Cryotherapy, or the use of freezing temperatures to elicit a specific tissue response, has a long history of safe and effective use in medicine. Cryothermal ablation results in discrete homogenous lesions that are sharply demarcated, with preserved ultrastructural tissue integrity and low propensity for thrombosis.1–3 Its unique safety profile is well established. Although cryoenergy has been used in modern surgical procedures for more than 50 years, the development of steerable percutaneous cryocatheters represents a more recent landmark in the history of clinical cardiac electrophysiology. This review examines the current state of knowledge regarding cryothermal catheter ablation. Pertinent features related to biophysics and biomechanics of cryothermic tissue injury are summarized, potential advantages compared with standard radiofrequency (RF) catheter ablation (RFCA) are discussed, and the contemporary clinical experience with transcatheter cryoablation is reviewed. Practical aspects relevant to clinical electrophysiologists are emphasized throughout.

A Brief Background

The concept of cooling to treat medical disorders dates back to the ancient Egyptians, where the use of hypothermic therapy was described in ≈1600 to 3000 BCE.4 More recently, iced saline was used in the mid-1800s for the treatment of carcinomas of the breast and uterine cervix, followed by the topical use of liquid oxygen, nitrogen, and hydrogen for superficial carcinomas in the early 1900s. Preceded by a near half-decade of experimentation, the modern era of cryosurgery was initiated by Cooper and Lee5 in 1961 when vacuum-insulated cryosurgical probes cooled by liquid nitrogen (−196°C) were introduced. Novel cryoprobes were subsequently developed using thermoelectric cooling (Peltier effect) or cooling by the Joule–Thomson effect (ie, from the expansion of a highly compressed nonideal gas into a region of low pressure). Whereas the thermoelectric method (cooling by the passage of a direct current through dissimilar metal junctions) offered limited thermal efficiency, the Joule–Thomson effect was relatively efficacious. Thus, the inclusion of pressurized gases as refrigerants (nitrous oxide, carbon dioxide, and argon) spurred the development of diverse instruments (thin needle-like probes, clamp devices, catheter probes, and balloon structures), which in turn expanded the indications of cryoenergy for the treatment of a wide spectrum of diseases including dermatologic, prostatic, hepatic, gynecologic, ophthalmologic, neurosurgical, and oncological disorders.

In the 1970s, rigid hand-held cryothermal ablation probes were adapted for cardiac surgical applications.5–8 Although insights gained from the extensive cryosurgical experience invaluably contributed to the conceptualization of the modern transvenous catheter cryoablation system, significant engineering advances were required to achieve the safe and effective delivery of pressurized cryorefrigerant to the tip of a steerable percutaneous catheter. The current transvenous cryocatheter system consists of a hollow shaft deflectable catheter with a closed distal end containing a cooling electrode tip, 3 proximal ring electrodes, and a proximal thermocouple. The catheter is connected to a specialized external console via an electric cable and gas umbilical tube. Ablation is realized through the delivery of pressurized cryorefrigerant to the catheter tip via an ultraline injection tube. Just before release into the tip, the cryorefrigerant is further pressurized through a restriction tube that is designed to maximize the temperature drop via the Joule–Thomson effect. This accelerated liquid-to-gas phase change results in rapid cooling of the distal tip. The cryorefrigerant then absorbs heat from the surrounding tissue before returning to the console via a second coaxial return lumen maintained under vacuum.

Although the core tenets of its design have remained largely unchanged, the transvenous cryoablation catheter has undergone significant evolutionary advances throughout the past decade. The refrigerant was modified from Halocarbon 502 (Freon) to Genetron AZ-2067 to the current nitrous oxide to allow lower temperatures and faster freezing rates. Catheter diameter was reduced from 9F to 7F; whereas larger electrode tip sizes were introduced (4 mm to 6 mm to 8 mm). Steering mechanisms were developed and refined. Finally, with the introduction of innovative catheter configurations (focal, linear, circular, and balloon-based apparatuses), diverse clinical applications have been explored. Thus, within a relatively brief time frame, the initial 9F focal cryoablation catheter with slow cooling and a temperature limit of −50°C was transformed into the modern 7F version with rapid cooling and achievable temperatures below −80°C.

Lesion Formation

By the early 1960s, a synthesis of experiments predominantly focused on frostbite and cryopreservation demonstrated that the major mechanisms of cold-induced cellular and tissue injury result from a combination of (1) direct cellular damage attributable to the deleterious effects of ice crystal formation...
during hypothermia and (2) ischemic cell death attributable to microcirculatory failure and subsequent vascular stasis during thawing. As currently understood, the complex mechanisms underlying cryothermal lesion formation can be divided into sequential stages: freeze, thaw, hemorrhage and inflammation, and replacement fibrosis.

During the first phase, progressive hypothermia results in a slowing of cellular metabolism. Ion pumps lose transport capabilities, and the intracellular pH becomes more acidic. In general, the early effects are transient, provided that the duration of nonfreezing cooling does not exceed a few minutes. Thereafter, progressive cooling is associated with the formation of ice crystals. Initially, ice crystals form exclusively in the extracellular space as the tissue temperature drops below −15°C. Progressive cooling to below −40°C results in the formation of intracellular ice crystals. Whereas ice crystals are associated with mechanical cellular disruption, the predominant mechanism of cellular injury is biochemical. The formation of ice crystals in the extracellular space results in it becoming relative hypertonic. In an attempt to re-establish osmotic equilibrium, there is a compensatory egress of water from the intracellular to the extracellular space, with subsequent cellular shrinkage. Furthermore, the newly established osmotic gradient precipitates a diffusion gradient between extracellular and intracellular spaces, resulting in the net movement of H⁺ ions out of the cell, and the migration of solute ions into the cell. Concomitant increase in the intracellular saline concentration with a reduction in intracellular pH results in cellular protein damage, enzyme system impairment, and adverse effects on lipoprotein components of the plasma membrane. Of all the cytoplasmic components, the mitochondria are particularly sensitive and are the first structures to have irreversible damage.

On completion of the freezing phase, the tissue passively returns to body temperature (thawing effect). This second phase induces cellular damage through a combination of 2 mechanisms. First, recrystallization and coalescence of intra- and extracellular ice crystals increase the osmotic damage and generate shear forces, which further disrupt tissue architecture. Second, restoration of microcirculatory function is associated with a hyperemic vascular response characterized by hemorrhage and inflammation, which further disrupt tissue architecture. Specifically, blood vessel walls become porous, leading to increased capillary permeability, and subsequent interstitial edema. This vascular congestion, combined with endothelial-injury induced platelet aggregation and microthrombi formation, culminates in vascular obliteration and ischemic cellular necrosis. As such, whereas the central region subjected to the coldest freezing temperatures undergoes direct cellular damage, surrounding microvascular injury results in the extension of tissue destruction.

The final phase of cryoinjury begins concurrent to thawing and is characterized by reactive inflammation, followed by tissue repair and replacement fibrosis. During the subsequent weeks, these processes culminate in the generation of a mature lesion, which has a distinct, well-circumscribed central region of dense fibrosis surrounded by a narrow border zone of variable cellular death (attributable to microvascular injury and apoptosis).

Theoretical Benefits of Cryotherapy
RF energy has proven to be highly effective in the treatment of supraventricular and ventricular arrhythmias with a reasonably low complication rate. Despite its prominence in the field of electrophysiology, it has several inherent disadvantages. As a result, alternative energy sources have been developed, of which cryothermal ablation has positioned itself at the forefront. When compared with RF energy, cryothermal ablation offers several theoretical advantages.

Catheter Adhesion
In contrast to RFCA, where the catheter remains free-floating during ablation, cryothermal ablation is associated with freeze-mediated catheter adhesion to the target tissue. This catheter–tissue attachment provides several advantages. First, freeze-mediated catheter stability facilitates the efficacious ablation of technically challenging regions, such as sites where contact is difficult to maintain. Second, cryoadhesion eliminates the brushing effect, whereby RF energy is applied to the target and surrounding nontarget tissue because of cardiac and respiratory motion. It can be expected that increased catheter stability would result in less collateral damage to nearby critical structures, such as the conduction system, epicardial coronary arteries, or pulmonary veins (PVs). Finally, catheter adhesion allows for the dynamic assessment of lesion efficacy. Specifically, the ablation lesion can be safely delivered during arrhythmia, or programmed electric stimulation, as there is no concern for catheter dislodgement on arrhythmia termination.

Reversible Suppression
Another major advantage of cryotherapy is the ability to assess the safety and efficacy of a potential ablation lesion site dynamically and prospectively, because a period of reversible tissue inhibition obligatorily precedes irreversible tissue destruction. Whereas extreme freezing (ie, tissue temperatures colder than −50°C) results in near instantaneous permanent tissue injury, the degree of permanent cellular damage with relatively warmer tissue temperatures (−10°C to −25°C) is directly related to duration of freezing. Thus, the use of milder freezing temperatures and shorter ablation times facilitates the assessment of clinical effect at the target lesion site (so-called efficacy mapping), and confirmation that a target site does not result in adverse clinical outcomes (so-called safety mapping). For example, when the atrioventricular (AV) node is subjected to mild hypothermia (probe temperature 0°C to −30°C; tissue temperature 0°C to −5°C) a temporary loss of function (ie, heart block) will result until the tissue is rewarmed. Whereas partial damage and delayed recovery will occur with longer exposures to tissue temperatures in the −5°C to −15°C range, permanent AV block can be produced by maintaining a tissue temperature of −20°C for 3 to 4 minutes (probe temperature −75 to −80°C).

It is important to note that although safety and efficacy mapping may be realized through the use of the CryoMapping feature on the CryoConsole (Medtronic CryoCath LP, Pointe-Claire, Canada), a dynamic cryomapping process will naturally occur during the course of a cryoapplication as the hypothermic wavefront spreads centrifugally from the catheter tip to the surrounding tissue.

As such, vigilant monitoring
must be maintained when treating critical (eg, perinodal) substrates, because tissues not initially affected have the potential to undergo reversible suppression as the cryolesion continues to expand during cryoablation.

Lesion Characteristics, Endothelial Integrity, and Associated Thrombosis

In comparison with RFCA, lesions associated with focal cryothermal ablation have a smaller surface area attributable, in part, to cryoadhesion-induced loss of the bruising effect, with no difference in lesion depth (Figure 1). Histologically, cryothermy results in a dense, homogeneous fibrosis that is clearly demarcated from normal myocardium (Figure 2). In contrast, the hyperthermic injury induced by RF results in diffuse cellular destruction characterized by intralesional hemorrhage and ragged edges less clearly demarcated from underlying normal myocardium. In addition, although devitalized, lesions produced by cryothermal ablation are associated with preservation of ultrastructural integrity, an observation that is attributed to the remarkable resilience of fibroblasts and collagen fibers to hypothermia. Preservation of tissue ultrastructural integrity should theoretically result in a lower risk of myocardial perforation, esophageal injury, and aneurysmal dilation. It may be speculated that lesions produced with cryoablation should be less arrhythmogenic (given that distinct border zones are less susceptible to spontaneous depolarization) and associated with a lower incidence of venous or arterial stenosis (given the minimal tissue contraction observed with lesion healing). However, it is important to note that when applied to immature myocardium, the rate of expansion of cryoablation lesions is similar to RFCA.

In addition, cryothermal ablation lesions are associated with minimal endothelial surface disruption and a lesser degree of platelet and the coagulation cascade activation when compared with RFCA. Preclinical studies have demonstrated a significantly lower incidence of overlying thrombus (30.1% versus 75.8% despite the use of aspirin and heparin), and a lesser thrombus volume with cryothermal ablation compared with RF. Moreover, in contrast to RF lesions where the extent of hyperthermic tissue injury was positively correlated with thrombus bulk, cryoablation lesion dimensions were not predictive of overlying thrombus volume. Taken together, these effects suggest a possible pathophysiologic mechanism as to why cryoablation is less thrombogenic than RFCA.

Safety Near Coronary Arteries

Catheter ablation within the coronary venous system may be required for focal atrial tachycardias, epicardial accessory pathways, and for completion of linear left atrial lesions. The use of intracoronary sinus RFCA has been associated with venous injury (including acute perforation and tamponade, and delayed fibrosis/stenosis), acute or subacute venous thrombosis, and collateral damage to the esophagus and adjacent coronary arteries. In contrast, and in addition to the extensive surgical experience that has demonstrated the safety of cryothermal ablation adjacent to coronary arteries, preclinical studies of catheter-based cryoablation suggest a lower incidence of vascular injury, a reduced propensity for thrombosis, and a lower risk of coronary artery injury/stenosis when cryoablation is performed within or adjacent to the coronary sinus. These observations have been attributed to the resilience of fibroblasts and collagen fibers to hypothermic injury and to the protective heating effect of coronary arterial blood flow.

Pain-Free Ablation

Patient discomfort may occur with RF through direct stimulation of cardiac sensory nerves or pericardial or collateral visceral irritation, particularly when ablating in the posterior left atrium, coronary sinus, or posterior cavo-tricuspid isthmus. This may require increased sedation or analgesia. In contrast to RFCA, cardiac cryoablation is not associated with patient discomfort. Thus, for select procedures associated with substantial patient discomfort, the use of cryoablation may theoretically result in lower anesthetic and analgesic requirements. This is especially relevant for electrophysiology laboratories that do not use general anesthesia.

Clinical Applications

Ironically, the first clinical use of catheter-based cryothermal ablation was for AV node ablation in patients with recalcitrant rapid atrial fibrillation (AF). Since publication of the initial feasibility case series, indications for cryoablation have expanded.

AV Nodal Reentrant Tachycardia

Although acute and long-term success rates with RF for slow pathway ablation in AV nodal reentrant tachycardia (AVNRT) are consistently high, the occurrence of complete AV block

<table>
<thead>
<tr>
<th>RF – 4 mm</th>
<th>CRYO – 4 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>+70°C - 50W • 60 seconds</td>
<td>-75°C • 1 x 4 minutes</td>
</tr>
<tr>
<td>5.7 mm</td>
<td>4.3 mm</td>
</tr>
<tr>
<td>Area ~ 25 mm²</td>
<td>Area ~ 14 mm²</td>
</tr>
<tr>
<td>Vol ~ 89 mm³</td>
<td>Vol ~ 49 mm³</td>
</tr>
</tbody>
</table>

Figure 1. Comparison of radiofrequency (RF) and cryothermal (Cryo) ablation lesions created with a 4 mm tip catheter. Although the depths of the 2 lesions are comparable, the RF lesion has a greater surface area (P=0.0018), and thus a greater volume (P=0.0585). Reproduced with permission from Khairy et al.
necessitating pacemaker implant remains relevant (0.8%–2.0%). In contrast, inadvertent permanent high-degree AV block has yet to be reported with cryoablation for AVNRT. Although preferences and practice patterns continue to vary, this superior safety profile has prompted some centers, including ours, to adopt cryoablation as the treatment of choice for AVNRT. Cryoablation also allows for the electrophysiological evaluation of slow pathway conduction during mapping and ablation. Once the cryocatheter becomes adherent, atrial extrastimulus testing may be performed without risk of catheter dislodgment. End points such as disappearance of an A2-H2-jump, arrhythmia termination, and noninducibility may be assessed during the cryoapplication.

In contrast to the well-established exceptional safety profile, some debate remains about long-term efficacy. During the past 15 years, several studies have described outcomes for cryoablation of AVNRT. In a systematic review that combined 22 published studies (including 2654 patients), cryothermal ablation had a high procedural success rate (95%; range, 85%–99%) that was comparable with RFCA (95%–98%). Long-term freedom from recurrent arrhythmia with cryoablation was reported to be 89% (range, 81.3%–98%), which was lower than historical observations with RF (3%–7% recurrence). Although historical comparisons between observational studies are fraught with potential biases, 11 comparative studies between cryothermy and RFCA for AVNRT (8 retrospective observational studies and 3 prospective randomized studies; Table 1), reported comparable acute success rates. Although the longer term recurrence rate was statistically similar in 7 of the 11 studies, there was an overall trend that favored RFCA. Procedural duration was globally similar, with a shorter fluoroscopy time with cryoablation.

Importantly, the risk of recurrence with cryoablation is sensitive to several modifiable factors, which are largely based on the fact that cryoablation for AVNRT differs from RFCA in several respects. For example (1) precise mapping is more critical than with RF attributable to the more focused nature of the cryolesion. (2) The ideal ablation site is generally more proximal (more atrial) and superior (higher up the septum

### Table 1. Studies Comparing Cryothermal With Radiofrequency Ablation for the Treatment of AVNRT

<table>
<thead>
<tr>
<th>Year</th>
<th>Cryo Catheter</th>
<th>Patients</th>
<th>Acute Success</th>
<th>Chronic Success</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cryo RF P</td>
<td>Cryo RF P t/u</td>
</tr>
<tr>
<td>Randomized</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kimman et al42,43</td>
<td>2004</td>
<td>4 mm</td>
<td>30 33</td>
<td>93 91</td>
</tr>
<tr>
<td>Zrenner et al47</td>
<td>2004</td>
<td>4 mm</td>
<td>100 100</td>
<td>97 98</td>
</tr>
<tr>
<td>Deisenhofer et al40</td>
<td>2010</td>
<td>6 mm</td>
<td>251 258</td>
<td>96.8 98.4</td>
</tr>
<tr>
<td>Nonrandomized</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collins et al39</td>
<td>2006</td>
<td>4 mm</td>
<td>57 60</td>
<td>95 100</td>
</tr>
<tr>
<td>Gupta et al31</td>
<td>2006</td>
<td>4 and 6 mm</td>
<td>71 71</td>
<td>85 97</td>
</tr>
<tr>
<td>Avari et al36</td>
<td>2008</td>
<td>4 and 6 mm</td>
<td>38 42</td>
<td>97 95</td>
</tr>
<tr>
<td>Chan et al38</td>
<td>2009</td>
<td>6 mm</td>
<td>80 80</td>
<td>97.5 95</td>
</tr>
<tr>
<td>Opel at al46</td>
<td>2010</td>
<td>6 mm</td>
<td>123 149</td>
<td>93 95</td>
</tr>
<tr>
<td>Papagiannis et al45</td>
<td>2010</td>
<td>6 mm</td>
<td>20 20</td>
<td>90 100</td>
</tr>
<tr>
<td>Schwagten et al48</td>
<td>2011</td>
<td>4 mm</td>
<td>150 124</td>
<td>96.5 96</td>
</tr>
<tr>
<td>Chan et al37</td>
<td>2012</td>
<td>8 mm</td>
<td>20 20</td>
<td>90 95</td>
</tr>
</tbody>
</table>

AVNRT indicates atrioventricular nodal reentrant tachycardia; and NS, not significant.
The ability to test slow pathway conduction during ablation allows for an assessment of relative proximity of the catheter tip to the target tissue. An early time to effect is associated with a higher likelihood of delivering an efficacious lesion. Repeated freeze–thaw cycles produce faster and more extensive tissue cooling, which extend the lethal effect of ablation to the outer limit of the frozen volume. Larger catheter tip dimensions (6 mm and 8 mm) have been associated with increased procedural and long-term efficacy (ie, 2.5-fold lower recurrence rate with a 6- versus 4-mm electrode tip). The usual end points used with RFCA do not seem to apply with cryoablation. Specifically, an accelerated junctional rhythm is rarely observed. Moreover, whereas persistent AV nodal physiology without more than a single echo beat on isoproterenol is an acceptable end point for RFCA, it remains unresolved whether complete abolition of the slow pathway is required after cryoablation. Long-term efficacy outcomes may continue to improve as operators gain experience, the procedure is further refined, and catheter designs evolve.

Other Arrhythmia Substrates Amenable to Focal Cryoablation

Given its favorable safety profile, cryoablation for arrhythmia substrates in high-risk anatomic locations has likewise been investigated. Typically these include focal tachycardias or accessory pathways in perinodal or peri-Hisian locations, and arrhythmia substrates near or within the coronary sinus (Figure 4). In the case of septal accessory pathways, acute procedural success with cryoablation has been observed in 90% to 95%, with no reported case of permanent inadvertent AV block. Although long-term success seems lower than for AVNRT (70%–80%), cryoablation offers a safe therapeutic option for arrhythmia substrates deemed to be associated with an unacceptably high risk of AV block using other energy modalities.

The use of cryothermy has also been explored for the treatment of atrial flutter. In comparison with conventional RFCA, a similar freedom from recurrence (86% versus 87% with RFCA at 11.6 months of follow-up; P=0.84) and fluoroscopy time (27.5 versus 27.3 minutes with RFCA; P=0.28) have been reported with cryothermal ablation. Although the procedural time has been reported to be significantly longer with cryothermal ablation (171.7 versus 134.5 minutes with RFCA; P<0.001), cryothermy results in a lesser degree of patient discomfort than RFCA.

Atrial Fibrillation

Focal point-by-point RFCA of AF to isolate PV electrically has shown considerable success in treating paroxysmal AF. However, the procedure is complex, time-consuming, and highly dependent on operator competency. It is subject to inherent difficulties associated with creating contiguous curvilinear lesions using techniques originally developed for discrete ablation. Moreover, major complications include cardiac perforation, collateral damage to adjacent structures (esophagus, phrenic nerve, and aorta), and PV stenosis. As such, considerable effort has been directed toward developing technologies to achieve safer and more effective PV isolation (PVI) that is less reliant on operator dexterity.

Early attempts at PVI with cryoenergy were performed in a manner similar to contemporary RFCA. This strategy was associated with arguably prohibitive ablation and procedural durations (mean cryoablation time 65±39 minutes per vein; mean total procedural time 7.5±2 hours) and a disappointing overall success rate (6% freedom from recurrent AF at 18±9 months of follow-up). Thereafter, specialized catheters such as the curvilinear self-expanding 7F Arctic Circler (Medtronic CryoCath LP) were developed. Although isolation could be achieved in 91% of targeted PVs (41/45 PVs; 4 PVs requiring focal RFCA for isolation), only 22% of patients (4/18) remained arrhythmia-free after 14.8±6.2 months of follow-up. Efforts
to further refine the cryothermal energy delivery system led to the creation of a balloon catheter (Artic Front, Medtronic CryoCath LP, Pointe-Claire, Québec, Canada).67

The basic design and function of the cryoballoon (CB) catheter differs from the focal catheter in 3 major respects. First, instead of a rigid cooling electrode tip, the distal CB catheter consists of dual polyurethane and polyester balloons. Second, the CB is larger than the focal catheter (10.5F outer diameter versus 7F for the focal catheter) and requires the use of a 15F deflectable delivery sheath (FlexCath, Medtronic CryoCath LP). Third, the CB is deployed using an over-the-wire technique with a central lumen that permits a guide wire for positioning/support, or a small diameter circular diagnostic catheter for monitoring of PV potentials, as well as contrast injection to ensure adequate positioning.

Efficacy and Safety of CB Ablation for Paroxysmal AF
To date, more than 35,000 CB-based ablation (CBA) procedures have been performed worldwide (Figure 5). In a recent meta-analysis, we reported that CBA resulted in a high procedural success rate (>98% of patients achieving complete
Table 2. Studies Comparing Cryoballoon-Based Ablation With Other Rhythm Control Methods for the Treatment of Atrial Fibrillation

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-Up</th>
<th>Blanking</th>
<th>Comparator</th>
<th>Freedom From Recurrent AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Packer et al&lt;sup&gt;69&lt;/sup&gt;</td>
<td>12 mo</td>
<td>3 mo</td>
<td>AAD</td>
<td>69.9% (114/163) 7.3% (6/82) &lt;0.001</td>
</tr>
<tr>
<td>Linhart et al&lt;sup&gt;70&lt;/sup&gt;</td>
<td>6 mo</td>
<td>1 mo</td>
<td>Irrigated RF</td>
<td>45% (9/20) 55% (11/20) NS</td>
</tr>
<tr>
<td>Kojodjojo et al&lt;sup&gt;71&lt;/sup&gt;</td>
<td>12 mo</td>
<td>3 mo</td>
<td>Irrigated RF</td>
<td>77% (69/90) 72% (38/53) NS</td>
</tr>
<tr>
<td>Kühe et al&lt;sup&gt;72&lt;/sup&gt;</td>
<td>12±3 mo</td>
<td>3 mo</td>
<td>Irrigated RF</td>
<td>88% (22/25) 92% (23/25) NS</td>
</tr>
<tr>
<td>Herrera Siklody et al&lt;sup&gt;73&lt;/sup&gt;</td>
<td>Median 12 mo (3–29 m)</td>
<td>3 mo</td>
<td>Irrigated RF</td>
<td>63% (19/30) 80% (24/30) NS</td>
</tr>
<tr>
<td>Sorgente et al&lt;sup&gt;74&lt;/sup&gt;</td>
<td>12.6±6 mo</td>
<td>2 mo</td>
<td>Irrigated RF</td>
<td>65.7% (23/35) 65.5% (19/29) NS</td>
</tr>
<tr>
<td>Abdelaal et al&lt;sup&gt;75&lt;/sup&gt;</td>
<td>8±3 mo</td>
<td>NR</td>
<td>Duty-cycled multielectrode RF</td>
<td>83% (30/36) 72% (26/36) NS</td>
</tr>
<tr>
<td>Hofmann et al&lt;sup&gt;76&lt;/sup&gt;</td>
<td>6 mo</td>
<td>2 mo</td>
<td>Mesh ablator</td>
<td>69% (25/36) 44% (19/43) &lt;0.05</td>
</tr>
<tr>
<td>Sorgente et al&lt;sup&gt;74&lt;/sup&gt;</td>
<td>12.6±6 mo</td>
<td>2 mo</td>
<td>Magnetic guided RF</td>
<td>65.7% (23/35) 66.7% (20/30) NS</td>
</tr>
</tbody>
</table>

AAD indicates antiarrhythmic drugs; NR, not reported; NS, not significant; and RF, radiofrequency.

PVI and 1-year freedom from recurrent AF (1-year single procedure off antiarrhythmic drugs [AAD] success of 60%; 73% if a 3-month blacking period was included).<sup>67</sup> In comparison, longer term freedom from recurrent AF after RFCA has been reported to be 50% to 64% after a mean follow-up of 14 months in the meta-analysis by Calkins et al<sup>61</sup> and 40% at 1 year in the prospective long-term cohort study by Weera-sooriya et al.<sup>58</sup> Thus, the early experience suggests that CBA is efficacious for maintaining sinus rhythm at 1 year in patients with paroxysmal AF. Cost-effectiveness analyses are yet to be performed.

The first randomized trial comparing AAD therapy and CBA, the Sustained Treatment of Paroxysmal AF (STOP-AF) trial, enrolled 245 patients with paroxysmal AF and randomized them (2:1) to CBA (n=163) or AAD therapy (n=82).<sup>69</sup> Balloon-only PVI was realized in 90.8% of participants, with an overall procedural success (≥3 PVs isolated) of 98.2% when focal cryoablation touch-ups were added. Nineteen percent of patients required a repeat procedure within the 3-month blanking period. At 12 months of follow-up, 69.9% of the CB group versus 7.3% of the AAD group were free of recurrent AF (<0.001). Moreover, there was a statistically significant improvement in symptoms and quality of life in the CBA group.

CB ablation likewise compares favorably with other contemporary AF ablation technologies (Table 2).<sup>69–76</sup> In general, CBA is associated with procedure and fluoroscopy times that are somewhat longer than duty-cycled multielectrode RFCA but shorter than conventional irrigated-RFCA.<sup>70–74</sup> Despite these procedural differences, the efficacy outcomes did not differ between CBA and conventional irrigated-RFCA, magnetic-guided RF, and duty-cycled multielectrode RFCA.<sup>70–74</sup> The rate of major complications with CBA is relatively low (<3%–5%) in comparison with irrigated-RFCA and duty-cycled multielectrode RFCA (5%–6%).<sup>61–63,77</sup> With CBA, the reported rate of peri-procedural stroke or transient ischemic attack is 0.3%, cardiac tamponade 0.6%, and groin complications 1.8%. Corresponding complication rates with RFCA are 0.3 to 0.9% for stroke or transient ischemic attack, 0.8 to 1.3% for cardiac tamponade, and 1 to 1.5% for groin complications.<sup>67</sup> Longer term complications, such as symptomatic PV stenosis and esophageal injury, occurred infrequently with CBA (0.17% for symptomatic PV stenosis and 2 suspected cases of atrial-oesophageal fistula).<sup>67</sup>

Although the global complication rate with CBA seems comparable with conventional irrigated-RFCA, 2 complications merit further discussion. Phrenic nerve palsy (PNP) is the most frequently observed complication, occurring in 6% (range, 3%–11%).<sup>21,67,78</sup> Although PNP has been observed with other energy sources, it occurs more frequently with balloon-based technologies.<sup>61–63</sup> Fortunately, the majority of cases are transient with <0.4% of PNP persisting more than 1 year.<sup>67</sup> The incidence of persistent PNP nevertheless seems to be approximately twice that reported with RFCA (0.17%) even despite the interruption of ablation when less vigorous diaphragmatic excursion is detected by continuous abdominal palpation during phrenic nerve pacing.<sup>62</sup> Although alternative monitoring techniques, such as continuous diaphragmatic visualization and auditory monitoring of diaphragmatic contraction, have been proposed, the use of diaphragmatic electromyography represents a potentially more sensitive technique.<sup>73</sup> During phrenic nerve pacing, a reliable diaphragmatic signal (the diaphragmatic compound motor action potential, or CMAP) can be easily recorded using surface electrodes. In a recent animal study, we demonstrated that a 30% reduction in diaphragmatic CMAP amplitude predicted impending hemidiaphragmatic paralysis (presaging diaphragmatic paralysis by abdominal palpation by 31±23 seconds).<sup>78</sup>

The other complication that warrants a more detailed discussion is systemic thromboembolism. Cerebral ischemic events are a recognized complication of percutaneous endocardial left atrial catheter ablation. In the recent systematic review of CBA, the incidence of thromboembolic complications, including peri-procedural stroke or transient ischemic attack, was 0.32%, which compares favorably with conventional RFCA (0.3%–0.9%).<sup>61–63</sup> Recognizing that not all embolic cerebral events lead to clinical symptoms, recent studies quantified microembolic signals as a surrogate of subclinical disease. In a series of 30 patients, a significantly lower incidence of microembolic signals was noted in the middle
cerebral arteries with CBA and irrigated-RF catheters when compared with conventional nonirrigated RF.79 Similarly, 2 recent studies comprising a total of 182 patients compared the incidence of silent cerebral ischemic lesions after PV isolation with duty-cycled multielectrode ablation, conventional irrigated-tip RFCA, and CBA. In both studies, the incidence of new silent cerebral ischemic lesions was found to be significantly higher with multielectrode ablation (37.5%–38.9%) when compared with irrigated RF (7.4%–8.3%) or CBA (4.3%–5.6%).22,23 Whereas the clinical importance of cerebral ischemic lesions after interventional cardiac procedures remains to be demonstrated, an association with neuropsychological decline has been described.80–82 In short, a single CBA procedure for paroxysmal AF results in high acute and medium term efficacy rates with a relatively low incidence of complications. The most frequent complication, PNP, is often transient and may be preventable. Moreover, rates of ischemic thromboembolic complications seems lower with CBA than other technologies, which may reflect maintenance of endocardial integrity and lower risk of thrombosis.

**Efficacy of CB Ablation for Persistent AF**

CB-based PVI alone for patients with persistent AF has been associated with high rates of arrhythmia recurrence (45% 1-year freedom from recurrent AF),67 consistent with the RF literature, suggesting that more extensive ablation beyond PVI may be required.83 In this patient population, the left atrial substrate plays a prominent role in AF maintenance. Staged ablation strategies involving additional linear ablation and complex fractionated atrial electrogram-based ablation have yielded superior results.84 Recently, a small hypothesis-generating study by Mansour et al84 investigated an approach of CB PVI combined with conventional irrigated-RF based substrate modification in 22 participants with persistent AF. The authors explored the usability of a stepwise approach beginning with CB-based PVI followed by complex fractionated atrial electrogram-based ablation in patients with persistent or inducible AF (N=19). Thereafter, linear ablation of the roof, mitral isthmus, and septum was performed if ablation did not terminate AF or if the arrhythmia changed to an atrial tachycardia or flutter (N=10). After a mean follow-up of 6 months, freedom from recurrent AF off AAD after a single procedure was a remarkable 86%. The authors concluded that a combined CBA and RF approach is feasible with favorable short-term maintenance of sinus rhythm. Prospective studies are required to determine whether the safety and efficacy of a hybrid CBA approach merits adoption in clinical practice.

**Conclusion**

The development of steerable percutaneous cryocatheters represents a more recent landmark in the history of cardiac electrophysiology. Evolving from the initial treatment of focal tachycardias to simultaneous circumferential PV isolation, cryothermal catheter therapy represents an important and safe addition to the armamentarium of cardiac electrophysiologists.

**Sources of Funding**

Dr Khairy is supported by a Canada Research Chair in Electrophysiology and Adult Congenital Heart Disease.

---

**Disclosures**

Drs Dubuc, Andrade, and Khairy have received research support or honoraria from Medtronic.

**References**


Key Words: ablation ▪ arrhythmia ▪ catheter ablation ▪ electrophysiology
Catheter Cryoablation: Biology and Clinical Uses
Jason G. Andrade, Paul Khairy and Marc Dubuc

_Circ Arrhythm Electrophysiol_. 2013;6:218-227
doi: 10.1161/CIRCEP.112.973651

_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/6/1/218