Atrial Fibrillation Ablation using Cryothermy: Comparisons with Radiofrequency

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Rationale for Nonpharmacologic Treatment of Atrial Fibrillation

Atrial fibrillation is the most common symptomatic arrhythmia with a total incidence of 2.2 million cases in the United States alone [1]. The number of people with atrial fibrillation has been, and is expected to continue increasing; in fact, the number of affected people in the US alone is expected to more than double by the year 2050. [2, 3] The increased incidence is due in part to the increasing age of the population and also due to the increasing number of myocardial infarction survivors and perhaps also to the obesity epidemic (4). Additionally, there are data from the European community showing a similar incidence of atrial fibrillation in that cohort (5) Recent large randomized studies, including the AFFIRM and RACE trials, have failed to show an advantage of pharmacologic attempts at sinus rhythm restoration over rate control. All of these studies suggest that rate control may be a reasonable or even preferable option. However, there are two countervailing factors, a known increased mortality associated with atrial fibrillation and persistent symptoms associated with the condition. First, population based studies have consistently shown an increased mortality by a factor of 1.5-1.9 times [6] in patients with atrial fibrillation as compared to matched patients without atrial fibrillation (7). This suggests that the absence of improved or reduced mortality in the rhythm control arms of the randomized studies may be due to combination of very little success in restoration and maintenance of sinus rhythm, and/or the possible toxic effects of the medications. It remains to be proven, however, that successful restoration of sinus rhythm over the long term would result in a return of mortality reduction. A single center nonrandomized study from Milan, Italy (8) did suggest that atrial fibrillation ablation resulted in reduced mortality when compared to a matched group treated medically but it is not clear if the ablation and medically managed groups really were equivalent in underlying risks. The study from Taiwan published by Hsi E.H. (9) compared a nonrandomized group of elderly patients undergoing either catheter ablation for atrial fibrillation or AV junction ablation and permanent pacing. There were approximately 35 patients in each group. The freedom from symptomatic atrial fibrillation was better in the AV junction ablation group than in the ablation group, 100% vs 80%. However persistent atrial fibrillation was present in follow-up in close to 70% of patients in the AV junction ablation group versus only 8% in the pulmonary vein isolation group. Perhaps as a consequence of the persistent atrial fibrillation, heart failure

developed in over 50% of subjects in the AV junction ablation group compared to only about 25% of subjects in the pulmonary vein isolation group. New York heart function class was also better in follow up in the pulmonary vein isolation group. There were more deaths in the AV junction ablation group (16%) than the pulmonary vein isolation group (8%), although this was not statistically significant due to the small size of the study.

Even in the absence of potential mortality benefit for maintaining sinus rhythm, many patients with atrial fibrillation remain intolerably symptomatic. Dorian et al (10) compared quality of life in patients with atrial fibrillation to two groups, healthy subjects and patients undergoing percutaneous transluminal coronary angioplasty (PTCA). Patients with atrial fibrillation had markedly increased symptom frequency as well as symptom severity not only compared to healthy subjects but also compared to PTCA patients. Functional capacity was similar in the AF and PTCA groups and different from the healthy subjects.

In 1998 Michelle Haissaguerre (11) made the breakthrough observation that pulmonary venous ectopic foci are the most common trigger for episodes of atrial fibrillation and that catheter ablation of these foci can cure atrial fibrillation in some patients. This led to a reappreciation of previous anatomic work (12) that showed muscle sleeves extending from the left atrium on to the pulmonary veins in a variable but complex pattern.

Catheter Based Cryoablation of Atrial Fibrillation

A number of ablation energy modalities have been used in an effort to eliminate atrial fibrillation, either in a percutaneous approach via catheter techniques or with a surgically based approach. These include unipolar radiofrequency energy, irrigated and non irrigated bipolar radiofrequency energy, microwave, laser, cryothermy, and ultrasound. While the safety and efficacy of radiofrequency ablation has made it the mainstay of ablative therapy for cardiac arrhythmias, there are possible advantages to cryothermal ablation.

Initially used by Guiraudon and Klein (13) for treatment of the Wolff-Parkinson-White syndrome, cryoablation works by exploiting the Joule Thompson effect to create temperatures ranging from -30 to -90 degrees centigrade at the catheter/probe tissue interface. Cooling of the myocardium to these temperatures results in effective ablation lesions via several mechanisms (14). The first effect is the result of extracellular ice formation which occurs at temperatures of minus 20 degrees Celsius. This leads to an osmotic shift and hence an escape of water from the intracellular space to

the extracellular space. The second effect occurs at temperatures of about minus 40 degrees Celsius at which point intracellular ice begins to develop resulting in injury to the intracellular organelles. The third effect is related to vascular injury with cessation of blood flow due to freezing at the local level and then with thawing further injury is caused by hyperemic response and vascular leak. As with other energy sources such as radiofrequency energy, there is a gradient of injury due to a gradient of temperature. Cryothermal ablation can be either permanent, reversible, or in some cases even progressive due to vascular and other injuries after the conclusion of the cryoablation. In general, lesions produced at temperatures of minus 30 degrees or warmer, unless there is a prolonged application of energy, are reversible. This is an extremely attractive feature of cyroablation as it allows for “cryomapping” in areas where there is a higher risk of injury to the normal conducting system. It is important however to remember cryoablation lesions have been demonstrated cause some degree of permanent injury at temperatures as warm as minus 10 degrees with applications as brief as thirty seconds. For these reasons one must still remain vigilant with respect to catheter position as well as surface and intracardiac electrogram recordings to avoid unwanted injury. (15)

In the early years of atrial fibrillation ablation pulmonary vein stenosis occurred quite frequently with reported incidences ranging from roughly 8 percent to as much as 30 percent [2, 16], since at that time it was common to ablate within the pulmonary veins themselves. While contemporary techniques which focus on confining ablation to the pulmonary venous antra and or ostia have reduced the incidence of pulmonary vein stenosis to roughly five percent or less, it has not eliminated it altogether [17]. It also seems that there is a ”learning curve” effect with respect to this issue, suggesting that, at least in part, the higher incidence seen is some studies was due to a lesser volume of experience. For example Packer et al reported on a series of roughly 200 consecutive AF ablation patients from the Mayo Clinic. In their series they found a PV stenosis rate of 11% in the first hundred patients whereas the rate in the second hundred patients was only one percent. [18]

The mechanism of pulmonary vein stenosis is poorly understood but may due to contraction of collagen and other cytoskeletal elements seen with radiofrequency ablation, importantly, cryoablation do not cause similar cytoskeletal changes. A canine model of pulmonary vein stenosis (19) used radiofrequency catheter application beginning with ablation inside the pulmonary veins and withdrawing the catheter 2 to 3 mm every 30 seconds until the catheter re-entered the left atrium. These ablations were repeated several times using 2 minute RF applications in each pulmonary vein with temperatures between 60 and 80 degrees centigrade.

Clearly these techniques did not mimic what is sought with clinical catheter ablation in this era and the histologic affects seen may not be equivalent or assure the exact same mechanism as clinical episodes of catheter ablation. Species differences may pertain as well, of course. Nevertheless, histopathology showed replacement of muscle, which had necrosed by collagen, disruption of the internal elastic lamina, and contraction of the elastic lamina resulting in luminal narrowing. In contrast, cryoablation in a dog model (20) despite delivery of lesions within the pulmonary veins did not result in any instances of pulmonary vein stenosis. An additional argument for cryoablation was provided by work from Khairy (21) who found that in an animal model, thrombus formation was much more prevalent and extensive with radiofrequency ablation than with cryoablation. The incidence of thrombus formation approached 80% with RF ablation and was approximately 30% with cryoablation. These investigators found that cryoenergy had a smoother more sharply demarcated lesion where RF lesions were less well defined and had irregular margins; while the reasons for this are not entirely worked out, it seems to be due at least in part to the fact that the cryocatheter adheres to the myocardium during ablation thereby negating and “to and fro” motion seen with RF catheters.

More recently Sarabanda and colleagues evaluated the use of a cryothermal balloon in the canine model (22). They used a non deflectable double lumen 10 french catheter which had on its distal end a cryoenergy balloon with a maximal diameter of 23mm. The catheter was delivered to the left atrium via standard techniques and was then advanced into the right and left superior pulmonary veins of eight mongrel dogs in sequence. Once the catheter was in the respective vein, the balloon was inflated to achieve occlusion of the vein and cryoenergy was delivered for either 4 or 8 minutes with a minimum temperature of minus 80 degrees centigrade. After the application of energy, a lasso catheter was used to confirm electrical isolation. Two of the eight dogs were immediately euthanized and their hearts explanted for histologic analysis, the remaining six dogs underwent contrast enhanced spiral CT analysis of the pulmonary vein diameter at baseline, 4 weeks and 16 weeks after the procedure. The authors were able to successfully isolate 83% of the treated veins with this technique. Of note is the fact that all of the failures were in veins where ICE revealed an incomplete occlusion of the vein by the cryo balloon. While an immediate decrease in the PV diameter post ablation was noted, serial CT follow up showed no significant difference from baseline to 4 and 16 weeks respectively. The authors suggest that this may have been a result of local edema which then resolved.

A third impetus for considering cryoablation emanated from the startling case reports published by Pappone (23) detailing 2 cases of life-threatening or fatal left atrial esophageal fistula occurring

after circumferential pulmonary vein radiofrequency catheter ablation. These cases recalled earlier surgical reports especially using unipolar radiofrequency energy leading to endocarditis, air embolisms, stroke, or massive gastrointestinal bleeding. Recently Teplitsky and colleagues compared the effects of radiofrequency and cryoablation with respect to their ability to alter esophageal luminal temperature (24). The authors used a hybrid cryo and RF approach in 10 patients with atrial fibrillation while monitoring real time changes in esophageal luminal temperature with an inserted probe. They essentially began with an RF technique with an 8 mm tip catheter at energies of 35 – 60 and switched to a 6mm cryocatheter any time an increase in esophageal temperature was noted. The results revealed that a temperature rise was evident in all patients at some point during the initial RF ablation. Similarly they all exhibited esophageal cooling with cryoablation. Also of note was that there was a thermal latency observed with both modalities, meaning that the maximal temperature increase or decrease was often realized after cessation of energy delivery. There were no complications noted, and to date, no reports of atrio-esophageal fistula with a purely cryoablative technique.

Tse (25) studied the biophysics of cryoablation in a blood perfused swine thigh model. These investigators found that the lesion size was proportional to freeze duration, tipped orientation, number of freeze-thaw cycles, target temperature and contact area. They found that a 10 mm tip electrode was able to circumvent variations in catheter tip orientation and give larger lesion diameter, volume and depth, especially when coupled with a lower tip electrode temperature. Lesion depth was most closely related with tip electrode temperature with a more negative tip temperature generating deeper lesions. Ripley et al (26) explored the time factor of cryoablation in an animal model using calves treated with epicardial beating heart cryoablation while using a circulating body temperature saline bath. These investigators found that the majority of the cryolesion was produced in the first 30 seconds of the lesion suggesting a more efficient approach could be developed than initial studies using dual 5-minute cryothermal applications.

In 2003 Tse and coworkers publishing on behalf of the European and Hong Kong atrial fibrillation feasibility trial (27) reported the results from 3 centers treating 52 patients with atrial fibrillation. Patients had failed 2 or more antiarrhythmic drugs and had 2 or more symptomatic episodes of atrial fibrillation within a 6-week period. Patients had normal to slightly enlarged atrial size and most had normal ejection fraction. The targeted pulmonary veins were isolated in 94% of patients totaling 3 ± 0.7 veins per patient. The procedures were long at 7.5 ± 2 hours with ablation times approaching 2 hours on average. An average of 48 lesions per patient and 14 lesions per vein, with a greater number in the superior veins, were required. They also reported complications in

several patients, including 1 transient phrenic injury, 1 pulmonary embolism 2 months after the procedure with a subtherapeutic INR and 1 peri-procedural stroke. An additional patient had a 75% left inferior pulmonary vein stenosis; a technical failure of the cryoablation console had occurred and this patient was treated with radiofrequency ablation in the left inferior pulmonary vein. Twenty-nine out of 52 patients at 6-month followup reported no AF with 18 of the 29 being off antiarrhythmic drugs and an additional 7 of the 23 were improved with greater than 50% reduction in episodes. Pulmonary vein stenosis other than the patient treated with radiofrequency ablation was not noted at 3 or 12 months of follow up compared to baseline CT scans. Quality of life improved markedly in the 52% of patients without AF recurrence and marginally in the overall group.

Additionally, U.S. feasibility data were published by Hoyt et al (28) who reported on 32 patients with a mean age of 57 years having paroxysmal atrial fibrillation. These patients had also failed 2.2 ± 1.1 Class I or III antiarrhythmic drugs and had a mean ejection fraction of 0.57 with the lowest EF being 0.44. Segmental ostial pulmonary vein based isolation was performed using double 5 minute cryoablation lesions. The end point of the procedure was elimination of all pulmonary vein potentials in the targeted veins. The right inferior pulmonary vein was treated in 6 of the 32 patients. Patients received an event monitor for 1 month before and for 6 months after cryoablation. The primary end point of this study was event monitor data for 1 month at baseline and for 6 months post ablation. Eighteen of the 22 patients undergoing a single cyroablation procedure (82%) were free of AF at 6 months. Indeed preliminary data kindly provided by Dr. L. Rodriguez from the Maastricht group in the Netherlands [personal communication], showed that AF recurrences continue to decrease for even beyond 6 months after cryoablation. In the U.S. feasibility trial, complications were reported in several patients including respiratory depression, transient leg weakness, transient sinus node swelling, femoral pseudoaneurysm and endocarditis with an incidence of 1 each. After radiofrequency ablation, a TIA was noted in 1 patient. Follow up of the extension of the U.S. feasibility study including 15 patients, found acute success in 14 of 15 patients with follow up still in progress.

A larger, very important atrial fibrillation ablation trial is also currently in progress. This is the ICE-PAF study, which is targeting 160 patients and employing a 1 to 1 randomization between cryoablation and medical management. The study is occurring at 25 sites in the United States. Patient enrollment characteristics include paroxysmal atrial fibrillation patients only with patients having atrial fibrillation for longer than 7 days being excluded. Exclusions include left atrial size ≥ 50 mm, previous stroke or prior AF ablation. Prior to randomization, patients must have failed at

least 1 antiarrhythmic drug but not more than 4. Prior to randomization, patients undergo a baseline CT scan to serve as a follow up for pulmonary vein stenosis. Patient randomized to cryoablation undergo ablation procedure as soon as it can be scheduled. In the other arm, patients assigned to the medical treatment arm receive a new or increased dose of a class I or class III antiarrhythmic drug. If the medical treatment arm patients continue to have episodes of atrial fibrillation after 3 months of medical treatment (documenting 3 or more episodes occurring beyond the 90 day point) they are eligible for early cross over to catheter ablation. The study end points are acute and chronic safety and efficacy of cryoablation compared to medical management. This study will be an important study, not only for cryoablation, but also for catheter ablation of AF in general where very few large multicenter randomized studies, if any, have been performed. The ICE-PAF trial is sponsored by the CyoCor Company (San Diego, CA) and is using a 6 mm, 10 French cryoablation catheter. Cryo temperatures down to about –80 degrees Celsius are typically achieved with this system and 2-minute freezes are delivered. The acute end point of the procedure is isolation of all 4 pulmonary veins plus cavo tricuspid isthmus block.

While one advantage of cryoablation is catheter stability due to development of the ice ball and locking the catheter in contact with the tissue during the ablation, this is one effect that tends to result in longer procedure duration than radiofrequency ablation where the catheter can be dragged at any point during the delivery of the RF energy. One approach to expediting the cryoablation procedure was pioneered by the CryoCath Company in Montreal, Quebec, Canada. Vogt and colleagues from Germany reported on 37 patients treated with the Arctic Circler™ which is a self-expanding cryoablation catheter that can expand a maximum of 30 mm in diameter and achieve temperature of –75 degrees Celsius ablating around the pulmonary vein orifice. The 37 patients (26 men and 11 women) were age 58 ± 8 years and refractory to antiarrhythmic therapy. Thirty-four of the patients had paroxysmal atrial fibrillation and 3 had persistent atrial fibrillation that had occurred for a mean of 7 years. Twenty-four patients were undergoing their first atrial fibrillation ablation and 13 had undergone ablation 3 months or more previous because of AF recurrence. Of 118 pulmonary veins treated with the Arctic Circler™, 53% (63 pulmonary veins) were able to be isolated with the Arctic Circler™ alone. In the remaining 47% of pulmonary veins (55 pulmonary veins) additional lesions were required with a standard-type cryoablation catheter. The left upper pulmonary vein required additional focal cryolesions in 64% of veins. Pulmonary vein stenosis was not present in any veins at a mean of 5.5 months. After 1.5 cryoablation procedures per patients, of 17 patients who had reached the 6-month follow up point, 7 had no recurrence and 7 had a remarked reduction in AF burden with clinical improvement calculated at 82%. In 7 patients who underwent repeat ablation, 50% of the targeted veins either remained

isolated as confirmed by lasso catheter mapping techniques or had only 1 to 2 focal pulmonary vein sleeves needing ablation. Approximately 4 to 6 four-minute lesions were required with the Arctic Circler™ to achieve the approximately 55% success in isolating pulmonary veins.

At the Heart Rhythm Society Annual Scientific Sessions in 2004, Doshi and colleagues reported multi-center results with a balloon cryoablation catheter developed by CryoCath. (29) Enrolled at 3 centers, 24 patients underwent pulmonary vein isolation using the Arctic Circler™ plus standard design cryoablation catheters at 3 centers. In a non-randomized separate study conducted at 2 centers, 20 patients underwent pulmonary vein isolation using a novel Cryo balloon ablation catheter (CryoCath) as well as the Arctic Circler™ and/or a focal standard design catheter if necessary. The acute procedural success was similar at 98 and 95% respectively. Pulmonary vein imaging by MR at three months revealed no pulmonary vein stenosis in either group. For patients who had reached the six month follow-up point, including all 24 patients in the Arctic Circler™ group and 13 of 20 patients in the Cryo Balloon Group, subacute or chronic success was significantly better in the Cryo balloon group. Of patients in the Cryo Balloon Group, 70% of patients were in sinus rhythm without anti-arrhythmic drugs compared with 20% in the Arctic Circler™ group. In addition, including patients in sinus rhythm either off or on anti-arrhythmic drugs the Cryo balloon group had a higher success rate of 85% compared to 45% for the Arctic Circler™ group.

More recently Vogt and colleagues reported their results with 68 patients using the Arctic Circler 30mm catheter (30). Their cohort was largely comprised of patients with paroxysmal atrial fibrillation and no structural heart disease however it also included 10 patients with structural heart disease and 6 with persistent atrial fibrillation. They used the Arctic Circler to deliver 4 minute ablations encircling the PV ostia. They then used a 6 or 8 mm tip cryocatheter to “close the gaps”. They followed their patients for 16±9 months for recurrence of atrial fibrillation. Twenty-one patients required repeat ablation and in those patients 73% were found to have recurrent conduction at the previous ablation lines whereas 27% did not have recurrent pulmonary vein conduction. During follow up 52% remained AF free, 28% had a significant reduction in AF burden and 20% of patients remained unchanged. When the group of persistent atrial fibrillation was excluded they found an 88% efficacy at 16 months for elimination or reduction in AF. The average number of procedures per patient was 1.4 and importantly no evidence of PV stenosis was found.

Doug Packer’s group at the Mayo clinic recently reported at the Heart Rhythm Society in 2005, (31) their animal model using balloon cryoablation to look for CT evidence of pulmonary vein stenosis.

They found slight narrowing in several veins, but no progression or significant pulmonary vein stenosis in 6 dogs. At the Heart Rhythm Society 2005 Scientific Sessions, Avitall and colleagues at the University of Illinois reported results using a Cryo balloon ablation in the left atrium (32) regarding the effect on esophageal tissue in 4 dogs. The authors delivered 42 lesions with a catheter temperature averaging –77° Celsius for 2 minutes. Esophageal temperatures were recorded and the lowest average intra-esophageal temperature was 94° Fahrenheit. The lowest temperatures were recorded in the esophagus during left inferior pulmonary vein and posterior left atrial wall ablation. Pathologic evaluation of the esophagus one week after ablation did reveal hemorrhaghic lesions up to 19 mm in diameter in the adventitia and external muscular coat of the esophagus without injury to the submucosa or mucosa. In 2005 Heike and Doll evaluated the effects of left atrial endocardial and epicardial ablation in an ovine model using microwave, laser, cryo and both unipolar as well as bipolar radiofrequency energy. They found the most dramatic degree of esophageal injury occurred after endocardial cryolesions and endocardial unipolar radiofrequency lesions. [33]

Comparison of Cryothermal and Radiofrequency for Atrial FibrillationAblation

While both cryoablation and radiofrequency have been used to ablate atrial fibrillation the comparative efficacy of the two modalities is unclear. Catheter based cryoablation has mainly been performed in several multi-center trials, sponsored by either CryoCor or CryoCath, using either a conventional shaped ablation catheter or a circular or balloon type catheter. Radiofrequency ablation has only been performed with a standard shaped ablation catheter. All of the radiofrequency experience has been single center or several center, off-label case series or several randomized trials [21, 34-36]. A multicenter, clinical trial using irrigated radiofrequency catheter ablation is currently underway in an effort to obtain an indication for atrial fibrillation ablation. There are no head to head comparisons between cryoablation and radiofrequency. The reported trials differ considerably in terms of patient composition, number of centers and prior experience as well as follow-up methodology making comparisons difficult. Almost all series have relatively short follow-up. Cryoablation trials reviewed above report success rates that are generally similar to or somewhat lower than the radiofrequency ablation reports, although few multi-center RF reports are available. [21, 34-40].

The safety of the ablation procedure is obviously critical and a multicenter worldwide registry recently found about a 6% serious complication rate [42]. Pulmonary vein isolation using cryothermal techniques may have a lower occurrence of pulmonary vein stenosis than RF ablation. [17, 18, 42, 43] One animal study could not induce pulmonary vein stenosis with cryothermal

ablation. [44] Atrial-esophageal fistula has not been reported with cryoablation, although the reported experience is much smaller with cryoenergy than RF ablation. In an animal study, Ripley and colleagues [45] could not produce atrial-esophageal fistula despite direct application of cryoenergy to the esophagus, whereas this could be replicated with radiofrequency based ablation directly on the esophagus. In vitro data suggest cryoenergy may activate the coagulation system less than radiofrequency based ablation, although clearly stroke can occur with a cryoablation approach due to air embolism or thrombosis of sheaths or catheters even if the cryolesions themselves might be less thrombogenic. Cardiac tamponade or other vascular insults can occur with either approach.

In conclusion, transvenous endocardial based cryoablation approaches is a promising technique for non-pharmacologic treatment and potential cure of atrial fibrillation. Further technological development of catheters and more extensive larger series with randomization to medical therapy and longer-term follow-up are necessary to determine the true clinical utility, success and complication profile of the this technique.

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