Clinical research

Transvenous cryoablation versus radiofrequency ablation of the slow pathway for the treatment of atrioventricular nodal re-entrant tachycardia: a prospective randomized pilot study

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Received 19 March 2004; revised 25 June 2004; accepted 15 July 2004

Aims This is a prospective, randomized study comparing transvenous cryoablation with radiofrequency (RF) ablation of atrioventricular nodal re-entrant tachycardia (AVNRT).

Methods and results In this pilot trial, 200 patients with AVNRT were randomized to undergo cryoablation or RF ablation of the slow pathway. A 7 Fr 4-mm-tip cryocatheter (Cryocath®) was used for cryomapping and cryoablation. Cryomapping was performed at the temperature of −30°C to test the effect on the candidate ablation site. Following successful cryomapping, cryoablation was performed to produce an irreversible lesion by freezing to −75°C. Procedural success, defined as elimination of the slow pathway or noninducibility of AVNRT, was achieved in 97/100 (97%) patients in the Cryo group vs. 98/100 (98%) patients in the RF group. No permanent complete AV-block occurred in either group. During a median of 246 days of follow-up, 8 patients in the Cryo group and 1 in the RF group had AVNRT recurrence. The cumulative incidence of primary endpoint (a combination of procedural failure, permanent complete AV-block and AVNRT recurrence) was significantly higher in the Cryo group than in the RF group (P = 0.03, Log-rank test).

Conclusions The results of this pilot study indicate that transvenous cryoablation using a 4-mm-tip cryocatheter is associated with a comparable acute success rate but a higher recurrence rate as compared with RF ablation in patients with AVNRT. Potential benefits of cryoablation for ablation of AVNRT need to be determined in a larger multi-centre trial.

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KEYWORDS
Atrioventricular node; Tachycardia; Mapping; Catheter ablation

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Introduction

Radiofrequency (RF) catheter ablation of the slow pathway has been established as the first line curative strategy for atrioventricular nodal re-entrant tachycardia (AVNRT). Although this approach is highly effective, inadvertent complete AV-block requiring implantation of a permanent pacemaker occurs in 1.3–2% of patients.1,2 Cryoablation was used as a curative approach to AVNRT in the operation room.3,4 Recently, transvenous cryoablation has become available. A previous study enrolling a small number of patients showed that transvenous cryoablation can eliminate AVNRT and has a potential advantage with respect to obviating inadvertent AV-block.5 There are currently no prospective studies comparing the two approaches.

The objective of this prospective randomized pilot study was to compare transvenous cryoablation with RF ablation for the treatment of AVNRT with regards to efficacy and safety.

Methods

Study patients

Patients eligible for this study were those who were referred to our center for catheter ablation of AVNRT. We excluded patients who aged less than 18 or over 80 years of age, those who had previous AVNRT ablation procedures and those who had congenital heart disease. After giving informed consent and the diagnosis of AVNRT was confirmed by electrophysiological study, the patients were randomly assigned to either RF ablation or cryoablation of the slow pathway, by means of sealed envelopes containing a computer-generated randomization scheme. Blocks of 50 patients were used to enable equal numbers in each group. No stratification was used. The study was approved by the ethics committee of the German Heart Center Munich.

Electrophysiological study and catheter ablation

Patients were investigated in the fasting state without sedation. Antiarrhythmic drugs were discontinued for at least 5 half-life periods. A standard electrophysiological (EP) study was performed. Briefly, 3 EP catheters were positioned to the His bundle position, coronary sinus and right ventricular apex, respectively. Incremental atrial and ventricular pacing and extrastimulus testing from the proximal coronary sinus and right ventricular apex were performed. If sustained tachycardia could not be induced, orciprenaline was infused to facilitate tachycardia induction. Dual AV nodal physiology was identified by a sudden AH or HA jump of at least 50 ms in response to programmed atrial or ventricular extrastimulation. AVNRT was diagnosed on the basis of standard diagnostic criteria.6

For both RF ablation and cryoablation, a combination of the electrogram and anatomical approaches was conducted to identify appropriate target sites for ablation of the slow pathway.7 Procedural success was defined as complete elimination of the slow pathway or non-inducibility of AVNRT (no more than a single AV nodal echo beat) at baseline and after orciprenaline administration.

RF ablation was performed with the use of a 4-mm-tip catheter (Marinr®, Medtronic Inc.). At the target site, RF current was delivered through a generator (Stockert, Biosense-Webster) with a preset temperature of 65 °C and a power limit of 30 W. If no junctional ectopy occurred within the first 20 s of RF current delivery, the energy application was discontinued. If even a single beat of junctional ectopy occurred, energy was applied for up to 60 s. However, RF current delivery was terminated immediately if ventriculoatrial (VA) block during junctional ectopy or PR prolongation with conducted sinus beats occurred. Programmed stimulation was performed after each application. If AVNRT was still inducible, the catheter was repositioned and RF energy was applied at new target sites.

Cryoablation ablation of the slow pathway was performed by using a cryoablation system (CryoCath, Inc.) which has been described in detail elsewhere.8 The system consists of a control console and a 7F steerable catheter with a 4-mm-tip electrode and uses N2O as the refrigerant fluid. The protocol of cryoablation is shown in Fig. 1. Cryomapping was carried out first at a cryocatheter tip temperature of −30 °C for a maximal duration of 60 s to test the electrophysiological effect on the target sites by using programmed stimulation which reproducibly demonstrated dual nodal physiology or induced AVNRT. In case of ineffective results or AV-block, cryomapping was terminated and then repeated at new target sites. Cryoablation, which created a permanent lesion by cooling the tip temperature to −75 °C for 5 min, was initiated immediately following successful cryomapping defined as block of the slow pathway or noninducibilty of AVNRT. Programmed stimulation was also performed to test the effectiveness of the ablation during cryoablation. If AVNRT was still inducible or AV-block occurred, cryoablation was stopped and cryomapping at new target sites was repeated.

EP study was repeated after a waiting period of 30 min after RF or cryoablation to check the effectiveness of the slow pathway ablation at baseline and during orciprenaline infusion.

Post-ablation management and follow-up

The patients were discharged on no antiarrhythmic drugs. At follow-up visits at our ambulatory arrhythmia clinic or their referring physicians (3, 6, 12 and 18 months), patients underwent assessment of symptoms, rest ECG and 24-h Holter recording.

The study design did not allow a crossover of the ablation energy source within the same EP procedure. The patients without procedural success were advised to undergo a second EP study with RF ablation, as cryoablation is presently not the standard ablation procedure for the treatment of AVNRT.

Study endpoint

The primary endpoint of this study was the composite of procedural failure, permanent complete AV-block and recurrence of AVNRT.

Statistical analysis

No sample size calculation was conducted for this pilot study due to lack of firm data regarding efficacy and safety of cryoablation for AVNRT. The results of the pilot study will serve as the basis for sample size calculation of a planned multi-centre trial. As planned, we stopped enrolling after 200 patients were recruited and reported the preliminary results when the 200 patients completed a minimum follow-up of 3 months.
The results of this analysis are presented as means ± SD, counts or percentages or median and 25th, 75th percentile. The Student t test was used to compare the two groups for continuous variables and the \( \chi^2 \) test or Fisher’s exact test for categorical variables. Incidence of primary end point was analysed according to the Kaplan–Meier method; comparisons were made by means of the log-rank test. All tests were two-tailed; \( P < 0.05 \) was considered significant.

**Results**

**Patient characteristics**

Two hundred patients were enrolled in the study. Of them, 100 patients were randomly assigned to undergo RF ablation and 100 to undergo Cryoablation. The patient characteristics are shown in Table 1. There were no significant differences in terms of these variables between the two groups.

**Acute results**

The number of ablations was 3.6 ± 3.4 per patient in the Cryo group following a median of 4 (25th and 75th percentile, 2 and 10) cryomapping attempts and 7.6 ± 5.5 in the RF group (\( P = 0.002 \)). Procedural success was achieved in 97% of patients in the Cryo group and 98% in the RF group. The incidence of residual dual AV nodal physiology, as evidenced by the presence of AH or HA jump and/or single AV nodal echo beat did not differ significantly between the two groups (see Table 2).

No junctional ectopy occurred during cryomapping or cryoablation. During both cryomapping and cryoablation the catheter tip firmly adhered to the target site (cryo-adherence), preventing catheter dislodgment and fluoroscopic check of catheter position.

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**Fig. 1 Protocol of cryoablation. See text for a further description.**
The procedure and fluoroscopy times were 140 ± 63 and 12 ± 9.3 min in the Cryo group and 112 ± 35 and 14 ± 11 min in the RF group, respectively (P < 0.001 and P = 0.25, respectively).

### AV-blocks

No permanent complete AV-block occurred in either group. One patient in the RF group suffered from permanent AV-block I° although energy delivery was terminated 1.3 s after the occurrence of VA-block during junctional ectopy. No permanent AV-block occurred in the Cryo group. Transient AV-block was encountered in 18 (18%) patients in the Cryo group and in 8 (8%) patients in the RF group (P < 0.04). There were, in total, 21 episodes of transient AV-block occurring during cryomapping (n = 4) or cryoablation (n = 17) and 8 episodes during RF applications. The duration of transient AV-block ranged from 2 to 420 s in the Cryo group and from 2 to 180 s in the RF group (see Table 3).

### Follow-up results

During a median of 246 days (25th and 75th percentile, 159 and 379 days) of follow-up, 8 patients in the Cryo group and 1 in the RF group had AVNRT recurrence. Of those, 2 patients in the Cryo group had tachycardia recurrence manifesting beyond 6 months. Two of the three patients with procedural failure in the Cryo group had successful RF ablation in the second session, including one in whom the slow pathway was ablated in the left atrium; both had no further recurrence. The third patient had no documented tachycardia recurrence and no symptoms consistent with AVNRT recurrence over a follow-up period of 6 months. Of the two patients with procedural failure in the RF group, one was successfully reablated in the second session, the other underwent EP study 3 days after the 1st session, but no tachycardia was inducible. Neither had tachycardia recurrence during further follow-up.

### Primary endpoint

The primary endpoint was reached in 11 patients in the Cryo group (3 patients with procedural failure, 8 patients with AVNRT recurrence) and 3 patients in the RF group (2 patients with procedural failure and 1 patient with AVNRT recurrence (P = 0.03, Log-rank test, see Fig. 2)).

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**Table 1** Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cryo (n = 100)</th>
<th>RF (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>58 (58%)</td>
<td>68 (68%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51 ± 18</td>
<td>51 ± 17</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>25 (25%)</td>
<td>19 (19%)</td>
</tr>
<tr>
<td>Tachycardia CL (ms)</td>
<td>357 ± 69</td>
<td>359 ± 62</td>
</tr>
<tr>
<td>No. of AVNRT</td>
<td>100</td>
<td>101*</td>
</tr>
<tr>
<td>Slow–fast</td>
<td>89 (89%)</td>
<td>93 (92%)</td>
</tr>
<tr>
<td>Fast–slow</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Slow–slow</td>
<td>9 (9%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Duration of follow-up (day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>226</td>
<td>270</td>
</tr>
<tr>
<td>25th and 75th percentile</td>
<td>153, 378</td>
<td>160, 390</td>
</tr>
</tbody>
</table>

Values are given as n (%) or as means ± SD or as median and 25th, 75th percentile.

* One patient had 2 types of AVNRTs.

**Table 2** Acute results

<table>
<thead>
<tr>
<th></th>
<th>Cryo (n = 100)</th>
<th>RF (n = 100)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cryomapping</td>
<td>4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Median</td>
<td>2</td>
<td>10</td>
<td>—</td>
</tr>
<tr>
<td>25th and 75th percentile</td>
<td>140 ± 63</td>
<td>112 ± 35</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No. of ablations</td>
<td>3.6 ± 3.4</td>
<td>7.6 ± 5.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Procedural success</td>
<td>97 (97%)</td>
<td>98 (98%)</td>
<td>1</td>
</tr>
<tr>
<td>Residual dual nodal physiology</td>
<td>54/97 (52%)</td>
<td>50/98 (48%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Procedural time (min)</td>
<td>12 ± 9.3</td>
<td>14 ± 11</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Values are given as n (%) or as means ± SD or as median and 25th, 75th percentile.

**Table 3** Episodes of AV-block

<table>
<thead>
<tr>
<th></th>
<th>Cryo (n = 100)</th>
<th>RF (n = 100)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient AV block</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>18 (18%)</td>
<td>8 (8%)</td>
<td>0.04</td>
</tr>
<tr>
<td>No. of episodes (duration)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVB I° Cryomapping</td>
<td>1 (40 s)</td>
<td>6 (2–256 s)</td>
<td>4 (2–180 s)</td>
</tr>
<tr>
<td>AVB II° Cryomapping</td>
<td>1 (30 s)</td>
<td>5 (7–32 s)</td>
<td>2 (20–36 s)</td>
</tr>
<tr>
<td>AVB III° Cryomapping</td>
<td>2 (4–29 s)</td>
<td>6 (4–20 s)</td>
<td>2 (6–15 s)</td>
</tr>
<tr>
<td>Permanent AV block</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVB I°</td>
<td>0</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>AVB II° or III°</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Values are given as n (%) or as n and duration (minimum–maximum) of AV block episodes in seconds (s).
Discussion

To our knowledge, the current pilot study represents the first prospective randomized investigation comparing transvenous cryoablation with RF ablation for the treatment of AVNRT. This study was conducted to evaluate the possible advantages of cryoablation over RF ablation for the treatment of AVNRT. In contrast to RF ablation whose effect can only be assessed after formation of a permanent lesion, cryotechnology enables to test the effect of prospective ablation by creating a reversible lesion at a less critical temperature and therefore has the potential to lower or even avoid permanent AV-block, however low it can be with RF ablation. If this is the case, there will be a significant proportion of patients, especially the young patients and those with abnormal AV node anatomy, in whom a reduced efficacy may be preferred over the risk for a pacemaker implantation.

This study confirmed that RF ablation is a highly effective and safe approach for AVNRT ablation. Although carrying a high acute success rate, cryoablation using a 4-mm-tip cryocatheter appears to be inferior to RF ablation due to its markedly higher recurrence rate and significantly longer procedure time. The former directly contributed to the significantly higher incidence of the combined primary endpoint observed in the Cryo group in comparison to RF ablation; the latter is mainly due to the nature of longer duration of energy application in cryoablation, although a learning curve should also be taken into consideration. The significantly higher recurrence rate in cryoablation patients may relate to smaller lesion size created by cryoablation as compared with RF ablation. Since the use of cryoenergy results in cryoadherence during ablation, the catheter is not passively sliding along a larger area, as under RF ablation. Whether the usage of a 6-mm-tip cryoaablation catheter and the technique of “safety application” aiming at creating a larger lesion may reduce the recurrence rate in cryoablation needs further investigation.

Complete AV-block, the most important complication in RF ablation, is rare in experienced centres. This requires a huge sample size to manifest the potential advantages, if any, of an alternative ablation energy such as Cryo in obviating complete AV-block. However, several unique features of cryoablation observed in this pilot study may lead to ultimately obviate complete AV-block in AVNRT ablation. First, Cryo energy offers the possibility to test the effectiveness of a potential target site by producing reversible electrophysiological effects at less critical temperatures. Second, cryoadherence prevents dislodgment of the catheter tip and therefore avoids unwanted energy delivering at the compact AV node or His bundle. Third, junctional ectopy — a sensitive marker of successful RF ablation — does not occur during cryoablation, which facilitates monitoring the completeness of the fast pathway. Finally, all AV-blocks encountered during cryomapping or cryoablation were reversible. The high incidence of transient AV-block encountered during cryoablation, a finding that was not reported in the previous study, may relate to the lower cryoablation temperature used in the present study which creates larger lesions.

In conclusion, the results of this pilot study indicate that transvenous cryoablation using a 4-mm-tip cryocatheter is associated with a comparable acute success rate but higher recurrence rate as compared with RF ablation of AVNRT. RF ablation remains the standard approach for AVNRT ablation. In the young patients and those with abnormal AV node anatomy, the use of cryoenergy might be justified, taking a higher recurrence rate into account. Potential benefits of transvenous cryoablation for ablation of AVNRT need to be determined in a larger multi-centre trial.

Acknowledgement

The trial was not funded.

References


