

Cryoablation: how to improve results in atrioventricular nodal reentrant tachycardia ablation?

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Ablation for atrioventricular nodal reentry tachycardia is very effective, with a potential for damage to the normal conduction system. Cryoablation is an alternative, as it allows cryomapping, which permits assessment of slow pathway elimination at innocent freezing temperatures, avoiding permanent damage to the normal conduction system. It is associated with shorter radiation times and the absence of heart block in all published data. We discuss in this overview different approaches of cryoenergy delivery (focusing on spot catheter ablation), and how lesion formation is influenced by catheter tip size, application duration, and freezing rate. Some advantages of cryoenergy are explained. Whether these features also apply for an approach with a cryoballoon, e.g. for atrial fibrillation is unclear.

Keywords

Arrhythmia • Atrial fibrillation • Atrioventricular nodal reentrant tachycardia • Catheter ablation • Cryoenergy • Radiofrequency

Introduction

In the past decade, a significant amount of basic and clinical research has been conducted regarding the use of cryoablation. The different clinical trials leave no doubt on the advantageous safety profile of this ablation technique, with not a single permanent heart block reported till now for atrioventricular nodal reentrant tachycardia (AVNRT).^{1–4} This has led to the use of cryoablation as the technique of choice in medical or health care environments where safety is the primary concern, e.g. in pediatric patients, or when ablation is performed close to normal conduction system.⁵ Still, some debate remains about the long-term efficacy of cryoablation. *Table 1* shows the average success rate and the long-term outcome of studies analysing cryoablation versus radiofrequency (RF) in AVNRT. Acute success is similar, but it cannot be denied that slightly more recurrences are observed with cryotherapy.^{1,2,5–10} However, it is possible that cryoablation procedures can be improved. Issues such as catheter tip size, application duration, and the temperature constant will be discussed in this paper. In *Table 2*, we show procedure and radiation times as reported by investigators, directly comparing cryoenergy, and RF,

clearly demonstrating that less fluoroscopy is needed with AVNRT, with a similar procedure time as for RF.

Lesion formation

The creation of a permanent cryolesion is characterized by three phases: (i) the freeze/thaw phase, (ii) the haemorrhagic and inflammatory phase, and (iii) the replacement of this acute lesion by fibrosis.¹¹ In the first phase, intracellular and extracellular ice crystals are formed with variable size. Ice crystals formed more closely to the catheter tip are intra- and extracellular, in contrast to more peripheral ice crystals, which tend to appear only in the extracellular space. During the thawing phase, mitochondria develop irreversible damage due to increased membrane permeability. These changes are less marked towards the periphery.¹² The second phase, occurring within the first 48 h, is characterized by the development of haemorrhage, oedema, and inflammation.^{12,13} After 1 week, a sharply demarcated lesion is formed.¹² The final phase of lesion formation takes place within 2–4 weeks. At this time, the lesion consists of dense collagen and is infiltrated by fatty tissue. At its border many small blood vessels are found.

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Table 1 Acute procedural and long-term outcome data in studies comparing cryotherapy vs. radiofrequency

Authors	Patient nr		Acute success (%)		Recurrences (%)	
	Cryo	RF	Cryo	RF	Cryo	RF
Kimman <i>et al.</i> ¹	30	33	93	91	10	9
Zrenner <i>et al.</i> ²	100	100	97	98	8	1
Gupta <i>et al.</i> ⁶	71	71	85	97	19.8	5.6
Collins <i>et al.</i> ⁵	57	60	95	100	8	2
Avari <i>et al.</i> ⁷	38	42	97	95	2	2
Chan <i>et al.</i> ⁸	80	80	97.5	95	9	1.3
Schwagten <i>et al.</i> ⁹	144	130	97	95	7.5	6.5
Opel <i>et al.</i> ¹⁰	123	149	83	93	11	3
Total	643	665	93	96	10	4.2

Cryo, cryotherapy; RF, radiofrequency

Table 2 Comparison of procedural parameters in studies using cryotherapy vs. radiofrequency

Authors	Procedure time (min)		Fluoroscopy time (min)	
	Cryo	RF	Cryo	RF
Kimman <i>et al.</i> ¹	142,5	144	29	35
Zrenner <i>et al.</i> ²	140	112	12	14
Gupta <i>et al.</i> ⁶	96	90	17	13
Collins <i>et al.</i> ⁵	146	112	20	21
Avari <i>et al.</i> ⁷	176	174	19	21
Chan <i>et al.</i> ⁸	150	159	19	26
Schwagten <i>et al.</i> ⁹	149	152	22	29
Opel <i>et al.</i> ¹⁰	90	90	16	14

Cryo, cryotherapy; RF, radiofrequency.

Medians are in bold, italic; means are in a regular font.

At 1 month, the lesion is composed of dense fibrosis.¹⁴ In summary, cryolesions are formed by consecutive freezing, inflammation, and fibrosis, leading to tissue with intact extracellular matrix. The advantage of preservation the endothelium is a decreased risk of thromboembolism.¹¹ A theoretical advantage could be that cryolesions are less proarrhythmic as the lesion is more homogeneous.

At this moment, cryoenergy is applied at the epicardium by surgeons and by spot, and balloon catheters by the cardiologist. It is evident that these methods will result in different ways of lesion formation. Most of what we will address in this review will be based on data from spot catheters, as used for AVNRT.

Cryomapping

One of the major advantages of cryoablation is the possibility of cryomapping, a feature which was initially introduced by Dubuc.¹⁵ After cryoadhesion at -30°C , freezing is continued at this temperature, to evaluate the clinical effect of the application,

and to proof that no collateral damage is present. Some authors reported that temporary AV block may happen, even after such cautious approach.^{16,17} Nevertheless, this should not lead to persisting block. Even fast freezing till -70°C on the target site was applied to perform cryomapping, and did not lead to permanent block in the hand of other investigators.⁶ However, it has to be pointed out that this 'aggressive' approach was associated with a lower procedural success than for other groups, with substantially more recurrences (Table 1). One of the reasons might be that the 'stunned' area becomes larger, and that real (i.e. long-term) success becomes more difficult to predict. More moderate attempts, using -40°C resulted as well in local damage.¹⁸

Catheter tip size

Catheter tip size can be a very important determinant of procedural success. Nowadays, 4, 6, and 8 mm tip catheters are available. In everyday practice, the 4 and 6 mm tip catheters are used most frequently for treating AVNRT, although the 8 mm tip catheter can be very useful in other areas as ventricular tachycardia, Wolff–Parkinson–White (WPW), and atrial flutter.¹⁹ The 4 and 6 mm tip catheters create a lesion size, which is smaller than the lesions of the 8 mm tip.¹² The difference seems to be mostly dependent on the angle of the catheter tip in relation to the surface.²⁰ Moreover, when comparing the 4 and 6 mm tip catheters in AVNRT in clinical practice (Table 3), there seems to be a difference in efficacy in favour of the 6 mm tip catheters: acute success is similar in both groups, but there is a higher recurrence rate in the 4 mm tip group.^{21,22}

Apart from the lesion size and depth, lesion quality or degree of tissue damage created by cryoablation is influenced by the selected catheter tip size and by the tissue contact reached during the ablation, as shown in the recent experimental paper of Atienza *et al.*²³

Application duration

It was shown in several experimental settings that lesion depth is determined by the duration of freezing. During the first minute a stable temperature gradient is reached, and a plateau phase is

Table 3 Comparison of procedural and outcome data in studies comparing 4 and 6 mm tips for slow pathway ablation

Authors	Nr of cryoablation patients	Study design	Acute success	Follow-up (months)	Recurrences	Temporary AV block (first, second, third)	Complete, permanent AV block
De Sisti et al. ¹⁷	8 (4 mm)	SC, cohort, prospective, 4 and 6 mm	4/8	18 ^a	4/4	NR (21/69)	0
	61 (8 mm)		56/61				
Sandilands et al. ²¹	59 (4 mm)	SC, cohort, prospective, 4 vs 6 mm	54/59	18 ^a	12/54	NR (13/160)	0
	101 (6 mm)		95/101				
Rivard et al. (2007) ³¹	152 (4 mm)	SC, 2 cohort, retrospective, 4 vs 6 mm	139/152	6	22/139	6/152	0
	137 (6 mm)		123/137				

NR, not reported; SC, single centre.

^aSubgroup not specified.

achieved at 5–6 min.^{11,13,21} This is reflected in most clinical settings, where cryoenergy is applied for 4–5 min.

A recent experimental paper describing the electrophysiologic and histologic changes in correlation to the duration of the cryoapplication using an 8 mm tip catheter on the compact AV node in pigs showed that recovery of AV nodal function was less likely if the application lasted longer.²³ They observed that isolated viable cells surrounded by necrotic tissue in the compact AV node were associated with acute AV conduction recovery. Moreover, they witnessed a variation in the degree of myolytic changes between the animals with and without persistent AV block at 1 week.

Some suggestions have been made to improve lesion formation by applying a double freezing cycle (freezing–thawing–freezing).²⁴ First, a freezing phase of 4 min is applied. Then the catheter rewarms and immediately a new freezing cycle is performed at exactly the same site for 2 min. Data in hepatocellular ablation show that repetitive freeze–thaw cycles create larger lesions than those obtained by longer freezing at a certain temperature.²⁵ The rate and extent of conduction of the cold front increases with repetitive exposure, what suggests a progressive increase in thermal conductivity of tissue. Although poorly understood, this could be related to basic cellular structure changes and/or modification of local microperfusion.²⁶ So far, no cardiovascular data exist to support the routine use of this technique, which was tested in hepatic disorders.

Temperature time constant

Several suggestions have already been made to improve the quality of the lesion. Fast freezing, with a steep decrease in temperature is more effective than a slow progression to the target temperatures.²⁷ It was demonstrated in a group of WPW patients that successful ice mapping attempts were characterized by a short time-constant. This parameter reflects the time interval between the onset of ice mapping and the steady-state mapping temperature of -30°C .

Catheter adhesion

The formation of ice during ablation at the tip of the catheter causes the catheter to adhere to the adjacent tissue

(cryoadherence). This allows pacing manoeuvres in the atrium and the ventricle during ablation without the risk of catheter dislodgement, what is very useful to show persistence or absence of slow pathway conduction. Moreover, ablation can be performed during tachycardia without a risk of dislodging the catheter when normal rhythm is restored. Also, small patient movements and even deep breaths do not affect ablation catheter position during ablation. Unlike the 'brush lesions' formed by radiofrequency ablation, cryoablation creates very focal lesions. This is similar to lesions as described with magnetic navigation.²⁸

Recurrence

It is not impossible that some of the recurrences are due to reconnection, a phenomenon which is well known in the pulmonary veins, where reconnection is often detected, and almost always when a patient is restudied because of recurrences.²⁹ Asymptomatic reconnection is also seen in a recent study on cryoablation of the cavotricuspid isthmus in 23% of cases during restudy after several weeks.³⁰ This might be a reason to strictly adhere to some observation time after ablation, and to ascertain that there is no more slow pathway conduction after this time.

Conclusion

In conclusion, cryoablation is a safe and effective approach for AVNRT, but care should be taken to use it in a way with full understanding of its possibilities and limitations, otherwise it could lead to disappointing results.

This means that cryomapping should be performed to demonstrate that the catheter is over the slow pathway, which is impossible with RF techniques. Further, application times should be long enough to create full lesions. A 6 mm tip is probably better than the 4 mm tip, which still may have a place in some pediatric indications. Energy sources should allow very fast freezing to improve penetration of the cold in the tissue. Finally, waiting times should be respected, as recovery within a short time may indicate that more applications are necessary. In this way, cryoablation is an elegant technique, with few important side effects. The

complete absence of AV nodal conduction defects in AVNRT, should make it a strategy of first choice. The small excess number of patients requiring a second approach makes the extra amount of radiation and catheterization related complications of a second procedure acceptable, due to the absence of the main RF related complication. Further studies should be undertaken to improve the long-term outcome, as the value of freeze–thaw–freeze cycles and different application times; more flexible catheters, e.g. steerable with robotics or magnetic navigation (and without pull wires) could make the procedure even more safe.

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