Driver characteristics associated with structurally and electrically remodeled atria in persistent atrial fibrillation

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BACKGROUND Recent studies suggest persistent atrial fibrillation (AF) is maintained by localized focal or rotational electrical activations termed drivers.

OBJECTIVE The purpose of this study was to evaluate how left atrial (LA) dilation and time in AF impact persistent AF mechanisms.

METHODS Patients with persistent AF <2 years underwent electrocardiographic image mapping. Potential drivers (PDs) were defined as rotational wavefront activity ≥1.5 revolutions or focal activations. Distribution of PDs was recorded using an 18-segment model.

RESULTS One hundred patients were enrolled (age 61.3 ± 12.1 years). Of these patients, 47 were hypertensive, 14 had diabetes mellitus, and 10 had ischemic heart disease. AF duration was 8 [5–15] months. Median LA diameter was 39 [33–43] mm. Although LA dimensions did not correlate with overall PD burden or distribution, there was a modest correlation between increasing LA area (r = 0.235; *P* = .024) and LA volume (r = 0.216; *P* = .039) with

proportion of PDs that were rotational. Although time in AF did not correlate with overall PD burden or distribution, there was a correlation between time in AF and the number of focal PDs (r = 0.203; *P* = .044). Female gender, increasing age, and hypertension also were associated with an increase in focal PDs.

CONCLUSION This is the first study to demonstrate different AF mechanisms in patient subgroups. Greater understanding of patient-specific AF mechanisms may facilitate a tailored approach to AF mapping and ablation.

KEYWORDS Arrhythmia; Atrial fibrillation; CardioInsight; Electrocardiographic imaging; Mapping; Remodeling

Introduction

The underlying mechanisms of persistent atrial fibrillation (AF) remain poorly understood. Recent mapping studies have suggested persistent AF is maintained by intermittent localized focal or rotational activity that can originate in either atrium, the pulmonary veins (PVs), or the vena cava.[1–4] These activations have been termed "drivers," and it has been suggested that the burden and distribution of these drivers are patient-specific and may influence the success rates of catheter ablation for AF.[5,6]

Numerous factors can affect atrial substrate and the likely success rates after catheter ablation. Perhaps the best recognized factors are the time spent in persistent AF, which

causes progressive electrical remodeling, and increasing left atrial (LA) dimensions, which is associated with predominantly structural remodeling in terms of scarring and disruption of architecture.[7]

The CardioInsight electrocardiographic imaging (ECGI) system (Medtronic, Minneapolis, MN) is a noninvasive mapping technology that is able to panoramically map both atria simultaneously to identify focal and rotational activity that may act as potential drivers (PDs) of AF.[5,8,9] ECGI has been used to study the underlying mechanisms and to target PDs in AF.[4,5,8–11]

This study sought to evaluate the relationship between structural remodeling in terms of increasing LA dimensions and electrical remodeling as a result of greater duration of persistent AF and the burden and distribution of PDs in patients with persistent AF utilizing ECGI panoramic mapping. We hypothesized that increasing duration of AF and increasing LA dimensions would correlate with a greater burden and distribution of PDs.

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KEY FINDINGS

- Increasing left atrial (LA) dimensions had no impact on driver burden or distribution but was associated with an increase in the proportion of rotational potential drivers (PDs).

- Time in atrial fibrillation (AF) did not have an impact on PD burden or distribution but did correlate with shorter AF cycle lengths in the LA and pulmonary veins.

- Female gender, increasing age, and hypertension were associated with increased focal PDs.

Methods

Patient population

Patients undergoing first-time catheter ablation for persistent AF of <2 years' duration were prospectively enrolled. This is a substudy of a trial registered on ClinicalTrials.gov (NCT03394404), and the research reported adhered to CONSORT guidelines. Ethical approval was provided by the East Midlands–Leicester South Research Ethics Committee. REC Reference: 17/EM/0333, IRAS project ID: 218367. All participants provided written informed consent. Exclusion criteria included LA diameter >5 cm, left ventricular ejection fraction <40%, New York Heart Association functional class III or IV heart failure, age <18 years or >80 years, hypertrophic cardiomyopathy, or greater than moderate valve disease.

Noninvasive ECGI mapping

Our noninvasive mapping method has been reported previously.[4] In brief, patients were fitted with an ECGI 252-electrode mapping array vest (CardioInsight, Medtronic). Noncontrast computed tomographic scan was performed and then segmented using the ECGI system workstation (CardioInsight, Medtronic) to produce a 3-dimensional biatrial shell.

All ECGI mapping was performed before the patient underwent pulmonary vein isolation (PVI) with cryoablation. If patients were in sinus rhythm upon arrival to the catheter laboratory, AF was induced by pacing, and the rhythm was allowed to settle for at least 10 minutes before mapping. The ECGI software collects short individual segments of atrial rhythm (minimum duration of 840 ms) with a cumulative 15 seconds of atrial activity required to generate each map. If the ventricular rate was too rapid to allow acquisition of segments, intravenous metoprolol or verapamil was administered. If the drug failed to slow the ventricular rate sufficiently, then adenosine was administered.

Offline ECGI analysis

The method for offline ECGI analysis has been reported previously.[4] In brief, ECGI PD maps were analyzed offline by 2 operators. First, the surface ECGI recordings were reviewed, and leads with excessive noise were removed. Second, the raw unipolar electrograms were reviewed, and those with excessive noise were removed. The ECGI software then computed and transposed PDs onto a composite biatrial shell. The 2 operators then assessed each individual PD and removed those that were deemed implausible from the final analysis. PDs were defined as either rotational activations completing ≥1.5 revolutions or focal activations with radial spread, as this definition has been used in similar studies.[2–4] PDs were assessed in terms of the total number of PD occurrences, the stability of rotational activation patterns (mean number of rotations), and the distribution of PDs utilizing an 18-segment biatrial map used previously.[4] PDs were assessed for the atria in total and subdivided to investigate the PVs and posterior wall together, or elsewhere in the atria excluding the PVs and posterior wall.

Contact electrogram recordings

During the ablation procedure, electrogram data were displayed and recorded using the LabSystem Pro system (Boston Scientific, Marlborough, MA). Contact electrograms were recorded at the LA and right atrial (RA) appendages, proximal coronary sinus (CS), and each PV before PVI using either a quadripolar catheter or the Achieve mapping catheter (Medtronic). Cycle lengths (CLs) were recorded over 30 cycles at each location.

Study endpoints

The primary endpoints of this study were the association between PD burden and distribution as defined on the ECGI system and correlation with LA dimensions and time in persistent AF. To determine other interacting factors, the relationship between PDs and other key demographic parameters were investigated individually and as part of a multivariate analysis.

Statistical analysis

All statistical analysis was performed using IBM SPSS Statistics, Version 25 (IBM Corp., Armonk, NY). $P <.05$ was considered significant. Normally distributed data are expressed as mean ± SD and not normally distributed data as median [interquartile range]. The Student t test was performed for normally distributed variables, and the Mann-Whitney U test was performed for nonparametric variables. Correlation was assessed for nonlinear relationships by Spearman rank correlation. Multivariate analysis was performed using binary logistic regression to determine whether there were predictors of PD burden or PD distribution, with the top quartile taken as a positive result. Factors included as categorical covariates were gender, hypertension, diabetes mellitus, and ischemic heart disease. Continuous factors included age, body mass index (BMI), LA diameter, left ventricular function, duration of AF, and time from initial AF diagnosis. Factors were removed from the model in a stepwise fashion until only factors with $P <.10$ remained in the final model.

Table 1   Baseline characteristics of the study participants (N = 100)

Age (y)	61.3 ± 12.1
Male	74 (74.0)
Hypertension	47 (47.0)
Diabetes mellitus	14 (14.0)
Ischemic heart disease	10 (10.0)
Cerebrovascular accident	9 (9.0)
Obstructive sleep apnea	3 (3.0)
Body mass index (kg/m^2)	29.8 ± 4.6
CHA_2DS_2VASC score	1 [0–3]
NYHA functional class	1 [1–1]
EHRA classification	1 [1–2]
LA diameter (mm)	39 [33–43]
LA Volume (mL)	62 [49–83]
Median duration of AF: diagnosis to procedure (mo)	24 [16–48]
Duration of persistent AF (mo)	8 [5–15]
Persistent AF duration <12 mo	67 (67.0)
Persistent AF duration >12 mo	33 (33.0)

Values are given as mean ± SD, n (%), or median [interquartile range].
AF = atrial fibrillation; EHRA = European Heart Rhythm Association; LA = left atrium; NYHA = New York Heart Association.

Results

A total of 100 patients were enrolled between January and December 2018. Demographic data are given in Table 1. Of the 100 patients, mean age was 61.3 ± 12.1 years; 74 (74%) were male; 47 patients (47%) were diagnosed with hypertension, 14 (14%) with diabetes mellitus, 10 (10%) with ischemic heart disease, 9 (9%) with cerebrovascular accident, and 3 (3%) with obstructive sleep apnea. Mean BMI was 29.8 ± 4.6 kg/m^2. Median time from diagnosis to ablation was 24 [16–48] months, and median duration of continuous AF (time spent in AF) was 8 [5–15] months. Median LA diameter was 39 [33–43] mm. At the time of ablation, 67 patients had persistent AF of <12 months' duration, and 33 had AF >12 months' duration. ECGI maps were generated in 99 of 100 patients (in 1 patient the ventricular rate could not be reduced sufficiently and adenosine produced frequent ectopics). Analysis of the baseline ECGI maps is given in Supplemental Table 1.

Correlation with ECGI PD analysis

Correlations with PD burden and PD distribution are given in Tables 2 and 3, respectively. Comparisons of PD burden and distribution with categorical factors are given in Supplemental Tables 2 and 3, respectively. Figure 1 summarizes the factors that had a significant impact on PDs of persistent AF.

Impact of LA structural remodeling on AF mechanisms

PD burden

Spearman rank correlation analysis comparing PD burden to LA diameter (r = 0.164; P = .113), LA area (r = –0.059;

P = .575), and LA volume (r = –0.030; P = .775) did not reveal a significant correlation (Table 2). There was a significant but modest correlation between increasing LA area (r = 0.235; P = .024) and LA volume (r = 0.216; P = .039) with proportion of PDs that were rotational.

PD distribution

There was no significant correlation between PD distribution (total number of segments harboring PDs within the 18-segment biatrial model) and LA diameter (r = 0.099; P = .340), LA area (r = –0.089; P = .395), and LA volume (r = –0.090; P = .394) (Table 3).

Contact mapping

There was no correlation between LA dimensions and LA and RA appendages, proximal CS, or mean PV CL (Supplemental Table 4).

Impact of electrical remodeling

PD burden

Neither the time from initial diagnosis of AF nor the duration of continuous persistent AF correlated with PD burden (r = 0.079; P = 0.434; and r = 0.104; P = .304, respectively) (Table 2). However, duration of continuous persistent AF did correlate significantly with the number of focal PDs (r = 0.203; P = .044) (Table 2). Figure 2 shows ECGI composite maps for 2 patients: patient no. 93 who spent 16 months in AF with multiple risk factors for AF progression who had fewer PDs compared to patient no. 77 who spent 11 months in AF with no risk factors.

PD distribution

There was no significant correlation between PD distribution (total number of segments harboring PDs within the 18-segment biatrial model) and time from initial diagnosis of AF (r = –0.023; P = .822) or duration of continuous persistent AF (r = –0.070; P = .487). Time from initial diagnosis correlated with proportion of PDs identified at the septum (r = –0.245; P = .014) and trended toward significance with proportion in the LA (r = 0.180; P = .075) (Table 3).

Contact mapping

There was a significant correlation between duration of persistent AF and shortening of CL recorded at the proximal CS (r = 0.210; P = .036), and there was a trend toward significance with average of the PVs (r = 0.181; P = .072) (Supplemental Table 4).

Impact of other factors on PD<.case> burden and distribution

Hypertension

There was no significant difference in PD burden or distribution in patients with hypertension compared to those without (Supplemental Tables 3 and 4). The number of focal PDs was significantly higher in patients with hypertension compared

Table 2   Correlation between factors and PD burden

	PD burden	Proportion of PD at PVs and posterior wall	Proportion of rotational PDs (%)	Sum rotations	Sum foci	Rotational stability
Age						
r	0.053	−0.041	−0.099	−0.026	0.210	−0.002
P value	.598	.684	.330	.794	.037*	.986
BMI						
r	−0.283	−0.029	−0.138	−0.304	−0.052	0.105
P value	.005*	.779	.176	.002*	.611	.307
LA diameter						
r	0.164	−0.067	0.109	0.146	0.073	−0.012
P value	.113	.520	.297	.159	.483	.909
LA area						
r	−0.059	−0.093	0.235	0.063	−0.138	−0.071
P value	.575	.377	.024*	.547	.191	.501
LA volume						
r	−0.030	−0.022	0.216	0.063	−0.112	−0.127
P value	.775	.835	.039*	.551	.292	.230
LV function						
r	0.135	−0.004	0.052	0.106	0.030	0.079
P value	.186	.967	.612	.302	.773	.446
CHA$_2$DS$_2$-VASc score						
r	−0.039	−0.114	−0.155	−0.133	0.211	−0.022
P value	.701	.262	.125	.188	.036*	.828
Initial AF diagnosis						
r	0.079	0.098	−0.010	0.033	0.114	−0.001
P value	.434	.333	.921	.741	.263	.991
Duration of persistent AF						
r	0.104	0.097	0.025	0.020	0.203	0.158
P value	.304	.341	.810	.840	.044*	.118

Potential driver (PD) burden defined as total number of PD occurrences.

$P <$ .05 was considered significant.

BMI = body mass index; LV = left ventricle; PV = pulmonary vein; r = Spearman rho; other abbreviations as in Table 1.

*Factors with a significant P value $<$ .05.

to those without (14.13 ± 6.75 vs 10.77 ± 5.49; P = .008). This corresponded to a trend toward a reduction in the proportion of PDs that were rotational in patients who were hypertensive compared to those who were not (80.85% ± 10.15% vs 84.39% ± 9.45 %; P = .075) (Supplemental Table 3). There was no significant difference in CL measurements between patients with vs those without hypertension (Supplemental Table 5).

BMI
Increasing BMI was negatively correlated with PD burden (r = −0.283; P = .005) and negatively correlated with the

Table 3   Correlation between factors and PD distribution

	Total segments	Proportion of segments at the PVs and posterior wall	Proportion of segments in LA (%)	Proportion of segments in RA (%)
Age (y)	0.119 (.237)	−0.041 (.684)	−0.002 (.987)	0.140 (0,167)
Body mass index	−0.168 (.097)	−0.029 (.779)	0.012 (.909)	−0.072 (.483)
LA diameter	0.099 (.340)	−0.067 (.520)	0.132 (.204)	−0.145 (.162)
LA area	−0.089 (.395)	−0.093 (.377)	−0.077 (.464)	−0.086 (.415)
LA volume	−0.090 (.394)	−0.022 (.835)	0.037 (.729)	−0.107 (.311)
LV function	−0.032 (.754)	−0.004 (.967)	−0.099 (.339)	0.002 (.986)
CHADsVASc score	0.002 (.985)	−0.114 (.262)	0.069 (.499)	0.025 (.805)
Initial AF diagnosed	−0.023 (.822)	0.098 (.333)	0.180 (.075*)	−0.036 (.725)
Duration of persistent AF	−0.070 (.487)	0.097 (.341)	0.071 (.482)	−0.126 (.214)

Values are given as r (P value).

PD distribution defined as total number segments harboring PDs.

$P <$ .05 was considered significant.

RA = right atrium; other abbreviations as in Tables 1 and 2.

*$P <$ .10.

Factors impacting drivers of persistent AF

↑Focal PDs
- Continuous time in AF
- Female gender
- Increasing age
- Hypertension
- ↑CHA$_2$DS$_2$.VASc

↑Rotational PDs
- Increasing LA dimensions

PD (Potential Driver). p < 0.05 taken to be significant.
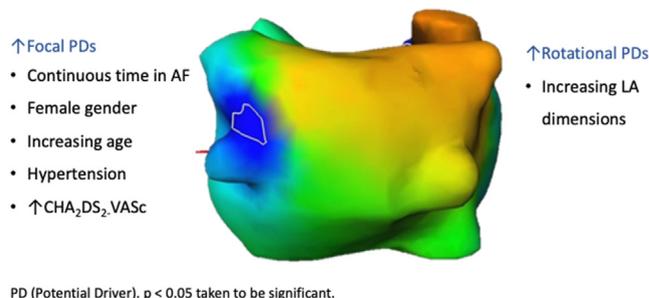
Figure 1   Factors impacting drivers of persistent atrial fibrillation (AF). Posterior-anterior view of an electrocardiographic imaging activation map is shown. There is a focal driver with radial spread originating from the left inferior pulmonary vein. **Left:** Factors that were found to be significant predictors of increased focal PDs (potential drivers). **Right:** Factors that were predictors of increased rotational potential drivers. LA = left atrium.

sum of revolutions (r = –0.304; P = .002). There was a trend toward significance with BMI and PD distribution (r = –0.174; P = .089). There was no correlation between BMI and proportion of rotational PDs, sum of revolutions, or CL measurements.

Obstructive sleep apnea
Comparison of PD burden and distribution in patients with obstructive sleep apnea to those without revealed a significant difference in rotational stability only (2.82 ± 1.00 vs 2.28 ± 0.38; P = .026). There was no significant difference in PD burden, PD distribution. or CL measurements.

Diabetes mellitus
There was no significant difference in PD burden, PD distribution, or CL measurements in patients with diabetes mellitus compared to those without.

Gender
There was no impact of gender on total PD burden and distribution. Although there was no difference in the proportion of segments in the LA harboring drivers, there were significantly more segments at the septum harboring PDs in men (13.21 ± 4.37 vs 10.40 ± 6.41; P = .015) and significantly more segments in the RA harboring PDs in women (25.98 ± 6.98 vs 30.46 ± 7.43; P = 0.007) (Supplemental Table 3). There was a trend toward more focal PDs in women (11.73 ± 5.63 vs 14.15 ± 7.78; P = .092) and toward fewer PDs being located at the PVs and posterior wall (0.28 ± 0.07 vs 0.26 ± 0.08; P = .083) (Supplemental Table 2). There was a significantly shorter mean PV CL in male patients compared to female patients (179.72 ± 26.78 vs 193.30 ± 31.58; P = .037) (Supplemental Table 5).

Age
There was no significant correlation between age and total PD burden or distribution. However, there was a correlation between number of focal PDs and increasing age (r = 0.210; P = .037) (Table 2). There also was a trend toward increasing mean PV CL with greater age (r = 0.195; P = .052) (Supplemental Table 4).

Multivariate analysis
Results of the multivariate analyses are given in Table 4 and Supplemental Table 6. The only factor remaining in the final model predicting PD burden was BMI (odds ratio [OR] 0.808; 95% confidence interval [CI] 0.710–0.919; P = .001), and the only factor predicting PD distribution in the final model was age (OR 1.087; 95% CI 1.022–1.157; P = .008).

Factors remaining in the final model associated with a higher burden of focal PDs were male gender (OR 0.248; 95% CI 0.079–0.783; P = .017); BMI (OR 0.874; 95% CI
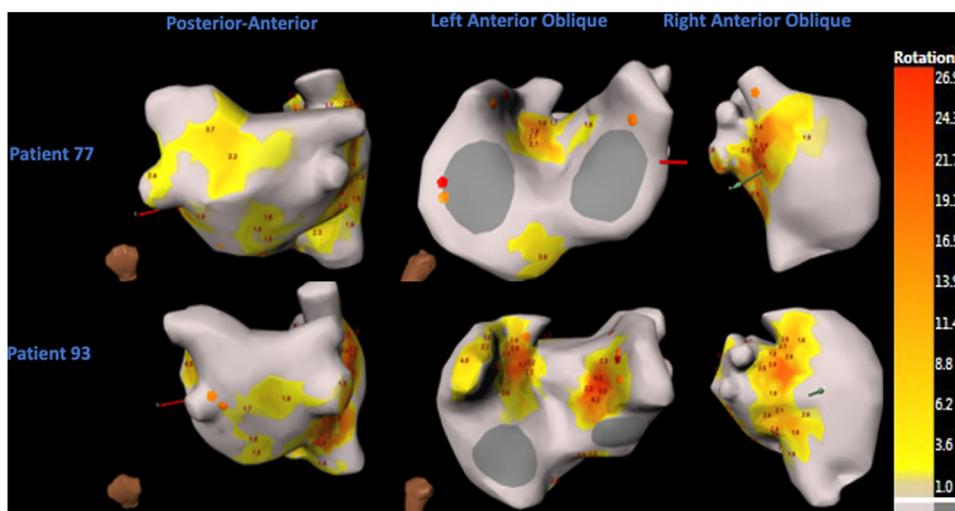

Figure 2   Electrocardiographic imaging (ECGI) composite maps of 2 patients with different risk factors. Comparison of ECGI composite maps shows patient no. 93 **(bottom)** who spent 16 months in atrial fibrillation (AF) and had cardiac risk factors of diabetes mellitus and hypertension who unexpectedly recorded fewer drivers compared to patient no. 77 **(top)** who was in AF for 11 months and had no other significant risk factors.

Table 4 Multivariate analysis of factors predicting PD burden and distribution

	Odds ratio	95% Confidence interval	P value
Multivariate analysis in predicting PD burden			
Age	1.007	0.944–1.074	.839
Male gender	1.589	0.359–7.034	.542
Body mass index	0.809	0.688–0.952	.011*
Hypertension	2.188	0.618–7.740	.225
Diabetes mellitus	0.325	0.031–3.445	.351
Duration of persistent AF	0.974	0.895–1.059	.535
Time from initial AF diagnosis	1.001	0.990–1.012	.894
Left atrial diameter	1.012	0.909–1.127	.829
Left ventricular ejection fraction	1.050	0.956–1.155	.307
Ischemic heart disease	0.754	0.088–6.487	.797
Multivariate analysis in predicting PD distribution			
Age	1.066	0.991–1.147	.084
Male gender	0.965	0.243–3.841	.960
Body mass index	0.914	0.792–1.056	.223
Hypertension	2.308	0.652–8.165	.194
Diabetes mellitus	0.583	0.118–2.886	.509
Duration of persistent AF	1.015	0.931–1.106	.737
Time from initial AF diagnosis	1.009	0.998–1.021	.117
Left atrial diameter	1.040	0.934–1.158	.471
Left ventricular ejection fraction	0.990	0.902–1.088	.839
Ischemic heart disease	0.878	0.136–5.669	.891
Multivariate analysis in predicting focal PD burden			
Age	1.002	0.945–1.063	.943
Male gender	0.228	0.057–0.912	.037*
Body mass index	0.865	0.748–1.000	.050*
Hypertension	3.356	0.893–12.614	.073
Diabetes mellitus	0.469	0.088–2.486	.373
Duration of persistent AF	1.101	1.017–1.192	.017*
Time from initial AF diagnosis	0.995	0.981–1.009	.456
Left atrial diameter	1.003	0.902–1.114	.961
Left ventricular ejection fraction	1.033	0.943–1.132	.485
Ischemic heart disease	2.058	0.322–13.141	.446

P < .05 was considered significant.
Abbreviations as in Tables 1 and 2.
*Factors for which P < .1.

0.772–0.990; P = .034); and duration of persistent AF (OR 1.104; 95% CI 1.022–1.193; P = .012). Hypertension trended toward significance (OR 2.956; 95% CI 0.958–9.122; P = .059).

There were no significant factors in the final model associated with a higher proportion of PDs being rotational, but hypertension trended toward significance (OR 0.365; 95% CI 0.133–1.003; P = .051). There were no predictors of proportion of PDs located at the posterior wall and PVs.

Discussion
Main findings
This is the first study to noninvasively evaluate driver characteristics in structurally and electrically remodeled atria in persistent AF. (1) Increasing LA dimensions had no impact on driver burden or distribution but was associated with an increase in the proportion of PDs that were rotational. (2) Time in continuous AF had no impact on total PD burden but did correlate with the burden of focal PDs, which was borne out in the multivariate analysis. Time in AF did not have an impact on how distributed PD were throughout the atria but was associated with a greater proportion of drivers being found in the LA and septum. Increasing time in persistent AF also correlated with shorter AF CL in the LA and PVs. (3) Female gender, increasing age, and hypertension were associated with increased focal PDs. (4) Gender had no impact on total PD burden or distribution in terms of the number of segments harboring PD. However, there was a higher proportion of PDs at the septum in men and in the RA in women. Women also had more focal PDs, which was borne out on multivariate analysis. PV CL was shorter in men. (5) Age did not affect total PD burden and distribution, but it was associated with an increase in focal PDs and longer PV CL.

Remodeling and AF mechanisms
There is uncertainty regarding how to customize antiarrhythmic drug therapy or catheter ablation strategies for treatment of AF. Evidence for any standardized ablation strategy beyond PVI for treatment of persistent AF is limited. Therefore, there is increasing interest in understanding AF mechanisms in order to facilitate customized patient-specific strategies for ablation. Although numerous studies have examined how atrial histology and tissue electrophysiology are impacted by different types of remodeling, no studies have evaluated how they affect AF mechanisms in the fibrillating human atria.

Impact of LA structural remodeling of AF mechanisms
Conditions causing increased atrial stretch were found to underlie AF in the majority of patients in the Framingham study and is a consistent etiologic factor in the development of AF.[12–18] Conditions such as valvular heart disease, heart failure, and hypertension all cause chronic atrial stretch leading to LA dilation, with heterogeneous changes in atrial architecture such as myocyte hypertrophy and fibrosis.[19–23] Atrial stretch causes reduced voltage throughout the atria and discrete areas of electrical scar, reduced conduction velocity with conduction heterogeneity, anisotropy and areas of block, complex fractionated atrial electrograms and double potentials, and greater inducibility of AF.[21–23] Interestingly, atrial stretch does not seem to lengthen refractory periods, as occurs after time spent in AF, but in most of these studies the effective refractory period actually was increased.[21–23]

In this study, increasing LA measurements (LA diameter, area, and volume) did not correlate with either PD distribution or burden overall. However, there was modest correlation between increasing LA area and LA volume with proportion of PDs that were rotational (r = 0.235; P =

.024; and r = 0.216; *P* = .039, respectively). This finding suggests that scarring and localized conduction velocity slowing may promote localized reentry,[24,25] despite the increased effective refractory period that occurs with atrial stretch and increasing LA dimensions.

Figure 2 shows PD burden and distribution in patient no. 77 (AF duration 3 months and no significant risk factors for developing AF) and patient no. 93 (AF duration 22 months, diabetes mellitus, and hypertension). ECGI mapping arguably demonstrates similar PD burden and distribution despite a difference in AF duration and risk factors. Therefore, progression of AF mechanisms may not be linear and clearly dependent on risk factors conventionally thought to determine progression of AF. Patient-tailored substrate ablation ultimately may depend on AF mapping rather than risk factor profiling.

Impact of duration on mechanisms of AF
Animal models have demonstrated that time spent in AF causes heterogeneous shortening of refractory periods and hence a reduction in AF CL.[26] This is thought to be predominantly to downregulation of L-type calcium channels, although other cellular changes also occur.[27] Time spent in AF also causes structural remodeling, which overlaps with that seen with atrial stretch, including a degree of fibrosis and atrial dilation.[28] Therefore, it may not be possible to untangle fully which changes relate to mechanical stretch and structural remodeling, and which relate to longer time in AF and predominantly electrical remodeling.

The duration of AF correlated with the number of focal PDs but did not have an impact on rotational PDs or PD distribution. Reduced refractory periods might be expected to involve increased reentry. This was not evident in terms of rotational PDs, which are thought to be rotors, but could have had an impact on "wandering wavelet" mechanisms, which are not assessed by the ECGI system. The increase in focal PDs may be related to cellular calcium loading in AF or perhaps may be due to progressive autonomic remodeling causing increased automaticity.

Other factors and AF
It is recognized that outcomes for AF ablation are worse in women.[29] In this study, female gender was associated with an increase in RA PDs and an increase in focal PDs. This may explain the diminished impact of a standard PVI lesion set for women. Likewise, increasing age and a history of hypertension also were associated with an increase in focal PDs. This may be related to autonomic remodeling in these subsets of patients. Further exploration of how the mechanisms of AF differ between subgroups may highlight which patients are most likely to benefit from which customized ablation approach.

There currently is interest in prevention of AF by managing the risk factors and a move toward holistic management of AF by combining risk factor modification with catheter ablation.[30]

In this study, there was a significant negative correlation between increasing BMI and number of PDs, and also reduced distribution of drivers. Studies have shown that patients who are overweight or obese have increased AF incidence, increased postoperative AF, and increased recurrence after catheter ablation.[31] It would have been expected that the burden and distribution of PDs would increase in patients as BMI increases. It may be that as BMI increases, the ECGI mapping vest is farther from the heart, thus hindering mapping. Decreased atrial voltage also may reduce detection of PDs. This may highlight the limitations of ECGI mapping of AF in obese patients.

Study limitations
This study relied on the ECGI mapping system to identify PDs. It is accepted that not all PDs visualized using the system are necessarily real or mechanistically important. Although several published studies reported using this technology, further validation of the ECGI system is required to improve the accuracy of the system.

Ideally, to determine the impact of time in AF or increasing LA dimensions, the atria before and after a period in AF, or before and after LA dilation, should be studied. Strictly, this study showed an association between driver characteristics as determined by ECGI mapping and both increasing time in AF and increasing LA dimensions.

The correlations demonstrated were modest. This may be partly due to methodologic constraints with driver mapping but also may be related to overlap between different forms of atrial remodeling and the complex interplay between different etiologic factors for this multifactorial disease. In addition, other factors remain difficult to quantify, such as autonomic remodeling. Nevertheless, it was possible to show different effects on AF mechanisms in various patient subgroups and with time in AF vs LA dilation specifically.

Conclusion
This is the first study to demonstrate different impacts on AF mechanisms in various patient subgroups. The predominantly structural remodeling seen with LA dilation was associated with increased rotational PDs, and the predominantly electrical remodeling seen with increasing duration of AF was associated with increased focal PDs. Female gender, increasing age, and hypertension were associated with increased focal PDs. The low r values likely are impacted by methodologic difficulties with driver mapping and with overlap in terms of these remodeling processes. Further elucidation of patient-specific AF mechanisms may facilitate a patient-tailored approach to AF mapping and ablation.

Appendix
Supplementary data
Supplementary data associated with this article can be found in the online version at 10.1016/j.hroo.2022.09.016.

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