Original Article

Pulmonary vein isolation for atrial fibrillation: Does ablation technique influence outcome?

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Background: Over the last 20 years various techniques have been developed striving for safer and more
durable pulmonary vein isolation (PVI). The three most commonly used tools are pulmonary vein
ablation catheter (PVAC) and cryoballoon ('single-shot' techniques), and point-by-point (PBP) radio-
frequency ablation using 3D electroanatomical mapping (EAM).

Objective: Evaluate the safety and efficacy of the different techniques in an unselected population un-
dergoing de-novo ablation for persistent or paroxysmal atrial fibrillation (AF) at Royal Papworth Hospital
(RPH).

Method: Retrospective, single-centre study of consecutive AF ablations at RPH between March 2017 and
April 2018. Demographic, procedural and outcome data were analysed.

Results: Over the study period 329 first-time PVI procedures were performed. 37.4% were performed
using PBP, 39.8% using cryoballoon and 22.8% using PVAC. There was no significant difference in age or
sex between different ablation technique groups. 238 procedures were performed for paroxysmal AF and
91 for persistent AF. A higher proportion of the persistent cases were performed using point-by-point
techniques compared to paroxysmal cases (58.2% vs 29.0%, p < 0.05).

Procedural times were significantly longer in the group undergoing PBP ablation compared to cryo-
balloon or PVAC. However, there was no statistically significant difference in 12-month freedom from
symptomatic AF or procedural complications between the groups.

Conclusions: PBP, PVAC and cryoballoon AF ablation all appeared equally efficacious in an unselected
population, though PVAC and cryoballoon procedures were shorter. All procedures were associated with
a low adverse event rate. Prospective examination is required to substantiate this finding.

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1. Introduction

The importance of focal ectopic triggers within the pulmonary veins (PVs) in the initiation of atrial fibrillation (AF), and the consequent necessity of preventing these triggers from propagating into the left atrium, has been well-recognised since the publication of Haïssaguerre’s landmark paper in 1998.1 Over the following two decades invasive treatment of AF has continued to progress both conceptually and strategically. Procedures focussing on targeting and ablating these ectopic foci with radiofrequency (RF) energy could often be exceptionally protracted and laborious, and have

since made way for the practice of ‘electrically isolating’ the pulmonary veins (PVs). Pulmonary vein isolation (PVI) is now the standard of care for treatment of symptomatic AF in many cir-
cumstances, particularly in younger patients presenting with

paroxysmal AF.

The methodology of achieving pulmonary vein isolation has evolved also, with diverse techniques and technology having been developed with the aim of making the procedure quicker, safer and more durable. These techniques can be broadly divided into two categories: ‘point by point’ (PBP) ablation, wherein single ablation lesions are applied using a single-tip electrode catheter to create a contiguous line of transmural scar around the pulmonary veins, and ‘single-shot’ ablation, wherein multipolar lasso RF catheters (such as the pulmonary vein ablation catheter, PVAC) or freezing balloons (cryoballoon) are inserted into each PV in turn for the same purpose.

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Point-by-point ablation generally requires the creation of a 3D electroanatomical map (EAM) of the left atrium (LA) to guide real-time catheter navigation and location of ablation lesions. This is more time-consuming and demands higher skill levels from operators and cardiac physiologists alike but provides the benefit of versatility, allowing the operator to pursue noteworthy non-PV targets in the left or right atrium or negotiate unusual PV anatomy. The popularity and uptake of single-shot strategies, which by their nature are simpler and quicker, has risen in line with the growing worldwide prevalence of AF and the concomitant requirement to simplify and streamline AF ablation service delivery.

As novel equipment or fresh iterations of existing technology become available, they are often compared to contemporary standard-of-care to ensure equivalent efficacy and safety. However, trials are often limited to highly selective patient populations, and additionally some issues do not become apparent until several years after such technology has been introduced. It is also apparent that operator comfort with new technology changes with time, impacting outcomes such as procedural success, procedure times and complication rates. These important factors are often overlooked in initial head-to-head studies, and downstream ‘real world’ experiential data, though vital, is meagre.

Royal Papworth Hospital (RPH) is a high-volume ablation centre, in which approximately 400–500 AF ablations are performed per year. A variety of methods are utilised by experienced operators for both persistent and paroxysmal AF ablation, of which the most frequently used are PVAC, cryoballoon and PBP ablation using the CARTO EAM system. The three techniques have never before been compared simultaneously in a single study, and indeed newer generation PVAC and cryoballoon have never been compared head-to-head at all to date.

Our objective was to provide a real-world evaluation of the influence of AF ablation technique on procedural outcomes, medium-term durability and complication rates in an unselected patient population undergoing de-novo ablation for paroxysmal or persistent AF at RPH.
Patients were admitted to the ward at least 90 min prior to procedure commencement, during which time admission clerking was performed and informed consent confirmed, and were brought into the electrophysiology lab in a fasted, non-sedated state.

Ultrasound guidance for femoral venous access was not routine but was available if required for difficult cases. Trans-septal puncture was performed under fluoroscopic guidance, following which heparin was administered and topped up as necessary to maintain activated clotting times (ACTs) of over 300 s. TOE was available if necessary for difficult trans-septal access or where clarity was required over the presence of thrombus in the left atrial appendage.

At the end of the procedure heparin was routinely reversed with protamine prior to venous sheath removal. Groin haemostasis was achieved with manual pressure.

Patients undergoing their procedure under conscious sedation were transferred directly back to the ward post-procedure, whilst those receiving general anaesthetic (GA) were initially transferred to the theatre recovery area until the haemodynamic and sedative effects of GA had worn off sufficiently for them to be deemed safe for ongoing ward-based management. All patients routinely undertook 2 h of bed rest on return to the ward whilst connected to a cardiac monitor, during which time a post-procedure ECG was performed, hourly routine observations (blood pressure, heart rate and oxygen saturations) were recorded and groin haemostasis was assessed. Post-procedure echocardiography was only performed when there was clinical suspicion of pericardial collection. If groin haemostasis was acceptable and patients were clinically stable after this 2-h period they could be gently mobilised. If after a further 1-h observation there were no evident complications anticoagulation could recommence and the patient could be discharged as long as there was a suitable caregiver present on discharge. Discharge could be nurse-led if stipulated by the operator in the post-procedure plan. Anti-arrhythmic medication was continued until outpatient review at 3 months unless significant adverse effects were being experienced from them.

2.3. Follow up

Patients were initially followed up at 3-, 6- and 12-months post-procedure. A 12 lead ECG was performed and patients were surveyed for symptomatic improvement and late complications. A post-procedure ‘blanking period’ of 3 months was allowed for, during which time any symptomatic episodes were not classed as procedure failure but rather an expected and acceptable consequence of left atrial ablation. If patients did report symptomatic improvement after 3 months then antiarrhythmic drugs were discontinued unless required for an alternative clinical purpose (for example beta blockade for left ventricular systolic failure). If patients reported significant ongoing symptoms consistent with atrial arrhythmia at 6-month follow up, but were in sinus rhythm at the time of the clinic appointment, they were referred for ambulatory monitoring to help clarify the diagnosis. Routine ambulatory monitoring in asymptomatic patients was not performed as detection of subclinical AF was not considered a clinically-relevant endpoint.

12-month success was defined as complete lack of symptoms from AF or demonstrable AF on ECG regardless of the intake of antiarrhythmic drugs.

2.4. Statistical analysis

Continuous variables are presented as mean ± standard deviation, and categorical data as counts or percentages. Analysis and comparisons of parametric continuous data were performed using Student’s t-tests and analysis of variance (ANOVA), whilst categorical data were compared using the χ² test. A two-tailed probability level of <0.05 was considered significant.

For the purposes of data analysis, paroxysmal and persistent AF groups were examined separately due to the well-recognised differences in long-term outcome between the two entities.

3. Results

3.1. Patient demographics, procedural characteristics and clinical results

Over the study period 452 AF ablation procedures were performed in 448 patients, of which 334 were first-time procedures. 5 of these were carried out using AcQMap. Thus 329 cases were suitable for inclusion. Of these, 123 (37.4%) were performed using PBP, 131 (39.8%) using cryoballoon and 75 (22.8%) using PVAC.

The average age was 60.4 ± 10 years and 69.6% of patients were male. There was no significant difference in age, sex, left atrial diameter, CHADS2-Vasc score or cardiovascular co-morbidity profile between different ablation technique groups.

238 ablations were performed for paroxysmal AF and 91 for persistent AF. A higher proportion of the persistent cases were performed using point-by-point techniques compared to paroxysmal cases (58.2% vs 29.0%, p < 0.05).

Procedural times were significantly longer in the group undergoing ablation with CARTO compared to cryoballoon or PVAC (191.3 ± 39 vs. 126.7 ± 24 vs. 117.4 ± 30 min respectively, p < 0.05).

12-month follow up data was available for 315 cases (95.7%). The overall 12-month freedom from symptomatic AF was 76.5% for paroxysmal AF and 69.0% for persistent AF. Success rates did not vary between different techniques for paroxysmal AF ablation, and whilst success rates were higher with single shot techniques in persistent cases this was not statistically significant. Additionally, time to recurrence of symptoms or ECG-documented atrial arrhythmia was no different between groups (Fig. 1). In total 26 patients were listed for redo procedures.

Demographic data and procedural outcomes are shown in Table 1.

3.2. Clinical complications

The overall major and minor complication rate was low at 3.9%. There was a higher complication rate observed in the CARTO group but this did not reach statistical significance. A summary of complications is shown in Table 2.

One cryoablation case was complicated by intraprocedural phrenic nerve palsy from which a full recovery was made prior to discharge, and another by right leg numbness likely due to local infiltration of the femoral nerve, which resolved fully within 2–3 h. Neither led to delayed discharge or long-term adverse sequelae. One patient suffered chest tightness on removal of the ablation catheter from a sheath situated in the left atrium. This was associated with transient ST segment depression on their ECG which resolved fully. Given the patient’s relative youth, lack of cardiovascular risk factors or prior history of ischaemic heart disease and the circumstances of the event a diagnosis of air embolism was made.

One patient undergoing ablation with PVAC suffered a right femoral vein pseudoaneurysm and arteriovenous fistula which manifest after the patient was discharged home, requiring readmission and eventually surgical intervention.

Three of the CARTO complications pertained to vascular access: two of these were minor haematomas which resolved with either manual compression or application of a femstop, and one further case of pseudoaneurysm treated with thrombin injection. One
patient had to be admitted to intensive care post-procedure for respiratory support due to pulmonary oedema, but made a full recovery to discharge. Two patients underwent pericardiocentesis for tamponade; one case manifest during ablation and led to procedure abandonment following drain insertion whilst the other case manifest soon after return to the ward. A further case unfortunately resulted in atrio-oesophageal fistula and death three weeks post-discharge.

One case of transient ischaemic attack occurring four days post-discharge was reported at follow up, which manifest as transient slurring of speech and facial weakness lasting for approximately 1 h with spontaneous resolution. Brain imaging did not show any abnormality. A full neurological recovery was made with no recurrence. One migraine was reported at 6 month follow up, in which the patient reported classic unilateral headache with photophobia and visual aura lasting a few minutes and resolving without need for treatment. This patient was known to have a history of migraine. No other late complications were reported.

### Table 1

|                          | CARTO n = 123 | Cryoballoon n = 131 | PVAC n = 75 | p-value |
|--------------------------|---------------|---------------------|-------------|---------|
| Age/years                | 61.7 ± 9.2    | 59.5 ± 10.6         | 61.7 ± 9.7  | 0.14    |
| Male                     | 92 (74.8)     | 88 (67.2)           | 49 (61.3)   | 0.80    |
| Paroxysmal AF            | 70 (56.9)     | 106 (78.6)          | 62 (82.7)   | 0.14    |
| Cardiovascular risk factors |           |                    |             |         |
| Hypertension             | 73 (59.3)     | 79 (60.3)           | 43 (57.3)   | 0.58    |
| Diabetes                 | 23 (18.7)     | 19 (14.5)           | 16 (21.3)   | 0.62    |
| Ischaemic heart disease  | 40 (32.5)     | 45 (34.4)           | 22 (29.3)   | 0.24    |
| Cerebrovascular disease  | 2 (1.6)       | 0 (0)               | 1 (1.3)     | 0.24    |
| Heart failure            | 0 (0)         | 1 (0.8)             | 0 (0)       | 0.71    |
| Hypertension             | 12 (9.8)      | 16 (12.2)           | 10 (13.3)   |         |
| Left atrial diameter/cm  | 4.2 ± 0.7     | 4.1 ± 0.7           | 3.9 ± 1.0   | 0.69    |
| Mean CHADS2-Vasc         | 2.3 ± 0.6     | 2.1 ± 0.8           | 2.1 ± 0.5   | 0.82    |
| Procedure time/mins      | 191.3 ± 39    | 126.7 ± 24          | 117.4 ± 30  | 0.05    |
| PVI success              | 121 (98.4)    | 127 (96.9)          | 74 (98.7)   | 0.88    |
| 12 month success         |               |                     |             |         |
| Paroxysmal               | 50/66 (75.8)  | 78/103 (75.7)       | 48/61 (78.6) | 0.99    |
| Persistent               | 32/51 (62.7)  | 18/24 (75.0)        | 10/12 (83.3) | 0.80    |

Fig. 1. Kaplan-Meier plots showing time to recurrence of symptoms or documented atrial arrhythmia following ablation for paroxysmal AF (panel A) and persistent AF (panel B) with CARTO, cryoballoon or PVAC after a 90-day blanking period.
4. Discussion

In our retrospective, single-centre, high-volume study we demonstrate that single shot PVI using either PVAC or cryoballoon is equally as efficacious as point-by-point ablation using the CARTO EAM system at reducing symptomatic AF burden at 12 months in an unselected population undergoing ablation for paroxysmal or persistent AF, and is associated with a low complication rate. The study we have presented is the first to make direct comparison between point-by-point, PVAC and cryoballoon simultaneously (or, indeed, between second generation PVAC and cryoballoon head-to-head).

The overall observed success rates for both paroxysmal and persistent AF ablation are comparable to other data published on the subject and are likely to reflect, at least in part, operator experience. For paroxysmal AF the 12-month durability was almost identical for all three modalities at approximately 75%. For persistent AF the variability in 12-month freedom from symptomatic arrhythmia across techniques was more pronounced, though this is more likely due to lower patient numbers in this group and the associated amplification of individual data points. Likewise the overall complication rate of 3.9% is markedly lower than that reported by the near-contemporaneous review of ablation outcomes published by the European Society of Cardiology, in which the in-hospital complication rate was found to be 7.8% amongst 3594 patients undergoing AF ablation in 104 centres in 27 European countries between April 2012 and April 2015.3

Currently point-by-point, PVAC and cryoballoon are the three most commonly used AF ablation tools. The original PVAC catheter had previously been maligned for causing a higher incidence of silent cerebral micro-emboli,4 requiring a subtle design change. The new incarnation, PVAC gold, sported 9 gold electrodes, a 20° forward deflection of the electrode array to improve tissue contact and avoid bipolar interaction between the most distal and proximal electrodes to reduce thrombogenicity. Early trials with PVAC gold were promising, demonstrating lower observed complication rates but comparable success rates.5 The PVAC gold catheter was used in our study and accordingly fared well with no cerebrovascular events noted.

The cryoballoon is another over-the-wire system consisting of a 28 mm diameter balloon mounted on a bidirectionally deflectable catheter.6 Single trans-septal access is required, though the calibre of the introducer sheath is larger (15F). However, a remarkably low occurrence of major groin site haematoma or arteriovenous fistula formation is reported,7 and no significant access site haematomas were observed in our study. The incidence of persistent atrial septal defect is higher although this rarely appears to lead to any adverse clinical consequences.8,9 Phrenic nerve injury, mainly on ablation of the right PVs, is a concern with early studies demonstrating an incidence as high as 10%. Improvements in balloon design, more widespread use of the 28 mm balloon over the 23 mm balloon and uptake of diaphragmatic electromyographic signal monitoring with compound motor action potential (CMAP) have greatly reduced this. The overall recent published complication rate with newer generation cryoballoons is approximately 2%, exactly as observed here.10

With the CARTO electroanatomic mapping system movement of the catheter tip within the patient causes deflection of the magnetic field in the locator pad, and allows the position of the catheter tip to be triangulated in space. The introduction of contact force and directional sensing within the last decade has both improved success rates and markedly reduced the overall complication rate associated with use of CARTO for PBP ablation.1

Despite advances in AF ablation technology no strategy has yet been developed that can decisively ‘cure’ AF. Thus the arms race for any incremental improvement, be it in procedural efficacy, safety or duration, is ongoing and has proved fertile ground for research. Head-to-head studies between PVAC and point-by-point ablation have generated comparable outcomes, as have those between cryoballoon and point-by-point.

Jin et al evaluated 12 studies comparing cryoballoon to single-tip RF, comprising over 4000 patients in total (91% paroxysmal AF).11 The findings largely corroborate that of our study: recurrence rates of atrial arrhythmia were comparable at 9 months median follow up, particularly when contact force RF was compared to second generation cryoballoon (19.5% for cryoballoon vs 18.3% for RF, p = 0.58); and procedure times were markedly shorter when cryoballoon was used. Complications were selectively reported however and thus cannot be compared to our observed outcomes.

Only one prospective study has attempted to compare outcomes for PVAC vs cryoballoon ablation, though as this featured first-generation technology the results are no longer so clinically relevant.12 Among 110 AF patients, 12-month freedom from AF after a single procedure was rather low in this analysis, but comparable between PVAC and cryoballoon (34% vs 46% respectively, p = 0.2) with respective complication rates of 2% vs 8% (p = 0.2). Procedure duration was not significantly different between the groups.

Whilst individual studies are numerous,13-14 systematic reviews of PVAC vs point-by-point are lacking.

The aforementioned lack of trial data, prior to our study, comparing all three techniques directly did not stop Kabunga et al performing a network meta-analysis of comparative head-to-head analyses.15 Cross-analysing 31 studies (14 comparing point-by-point to PVAC, 16 comparing point-by-point to cryoballoon and one comparing PVAC to cryoballoon) comprising a total of 7839 patients they concluded that PVAC was significantly more efficacious than point-by-point or cryoballoon ablation; however, on analysis of randomised data alone this did not hold true and PVAC and point-by-point had equivalent success rate (OR 1.23, p = 0.35). PVAC procedure times were significantly shorter, confirming our findings. Interestingly, when comparing only randomised prospective data point-by-point ablation was found to be statistically more efficacious than cryoballoon (OR 0.43, p = 0.04), whilst procedure times were equivalent; this is at odds with our observed data. No conclusion could be drawn about complication incidence due to low event rates and heterogeneous reporting of outcomes. The authors identified operator experience and skill as a key intangible confounder of all outcome reporting. Furthermore, half of the trials analysed consisted of fewer than 100 patients, and such low patient numbers may serve to accentuate any inherent confounding factors. In our study all operators had more than 5 years’ experience at AF ablation and were well-practised (>50 procedures per operator per year), whilst the high patient number in this analysis ought to moderate many of the hidden confounding elements.

Table 2

| Complications         | CARTO n = 123 | Cryoballoon n = 131 | PVAC n = 75 | p-value |
|----------------------|---------------|---------------------|-------------|---------|
| Total                | 9 (7.3)       | 3 (2.3)             | 1 (1.3)     | 0.07    |
| Vascular             | 3             | 0                   | 1           |         |
| Pericardial effusion | 2             | 0                   | 0           |         |
| Air embolus          | 0             | 1                   | 0           |         |
| Phrenic palsy        | 0             | 1                   | 0           |         |
| Migraine             | 1             | 0                   | 0           |         |
| CVA                  | 1             | 0                   | 0           |         |
| Pulmonary oedema     | 1             | 0                   | 0           |         |
| Leg numbness         | 0             | 1                   | 0           |         |
| Death                | 1             | 0                   | 0           |         |
With equal procedural efficacy but longer procedural times one pertinent question is: why opt for PBP? The main benefit of using an EAM system, particularly in persistent AF, lies with the ability to identify and treat non-PV triggers, focal areas of diseased substrate, or typical and atypical flutters in the same procedure. Whilst this does not appear to be any clear additional benefit to this in routine practice this approach may be deemed suitable for individual cases. Substrate modification and ablation of non-PV triggers has been reported with cryoballoon and PVAC, but this is not standard practice at present. PBP may also be preferable in cases where anatomical PV variants, such as common or middle pulmonary veins, render single shot techniques less attractive. Pre-procedure radiological evaluation of the left atrial anatomy may help identify such variants in advance and thus help procedural planning; an added benefit of this is to enable co-registration of CT or MRI pulmonary venography with the EAM system.

Furthermore, the time lost due to longer procedure duration may be reclaimed in other areas. 3D EAM systems are regularly the technology of choice for redo PVI as well as other electrophysiological procedures, and given the technical proficiency required to use these systems it would appear logical to perform a proportion of first-time PVI cases using EAM to maintain skill levels amongst both physicians and physiologists.

The ‘traditional’ PVI methods used in this study are, by definition, well-established and have a wealth of favourable outcome and safety data as outlined above to justify their continued usage, though periodic hardware and software upgrades ensure that they continue to evolve to sustain optimal performance. However, completely novel technology to achieve safe and durable PVI continues to develop, and early outcome data regarding pulsed field ablation and expandable lattice tip RF, for example, appears promising. The results of long-term comparison and observational studies with these new techniques will be awaited with interest.

4.1. Study limitations

This was a single-centre, retrospective, observational analysis and not a prospective study wherein patients would be matched for age, sex, co-morbidities and other variables. To mitigate this somewhat, the number of patients included was sizable compared to other similar studies and ought to provide an additional degree of robustness to the findings. Nevertheless, whilst we have therefore provided useful data as to the respective benefits of the different AF ablation techniques, only limited generalizable conclusions can be drawn from this analysis.

RPH is a tertiary centre with no emergency or general cardiology department, and it is possible that late complications presenting to this in routine practice at present.17, 18

Prospective, randomised control trial data is necessary to further validate this finding.

The performance of novel PVI techniques in real-world populations over a significant period of time will be fascinating to observe.

Author's contributions

SAR-preparation of manuscript, study design, data collection and analysis. SLN- data analysis, aiding of manuscript preparation. BVK- aiding of manuscript preparation. MSV- project lead, study design, manuscript preparation. All authors read and approved the final manuscript.

Declaration of competing interest

No conflicts of interest to disclose.

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