Cryoablation Versus Radiofrequency Energy for the Ablation of Atrioventricular Nodal Reentrant Tachycardia
(the CYRANO Study) Results From a Large Multicenter Prospective Randomized Trial

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Background—Cryoablation has emerged as an alternative to radiofrequency catheter ablation (RFCA) for the treatment of atrioventricular (AV) nodal reentrant tachycardia (AVNRT). The purpose of this prospective randomized study was to test whether cryoablation is as effective as RFCA during both short-term and long-term follow-up with a lower risk of permanent AV block.

Methods and Results—A total of 509 patients underwent slow pathway cryoablation (n=251) or RFCA (n=258). The primary end point was immediate ablation failure, permanent AV block, and AVNRT recurrence during a 6-month follow-up. Secondary end points included procedural parameters, device functionality, and pain perception. Significantly more patients in the cryoablation group than the RFCA group reached the primary end point (12.6% versus 6.3%; P=0.018). Whereas immediate ablation success (96.8% versus 98.4%) and occurrence of permanent AV block (0% versus 0.4%) did not differ, AVNRT recurrence was significantly more frequent in the cryoablation group (9.4% versus 4.4%; P=0.029). In the cryoablation group, procedure duration was longer (138±54 versus 123±48 minutes; P=0.0012) and more device problems occurred (13 versus 2 patients; P=0.033). Pain perception was lower in the cryoablation group (P<0.001).

Conclusions—Cryoablation for AVNRT is as effective as RFCA over the short term but is associated with a higher recurrence rate at the 6-month follow-up. The risk of permanent AV block does not differ significantly between cryoablation and RFCA. The potential benefits of cryoenergy relative to ablation safety and pain perception are counterbalanced by longer procedure times, more device problems, and a high recurrence rate.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00196222.

Key Words: atrioventricular node ■ catheter ablation ■ cryoablation ■ radiofrequency catheter ablation ■ tachycardia, atrioventricular nodal reentry

Radiofrequency (RF) catheter ablation (RFCA) is still considered first-line treatment for atrioventricular (AV) nodal reentrant tachycardia (AVNRT) because of its high short-term and long-term success rates.1,2 Immediate noninducibility of tachycardia corresponding to RF modulation or ablation of the slow AV nodal pathway is achieved in 95% to 98% of patients,1,3 and recurrence rates are reported to range from 3% to 7%.1–3 The main complication of RFCA is inadvertent damage to the fast pathway of the compact AV node, leading to permanent

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2239
AV block. This complication is still reported to be in the range of 1% to 2.0%.1,3

Clinical Perspective on p 2245

Since the late 1990s, cryoenergy has evolved as an alternative energy source to conventional RF energy.3 The catheter tip is cooled to −70°C to −80°C by means of liquid N2O, instilled into the catheter. One advantage is the adhesion of the cryoablation catheter to the tissue, preventing accidental dislodgement of the catheter tip.4−6 The targeted tissue is frozen, and endocardial and myocardial tissue structures remain almost unchanged, in contrast to the collateral necrosis caused by RFCA.5 Overall, cryoenergy might offer a less aggressive and more titrated way to alter tissue with a better safety profile than RFCA and a comparable success rate.7−9 The use of 6-mm–tip cryoablation catheters seems to enhance short-term success rates.10,11 The present study was designed as a multicenter prospective randomized trial to test the hypothesis that cryoablation for AVNRT is as effective (both short term and long term) as RFCA with a lower risk of permanent AV block.

Methods

The study was conducted as a multicenter prospective randomized clinical trial including 6 centers in Europe and 1 center in China. All centers had considerable experience with the technique of cryoablation and had performed at least 50 cryoablutions for AVNRT before study participation. The study protocol was approved by the local ethics committees of the participating centers. The trial was registered in the US national clinical trials registry (http://www.clinicaltrials.gov; unique identifier, NCT00196222).

Study Inclusion and Exclusion Criteria

Patients were included in the study if they were 18 to 80 years of age, had inducible AVNRT during the electrophysiological study, and had signed a written informed consent for study participation. Exclusion criteria comprised prior ablation for AVNRT, congenital heart disease, prior pacemaker implantation, pregnancy, and inability to follow the study protocol.

Procedure

During the electrophysiological study, a standardized atrial and ventricular stimulation protocol was carried out. Atrial and ventricular stimulation to test for antegrade and retrograde Wenckebach interval was performed, and programmed atrial stimulation with a train cycle of S1 = 600 milliseconds and S1 = 500 milliseconds, each with up to 2 extrastimuli with decreasing coupling intervals, was carried out. If AVNRT was not inducible during baseline stimulation, intravenous orciprenaline or isoproterenol was applied (until an increase in heart rate of 20% to 30%). The atrial stimulation protocol was then repeated with a baseline train cycle of S1 = 400 milliseconds and up to 2 extrastimuli. AVNRT was diagnosed if there was evidence of dual AV nodal physiology and inducible tachycardia with typical electrophysiological features of slow-fast, slow-slow, or fast-slow AVNRT, including tachycardia termination by bolus application of 6 mg adenosine and failure to advance atrial activation by His-synchronous ventricular beats. After confirmation of AVNRT, patients were randomized to undergo either RFCA or cryoablation.

RF Ablation Group

The ablation catheter (7F, 4-mm solid tip, MarinR, Medtronic, Minneapolis, Minn) was placed in the left anterior oblique 45° fluoroscopic view in the posteroseptal slow AV pathway area. RF energy was applied at the most inferior localization showing a local slow pathway electrogram or an AV amplitude ratio from 1:4 to 1:2. If AVNRT was still inducible after RF application, the ablation catheter was moved sequentially to more superior sites without His bundle electrograms. At eligible sites, RF energy applications (maximum, 60 seconds; 60°C, 30 W) were delivered. The occurrence of junctional beats during ablation was judged as indicative of a successful ablation site. If no junctional beats occurred, ablation was stopped after 20 seconds, and the catheter was moved more midseptally. If ablation temperature did not exceed 45°C, a long nonsteerable sheath (SR 0, Daig, St. Jude Medical, St. Paul, Minn) was used to increase wall contact stability. Fifteen minutes after successful ablation, the preablation stimulation protocol was repeated to test for early arrhythmia recurrence. The presence of dual AV node conduction properties and the postablation antegrade and retrograde Wenckebach intervals were documented. Patients were asked to judge their pain during ablation on a visual scale from 0 (no pain) to 100 (maximal pain).

Cryoablation Group

Slow pathway mapping in the posteroinferior septum with the cryoablation catheter (7F, Freezer Max, 6-mm tip, CryoCath, Montreal, Canada) was performed in a manner similar to that for the RF catheter. Cryomapping (cooling the catheter tip to −30°C) was started at the most inferior localization showing a local slow pathway electrogram or an AV amplitude ratio from 1:4 to 1:2. If AVNRT was noninducible during cryomapping (using the same stimulation maneuvers that induced AVNRT before), the site was assumed to be a candidate site for successful ablation. If AVNRT was still inducible during cryomapping, mapping was stopped and the catheter subsequently placed at a more superior site for another cryomapping. During cryomapping, screening for fast pathway damage was performed by repeated short atrial pacing bursts and repeated measurements of the PQ interval. At successful and safe cryomapping sites, a 4-minute ablation freeze and, after thawing, a bonus 4-minute freeze at the same site were applied. For both applications, the ablation target temperature was −80°C. During the ablation freezes, atrial stimulation to induce AVNRT was repeated several times to control efficacy and to screen for fast AV pathway damage.

Ablation End Point

The end point for successful ablation in both groups was noninducibility of AVNRT and no more than a single atrial echo beat during atrial stimulation using the same protocol (with or without sympatohormetic drugs) compared with before ablation.

Postablation Management and Follow-Up

After the procedure, patients were continuously monitored in hospital for at least 24 hours with Holter ECG to screen for AV block or recurrent arrhythmia. Patients were instructed to report any symptoms suggestive of arrhythmia relapse or AV block to their study center or their treating physician, and efforts were made to document arrhythmia episodes by 12-lead ECG or Holter ECG. In patients with symptoms suggestive of AVNRT relapse, tachycardia had to be documented on a 12-lead ECG or on Holter to be classified as recurrence. Regardless of symptoms, all patients were routinely seen after 6 months in the outpatient arrhythmia clinic and intensively questioned for arrhythmia symptoms. At this time, a transthoracic echocardiography, a resting ECG, and a stress test (to judge the antegrade Wenckebach interval in suspicious cases) were performed.

Study End Points

The primary study end point was a combination of short-term ablation efficacy (noninducibility of AVNRT), efficacy after 6 months (no symptoms suggestive of AVNRT recurrence and no documented tachycardia), and ablation-induced AV block requiring pacemaker implantation. Secondary end points included procedure and fluoroscopy duration, handling and device functionality of the cryoablation console and catheter, number of tissue-altering applications, ablation-induced AV block without pacemaker indication, and patients’ perceived pain documented on the visual pain scale.
Case Number Calculation
A 98% short-term ablation success rate for RFCA was assumed with a midterm follow-up success rate of 91% and a 2% risk of complete AV block occurrence. Thus, the overall failure rate for RFCA was estimated to be 13%. For the cryoablation group, a failure rate of 23% (94% short-term success, 83% success in follow-up, <1% ablation-induced AV block) was anticipated. With a power of 80% and an $\alpha$ of 5%, using a 2-sided test, 250 patients per group were included into the study.

Primary End Point
The combined primary end point of procedural failure, ablation-induced complete AV block, and AVNRT recurrence was reached by 12.6% of the cryoablation group and 6.3% of the RFCA group ($P=0.018$; Figure 2).

Results

Patients
A total of 611 patients were eligible for study participation. Of these, 24 patients refused to participate and 5 were excluded because of age. AVNRT could not be induced in 73 patients during the electrophysiology study. Of the remaining 509 patients, 258 were randomized to RFCA and 251 to cryoablation. In total, 13 patients (7 in the RFCA group and 6 in the cryoablation group) were lost to follow-up. Overall, 251 patients in the RFCA group and 245 patients in the cryoablation group completed the follow-up and were included in the analysis (Figure 1).

Table 1 shows patients’ demographic characteristics, number of patients with structural heart disease, and type of AVNRT. A preexisting first-degree AV block was present in 18 patients in the cryoablation group and 17 patients in the RFCA group. PQ intervals ranged from 205 to 310 milliseconds (mean, 218±30 milliseconds) in the cryoablation group and from 205 to 305 milliseconds (mean, 226±26 milliseconds) in the RFCA group.

Statistical Analysis
Normally distributed data are expressed as mean±SD, and for comparison of both groups, a Student $t$ test was used. Nonnormally distributed data are given as median (with minimum and maximum), and the Mann-Whitney test was used to assess statistical significance. Categorical variables were assessed with the Fisher exact test or $\chi^2$ test. For the combined primary end-point analysis and the recurrence rate, the log-rank test and Kaplan-Meier survival analysis were performed.
Short-Term Procedural Success
Primary ablation success with noninducibility of AVNRT was achieved in 243 of 251 patients (96.8%) in the cryoablation group and 254 of 258 patients (98.4%) in the RFCA group \( (P=0.255) \).

Ablation-Induced AV Block
No ablation-induced AV block occurred in the cryoablation group (0%). The PQ interval did not prolong in any of the 18 patients with preexisting first-degree AV block.

In the RFCA group, 1 patient (0.4%) gradually developed a complete AV block 20 hours after ablation, necessitating pacemaker implantation. In this patient, the baseline PQ interval had been 180 milliseconds, which did not prolong during the ablation procedure. Ablation-induced permanent first-degree AV block was observed in 2 patients (PQ intervals after ablation were 230 and 270 milliseconds). In both patients, RF delivery had been stopped within 2 seconds after occurrence of ventriculoatrial block during junctional rhythm. No further PR interval prolongation was observed in the 17 patients with preexisting first-degree AV block.

Efficacy After 6 Months
A total of 246 of 251 patients (98.0%) in the cryoablation group and 249 of 258 patients (96.5%) in the RFCA group completed the 6-month follow-up (Figure 1). In the cryoablation group, 38 patients reported arrhythmia symptoms, and recurrent AVNRT was documented on the ECG in 23 patients. In 16 of the 23 patients, repeat electrophysiology study with ablation (all but one with RF) was performed successfully.

In the RFCA group, 18 patients reported symptoms suggestive of an arrhythmia relapse, and AVNRT was documented in 11 patients on the 12-lead ECG. Of these 11 patients, 8 underwent repeat electrophysiology study with successful repeat ablation (all with RF).

Overall, significantly more patients in the cryoablation group than in the RFCA group experienced documented AVNRT recurrence (9.4% of the cryoablation group patients versus 4.4% of the RFCA group patients; \( P=0.029; \) Figure 3). No further AV block occurred during the follow-up period.

Secondary End Points
Procedural Characteristics
Procedure duration was significantly longer in the cryoablation than the RFCA group, whereas fluoroscopy duration and fluoroscopy dose were comparable in both groups (Table 2). The median number of energy applications (\( n=4 \)) did not

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<thead>
<tr>
<th>Table 2. Secondary End-Point Results</th>
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<tbody>
<tr>
<td><strong>RF Ablation</strong></td>
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<td>------------------</td>
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<tr>
<td>Procedure time, min</td>
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<tr>
<td>Fluoroscopy</td>
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<tr>
<td>Time, min</td>
</tr>
<tr>
<td>Dosage, cGy/cm</td>
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<tr>
<td>Ablation-induced first- or second-degree AV block, n</td>
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<tr>
<td>Device functionality failure, n patients</td>
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<tr>
<td>Energy applications, median (minimum-maximum), n</td>
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<td>Subjective pain score during ablation (visual scale, 1–100)</td>
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differ between the groups (1 to 42 in the RFCA group and 2 to 33 in the cryoablation group; Table 2).

The pain perception score during ablation on the visual pain scale was significantly higher in the RF group than in the cryoablation group (20.3±22.0 versus 7.3±13.9; P<0.001; Table 2).

Device Functionality
A device functionality failure occurred in 2 of 258 patients of the RFCA group (ablation generator failure) and in 13 of 251 patients of the cryoablation group (P=0.0033). In 8 of 13 cryoablation patients, >1 type of dysfunction occurred, with a total of 21 dysfunctions. In 8 patients, the console aborted the cryomapping mode because the measured catheter tip temperature dropped to below −30°C. In 8 patients, the ablation catheter tip temperature did not fall below −60°C despite repeated attempts to improve catheter wall contact. In 2 patients, ablation was aborted because fluid was detected inside the console. In 17 of 18 instances, the problem was at least partially overcome by rebooting the console (for ablation, temperatures of −70°C were reached in 5 of 8 patients); in 1 instance, exchanging the coaxial umbilical cable and the ablation catheter finally resulted in acceptable ablation temperatures. In 2 patients, endocardial signals from the catheter tip showed heavy noise, which was overcome only by changing the ablation catheter once (1 patient) or twice (1 patient). In total, 18 of 21 dysfunctions were related to the cryoablation console and 3 to catheter failure (Table 2).

Discussion

Main Findings
This is the largest prospective randomized study dealing with short- and long-term efficacy and complications of RF versus cryoenergy for the ablation of the slow AV pathway in AVNRT. Our findings indicate that cryoablation is as effective as RF ablation in the short term but is associated with a significantly higher recurrence rate. Because there was only 1 case of permanent complete AV block with RFCA in this large series, the rate of ablation-induced AV block seems low with both energy forms.

Although cryoenergy procedures lasted significantly longer and did not save fluoroscopy time, patients perceived less pain during cryoablation than during RF ablation. The cryoablation console and catheter had significantly more functionality failures than the RF generator and catheter.

Short-Term Success
Data on the short-term success of AVNRT ablation with cryoenergy are inconsistent.4,7,8,10–17 A bigger cryoablation catheter tip (6 instead of 4 mm), longer freezing duration, and application of a bonus freeze seem to have a positive effect on short-term ablation success.4,7,8,10–15 Several authors report that using a 4-mm–tip ablation catheter achieved only moderate success rates.11,12 whereas in more recent series with 6-mm–tip cryoablation catheters, short-term success rates of 93% to 99% were reached.13,16,17 We used a 6-mm–tip catheter, an ablation time of 4 minutes, and a bonus freeze at the site of successful ablation. With this practice, a high short-term success rate (96.8%) comparable to RFCA (98.4%) was found. These data confirm the results from a randomized pilot study from our center14 including 200 patients and the findings of a recent nonrandomized study by Opel et al.17 in which the primary success rate in ablating AVNRT with cryoenergy was not significantly different from that with RF energy.

Ablation-Induced AV Block
As compared with published results, the overall incidence of ablation-induced AV block using RF energy was low in this study (only 1 complete AV block requiring pacemaker implantation) but consistent with former data from our center.3,14 In line with all previously published studies, we observed no persistent ablation-induced AV block in the cryoablation group. One might argue that an AV block incidence of 0.4% is still worse than 0.0%. However, the risk of AV block with RF was so low that a possible safety advantage of using cryoablation could not be demonstrated.

Long-Term Success
During the 6-month follow-up, significantly more patients experienced arrhythmia recurrence after cryoablation than after RFCA (9.4% versus 4.4% of patients). This is in line with the results of the pilot study at our center14 and with the findings of Opel et al.17 with an 11% recurrence in the cryoablation group versus a 3% recurrence in the RFCA group. In our pilot trial, catheter tip size (4 instead of 6 mm) and the lack of a bonus freeze were supposed to be parameters at least partially responsible for the high recurrence rate. As a consequence, these parameters were changed in the present study. Several other groups have described the problem of AVNRT recurrence after cryoablation in the range of 8% to 20%, which seems hard to accept compared with the significantly lower recurrence risk with RF.11–14,16,17 The most likely reason for the high recurrence rate after cryoablation is the different type of acute and the smaller size of definitive ablation lesions. Cryoablation leads to a more homogenous lesion with intact, smooth endothelium and the absence of a big colliquation necrosis.4 The structure of the tissue is more preserved, allowing better tissue regeneration. Once the ablation-created edema has disappeared, the size of the definitive lesion is supposedly smaller than that created by RF ablation. It might therefore be necessary to create a considerably larger acute lesion with cryoablation than with RF ablation to obtain a permanent scar of the same size. How this larger lesion might be created without inducing transient or long-term persistent AV block has to be evaluated.

Procedural Parameters

Procedure and Fluoroscopy Time
In line with the findings of the randomized pilot study by our center,14 cryoablation procedures lasted significantly longer than RF ablation, whereas fluoroscopy times did not differ. Several retrospective series8,12,16,17 did not find a significant difference in procedure duration between cryoablation and RF, and only Chan et al.16 reported a significantly shorter fluoroscopy time in the cryoablation group (18 versus 26 minutes). In our experience, the longer procedure duration is not so much due to the time needed to install the cryoablation
console and start the system but more to the time needed to perform multiple cryoablation mappings (each of 3 minutes’ duration) with a large number of sites sometimes tested before ablation. Repetitive search for a new cryomapping sites might also be the reason that fluoroscopy time was not reduced in the cryoablation group, with a mean absolute fluoroscopy duration (13 minutes) being relatively low with cryoablation and RF.

Device Functionality
It is notable that device failures of the cryoablation console, which prolonged the procedure and often necessitated rebooting of the cryoablation console, occurred in 13 patients. The (nonsignificant) lower primary success in the cryoablation group in our study was caused in part (3 of 8 patients) by a device functionality failure (target temperature of less than −70°C could not be reached). Considering that cryoablation is a relatively new and technically complex technique, this number may not seem exceedingly high, but in the daily routine, cryoablation will have to stand the test of time compared with the readily available, straightforward, and relatively cheaper RF technique.17

Pain Perception
Patients felt significantly less pain with cryoenergy than with RF energy. This finding corresponds to published reports showing that the use of cryoenergy results in less pain perception even in ablation locations known to be painful like the cavotricuspid isthmus. It has to be mentioned, however, that the pain perception score even in the RF group was relatively low with a mean of 20. Timmermans et al18 used the same scale from 0 to 100 for pain perception during cavotricuspid isthmus ablation. RF ablation reached a mean score of 38, whereas cryoablation reached a score of <1. It seems that the ablation site in AVNRT is in general less painful, so this feature of cryoenergy application maybe less important than in other ablation sites.

Limitations
If AVNRT had been inducible without sympathetic mimetic drugs before ablation, testing for inducibility after ablation was performed with the same protocol. It cannot be excluded that using sympathetic mimetic drugs in all cases after ablation might have detected earlier recurrences in both groups.

The follow-up was performed after 6 months, according to the follow-up time of most studies published on RF ablation of AVNRT. We observed that in a few patients ablated with cryoenergy (in contrast to RF), the first AVNRT relapse occurred as long as 12 to 14 months after ablation. However, this would only have enforced our study results.

Conclusions
Cryoablation in patients with AVNRT is associated with a short-term success rate as high as that for RF. However, the significantly higher recurrence rate after cryoablation is probably the main limitation of using this energy form for AVNRT ablation, especially because the potential safety benefit of cryoenergy seems negligible. The advantage of less pain perception with cryoablation is counterbalanced by longer procedure times and frequent device functionality failure.

Disclosures
Dr Schmitt received a restricted grant for equipment from CryoCath Inc. Drs Schmitt, Pitschner, and Kuniss received speakers’ fees from CryoCath Inc. The other authors report no conflicts.

References
This large prospective randomized study including 509 patients compares the short- and long-term efficacy and complications of radiofrequency catheter ablation (RFCA) versus cryoablation of the slow atrioventricular (AV) pathway in AV nodal reentrant tachycardia (AVNRT). Significantly more patients in the cryoablation than in the RFCA group reached the combined primary end point of immediate ablation failure, permanent AV block, and AVNRT recurrence (12.6% versus 6.3%; \(P=0.018\)). The difference in primary end point was driven almost exclusively by the significantly higher rate of AVNRT recurrence after cryoablation (9.4% versus 4.4%; \(P=0.029\)), although short-term success was equally high in both groups (96.8% for cryoablation versus 98.4% for RFCA). Occurrence of permanent AV block (0% for cryoablation versus 0.4% for RFCA) was rare. Cryoablation procedures lasted significantly longer than RFCA, and significantly more device-related problems occurred with cryoablation than with RFCA. Pain perception was lower in the cryoablation group (\(P<0.001\)). In summary, cryoablation in patients with AVNRT is associated with a comparably high immediate success rate as RF. However, the significantly higher recurrence rate after cryoablation is probably the main limitation of using this energy form for AVNRT ablation, especially because the potential safety benefit of cryoenergy seems negligible. The advantage of less pain perception with cryoablation is counterbalanced by longer procedure times and frequent device functionality failure.
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