Gurpreet Dhillon ORCID iD: 0000-0002-1197-9328

Shohreh Honarbakhsh ORCID iD: 0000-0003-0081-5739

Vinit Sawhney ORCID iD: 0000-0002-9947-2037

Rui Providência ORCID iD: 0000-0001-9141-9883

Impact of pulmonary vein isolation on mechanisms sustaining persistent atrial fibrillation: predicting the acute response.

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Dhillon GS MRCP BSc, Schilling RJ MD FRCP, Honarbakhsh S MRCP BSc, Graham A MRCP BSc, Abbass H, Waddingham P MRCP, Sawhney V MRCP, Creta A, Sporton S MD FRCP, Finlay M PhD, Providencia R PhD, Chow A FRCP MD, Earley MJ MD FRCP, Lowe M MD FRCP, Lambiase PD PhD FHRS, Hunter RJ PhD FESC FEHRA.

Barts Heart Centre, St Bartholomew's Hospital, Barts Health NHS Trust, London, United Kingdom.

Corresponding Author:

Dr Ross J Hunter

Barts Heart Centre

Barts Heart NHS Trust

EC1A 7BE

Email: Ross.Hunter@bartshealth.nhs.uk

02037658651

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ABSTRACT

Background:

Non-invasive mapping identifies potential drivers (PDs) in AF. We analysed the impact of pulmonary vein isolation (PVI) on PDs and whether baseline PD pattern predicted termination of AF.

Methods:

Patients with persistent AF < 2 years underwent ECGI mapping before and after cryoballoon PVI. We recorded the number of PD occurrences, characteristics (rotational wavefronts ≥ 1.5 revolutions or focal activations) and distribution using an 18-segment atrial model.

Results:

Of 100 patients recruited, PVI terminated AF in 15 patients. 21.3 ± 9.1% (8.7 ± 4.8) of PDs occurred at the PVs and posterior wall. PVI had no impact on PD occurrences outside the PVs and posterior wall (33.2 ± 12.9 vs 31.6 ± 12.5, p = 0.164), distribution

over the remaining 13 segments (9 (8 – 11) vs 9 (8 -10), p = 0.634), the proportion of PDs that were rotational (82.9 ± 9.7% vs 83.6 ± 10.1%, p = 0.496) or temporal stability (2.4 ± 0.4 vs 2.4 ± 0.5 rotations, p = 0.541). Fewer focal PDs (AUC 0.683,95% CI 0.528 – 0.839, p = 0.024) but not rotational PDs (p = 0.626) predicted AF termination with PVI.

Conclusions: PVI did not have a global impact on PDs outside the PVs and posterior wall. Although fewer focal PDs predicted termination of AF with PVI, the burden of rotational PDs did not. It is accepted though not all PDs are necessarily real or important. Outcome data is needed to confirm whether non-invasive mapping can predict patients likely to respond to PVI.

KEYWORDS: Persistent Atrial Fibrillation, Pulmonary Vein Isolation, Non-invasive Mapping, Drivers, Mechanisms of Atrial Fibrillation.

INTRODUCTION

Recent studies have suggested that pulmonary vein isolation (PVI) alone is as effective as strategies incorporating atrial substrate modification[1,2]. It is unclear why PVI should be effective for persistent AF. It could simply remove the triggers which initiate AF, or it may fundamentally impact the mechanisms sustaining persistent AF.

The mechanisms sustaining persistent AF remain controversial. Recent studies using contact electrograms from basket catheters have suggested that AF is maintained by focal and rotational activation patterns which are intermittent but recur at certain sites[3–5]. The Electrocardiographic Imaging (ECGI) system (CardioInsight, Medtronic, USA) is a novel non-invasive mapping technology that performs simultaneous 3D

panoramic mapping of both atria. The ECGI has demonstrated comparable focal and rotational activity which may act as potential drivers (PDs)[6–8].

Mapping data suggests that mechanisms supporting AF are patient specific in terms of the location and characteristics of drivers, and that these mechanisms evolve over time with remodelling in terms of the number and distribution of drivers[3,4,6–10]. Despite this, for reasons that remain unclear, PVI remains a relatively effective treatment for persistent AF, particularly when AF terminates during PVI[1,2,11].

Mapping studies have shown that the burden of fractionated electrograms, the cycle length of electrograms, and the dominant frequency of the atria are reduced following PVI which suggests an impact on mechanism sustaining AF in the body of the atria[12–14]. Targeting of ganglionated plexi has been shown to eliminate areas of continuous fractionation, both locally and at distant sites, and hence damage to ganglionated plexi at the PV ostia has been suggested as one potential mediator of wider spread changes in AF mechanisms[15]. A better understanding of how PVI affects mechanisms sustaining AF may clarify the rationale for what ablation should be considered beyond PVI.

In this study the ECGI system was used to map the atria in persistent AF before and after PVI to determine what effect this has on mechanisms sustaining persistent AF. We hypothesized that patients with a lower burden of PDs that were less widely distributed throughout the atria would be more likely to terminate to sinus rhythm with PVI.

METHODS:

Patient Population

Patients undergoing first time catheter ablation for persistent atrial fibrillation of less than two years duration were prospectively enrolled. All participants provided written informed consent. The study was approved by the national ethics committee and is a sub-study of a trial registered on clinicaltrials.gov (NCT03394404). 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.

Catheter Ablation

Patients underwent ablation using the cryoballoon as described in Supplemental Methods 1.

Non-invasive ECGI Mapping

ECGI mapping has been described elsewhere in detail, and was performed as described in Supplemental Methods 2[7,8]. All ECGI mapping was performed intra-procedurally. If patients were in sinus rhythm AF was induced through pacing and left to stabilize for 10 minutes prior to mapping. Although this analysis was largely automated there were three steps for quality control which were carried out together by 2 operators:

1. The surface ECG recordings were reviewed and segments with excessive noise were discarded (Figure 1A).
2. The raw surface unipolar electrograms were then reviewed and signals from individual electrodes with significant noise were excluded (Figure 1B).

3. The subsequent analysis was then reviewed as in Figure 1C. The composite map was viewed as seen on the left of the panel with all PD detections shown. The phase map with the activation sequence was reviewed for each PD detection as on the middle panel. The timings around the area of interest were then reviewed (as for the example electrograms on the far right of this panel). The raw reconstructed atrial electrogram and the resultant waveform following the Hilbert Transform was then reviewed for sites along the wavefront (as shown at the bottom panel in Figure 1C) to review plausibility of the source data. Where any of these steps were thought unsatisfactory or implausible the PD was discarded as artefact.

An ECGI map was acquired at the start before any ablation and again following PVI. The operator performing ablation was blinded to these maps. It is also important to clarify that no post PVI map was created in patients whose AF terminated with PVI.

ECGI Map Analysis

ECGI Maps were analysed offline (post procedure) by an operator blinded to patient and procedural details including whether AF terminated and whether ECGI maps were generated pre or post PVI. Step 3 in the above quality control analysis was conducted at this stage where PDs are accepted or rejected. PDs were assessed in terms of the total number of PD occurrences, the stability of rotational activation patterns (the mean number of rotations per PD occurrence), the proportion of PDs that were rotational or focal, and the distribution of PDs using an 18-segment bi-atrial shell (Figure 2). Rotational wavefronts with an unstable wandering core are disregarded by the system. Where a PD occupied an area that straddled more than one segment on the 18 segment model, it was counted as a single driver occurrence but

ascribed to more than one segment for the purposes of assessing distribution. An example of ECGI composite maps from two different patients are shown in Figure 3.

Study End Points

The primary end point was the association between PD burden (defined as the number of driver occurrences) and distribution (defined as the number of segments harbouring drivers on the 18-segment model) on baseline ECGI maps, and an acute response to PVI. Termination of AF to either sinus rhythm or an atrial tachycardia was chosen as the clearest response to PVI that could be studied. Secondary end points included an assessment of the impact of PVI on PD burden, distribution, temporal stability, and the proportion of PDs that were focal or rotational.

Statistical Analysis

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. The association between different factors and termination of AF with PVI was tested using receiver operating characteristic (ROC) analysis. Optimal cut offs were determined manually from ROC curves aiming for balanced sensitivity and specificity. A multivariate analysis was performed of factors predicting acute AF termination using binary logistic regression. Gender, hypertension, diabetes mellitus, were included as binary variables and BMI, LA diameter and duration of persistent AF were included as continuous variables. Any factors showing a significant relationship with AF termination on ROC analysis were tested through this multivariate analysis. All Statistical analysis were 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.

RESULTS

In total 100 patients were enrolled. Patient demographics are displayed in Table 1. Mean age was 61.3 ± 12.1 years with 74 (74.0%) being male. The median time from diagnosis of AF to ablation was 24 (16 – 48) months with mean duration of continuous persistent AF being 8 (5 – 15) months. Median LA diameter was 39 (33 – 43) mm.

Procedural Factors

Procedure time defined from needle to skin to removal of the venous sheaths was 57 (48 – 68) minutes. All PVs were isolated in all patients. Termination of AF occurred in 15 (15.0%) patients. The median number of applications per vein was 1.5 (1.25 – 1.75) including applications that were abandoned. The median total freeze time was 15.7 (13.0 – 20.3) minutes per patient. Median fluoroscopy time was 4.1 (3.0 – 6.0) minutes. Seven (7.0%) cases were performed under general anaesthesia. In ten (10.0%) cases a cavotricuspid isthmus line was also ablated. There were two major complications, one tamponade detected at the end of the procedure (but thought related to a difficult transseptal puncture) requiring percutaneous drainage, and one persistent phrenic nerve palsy.

Pre-PVI ECGI Baseline Maps

Pre-PVI ECGI maps were successfully generated in 99 of 100 patients. In one patient the ventricular rate could not be reduced sufficiently and adenosine produced frequent ectopics which precluded mapping. In 39/99 (39.4%) cases adenosine was required to

obtain the required intervals of 840ms. The mean duration of cumulated intervals per map was 15377 ± 402 ms comprised of 15 (12 – 16) intervals. The mean duration of individual atrial intervals recorded was 1228 ± 516 ms.

The total number of PD occurrences per map was 41.5 ± 15.3 with a mean of 8.7 ± 4.8 (21.3 ± 9.1%) confined to the posterior wall and PVs and 32.1 ± 12.7 (78.7 ± 9.1%) elsewhere. The proportion of PDs that were re-entrant was 82.7 ± 9.9% with the remainder being focal. The mean number of rotations per rotational PD occurrence was 2.4 ± 0.4.

Allocation of PDs utilising the described 18-segment bi-atrial geometry to further assess the distribution of PDs revealed that the median number of segments harbouring PDs pre-PVI was 13 (11 – 15). Of five segments that comprise the posterior wall and PVs, the median number of segments harbouring PDs was 3 (3 – 4). Although all patients had some PDs located at the PVs and posterior wall, only 27.7 ± 7.2% of segments harbouring PDs were located there and the remainder were widely distributed throughout the atria: 27.2 ± 7.4% were in the right atrium, 12.5 ± 5.1% were found at the septum, and 32.7 ± 7.6% were located in the body of the LA (excluding the PVs and posterior wall and also the septum).

The Impact of PVI on mechanisms sustaining AF

84 post PVI ECGI maps were generated (AF terminated in 15 patients and rate control was insufficient in one case). Analysis of the impact of PVI included a paired analysis of these 84 patients. Of these 32 (38.1%) required the administration of Adenosine (if adenosine was required for the baseline map then this was also used to acquire the post-PVI map for consistency). The mean duration of these maps was 15067 ± 788 ms

with a median number of consecutive windows required for collection was 14 (10 – 16).

PD occurrence was reduced from 41.5 ± 15.3 pre- PVI to 31.6 ± 12.5 post PVI ($p < 0.001$), representing a reduction of 22.7 ± 22.6%. However, when excluding the PVs and posterior wall segments, there was no demonstrable impact on the number of PDs occurring elsewhere in the atria following PVI (33.2 ± 12.9 vs 31.6 ± 12.5, $p = 0.164$). There was no change in the proportion of PDs that were rotational (82.9 ± 9.7% pre-PVI compared to 83.6 ± 10.1% post PVI, $p = 0.496$) relative to focal drivers and no significant reduction in driver temporal stability following PVI in terms of the mean number of rotations per rotational PD occurrence (2.4 ± 0.4 rotations pre-PVI vs 2.4 ± 0.5 post PVI, $p = 0.541$)

Comparison of the number of segments harbouring drivers excluding the PVs and posterior wall (so out of 13 potential segments) revealed no significant reduction (9 (8 – 11) vs 9 (8 -10), $p = 0.634$). Examining this on a regional basis the number of segments harbouring PDs in the body of the left atrium (4 (3 – 5) vs 4 (3 - 5), $p = 0.890$), in the right atrium (4 (3 - 4) vs 4 (3 – 4), $p = 0.691$) and at the septum (2 (1 - 2) vs 2 (1 – 2) $p = 0.070$) were unchanged post PVI.

To determine whether the duration of recorded intervals impacted significantly on the number of detected PDs, or the number of rotations completed by rotational PDs, the pre PVI baseline maps in patients with all data intervals recorded 840 - 1200ms were compared to patients where all recorded intervals were >1500 ms. The number of patients in each group of this sub-analysis were 15 and 10. The mean duration of recorded intervals in each group was 937 ± 30 ms versus 2269 ± 554 ms ($p < 0.001$). The mean number of PD detections was 42.9 ± 15.0 versus 46.8 ± 19.7, $p = 0.582$) the

mean number of revolutions completed by a rotational PD was 65.5 ± 25.9 versus 85.0 ± 45.4 p = 0.185).

Cycle Length Measurements

CLs pre- and post PVI are shown in Supplemental Table 1. The mean of the PV CLs were longer than that in the LAA ($p < 0.001$). PVI caused a small but significant CL prolongation in all 3 sites studied (all $p < 0.05$).

Comparison of AF mechanisms in patients whose AF terminated with PVI to those that remained in AF

Comparison of the burden of PDs in patients in whom PVI terminated AF to those who remained in AF did reveal a significant difference in the number of PD occurrences at the PVs and posterior wall (6.40 ± 3.85 vs 9.11 ± 4.84, p = 0.043). Comparison of the number of PDs outside the PVs and posterior wall, and total number of PD occurrences did not reach significance (29.93 ± 13.23 vs 33.24 ± 12.89, p = 0.364; and 36.73 ± 15.62 vs 42.38 ± 15.12, p = 0.188 respectively). Comparing stability of rotational activations did not reveal a significant difference (2.34 ± 0.44 vs 2.36 ± 0.44, p = 0.890.

There was no significant difference comparing the distribution of PDs in terms of the number of segments harbouring PDs at the PVs and posterior wall (3 (2 – 4) vs 4 (3 – 5), p 0.56) or the total number of segments harbouring drivers 12 (12 – 13) vs 13 (11 – 15), p = 0.085.

Prediction of Acute Response to PVI

Table 2 shows the ROC analysis of factors predicting termination of AF with PVI. The relationship between these factors and termination of AF is summarised below.

(i) PD factors and termination of AF

Fewer PD occurrences (AUC 0.633, 95% CI 0.473 – 0.792, p = 0.103) did not reach significance in predicting termination of AF with PVI, but examining the breakdown of PD sub-types, a smaller number of focal activations predicted termination of AF (AUC 0.683, 95% CI 0.528 – 0.839, p = 0.024) whereas the number of rotational activations had no significant association with AF termination (AUC 0.540, 95% CI 0.376 – 0.704, p = 0.626).

Looking at the distribution of PDs, fewer PDs present at the PVs and posterior wall (AUC 0.675, 95% CI 0.529 – 0.820, p = 0.032) and fewer segments harbouring PDs at the PVs and posterior wall (AUC 0.662, 95% CI 0.535 – 0.788, p = 0.047) were both significant predictors of AF termination with PVI. PDs being less widely distributed in terms of the total number of segments harbouring drivers seemed less important and did not reach significance in predicting termination of AF (AUC 0.604, 95% CI 0.479 – 0.730, p = 0.199).

(ii) Cycle Length and termination of AF

The LAA, RAA, Proximal CS, and average of these CLs were all found to predict termination of AF with PVI (Table 2; all $p < 0.05$). A longer average PV CLs and a smaller ratio of the average of the PV CLs to LAA CL also predicted AF termination (p = 0.012 and p = 0.018) respectively.

(iii) *Patient factors and termination of AF*

ROC analysis showed that left atrial dimensions and time in persistent AF did not predict termination of AF with PVI (Table 2).

IV) Multivariate analysis of factors predicting termination of AF

To determine whether driver patterns independently predicted termination of AF a multivariate analysis was conducted. The ECGI determined PD patterns which reached significance on the ROC analysis (the number of PD occurrences at the PVs and posterior wall, the number of segments occupied by PDs at the PVs and posterior wall, and the total burden of focal PDs) were included. Since all factors in a multivariate analysis must be independent, the analysis was repeated to test each of these factors separately. The multivariate analysis including the number of PD occurrences at the PVs and posterior wall is shown in Supplemental Table 2. After stepwise removal from the model of factors with a p-value > 0.10, the factors remaining were the presence of hypertension (OR 0.130, 95% CI 0.019 – 0.892, p = 0.038) and the number of PD occurrences at the posterior wall and PVs (OR 0.783 95% CI 0.626 – 0.979, p = 0.032).

Repeating the analysis with the number of segments occupied by PDs at the PVs and posterior wall gave nearly identical results. After stepwise removal from the model of factors with a p-value > 0.10, the factors remaining were hypertension (OR 0.144, 95 CI 0.023 – 0.911, p = 0.039) and number of segments occupied by PDs at the PVs and posterior wall (OR 0.470 95% CI (0.236 – 0.940, p = 0.033). Repeating the analysis with the number of focal PDs gave nearly identical results. After stepwise removal from the model of factors with a p-value > 0.10, the factors remaining were

hypertension (OR 0.148, 95 CI 0.031 – 0.710, p = 0.017) and number of focal PDs (OR 0.909 95% CI (0.856 – 0.966, p = 0.002).

DISCUSSION

Main Findings

This is the first study to comprehensively evaluate the effect of PVI on the mechanisms sustaining persistent AF. Baseline maps prior to PVI showed that there was significant variation in the burden and distribution of PDs between patients. Comparison of pre and post-PVI maps revealed that PVI had no discernible impact on the occurrence of PDs, the distribution of PDs, or the temporal stability of PDs outside of the PVs and posterior wall. Clinical factors such as time in AF and left atrial dimensions did not predict termination of AF with PVI, but atrial CL from contact electrograms was strongly predictive. Non-invasive mapping showed that fewer focal activations predicted termination of AF, but the number of rotational activations did not. Although the total number of PD occurrences (focal and rotational combined) did not predict termination of AF, fewer PD occurrences at the PVs and posterior wall and also a more limited distribution of PDs at the PVs and posterior wall segments predicted termination of AF with PVI.

Baseline Driver Distribution and Characteristics

Baseline maps showed that all patients had both rotational and focal PDs which were intermittent and repetitive in localised regions. This is in keeping with prior studies with this non-invasive mapping system[7,8], and is also compatible with studies using basket catheters for contact mapping[3,4,9,10,16]. Studies utilizing the ECGI system have described a greater number of drivers per patient than studies using analysis of contact electrograms from basket catheters. However, studies using other technologies

typically describe the number of driver sites rather than the number of driver occurrences. We observed 41 PD occurrences in 15 seconds which often recurred in similar locations, although overall were still distributed over a median of 13 out of 18 segments. It is possible that the ECGI detects a greater number of drivers due to better coverage, or possibly that it detects some 'false positives' due to the limitations of non-invasive mapping or phase analysis.

Although on average only 21.3 ± 9.1% of PDs were located at the PVs and posterior wall, PDs were identified here in all patients, and were usually widely distributed across this area (a median of 4 out of 5 segments here harboured PDs). However, the median number of segments harbouring PDs was 13 (11 – 15) of 18 segments (69.6 ± 15.5%), suggesting that although PDs had a predilection for the PVs and posterior wall, they were widely distributed throughout the atria.

The impact of PVI on the burden, distribution and characteristics of drivers

Recent studies have suggested that PVI alone is as effective as strategies incorporating atrial substrate modification[1,2]. However, it is unclear why PVI should be effective for persistent AF. Previous studies investigating the impact of PVI on mechanisms sustaining AF have used surrogates for drivers such as fractionated electrograms or dominant frequency. PVI has been shown to reduce dominant frequency[14] and the burden of fractionated electrograms[12–14,17]. However, fractionated electrograms and peaks in dominant frequency correlate poorly with drivers in AF[18,19]. Fractionated electrograms may have many causes including wave collision[20], and the intermittent nature of drivers may impair detection through dominant frequency[18].

By mapping drivers directly pre- and post PVI we have been able to dispense with surrogate markers. Although PVI caused an overall reduction in PD burden, this was exclusively through its impact at the PVs and posterior wall and there was no significant impact on PD burden, distribution or temporal stability outside of the pulmonary veins and posterior wall. This arguably lends weight to the 'driver hypothesis' as a mechanism for maintaining AF, and provides a rationale for targeting drivers elsewhere in the atria where AF persists after PVI.

The minimum duration of recorded intervals collected by the ECGI system was 840 ms, with the mean duration of 1228 ± 516 ms pre PVI. Although focal activations simply need to occur during the recorded interval, rotational activations needed to complete 1.5 revolutions raising the question as to whether shorter recorded intervals might not record the full duration of a rotational PD occurrence, thus reducing the number of detections and shortening the apparent duration of detected rotational PDs. Others have shown that sites where ablation has terminated persistent AF can be associated with rotational activation where less than a full rotation has been completed, possibly due to the rotational activation being truncated by the recording[9]. Our data suggests that using a minimum duration of 840 ms did not significantly impact on the number of rotational PDs detected, or on their apparent duration compared to longer segments.

Baseline drivers and the response to PVI

This is the first study to assess whether the baseline pattern of drivers in AF predicts the acute response to PVI. Several potential factors were studied. A lower total PD burden trended towards significance in predicting AF termination ($p = 0.103$). Examining the two components of this, a lower burden of focal activations predicted

termination of AF with PVI whereas the burden of rotational activations did not. This may suggest greater mechanistic importance of focal activations in maintaining AF than rotational activations. Termination of AF has been achieved exclusively through targeting focal activations using other technologies and may predict AF termination better than ablation of rotational activation patterns[21,22]. Another possibility though is that with current technology there may be more false positive detections for rotational activations which may obscure any relationship.

Although the total PD burden did not reach significance, a lower PD burden at the PVs and posterior wall was a significant predictor of AF termination. Likewise, although the PD distribution in terms of the number of segments harbouring drivers did not reach significance, a distribution of PDs across fewer segments at the PVs and posterior wall did predict AF termination. This may suggest that PDs observed at the PVs and posterior wall are of particular importance in maintaining AF. It is not clear from these data why this should be, although this finding would explain the reasonable success rates with PVI alone for persistent AF. Ganglionated plexi innervation occurs predominantly in this region and PD associated with these may be particularly important[23].

Notably duration of persistent AF and left atrial dimensions did not predict AF termination with PVI. Hypertension was the only clinical factor that predicted failure to terminate AF on the multivariate analysis. This highlights the variability in the patient specific mechanisms sustaining AF. The multivariate analyses confirmed that non-invasive mapping data predicted termination of AF independent of these clinical parameters. In terms of the strength of these relationships, the AUC for the factors reaching significance were all between 0.65 and 0.70, which strongly suggests a

biological relationship but would be regarded as poor for a diagnostic test. CL data from contact electrograms had a better predictive value for AF termination, but this is the first-time non-invasive mapping data has shown potential utility in this regard. Further refinement of ECGI mapping and ongoing study of these relationships will clarify the strength of these associations and the usefulness of ECGI in this capacity.

Termination of AF was chosen as the clearest response to PVI that could be studied. It is recognised that the clinical outcome in terms of freedom from AF is very good in those patients whose persistent AF terminates with PVI [11]. Nevertheless, the focus of this study was on the acute impact of PVI on AF mechanism, and whether the acute response was predictable based on patient specific AF mechanisms. However, it is recognised that termination of AF is not synonymous with long term success. This is a sub-study of an outcomes based study to determine whether baseline PD burden and distribution in persistent AF predict long term outcome with PVI (NCT03394404) which will yield complimentary data.

Atrial Fibrillation is arguably the most difficult arrhythmia to map non-invasively. Validation work in the ventricle has shown a moderate correlation between ECGI predicted activation times and that on epicardial contact mapping[24–26]. The accuracy may be further reduced in areas of low voltage and the system may have difficulty identifying lines of block. The atria are also anatomically complex and the atria cannot be separated at the septum. The moderate accuracy of ECGI mapping combined with the limitations of phase mapping may predispose to false rotor detections. In order to mitigate these limitations so much as is possible we reviewed each rotor detection individually and inspected electrograms for noise and clarity, in addition to reviewing the plausibility of timings constituting the rotational activation.

Furthermore, we recorded the breakout of PDs either side of the septum rather than attempting to attribute them to either atria.

LIMITATIONS

This study has relied on the ECGI mapping system for mapping of PDs. Although there are several published studies using this technology it is accepted that not all PDs visualised using the system are necessarily real or mechanistically important. Arguably the fact that driver patterns predicted the response to PVI lends some internal validation to this mapping technique. Nevertheless, we were not using the system to target any one driver and instead were using it for a mechanistic overview in a relatively large cohort of patients. Not using an internal mapping system has meant that voltage mapping could not be performed following PVI and hence the site of ablation has been assumed rather than specifically assessed. We have studied acute electrophysiologic end-points in this study to gain a greater understanding of the mechanistic impact of PVI in AF. It remains to be seen whether any relationships exist between driver patterns and the long-term freedom from AF following PVI.

CONCLUSION

PVI did not have a global impact on driver burden, distribution or temporal stability outside of the PVs and posterior wall, which suggests these drivers are independent of the PVs and may represent a viable target for patients not responding to PVI. A lower burden of focal but not rotational activation patterns predicted termination of AF with PVI suggesting that focal activations may be more important in maintaining AF. Although total PD burden and distribution did not predict AF termination, a smaller burden and distribution at the PVs and posterior wall did predict termination of AF with PVI, suggesting PDs in this area may be of particular mechanistic importance.

Outcome data is needed to determine whether non-invasive mapping might be of use in determining outcome after PVI for persistent AF.

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FIGURES

Figure 1A-C – Diagram demonstrating the required steps to analyse potential drivers using the ECGI Mapping System.

1A – Diagram showing surface ECG recordings. Segments with excessive noise can be reviewed and discarded.

1B – Diagram showing the raw surface unipolar electrograms allowing signals from individual electrodes with significant noise to be excluded.

1C – Diagram showing how analysis of PDs are performed. The composite map of PDs is displayed on the left. The phase map with the activation sequence can be reviewed for each PD detection on the middle panel. The timings around the area of interest are reviewed (as for the example electrograms on the far right of this panel). The raw reconstructed atrial electrogram and the resultant waveform following the Hilbert Transform is displayed at the bottom to allow sites along the wavefront to be reviewed for plausibility of the source data.

1A-C – Diagram demonstrating the required steps to analyse potential drivers using the ECGI Mapping System

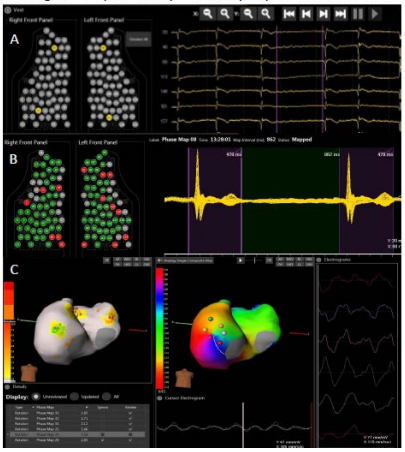

Figure 2 – Diagram showing the 18 bi-atrial segment model used to record the distribution of potential drivers (including rotational and focal activations). Posterior-Anterior view on left and Anterior-Posterior view on right.

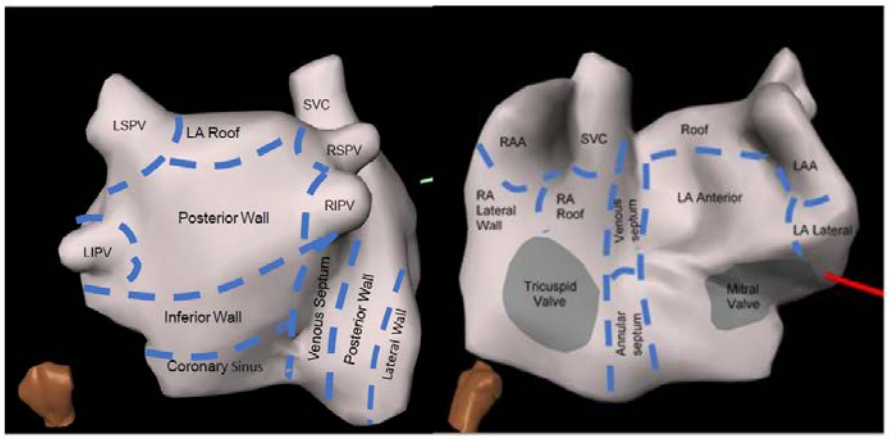

Figure 3 – Diagram showing ECGI Composite maps from two patients. Patient A in which PVI led to termination of AF has fewer PDs compared to Patient B in which PVI did not terminate AF.

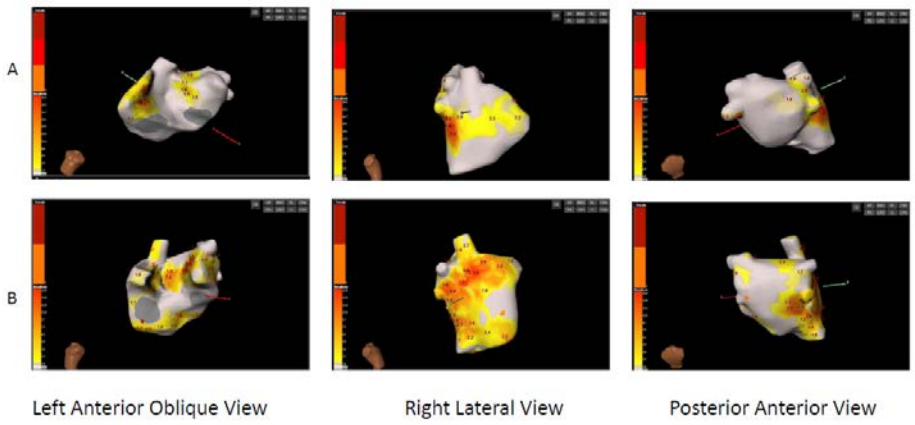

Table 1: Demographics of Participants

Baseline Characteristics	
Number of Patients	100
Age (years) Mean ± SD	61.3 ± 12.1
Male n (%)	74 (74.0)
Hypertension n (%)	47 (47.0)
Diabetes Mellitus n (%)	14 (14.0)
Ischaemic Heart Disease n (%)	10 (10.0)
Cerebrovascular Accident n (%)	9 (9.0)
CHA2DS2VASC Score mean ± SD	1 (0 – 3)
LA Diameter (mm)	39 (33 – 43)
LA Volume (ml)	62 (49 – 83)
Median duration of AF: diagnosis to procedure (months)	24 (16 – 48)

Duration of Persistent AF (months)	8 (5 -15)
Persistent AF (< twelve months)	67 (67.0)
Longstanding AF (> twelve months)	33 (33.0)
Number of Anti-arrhythmic Drugs failed	1 (1 - 1)
Anticoagulation with direct oral anticoagulant n (%)	93 (93.0)

Values are given as no. (%), mean ± standard deviation or median (Interquartile Range).

Table 2: ROC analysis of factors predicting Termination of AF

Factor	Area Under Curve	95% Confidence Interval	P Value	Optimal Value	Sensitivity (%)	Specificity (%)
Burden of PDs						
Total PD Occurrences	0.633	0.473 – 0.792	0.103	34	66.7	60.0
Total Number of Foci	0.683	0.528 – 0.839	0.024	11	66.7	60.7
Total Rotations	0.540	0.376 – 0.704	0.626	62.8	60.0	47.6
No of PD Occurrences at PV and PW	0.675	0.529 – 0.820	0.032	6	67.9	60.0
Proportion of PDs at PVs and PW (%)	0.569	0.424 – 0.714	0.399	0.24	57.1	53.3

Distribution of PDs						
Total Segments with PDs	0.604	0.479 – 0.730	0.199	12	57.1	73.3
No of Segments with PDs at PVs and PW	0.662	0.535 – 0.788	0.047	3	57.1	66.7
Proportion of Segments with PDs at PVs and PW (%)	0.635	0.480 – 0.790	0.097	35	61.9	60.0
LA Diameter (mm)	0.639	0.433 - 0.844	0.124	33.5	81.8	67.7
LA Area (cm2)	0.490	0.316 – 0.665	0.914	22.8	58.4	3.33
LA Volume (ml)	0.485	0.321 – 0.649	0.866	56.4	59.7	41.7
Time from diagnosis AF to PVI (Months)	0.581	0.422 – 0.740	0.368	15.5	59.7	58.3
Duration of continuous Persistent AF (Months)	0.568	0.429 – 0.707	0.449	7.5	59.7	50.0
LAA CL	0.750	0.621 – 0.879	0.002	179.9	80.0	71.1
RAA CL	0.753	0.651 – 0.855	0.002	172.0	80.0	61.4
Prox CS CL	0.734	0.598 – 0.869	0.004	194.0	73.3	59.0
Average of LAA, RAA and Prox CS	0.777	0.670 – 0.884	0.001	184.2	80.0	69.9
Average of PVs	0.704	0.569 – 0.840	0.012	185.4	73.3	69.9
Ratio CL of PVs to LAA	0.693	0.544 – 0.843	0.018	1.0	67.5	67.7

CL: Cycle Length in (ms), LAA: Left atrial appendage, RAA: Right atrial appendage, Prox CS: Proximal Coronary Sinus. LA: Left atrium.