Cryothermal slow pathway modification for atrioventricular nodal reentrant tachycardia

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Aims Predictors of recurrence following transcatheter cryoablation for atrioventricular nodal reentrant tachycardia (AVNRT) are currently unknown. Our objective was to explore predictors of recurrence post-cryoablation for AVNRT, including the impact of procedural endpoints such as complete elimination of slow pathway conduction vs. persistent dual atrioventricular (AV) nodal physiology with or without echo beats.

Methods and results A single center cohort study was performed on patients undergoing a first cryoablation procedure for AVNRT between May 1999 and December 2004. Cryoablation for AVNRT was attempted in 185 consecutive patients (79.2% female), age 43.1 ± 15.2 years. Acute success was achieved in 170 (91.9%) patients with 4.4 ± 3.5 cryoapplications and a total procedural duration of 2.8 ± 0.8 h. Complete elimination of slow pathway conduction was noted in 47.6% of acutely successful interventions, absence of AV nodal echoes despite dual AV nodal physiology in 8.8%, and presence of echoes but no inducible AVNRT on and off isoproterenol in 43.5%. Actuarial recurrence-free survival following acutely successful cryoablation at 1, 3, 6, 12, and 24 months was 94.8, 93.1, 91.7, 90.8, and 90.8%, respectively. Independent predictors of recurrence were younger age (P = 0.0045) and valvular heart disease (P = 0.0186). The achieved procedural endpoint did not modulate recurrence rates. Eight patients (4.3%) experienced transient third degree AV block; none required permanent pacing.

Conclusions As a cryoablation procedural outcome for AVNRT, persistent dual AV nodal physiology with or without echo beats is not associated with higher recurrence rates than complete elimination of dual AV nodal physiology if AVNRT remains non-inducible on and off isoproterenol.

Keywords Arrhythmia; Catheter ablation; Cryothermal energy; AV nodal reentrant tachycardia

Introduction

Radiofrequency (RF) catheter ablation is an effective treatment for atrioventricular nodal reentrant tachycardia (AVNRT), with a low complication rate.1–3 In view of its superior safety profile, catheter cryoablation has emerged as an alternative ablation modality, shown to be effective and safe for AVNRT.4–8 However, for reasons not fully elucidated, cryoablation may be associated with a modestly higher recurrence rate following slow pathway modification.4,8 Speculations include comparatively smaller lesions, in part due to cryocatheter adherence to underlying endocardium that eliminates a ‘brushing effect’.9 If lesion size is limiting, additional benefit may potentially be expected from cryocatheters with larger distal electrode tips (e.g. 6 vs. 4 mm). In addition, it may be hypothesized that pursuing a more aggressive procedural endpoint may improve long-term success. With RF energy, persistence of dual AV nodal physiology post-ablation with no more than single echo beats on an isoproterenol infusion does not appear to incur a higher risk of recurrence when compared with complete elimination of slow pathway conduction.10–15 It is unknown whether a similar endpoint should be targeted with cryoablation or if complete slow pathway elimination is preferable.

The purpose of this study was to explore predictors of recurrence post-cryoablation for AVNRT, including the impact of procedural endpoints such as complete elimination of slow pathway conduction vs. persistent dual AV nodal physiology with or without echo beats.

Methods

Study design

The study population consisted of all patients having undergone a first transcatheter ablation procedure for AVNRT with cryothermal energy at the Montreal Heart Institute between May 1999 and December 2004. Patients with prior ablation of a different arrhythmia substrate were included if AVNRT had not been previously targeted. Those presenting with recurrent AVNRT were excluded, regardless of whether the initial procedure utilized RF or cryothermal energy.

A retrospective cohort study was performed. Patient records were reviewed to determine clinical variables and arrhythmia-free survival based on routine follow-up, including clinical visits,
Electrophysiology procedures were performed in the fasting state, off all AV nodal blocking agents and antiarrhythmic drugs, and under conscious sedation provided by an anaesthesiology service (i.e. continuous propofol infusion with boluses of midazolam and fentanyl). A diagnostic electrophysiology study was performed using three 5F quadripolar catheters (Supreme, St Jude Medical, Minnetonka, MN, USA) with or without a 6F or 7F decapolar catheter (Livewire, St Jude Medical, Minnetonka, MN, USA) introduced through right and left femoral veins and placed in standard high right atrium, His, right ventricular apex, and coronary sinus positions. All patients underwent atrial and ventricular programmed electrical stimulation at two drive trains (600 and 400 ms) with up to two extrastimuli, using an EP-3 computerized stimulator (EP Medsystems Inc., West Berlin, NJ, USA). If AVNRT was not induced, the protocol was repeated on an isoproteronol infusion titrated up to 2 g/min. All recordings were bipolar with the gain set at 0.5 mV/mm and filtered at 30–500 Hz.

After completing the diagnostic study, a 7F cryocatheter was introduced through the femoral vein and an intravenous bolus of 2500 IU of unfractionated heparin was administered. One of two 7F quadripolar steerable cryoblation catheter models was used, with either a 4 mm (Freezor) or 6 mm (Freezor Xtra) distal electrode tip (catheter selection was not randomized as the 6 mm tip catheter was not available for commercial use until the latter part of our study period). Consoles and catheters (CryoCath Technologies Inc., Montreal, QC, Canada) have been previously detailed.4,5,16,17 In short, the console allows two modes of operation, cryomapping and cryoablation. In the cryomapping mode, temperature of the distal tip may be decreased to –30°C for up to 80 s to deliver a reversible application. In the cryoablation mode, this temperature may be further lowered to –80°C for up to 4 min (this represents a standard cryoablation application), thereby producing a permanent lesion.

After cryocatheter positioning, a cryomapping application was performed to assess safety (i.e. failure of AH prolongation by more than 25% from baseline) and efficacy (i.e. failure to induce tachycardia using a previously successful stimulation protocol). Cryoablation was then performed. Programmed stimulation was pursued during cryoablation and, if tachycardia was inducible, cryoablation was terminated and the catheter repositioned. If no tachycardia was inducible, the application was continued for a total of 4 min, provided no AH interval prolongation or AV block occurred. Programmed stimulation was repeated following ablation. If acutely successful, observation with programmed stimulation on or off isoproteronol was performed, typically for 30 min or more. Patients were discharged the following day barring any complication. Outpatient follow-up was scheduled at 3 months with a 12-lead ECG. Holter monitoring, event recorders, and further clinical follow-up was at the discretion of the treating cardiologist. The study terminated on 1 June 2005.

### Transcatheter cryoablation

Electrophysiology procedures were performed in the fasting state, off all AV nodal blocking agents and antiarrhythmic drugs, and under conscious sedation provided by an anaesthesiology service (i.e. continuous propofol infusion with boluses of midazolam and fentanyl). A diagnostic electrophysiology study was performed using three 5F quadripolar catheters (Supreme, St Jude Medical, Minnetonka, MN, USA) with or without a 6F or 7F decapolar catheter (Livewire, St Jude Medical, Minnetonka, MN, USA) introduced through right and left femoral veins and placed in standard high right atrium, His, right ventricular apex, and coronary sinus positions. All patients underwent atrial and ventricular programmed electrical stimulation at two drive trains (600 and 400 ms) with up to two extrastimuli, using an EP-3 computerized stimulator (EP Medsystems Inc., West Berlin, NJ, USA). If AVNRT was not induced, the protocol was repeated on an isoproteronol infusion titrated up to 5 µg/min. All recordings were bipolar with the gain set at 0.5 mV/mm and filtered at 30–500 Hz.

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### Statistical analysis

Continuous variables are presented as mean ± SD or median and range depending on their distribution. Categorical variables are summarized as frequency and percentage. In the analyses of determinants of acute success, two-group comparisons were assessed by independent sample t-tests or non-parametric Mann–Whitney tests where appropriate. Nominal variables were cross-tabulated with relationships analysed by the Pearson χ² test. Event-free survival curves were plotted and compared using the Kaplan–Meier method and log-rank statistic. To assess predictors of recurrent AVNRT while controlling for follow-up duration, Cox proportional hazards models were used. Two-tailed P-values < 0.05 were considered statistically significant. Testing was performed with SAS software version 9.1 (SAS Institute, Cary, NC, USA).

### Results

#### Baseline characteristics

A total of 191 patients underwent transcatheter cryoablation for AVNRT between May 1999 and December 2004 (Figure 1). Six patients had prior AVNRT ablation procedures and were therefore excluded from further analysis. Of the 185 remaining patients, mean age at the time of procedure was 43.1 ± 15.2 years, and 79.2% were female. Baseline characteristics are summarized in Table 1.

#### Acute procedural success with cryoablation

Acute procedural success with cryoablation was achieved in 170 of 185 patients (91.9%) (Figure 1). In one patient, the cryoablation procedure was abandoned due to technical difficulties with the ablation console. An additional 14 patients (7.5%) failed an attempt at cryoablation and had successful RF slow pathway modification.

In patients with acutely successful cryoablation, complete elimination of slow pathway conduction was achieved in 81 (47.6%), absence of AV nodal echoes despite dual AV node physiology in 15 (8.8%), and presence of AV nodal echoes in 185 remaining patients, mean age at the time of procedure was 43.1 ± 15.2 years, and 79.2% were female. Baseline characteristics are summarized in Table 1.

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Acute success rates were similar with the 6 mm (n = 39) and 4 mm (n = 146) electrode-tip cryocatheters (94.9 vs. 91.8%, P = NS). As summarized in Table 2, no differences in procedure and fluoroscopy times were noted between patients having cryoablation with 4 vs. 6 mm electrode tips. Although procedures utilizing 6 mm tip electrodes
were associated with more cryoapplications, total cryoablation time was similar between the two groups.

Long-term arrhythmia-free survival with cryoablation

Patients were followed in outpatient electrophysiology clinics for a median of 2.0 years (range 0.4–6.1 years) following the index ablation procedure. Of the 170 patients with acute procedural success, 15 (8.8%) had recurrences. Actuarial arrhythmia-free survival rates at 1, 3, 6, and 12 months were 94.8, 93.1, 91.7, and 90.8%, respectively, with no later recurrence.

As depicted in Figure 2, recurrences were similar regardless of whether dual AV nodal echo beats were eliminated or persisted with or without AV nodal echo beats. Univariate and independent predictors of recurrence are summarized in Table 3. The only independent predictors of recurrence were younger age (HR 0.88 per year, 95% CI 0.80, 0.96, P = 0.0045) and presence of valvular heart disease [HR 13.0, 95% CI (1.5, 111.1), P = 0.0186]. A non-significant trend favored the 6 mm over the 4 mm tip catheter [HR 2.6, 95% CI (0.4, 20.0), P = NS], with arrhythmia-free survival rates of 100 vs. 92.9% at 3 months, 97.2 vs. 90.2% at 6 months, and 97.2 vs. 84.6% at 7.5 months, and unstable rates thereafter.

Cryoablation-induced atrioventricular block

Transient complete AV block occurred in eight patients, all of whom completely recovered AV node conduction during the procedure. Two transient AV blocks were induced by mechanical trauma (4 mm tip catheter in one; 6 mm in the other), five occurred during cryomapping (4 mm tip catheter in three; 6 mm in two), and one transpired 19 s into cryoablation (4 mm tip catheter). Overall rates were somewhat higher with 6 mm vs. 4 mm electrode tip cryocatheters, although not significantly so (7.7 vs. 3.4%, P = NS). The mean duration of complete AV block was 5.3 ± 1.6 s with no significant difference in duration between 4 and 6 mm catheters. No patient experienced permanent AV block or required a permanent pacemaker during follow-up.

Discussion

Transcatheter cryoablation was first performed at our institution, allowing for extended follow-up in the current study on AVNRT. Our results confirm that cryoablation is an effective and safe alternative to RF ablation in this setting, albeit with a non-negligible risk of recurrence. The acute success rate of 92% is comparable with the reported 91% from the Frosty trial and 97% by Zrenner et al. Although direct comparisons to RF ablation were
investigators and 91% at 246 days by Zrenner were consistent with 94% at 6 months reported by Frosty. Rates of 93.1 and 90.8% at 3 and 12 months, respectively, are required to substantiate this assertion.

Is not akin to equivalency, as adequately powered studies while noting, however, that lack of statistical significance is not made, reported acute success rates with RF energy are somewhat higher, between 95 and 98%. Interestingly, the 95% acute success rate utilizing the 6 mm tip cryocatheter approaches these figures. In a pilot study that randomized 63 patients with AVNRT to RF or cryoablation, equivalent acute procedural success rates were noted. The number of cryoapplications was lower than RF applications (2 vs. 7, \(P < 0.005\)), and fluoroscopy and procedural times were comparable. A second study likewise reported no differences in acute success rates with cryoablation vs. RF ablation for AVNRT (97 vs. 98%). It is worthwhile noting, however, that lack of statistical significance is not akin to equivalency, as adequately powered studies are required to substantiate this assertion.

On long-term follow-up, our recurrence-free survival rates of 93.1 and 90.8% at 3 and 12 months, respectively, were consistent with 94% at 6 months reported by Frosty investigators and 91% at 246 days by Zrenner et al. By further extending follow-up to 2 years, we report a persisting actuarial event-free survival of 90.8%, with no recurrence after the first year. Overall, these long-term success rates appear somewhat lower than reported with RF ablation: 95% at 12 months, 93% at 20 months, and 94.8% at almost 3 years. Of the two randomized comparative pilot studies, one reported no difference in long-term outcomes and the second favoured RF ablation.

We additionally considered cryocatheter electrode-tip size as a modulator of acute and long-term success, but our study was inadequately powered for definitive comparisons. Post hoc analyses revealed 80% power to detect a 22% difference between 4 and 6 mm electrode-tip sizes, such that the risk of a type II error is substantial for differences of lesser magnitude. The trend favouring the larger tip catheter does, however, merit further investigation. Although the number of cryoapplications was greater with 6 vs. 4 mm electrode tip catheters (i.e. 5.7 vs. 4.1, \(P = 0.0012\)), this did not translate into increased cryoablation time. Reasons for the higher number of briefer cryoapplications with 6 mm tip cryocatheters remain speculative but may include PR prolongation, placement of initial lesions more inferiorly in Koch’s triangle with larger-tip catheters, and a chance finding.

Our study also identified two independent risk factors for AVNRT recurrence: younger age and valve disease. Younger age has been previously described as a predictor of recurrence following RF ablation and a lower acute success rate (83%) was noted in pediatric patients undergoing cryoablation. One proposed explanation for this lesser efficacy involves operator bias, with less aggressive ablation in younger patients. Other hypotheses include age-related changes in AV node morphology and function; tissue that is more recalcitrant to damage in the young; and perhaps some regenerative potential following ablation.

In addition to identifying predictors of recurrence, our main objective was to assess whether a more stringent post-ablation endpoint improved longer term outcomes. Given the increased safety profile of cryoablation, persisting

<table>
<thead>
<tr>
<th>Procedure (h)</th>
<th>Fluoroscopy (min)</th>
<th>Cryoablation (min)</th>
<th>Number of cryoablations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.8 ± 0.8</td>
<td>18.0 ± 12.8</td>
<td>10.5 ± 7.8</td>
<td>4.4 ± 3.5</td>
</tr>
<tr>
<td>2.8 ± 0.8</td>
<td>18.1 ± 12.5</td>
<td>10.5 ± 8.1</td>
<td>4.1 ± 3.3</td>
</tr>
<tr>
<td>2.7 ± 0.8</td>
<td>17.9 ± 14.0</td>
<td>10.4 ± 6.8</td>
<td>5.7 ± 3.9</td>
</tr>
</tbody>
</table>

\(n = 170\) for all patients with acute success, \(n = 133\) for 4 mm tip cryocatheter, \(n = 37\) for 6 mm tip cryocatheter.

**Table 2** Procedural parameters with successful cryoablation according to the electrode tip size

<table>
<thead>
<tr>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.94 (0.88, 0.99)</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>9.9 (1.1, 90.9)</td>
</tr>
<tr>
<td>Bicuspid aortic valve</td>
<td>11.6 (1.3, 100.2)</td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td>11.6 (1.3, 100.2)</td>
</tr>
<tr>
<td>History of presyncope</td>
<td>13.9 (1.6, 125.0)</td>
</tr>
<tr>
<td>Maximum A2-H2</td>
<td>1.01 (1.00, 1.01)</td>
</tr>
</tbody>
</table>

**Table 3** Clinical and electrophysiologic predictors of recurrent AVNRT post-cryoablation

CI denotes confidence interval.
until complete elimination of slow pathway conduction may be justified if associated with fewer recurrences. However, no differences or trends were identified, regardless of whether the achieved endpoint was complete elimination of dual AV nodal physiology, presence of slow pathway conduction but no echo beats, or persistent AV nodal echoes, but non-inducibility with and without isoproterenol. Our results suggest that non-inducibility despite an isoproterenol infusion may be an acceptable outcome for slow pathway modification using cryoenergy. However, in light of the potentially higher recurrence rate with cryoablation, confirmation from further studies may be prudent before rejecting a more demanding endpoint. Recently, similar conclusions were drawn with RF ablation for AVNRT, as a non-significant trend favoured complete elimination of slow pathway conduction. Whether a greater than 30-min observation and testing period post-acute success-ful cryoablation could contribute to further improving long-term success rates is worthy of further study.

Finally, another important aim of this study was to further assess safety of cryoablation for AVNRT. Although transient complete AV block occurred in eight patients, AV node conduction normalized in all, and no permanent pacemakers were required. The incidence of 4.3% observed in our study included two cases of mechanically-induced AV block and is consistent with prior reports of up to 11%. In all such patients, AV block was brief. Indeed, inadvertent permanent high degree AV block has yet to be reported with cryoablation for AVNRT. This lends further credence to the superior safety profile when compared with the 0.3–1.3% risk of complete AV block with RF ablation of AVNRT.

Transient block may be explained, in part, by the concept of ‘dynamic cryomapping’ and the resistant nature of the AV node to cryothermal injury. A temperature gradient spreads centrifugally from the catheter tip in contact with the endocardial surface. Once the AV node achieves a temperature in the range of −30°C, reversible effects on conduction occur. This transpires prior to attaining a temperature of −50 to 60°C, at which point permanent damage is expected. Thus, complete resolution of AV block shortly follows termination of the cryoapplication. A greater radius of tissue is subject to dynamic cryomapping with larger catheter tips, which may account for the trend towards a higher incidence of transient AV block with the 6 mm tip catheter. When compared with RF energy, an additional contributing factor may be the delivery of lesions more superiorly in Koch’s triangle, incited by a stringent definition for acute success and cryoenergy’s enhanced safety profile.

Study limitations

This investigation was retrospective in nature and subject to the limitations inherent to such study designs. Nevertheless, most of the data utilized for this study was prospectively entered into a systematic database. The cryocatheter type was not randomly allocated, with 6 mm electrode tip catheters more frequently utilized in the latter half of the study. However, as transcatheter cryoablation was first performed in our institution in August 1998 and the study was initiated in May 1999, bias favouring the 6 mm cryocatheter from a learning curve effect is unlikely to be substantial. Finally, if tachycardia was reinducible by programmed stimulation during cryoablation, the application was interrupted. Given the complex anatomy of the slow pathway region, more than one complete ablation lesion may be required to render AVNRT non-inducible. Cryoablation was generally pursued if some effect on slow pathway conduction was appreciated (e.g. non-inducibility despite persistence of an A2-H2 jump). However, the practice of terminating a cryoapplication if deemed unsuccessful may influence acute outcomes.

Conclusions

Cryoablation is an effective treatment for AVNRT, with an overall acute success rate of 92%. The absence of complete AV block requiring pacemaker implantation represents a distinct advantage of this ablation modality. As a cryoablation procedural outcome for AVNRT, persistent dual AV nodal physiology with or without AV nodal echo beats is not associated with higher recurrence rates than complete elimination of dual AV nodal physiology if tachycardia remains non-inducible for at least 30 min of testing, on and off isoproterenol.

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Conflict of interest: D.R. is chair of the clinical events committee for CryoCath Inc. M.D. is a consultant for CryoCath Inc.

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