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Associations of Electrocardiographic P-wave Characteristics with Left Atrial Structure, Function and Diffuse Left Ventricular Fibrosis Defined by Cardiac Magnetic Resonance: the PRIMERI Study

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Abstract

Background—Abnormal P-terminal force in V1 (PTF_{V1}) is associated with an increased risk of heart failure, stroke, atrial fibrillation (AF) and death.

Objective—Our goal was to explore associations of left ventricular (LV) diffuse fibrosis with left atrium (LA) function and ECG measures of LA electrical activity.

Methods—AF-free patients (n=91, mean age 59.5, 61.5% men, 65.9% Caucasian) with structural heart disease (wide spatial QRS-T angle≥105° ± Selvester QRS score≥5 on ECG) but LV ejection fraction >35% underwent clinical evaluation, cardiac magnetic resonance and resting ECG. LA function indices were obtained by multimodality tissue tracking using 2 and 4-chamber long-axis images. T_1 mapping and late gadolinium enhancement were used to assess diffuse LV fibrosis and presence of scar. P-prime in V_1 amplitude ($PPaV_1$) and duration ($PPdV_1$), averaged P-duration, PR interval and P-axis were automatically measured using 12SL TM algorithm. PTF_{V1} was calculated as product of $PPaV_1$ by $PPdV_1$.

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Conflict of Interest Disclosures

None. The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services.

Results—In linear regression after adjustment for demographic, body mass index, LA $volume_{max}$ index, presence of scar and LV mass index, each decile increase in LV interstitial fibrosis was associated with 0.76mV*ms increase in negative abnormal PTF_{V1} [(95%CI −1.42 to −0.09), P=0.025], 15.3ms prolongation in $PPdV_1$ [(95%CI 6.9 to 23.8), P=0.001], and 5.4ms widening in averaged P-duration [(95%CI 0.9 to 10.0), P=0.020]. LV fibrosis did not affect LA function. $PPaV_1$ and PTF_{V1} were associated with an increase in LA volumes, decrease in LAEF and LA reservoir function.

Conclusion—LV interstitial fibrosis is associated with abnormal PTF_{V1}, prolonged $PPdV_1$ and P-duration, but does not affect LA function.

Keywords

P-terminal force in V_1; left atrium function; fibrosis; left ventricle; atrial fibrillation

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the United States where the prevalence in adults < 65 years of age is about 1% to 2%; it increases up to 9% in elderly[1, 2]. AF is associated with a two-three-fold risk of cardiovascular mortality and sudden cardiac death[3, 4], five-fold risk of stroke[5], and a three-fold risk of heart failure (HF)[6]. Selection of a high-risk subgroup of patients amongst overall low-risk individuals early in the continuum of structural heart disease is needed for successful primary prevention of AF.

Common risk factors of AF (hypertension, coronary heart disease, HF, diabetes) are well acknowledged[7, 8]. In response to hemodynamic stress or injury, atria undergo structural remodeling with progressive fibrosis[9]. Cardiac magnetic resonance (CMR) imaging with T_1 mapping is a gold standard for quantification of interstitial fibrosis[10]. However, CMR is not a method of choice for screening of a large population given its complexity, limited accessibility and cost.

ECG carries important information about electrophysiological properties of the heart. P-wave characteristics reflect underlying atrial electrophysiology, as well as structure and function. Prolonged P-wave duration and abnormal P-axis[11] are associated with increased risk of AF[12], stroke and cardiovascular disease mortality[13]. Abnormal P-wave terminal force in V_1 (PTF_{V1})[14] is associated with increased risk of AF and stroke,[15,16] HF and post- MI death[17]. In a large sample of the adult population in the United States, deep terminal negativity of P-prime in V_1 was shown independently associated with increased risk of death due to all-cause, cardiovascular, and ischemic heart disease mortality[18]. However, while epidemiological data demonstrated a strong association between P-terminal force, deep terminal negativity in lead V1 and mortality, mechanisms behind such association in the absence of left atrial (LA) enlargement remained elusive.

In the Personalized Risk Identification and Management for Arrhythmias and Heart Failure by ECG and CMR (PRIMERI) study[19–21], both ECG and CMR were acquired within the same day. We hypothesized that LV interstitial fibrosis is associated with altered atrial electrophysiology and function in PRIMERI study participants.

Methods

Study population

The PRIMERI study is an ongoing prospective observational cohort study[19–21] of the Johns Hopkins Hospital patients with ECG signs of structural heart disease. The study protocol was approved by the Johns Hopkins Hospital Institutional Review Board. All study participants signed informed consent upon entering the study. PRIMERI study inclusion criteria were: general hospital population with 12-lead ECG criteria (spatial QRS-T angle[22] ≥105° and/or the Selvester QRS score[23] ≥5). Exclusion criteria were: age >70 years, LVEF <35%, eGFR<45mL/min, implanted ICD or pacemaker, concomitant non-cardiac diseases with high risk of non-cardiac death within 3 years of follow-up, and other general contraindication to CMR, or claustrophobia. Enrolled patients underwent a comprehensive clinical evaluation, routine 12-lead ECG, and CMR study. PRIMERI participants in sinus rhythm were included in this study, and those with AF on 12-lead ECG (recorded at enrollment) were excluded.

ECG data acquisition and analysis of P-wave indices

A standard 12-lead ECG was recorded at rest on the same day of the CMR by the Marquette MAC 5000 ECG system with 12SL TM algorithm (GE Medical Systems, Milwaukee, WI) and automatically analyzed by Magellan ECG Research Workstation (Magellan ECG Research Workstation Software, GE Healthcare, Wauwatosa, WI, USA). P-wave duration and PR interval were measured on an averaged median beat (averaged across all recorded beats and all 12 leads). Amplitude ($PPaV_1$) and duration ($PPdV_1$) of a second P-wave deflection (P-prime) in lead V_1 were measured (Figure 1) on the median beat (averaged across all recorded beats in V_1). PTF_{V1} was calculated as a product of the duration by the amplitude of the P-prime in lead V_1.

Cardiac Magnetic Resonance Study Protocol

Enrolled participants underwent CMR using 1.5T whole body MRI scanners (Avanto; Siemens Medical Systems, Erlangen, Germany) on the same day as the ECG recordings.

Maximum and minimum LA volume (V_{max} and V_{min}), LA volume before atrial systole (V_{preA}), maximum LA strain (S_{max}), and strain rate (SR_{max}) (Figure 2) were obtained as relevant LA parameters using a tissue tracking method with semi-automated software (multimodality tissue tracking (MTT) version 5.0, Toshiba, Japan) in untagged long-axis 2-chamber and 4– chamber cine CMR images (Figure 3). V_{max} was indexed by body surface area ($LAVi_{max}$).

T_1 mapping was used to assess diffuse LV fibrosis. One short-axis image in the mid-ventricular level was acquired by modified look-locker inversion recovery[24] at three phases; pre-contrast, 12-minute post-contrast, and 25-minute post-contrast using the MASS research software (Medis, Leiden University Medical Center, Leiden, Netherlands) (Figure 3). LV fibrosis index was calculated as following:

Fibrosis index = slope {$R1_{myocardium}$ (pre, post-12min, post-25 min) / $R1_{blood}$ (pre, post-12min, post-25 min[25, 26])}. Detailed CMR protocol is provided in Supplemental Methods.

Late gadolinium enhancement CMR (LGE-CMR) was used to detect the presence of regional scar replacement. The images were analyzed using QMass (Medis, The Netherlands). The region of interest for myocardium was manually placed on short-axis slices, and the scar replacement area was then detected as the area with increased intensity manually by the user for each slice.

Statistical Analysis

STATA 13 (StataCorp LP, College Station, TX) was used for statistical analysis. Continuous variables are expressed as mean ± SD after verification of the normal distribution. Categorical data were summarized as frequencies and percentages. The association of LV interstitial fibrosis with P-wave indices (PTF_{V1}, P-duration, P-axis, PR interval) was estimated using general linear models with each of P-wave indices as dependent variables. LV fibrosis index was included in the models as a continuous variable. The difference in P-wave indices associated with increasing LV fibrosis was estimated adjusting for age, race, sex and body mass index (BMI) (Model 1), due to previously reported demographics (age, race, and sex) specificity of P-wave indices[27], and their association with BMI[28]. Model 2 adjusted for all variables from model 1 and included $LAVi_{max}$. Model 3 adjusted for all variables from model 2 and included LV mass index and the presence of scar on LGE-CMR. Sensitivity analysis was performed after exclusion of participants with LVEF ≤45% (n=3). In addition, statistically significant models were further adjusted by left ventricular ejection fraction (LVEF), and history of myocardial infarction. We examined the possibility of a nonlinear relationship between LV fibrosis and the P-wave indices using restricted cubic splines of LV fibrosis index. All cubic spline analyses were adjusted for demographics, BMI, $LAVi_{max}$, the presence of LGE-CMR scar and LV mass index.

The associations of P-wave indices (PTF_{V1}, P-duration, P-axis, PR interval) with LA size and function were estimated using general linear models with each of LA function parameters (LA volume index, S_{max}, SR_{max}, LAEF) as dependent variables, and each of P-wave indices as predictors. Model 1 was adjusted for age, sex, and race. Model 2 was adjusted for demographics and BMI.

Analysis of associations of LV fibrosis with LA function parameters was performed. Model 1 was adjusted for age, race, sex and BMI. Model 2 included variables from Model 1 and the presence of LGE-CMR scar and LV mass index.

Results

Study population: Comparison of participants with and without atrial fibrillation

The clinical characteristics of participants are reported in Table 1. Less than 20% had a history of MI, less than third patients had NYHA HF class ≥ II. At the same time, risk factors profile was unfavorable in most of the study participants: up to 75% have had

hypertension; more than 50% were obese. Systolic blood pressure was not adequately controlled in the study population. LA function and P-wave ECG parameters were normal.

Myocardial interstitial fibrosis index and P-wave indices

Increasing diffuse LV fibrosis was borderline associated with more abnormal PTF_{V1} in unadjusted analysis (Table 2). After adjustment for $LAVi_{max}$, presence of LGE-CMR scar and LV mass index, association between LV fibrosis and PTF_{V1} strengthened and reached statistical significance: increase in LV fibrosis by each decile of fibrosis index was associated with 0.76 mV*ms increase in negative abnormal PTF_{V1}. LV fibrosis predominantly affected $PPdV_1$, rather than $PPaV_1$. In a fully adjusted model increase in LV fibrosis by each decile of fibrosis index was associated with 15.3 ms prolongation of $PPdV_1$. LV fibrosis impacted averaged P-duration to a lesser degree: increase in the decile of fibrosis index was associated with P-duration prolongation only by 5.4 ms. Association of LV fibrosis with $PPdV_1$, PTF_{V1}, and P-duration was non-linear (Figure 4), with the strongest association in mild and moderate fibrosis. Additional adjustment for LVEF, presence of LGE-CMR scar and history of MI did not attenuate the association between LV fibrosis and $PPdV_1$/PTF_{V1}, or P-duration. Increase in LV fibrosis by each decile of fibrosis index was associated with 0.74 mV*ms increase in negative abnormal PTF_{V1} [(95%CI from −1.42 to −0.07); P=0.030]. Increase in LV fibrosis by the decile of LV fibrosis index was also associated with 14.7 ms prolongation in PPdV1 [(95%CI 6.2 to 23.2 ms); P=0.001], and 5.2 ms widening in P-duration [(95%CI 0.55 to 9.77 ms); P=0.029]. Neither PR interval nor P-axis was associated with LV fibrosis index. After excluding the participants with LVEF ≤ 45% (n=3), all the previously significant associations became stronger (Supplemental Table 1). LGE-CMR LV scar did not associate with P-wave parameters. LV compliance (assessed by early diastolic global circumferential strain rate) did not associate with P-wave characteristics (data not shown). Adequately adjusted effect of LV interstitial fibrosis on QRS duration was weaker [+2.7 (95%CI −2.4 − 7.9 ms); P=0.298] than on P-wave.

LA function and P-wave indices

Deepening of PPaV1 and more abnormal PTF_{V1} was associated with an increase in LA volumes, decrease in LAEF, and LA reservoir function (Table 3). Deepening of $PPaV_1$ by 0.1 mV was associated with a decrease in LA strain by 7.5 units. While prolongation of PR interval was associated with LA function impairment, effect size was relatively small. P-duration weakly associated with LA minimum volume index. P-axis did not associate with LA function parameters. LV interstitial fibrosis did not affect LA function parameters (Supplemental Table 2).

Discussion

In this study of patients early in the continuum of structural heart disease, diffuse LV interstitial fibrosis was independently associated with abnormal PTF_{V1} after adjustment for demographics, BMI, LV mass index, and LV scar detected by LGE-CMR. Specifically, increased LV interstitial fibrosis (and hence potentially LA fibrosis[29]) resulted in gradual prolongation of $PPdV_1$ and averaged P-duration. LV interstitial fibrosis did not affect LA function. This finding represents the first evidence of the association of LV interstitial

fibrosis with interatrial conduction in patients without LA enlargement before impairment of LA function, supports previously reported association of LV fibrosis with LA fibrosis[29], and is consistent with previous works[30, 31] of the causative role of diffuse fibrosis for cardiac arrhythmias development. $PPaV_1$ demonstrated the strong associations with LA function.

Hospital ECG database screening: the PRIMERI study population

While it is well recognized that primary prevention of cardiac arrhythmias strategy has to be developed, the best screening approach is yet unclear. The PRIMERI study utilized hospital ECG database screening, and enrolled patients with wide QRS-T angle, or high QRS score, who are known to be at risk for cardiac arrhythmias (both AF and ventricular arrhythmias)[32, 22, 33, 34].

Effect of LV interstitial fibrosis on atrial electrophysiology and LA function

Fibrosis is categorized into distinct patterns: compact, patchy, interstitial, and diffuse[35]. Compact/patchy fibrosis is a replacement fibrosis[10], quantified by LGE-CMR[10]. Among patients with AF, atrial fibrosis estimated by LGE-CMR is associated with AF recurrence post-ablation[36]. LV fibrosis was detected by LGE-CMR in 13% of AF patients, and strongly associated with mortality[37]. Unfortunately, numerous technical challenges reduce reproducibility of atrial LGE fibrosis quantification[38]. In this study compact/patchy LV fibrosis did not affect atrial electrophysiology.

Our observation showed that diffuse interstitial LV fibrosis (likely via associated LA fibrosis[29]) directly affects and impairs interatrial conduction, leading to characteristically abnormal $PTF_{V1.}$ It is known that individuals with PTF_{V1} in an upper 5^{th} percentile have two-fold increased risk of incident AF[15]. Interestingly, an association with P-wave measures was observed in the presence of mild-moderate LV fibrosis, but not severe diffuse LV fibrosis which could be explained by the different nature of mild-moderate vs. severe LV fibrosis. Potentially different causes (besides collagen accumulation) could be associated with extreme expansion of extracellular matrix as measured by the high fibrosis index[26]. Our study is the first study, which quantified diffuse interstitial fibrosis in association with atrial electrophysiology. Further studies of diffuse interstitial fibrosis in patients at risk of cardiac arrhythmias are needed. Interestingly, in this study LV interstitial fibrosis impacted P-wave to a greater degree, as compared to QRS duration. This fact suggests that P-prime in V1 better than QRS duration reflects extend of interstitial fibrosis. Indeed, electrical excitation in atria propagates largely cell-to-cell, whereas QRS duration primarily reflects conduction thru His-Purkinje system, rather than thru LV myocardium, especially in patients early in the continuum of structural heart disease.

Associations between P-wave indices and LA function

LA size is a known predictor of morbidity and mortality. LA volume index predicts survival post-MI[39]. The present study also showed that PTF_{V1} and especially $PPaV_1$ can be used as a tool to predict LA size and function. The larger the LA size, the deeper the terminal negativity of P-wave in lead V_1, and the larger the $PTF_{V1.}$ Traditionally, LA size and function was characterized by $LAVi_{max}$. Results of our study are consistent with previously reported studies of P-wave indices association with LA volume[40–42]. Importantly, in

addition, we demonstrated a significant association between negative $PPaV_1$ and LA minimum volume index, global LAEF, and LA reservoir function. We also showed that the weaker the LA strain, the deeper the terminal negativity of P-wave in lead V_1. Altogether these observations characterize $PPaV_1$ as a marker of LA dysfunction, which, in turn, can signify the presence of LV diastolic dysfunction.

Out of all P-wave indices $PPaV_1$ showed the strongest association with LA volume, strain, global LAEF and LA reservoir function. Mechanistically, the following sequence of events likely takes place. In consequence of diastolic LV dysfunction in the setting of structural heart disease, LV filling pressure and then LA pressure rise, which leads to increase the LA wall tension. When the LA is overloaded, the vector of P wave rotates to the left and posteriorly in the horizontal plane causing a prominent negative component of the P wave in V_1.

Clinical importance and future directions

Our study uncovered underlying mechanisms of electrocardiographic P-wave indices presentation and further advanced our understanding of subclinical structural heart disease. Interstitial fibrosis in LV and possibly in LA is associated with abnormal PTF_{V1}, prolonged PPdV1 and P-duration, which could be used for screening of asymptomatic adults to identify individuals at risk, and serve as an intermediate outcome to track effect of future anti-fibrotic treatment.

At the same time, our study revealed strong association between LA function and $PPaV_1$. We speculate that vasodilators (e.g. ACEI, ARBs), which can unload LV and decrease LA volume[43], could possibly acutely affect PTF_{V1}, predominantly $PPaV_1$. Thus, PTF_{V1}, and $PPaV_1$ could be potentially helpful to guide therapy on the day-to-day basis. Future studies are needed to test this hypothesis.

Limitations

Our results must be interpreted in the face of certain methodological limitations. First, because LGE and T_1 mapping were not performed in the LA in our study, we were unable to obtain measures of atrial fibrosis. However, association between LV and LA fibrosis was previously shown[29]. Second, we did not calculate extracellular volume because hematocrit was obtained only in half of our study population. Third, diastolic dysfunction was not the focus of this study. Despite these limitations, our study uncovered mechanisms of abnormal PTF_{V1} appearance, reflecting interplay between primary and secondary changes in LA electrophysiology. While prolonged $PPdV_1$ reflects interstitial fibrosis in LV and potentially in LA, negative $PPaV_1$ characterizes abnormal LA size and function. Abnormal PTF_{V1} encompasses both mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AF	atrial fibrillation
LA	left atrium
LV	left ventricle
PTF_{V1}	P-terminal force in V_1
$PPaV_1$	P-prime in V_1 amplitude
$PPdV_1$	P-prime in V1 duration
HF	heart failure
CMR	cardiac magnetic resonance
LVEF	left ventricular ejection fraction
LAEF	left atrium emptying fraction
LGE	Late gadolinium enhancement
V_{max}	Maximum left atrial volume
V_{min}	minimum left atrial volume
V_{preA}	left atrial volume before atrial systole
Smax	maximum left atrial strain
SR_{max}	maximum left atrial strain rate
$LAVi_{max}$	left atrial volume indexed by body surface area
BMI	Body mass index

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Clinical Perspectives

Our work for the first time showed that LV diffuse interstitial fibrosis (but not patchy LV scar) is associated with slowing of conduction through LA (measured as duration of P-prime in V1 and averaged P-wave duration) very early in the continuum of structural heart disease, before LA enlargement, impairment of LA function, systolic and diastolic LV function. We also confirmed that impairment of LA function and increase in LA size is associated with deepening of P-prime amplitude in V1, whereas P-terminal force in V1 encompasses both mechanisms.

ECG is an inexpensive and easily available tool, which could be used to identify individuals with interstitial LV fibrosis who have indications for CMR. Duration of P-prime in V1 could serve as an intermediate marker to monitor effect of anti-fibrotic therapy. Amplitude of P-prime in V1 could be used to monitor effect of medications on LA size and function.

Our study is the first cross-sectional observation of an association between LV interstitial fibrosis and duration of P-prime in V1. Therefore, validation of our findings in a prospective cohort study is needed. Then, knowledge about mechanisms behind P-prime in V1 presentation should be disseminated amongst electrophysiologists, cardiologists, primary care physicians and other medical professionals. Routine resting 12-lead ECG is easily available at any medical institution, and healthcare facility. Measurement of P-prime in V1 duration and amplitude could be performed manually with the use of ruler, or automatically by ECG software. Manufacturers of ECG equipment should be encouraged to routinely report P-prime in V1 parameters.

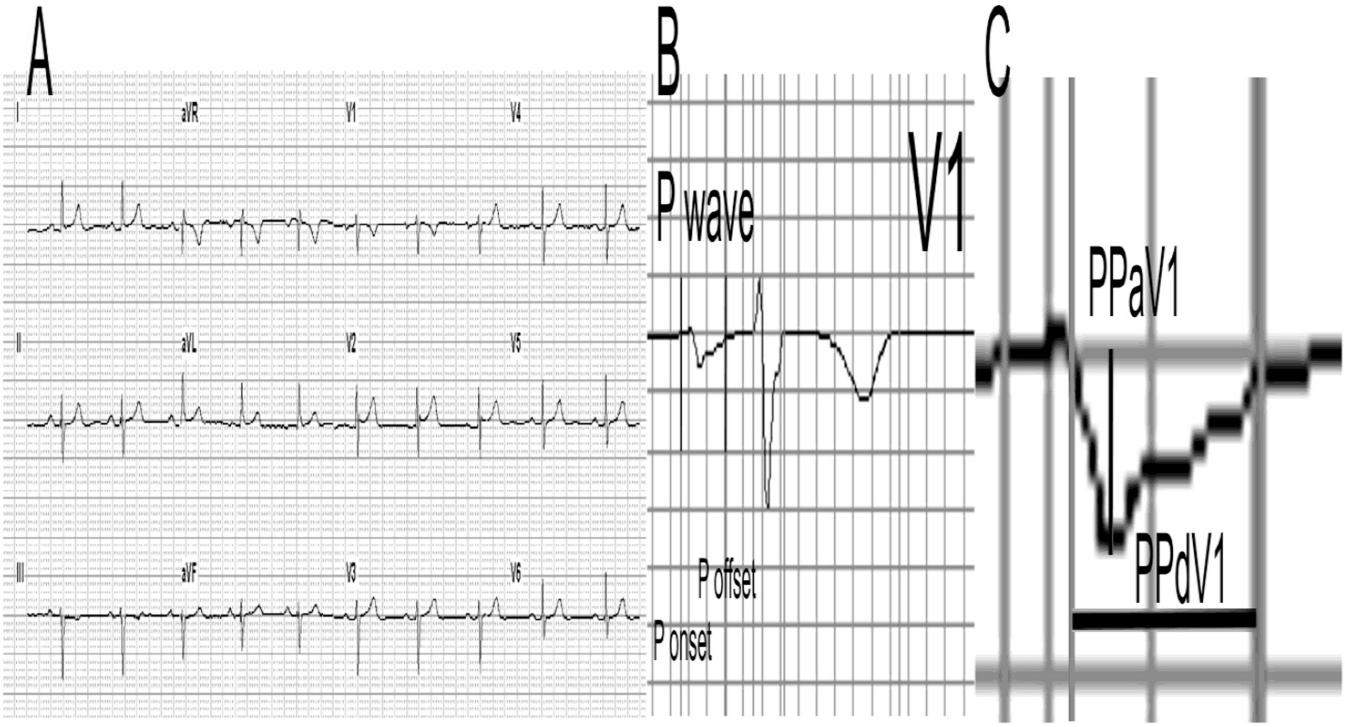

Figure 1.

Measurement of P-prime amplitude ($PPaV_1$) and P-prime duration ($PPdV_1$) in V_1 on a median beat. **A**. 12-lead ECG; **B**. Lead V_1 PQRST waveform with marked P onset and offset; **C**. P-wave in V_1 with marked $PPaV_1$ and $PPdV_1$. $PPaV_1 = -58$ μV; $PPdV_1 = 88$ ms.

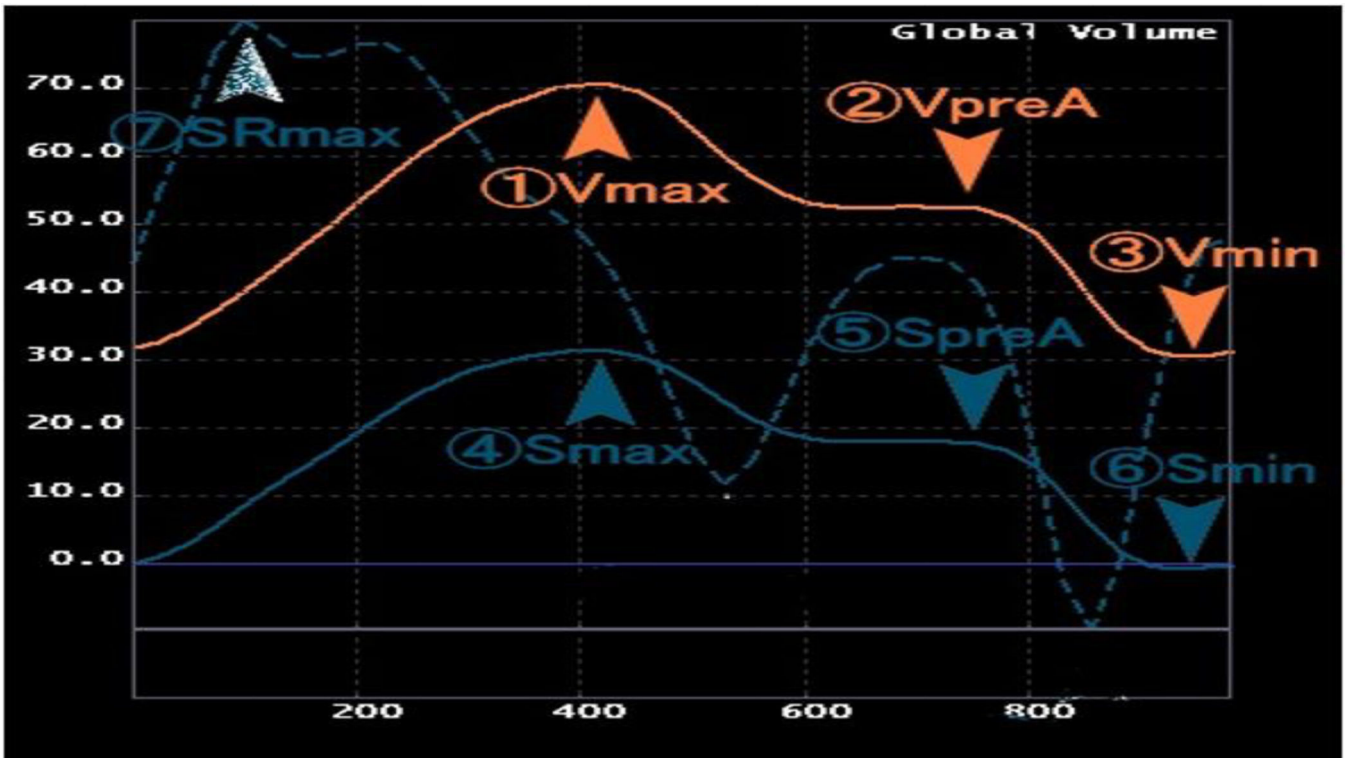

Figure 2.

Left atrial parameters: Definitions of parameters from volume (orange), strain (solid blue) and strain rate curves (dotted blue). Vmax=Maximum LA volume, VpreA= LA volume before atrial systole, Vmin=Minimum LAvolume, Smax=Maximum LA strain, SpreA=LA strain before atrial systole, Smin=Minimum LA Strain, SRmax=Maximum LA strain rate.

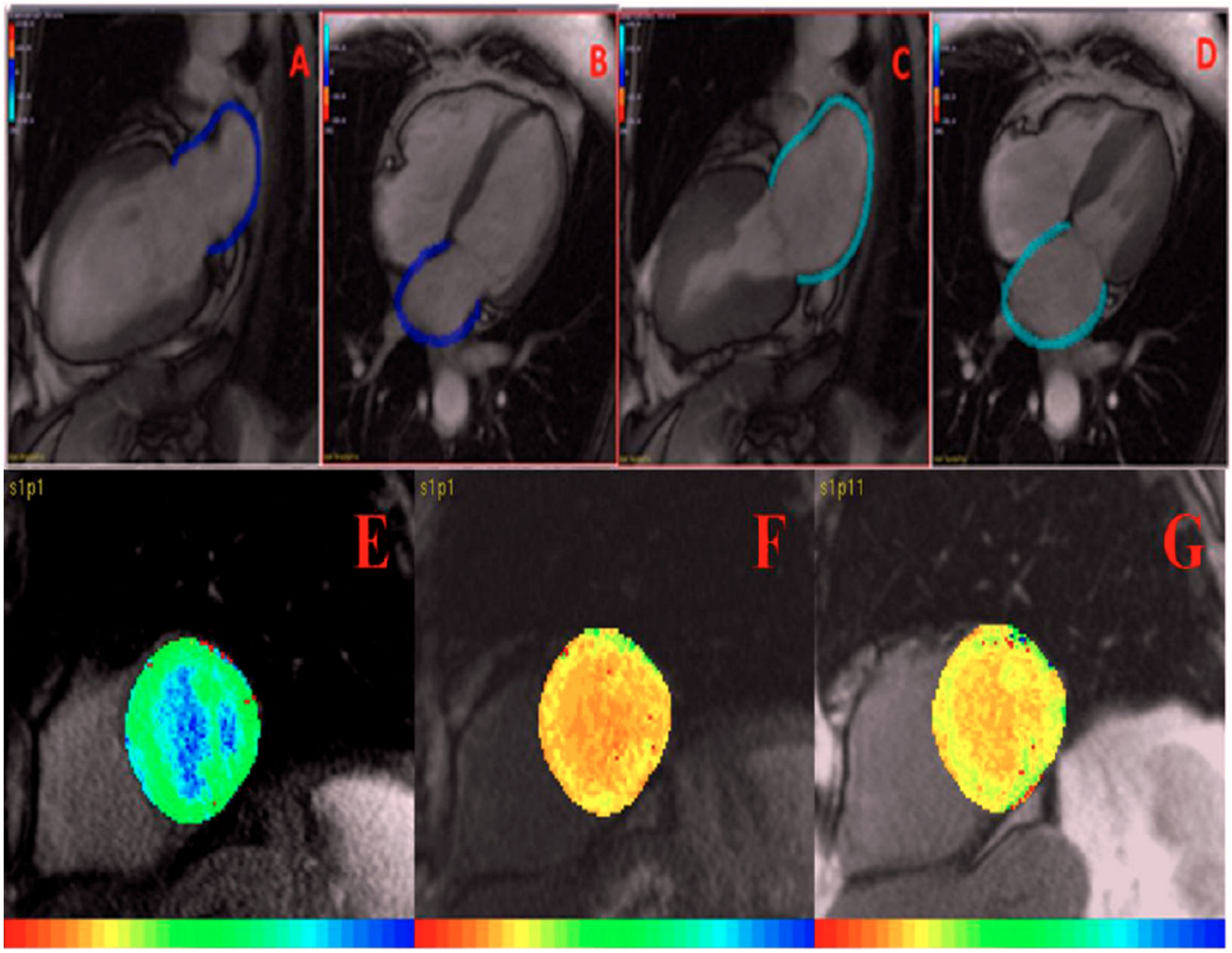

Figure 3.

(**A–C**) Cardiac Magnetic Resonance multimodality tissue tracking. **A**: end-diastolic 2 chamber view; **B**: end-diastolic 4-chamber view; **C**: end-systolic 2-chamber view; **D**: end-systolic 4 chamber view. (**E–G**) Cardiac Magnetic Resonance T_1 Mapping. **E**: Pre-contrast; **F:** 12 minutes post contrast; **G**: 25 minutes post contrast showing reduction in T_1 time in the presence of diffuse interstitial myocardial fibrosis.

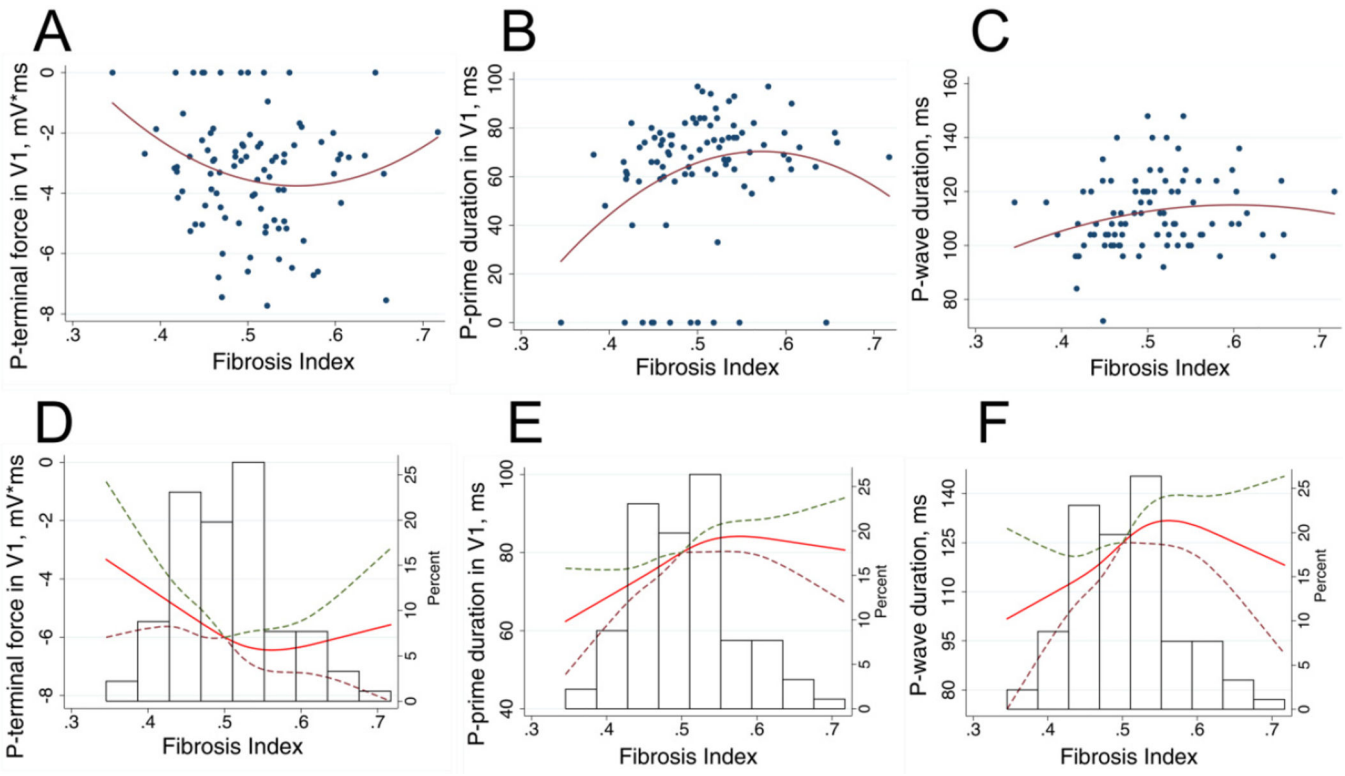

Figure 4.

Unadjusted (**A–C**) and adjusted (**D-F**) associations of P-wave indices and fibrosis. Scatterplots of (**A**) P-terminal force in V_1, (**B**) P-prime duration in V_1, (**C**) average P-wave duration (Y) against fibrosis index (X). Quadratic best fit line is shown. Cubic restricted splines depicting the association of (**D**) P-terminal force in V_1, (**E**) P-prime duration in V_1, (**F**) average P-wave duration and fibrosis index, adjusted by age, sex, race, body mass index, LA $volume_{max}$ index and LV mass index. Dashed lines represent 95% confidence intervals surrounding the estimate.

Table 1

Characteristics of study participants

	n=91
Age(SD),y	59.5(9.4)
Men,n(%)	56(61.5)
Whites,n(%)	60(65.9)
Body mass index,kg/m2	30.5(6.9)
Hypertension,n(%)	65(71.4)
Diabetes,n(%)	24(26.4)
Current or former smoker,n(%)	46(50.6)
History of MI,n(%)	14(15.4)
History of PCI/CABG,n(%)	24(26.4)
NYHA class≥II,n(%)	22(24.2)
Valvular Heart Diseases (mild),n(%)	7(13)
Systolic BP(SD),mmHg	144.3(26.2)
Diastolic BP(SD),mmHg	85.1(16.4)
eGFR(SD),ml/min/1.73m2	90.5(2.6)
Beta-blockers,n(%)	33(36.3)
ACE-I or ARBs,n(%)	36(39.6)
Ca-channel blockers,n(%)	16(17.6)
Statins,n(%)	51(56.0)
LA and LV structure and function parameters	
LA Volume index max(SD),ml/m^2	34.8(11.0)
LA Volume index min(SD),ml/m^2	16.7(7.0)
Global LAEF,ml/min	52.9(9.0)
LA conduit function(Passive EF)	28.0(9.0)
LA booster pump function(Active EF)	34.0(14.5)
LA reservoir function	122.3(56.5)
Max LA strain(SD),	26.4(8.6)
Max LA strain rate(SD),	1.18(0.42)
LV ejection fraction(SD),%	60.64(8.6)
LV mass index(SD),g/m^2	64.4(16.7)
LV Fibrosis index	0.51(0.07)
ECG parameters	
Heart rate(SD),bpm	65.0(10.7)
QRS duration(SD),ms	104.7(23.5)
P-duration(SD),ms	111.9(13.7)
P-axis(SD),deg	46.8(33.3)
PR interval(SD),ms	181.3(43.1)
PTF_{V1}(SD),mV*ms	−3.3(1.9)
P-prime amplitude in V1(SD),μV	−46.3(25.1)
P-prime duration in V_1,ms	62.7(26.1)

Table 2

Difference (95%CI) in P-wave indices by LV fibrosis index deciles

	Model	Per 1 decile of LV fibrosis index	P
PTF_{V1}, mV*ms	1	−0.57(−1.22 to +0.08)	0.086
	2	−0.62(−1.23 to +0.03)	0.061
	3	−0.76(−1.42 to −0.09)	**0.025**
P-prime amplitude in V1,μV	1	−4.86(−13.46 to +3.73)	0.264
	2	−5.68(−14.21 to +2.85)	0.189
	3	−7.12(−15.90 to +1.66)	0.110
P-prime duration in V_1,ms	1	+12.34(+3.91 to +20.77)	**0.005**
	2	+14.39(+6.05 to +22.71)	**0.001**
	3	+15.34(+6.88 to +23.79)	**0.001**
PR interval,ms	1	−1.26(−15.29 to +12.78)	0.859
	2	−5.39(−19.05 to +8.28)	0.435
	3	−5.79(−19.39 to +7.79)	0.398
Average P-duration,ms	1	+4.76(+0.30 to +9.22)	**0.0373**
	2	+5.06(+0.65 to +9.46)	**0.0253**
	3	+5.42(+0.87 to +9.97)	**0.020**
P-axis,deg	1	+6.37(−4.87 to +17.62)	0.263
	2	−1.00(−8.19 to +6.19)	0.782
	3	+1.39(−6.21 to +8.99)	0.716

General linear models. Model1 is adjusted for age, race, sex, and body mass index. Model 2 includes variables from Model 1 and LA $Volume_{max}$ index. Model 3 includes variables from Model 2, and scar and LV mass index.

Table 3

Difference (9 5% CI) in LA structure and function indices by ECG P-wave indices participants

	Per 1 mV*ms of PTF_{V1}	P	Per 0.1 mV of Pprime V_1 amp	P	Per 1ms of Pprime V_1 dur	P	Per 10 ms of PR interval	P	Per 10 ms of P-duration	P	Per 10 degrees of P-axis	P
LA Volume index max,ml/m^2	**−1.6(−2.8 to −0.4)**	**0.010**	**−11.9(−21.2 to −2.57)**	**0.013**	+0.07(− 0.03 to +0.16)	0.155	**+0.9(+0.4 to +1.5)**	**0.001**	+1.6(−0.3 to +3.4)	0.093	−0.1(− 1.3 to +1.1)	0.902
LA Volume index min,ml/m^2	**−1.2(−1.9 to −0.4)**	**0.003**	**−8.8(−14.7 to −2.9)**	**0.004**	+0.04(− 0.02 to +0.10)	0.153	**+0.7(+0.3 to +1.0)**	**<0.0001**	**+1.2 (+0.01 to +2.3)**	**0.049**	−0.3(− 1.0 to +0.5)	0.495
Global LAEF,%	**+1.1(+0.1 to +2.1)**	**0.026**	**+8.4(+0.9 to +15.9)**	**0.029**	−0.03(− 0.10 to +0.05)	0.515	**−0.5(−0.9 to − 0.004)**	**0.048**	−0.9 (− 2.4 to +0.6)	0.236	+0.5(− 0.5 to +1.4)	0.318
LA reservoir function,%	**+7.2(+1.1 to +13.3)**	**0.021**	**+54.7(+7.8 to +101.5)**	**0.023**	−0.28(− 0.75 to +0.20)	0.253	−2.6(−5.5 to +0.4)	0.084	−5.7(− 15.0 to +3.6)	0.226	+2.0(− 4.0 to +8.0)	0.509
LA conduit function,%	+0.8(−0.2 to +1.8)	0.107	+7.5(−0.1 to +15.2)	0.053	−0.06(− 0.14 to +0.01)	0.090	−0.3(−0.7 to +0.1)	0.168	−0.2(− 1.7 to +1.3)	0.830	+0.7(− 0.3 to +1.6)	0.164
LA booster pump function,%	+0.8(−0.9 to +2.4)	0.378	+3.5(−9.5 to +16.5)	0.591	+0.05(− 0.08 to +0.17)	0.455	−0.3(−0.1 to +0.5)	0.482	−1.4(− 3.8 to +l.l)	0.277	−0.3(− 1.9 to +1.3)	0.717
LA Strain	+0.9(−0.1 to +1.8)	0.064	**+7.5(+0.4 to +14.5)**	**0.037**	−0.05(− 0.12 to +0.02)	0.190	**−0.5(−0.9 to −0.1)**	**0.027**	−0.8(− 2.2 to +0.6)	0.259	−0.6(− 1.5 to +0.3)	0.167
LA strain Rate	+0.04(− 0.01 to +0.08)	0.129	+0.3(−0.04 to +0.7)	0.083	−0.003(− 0.006 to +0.001)	0.144	**−0.03(−0.05 to − 0.01)**	**0.007**	−0.04(− 0.1 to +0.02)	0.163	−0.00(− 0.05 to +0.04)	0.922

All models are general linear models. All models are adjusted for age, race, sex, and body mass index