Cryosurgical ablation of atrioventricular nodal reentry: histologic localization of the proximal common pathway*

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ABSTRACT A method using cryosurgery has been previously described to selectively ablate atrioventricular nodal reentry tachycardia while preserving intact atrioventricular conduction. The purpose of the present study was to define the histologic features of the cryolesions in relationship to the specialized conduction system. In 12 adult dogs a series of nine discrete cryolesions was placed along the perimeter of the triangle of Koch while continuously monitoring the His bundle electrogram. All animals survived the operation and maintained intact atrioventricular conduction. At 14 weeks after surgery the hearts were sectioned and examined. In all 12 animals there was a confluent mass of dense fibrous tissue present in the lower atrial septum that was in immediate proximity to but did not involve the atrioventricular node—His bundle. The ablation of perinodal tissue with preservation of the specialized conduction system with the use of this cryosurgical technique was confirmed. It is likely that the cryoaablated perinodal tissue represents the proximal common pathway of the circuit for atrioventricular nodal reentry tachycardia.

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IN 1979 a case report was published by Pritchett et al. that described the fortuitous ablation of atrioventricular nodal reentrant (AVNR) tachycardia with preservation of intact atrioventricular conduction. This report stimulated our group to develop a reproducible and safe surgical method for the ablation of AVNR tachycardia refractory to medical therapy. One concept central to the development of this operation was that perinodal atrial tissue is necessary for the AVNR circuit to exist, and that if this perinodal tissue can be ablated without destroying the atrioventricular node, then the goal of reproducibly ablating the circuit required for AVNR tachycardia while preserving intact atrioventricular conduction will have been achieved.

A method using cryothermia to ablate perinodal tissue and preserve the atrioventricular node was subsequently devised by our group, and the electrophysiologic effects of perinodal cryoablation on antegrade and retrograde atrioventricular nodal function, dual atrioventricular nodal conduction, and the ventricular echocardiographic phenomenon was published. This procedure has been used successfully in a series of patients at Duke University Medical Center and Barnes Hospital, St. Louis, and similar procedures for selectively ablating atrioventricular nodal reentry have been reported from other institutions. The purpose of the present study was to complete our description of the surgical procedure for selective cryoablation of AVNR tachycardia with preservation of intact atrioventricular conduction by defining the histologic sequel of this cryosurgical procedure in a canine preparation. The conclusions of our studies are then discussed in light of other clinical and experimental investigations of AVNR tachycardia as they relate to the exact localization of the proximal portion of the reentry circuit.

Methods

The experimental protocol included 12 adult mongrel dogs that were subjected to the cryosurgical procedure as follows. After induction of anesthesia with morphine and thiamylal sodium (Surital), the animals were intubated and maintained on a

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volume-cycled respirator (Bennett MA-1) at an FIO2 of 0.40. Arterial blood gases and serum electrolytes were monitored throughout the procedure and early postoperative period, and were maintained within physiologic ranges. The femoral arteries were cannulated for arterial pressure monitoring and systemic perfusion during cardiopulmonary bypass. Under sterile conditions, the heart was exposed via a right thoracotomy. Two bipolar epicardial electrodes were placed on the right atrium. The first pair was placed on the right atrial appendage for the recording of atrial electrograms. The second electrode pair was placed on the right atrial free wall and was used for right atrial pacing at twice diastolic threshold. One bipolar epicardial electrode was placed on the right ventricular outflow tract to record the ventricular electrogram. A No. 6F bipolar electrode catheter (USCI, C.R. Bard, Inc., Billerica, MA) was wedged into the noncoronary cusp of the aortic valve to record the His bundle electrogram. Surface limb lead II was also recorded. After completion of this portion of the operation, baseline data were collected at atrially paced cycle lengths of 300, 350, and 400 msec for the subsequent measurements of the following intervals: pacing artifact–to–atrial depolarization (PA) interval, atrial depolarization–to–His bundle depolarization (AH) interval, and His bundle–to–ventricular depolarization (HV) interval.

After collection of the baseline electrophysiologic data, the venae cavae were cannulated, tapes were passed around them, and cardiopulmonary bypass was initiated at normothermia. The caval tapes were made occlusive, the atrial septum was exposed via a longitudinal right atriotomy, and a hand-held bipolar probe was used to delineate the His bundle within the triangle of Koch. A series of nine cryolesions was then created with a 4 mm cylindrical cryoprobe (Frigitronics, Inc., Shelton, CT) at endocardial sites on the lower atrial septum along the perimeter of the triangle of Koch (figure 1). The cryolesions were generated with a negative 60° C probe tip temperature applied for 120 sec while carefully monitoring the AH and AV intervals. Typically, the AH and AV intervals lengthened greatly during the cryothermic exposure, but if complete atrioventricular block or Wenckebach block occurred, the cryothermic exposure was immediately terminated. When three animals were noted to have postoperative chronic right bundle branch block, the protocol was further modified so that cryothermia was immediately terminated if a sudden increase in the atrioventricular interval occurred in association with widening of the QRS complex as observed in limb lead II.

After completion of these procedures, the atriotomy was closed, the animals were weaned from cardiopulmonary bypass, and the thoracotomy was closed in standard fashion. No inotropic support was required, but postoperative analgesics and perioperative antibiotics were administered. All animals received humane care in compliance with the guiding principles of the American Physiological Society. During the period of convalescence none of the animals developed signs of congestive heart failure, and serial surface electrocardiograms failed to reveal tachycardias except in the one animal that had been previously reported with atrial flutter and an acceptably slow ventricular response. At week 14, the animals were again anesthetized and their hearts were arrested with potassium chloride and removed. The right atrium was opened through the previous atriotomy and the area of the cryolesions was visually inspected. A block of tissue that included portions of the aortic valve, mitral valve, and tricuspid valve surrounding the atrioventricular node, His bundle, and proximal portions of the left and right bundle branches was then excised (figure 2) and serially sectioned (figure 3) transversely into seven tissue slabs across the atrial septum starting at the anterior edge of the coronary sinus and terminating at the most anterior septal attachment of the tricuspid valve septal leaflet (conal papillary muscle or papillary muscle of Lancisi).

The seven slabs of tissue were preserved in formaldehyde and subsequently fixed, step-sectioned, and stained by Masson’s trichrome technique. At 14 weeks, the cardiac lesion produced

**FIGURE 1.** The sites of the nine cryolesions in relation to the atrioventricular node–His bundle, coronary sinus, and tricuspid valve anulus. Mapping of the His bundle at the time of operation was used to confirm the location of the specialized conduction system before the application of the cryolesions.

**FIGURE 2.** The tissue block excised from the heart at 14 weeks postcryosurgery included the atrioventricular node, bundle of His, and proximal portion of the right and left bundle branches as shown in black within the atrial septum. Ao = aortic valve; MV = mitral valve; TV = tricuspid valve; CS = coronary sinus.
The atrioventricular node moves by cryothermia consisted of dense, fibrous, scar tissue with a sharply defined border. With the Masson trichrome technique the location of scar tissue was optimally displayed since the scar tissue stains bright green, in contrast to normal myocardium, which stains red. The stained sections were examined (D. B. H.) and the positions of the cryolesions were noted according to a standard format (table 1) defined as follows based on the descriptions of the atrioventricular conduction system by Davies et al.10 and Hackel.11 The atrioventricular node is visible histologically as a compact, oval nodule containing interconnecting relatively small myofibers that are located within the atrial septum, beneath the tendon of Todaro, and above the anulus of the tricuspid valve near the apex of the triangle of Koch. The atrioventricular node moves anteriorly into the apex of the triangle of Koch, then it passes into the central fibrous body (right trigone) as a compact strand of regularly arrayed myofibrils embedded in fibrous tissue. At this point, the atrioventricular node becomes the penetrating portion of the common bundle of His. As the penetrating portion of the bundle passes out of the central fibrous body along the crest of the ventricular septum and the posteriorinferior border of the membranous septum, it becomes the branching portion of the common bundle of His. Myofibrils fanning off of the branching bundle come to occupy a subendocardial position in the left ventricle as the left bundle branch, with the remaining cells passing on to the right ventricle as the right bundle branch.

Results

Each of the 12 animals in the study survived surgery without complications and had an uneventful convalescence. All of the animals demonstrated the early and late electrophysiologic changes that occur with cryoablation of the lower atrial septum.2-4 During application of cryothermia the AH interval lengthened, and in some instances progressed to Wenckebach block. When Wenckebach block occurred, the cryothermic exposure was immediately terminated, and within 3 to 5 min, 1:1 atrioventricular conduction returned in all cases. No instances of complete heart block were noted during follow-up electrocardiographic determinations, although in three of the dogs studied earlier, permanent right bundle branch block developed after application of cryolesions near the apex and along the inferior border of the triangle of Koch. This problem was subsequently eliminated by monitoring the total atrioventricular interval and the QRS morphology in the limb lead II electrograms. When right bundle branch block occurred during application of a cryolesion, the cryothermia was immediately terminated.

Gross description. The epicardial surface of the heart, caval cannulation sites, and atriotomy site all had the appearance of normal healing tissue. The abnormal findings were confined to the region of the lower right atrial septum. The os of the coronary sinus was patent in all cases but was frequently deformed by nearby scar tissue. Within the triangle of Koch there was a firm confluent mass of white scar tissue that frequently (10 of 12 dogs) extended down onto the base of the septal leaflet of the tricuspid valve. There were no atrial septal defects, nor was there evidence of thinning of the tissue within the lower atrial septum on cross section. The scar tissue within the triangle of Koch extended from 1 to 3 mm beneath the endocardial surface, and in three cases by visual inspection involved a small portion of the ventricular septum. The subvalvular apparatus of the tricuspid valve was normal, and the free edges of the tricuspid valve leaflet had no thickening or nodularity.
Histologic description. The findings of the microscopic examination of the cryolesions are summarized in table 1. As predicted by our previous experience, the cryolesions produced dense uniform scars with histologically sharp borders to normal tissue. In 12 of 12 specimens examined there were easily identifiable large cryolesions extending into the lower atrial septum from the right atrial endocardial surface. In no instance did the cryolesion extend into the tissue comprising the histologically identified atrioventricular node (figures 4 and 5), although the edge of the lesions were very close to the atrioventricular node (figure 4) or actually abutted on the atrioventricular node (figure 5). The confluent scar could easily be traced into the apex of the triangle of Koch through the serial sections of the atrial septum. The scar from the cryolesions was always first noted in a portion of the septum proximal to the atrioventricular node (i.e., between the atrioventricular node and the coronary sinus) and never involved the atrial septum transmurally. As the cryolesion passed beyond the apex of the triangle of Koch, it remained in close proximity to the penetrating and branching portions of the bundle of His (figure 6), but the scar never involved the bundle of His.

In four animals there was histologic evidence of extension of the cryolesion onto the uppermost portion of the ventricular septum, and in the three animals with permanent right bundle branch block this ventricular extension of the cryolesion involved the right bundle branch (figure 7).

The base of the septal tricuspid valve leaflet was included in the lower atrial septal cryolesion in 10 of 12 animals. Although in some instances the scarring produced rather marked thickening of the base of the valve leaflet with chondroid metaplasia of normal valve tissue (figure 8), the peripheral portions of the valve and the subvalvular apparatus were invariably normal.

Discussion

Previous studies from this laboratory have defined a cryosurgical procedure for the ablation of AVNR tachycardia and described the electrophysiologic sequelae of this operation. In the immediate postoperative period, the AH and VA intervals are lengthened.
and the Wenckebach point, functional refractory period, and effective refractory period of the atrioventricular node are lengthened. However, by 14 weeks postoperatively all of these variables except for the AH interval return to normal. We believe that these electrophysiologic data confirm the selective ablation of perinodal tissue in the lower atrial septum, with sublethal injury to the atrioventricular node that resolves completely over time. The elimination of ventricular echoes in a group of animals subjected to the cryosurgical procedure provides further evidence to support the hypothesis that cryoablation of perinodal tissue can ablate AVNR. Finally, in a previous study, three animals fortuitously demonstrated the phenomenon of dual atrioventricular nodal conduction that is necessary for AVNR, and this dual atrioventricular node conduction was ablated postoperatively by the cryosurgical procedure.

These data from the animal preparation subsequently led to the successful use of this cryosurgical procedure in humans suffering from intractable AVNR tachycardia. Other groups have reported similar results for the surgical treatment of AVNR tachycardia, although some surgeons have a preference for sharp dissection rather than cryosurgery for ablation of the reentry circuit.

The present study was undertaken to histologically describe the site of the cryolesions to confirm the preservation of the specialized conduction tissue and provide further data regarding the location of the proximal common pathway for the circuit of AVNR. In the present study, we found that the scar tissue resulting from multiple cryolesions within the triangle of Koch in the lower atrial septum was a confluent area of dense homogenous fibrous tissue that extended from just above the os of the coronary sinus into the apex of the triangle of Koch. The atrioventricular node and His bundle as defined histologically were never involved

**FIGURE 6.** The cryolesions created at the apex of the triangle of Koch remained in close proximity to the specialized conduction system, but as documented in this photomicrograph, never involved the bundle of His. CL = cryolesion; HB = bundle of His. (Masson trichrome, original magnification × 25.)

**FIGURE 7.** The atrial cryolesions extended into the ventricular septum in four of 12 animals. In three of 12 animals the right bundle branch was included within the cryolesion where the cryolesion ablated the right bundle branch as it straddled the ventricular septum. CL = cryolesion. (Masson trichrome, original magnification × 25.)

**FIGURE 8.** The base of the septal tricuspid valve leaflet was frequently subjected to cryothermia. This valve leaflet demonstrated a marked degree of thickening, together with changes compatible with chondroid metaplasia. (Hematoxylin-eosin, original magnification × 25.)
by the scar tissue, although the scar was in immediate proximity to the atrioventricular node or in some cases actually abutted the node. In three animals the right bundle branch was ablated by extension of the cryolesion onto the ventricular septum, but this complication was subsequently eliminated by more careful monitoring of the electrograms during application of cryothermia. Extension of the cryolesion onto the base of the septal tricuspid valve leaflet was also noted, and the leaflet base was thickened at 14 weeks postoperatively. However, this failed to produce detectable tricuspid valve dysfunction and is probably not clinically relevant to humans since the chondroid metaplasia that caused the most marked valve thickening is a healing phenomenon characteristic of the canine species.*

Although the nature of the dual atrioventricular node conduction phenomenon and associated AVNR tachycardia has been studied extensively, the exact location of the circuit for AVNR remains controversial. Many studies in man,12-16 as well as with animal preparations in vivo and in vitro,17, 18 have concluded that the reentry circuit is entirely confined to the atrioventricular node. However, it should be noted that in all of these studies periatroventricular nodal tissue could not conclusively be excluded from participation as the proximal common pathway of the AVNR circuit. Specifically, the method for determining that the atrium was not involved with the circuit of AVNR in all but one17 of these studies depended on documentation of atrioventricular dissociation or block during AVNR tachycardia14-16 or the inability of critically timed atrial premature depolarizations to interrupt AVNR.12, 13, 18 While these studies proved that involvement of the entire atrium is not required for AVNR, they fail to provide direct evidence for the noninvolvement of perinodal tissue. One study17 did map the lower atrial septum in a superfused rabbit heart preparation with use of a 10 point microelectrode brush. Based on isochronous maps of atrioventricular node reentry, in addition to noting an inability of an atrial premature depolarization to disrupt the reentrant circuit, the authors concluded that the majority of the atrium was not involved with the reentrant circuit. They did, however, concede that "It is possible that a small part of the atrium close to the atrioventricular node participated in the circuit."

The report of Pritchett et al.1 illustrates a case of the ablation of AVNR tachycardia with preservation of atrioventricular conduction in a patient after extensive dissection of the lower atrial septum, implying that at least a portion of the lower atrial septum is necessary for the reentrant circuit. This report led us to develop a reproducible method for the selective ablation of perinodal tissue in the lower atrial septum based on the hypothesis that even though the entire atrium is not required for the atrioventricular node reentry circuit, tissue immediately adjacent to the atrioventricular node in the lower atrial septum constitutes the proximal common pathway of AVNR and is necessary for reentry to occur. This hypothesis is supported by multiple successful cases of surgical ablation of AVNR tachycardia in man,5-8 as well as the early work of Mendez and Moe19 and the recent work of Inuma and Mazgalev and their colleagues20, 21 that describe the role of the periautoventricular nodal tissue in AVNR, as defined by mapping studies of AVNR in isolated superfused rabbit heart preparations.

One potential criticism of the present study is that, although the scar resulting from cryosurgery does not directly involve the atrioventricular node, indirect damage to the atrioventricular node from sublethal exposure to cold, cryoablation of the autonomic neural input to the node, or alteration of the blood supply to the node may have caused the electrophysiologic effects that we attribute solely to the cryoablation of perinodal tissue. A similar criticism of sharp dissection for the ablation of AVNR tachycardia was made by Scheinman22 and may be relevant to this study in view of the high sensitivity of nervous tissue to cryothermic injury and the late effects of cryothermia that may result in stenosis or occlusion of blood vessels. However, since the atrioventricular node remains histologically intact and atrioventricular node function returns to preoperative values by 14 weeks postoperatively,2, 4 we believe that any indirect effects on the node are far less likely an explanation of success of the procedure in ablating AVNR tachycardia than direct ablation of perinodal tissue. Furthermore, we also subjected a small group of animals to sympathetic blockade with reserpine or propranolol or to parasympathetic blockade with atropine before the cryosurgical procedure. The results of cryosurgery paralleled those noted in animals without autonomic blockade with atrioventricular conduction appropriately accelerated or slowed according to the medication given. Since the atrioventricular node remained appropriately responsive to autonomic manipulation, it is unlikely that our results are due to cryoablation of autonomic neural input to the atrioventricular node.

Another interesting point to be considered is the complexity added to our histologic analysis by the differences between the boundaries of the atrioventricular node as defined by morphologic or electrophys-

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*Hackel DB: Personal communication.
The compact nodule of small cells defined as the atrioventricular node in this study excludes the more loosely organized cells that surround the histologically defined atrioventricular node in the so-called transitional zone of the electrophysiologically defined atrioventricular node. Cells in the transitional zone have been shown to exhibit typical nodal potentials, as characterized by a slow upstroke, and these cells may have been included in the cryolesions. Nevertheless, the fact that the only observed long-term effect of the cryosurgical procedure on atrioventricular conduction is prolongation of the AH interval argues against an important role of these transitional cells in the ablation of the AVNR circuit.

We conclude that cryotherapy can be used to reproducibly ablate periatrioventricular nodal tissue while preserving the integrity of the atrioventricular conduction system. Although sharp dissection can achieve the same result as cryosurgery in ablating AVNR tachycardia, the ability to discern changes in conduction that occur with cooling before lethal damage ensues is a distinct advantage of cryothermia when it is used in immediate proximity to the atrioventricular node—His bundle. We believe that the cryosurgical technique described can successfully ablate AVNR tachycardia and possibly can be modified for the safe and reproducible ablation of Mahaim fibers or other abnormal conduction pathways that are immediately adjacent to the normal conduction pathways.

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References
17. Janse WJ, Van Capelle FJL, Freud GE, Durrer D: Circus movement within the A-V node as a basis for supraventricular tachycardia as shown by multiple microelectrode recordings in the isolated rabbit heart. Circulation 28: 403, 1971
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