Relation of Echocardiographic Markers of Left Atrial Fibrosis to Atrial Fibrillation Burden

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In patients with atrial fibrillation (AF), left atrial (LA) fibrosis is a major determinant of the progression to, and burden of AF. LA reservoir strain and total atrial conduction time (PA-TDI) reflect LA fibrotic content. We aimed to investigate the relation between LA reservoir strain and PA-TDI in AF patients and control subjects. Six-hundred two patients (mean age 56 years, 53% men) with first episode of AF and 342 controls (mean age 64 years, 71% men) without structural heart disease underwent echocardiography. LA volumes, PA-TDI, LA reservoir strain, and left ventricular global longitudinal strain (GLS) were compared. Compared with controls, patients with paroxysmal AF and patients with persistent AF had longer PA-TDI (128 ± 25 millisecond, 140 ± 31 millisecond, and 154 ± 33 millisecond, respectively; $p < 0.001$) and a progressive decline in LA reservoir strain (36.9 ± 11.6%, 29.8 ± 13.4%, 24.2 ± 12.3%, respectively; $p < 0.001$). LA reservoir strain was negatively correlated with PA-TDI ($r = -0.43$, $p < 0.001$). On multivariate analyses, LA reservoir strain, diabetes mellitus, and burden of AF were independent correlates of PA-TDI ($R^2 = 0.23$, $p < 0.001$); whereas only PA-TDI was an independent correlate of LA reservoir strain ($R^2 = 0.43$, $p < 0.001$); controlling for age, hypertension, coronary artery disease, body mass index, severity of mitral regurgitation, left ventricular global longitudinal strain, and LA volume. In conclusion, PA-TDI and LA reservoir strain are negatively correlated in all subjects, irrespective of the presence or burden of AF. Patients with persistent AF have longer PA-TDI and impaired LA reservoir strain compared with paroxysmal AF and controls, suggesting increasing burden of fibrosis and LA structural remodeling in the progression of AF. **(Am J Cardiol 2018;122:584−591)**

Atrial fibrillation (AF) leads to progressive structural and functional changes in the left atrium (LA) over time. LA fibrosis is a major determinant of the progression to, and burden of AF and its substrate,[1−3] leading to an increase in total atrial activation time.[4] The time delay between the P-wave on the surface electrocardiogram (ECG) and mechanical activation of the LA measured using color-coded tissue Doppler echocardiography, the so-called PA-TDI, provides a reliable estimate of total atrial activation time, reflecting the degree of atrial fibrosis on biopsy specimens.[5] LA compliance by echocardiographic LA reservoir strain in AF patients has been shown to inversely correlate with LA fibrosis burden demonstrated on late gadolinium contrast enhanced cardiac magnetic resonance.[6] There is evidence of progressive remodeling of the LA once AF develops with increasing fibrosis alongside lower LA reservoir strain in patients with persistent AF compared with patients with paroxysmal AF (PAF).[6] However, the relation between AF burden and LA reservoir strain and PA-TDI is unknown. The present study investigated the relation between AF burden and LA reservoir strain and PA-TDI in patients with AF, and in control individuals without structural heart disease. We hypothesized that increasing AF burden is associated with more impaired LA reservoir strain and longer total atrial activation time (PA-TDI).

Methods

This retrospective case-control analysis included patients presenting with their first episode of AF to our tertiary referral center. Cases comprised patients in sinus rhythm at the time of the echocardiogram. Echocardiograms performed within 3 weeks after cardioversion were excluded to avoid the effects of atrial stunning. Patients with congenital heart disease were excluded, as well as patients without appropriate echocardiographic images for measurement of PA-TDI.

Controls comprised subjects clinically referred for echocardiography for the following indications: evaluation of chest pain, palpitations, dyspnea, syncope, or preoperative

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assessment for noncardiac surgery. Subjects were excluded if they had evidence of structural heart disease, or arrhythmias that were documented on the cardiology department and hospital information systems (EPD-Vision and EZIS; Leiden University Medical Centre, Leiden, The Netherlands).

Demographic and anthropometric data, medication, traditional cardiac risk factors, co-morbidities, and New York Heart Association functional class were collected. In accordance with current European Society of Cardiology Guidelines, PAF was defined as self-terminating within 48 hours, but may have continued up to 7 days; persistent AF was defined as an episode lasting longer than 7 days or requiring termination by either electrical or pharmacological cardioversion.[7] AF burden was categorised as: "no AF," "paroxysmal AF," and "persistent AF," The Institutional Review Board approved this retrospective analysis of clinically acquired data and waived the need for patient written informed consent.

Transthoracic echocardiography was performed with the patient in the left lateral decubitus position using a commercially available ultrasound transducer and equipment (3.5 Mhz or M5S probe, Vivid 7 and Vivid E9, GE-Vingmed, Horten, Norway). All images were digitally stored for offline analysis (EchoPAC, version 113 1.1, GE-Vingmed, Horten, Norway). All standard echocardiographic and Doppler parameters of left ventricular (LV) systolic and diastolic function were measured. The LV ejection fraction was calculated using the Simpson's biplane method of discs as per current recommendations.[8] Maximal LA volume was measured in the apical 4-chamber view using Simpson's single plane method of discs.

Atrial tissue Doppler imaging (TDI). The PA-TDI duration was measured on color-coded TDI images of the LA obtained in the apical 4-chamber view. The sector width and depth were minimized to obtain the highest possible frame rate. A fixed 9×9 pixel region of interest was placed on the lateral LA wall, just above the mitral annulus, to obtain the tracing of mechanical activation in that area. The PA-TDI duration was obtained by measuring the time delay between the onset of the P-wave on the surface ECG and the peak of the A'-wave on the tissue Doppler tracing (Figure 1).[9]

Strain imaging. Global longitudinal strain (GLS) of the left ventricle was measured with 2-dimensional (2D) speckle tracking echocardiography in the apical 4-, 2-chamber and long-axis views using the highest possible frame rates. LV GLS was calculated from the average longitudinal strain curve of the 3 apical views. LA reservoir strain was evaluated using 2D speckle tracking on images obtained from the apical 4-chamber view. Care was taken to avoid images with LA or LV foreshortening. LA reservoir strain was measured as the peak longitudinal strain during ventricular systole (Figure 2).[10]

Continuous variables were presented as mean ± standard deviation for normally distributed variables, and median (interquartile range) for non-Gaussian variables. Continuous variables were compared with the unpaired Student's *t*-test, analysis of variance, and Wilcoxon rank sum test, as appropriate. Categorical data are summarized as frequencies and percentages, and compared using the chi-square test. Multiple linear regression analysis was performed to identify factors independently associated with PA-TDI duration. Clinical and echocardiographic parameters were chosen a priori based on biological plausibility, published studies.[6,11–13] Parameters with p-values <0.2 on univariate analysis were entered into the final multivariate model as independent variables. Independent contribution was assessed and there was no evidence of multicollinearity. Case elimination was used for missing data. A 2-tailed p-value <0.05 was considered statistically significant. Statistical analyses were performed using STATA v12 (STATA Corporation, Texas).

Results

A total of 602 patients with AF and 342 controls with complete echocardiographic examinations were included. Clinical characteristics of AF patients compared with controls are presented in Table 1. There were 364 patients with PAF and 238 patients with persistent AF. Patients with AF were older and more frequently men, with higher body mass index (BMI) and body surface area compared with controls. A larger number of AF patients had hypertension and dyslipidemia, and had greater use of cardiac medications compared with controls.

Echocardiographic parameters are presented in Table 2. Patients with AF had increased LV wall thickness and chamber size, with normal LV ejection fraction but impaired GLS (-16.7 ± 6.0%). Indexed LA volumes were enlarged, and the LA reservoir strain was reduced in AF patients. PA-TDI was significantly increased in patients with AF compared with controls.

Compared with controls, patients with PAF and patients with persistent AF showed a lengthening in PA-TDI (128 ± 25 millisecond, 140 ± 31 millisecond, and 154 ± 33 millisecond, respectively, p <0.001). On multivariate analysis, LA reservoir strain, diabetes mellitus, and burden of AF (no AF, PAF, or persistent AF) were independent correlates of PA-TDI when controlling for age, hypertension, BMI, coronary artery disease, the severity of mitral regurgitation, LV GLS, and LA volume ($R^2 = 0.23$, p <0.001; Table 3).

Compared with controls, patients with PAF and patients with persistent AF showed a progressive decline in LA reservoir strain (36.9 ± 11.6%, 29.8 ± 13.4%, 24.2 ± 12.3%, respectively, p <0.001). On multivariate analysis, PA-TDI was an independent correlate of LA reservoir strain when controlling for age, hypertension, BMI, coronary artery disease, the severity of mitral regurgitation, LV GLS and LA volume ($R^2 = 0.43$, p <0.001; Table 4). The burden of AF and diabetes mellitus were not significantly associated with LA reservoir strain.

There was a significant linear relation between LA reservoir strain and PA-TDI in all subjects (r = -0.43, p <0.001) such that impaired LA reservoir strain, indicating poor LA compliance, was associated with prolonged PA-TDI. This relation was maintained when controlling for the type of AF (paroxysmal or persistent). To further assess the influence of the burden of AF on the relation between LA

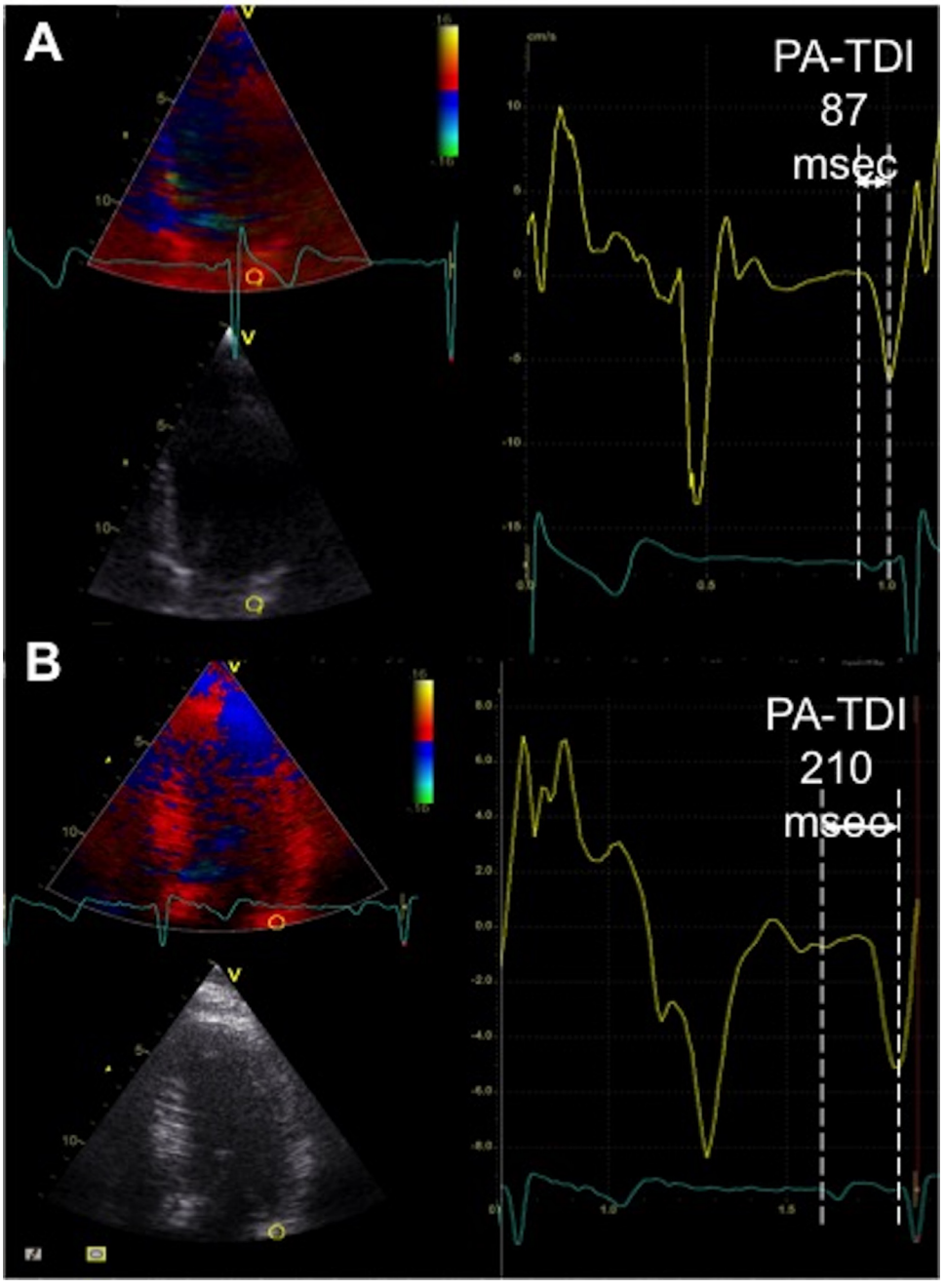

Figure 1. Example of PA-TDI in a patient with PAF, and a control subject. The PA-TDI measurement was performed during sinus rhythm in both individuals. The PA-TDI duration is obtained by measuring the time delay between the onset of the P-wave on the surface ECG and the peak of the A'-wave on the tissue Doppler tracing (time interval between the two dotted white lines, indicated by the white arrow). In this example, the control shown in panel *(A)* has a short PA-TDI of 87 millisecond, in contrast to a prolonged PA-TDI of 210 millisecond in a patient with PAF.

reservoir strain and PA-TDI, the mean LA reservoir strain of 37% and mean PA-TDI of 128 millisecond of controls were used as cut-off points (Figure 3). A larger proportion of patients with persistent AF showed LA reservoir strain less than 37% and PA-TDI longer than 128 millisecond compared with patients with PAF (65% vs 51%, $p = 0.001$). This demonstrates that increasing AF burden is associated with more impaired LA reservoir strain and longer total atrial activation time (PA-TDI).

Discussion

The present study demonstrated that both the presence and burden of AF were associated with morphofunctional abnormalities of the left atrium, represented by larger LA volumes, longer PA-TDI duration, and more impaired LA reservoir strain. Our results also provide echocardiographic evidence of a linear relation between total atrial conduction time and atrial reservoir function in all subjects, irrespective of the presence or burden of AF.

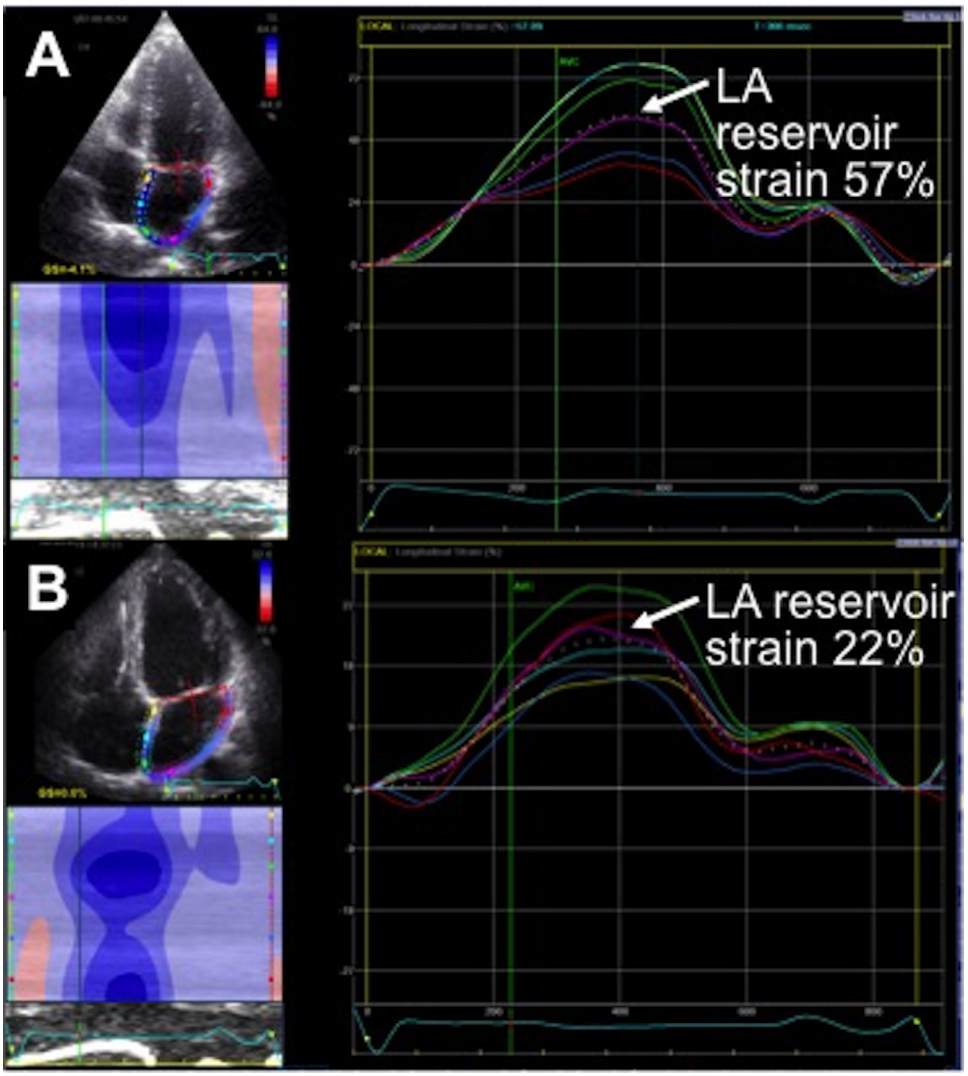

Figure 2. Example of measurement of LA reservoir strain in a patient with AF, and a control subject. The LA reservoir strain measurement was performed during sinus rhythm in both individuals. The LA endocardium is manually traced in the apical 4-chamber view, and region of thickness adjusted to the LA wall. LA reservoir strain is measured as the peak global longitudinal strain during ventricular systole (white dotted curve, arrow). Panel *(A)* demonstrates normal LA reservoir strain of 57% in a control individual, and panel *(B)* shows reduced LA reservoir strain of 22% in a patient with PAF.

It is well established that AF is accompanied by electrical, contractile, and structural remodeling of the left atrium that plays a role in the persistency of the arrhythmia.[14,15] The remodeling process that occurs within the atria culminates in the loss of atrial myocytes with increased collagen content and consequent LA interstitial fibrosis.[14] Hence, fibrosis is considered a prime driver of AF, resulting in the formation of micro re-entry circuits that may initiate and perpetuate the atrial arrhythmia.[16]

Animal studies have demonstrated that AF is more likely when atrial fibrosis is experimentally induced.[17,18] In a canine model, rapid atrial pacing was shown to result in a fourfold release of collagen-I and fibronectin-I from cardiac myocytes in atrial tissue that caused structural remodeling by altering cardiac fibroblast function, and contributed to the upregulation of extracellular matrix genes.[19]

Fibrosis, demonstrated on postmortem biopsy specimens, has been related to the burden of AF independent of age, with control patients exhibiting no significant fibrosis.[1] Clinical studies examining histological biopsies have demonstrated increased fibrosis in patients with AF,[20] the higher atrial fibrotic content was associated with the occurrence of AF after cardiac bypass surgery,[21] and the success of Maze ablation.[20,22] The extent of atrial fibrosis, demonstrated on late gadolinium enhancement cardiac magnetic resonance, has also been related to the burden of AF in some studies, whilst other have shown that the degree of structural remodeling is independent of AF type and comorbidities.[6,23,24] Regardless of the relation with AF burden, the degree of fibrosis on late gadolinium contrast enhanced cardiac magnetic resonance in these studies was shown to be a predictor of ablation success.[3,23,24]

The PA-TDI duration on TDI echocardiography measures the total atrial activation time, and is a novel noninvasive surrogate for fibrosis.[5] Longer PA-TDI has been demonstrated alongside higher degrees of atrial fibrosis on biopsy specimens in patients who develop new-onset AF after cardiac surgery compared with those who remain in

Table 1
Clinical characteristics of controls and atrial fibrillation patients

Characteristic	Controls (n = 342)	Atrial fibrillation patients (n = 602)	p value
Age (years)	56 ± 16	64 ± 12	<0.001
Men	180 (53%)	429 (71%)	<0.001
Body mass index (kg/m^2)	26 ± 4	27 ± 5	<0.001
Body surface area, /m^2	1.91 ± 0.21	2.03 ± 0.24	<0.001
Hypertension	122 (36%)	411 (68%)	<0.001
Current smoker	31 (9%)	80 (13%)	0.073
Dyslipidemia	63 (18%)	294 (49%)	<0.001
Diabetes mellitus	39 (11%)	87 (14%)	0.175
Medications:			
Aspirin or clopidogrel	0	137 (23%)	
Anticoagulant (warfarin or novel oral anticoagulant)	0	377 (63%)	
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	80 (23%)	334 (56%)	<0.001
Calcium channel blocker	28 (8%)	128 (21%)	<0.001
Beta-blocker	60 (18%)	402 (67%)	<0.001
Amiodarone	0	48 (8%)	
Diuretic	50 (15%)	194 (32%)	<0.001
Aldosterone antagonist	0	53 (9%)	
Statin	68 (20%)	268 (45%)	<0.001

Dyslipidemia was defined as previously diagnosed dyslipidemia, treatment with lipid-lowering agents, low-density lipoprotein ≥3.0 mmol/L in low-to-moderate risk groups, ≥2.6 mmol/L in high-risk groups, and ≥1.8 mmol/L in very high-risk groups.

Table 2
Echocardiographic characteristics of controls compared with atrial fibrillation patients

Variable	Controls (n = 342)	Atrial fibrillation patients (n = 602)	p value
Interventricular septal thickness (mm)	10 ± 2	12 ± 3	<0.001
Left ventricular end diastolic diameter (mm)	48 ± 6	50 ± 8	0.006
Posterior wall thickness (mm)	10 ± 2	11 ± 2	<0.001
Left ventricular end-systolic diameter	31 ± 6	32 ± 9	0.003
Left atrial dimension (mm)	35 ± 5	43 ± 7	<0.001
Left ventricular end-diastolic volume (ml)	103 (40)	116 (53)	<0.001
Left ventricular end-systolic volume (ml)	41 (24)	49 (30)	<0.001
Left ventricular ejection fraction, %	60 (11)	57 (14)	<0.001
Left atrial volume indexed (ml/m^2)	24 ± 8	43 ± 18	<0.001
Left ventricular global longitudinal systolic strain, %	−18.5 (2.6)	−16.7 (6.0)	<0.001
Left atrial reservoir strain, (%)	36.9 ± 11.6	27.6 ± 13.3	<0.001
PA-TDI (millisecond)	128 ± 25	146 ± 32	<0.001

Table 3
Univariate and multivariate linear regression examining correlates of PA-TDI

Variable	Univariate			Multivariate model (R^2 = 0.23, p <0.001)		
	Coefficient	95% confidence interval	p value	Coefficient	95% confidence interval	p value
Age (years)	0.92	0.79 − 1.05	<0.001	0.63	0.41 − 0.85	<0.001
History of hypertension	10.02	6.09 − 13.96	<0.001	−3.62	−8.9 − 1.67	0.180
Diabetes mellitus	11.17	5.40 − 16.94	<0.001	8.28	1.26 − 15.31	0.021
Coronary artery disease	19.45	14.83 − 24.08	<0.001	3.43	−2.03 − 8.89	0.218
Body mass index (kg/m^2)	0.73	0.29 − 20.25	0.001	0.04	−0.5 − 0.57	0.895
Atrial fibrillation burden	13.02	10.61 − 15.43	<0.001	6.99	2.05 − 11.93	0.006
Mitral regurgitation grade	5.30	1.24 − 9.35	0.011	−0.88	−4.75 − 2.99	0.656
Left atrial volume indexed (ml/m^2)	0.59	0.48 − 0.69	<0.001	0.17	0.02 − 0.31	0.026
Left ventricular global longitudinal strain (%)	1.70	1.23 − 2.17	<0.001	−0.17	−0.77 − 0.43	0.575
Left atrial reservoir strain, (%)	−0.98	−1.12 − 0.85	<0.001	−0.58	−0.81 − 0.36	<0.001
Constant				94.80	85.96 − 121.06	<0.001

Atrial fibrillation burden categorized as: “no AF,” “paroxysmal AF,” and “persistent AF.”

Table 4
Univariate and multivariate linear regression examining correlates of LA reservoir strain

Variable	Univariate			Multivariate model ($R^2 = 0.43$, $p < 0.001$)		
	Coefficient	95% confidence interval	p value	Coefficient	95% confidence interval	p value
Age (years)	−0.36	−0.41 − 0.30	<0.001	−0.16	−0.24 − 0.08	0.000
History of hypertension	−4.82	−6.53 − 3.11	<0.001	0.66	−1.21 − 2.53	0.490
Diabetes mellitus	−2.89	−5.42 − 0.36	0.025	1.13	−1.36 − 3.62	0.372
Coronary artery disease	−10.46	−12.43 − 8.49	<0.001	−1.23	−3.16 − 0.70	0.210
Body mass index (kg/m^2)	−0.48	−0.67 − 0.29	<0.001	−0.19	−0.38 − 0.01	0.043
Atrial fibrillation burden	−6.38	−7.41 − 5.35	<0.001	−0.02	−1.77 − 1.74	0.985
Mitral regurgitation grade	−3.28	−4.95 − 1.62	<0.001	0.59	−0.78 − 1.95	0.399
Left atrial volume indexed (ml/m^2)	−0.36	−0.40 − 0.32	<0.001	−0.24	−0.29 − 0.2	0.000
PA-TDI (millisecond)	−0.19	−0.21 − 0.16	<0.001	−0.07	−0.10 − 0.04	0.000
Left ventricular global longitudinal strain (%)	−1.46	−1.64 − 1.27	<0.001	−1.06	−1.25 − 0.86	0.000
Constant				47.17	38.07 − 56.28	0.000

Atrial fibrillation burden categorized as: "no AF," "paroxysmal AF," and "persistent AF."

sinus rhythm.[25] The requirement of a P-wave, and thus sinus rhythm, on the ECG to measure this interval, however, limits its use during AF. Nonetheless, the value of PA-TDI in predicting new-onset AF and the success of radiofrequency catheter ablation has been previously demonstrated.[9,26] We demonstrated that the burden of AF and co-morbidities is related to the degree of structural remodeling as represented by the PA-TDI duration, and is in support of the previously mentioned invasive and noninvasive studies. Furthermore, they reinforce the feasibility of this noninvasive echocardiographic technique for atrial substrate evaluation.

The imbalance in collagen synthesis and degradation leading to myolysis and the development of a fibrotic atrial substrate has consequent effects on LA electromechanical function, manifest as longer atrial conduction times and reduced atrial compliance and contractility.[27,28] LA reservoir strain represents LA relaxation and lengthening during ventricular systole and is an indicator of LA compliance. We proposed that remodeling of the atrial substrate and increasing fibrosis may reduce LA compliance during the LA reservoir phase. A previous study has demonstrated a relation between LA reservoir strain and the degree of fibrosis on late gadolinium contrast enhanced cardiac magnetic resonance that was evident in patients with persistent but not in patients with PAF, and the authors proposed that LA reservoir strain is a surrogate for fibrosis.[6] Our study confirmed the hypothesis that LA compliance is impaired in AF, and together with the significant negative relation with PA-TDI, suggests that these changes may be due to atrial fibrosis. We believe this also explains the relation in the previously mentioned study, that LA reservoir strain is reduced as a functional consequence of the structural remodeling that prolongs electrical, and therefore, mechanical activation of the LA. These improved mechanistic insights may lead to innovative and improved therapeutic approaches for rhythm control in patients with AF.

To our knowledge, the present study is the first to demonstrate this relation between PA-TDI and LA reservoir strain in AF patients, providing a better understanding of the relation between structure and function. Additionally, this is the first study to evaluate PA-TDI in a control

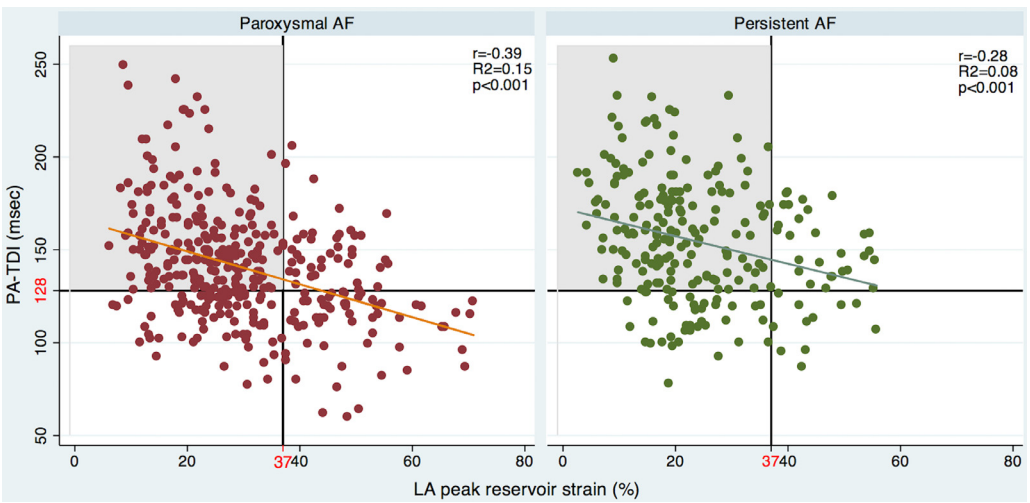

Figure 3. Relation between LA reservoir strain and PA-TDI in patients with paroxysmal and persistent AF. To assess the influence of the burden of AF on the relation between LA reservoir strain and PA-TDI, the mean LA reservoir strain of 37% and mean PA-TDI of 128 millisecond of controls were used as cut-off points. There were more patients (65%) in the persistent AF group that had LA reservoir strain less than 37% and PA-TDI higher than 128 millisecond, compared with 51% of patients in the PAF group ($p = 0.001$).

population and, beyond that, to show that the relation with LA reservoir strain exists even in patients without AF. It is important to note that this study is subject to the inherent limitations of an observational study. Future prospective studies are required to establish reference ranges and evaluate determinants of PA-TDI in a control population; determine the applications, if any, of this noninvasive tool in non-AF populations; as well as examine the utility and therapeutic implications of LA reservoir strain and PA-TDI in predicting overall AF burden and conversion of paroxysmal to persistent AF.

In conclusion, total atrial conduction time (PA-TDI) and LA reservoir strain are negatively correlated in all subjects, irrespective of the presence or burden of AF. Patients with persistent AF have longer PA-TDI and impaired LA reservoir strain compared with PAF and controls, suggesting increasing burden of fibrosis and LA structural remodeling in the progression of AF.

Disclosures

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