Impact of variant pulmonary vein anatomy and image integration on long-term outcome after catheter ablation for atrial fibrillation


Aims
To investigate the impact of variant pulmonary vein (PV) anatomy and the use of three-dimensional image integration (3D-II) on long-term efficacy of catheter ablation for atrial fibrillation (AF).

Methods
Consecutive procedures from 2002 to 2007 were analysed from a prospective database. All patients underwent wide area circumferential ablation, with linear lesions added and complex fractionated electrograms targeted for persistent AF. Imaging was segmented on Carto to assess PV anatomy.

Results
Three hundred and fifty patients underwent 1.9 ± 0.9 procedures. The mean age was 57 ± 11 years, 73% males, and 55% paroxysmal AF. Freedom from AF/atrial tachycardia was 42% for paroxysmal AF and 20% for persistent AF at 3.1 years after the first procedure, or 86 and 66%, respectively, at 2.5 years after the last procedure. The Kaplan–Meier analysis showed a trend towards improved single-procedure efficacy with 3D-II (8.9% difference, \( P = 0.087 \)) and a reduction in the number of procedures per patient from 2.1 ± 1.1 to 1.8 ± 0.9 (\( P < 0.0001 \)). The use of 3D-II improved single-procedure efficacy with Carto (13.3% difference, \( P = 0.018 \)), but not with Ensite NavX. Variant PV anatomy was identified in 28% and was associated with a lower single-procedure efficacy (10.0% difference, \( P = 0.024 \)) but with no effect on final outcome. Multivariate analysis confirmed the impact of 3D-II [hazard ratio (HR) for recurrence of AF 0.67, \( P = 0.020 \)] and variant PV anatomy (HR 1.37, \( P = 0.044 \)).

Conclusion
The use of 3D-II improves single-procedure efficacy of PV isolation for AF. Variant PV anatomy was associated with a lower single-procedure success rate.

Keywords
AF • Catheter ablation • Outcome • Efficacy • Image integration • Venous anatomy • Atrial anatomy

Introduction
The anatomy of the junction between the pulmonary veins (PVs) and the left atrium is highly variable. Variations in anatomy at the veno-atrial junction may hinder attempts to isolate the PVs during catheter ablation for atrial fibrillation (AF), particularly if the operator is unaware of the abnormality. Confirmation of PV anatomy with computed tomography (CT) or magnetic resonance imaging (MRI), with or without three-dimensional image integration (3D-II) into mapping systems, highlights anatomical variation and may aid catheter navigation and lesion placement. However, evidence regarding the impact of 3D-II on outcome remains contradictory. There is also limited evidence that variation in anatomy of the veno-atrial junction actually influences outcome.

Catheter ablation of AF at St Bartholomew’s Hospital has remained consistent since 2002, with wide area circumferential ablation (WACA) and confirmation of electrical isolation of the PVs as a procedural endpoint in all patients. For persistent AF,
linear lesions have been added and complex fractionated electrograms (CFE) targeted. A prospective registry was examined to ascertain whether (i) the use of 3D-II or (ii) variations in anatomy of the veno-atrial junction impact on outcome after catheter ablation of AF.

Methods
Consecutive patients undergoing catheter ablation of AF between 1 April 2002 and 5 October 2007 were included for analysis. Procedural data and baseline patient information were obtained from a prospective registry. Patients were defined as paroxysmal or persistent AF according to the ACC/ESC guidelines. Patients with long-lasting persistent AF have been grouped with persistent AF.

Peri-procedural management
If patients were on warfarin, this was stopped 5 days pre-procedure and patients self-administered low-molecular-weight heparin (subcutaneous enoxaparin 1.5 mg/kg od). Patients underwent transoesophageal echocardiography within 24 h of catheter ablation to exclude intra-cardiac thrombus. Patients were given 5000 U of unfractionated heparin after insertion of sheaths, and a further 5000 U after transseptal puncture. The activated clotting time was checked every 30 min and maintained between 300 and 400 s with further heparin boluses. Low-molecular-weight heparin was administered while reloading warfarin.

Catheter ablation of atrial fibrillation
Our technique for catheter ablation of AF has been described previously. In brief, under local anaesthetic (lidocaine) and intravenous moderate sedation (midazolam and diamorphine), a quadripolar or decapolar catheter was inserted into the coronary sinus, and after double transseptal puncture, a PV mapping catheter and an irrigated 4 mm tip radiofrequency ablation catheter were introduced to the left atrium. Our catheter irrigation and power settings during ablation have been published previously.

Procedures were guided by 3D mapping systems, either Carto (Biosense Webster Inc., Diamond Bar, CA, USA) or Ensite NavX (St Jude Medical, Minneapolis, MN, USA). Computed tomography or MRI imaging was performed routinely for 3D-II and was segmented on proprietary software (Cartomerge or Ensite Verismo) and integrated as described previously.

Wide area circumferential ablation was performed for all patients in the cohort, with lesions placed 1–2 cm outside PV ostia to isolate them in ipsilateral pairs. Electrical isolation was confirmed with a multipolar PV mapping catheter. For persistent AF, linear lesions were added at the mitral isthmus (between the mitral valve and left WACA ring), the roof between WACA rings, and the cavotricuspid isthmus in patients with a history of atrial flutter. Conduction block was verified by examining activation sequence either side of linear lesions after restoration of sinus rhythm. From 2005, after PV isolation and linear lesions, CFE were systematically targeted throughout both atria. If at any point, AF organized into atrial tachycardia (AT), this was mapped and ablated. If sinus rhythm was not restored following these lesions, the patient was cardioverted with a DC shock.

Follow-up
Patients were discharged the day after the procedure. As early recurrences may settle spontaneously, a 3-month blanking period was observed during which recurrences were managed medically. Those with persistent AF/AT or symptomatic paroxysmal AF were offered a repeat procedure. Anticoagulation was continued for a minimum of 3 months and ongoing anticoagulation advised if the CHADS2 score was ≥2 (regardless of rhythm) as per the current guidelines.

Patients were followed up at 3 months, and again at 6 months if symptomatic initially, with a period of ambulatory electrocardiographic (ECG) monitoring of 2–7 days. There was open access to arrhythmia nurse specialists subsequently and further monitoring prompted by symptoms. Late follow-up with an ECG was obtained from the referring physician at 18 months. Attempts were made to contact all patients for review between 1 September 2009 and 16 October 2009 to determine any adverse events, recurrences of AF/AT, current medications, and symptoms. Success was defined as freedom from symptoms and/or documented AF/AT lasting >30 s following the 3-month blanking period and is reported after the first and last procedures.

Single-procedure success was compared for cases performed with and without 3D-II. The impact of 3D-II was also assessed for each mapping system (Carto and NavX). To investigate the impact of variant PV anatomy, imaging was segmented on Carto and assessed by two electrophysiologists independently with a third independent opinion sought in cases of disagreement. Anatomy was categorized as follows:

(i) normal, defined as four PV ostia at the respective corners of the posterior wall,
(ii) left common trunk, defined as a single left-sided ostium,
(iii) a right middle vein, defined as three right-sided ostia, and
(iv) other variants (including those with multiple variants).

The impact of common anatomical variations on single-procedure and final outcome was assessed.

Statistics
Continuous variables are reported as mean ± standard deviation, or median (range) if not normally distributed. Continuous data were compared by Student's t-test. The Kaplan–Meier curves were used to analyse AF-free survival and the curves were compared using the log-rank test. Multivariate analysis of predictors of recurrence was by Cox’s regression, with time of inclusion in the cohort included as a continuous variable.

Results
Patients and procedures
Three hundred and fifty patients were studied, aged 56.6 ± 10.7 years. Sixteen per cent were over 65 years of age and 73% were males. Patients had a history of AF for 65 ± 59 months. One hundred and eighty-three (55%) had paroxysmal AF, 152 (45%) had persistent AF, and the majority of these (92%) were long-lasting persistent AF (i.e. continuous for >1 year). Twenty per cent had structural heart disease and 31% had hypertension. Five per cent
had a history of stroke or transient ischaemic attack (TIA). The mean left atrial diameter was 4.3 ± 0.8 cm and 16% had left ventricular systolic dysfunction (defined as ejection fraction <50%).

Six hundred and fifty-six procedures were performed, with a mean per patient of 1.9 ± 0.9 (1.7 ± 0.8 for paroxysmal AF and 2.1 ± 1.1 for persistent AF). One hundred and forty-eight (42%) patients had 1 procedure, 128 (37%) had 2, 53 (15%) had 3, 13 (4%) had 4, 7 (2.0%) had 5, and 1 (0.3%) had 6. The procedure time was 220 (45–510) min and fluoroscopy time 57 (21–129) min.

Procedural complications consisted of: tamponade in 12 (1.8%) which were all drained without sequelae, stroke or TIA in 3 (0.5%) which all resolved without lasting deficit, and PV stenosis in 3 (0.5%) which all occurred in the first 100 cases. There were no deaths or atrio-oesophageal fistulas. One pseudo-aneurysm occurred and was successfully treated with thrombin injection and compression.

**Adverse events during follow-up**

Of the 350 patients, 15 could not be traced and were excluded from the analysis. Patients were followed up for a median of 3.1 (2.0–7.5) years from their last procedure. The seven deaths in the cohort were unrelated to AF or the ablation. Of the two cardiac deaths, one occurred at 27 days post-procedure due to a myocardial infarction and the other was a sudden cardiac death in a patient with pre-existing heart failure and an implantable cardioverter deﬁbrillator in situ more than 2 years post-ablation. The non-cardiac deaths were due to three malignancies and two pneumonias complicating pre-existing pulmonary disease. Other adverse events during follow-up included one myocardial infarction, two TIA’s, and a stroke which resolved without long-term neurological deﬁcit. There were no cases of new onset heart failure. Two patients went on to have atrioventricular node ablation and pacemaker implantation.

**Impact of image integration on outcome**

Of 335 patients with follow-up data, 227 (68%) underwent procedures involving 3D-II and 108 (32%) did not. More patients underwent catheter ablation without 3D-II early in the cohort; procedures involving 3D-II and 108 (32%) did not. More patients had 1 procedure, 128 (37%) had 2, 53 (15%) had 3, 13 (4%) had 4, 7 (2.0%) had 5, and 1 (0.3%) had 6. The procedure time was 220 (45–510) min and fluoroscopy time 57 (21–129) min.

Procedural complications consisted of: tamponade in 12 (1.8%) which were all drained without sequelae, stroke or TIA in 3 (0.5%) which all resolved without lasting deficit, and PV stenosis in 3 (0.5%) which all occurred in the first 100 cases. There were no deaths or atrio-oesophageal fistulas. One pseudo-aneurysm occurred and was successfully treated with thrombin injection and compression.

**Table 1 Long-term outcome after catheter ablation of AF**

<table>
<thead>
<tr>
<th></th>
<th>Single-procedure success (%)</th>
<th>Final success (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AF</td>
<td>31.9 (28.4)</td>
<td>76.7 (66.6)</td>
</tr>
<tr>
<td>3D-II used</td>
<td>34.8 (30.8)</td>
<td>—</td>
</tr>
<tr>
<td>3D-II not used</td>
<td>25.9 (23.1)*</td>
<td>—</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>42.1 (38.3)</td>
<td>85.6 (76.0)</td>
</tr>
<tr>
<td>3D-II used</td>
<td>43.8 (40.0)</td>
<td>—</td>
</tr>
<tr>
<td>3D-II not used</td>
<td>37.7 (34.0)</td>
<td>—</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>19.7 (16.4)</td>
<td>65.8 (55.3)</td>
</tr>
<tr>
<td>3D-II used</td>
<td>22.7 (18.6)</td>
<td>—</td>
</tr>
<tr>
<td>3D-II not used</td>
<td>14.5 (12.7)</td>
<td>—</td>
</tr>
<tr>
<td>Carto</td>
<td>31.1 (28.3)</td>
<td>—</td>
</tr>
<tr>
<td>3D-II used</td>
<td>34.4 (31.1)</td>
<td>—</td>
</tr>
<tr>
<td>3D-II not used</td>
<td>21.1 (19.7)*</td>
<td>—</td>
</tr>
<tr>
<td>Ensite NavX</td>
<td>36.5 (28.8)</td>
<td>—</td>
</tr>
<tr>
<td>3D-II used</td>
<td>40.0 (26.7)</td>
<td>—</td>
</tr>
<tr>
<td>3D-II not used</td>
<td>35.1 (29.7)</td>
<td>—</td>
</tr>
<tr>
<td>PV anatomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>35.9 (32.1)</td>
<td>75.5 (66.8)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>26.8 (23.9)*</td>
<td>76.1 (70.0)</td>
</tr>
</tbody>
</table>

Success was defined as freedom from symptoms and/or documented AF/AT lasting >30 s following the 3-month blanking period. The number in brackets shows the percentage achieving success without taking anti-arrhythmic medication. 3D-II is the abbreviation used for image integration.

*Statistical significance (P < 0.05).
Impact of pulmonary vein anatomy

Of 335 patients with follow-up data, imaging was available for review in 255. Pulmonary vein anatomy was normal in 184 (72%), a left common trunk in 39 (15%), a right middle vein in 23 (9%), and other abnormalities in 9 (4%) including aberrant PV ostia on either the roof or the posterior wall in 3 (1%).

The procedure time was increased from 220 (85–510) min in those with normal anatomy to 225 (110–500) min in those with variant anatomy ($P = 0.0001$). The fluoroscopy time was unchanged at 52 (14–129) min in those with normal anatomy compared with 51 (17–100) min in those with variant anatomy ($P = 0.983$).

Compared with those with normal anatomy, a left common trunk was associated with a 12.8% absolute decrease in first-procedure success (Figure 2A; $P = 0.033$). There was no effect of a right middle vein on success. Despite small numbers, there was a trend towards a lower single-procedure success rate in those with other miscellaneous abnormalities grouped together (13.7% absolute reduction, $P = 0.085$). Grouping together all PV abnormalities, there was a 10.5% absolute reduction in single-procedure success compared with those with normal anatomy ($P = 0.024$). There was no impact of PV anatomy on final outcome (Figure 2B) or the number of procedures required.

Multivariate analysis

Multivariate analysis of factors predicting recurrent AF after a single procedure is shown in Figure 3. The use of 3D-II was associated with a significantly reduced risk of recurrence [hazard ratio (HR) 0.67, confidence interval (CI) 0.48–0.94, $P = 0.020$]. Variant PV anatomy, including all variants grouped together, was associated with a higher risk of recurrence (HR 1.37, CI 1.01–1.96, $P = 0.044$). There was a trend towards improved success with the use of Ensite NavX rather than Carto (HR 0.73, CI 0.48–1.10, $P = 0.134$). The only other factor which reached significance was persistent AF which was associated with a higher risk of recurrence (HR 2.00, CI 1.52–2.62, $P < 0.0001$). There was no independent effect of a later time of inclusion in the cohort (HR 0.926, CI 0.81–1.06, $P = 0.247$).

Discussion

Main findings

This is the largest cohort with the longest follow-up to report on the impact of 3D-II and/or PV anatomy on outcome after catheter ablation for AF. Previous reports regarding potential benefits of 3D-II have been conflicting, and we have demonstrated a modest
improvement in outcome. Subgroup analysis showed a significant benefit for 3D-II in cases performed using Carto but not with NavX. Overall, there was a trend towards improved outcome with the use of NavX which did not reach significance. Compared with patients with four normal PVs, those with variant anatomy had a significantly lower single-procedure success rate, although this did not impact on final outcome.

**Impact of image integration**

Variability in anatomy of the PVs, the dimensions of their ostia, and other anatomical subtleties may influence the outcome of PV isolation. Tissue oedema is progressive once ablation has begun, and if continuous encircling lines of block are not achieved rapidly and efficiently, may cause temporary PV electrical isolation without creating lasting lesions, potentially contributing to PV reconnection and recurrence of AF. Registration of imaging with 3D mapping systems is accurate to within 2–3 mm \(^3,9,10\) and may facilitate catheter navigation and accurate lesion placement. This may help operators to customize their technique to individual patient anatomy. By allowing lesions to be placed into better circumscribed lines and with the opportunity to address gaps, the use of 3D-II may facilitate PV isolation.

Early non-randomized data from our centre demonstrated improved outcomes with 3D-II. \(^4\) A subsequent large randomized controlled trial by Della Bella et al. \(^6\) showed a 19% absolute increase in the single-procedure success rate with the use of 3D-II (with no imaging performed in those not randomized to 3D-II). However, a randomized controlled trial performed at our centre found that the use of 3D-II conferred no benefit. \(^5\) In that trial, patients underwent left atrial CT angiography, regardless of the group they were randomized to. This imaging was available to operators who were consequently aware of left atrial and PV anatomy. The present study demonstrated a more modest 8.9% increase in success with 3D-II. Multivariate analysis confirmed the use of 3D-II as an independent predictor of improved outcome. The randomized controlled trial at our centre was the only study not to suggest a benefit with 3D-II and the only one in which there was imaging available when 3D-II was not used. \(^5\) Therefore, it may be the availability of imaging and knowledge of individual patient anatomy rather than the use of 3D-II per se that improves outcome.

The number needed to treat with 3D-II to prevent one recurrence of AF was 11. The use of 3D-II reduced the number of procedures per patient, with a number needed to treat to prevent one repeat procedure of 3.6. Although the fluoroscopy time was not affected, the reduction in repeat procedures equated to a mean reduction in radiation exposure. Although this reduction in radiation exposure was more marked if MR was used to image the left atrium, there was still a net reduction when CT was used. Magnetic resonance angiography is difficult to perform adequately for segmentation, and availability may depend on local expertise. The greater success with 3D-II therefore comes with the added benefit of a mean reduction in radiation exposure, and this is not dependent on local availability of cardiac MRI.

**Image integration with different mapping systems**

It is a point of note that the three studies investigating the impact of 3D-II have all used Carto exclusively. \(^4,6\) The present study showed improved outcomes with the use of 3D-II only in cases

![Figure 2](https://example.com/f2.png) **Figure 2** Impact of PV anatomy on AF-free survival. Pulmonary vein anatomy is grouped as normal (i.e. four PV ostia in normal positions), left common trunk, a right middle vein, or other miscellaneous abnormality. Kaplan–Meier analysis shows survival free of AF or other atrial tachyarrhythmia lasting >30 s following (A) the first procedure and (B) the final procedure.

![Figure 3](https://example.com/f3.png) **Figure 3** Multivariate analysis of factors predicting recurrence of AF. Figures show HRs for recurrence of AF derived from Cox’s regression analysis, with P-values shown to the right. SHD, structural heart disease; 3D-II, three-dimensional image integration. Three-dimensional mapping was used for all cases, and success using Ensite NavX is compared with Carto.
involving Carto and not NavX, although the number of cases using NavX were smaller. There was also a trend towards improved outcomes with the use of NavX rather than Carto, driven mostly by the lower success rate in those without 3D-II in the Carto group. These findings may relate to the shape of the left atrial shell created on the respective mapping systems. The geometry created using NavX may better resemble the left atrium and veno-atrial junction than that produced using Carto. The use of 3D-II, with the small inherent error introduced by the registration process, may therefore only offer additional benefit for cases involving Carto.

Multivariate analysis
The impact of 3D-II and variant PV anatomy was confirmed on multivariate analysis. Otherwise, the findings mostly confirmed those of others, with persistent AF found to be a predictor of recurrence and factors such as hypertension, diabetes, or structural heart disease found to have little or no impact.15

Impact of pulmonary vein anatomy on outcome
The proportion of patients in this study with a left common trunk, a right middle vein, and other more unusual variants is similar to that observed by others.2,6 Hof et al investigated the impact of PV anatomy on outcome after PV isolation for AF. In 146 patients, they demonstrated no impact of variant PV anatomy on outcome at 19 months. This is in contrast to the results of the present study in which a 10.5% absolute decrease in single-procedure success was demonstrated in those with variant anatomy. The reason for this difference is uncertain, as both groups used WACA with confirmation of electrical isolation as a procedural endpoint, and the overall results achieved were comparable. However, Hof et al. conducted ambulatory monitoring only in the event of symptoms, and as patients were routinely monitored in the present study, our results may better reflect lasting PV isolation. The effect on outcome was relatively small and it is also possible that there may have been a type 2 error. The present study reports more than twice the number of patients over nearly double the follow-up period.

It had initially been hypothesized that fewer veins would be easier to isolate, and hence a left common trunk might improve outcome and a right middle vein might be detrimental. However, the lower single-procedure success rate in those with variant PV anatomy was driven mostly by a worse outcome in those with a left common trunk. It is possible that a single wider ostium might decrease catheter stability, jeopardizing the transmurality of lesions. A wider ostium, according to the law of La Place, would be expected to increase wall stress at and around the veno-atrial junction, perhaps leading to subtle differences in wall thickness and greater resistance to transmural lesions. It may also be more difficult to confirm electrical isolation in a large common ostium, where achieving simultaneous tissue contact of the multiple electrodes on a PV mapping catheter may not be possible. Inability to verify this important endpoint with certainty may be detrimental to outcome.16

Limitations
Frequent monitoring has revealed that a proportion of apparently cured patients have episodes of asymptomatic AF.17 Although patients underwent ambulatory monitoring, it is recognized that this approach may fail to detect up to a third of asymptomatic recurrent AF.18 Fewer patients had 3D-II used early in this cohort, meaning that other changes in practice including an increase in operator experience may have improved outcomes over the same period of time. However, inclusion of time as a covariate in the multivariate analysis showed no independent effect of later inclusion in the cohort, and identified use of 3D-II as an independent predictor of success. It is also recognized that registry data can be prone to bias, and hence whether choice of mapping system impacts on outcome and whether image integration with NavX is beneficial should be clarified through randomized controlled trials.

Conclusion
The use of 3D-II is associated with a modest improvement in single-procedure efficacy of PV isolation for AF. Although the use of 3D-II improved outcome with Carto, there was no impact when used in conjunction with NavX. It remains unclear whether 3D-II per se improves outcome or simply the knowledge of PV and left atrial anatomy from imaging. Variant PV anatomy, and in particular a left common trunk, adversely affects single-procedure outcome even when the operator is forewarned by imaging.

Conflict of interest: R.J.S. is a member of the scientific advisory board for Biosense Webster. He is listed on the Speakers Bureau for Endocardial Solutions and has received payment for lectures sponsored by them. All authors have received support for travel to international meetings from Guidant, Medtronic, St Jude Medical, Endocardial Solutions, and Biosense Webster.

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