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Cryoablation compared with radiofrequency ablation for atrioventricular nodal re-entrant tachycardia: analysis of factors contributing to acute and follow-up outcome

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Aims The efficacy of transvenous Cryoablation (Cryo), for the treatment of atrioventricular nodal re-entry tachycardia (AVNRT), when compared with radiofrequency (RF) ablation, requires further investigation.
Methods and results We sought to compare the acute- and follow-up results of 71 cases each of Cryo and RF for AVNRT using a retrospective matched case–control study design and aimed at identifying patient and procedural factors that may predict success with each strategy. Primary failure of Cryo (thus necessitating RF at the same sitting) was seen in 11 (15.4%) cases, whereas there were two (2.8%) primary failures with RF ($P < 0.01$). Patients in the Cryo group had significantly higher arrhythmia recurrence [14 (19.8%)] when compared with the RF group [4 (5.6%)] ($P < 0.01$). The incidence of recurrence following Cryo was significantly higher if an echo beat was still inducible after ablation than if complete slow pathway block was achieved (7/19, vs. 4/46, $P < 0.001$). The median number of Cryo lesions was significantly lower in patients who had recurrence compared with those who did not (1.5 vs. 3.0, $P = 0.02$).
Conclusion We have observed a much higher primary failure and recurrence rate with Cryo when compared with RF for AVNRT. It may be possible to decrease this high recurrence rate by aiming to achieve complete slow pathway block and by increasing the number of Cryo lesions.

Introduction

Transvenous radiofrequency (RF) of the slow pathway has become the treatment of choice for atrioventricular nodal re-entry tachycardia (AVNRT) with wide success rates of over 90%.[1,2] However, up to 1% of these cases develop atrioventricular nodal (AVN) block necessitating the insertion of a permanent pacemaker.[3] Cryoablation (Cryo) is an alternative ablation modality which may not be associated with this serious complication.[4] Although several studies have demonstrated similar acute success rate with Cryo compared with RF,[5,6] it is recognized that the results of new ablation techniques in a non-research setting may not match those of the trials conducted by enthusiasts.[7] We sought to investigate this possibility and analysed our initial results with Cryo comparing these with those of RF. We also aimed to identify patient and procedural factors that may predict success with each strategy.

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Methods

Patient groups

Seventy-one consecutive patients who had been treated for AVNRT with Cryo at a single institution from November 2003 to August 2005 were selected. These patients were then matched to 71 consecutive patients who underwent RF for AVNRT over the same period according the order of priority of sex, age, and incidence of structural heart disease. The doctor selecting the RF patients was blinded to the subsequent outcome. The choice of energy used for an individual patient was at the discretion of the operators, and a systematic approach of applying exclusion criteria for either of the two energy sources was not followed. All Cryo cases were performed by one of the two operators (A.W.N. and S.C.S.).

Electrophysiological procedure and catheter ablation

All patients had stopped anti-arrhythmic drugs at least five half lives before the procedure and entered the laboratory in the fasting state. A standard electrophysiological (EP) study was performed with quadripolar diagnostic catheters positioned at the high right atrium, His bundle, right ventricular apex, and a decapolar catheter positioned in the coronary sinus. Access for all catheters was via the femoral veins. A diagnosis of AVNRT was made by demonstration of dual AV nodal physiology and induction of sustained supraventricular tachycardia with earliest retrograde atrial activation at the His bundle catheter and failure to reset atrial activation with His synchronous ventricular premature paced beats. If tachycardia could not be induced, 2–4 μg boluses of isoprenaline were given to maintain a resting heart rate of greater than 90 bpm, and the EP study was repeated.

For RF ablation, a 4 mm tip catheter (Celsius™, Biosense Webster, Diamond Bar, CA) was used to target a slow pathway signal at the inferior tricuspid valve annulus. Energy was delivered via an RF generator (Stockert, Biosense Webster), power limited to a maximum of 60 W, and temperature limited to 60°C. If junctional activity was seen within 15 s, ablation was continued for 60 s and inducibility of AVNRT re-tested. The endpoint for slow pathway ablation was either slow pathway block or a single atrial echo beat where AVNRT previously had been sustained. If isoprenaline had been given to induce or sustain the AVNRT prior to ablation, it was given prior to endpoint testing.

For Cryo, we followed the techniques described in previous studies.[5,6,8] A 4 mm tip catheter was used for 61 cases (Freezor 3™, Cryocath Technologies, Montreal, Canada) and a 6 mm tip catheter (Freezor Extra™, Cryocath Technologies) in the last 10 cases. At suitable slow pathway signals on the inferior tricuspid annulus, cooling (cryomapping) was performed to −30°C, for 20 s. If no prolongation of AVN conduction was seen, Cryo was performed by cooling to −70°C. After 90 s at this temperature induction of AVNRT was attempted (while continuing to deliver energy) by programmed atrial stimulation looking for inducibility of AVNRT or greater than single atrial echo beats. If these were not seen, Cryo was continued for a total of 4 min. Testing was continued for 30 min after a successful freeze and repeat lesions performed if the tachycardia was still inducible or if multiple echo beats were still inducible.[5,6,8] If these endpoints could not be achieved with Cryo, RF was used instead.

Post-procedure and follow-up

All patients were discharged with no anti-arrhythmic drugs and out-patient follow-up was arranged 6 weeks after the procedure. The patients were also followed-up at any time after this 6-week period if they had a relapse of their presenting symptoms. If a recurrence of AVNRT was documented or patients had symptoms strongly suggestive of a recurrence, then they were offered a further procedure. All patients in whom the medical notes were incomplete were followed-up by telephone.

Cost analysis

Cost of catheters was calculated in units where one unit equals the UK list price of a quadripolar diagnostic catheter. Thus the catheter cost for a successful RF procedure was calculated as 7.5 units (three quadripolar catheters, one decapolar catheter, and one RF catheter), whereas that of a successful Cryo procedure was 8.5 units (three quadripolar catheters, one decapolar catheter, and one Cryo catheter with umbilical tubing). A case in which RF had to be used at the same sitting following an unsuccessful Cryo cost 11.5 units.

Study endpoints

The primary endpoint was a composite of change to alternative ablation energy during index procedure, procedural complications, and documented recurrence of AVNRT during follow-up or induction of AVNRT during repeat EP study. The secondary endpoints were acute procedural success, procedural complications, procedure duration, fluoroscopy time, radiation dose, number of energy deliveries, requirement for repeat EP study based on recurrence of symptoms, and catheter costs per patient: in catheter units.

Statistical analysis

Between the two groups only age was normally distributed and this is expressed as mean (SD). All other continuous variables are presented as median (range). Student's *t*-test was used to compare age and a Mann–Whitney *U* test for all other continuous data. For categorical data, proportions were analysed using the χ^2 test. Statistical analyses were performed using commercially available software (WinSTAT™, R. Fitch Software, Bad Krozingen, Germany). A *P*-value (two tailed) of less than 5% was considered significant.

Results

Acute procedure characteristics

The baseline characteristics of these patients were closely matched (*Table 1*).

The study endpoints are compared in *Table 2*. There was no difference in procedure time, fluoroscopy time, and radiation dose between the groups. There was no significant difference in the number of energy deliveries, and the acute procedural success rate was identical in the two groups. However, Cryo was unsuccessful in 11 (15.4%) cases in whom RF had to be used at the same sitting to achieve acute procedural success. In one (1.4%) patient in whom Cryo was not successful, the case had to be abandoned due to patient fatigue. She went on to have successful RF at a later date. RF was acutely unsuccessful in one patient after 18 energy applications. This patient turned down a repeat attempt and opted for pharmacological therapy.

Junctional rhythm of varying duration was observed in all cases in the RF group, but in no patient in the Cryo group during the lesion application. In one patient in whom Cryo was successful, junctional rhythm was observed following the cessation of the energy delivery.

One 84-year-old woman who developed first degree AV block during her only (successful) RF application developed second degree heart block at 4 weeks follow-up. She was prescribed a permanent pacemaker. AV conduction damage was not observed in any patient in the Cryo group.

Follow-up

Follow-up was available in all patients at a median duration of 66 and 57 days, respectively for the Cryo and RF groups.

Table 1 Baseline characteristics of the study population

	Cryoablation (*n* = 71)	Radiofrequency ablation (*n* = 71)	*P*-value
Male/female	16/55	16/55	1.0
Age (years)	52 ± 16	52 ± 15	0.74
Prevalence of structural heart disease (%)	5 (7%)	4 (5.6%)	0.65
Median follow-up (days)	66 ± 12	57 ± 11	0.53

Table 2 Primary and secondary endpoints

	Cryoablation ($n = 71$)	Radiofrequency ablation ($n = 71$)	*P*-value
Procedure time (min)	96.1 (60–180)	90.4 (60–180)	0.27
Fluroscopy time (min)	16.8 ± 12.6	13.2 ± 13.5	0.13
Radiation dose (cGy)	1670 ± 1669	1395± 1960	0.36
Median number of energy deliveries[a]	3 (1–20)	2 (1–25)	0.50
Primary failure	11 (15.4%)	2 (2.8%)	<0.01
Acute procedural success	69 (97%)	69 (97%)	1.0
Permanent AV nodal damage	0	1 (1.4%)	0.89
Documented recurrence	14 (19.7%)	4 (5.6%)	0.01
Primary endpoint	25 (35.2%)	7 (9.8%)	<0.001
Suspected arrhythmia recurrence[b]	2 (2.8%)	0	0.20
Cost, catheter units (range)	10.9 ± 3.8 (8.5–26)	7.8 ± 1.5 (7.5–15)	<0.001

[a]Number does not include Cryomapping lesions in the Cryo group.
[b]No arrhythmia induced on repeat electrophysiology study.

Excluding those with failed procedures, 14 (19.7%) of the patients in the Cryo group and four (5.6%) patients in the RF group had documented arrhythmia recurrence ($P = 0.01$). All the 14 cases of arrhythmia recurrence in the Cryo group were seen in those cases ($n = 60$) where RF was not used, i.e., no recurrence was observed in any of the 11 cases in the group who had switched from Cryo to RF. In 9 of these 11 crossover patients, slow pathway block had been achieved while the other two still had single echo beats. Further two patients in the Cryo group required diagnostic EP studies for suspected recurrence on which no arrhythmia could be induced. The primary endpoint was thus met by 25 (35.2%) patients in the Cryo group and six (8.4%) patients in the RF group ($P < 0.001$).

We analysed the recurrence rates according to the endpoints achieved at the end of all cases (*Figure 1*). Forty-six (64.8%) patients in the RF and 47 (66.2%) in the Cryo groups had evidence of slow pathway conduction block ($P = $ NS). Of these, no patient in the RF group had arrhythmia recurrence while four (8.5%) of the patients in the Cryo group had recurrence ($P < 0.05$). Single echo beats could be induced in 20 (28.2%) patients in the RF group and 19 (26.8%) patients in the Cryo group ($P = $ NS). Of these, one (5%) and seven (36.8%) patients, respectively, had documented arrhythmia recurrence ($P < 0.05$). In three patients in the RF group, the final lesion delivery had to be discontinued at 30 s or less because of transient impairment of AV conduction and proximity to the compact AV node. As the tachycardia was not inducible at this point, further energy was not delivered. All three of these patients had arrhythmia recurrence. Similarly three patients in the Cryo group had their therapy curtailed by impairment of AV conduction at the time of Cryo; all three had arrhythmia recurrence.

We compared the demographic and procedural characteristics of the 14 patients with documented arrhythmia recurrence following successful Cryo therapy with the 55 patients who did not (*Table 3*). Those with recurrences had a significantly lower median number of Cryo lesions (1.5) when compared with those who did not (3.0) ($P = 0.02$). These patients also had a significantly greater proportion of inducible echo beats when compared with complete slow pathway block at the end of the case ($P < 0.001$).

Of the 10 patients in which 6 mm tip Cryo catheters were used, four were acutely unsuccessful after a median number of 3.5 (1–8) Cryo lesions. These patients were successfully treated with RF at the same sitting. There was no recurrence in any of these 10 patients at a mean follow-up period of 58 ± 16 days.

We attempted to detect any 'learning curve' effect in the Cryo group by comparing the results of our initial experience with Cryo with the subsequent one. The number of primary failure, recurrence, and combined primary endpoint were 5, 8, 13 and 6, 6, 12 among our first 36 and last 35 Cryo cases, respectively ($P = $ NS).

Discussion

Cryoenergy has been promoted as a safer alternative to RF energy to ablate arrhythmias. The ability to 'Cryomap' potential ablation sites by creating reversible lesions, and the phenomenon of 'Cryoadherence' preventing catheter dislodgement during ablation are two characteristics of Cryo that are thought to provide safety.[4] This is especially desirable while ablating perinodal structures like the slow pathway (for AVNRT) or paraHisian accessory pathways. Hence, Cryo is becoming the ablation modality of choice for AVNRT cases in some institutions.

There is a surprisingly large variation in the published success rates using Cryo for AVNRT. Two prospective randomized multicentre studies by Zrenner *et al.*[6] and Kimman *et al.*[5] showed equally high acute procedural success rates of >90% using Cryo and RF, although Kimman *et al.* did experience a higher recurrence rate in the patients who received Cryo. However, subsequent single centre series, while confirming the safety of the technique, demonstrated more modest success rates. Both Kriebel *et al.*[9] and Greiss *et al.*[10] experienced acute and long-term failure rates with Cryo of 15%. In the paediatric series by Kriebel *et al.*,[9] the success rates of Cryo for ablation of supraventricular tachycardia were only 75% which were increased to 90% by the use of RF at the same sitting in several cases. Greiss *et al.* too observed in their retrospective analysis that RF was required in 6% of cases to achieve success.

We have shown that Cryo is less effective than RF when used for AVNRT not only in terms of the high requirement for RF in many patients due to primary failure but also by

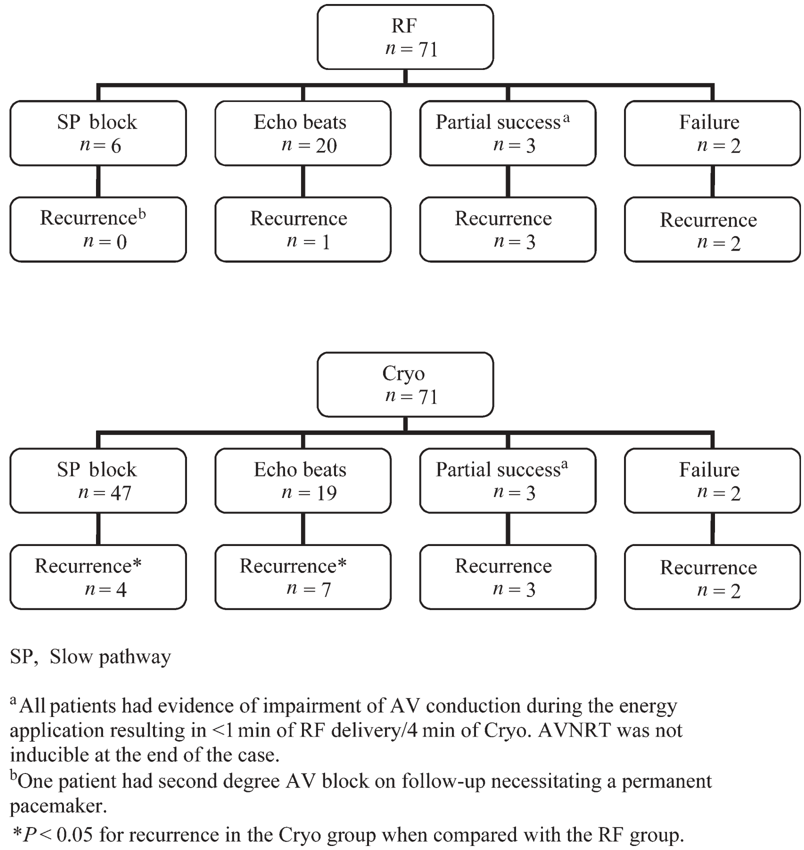

Figure 1 Flowchart of recurrence rates of AVNRT according to the endpoints achieved at the end of the index ablation procedure.

Table 3 Comparison of patients with arrhythmia recurrence and those with no recurrence following cryoablation[a]

	Recurrence ($n = 14$)	No recurrence ($n = 55$)	*P*-value
Sex (M/F)	4/10	11/44	0.85
Age (years)	44.6 ± 14.6	54.0 ± 16.1	0.06
Median number of Cryo lesions	1.5	3	0.02
Cryoablation catheter tip (4 mm/6 mm), *n*	14/0	45/10	0.09
Procedure time (min)	80.7 ± 24.6	91.6 ± 28.6	0.19
Fluroscopy time (min)	16.7 ± 12.8	15.9 ± 11.1	0.82
Radiation dose (cGy)	23.3 ± 27.4	14.8 ± 12.7	0.09
Use of RF, *n* (%)	0	11 (20%)	0.09
Slow pathway block achieved, *n* (%)	4 (28.5)	43 (78.2)	<0.001
Echo beat inducible, *n* (%)	10 (71.5)	12 (21.8)	<0.001

[a]Excluding two failures.

the higher rate of arrhythmia recurrence on follow-up. This has obvious cost implications, which we have demonstrated in our study. Moreover, as we only had one delayed complication of AV node damage as a complication of RF, the safety benefit of Cryo was modest. Recent reports from other centres suggest that the incidence of serious permanent AV nodal damage with RF for slow pathway ablation is much lower than previously thought, and should now be less than 0.5%.[11]

There may be several reasons for the difference in success rates we observed between Cryo and RF. The most obvious one relates to the lesion size whereby the phenomenon of Cryoadherence with Cryo limits the size of the ablation lesion by preventing the movement of the catheter across cardiac tissues that occurs as a result of cardiac and respiratory movement during RF.[11] We have noted in this study that the number of patients who had recurrences following Cryo had on average half the number of lesions compared with those who did not (*Table 3*). This might reflect the greater area of ablation caused by the increased number of lesions, and it is our routine policy now to deliver at least a total of three Cryo lesions in the slow pathway region even if the arrhythmia is not inducible after the first lesion application. It has also been suggested that efficacy of Cryo may be enhanced by the use of larger 6 mm tip catheters which produce larger and deeper ablation lesions.[12] While this may indeed turn out to be the case in future, it was not the experience of Kriebel *et al.*[9] Our limited experience with the 6 mm tip catheter in our first 10 cases too was similar to that with the smaller tip catheters.

Another plausible reason for the difference in recurrence rates between Cryo and RF is the difference in late lesion maturation characteristics. It is well known that RF lesions often exhibit late progression due to fibrosis and vascular damage,[13,14] and delayed AV block as a complication of RF for AVNRT has been well described.[15,16] Indeed, the only patient in our study with this complication developed it 4 weeks after her RF procedure. On the other hand, Cryo lesions tend to contract slightly over time as border zone re-warming occurs.[17] This might explain why the long-term success rates of RF are higher than those of Cryo. This hypothesis is given weight by the fact that more than one-third of our patients with reproducible echo beats following 'successful' Cryo had documented recurrence when compared with less than 10% of those who had evidence of complete slow pathway block (*Figure 1*). While this difference in recurrence rates according to the endpoint achieved was also observed in the RF group, it was considerably less pronounced than in the Cryo group. This suggests that the ideal endpoint following Cryo for AVNRT should be complete block of slow pathway conduction, and energy delivery should be repeated till all echo beats are seen to disappear.

In light of our experience with Cryo and RF for AVNRT, we now advise the use of Cryo in specific circumstances where the use of RF may be more likely to cause AV nodal damage. These include patients with unusual cardiac anatomy making safe RF delivery difficult, or those with evidence of impaired AV conduction at baseline. We also use Cryo in patients who need ablation in the close vicinity of the compact AV node following unsuccessful RF at more posterior sites. Given the reported age-dependent complication of AV block following RF,[18] and as borne out by our experience too, we also have a lower threshold for using Cryo in more elderly patients. While using Cryo, it is our policy now to give multiple lesions and to aim for total abolition of slow pathway conduction.

Limitations

A limitation of our study is its retrospective nature. We attempted to overcome this by including all cases and by carefully matching the two groups to minimize any bias. Another possible limitation is the relatively small number of patients in our study, although our sample size of 142 patients compares well with the published literature. The adequacy of the sample size is also suggested by the lack of a demonstrable learning curve effect in our analysis.

Conclusion

We have found that, compared with RF, cryo for AVNRT is associated with a higher rate of primary failure as well as arrhythmia recurrences in follow-up resulting in a significantly higher catheter cost. The recurrence rate with Cryo is particularly high in those patients with evidence of residual slow pathway conduction at the end of the ablation procedure.

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