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Evaluating subclinical left ventricular and left atrial dysfunction in idiopathic atrial fibrillation: A speckle-tracking based strain-analysis

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ABSTRACT

Objective: A subset of patients with atrial fibrillation (AF) presents without established AF risk factors and normal left ventricular (LV) systolic function, called idiopathic AF (IAF). Traditionally, echocardiography derived LV dimensions and ejection fraction (EF) are used to exclude LV dysfunction in IAF, but their sensitivity is limited. Our objective is to evaluate the presence of subtle alterations in LV function despite normal LVEF in patients with IAF compared to healthy controls, using speckle-tracking echocardiography (STE) based global longitudinal strain (GLS).

Methods: Standard transthoracic echocardiography was performed in 80 patients with IAF and 129 healthy controls. Patients with overt cardiac disease as well as known established AF risk factors were excluded. STE analysis was performed to assess GLS of the LV, and left atrial strain (LAS).

Results: LVEF was normal and comparable between patients with IAF and healthy controls (63 ± 4% for both groups; $p = 0.801$). Mean GLS was within normal limits for both groups but statistically significantly more negative in patients with IAF (−20.6 ± 2.5% vs. -19.7 ± 2.5%; $p = 0.016$), however not when indexed for ventricular cycle length ($p = 0.784$). No differences in LA volume or non-indexed LAS were seen in patients with IAF compared to healthy controls.

Conclusions: In this selected group of IAF patients, STE did not detect any overt LV or LA dysfunction compared to healthy controls. Thus, IAF occurred in these patients not only in the absence of established AF risk factors but also without evidence of ventricular or atrial dysfunction.

1. Introduction

Atrial fibrillation (AF) is the most frequent arrhythmia. Most patients have relevant cardiovascular comorbidities that lead to or are associated with AF. Still, there is a small population where AF is thought to be 'idiopathic' (IAF), thus occurring in the absence of established AF risk factors and without overt (or detectable) structural heart disease [1]. Current AF guidelines recommend a structured work-up of patients with AF, including echocardiography to rule out any underlying disease such as valvular disease, left ventricular (LV) dysfunction and other structural alterations [2]. Nevertheless, the more thoroughly is searched, the more underlying disease can be identified. For example, coronary artery

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disease (CAD) is present in many patients, which has not yet been manifested in LV structural changes [3].

In general, the definition of IAF is based on classical echocardiographic measurements such as LV ejection fraction (EF) and LV dimensions. However, such volumetric parameters may just capture global changes in LV function which often occur late during the course of a disease, while subtle impairments in LV function could be missed [4]. Speckle-tracking echocardiography-derived (STE) global longitudinal strain (GLS) has been shown to identify subclinical changes in LV function and structure in a number of cardiac diseases and may, therefore, represent a better measurement to detect early and subtle alterations in LV function in IAF. Consequently, more detailed changes of LV function that cannot be captured by volumetric parameters alone, may fuel the discussion whether AF is primarily an atrial disease or a ventricular disease and being an early symptom of a cardiomyopathy.

Thus, we hypothesized that early-stage LV pathology, revealed by a subtle change of GLS, exists in patients with IAF, despite having a normal LVEF.

2. Methods

2.1. Original study population

The present study is an echocardiographic sub-analysis of patients with IAF and healthy controls based on a previously published matched case-control study [3]. For the initial study, participants were consecutively enrolled between January 2008 and March 2011 at the outpatient clinic of the Cardiology department in the Maastricht University Medical Center+, the Netherlands. Patients with IAF were recruited during work-up for prior to AF ablation. Healthy controls were patients who underwent additional examination for cardiovascular screening purposes, in absence of any cardiac complaints. Details of this previous study are outlined elsewhere. The study was approved by the institutional review board, and all patients gave written informed consent. As this study is a retrospective sub-analysis and rather hypothesis generating, there was no patient or public involvement during development of the research question. There was no prospective recruitment as analysis was done on an existing data base. In turn, results were presented during patient congresses of the Health Foundation Limburg by authors of this study.

2.2. Definition of current study population

For this current analysis, only participants with an available echocardiogram during sinus rhythm were eligible. In total, 80 patients with IAF (paroxysmal ($n = 78$) or persistent ($n = 2$)) and 129 healthy controls were included in this sub-analysis. Patients in the control group underwent coronary computed tomography for cardiovascular screening purposes. They had to be healthy (based on past medical history and known information) and had to have permanent sinus rhythm. More specifically, symptoms such as angina had to be absent and an abnormal stress test was never an indication for computed tomography. In the initial publication [3], patients and controls were matched based on sex, age at time of computed tomography (range of ±1 year), and the value of the PROCAM risk score (±2%).

Importantly, the following definition was applied for the inclusion of patients in order to be as restrictive as possible regarding underlying disease:

IAF and healthy controls were defined as the absence of any cardiovascular disease, including hypertension (defined as antihypertensive drug use, or systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg on CTA visit, or left ventricular hypertrophy [interventricular septum width > 10 mm, posterior wall width > 10 mm]), diabetes mellitus (fasting blood glucose >7.0 mmol/L), or hypercholesterolemia (total fasting cholesterol >7.0 mmol/L).

In addition, no history of CAD (i.e, typical exercise-related angina pectoris, exercise stress test with significant ST-segment depression if available, previous acute coronary syndrome, percutaneous or surgical coronary revascularization, or previous angiographically documented CAD), no significant renal dysfunction (calculated creatinine clearance <60 mL/min, Cockcroft and Gault formula), no congestive heart failure (left ventricular ejection fraction >55%), no previous stroke, no malignancy, no thyroid disease or pulmonary disease, and no evidence of structural cardiovascular disease on echocardiogram, including valvular heart disease and left ventricular hypertrophy as defined earlier.

2.3. Subgroup analysis

Subgroup analysis was performed, to pursue the phased diagnostic assessment in clinical practice, by a stepwise approach of excluding potential preliminary risk factors. Subgroup selection is shown in Fig. 1. The following exclusion criteria were applied successively per subgroup:

(1) *presence of (non-significant) coronary plaques;*
(2) *BMI ≥ 25 kg/m^2;*
(3) *use of medication potentially indicating underlying disease* (i.e. *statins (in both groups) or use of betablocker (only in healthy controls)). Of note, the use of betablockers is only excluded in healthy controls as this may be related to masked hypertension without known diagnosis.*

2.4. Transthoracic echocardiography

Standard transthoracic echocardiography was performed according to the guidelines using commercially available ultrasound systems (Sonos 5500, Philips Medical Systems, Best, the Netherlands). All images were acquired in the left lateral decubitus position and recorded as electrocardiographically gated digital loops and stored for offline analysis. Atrial and ventricular dimensions, and valvular function were assessed according to guidelines. LVEF was measured using the Simpson biplane method of discs.

2.5. Speckle-tracking echocardiography

Longitudinal strain analysis of the LV and LA was performed offline using vendor-independent software (TOMTEC-ARENA 2.20.10, TOMTEC Imaging Systems, Unterschleissheim, Germany). Only studies during sinus rhythm were assessed. GLS of the LV was measured in the apical two-, three-, and four-chamber images using an automated software tool (AutoLV© module). The separate views were labeled manually as the software does not recognize the images automatically. Automated contour detection provided standard LV strain parameters, including combined GLS (peak systolic strain based on the 18-segment model) and individual GLS values of the separate apical views. All automated contours were reviewed by two experienced readers (MvM, CK) for tracking quality. Readers were blinded to clinical data. Suboptimal automated tracking was manually corrected.

Left atrial strain (LAS) was assessed in the apical four-chamber view (A4CH) only, by two independent readers (MvM, HV) blinded to clinical data, using the manual software tool (2D-CPA). The regions of interest were manually outlined by marking the endocardial borders in the left ventricular end-systolic frame. End-systole was defined as the frame before mitral valve opening. The software automatically tracked myocardial speckle patterns frame-by-frame during one cardiac cycle (RR-interval) and generated an atrial strain curve. Atrial strain was determined during reservoir phase (LASr) and during active contraction phase (LASct) in accordance with the consensus document. Atrial strain during conduit phase (LAScd) was calculated from LASr minus LASct. Suboptimal tracking was manually adjusted. If suboptimal tracking persisted despite multiple attempts, the analysis was eliminated.

In addition, to adjust for difference in heartrate, both ventricular and atrial strain parameters were indexed with the square root of the ventricular cycle length (calculated RR-interval in seconds) (i.e. GLS/$\sqrt{}$(RR)

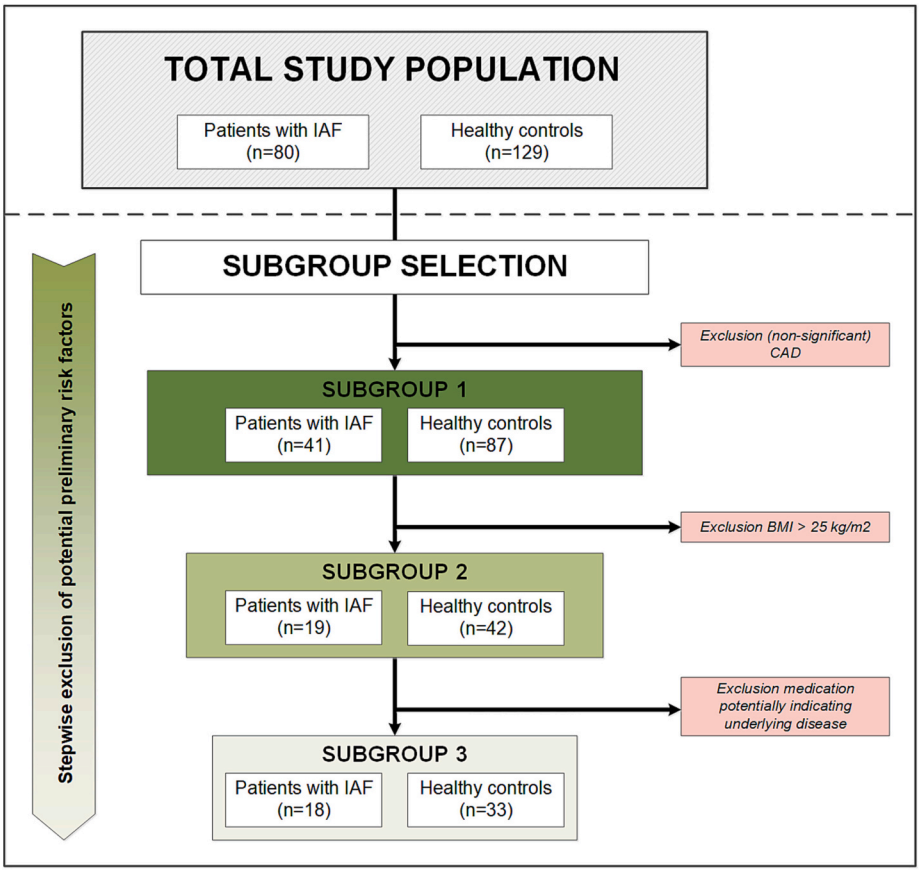

Fig. 1. Patient selection and subgroup classification.
CAD = coronary artery disease; IAF = idiopathic atrial fibrillation; BMI = body mass index.

and LAS/$\sqrt{}$(RR)) [5]. For the analyses, the lower limit of normal for (non-indexed) GLS was defined using a sex-specific vendor-independent value of −17% for males and − 18% for females. For (non-indexed) LAS we used sex- and vendor-independent lower limit of normal for the different phases, i.e. 26.1% for LASr, 12.0% for LAScd and 7.7% for LASct [6].

2.6. Statistical analysis

Continuous variables with normal distribution are expressed as mean ± 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. For categorical variables Chi-square or Fisher's exact test were used to evaluate differences. SPSS version 27.0 (SPSS Inc., Chicago, Illinois) was used for all statistical analyses. A two-tailed value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

In total, 80 consecutive patients with IAF and 129 healthy controls were included in this echocardiographic analysis. Baseline characteristics are presented in Table 1. Age and sex did not differ significantly between groups and the majority was male (64%). Both patients with IAF and healthy controls were free of other overt cardiac diseases (i.e. CAD, heart failure or other), thromboembolic complications, and diabetes. Healthy controls more often had a positive family history for CAD compared to patients with IAF (36% vs. 15%, $p = 0.001$). In addition, none of the subjects was diagnosed with COPD or sleep apnea syndrome. Only patient with IAF was diagnosed with peripheral artery disease previously. Furthermore, differences were seen in medication use according to treatment for AF, Table 1. In addition, patients with IAF had a lower baseline heart rate compared to healthy controls (60 ± 10 vs. 66 ± 9 bpm, $p < 0.001$), likely due to drugs use that lower heart rate. According to the definition of this study population, both patients with IAF and healthy controls did not use any ACE-inhibitors, angiotensin receptor blockers or diuretics.

3.2. Echocardiographic left ventricular characteristics

Between the two groups, there was no difference in LV function based on LVEF, Table 2. However, GLS was more negative in patients with IAF compared to healthy controls (−20.6 ± 2.5% vs. -19.7 ± 2.5%; $p = 0.016$), Fig. 2, and LV mass index was lower in patients with IAF compared to healthy controls (80 ± 14 vs. 88 ± 20 g/m^2, $p = 0.003$). In absolute numbers, 7 (9%) patients with IAF had an impaired GLS versus 24 (19%) healthy controls ($p = 0.051$). Heart rate during echocardiography was lower in patients with IAF compared to healthy controls (60 ± 10 vs. 66 ± 9 bpm; $p < 0.001$). When GLS was indexed for ventricular cycle length there was no difference between groups (GLS/$\sqrt{}$(RR) -20.7 ± 3.0% vs. −20.6 ± 2.5% respectively; $p = 0.784$).

3.3. Echocardiographic atrial characteristics

Between the two groups, there was no difference in indexed left atrial volume (LAVI) or non-indexed LAS throughout the three different phases, Table 2. In absolute numbers, patients with IAF (19 (24%)) had more often an impaired LASct compared to healthy control (15 (12%); $p = 0.021$). There was no statistically significant difference in numbers of

Table 1
Baseline characteristics.

	Patients with IAF ($n = 80$)	Healthy controls ($n = 129$)	p-value
Age (years)	55 ± 10	57 ± 10	0.143
Male sex	55(69)	79(61)	0.301
BSA	BSA 2.0 ± 0.2	1.9 ± 0.2	$p =$ 0.002
History			
Time since diagnosis (months)	23(6–66)	–	–
Peripheral artery disease	0(0)	1(1)	>0.99
Smoking	12(15)	25(20)	0.392
Family history of CAD	12(15)	47(36)	**0.001**
Physical examination			
BMI (kg/m^2)	26 ± 3	26 ± 3	0.362
Heartrate (bpm)	60 ± 10	66 ± 9	**<0.001**
Systolic blood pressure (mmHg)	125 ± 12	126 ± 10	0.287
Diastolic blood pressure (mmHg)	80 ± 11	80 ± 10	0.812
Blood sample			
Fasting blood glucose	5.4 ± 0.7	5.6 ± 0.8	0.062
LDL	3.6 ± 0.9	3.5 ± 1.0	0.689
HDL	1.2 ± 0.3	1.3 ± 0.4	**0.036**
GFR	91 ± 18	89 ± 17	0.674
NT-proBNP	7(3–13)	6(3–13)	0.891
Medication			
β-Blocker	27(34)	23(18)	**0.008**
Verapamil/Diltiazem	8(10)	1(1)	**0.002**
Digoxin	7(9)	0(0)	**0.001**
Antiarrhythmics			
Sotalol	23(29)	0(0)	**<0.001**
Flecainide	22(28)	0(0)	**<0.001**
Disopyramide	2(3)	0(0)	0.145
Propafenone	2(3)	0(0)	0.145
Amiodarone	5(6)	0(0)	**0.007**
ACE-inhibitor	0(0)	0(0)	–
Angiotensin Receptor Blocker	0(0)	0(0)	–
Diuretics	0(0)	0(0)	–
Statins	9(11)	14(11)	0.929

Bold denotes statistical significance.

Table 2
Echocardiographic characteristics.

	Patients with IAF (n = 80)	Healthy controls (n = 129)	p-value
Heart rate (bpm)	60 ± 10	66 ± 9	**<0.001**
Ventricular cycle length (ms)	1014 ± 178	925 ± 144	**<0.001**
BSA	2.0 ± 0.2	1.9 ± 0.2	**0.002**
Echocardiography			
LVEF (%)	63 ± 4	63 ± 4	0.801
LV mass index (g/m^2)	80 ± 14	88 ± 20	**0.003**
LAVI (ml/m^2)	36 ± 10	33 ± 9	0.090
Speckle-tracking echocardiograph			
Left ventricle			
GLS (%)	-20.6 ± 2.5	−19.7 ± 2.5	**0.016**
A4CH (%)	−21.4 ± 2.5	−20.4 ± 2.8	**0.015**
A2CH (%)	−21.0 ± 2.4	−20.4 ± 2.6	0.109
ALAX (%)	−21.1 ± 2.8	−20.0 ± 2.8	**0.013**
GLS/$\sqrt{}$(RR)	−20.7 ± 3.0	−20.6 ± 2.5	0.784
Left atrium			
LASr (%)	34 ± 11	36 ± 12	0.118
LASr/$\sqrt{}$(RR)	34 ± 12	38 ± 13	**0.011**
LAScd (%)	21 ± 7	22 ± 9	0.246
LAScd/$\sqrt{}$(RR)	21 ± 8	23 ± 10	0.108
LASct (%)	13 ± 8	14 ± 7	0.290
LASct/$\sqrt{}$(RR)	12 ± 7	15 ± 7	**0.020**
Computed tomography			
Coronary plaque burden	39(49)	42(33)	**0.020**
Calcified plaque	21(26)	24(19)	0.191
Soft plaque	16(20)	11(9)	**0.016**
Mixed plaque	22(28)	26(20)	0.220
Significant plaque	4(5)	1(1)	0.072
Agatston score (coronary)	0(0–27)	0(0–4)	0.069

A2CH = apical 2-chamber view; A4CH = apical 4-chamber view; ALAX = apical long axis view; BSA = body surface area; GLS = global longitudinal strain; LAScd = left atrial conduit strain; LASct = left atrial contractile strain; LASr = left atrial reservoir strain; LAVI = left atrial volume index. Bold denotes statistical significance.

impaired LASr and LAScd between patients with IAF compared to healthy controls (for LASr respectively 17 (21%) vs. 22 (17%), $p = 0.449$; for LAScd respectively 8 (10%) vs. 11 (9%), $p = 0.719$). When indexed for ventricular cycle length, LAS during reservoir and active contraction phase were statistically significant lower in patients with IAF compared to healthy controls (LASr/$\sqrt{}$(RR) 34 ± 12 vs. 38 ± 13 respectively, $p = 0.011$); LASct/$\sqrt{}$(RR) 12 ± 7 vs. 15 ± 7 respectively, $p = 0.020$).

3.4. Subgroup analysis

Echocardiographic results according to subgroup classification are shown in Table 3, and the selection process with applied exclusion criteria is shown in Fig. 1. In all subgroups, patients with IAF are statistically significant younger compared to healthy controls. Mean GLS remains within normal limits in all groups when applying further differentiation by excluding potential preliminary risk factors. GLS and LAS, indexed for cycle length, do not show any statistically significant difference between patients with IAF and healthy controls in the subgroup analysis. The statistically significant difference in LV mass index holds true when excluding (non-significant) coronary plaques, but not when excluding increased BMI. Regarding the third subgroup analysis excluding use of medication potentially indicating underlying disease, we saw the following numbers of antiarrhythmic drugs: β-blocker $n = 7$ (IAF) vs. 0 (HC), $p \leq 0.001$; verapamil/diltiazem $n = 1$ (IAF) vs. 0 (HC), not significant (n.s.); digoxin $n = 2$ (IAF) vs. 0 (HC), $p = 0.051$; sotalol $n = 3$ (IAF) vs. 0 (HC), $p = 0.016$; flecainide n = 2 (IAF) vs. 0 (HC), $p = 0.051$; disopyramide n = 1 (IAF) vs. 0 (HC), n.s.; propafenone n = 1 (IAF) vs. 0 (HC), n.s.; amiodarone n = 1 (IAF) vs. o (HC), n.s.

4. Discussion

This study does not demonstrate any LV dysfunction in a selected group of patients with IAF using extensive echocardiographic phenotyping by means of STE. GLS was within normal limits in patients with IAF, and comparable with healthy controls when indexed for cycle length. On the other hand, indexed LAS during the reservoir and active contraction phase were lower in patients with IAF, which could suggest early atrial dysfunction. However, when adjusting for additional potential preliminary risk factors, this did not hold true anymore. Overall, these findings do not support the hypothesis that subtle ventricular dysfunction is leading to IAF.

4.1. In-depth cardiovascular imaging

The most recent guidelines for the diagnosis and management of AF state 'lone AF' as a historical descriptor that should be abandoned, as increasing knowledge about the pathophysiology of AF suggests that in every patient a cause is present [2,7]. This underlines the importance of a comprehensive cardiovascular assessment. In daily clinical practice, management of AF is inextricably accompanied with examination and treatment of associated cardiovascular disease. Nevertheless, there is still a small number of patients that present at young age in absence of any apparent comorbidities or underlying cardiovascular disease detectable with the current imaging modalities. Therefore, it is of

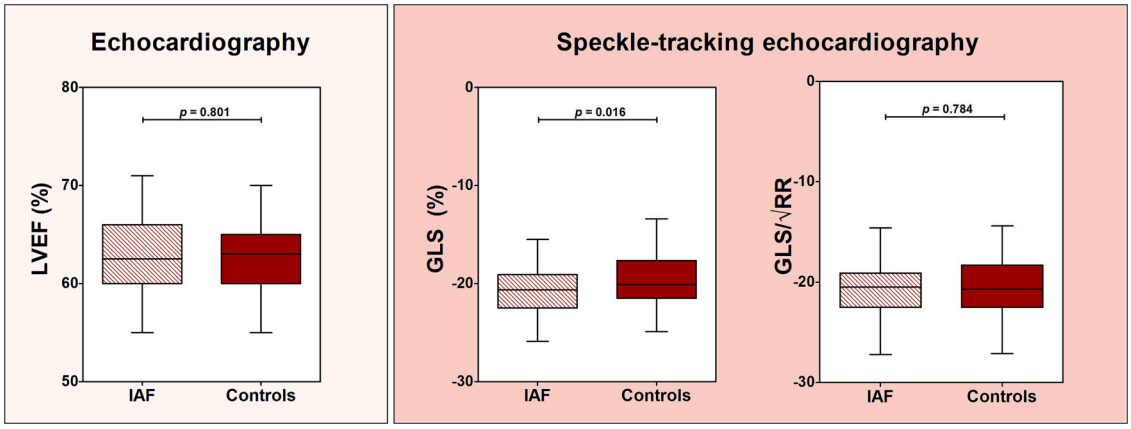

Fig. 2. Left ventricular function as measured by LVEF in routine echocardiography (left panel), and STE based GLS and indexed GLS/$\sqrt{}$(RR) (right panel), compared between patients with IAF and healthy controls.
IAF = idiopathic atrial fibrillation; LVEF = left ventricular ejection fraction; GLS = global longitudinal strain; STE = speckle-tracking echocardiography.

Table 3
Echocardiographic comparison in subgroup analysis.

	Subgroup 1			Subgroup 2			Subgroup 3		
	Patients with IAF (n = 41)	Controls (n = 87)	p-value	Patients with IAF (n = 19)	Controls (n = 42)	p-value	Patients with IAF (n = 18)	Controls (n = 33)	p-value
Age (years)	50 ± 10	55 ± 10	**0.032**	50 ± 11	56 ± 8	**0.030**	50 ± 11	55 ± 8	**0.042**
Male sex	26(63)	46(53)	0.262	8(42)	17(41)	0.905	8(44)	13(39)	0.726
Echocardiography									
Heart rate (bpm)	60 ± 10	67 ± 9	**<0.001**	62 ± 10	67 ± 9	0.090	63 ± 9	67 ± 10	0.150
Ventricular cycle length (ms)	1016 ± 173	910 ± 144	**<0.001**	980 ± 179	900 ± 137	0.067	962 ± 166	897 ± 147	0.163
LVEF (%)	63 ± 4	62 ± 4	0.346	63 ± 5	63 ± 4	0.490	63 ± 5	63 ± 4	0.708
LV mass index (g/m^2)	77 ± 14	87 ± 19	**0.005**	77 ± 15	83 ± 18	0.302	76 ± 15	80 ± 17	0.501
LAVI (ml/m^2)	34 ± 8	32 ± 7	0.324	33 ± 9	29 ± 6	0.144	33 ± 10	29 ± 6	0.160
Speckle-tracking echocardiography									
GLS (%)	−21.5 ± 2.1	−19.7 ± 2.3	**<0.001**	−21.5 ± 2.0	−20.0 ± 2.0	**0.006**	−21.4 ± 1.9	−19.9 ± 2.0	**0.012**
Number of dysfunction	1(3)	15(17)	**0.019**	0(0)	7(17)	0.088	0(0)	5(15)	0.148
GLS/$\sqrt{}$(RR)	−21.5 ± 2.5	−20.8 ± 2.8	0.165	−22.0 ± 2.5	−21.2 ± 2.6	0.315	−22.1 ± 2.5	−21.2 ± 2.8	0.312
LASr (%)	35 ± 8	37 ± 12	0.319	35 ± 7	36 ± 10	0.673	35 ± 7	36 ± 9	0.775
Number of dysfunction	4(10)	13(15)	0.420	1(5)	6(14)	0.418	1(6)	4(12)	0.645
LASr/$\sqrt{}$(RR)	35 ± 8	39 ± 13	0.055	36 ± 9	39 ± 10	0.248	37 ± 9	39 ± 9	0.353
LAScd (%)	23 ± 6	23 ± 10	0.987	22 ± 4	22 ± 7	0.851	22 ± 5	22 ± 7	0.871
Number of dysfunction	2(5)	7(8)	0.718	1(5)	4(10)	>0.99	1(6)	2(6)	>0.99
LAScd/$\sqrt{}$(RR)	23 ± 6	24 ± 10	0.388	22 ± 5	23 ± 8	0.630	23 ± 6	24 ± 7	0.460
LASct (%)	12 ± 6	14 ± 7	0.101	13 ± 7	14 ± 6	0.452	14 ± 7	14 ± 5	0.821
Number of dysfunction	9(22)	11(13)	0.176	3(16)	5(12)	0.695	2(11)	3(9)	>0.99
LASct/$\sqrt{}$(RR)	12 ± 6	15 ± 8	**0.028**	14 ± 8	16 ± 7	0.269	14 ± 7	15 ± 7	0.593

Absolute numbers (%) of dysfunction are based on lower limit of normal: GLS > -17.0% for men; GLS > -18.0% for women; LASr <26.1%; LAScd <12.0%; LASct <7.7%.
GLS = global longitudinal strain; LAScd = left atrial conduit strain; LASct = left atrial contractile strain; LASr = left atrial reservoir strain; LAVI = left atrial volume index. Bold denotes statistical significance.

interest to study the incremental value of more sophisticated imaging modalities to detect subtle impairments in left ventricular function in IAF patients. Our study is the first to apply STE in IAF patients, which is a widely available and evolving technique to quantify myocardial function, and to detect even minor dysfunction.

4.2. Early ventricular dysfunction

Previous research showed that STE outperforms LVEF, and that GLS is able to detect early subclinical changes in numerous cardiac diseases, including ischemic heart disease, valvular heart diseases and heart failure with preserved ejection fraction [8]. Even in absence of any manifested cardiac disease, the presence of cardiovascular risk factors solely, i.e. hypertension, diabetes mellitus and obesity, may be associated with subclinical LV dysfunction as measured by impaired GLS [9].

GLS has been shown to be predictive of new-onset AF in various settings, after presentation with acute myocardial infarction or stroke, but also in the general population [10]. In patients with known AF and normal LVEF, GLS was impaired during AF compared to sinus rhythm. Recurrence of AF after successful catheter ablation is associated with worsening of (impaired) GLS, whereas strain parameters improve during maintenance of sinus rhythm. Furthermore, Dons et al. showed that indexed GLS measured during AF, indexed by cycle length, is associated significantly with increased risk of an adverse outcome and clearly outperforms LVEF [5].

In the current study, there was no evidence of systolic ventricular dysfunction based on STE in patients with IAF compared to healthy controls. Non-indexed GLS was even significantly better in patients with IAF, but not when indexed for ventricular cycle length. This observation suggests, that the presence of IAF in this population cannot be elucidated

by the presence of subclinical LV dysfunction and that there is no indication that IAF impairs LV performance during sinus rhythm.

4.3. Atrial dysfunction

In addition to ventricular dysfunction, AF is also associated with atrial structural and functional remodeling processes, which is described as 'atrial cardiomyopathy' [11]. This may suggest that imaging techniques of the left atrium as 'the scene of calamity' should be an additional focus, especially in patients with presumed IAF. Frustaci et al. found abnormal atrial histology in the absence of histologic ventricular alterations in patients with IAF [12]. Recent studies suggest that novel CMR techniques are able to detect atrial fibrosis, but these techniques have not yet been used in patients with IAF. Advanced echocardiography enables the assessment of both anatomical and functional alterations in the course of atrial cardiomyopathy. LAVI is well-established and related to increased risk of cardiovascular complications in patients with AF. However, it is hypothesized that functional remodeling precedes structural remodeling. Hong et al. showed that LA intrinsic myocardial properties, assessed by STE, may be impaired in patients with IAF without LA dilatation [13].

To our knowledge, this study is the first to use LAS indexed for cycle length. Adjustment according to cycle length has been applied for GLS previously, but not yet for LAS, although experimental research in dogs has shown that LA active function improves when lowering heart rate [14]. We show, that indexed LAS during the reservoir and active contraction phase was lower in patients with IAF compared to healthy controls, but this does not apply to non-indexed LAS. Furthermore, observing absolute numbers among patients with IAF in the total study population, still 21% had an impaired reservoir function, 10% an impaired conduit function and 24% an impaired active contraction function of the LA, although these numbers were lower after additional exclusion of potential preliminary risk factors [6]. Impaired LA active contraction function was more prevalent in patients with IAF compared to healthy controls, and as the active contraction function is more related to LA intrinsic function [15], this could support the hypothesis of local atrial disease. Although there was no difference in the number of impaired LA reservoir and conduit function compared to healthy controls, impairment was present in both groups. This apparent opposition could be explained by the atrial cardiomyopathy hypothesis, since this is not limited to the extent of (I)AF solely but is also key player in the course of heart failure with preserved ejection fraction and numerous of cardiovascular risk factors [11], and possibly even potential preliminary risk factors.

4.4. Non-conventional risk factors, genetic disposition and changes in autonomic system

In patients with IAF, non-conventional and pre-clinical risk factors as well as genetic contributors (genotype) may be important [7,16]. Various genetic variants are associated with the risk of AF. Independent of the presence of cardiovascular risk factors, heritability has been shown to contribute to development of AF, both in patients with IAF and in a combined AF population independent of the presence of cardiovascular risk factors. Hobbelt et al. found genetic predictors of specific types of AF and hypothesized that especially in patients with self-terminating AF this genetic background may play an even more important role than modifiable risk factors [17]. Furthermore, a recent study showed the presence of loss of function mutations from cardiomyopathy genes in patients with IAF [18] which could support the causal interplay of atrial cardiomyopathy.

Additionally, also exposure to conditions transiently increasing AF susceptibility, such as changes in autonomic nervous system observed in individuals with 'vagal AF', may lead to AF even in completely healthy individuals [19].

4.5. Limitations

In this study we examined patients with IAF and previously matched healthy controls. Since healthy controls were referred for cardiovascular screening purposes, referral bias may have played a role, but would—if anything—have led to a higher incidence of events in the control population rather than the opposite. In addition, healthy controls had more often a family history of CAD, therefore, they may have a potential greater risk to develop any cardiovascular disease in the future compared to the overall population. Because of the retrospective study design, it was not possible to obtain sufficient information on clinical presentation and symptoms. The small sample size, due to restrictive inclusion criteria, limits the extend of additional analyses. In the subgroup analysis we excluded potential preliminary risk factor therefore as good as possible, however in patients with IAF we cannot rule out that the use of betablockers is also related to masked hypertension without known diagnosis. Also, patients in the IAF used anti-arrhythmic medication which potentially has an influence on cardiac contractility. Still, given the limited size of the study population and the complexity of potential influential factors, not all effects on strain can be addressed an investigated. To evaluate LAS uniformly, only echocardiographic recordings during sinus rhythm were used. However, in absence of continuous rhythm monitoring, it is not possible to rule out the impact of atrial stunning on LAS in patients with IAF. Also, despite the fact that the initial study population was matched for age, we saw a difference in the subgroups with a lower age of patients having IAF. This might lead to an overestimation of GLS. However, due to the small sample size, we did not adjust for age in that subgroup analysis.

5. Conclusions

Extensive STE did not detect any overt LV or LA disease in a selected group of patients with IAF compared to healthy controls. Therefore, there is no evidence of systolic LV dysfunction as driving arrhythmogenic factor for IAF.

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CK has received research software and hardware from TomTec Imaging Systems. MvM, HV, JW and SB have also used software for study purposes from TOMTEC Imaging Systems. All other authors report no conflicts of interest related to this study.

Key messages

- What is already known on this topic:
  - o Idiopathic atrial fibrillation (AF) occurred in the absence of established AF risk factors.
- What this study adds:
  - o Global longitudinal strain was normal in patients with idiopathic AF.
  - o Speckle-tracking imaging did not detect any overt left ventricular dysfunction compared to healthy controls.
- How this study might affect research, practice or:
  - o There is a subgroup of patients in whom AF can occur in the absence of established AF risk factors but also without evidence of ventricular dysfunction

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Appendix A. Supplementary data

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