rhythm control prevents or even reverses decreases in atrial strain function warrants further study.

Disclosures

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2022.05.044>.

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