The time course of exit and entrance block during cryoballoon pulmonary vein isolation

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Introduction

Percutaneous pulmonary vein isolation (PVI) has shown considerable success in the treatment of atrial fibrillation (AF). Currently, the electrophysiological endpoint of PVI is defined as the ‘stable absence of any conduction into the pulmonary vein(s) (PV) from the left atrium (LA; entrance block) as well as in the opposite direction, i.e. from the PV into the LA (exit block)’.¹,² While the presence of entrance block appears to be effective in predicting bidirectional LA–PV block, recent reports have suggested that unidirectional entrance block may occur.³ Moreover, the dynamic time course of entrance and exit block during PVI is unknown. The purpose of this series was to dynamically evaluate the manifestation of entrance and exit conduction block during simultaneous circumferential PVI.

Methods

Thirty consecutive patients with a history of drug-refractory paroxysmal AF underwent cryoballoon ablation (Arctic Front³⁰ or Arctic Front Advance³⁰, Medtronic CryoCath LP, Pointe-Claire, Quebec) using standard techniques. Thirteen procedures were performed under conscious sedation techniques. Thirteen procedures were performed under conscious sedation using boluses of midazolam and/or remifentanyl, while 17 were performed with the use of general anaesthesia. Following a single echocardiographic-guided transseptal puncture, an intravenous bolus of midazolam and/or remifentanyl, while 17 were performed with the use of general anaesthesia. Following a single echocardiographic-guided transseptal puncture, an intravenous bolus of sedation using boluses of midazolam and/or remifentanyl, while 17 were performed with the use of general anaesthesia. Following a single echocardiographic-guided transseptal puncture, an intravenous bolus of sedation using boluses of midazolam and/or remifentanyl, while 17 were performed with the use of general anaesthesia. Following a single echocardiographic-guided transseptal puncture, a

Conclusion

Circumferential PV ablation results in progressive PVI, beginning with unidirectional exit block, and followed by entrance block. As exit block reliably precedes entrance block, we are able to provide justification for the exclusive use of entrance conduction block as the endpoint of cryoballoon-based PVI.

Keywords

Atrial fibrillation • Pulmonary vein isolation • Cryoballoon ablation • Pulmonary vein electrophysiology
What’s new?

- Exit block reliably precedes entrance block in pulmonary veins undergoing simultaneous circumferential cryoballoon isolation.
- The median time from exit block to entrance block was 5 s (interquartile range, 3, 12 s).

purposes of this report, only left-sided PVs were targeted due to the need to perform continuous vena caval pacing for phrenic nerve integrity monitoring during ablation of right-sided PVs. Prior to ablation, the CMC was positioned in the PV ostium to record baseline electrical activity and then advanced distally to optimize cryoballoon support at the LA–PV junction. To assess the exact position of the inflated balloon and the degree of occlusion, 1:1 diluted contrast medium was injected from the distal lumen of the cryoballoon catheter. Where possible the mapping catheter was withdrawn to the most proximal (ostial) position possible to maximize the ability to obtain real-time PV recordings without compromising the cryoballoon support, and by extension, adequacy of the cryoballoon–PV seal.

Prior to cryoablation, pacing at a cycle length of 600 ms was performed from both the targeted PV (via the small-diameter CMC) and the distal coronary sinus (CS; via a deflectable decapolar catheter) to verify the presence of baseline entrance and exit conduction, as well as to determine the capture threshold. Pacing was initiated at the CMC bipole with the largest local PV electrogram at an output of 10 mA and a pulse width of 1 ms. If there was no PV capture subsequent bipoles were interrogated. Once stable capture was established the output was immediately re-verified by sequentially pacing all the bipoles of the CMC. All PVs were interrogated after a minimum 20 min observation period post-PVI to exclude early reconnection.

Results

Characteristics of the 30 patients are presented in Table 1. In total, 58 left-sided PVs (including two left common ostia) were targeted for cryoballoon ablation. Real-time PV recordings were obtainable in 45 PVs (2 LCPVs, 25 LSPVs, and 18 LIPVs). In the remaining 13 PVs real-time PV recordings were not possible due to the requirement of a more distal CMC position (i.e. for cryoballoon stability and/or optimization of cryoballoon–PV tissue contact). Representative sequential tracings of baseline conduction, exit conduction, exit block, entrance conduction, and entrance block (i.e. isolation) are presented in Figures 1–3.

Exit block (i.e. loss of conduction from PV to LA despite continued local capture of the PV musculature), was demonstrated to occur at a median of 38 s [interquartile range (IQR) 25, 71 s] from the initiation of cryoablation at a median cryoballoon temperature of −39°C (IQR −45°C, −30°C). In all cases, when uninterrupted pacing was transitioned from the PV to the distal CS, entrance conduction from LA to

Figure 1   Cryoballoon ablation of a left superior PV. Shown are surface leads III, and V1; bipolar electrograms recorded from a CMC positioned near the ostium of the PV (distal PV 1–2, proximal PV 6–7, and PV 8–1); and bipolar electrograms recorded from the CS catheter (distal CS 1–2 and proximal CS 5–6). (A) Baseline PV electrograms in sinus rhythm [pulmonary vein potential, PVP (†)]; (B) Exit conduction [local capture of the PV musculature (†) with reliable conduction to the LA] during PV pacing (CL 600 ms; note the non-sinus P-wave morphology and altered CS activation sequence); (C) Exit block [loss of PV–LA conduction despite local capture of the PV musculature (†)]. On the second and third sinus beat entrance PV conduction is noted to be intact (PVPs obscured by pacing artefact on the first and fourth beat); (D) Entrance conduction during distal CS pacing [atrial capture with reliable conduction from LA to PV (*). Note the presence of significant LA to PVP delay but no change in the PV activation sequence from baseline]; (E) Entrance conduction block (fourth beat) is preceded by significant, and increasing LA–PVP delay during CS pacing (first three beats).
PV remained intact. While there was no change in the PV activation sequence, there was a universally significant delay in LA–PV conduction from baseline. Entrance block (i.e. the stable absence of conduction into the PV from the LA) occurred significantly later than exit block ($P < 0.0001$), a median of 55 s (IQR 34, 86 s) from initiation of cryoablation at a median cryoballoon temperature of $-42^\circ C$ (IQR $-46^\circ C$ to $-35^\circ C$). The median delta time from exit block to entrance block was 5 s (IQR 3, 12 s). In 37 cases, the time from exit block to entrance block was short (<15 s), and in two cases was extremely prolonged (85 and 161 s, respectively). In three cases, exit block was followed by an almost immediate transition from 1:1 to 2:1 entrance conduction block (Figure 3), although the time from 2:1 entrance block to PVI was relatively prolonged (33–145 s). Overall, the nadir cryoballoon temperature was $-53^\circ C$ (IQR $-48.25^\circ C$ to $-59^\circ C$). No acute reconnections were noted after a $\geq 20$ min observation period.

### Discussion

The electrophysiological endpoint of PVI procedures is defined as the ‘stable absence of any conduction into the PV(s) from the LA’ (entrance block). In most cases this is felt to be analogous to ‘stable absence of any conduction from the PV into the LA’ or exit block, which is the ultimate goal in the prevention of PV-induced AF.\textsuperscript{1,2}

The question of whether unidirectional conduction is possible at the LA–PV junction is controversial. Gerstenfeld et al.\textsuperscript{3} suggested that the incidence of apparent unidirectional entrance conduction block was as high as 60%. However, other centres have observed that ‘entrance block and exit block go hand in hand’.\textsuperscript{1,4}

Central to the discussion is the realization that PV electrogram interpretation is fraught with challenges. In the case of entrance conduction, the presence of neighbouring electrically active structures (such as the LA appendage) may mimic, or mask, PV electrical

### Table 1 Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>Number—patients/pulmonary veins</td>
<td>30/58</td>
</tr>
<tr>
<td>Male sex—number (%)</td>
<td>20 (66.7)</td>
</tr>
<tr>
<td>Age in years—mean ± SD</td>
<td>59.9 ± 9.7</td>
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<tr>
<td>AF duration in years—mean ± SD</td>
<td>4.6 ± 3.6</td>
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<tr>
<td>Left ventricular ejection fraction in %—mean ± SD</td>
<td>60.5 ± 5.5</td>
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<tr>
<td>Left atrial size in mm—mean ± SD</td>
<td>39.4 ± 5.7</td>
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<tr>
<td>28 mm Cryoballoon—number (% of PVs)</td>
<td>56 (96.6)</td>
</tr>
<tr>
<td>20 mm circular mapping catheter—number (% of PVs)</td>
<td>58 (100)</td>
</tr>
</tbody>
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mm, millimetres; SD, standard deviation.

Figure 2. Cryoballoon ablation of a left inferior PV. Shown are surface leads III, and V1; bipolar electrograms recorded from a CMC positioned near the ostium of the PV (PV 1-2, and PV 8-1); and bipolar electrograms recorded from the CS catheter (distal CS 1-2 and proximal CS 5-6). At the beginning of the tracing reliable PV–LA exit conduction is demonstrated during PV pacing (first four beats). The first sinus beat following the occurrence of exit block demonstrates intact entrance (LA–PV) conduction (PVP denoted as *). Subsequent PVPs are not visualized during continued PV pacing due to short coupling intervals or overlying pacing artefact; however, following the cessation of PV pacing continued entrance conduction is noted (**). Thereafter, PVI (entrance block) is observed.
Moreover, the use of focal point-by-point ablation may result in apparent entrance conduction block despite the persistence of bidirectionally conducting myocardial fibres, which were too discrete to be detected. Similarly, the assessment of exit conduction is complicated by the uneven distribution of myocardial sleeves (resulting in PV non-capture with apparent exit block), the obscuring effect of the stimulus artefact (thus complicating the assessment of PV capture by obfuscating local PV electrograms), as well as the potential for capture of adjacent electrically active structures (resulting in misinterpretation of apparent exit conduction).

In this series of patients, we demonstrated that exit block reliably precedes entrance block in a PV undergoing simultaneous circumferential isolation with a cryoballoon catheter. Mechanistically, the most likely explanation is source–sink mismatch, which is defined as the abnormalities of anterograde conduction (i.e. delay or block) observed when the size of a given excited region supplying depolarizing current (the current source) is ill-matched to the amount of depolarizing current necessary to excite the regions ahead (the current sink). In the case of circumferential PVI, the progressive delivery of ablation energy results in decreased excitability around the PVs. This ablation-induced excitability decrease, when coupled with the lower density of the PVs depolarizing diffusive current (i.e. source), results in a failure to bring the locally coupled unexcited LA cells (i.e. sink) to threshold, resulting in the onset of exit conduction block. However, at the same time, the larger electrical mass of LA tissue is able to overcome the injured, but still viable LA–PV junction tissue resulting in persistent entrance conduction despite exit block. Persistent bidirectional conduction block occurs following continued ablation and growth of the cryolesion.

This report demonstrates a novel concept in PV physiology. Specifically, we found that circumferential ablation results in progressive PVI, beginning with unidirectional exit block, and followed by entrance block. Since exit block reliably precedes, and thus is a necessary prerequisite of entrance block, the presence of entrance block implies bidirectional block and therefore may be justified as the endpoint for PVI procedures.

**Limitations**

The series is limited to left-sided PVs undergoing cryoballoon ablation due to the need to perform continuous vena caval pacing for phrenic nerve integrity monitoring during the cryoablation of right-sided PVs. As such, strictly speaking, our finding cannot be generalized to right-sided veins, although there is no reason to suspect that the isolation process would differ based on PV lateralization. Secondly, the energy source for PVI in this series was exclusively cryothermal, and delivered by a balloon catheter. As the goal of our current study was to conceptually demonstrate the dynamic time course of entrance and exit block, we chose ablation technology that provided simultaneous circumferential PVI. Unfortunately, neither multielectrode RF ablation nor point-by-point RF ablation was appropriate for our purposes due to the ‘step-by-step’ manner by which PVI is realized. As a result, it is possible, although unlikely, that the time course of entrance and exit block may differ between cryothermal and radiofrequency ablation. Another limitation is the use of a non-variable circular catheter, which may have altered the results due to variable tissue contact. However, we do not feel that this limitation is particularly relevant in the case of cryoballoon ablation.
ablation as the initiation of cryotherapy results in fixation of both the cryoballoon catheter (to the PV ostium) and the CMC (due to luminal freezing), thus negating the potential for mapping catheter movement to alter pacing reproducibility. In addition, we attempted to vigilantly monitor the PV electrograms on the CMC to ensure that exit block was true rather than ‘pseudo’ (i.e. loss of PV capture mimicking loss of exit conduction). Lastly, it is theoretically possible that pacing at a slower rate may have revealed remaining conduction after apparent conduction block; however, we were concerned that pacing at a lower rate would compromise the ability to detect a difference in bidirectional conduction block given the very short delta between the onset of entrance and exit block. In addition, pacing was performed at the same cycle length in both the PVs and the distal CS.

**Conclusion**

In PVs, undergoing simultaneous circumferential cryoballoon isolation, exit conduction block reliably precedes entrance block. Our observations may serve as a functional rationale as to why, in the majority of cases, entrance and exit block go hand in hand.

**Conflict of interest:** M.D., J.A., M.T., and P.K. have received research support or honoraria from Medtronic.

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