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

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An evaluation of electrical and structural remodelling in persistent atrial fibrillation using non-invasive mapping.

100 Persistent AF Patients
< 2 years duration

Factors impacting drivers of persistent AF

ECGI Mapping
- Jacket applied
- CT Scan performed
- Bi-atrial map segmented from CT
- 15 Seconds of AF recorded
- Correlation between PDs and factors performed.

↑Focal PDs
- Continuous time in AF
- Female gender
- Increasing age
- Hypertension
- ↑CHA₂DS₂-VASc

↑Rotational PDs
- Increasing LA dimensions

PD (Potential Driver), p < 0.05 taken to be significant.

Potential Drivers (PD) defined as either:
- Focal
- Rotational activations > 1.5 revolutions
Driver characteristics associated with structurally and electrically remodelled atria in persistent atrial fibrillation.

Short title: Driver characteristics and remodelling in Persistent AF

Word Count: 4940

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Conflict of Interest

Ross Hunter has received research grants from Medtronic, educational grants from Biosense Webster, and speaker fees from Medtronic and Biosense Webster.

Pier Lambiase receives research grants from Medtronic, Abbott and Boston Scientific. This work is supported by UCLH Biomedicine NIHR and Barts BRC.

Richard Schilling receives speaker fees and education grants from Biosense Webster, Medtronic, Boston Scientific and Abbott.

Ross Hunter, Richard Schilling, Shohreh Honarbakhsh were inventors of the STAR mapping system and are shareholders in Rhythm AI Ltd.

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ABSTRACT

Background:
Recent studies suggest persistent AF is maintained by localised focal or rotational electrical activations termed drivers.

Objective:
We sought to evaluate how left atrial (LA) dilatation and time in AF impact persistent AF mechanisms.

Methods:
Patients with persistent AF <2 years underwent ECGI 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:
100 patients were enrolled (age 61.3 ± 12.1 years) of these 47 were hypertensive, 14 had diabetes mellitus and 10 ischaemic 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 = 0.024) and LA volume (r = 0.216, p = 0.039) 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 = 0.044). Female gender, increasing age, and hypertension were also associated with an increase in focal PDs.

Conclusions:

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

Key words: Atrial fibrillation; Arrhythmia; Remodelling; Mapping; ECGI; CardioInsight.
INTRODUCTION

The underlying mechanisms of persistent atrial fibrillation (AF) remain poorly understood.

Recent mapping studies have suggested persistent AF is maintained by intermittent localised focal or rotational activity that can originate in either atria, the pulmonary veins or vena cava. 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 success rates of catheter ablation for AF.

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 remodelling, and increasing left atrial dimensions which is associated with predominantly structural remodelling in terms of scarring and disruption of architecture.

The Electrocardiographic Imaging (ECG-I) system (Cardioinsight, Medtronic, USA) is a non-invasive mapping technology that is able to panoramically map both atria simultaneously to identify focal and rotational activity which may act as potential drivers (PDs) of AF. ECGI has been used to study the underlying mechanisms and to target PDs in AF.

This study sought to evaluate the relationship between structural remodelling in terms of increasing left atrial dimensions, and electrical remodelling as a result of greater duration of persistent AF and the burden and distribution of PDs in patients with persistent atrial fibrillation utilising ECGI panoramic mapping. We hypothesised that increasing duration of AF
and increasing LA dimensions would correlate with a greater burden and distribution of potential drivers.
METHODS:

Patient Population

Patients undergoing first time catheter ablation for persistent atrial fibrillation of less than two years duration were prospectively enrolled. This is a sub-study of a trial registered on clinicaltrials.gov (NCT03394404) and the research reported adhered to CONSORT guidelines. Ethical approval by 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 > 5cm, LV EF < 40%, NYHA III or IV heart failure, age < 18 or > 80 years, hypertrophic cardiomyopathy or greater than moderate valve disease.

Non-invasive ECGI Mapping

Our non-invasive mapping method has been published previously\(^4\). To summarise, patients were fitted with an ECGI 252 electrode mapping array vest (Cardioinsights, Medtronic, USA). A non-contrast computed tomography (CT) scan was performed which was then segmented using the ECGI system workstation (Cardioinsight, Medtronic, USA) to produce a three-dimensional bi-atrial shell.

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

**Offline ECGI Analysis**

The method for offline ECGI analysis has been published previously\(^4\). In brief, ECGI PD maps were analysed offline by two operators. Initially the surface ECGI recordings were reviewed and leads with excessive noise were removed. Secondly, the raw unipolar electrograms were reviewed and those with excessive noise were removed. The ECGI software will then compute and transpose PDs onto a composite biatrial shell. The two 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 (the mean number of rotations), and the distribution of PDs utilising an 18-segment bi-atrial map used previously\(^4\). PDs were assessed for the atria in total, and also subdivided to look at the pulmonary veins (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 was displayed and recorded using the LabSystem Pro (Boston Scientific, Marlborough, MA, USA) system. Contact electrograms were recorded at the left and right atrial appendage (LAA and RAA respectively), proximal coronary sinus (Proximal CS) and at each pulmonary vein (PV) prior to PVI using either a quadripolar catheter or the Achieve mapping catheter (Medtronic, USA). Cycle lengths were recorded over 30 cycles at each location.

**Study End Points**

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

**Statistical Analysis**

All Statistical analysis was performed using SPSS (IBM SPSS Statistics, Version 25 IBM Corp, Armonk, NY, USA). A P-value of < 0.05 was taken to indicate statistical significance. Normally-distributed data were expressed as mean ± standard deviation or if not normally-distributed as median with interquartile range. Student’s t test was performed for normally-distributed variables and Mann-Whitney U test was performed for non-parametric variables. Correlation was assessed for nonlinear relationships by Spearman rank correlation. A multivariate
analysis was performed using binary logistic regression to determine if there were predictors of PD burden, PD distribution. With the top quartile taken as a positive result. Factors included as categorical covariates included gender, hypertension, diabetes mellitus and ischaemic heart disease. Continuous factors included age, body mass index (BMI), LA diameter, LV function, duration of AF and time from initial AF diagnosis. Factors were removed from the model in a stepwise fashion until only factors with a p-value of < 0.10 remained in the final model.
RESULTS

In total 100 patients were enrolled between January and December 2018. Demographic data is displayed in Table 1. Of 100 patients, mean age was 61.3 ± 12.1 years and 74 (74%) were male. 47 (47%) of patients were diagnosed with hypertension, 14 (14%) with diabetes mellitus, 10 (10%) with ischaemic heart disease, 9 (9%) with cerebrovascular accident (CVA) and 3 (3%) with obstructive sleep apnoea. Mean body mass index (BMI) was 29.8 ± 4.6.

Median time from diagnosis to ablation was 24 (16 – 48) months with 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 less than 12 months duration and 33 had AF > 12 months duration. ECGI maps were generated in 99 of 100 patients (in one patient the ventricular rate could not be reduced sufficiently and adenosine produced frequent ectopics). The analysis of the Baseline ECGI maps are shown in Supplementary Table 1.

Correlation with ECGI PD analysis

Correlation with PD burden and PD distribution are displayed in Table 2 and 3 respectively. Comparison of PD burden and distribution with categorical factors are shown in Supplementary Table 2 and 3. Figure 1 summaries the factors that had a significant impact upon potential drivers of persistent AF.

Impact of LA structural remodelling on AF mechanisms

i) PD burden
Spearman rank correlation analysis comparing PD burden to LA diameter ($r = 0.164$, $p = 0.113$), LA area ($r = -0.059$, $p = 0.575$) and LA volume ($r = -0.030$, $p = 0.775$) did not reveal a significant correlation as shown in Table 2. There was a significant but modest correlation between increasing LA area ($r = 0.235$, $p = 0.024$) and LA volume ($r = 0.216$, $p = 0.039$) with proportion of PDs that were rotational.

ii) PD distribution

There was no significant correlation between PD distribution (total number of segments harbouring PDs within the 18 segment bi-atrial model) and LA diameter ($r = 0.099$, $p = 0.340$), LA area ($r = -0.089$, $p = 0.395$) and LA volume ($r = -0.090$, $p = 0.394$), Table 3.

iii) Contact Mapping

There was no correlation between LA dimensions and LAA, RAA, Proximal CS or mean PV CL (Supplementary Table 4).

Impact of electrical remodelling

i) PD Burden

Neither the time from initial diagnosis of AF nor the duration of continuous persistent AF correlated with PD burden ($r = 0.079$, $p = 0.434$; $r = 0.104$, $p = 0.304$ respectively, Table 2). However, duration of continuous persistent AF did significantly correlate with number of focal PDs ($r = 0.203$, $p = 0.044$, Table 2). Figure 2 demonstrates two patients, Patient 93 who spent...
16 months in AF with multiple risk factors for AF progression who had fewer PDs compared to a Patient 77 who spent 11 months in AF with no risk factors.

ii) PD Distribution

There was no significant correlation between PD distribution (total number of segments harbouring PDs within the 18 segment bi-atrial model) and time from initial diagnosis of AF ($r = -0.023$, $p = 0.822$) or duration of continuous persistent AF ($r = -0.070$, $p = 0.487$). Time from initial diagnosis correlated with proportion of PDs identified at the Septum ($r = -0.245$, $p = 0.014$) and trended towards significance with proportion in the LA ($r = 0.180$, $p = 0.075$, Table 3) respectively.

iii) Contact Mapping

There was a significant correlation between duration of persistent AF and shortening of CL recorded at the proximal CS ($r = 0.210$, $p = 0.036$) and there was a trend towards significance with average of the PVs ($r = 0.181$, $p = 0.072$) as shown in Supplement Table 4.

Impact of other factors on PD Burden and Distribution

Hypertension

There was no significant difference in PD burden or distribution in patients with hypertension compared to those who were not Supplementary Tables 3 and 4. The number of focal PDs was significantly higher in patients with hypertension compared to those without (14.13 ± 6.75 vs 10.77 ± 5.49, $p = 0.008$). This corresponded to a trend towards a reduction in the
proportion of PDs that were rotational in patients that were hypertensive compared to those who were not (80.85 ± 10.15 % vs 84.39 ± 9.45 %, p = 0.075) as shown in Supplementary Table 3. There was no significant difference in CL measurements between patients with hypertension and those without (Supplementary Table 5).

**BMI**

Increasing BMI was negatively correlated with PD burden (r = -0.283, p = 0.005) and negatively correlated with sum of revolutions (r = -0.304, p = 0.002). There was a trend to significance with BMI and PD distribution (r = -0.174, p = 0.089). There was no correlation between BMI and proportion of rotational PDs, sum of revolutions or CL measurements.

**Obstructive Sleep Apnoea (OSA)**

Comparison of PD burden and distribution in patients with OSA to those without revealed a significant difference in rotational stability only (2.82 ± 1.00 vs 2.28 ± 0.38, p = 0.026). 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 harbouring drivers, there were significantly
more segments at the septum harbouring PDs in men (13.21 ± 4.37 vs 10.40 ± 6.41, p = 0.015)
and significantly more segments in the RA harbouring PDs in women (25.98 ± 6.98 vs 30.46 ±
7.43 p = 0.007) as shown in Supplementary Table 3. There was a trend towards more focal
PDs in women (11.73 ± 5.63 vs 14.15 ± 7.78, p = 0.092) and towards fewer PDs being located
at the PVs and Posterior Wall (0.28 ± 0.07 vs 0.26 ± 0.08, p = 0.083) as shown in Supplementary
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 = 0.037; Supplementary Table 5).

Age
There was no significant correlation between age and total PD burden or distribution. There
was however, a correlation between number of focal PDs and increasing age (r = 0.210, p =
0.037, Table 2). There was also a trend towards increasing mean PV CL with greater age (r =
0.195, p = 0.052; Supplementary Table 4).

Multivariate Analysis
Results of the multivariate analyses are shown in Table 4 and Supplementary Table 6. The
only factor remaining in the final model predicting PD burden was BMI (OR 0.808, 95 % CI
0.710 – 0.919, p = 0.001), and the only factor predicting PD distribution in the final model
was age (OR 1.087, 95 % CI 1.022 – 1.157, p = 0.008).

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 = 0.017), BMI (OR 0.874 95 % CI 0.772 – 0.990 p
= 0.034), and duration of persistent AF (OR 1.104 95 % CI 1.022 – 1.193 p = 0.012).

Hypertension (OR 2.956 95 % CI 0.958 – 9.122 p = 0.059) trended towards significance.

There were no significant factors in the final model associated with a higher proportion of PDs being rotational, but hypertension trended towards significance (OR 0.365 95 % CI 0.133 – 1.003, p = 0.051). There were no predictors of proportion of PDs located at the posterior wall and PVs.
DISCUSSION

Main Findings

This is the first study to non-invasively evaluate driver characteristics in structurally and electrically remodelled 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 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 harbouring PD. However, there were 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 also shorter in men.

5. Age did not affect total PD burden and distribution, but was associated with an increase in focal PDs and longer PV CL.

Remodelling and AF mechanisms

There is uncertainty regarding how to customise antiarrhythmic drug therapy or catheter ablation strategies for AF. Evidence is limited for any standardised ablation strategy beyond
pulmonary vein isolation for persistent AF. There is therefore increasing interest in understanding AF mechanisms in the hope that this might facilitate a customised patient specific strategy for ablation. Although there are numerous studies examining how atrial histology and tissue electrophysiology are impacted by different types of remodelling, there are no studies evaluating how this affects AF mechanisms in the fibrillating human atria.

**Impact of LA structural remodelling 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 aetiological factor in the development of AF\textsuperscript{12-18}. Conditions such as valvular heart disease, heart failure and hypertension all cause chronic atrial stretch leading to LA dilatation, with heterogeneous changes in atrial architecture such as myocyte hypertrophy and fibrosis\textsuperscript{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 (CFAE) and double potentials, and greater inducibility of AF\textsuperscript{21-23}. Interestingly, atrial stretch does not seem to lengthen refractory periods as occurs following time spent in AF, but in most of these studies the effective refractory period was actually increased\textsuperscript{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 ($r = 0.235$, $p = 0.024$ and $r = 0.216$, $p = 0.039$ respectively). This may suggest that the scarring and
localised conduction velocity slowing may promote localised reentry\textsuperscript{24,25}. This is despite the increased ERP occurring with atrial stretch and increasing left atrial dimensions.

Figure 2 shows PD burden and distribution in patients 77 (AF duration 3 months and no significant risk factors for developing AF) and patient 93 (AF duration 22 months, diabetes mellitus and hypertension). However, ECGI mapping arguably demonstrates a similar PD burden and distribution. 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 may ultimately 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 a heterogeneous shortening of refractory periods and hence a reduction in AF cycle length\textsuperscript{26}. This is thought to be predominantly due to down regulation of L-type calcium channels, although other cellular changes also occur\textsuperscript{27}. Time spent in AF also causes structural remodelling which overlaps with that seen with atrial stretch, including a degree of fibrosis and atrial dilatation\textsuperscript{28}. Therefore, it may not be possible to untangle fully which changes relate to mechanical stretch and structural remodelling, and which relate to a longer time in AF and predominantly electrical remodelling.
The duration of AF correlated with the number of focal PDs but did not impact on rotational PDs or on PD distribution. Reduced refractory periods might be expected to involve increased reentry. This was not evident in terms of rotational PD which are thought to be rotors, but could have impacted on ‘wandering wavelet’ mechanisms which are not assessed by the ECGI system. The increase in focal PDs may relate to cellular calcium loading in AF, or perhaps due to progressive autonomic remodelling causing increased automaticity.

Other Factors and Atrial Fibrillation

It is recognised that outcomes for AF ablation are worse in women. 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 pulmonary vein isolation lesion set for women. Likewise, increasing age and a history of hypertension were also associated with an increase in focal PDs. This may relate to autonomic remodelling in these sub-sets of patients. Further exploration of how the mechanisms of AF differ between subgroups may highlight which patients are most likely to benefit from which customised ablation approach.

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

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 post-operative AF and increased reoccurrence following catheter ablation. 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 further from the heart hindering mapping. Decreased atrial voltage may also reduce detection of PDs. This may therefore highlight limitations for ECGI mapping of AF in obese patients.

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

Ideally, to study the impact of time in AF or of increasing LA dimensions, one ought to study the atria before and after a period in AF, or before and after LA dilatation. Strictly, this study has shown an association between driver characteristics as determined by ECGI mapping and both increasing time in AF and increasing left atrial dimensions.

The correlations demonstrated are modest. This may be partly due to methodological constraints with driver mapping, but may also relate to overlap between different forms of atrial remodelling and the complex interplay between different aetiological factors for this multifactorial disease. There are also other factors that remain difficult to quantify such as...
autonomic remodelling. Nevertheless it was possible to show different effects on AF mechanisms in different patient subgroups and with time in AF versus left atrial dilatation specifically.
CONCLUSION

This is the first study to demonstrate differing impacts on AF mechanisms in different patient sub-groups. The predominantly structural remodelling seen with left atrial dilatation was associated with increased rotational PDs, and the predominantly electrical remodelling seen with increasing duration of AF was associated with increased focal PDs. Similarly, female gender, increasing age, and hypertension were associated with increased focal PDs. The low r values are likely impacted by methodological difficulties with driver mapping and also with overlap in terms of these remodelling processes. Further elucidation of patient specific AF mechanisms may facilitate a patient tailored approach to AF mapping and ablation.
REFERENCES:


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FIGURE LEGENDS

Figure 1. Factors impacting drivers of persistent AF

This figure displays a posterior-anterior view of an ECGI activation map. There is a focal driver with radial spread originating from the left inferior pulmonary vein. To the left of the figure are factors that were found to be significant predictors of increased focal potential drivers. To the right of the figure are factors that are predictors of increased rotational potential drivers.

Figure 2. ECGI Composite Maps in Two patients with differing risk factors

Comparison of ECGI composite maps showing Patient 93 who spent 16 months in AF and had cardiac risk factors of diabetes mellitus and hypertension who unexpectedly recorded fewer drivers compared to patient 77 who was in AF for 11 months and had no other significant risk factors.
Table 1: Demographics of Participants

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>100</td>
</tr>
<tr>
<td>Age (years) Mean ± SD</td>
<td>61.3 ± 12.1</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>74 (74.0)</td>
</tr>
<tr>
<td>Hypertension n (%)</td>
<td>47 (47.0)</td>
</tr>
<tr>
<td>Diabetes Mellitus n (%)</td>
<td>14 (14.0)</td>
</tr>
<tr>
<td>Ischaemic Heart Disease n (%)</td>
<td>10 (10.0)</td>
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<tr>
<td>Cerebrovascular Accident n (%)</td>
<td>9 (9.0)</td>
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<tr>
<td>Obstructive Sleep Apnoea (%)</td>
<td>3 (3.0)</td>
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<tr>
<td>Body Mass Index</td>
<td>29.8 ± 4.6</td>
</tr>
<tr>
<td>CHA2DS2VASC Score mean ± SD</td>
<td>1 (0 – 3)</td>
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<tr>
<td>NYHA</td>
<td>1 (1 -1)</td>
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<tr>
<td>EHRA</td>
<td>1 (1 – 2)</td>
</tr>
<tr>
<td>LA Diameter (mm)</td>
<td>39 (33 – 43)</td>
</tr>
<tr>
<td>LA Volume (mls)</td>
<td>62 (49 – 83)</td>
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<tr>
<td>Median duration of AF: diagnosis to procedure (months)</td>
<td>24 (16 – 48)</td>
</tr>
<tr>
<td>Duration of Persistent AF (Months)</td>
<td>8 (5 -15)</td>
</tr>
<tr>
<td>Persistent AF duration &lt; twelve months</td>
<td>67 (67.0)</td>
</tr>
<tr>
<td>Persistent AF duration &gt; twelve months</td>
<td>33 (33.0)</td>
</tr>
</tbody>
</table>

Values are given as no. (%), mean ± standard deviation or median (Interquartile Range).
Table 2. Correlation between Factors and Potential Driver Burden.

<table>
<thead>
<tr>
<th></th>
<th>PD Burden</th>
<th>Proportion of PD at PVPW</th>
<th>Proportion of Rotational PDs %</th>
<th>Sum Rotations</th>
<th>Sum Foci</th>
<th>Rotational Stability</th>
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<tbody>
<tr>
<td>Age (r)</td>
<td>0.053</td>
<td>-0.041</td>
<td>-0.099</td>
<td>-0.026</td>
<td>0.210</td>
<td>-0.002</td>
</tr>
<tr>
<td>P Value</td>
<td>0.598</td>
<td>0.684</td>
<td>0.330</td>
<td>0.794</td>
<td>0.037*</td>
<td>0.986</td>
</tr>
<tr>
<td>BMI (r)</td>
<td>-0.283</td>
<td>-0.029</td>
<td>-0.138</td>
<td>-0.304</td>
<td>-0.052</td>
<td>0.105</td>
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<tr>
<td>P Value</td>
<td>0.005*</td>
<td>0.779</td>
<td>0.176</td>
<td>0.002*</td>
<td>0.611</td>
<td>0.307</td>
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<tr>
<td>LA Diameter (r)</td>
<td>0.164</td>
<td>-0.067</td>
<td>0.109</td>
<td>0.146</td>
<td>0.073</td>
<td>-0.012</td>
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<tr>
<td>P Value</td>
<td>0.113</td>
<td>0.520</td>
<td>0.297</td>
<td>0.159</td>
<td>0.483</td>
<td>0.909</td>
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<tr>
<td>LA Area (r)</td>
<td>-0.059</td>
<td>-0.093</td>
<td>0.235</td>
<td>0.063</td>
<td>-0.138</td>
<td>-0.071</td>
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<tr>
<td>P Value</td>
<td>0.575</td>
<td>0.377</td>
<td>0.024*</td>
<td>0.547</td>
<td>0.191</td>
<td>0.501</td>
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<tr>
<td>LA Volume (r)</td>
<td>-0.030</td>
<td>-0.022</td>
<td>0.216</td>
<td>0.063</td>
<td>-0.112</td>
<td>-0.127</td>
</tr>
<tr>
<td>P Value</td>
<td>0.775</td>
<td>0.835</td>
<td>0.039*</td>
<td>0.551</td>
<td>0.292</td>
<td>0.230</td>
</tr>
<tr>
<td>LV Function (r)</td>
<td>0.135</td>
<td>-0.004</td>
<td>0.052</td>
<td>0.106</td>
<td>0.030</td>
<td>0.079</td>
</tr>
<tr>
<td>P Value</td>
<td>0.186</td>
<td>0.967</td>
<td>0.612</td>
<td>0.302</td>
<td>0.773</td>
<td>0.446</td>
</tr>
<tr>
<td>CHA2DS2-VASc Score (r)</td>
<td>-0.039</td>
<td>-0.114</td>
<td>-0.155</td>
<td>-0.133</td>
<td>0.211</td>
<td>-0.022</td>
</tr>
<tr>
<td>P Value</td>
<td>0.701</td>
<td>0.262</td>
<td>0.125</td>
<td>0.188</td>
<td>0.036*</td>
<td>0.828</td>
</tr>
<tr>
<td>Initial AF diagnosis (r)</td>
<td>0.079</td>
<td>0.098</td>
<td>-0.010</td>
<td>0.033</td>
<td>0.114</td>
<td>-0.001</td>
</tr>
<tr>
<td>P Value</td>
<td>0.434</td>
<td>0.333</td>
<td>0.921</td>
<td>0.741</td>
<td>0.263</td>
<td>0.991</td>
</tr>
<tr>
<td>Duration of Persistent AF (r)</td>
<td>0.104</td>
<td>0.097</td>
<td>0.025</td>
<td>0.020</td>
<td>0.203</td>
<td>0.158</td>
</tr>
<tr>
<td>P Value</td>
<td>0.304</td>
<td>0.341</td>
<td>0.810</td>
<td>0.840</td>
<td>0.044*</td>
<td>0.118</td>
</tr>
</tbody>
</table>

PD Burden defined as total number of PDs occurrences. R = Spearmans rho. P < 0.05 taken to be significant.
Table 3. Correlation between Factors and Potential Driver Distribution.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Total Segments</th>
<th>Proportion of Segments at the PVs and Posterior Wall</th>
<th>Proportion of segments in LA %</th>
<th>Proportion of segments in RA %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) R (P value)</td>
<td>0.119 (0.237)</td>
<td>-0.041 (0.684)</td>
<td>-0.002 (0.987)</td>
<td>0.140 (0.167)</td>
</tr>
<tr>
<td>Body Mass Index R (P value)</td>
<td>-0.168 (0.097)</td>
<td>-0.029 (0.779)</td>
<td>0.012 (0.909)</td>
<td>-0.072 (0.483)</td>
</tr>
<tr>
<td>LA Diameter R (P value)</td>
<td>0.099 (0.340)</td>
<td>-0.067 (0.520)</td>
<td>0.132 (0.204)</td>
<td>-0.145 (0.162)</td>
</tr>
<tr>
<td>LA Area R (P value)</td>
<td>-0.089 (0.395)</td>
<td>-0.093 (0.377)</td>
<td>-0.077 (0.464)</td>
<td>-0.086 (0.415)</td>
</tr>
<tr>
<td>LA Volume R (P value)</td>
<td>-0.090 (0.394)</td>
<td>-0.022 (0.835)</td>
<td>0.037 (0.729)</td>
<td>-0.107 (0.311)</td>
</tr>
<tr>
<td>LV Function R (P value)</td>
<td>-0.032 (0.754)</td>
<td>-0.004 (0.967)</td>
<td>-0.099 (0.339)</td>
<td>0.002 (0.986)</td>
</tr>
<tr>
<td>CHADSVASC Score R (P value)</td>
<td>0.002 (0.985)</td>
<td>-0.114 (0.262)</td>
<td>0.069 (0.499)</td>
<td>0.025 (0.805)</td>
</tr>
<tr>
<td>Initial AF Diagnosed R (P value)</td>
<td>-0.023 (0.822)</td>
<td>0.098 (0.333)</td>
<td>0.180 (0.075*)</td>
<td>-0.036 (0.725)</td>
</tr>
<tr>
<td>Duration of Persistent AF R (P value)</td>
<td>-0.070 (0.487)</td>
<td>0.097 (0.341)</td>
<td>0.071 (0.482)</td>
<td>-0.126 (0.214)</td>
</tr>
</tbody>
</table>

PD Distribution defined as total number segments harbouring PDs. R = Spearman's rho. P value in brackets. P < 0.05 taken to be significant. *P < 0.10.
### Table 4. Multivariate Analysis of factors predicting PD Burden and Distribution

<table>
<thead>
<tr>
<th>Multivariate Analysis in predicting PD Burden</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.007</td>
<td>0.944 - 1.074</td>
<td>0.839</td>
</tr>
<tr>
<td>Male Gender</td>
<td>1.589</td>
<td>0.359 – 7.034</td>
<td>0.542</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>0.809</td>
<td>0.688 - 0.952</td>
<td>0.011*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.188</td>
<td>0.618 - 7.740</td>
<td>0.225</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>0.325</td>
<td>0.031 – 3.445</td>
<td>0.351</td>
</tr>
<tr>
<td>Duration of Persistent AF</td>
<td>0.974</td>
<td>0.895 - 1.059</td>
<td>0.535</td>
</tr>
<tr>
<td>Time from Initial AF diagnosis</td>
<td>1.001</td>
<td>0.990 - 1.012</td>
<td>0.894</td>
</tr>
<tr>
<td>Left Atrial Diameter</td>
<td>1.012</td>
<td>0.909 - 1.127</td>
<td>0.829</td>
</tr>
<tr>
<td>Left Ventricular Ejection Function</td>
<td>1.050</td>
<td>0.956 - 1.155</td>
<td>0.307</td>
</tr>
<tr>
<td>Ischaemic Heart Disease</td>
<td>0.754</td>
<td>0.088 – 6.487</td>
<td>0.797</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multivariate Analysis in predicting PD Distribution</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.066</td>
<td>0.991 - 1.147</td>
<td>0.084</td>
</tr>
<tr>
<td>Male Gender</td>
<td>0.965</td>
<td>0.243 - 3.841</td>
<td>0.960</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>0.914</td>
<td>0.792 - 1.056</td>
<td>0.223</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.308</td>
<td>0.652 - 8.165</td>
<td>0.194</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>0.583</td>
<td>0.118 - 2.886</td>
<td>0.509</td>
</tr>
<tr>
<td>Duration of Persistent AF</td>
<td>1.015</td>
<td>0.931 - 1.106</td>
<td>0.737</td>
</tr>
<tr>
<td>Time from Initial AF diagnosis</td>
<td>1.009</td>
<td>0.998 - 1.021</td>
<td>0.117</td>
</tr>
<tr>
<td>Left Atrial Diameter</td>
<td>1.040</td>
<td>0.934 - 1.158</td>
<td>0.471</td>
</tr>
<tr>
<td>Left Ventricular Ejection Function</td>
<td>0.990</td>
<td>0.902 - 1.088</td>
<td>0.839</td>
</tr>
<tr>
<td>Ischaemic Heart Disease</td>
<td>0.878</td>
<td>0.136 - 5.669</td>
<td>0.891</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multivariate Analysis in predicting Focal PD Burden</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.002</td>
<td>0.945 – 1.063</td>
<td>0.943</td>
</tr>
<tr>
<td>Male Gender</td>
<td>0.228</td>
<td>0.057 – 0.912</td>
<td>0.037*</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>0.865</td>
<td>0.748 – 1.000</td>
<td>0.050*</td>
</tr>
<tr>
<td>Condition</td>
<td>Odds Ratio</td>
<td>95% CI</td>
<td>P Value</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>------------</td>
<td>--------------</td>
<td>---------</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.356</td>
<td>0.893 – 12.614</td>
<td>0.073</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>0.469</td>
<td>0.088 – 2.486</td>
<td>0.373</td>
</tr>
<tr>
<td>Duration of Persistent AF</td>
<td>1.101</td>
<td>1.017 – 1.192</td>
<td>0.017*</td>
</tr>
<tr>
<td>Time from Initial AF diagnosis</td>
<td>0.995</td>
<td>0.981 – 1.009</td>
<td>0.456</td>
</tr>
<tr>
<td>Left Atrial Diameter</td>
<td>1.003</td>
<td>0.902 – 1.114</td>
<td>0.961</td>
</tr>
<tr>
<td>Left Ventricular Ejection Function</td>
<td>1.033</td>
<td>0.943 – 1.132</td>
<td>0.485</td>
</tr>
<tr>
<td>Ischaemic Heart Disease</td>
<td>2.058</td>
<td>0.322 – 13.141</td>
<td>0.446</td>
</tr>
</tbody>
</table>

P < 0.05 taken to be significant. *factors where P < 0.1.
Factors impacting drivers of persistent AF

↑Focal PDs
- Continuous time in AF
- Female gender
- Increasing age
- Hypertension
- ↑CHA₂DS₂-VASc

↑Rotational PDs
- Increasing LA dimensions

PD (Potential Driver). p < 0.05 taken to be significant.

Figure 2. ECGI Composite Maps in Two patients with differing risk factors for AF

progressions.
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.
Key Findings

1. Increasing LA dimensions had no impact on driver burden or distribution but was associated with an increase in the proportion of rotational PDs.

2. Time in AF did not impact on how PD burden or distribution but did correlate with shorter AF cycle lengths in the LA and PVs.

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