In vitro assessment of induced phrenic nerve cryothermal injury

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BACKGROUND Phrenic nerve injury, both left and right, is considered a significant complication of cryoballoon ablation for treatment of drug-refractory atrial fibrillation, and functional recovery of the phrenic nerve can take anywhere from hours to months.

OBJECTIVE The purpose of this study was to focus on short periods of cooling to determine the minimal amount of cooling that may terminate nerve function related to cryo ablation.

METHODS Left and/or right phrenic nerves were dissected from the pericardium and connective tissue of swine (n = 35 preparations). Nerves were placed in a recording chamber modified with a thermocouple array. This apparatus was placed in a digital water bath to maintain an internal chamber temperature of 37°C. Nerves were stimulated proximally with a 1-V, 0.1-ms square wave. Bipolar compound action potentials were recorded proximal and distal to the site of ablation both before and after ablation, then analyzed to determine changes in latency, amplitude, and duration. Temperatures were recorded at a rate of 5 Hz, and maximum cooling rates were calculated.

RESULTS Phrenic nerves were found to elicit compound action potentials upon stimulation for periods up to 4 hours minimum. Average conduction velocity was 56.7 ± 14.7 m/s preablation and 49.8 ± 16.6 m/s postablation ($P = .17$). Cooling to mild subzero temperatures ceased production of action potentials for >1 hour.

CONCLUSION Taking into account the data presented here, previous publications, and a conservative stance, during cryotherapy applications, cooling of the nerve to below 4°C should be avoided whenever possible.

KEYWORDS Phrenic nerve injury; Atrial fibrillation; Cryoballoon ablation; Phrenic thermal tolerance; Compound action potential

ABBREVIATIONS AF = atrial fibrillation; **CAP** = compound action potential; **PNP** = phrenic nerve palsy

Introduction

Recently shown in the pivotal U.S. trial STOP-AF[1] and other multicenter trials,[2] phrenic nerve injury was noted as the highest non–access site-related complication of cryoballoon ablation for the treatment of drug-refractory atrial fibrillation (AF). This form of injury is not unique to cryoballoon ablation, yet a recent systematic literature review suggests it may occur more frequently in cryoballoon ablation than in radiofrequency ablation and may be highly susceptible to injury by high-intensity focused ultrasound.[3–5]

The right phrenic nerve generally follows the posterior or posterolateral aspect of the vena cava, and the left phrenic nerve passes over the marginal veins of the left ventricle. Both the right and left phrenic nerves terminate on the superior surface of the diaphragm; thus, injury to either phrenic nerve may result in diaphragmatic hemiparalysis or palsy.[6,7] Usually, only the right phrenic nerve has been reported to be injured during cryoballoon ablation, most frequently during ablation of the right superior pulmonary vein.[8,9] However, recent case reports have been published on left phrenic nerve injury,[6,10] and such occurrences may only increase with expanded cryoballoon adoption. Phrenic nerve palsy (PNP) is most commonly reported to occur during ablations of the right superior pulmonary vein. This may be due to the fact that the right inferior pulmonary vein is isolated before and the area may not be completely rewarmed, and/or that the right superior pulmonary vein is significantly closer to the phrenic nerve as demonstrated by Sanchez-Quintana et al[11] and by soon to be published data from our laboratory.

Reported rates of phrenic nerve injury vary in the literature, ranging from 4% to 17% for the first-generation balloon and 3.5% to 24% for the second-generation balloon (Table 1).[12–18] The reported time course of phrenic nerve functional recovery also differs considerably in the literature; the shortest recovery time periods reported are on the order of minutes whereas the longest recoveries extend to over a year.[19] Recently, a second generation of cryoballoons has become available for clinical use. The second-generation

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Table 1 Published incidences of phrenic nerve injury occurring clinically*

Cryoballoon studies	Incidence of PNP per procedure	Phrenic pacing	Resolution	Vein
Artic Front studies				
Vogt et al[12]	2% (12/605)		3–9 months	
Neumann et al[2]	8% (26/346)	Yes	Less than 1 year, 2 before procedure end	
Packer et al[1]	11% (29/259)		25/28 within 144 ± 27 days	
Jackson et al[13]	8% (15/200)	Yes, SVC	2 hours to 12 months, 9 before procedure end	
Martins et al[3]	5.6% (7/126)		Resolution within 0.5–20 minutes	
Casado-Arroyo et al[14]	6% (5/80)		Resolution before discharge	
Fürnkranz et al[15]	3% (1/30)		By 3-month follow-up	Right sided
Arctic Front advanced studies				
Martins et al[3]	13.6% (22/162)		Resolution within 0.5–20 minutes	RSPV/RIPV
Metzner et al[16]	3.5% (4/115)		As late as 10 months	RSPV
Casado-Arroyo et al[14]	20% (8/41)		Resolution by 7 months, except 1	
Fürnkranz et al[15]	3% (1/30)		1 day postprocedure, not related to ablation	Left sided
Multi and other balloon studies				
Bordignon et al[17] (total)	6% (7/140)	Yes, SVC	Recovered by 6-month follow-up	RSPV
Cryo	6% (4/70)			
Laser	4% (3/70)			
Horton et al[4] (total)	19% (7/37)	Yes, SVC		RSPV
Cryo	16% (1/6)			
HiFU	22% (4/18)			
Laser	15% (2/13)			
Sohara et al[18] (hot balloon)	1% (1/100)	Not in this patient, otherwise yes	Within 3 months	

HiFU = high-intensity focused ultrasound; PNP = phrenic nerve paralysis/palsy; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein; SVC = superior vena cava.

*Studies include (1) >200 patients, (2) those comparing balloon generations/modalities, or (3) the highest and lowest reported PNP with ArticFront Advanced. Studies are ordered from greatest to least number of patients. Entries left blank were not specified in the journal publication.

balloon has a different cooling profile that covers the distal half with more cooling jets to promote uniform cooling.[20] The cooling power of this catheter has also been increased, and, as evidenced by Table 1, PNP may be easier to cause. Use of phrenic monitoring and avoidance of deep seating of the new-generation cryoballoon should be mainstays of the treatment paradigm.

It may be the case that the nerves were not actually experiencing the temperatures produced by the probe. Nevertheless, the authors of these studies should be commended for their efforts to elucidate phrenic thermal tolerance. Again, 2 sources of error may have influenced the studies. One potential error is that the cooling device temperatures were monitored rather than the nerve temperatures themselves. Therefore, the exact temperatures that the nerves reached were unknown, but more than likely they were close to the probe temperatures. The second error to consider is that, in many experimental apparatuses, thermal contact resistances (ie, microscopic air pockets from surface roughness, etc) can significantly alter the degree of heat actually exchanged between 2 objects, which may also play a role.

From a clinical perspective, because a phrenic nerve typically is not in direct contact with an intracardiac ablation catheter and there is a large degree of convective warming from blood flow occurring, these nerves most likely are experiencing cooling excursions to damaging temperatures for short durations. Yet, one has to consider the clinical aspects of a cryoprocedure. Treatments generally extend for 3 to 4 minutes, and there is lag time associated with conduction of cooling to the nerve, indicating the nerve will only be cooled for a fraction of the treatment time. Therefore, the study we performed and present here focused on short periods of cooling in an attempt to determine the minimal amount of cooling that may terminate nerve function.

Methods

Castrated male Yorkshire Cross swine (average weight 85 ± 10 kg) were used for these studies, which were approved by the University of Minnesota's Institutional Animal Care and Use Committee. Anesthesia was induced with telazol and thiopental. Animals then were intubated and mechanically ventilated, maintaining a $Paco_2$ of 40 ± 2 mm Hg, with a surgical level of anesthesia maintained with isoflurane (>1.2 MAC). Access to the thoracic cavity was achieved via a medial sternotomy. The left and/or right phrenic nerves were carefully dissected from the pericardium and connective tissue, and then placed in modified Krebs-Henseleit buffer at room temperature. The fatty sheaths and remaining connective tissues were dissected from the nerves using a stereomicroscope. Nerves were then placed in a nerve-recording chamber (MLT016, ADInstruments, Dunedin, New Zealand), which was modified by the addition of a thermocouple array. The array consisted of a Styrofoam block with four 40-gauge T-type thermocouples (no. 5SRTC, Omega Engineering, Stamford, CT) embedded 2.5 mm apart. The apparatus was placed