

# Cryoablation for atrial fibrillation

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Cryoballoon ablation for the treatment of atrial fibrillation has established itself as an effective and efficient modality for achieving pulmonary vein isolation. Over the past 13 years more than 100,000 Cryoballoon ablation procedures have been performed with the first to fourth generation cryoballoons. Over that time there have been significant advances in our understanding regarding the optimal procedural techniques. The purpose of this "topic in review" is to focus on the practical aspects of performing a Cryoballoon ablation procedure, within the context of the contemporary literature. Specifically there is a focus on how contemporary

Atrial fibrillation (AF) is a chronic and progressive disorder characterized by exacerbations and remissions. Multiple large observational studies and randomized controlled trials have shown that catheter ablation, which is centered on electrical isolation of triggering foci within the pulmonary veins (PVs), is superior to antiarrhythmic drug (AAD) therapy in maintaining sinus rhythm and improving AF-related symptoms and quality of life.<sup>1</sup> Because the results of catheter ablation can be limited by arrhythmia recurrence, considerable effort has been directed toward developing technologies to achieve safer and more durable pulmonary vein isolation (PVI), including the development of dedicated catheters capable of achieving PVI with a single ablation lesion (eg, Arctic Front cryoballoon; Medtronic, Minneapolis, MN). The purpose of this article is to discuss practical procedural considerations related to cryoballoon-based PVI within the context of the contemporary evidence base.

## Occlusion is key

The cornerstone of an effective cryoballoon-based PVI procedure is the achievement of PV occlusion with the cryoballoon. Upon PV occlusion, the operator is able to achieve the combined goal of maximizing the surface area of cryoballoon–left atrium (LA) myocardial contact and ensuring colder freezing temperatures. Failure to fully occlude the targeted

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studies can inform clinical decision making and ensure operators are able to perform a safe and effective procedure.

**KEYWORDS** Ablation; Atrial fibrillation; Cryoablation; Pulmonary vein isolation

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PV results in convective heating from the intervening blood flow, which reduces the efficiency of freezing and the durability of the lesion. This was eloquently demonstrated by a study in which total occlusion of the PV was shown to successfully predict PVI with a positive predictive value of 93%–98%, whereas a persistent leak had a negative predictive value for successful PVI of 92%–100%.<sup>2</sup>

Typically, assessment of balloon occlusion is performed with injection of 50% diluted contrast (Figure 1). In addition to assessing occlusion, contrast injection provides information regarding the relative position of the inflated balloon with respect to the LA–PV junction. Alternative methods for assessing the adequacy of balloon occlusion include color flow Doppler on intracardiac echocardiography or PV pressure assessment (ie, transition from LA to pulmonary arterial pressure waveforms).<sup>2,3</sup> The latter methods offer the advantage of dynamic assessment of occlusion during the cryoapplication, a period when contrast venography is not possible due to freezing of the central lumen of the cryoballoon catheter.

Of note, although every effort should be made to achieve optimal cryoballoon occlusion before ablation, a small localized leak or delayed contrast emptying may be acceptable (Supplemental Video 1). This is because the transition from balloon inflation to cryoablation is associated with increased balloon pressure (from 2–4 to 18 psi) and increased balloon diameter (1.5 mm), which may improve the seal (Supplemental Video 2).

## Management of inadequate seal

Variability in ostial geometry and LA–PV orientation may impede adequate circumferential cryoballoon–PV contact. Specifically, increasing magnitudes of PV ovality, the

### KEY FINDINGS

- Decreasing the cryoablation dose results in significantly shorter ablation procedures and left atrial dwell times, with reduction in fluoroscopy exposure mostly related to omission of the bonus freeze.
- Dose-limitation strategies have not been definitively proven to reduce the rates of complications directly related to cryoablation.
- Overreduction in cryoablation dose may compromise efficacy, particularly in relation to ablation of the left pulmonary veins.

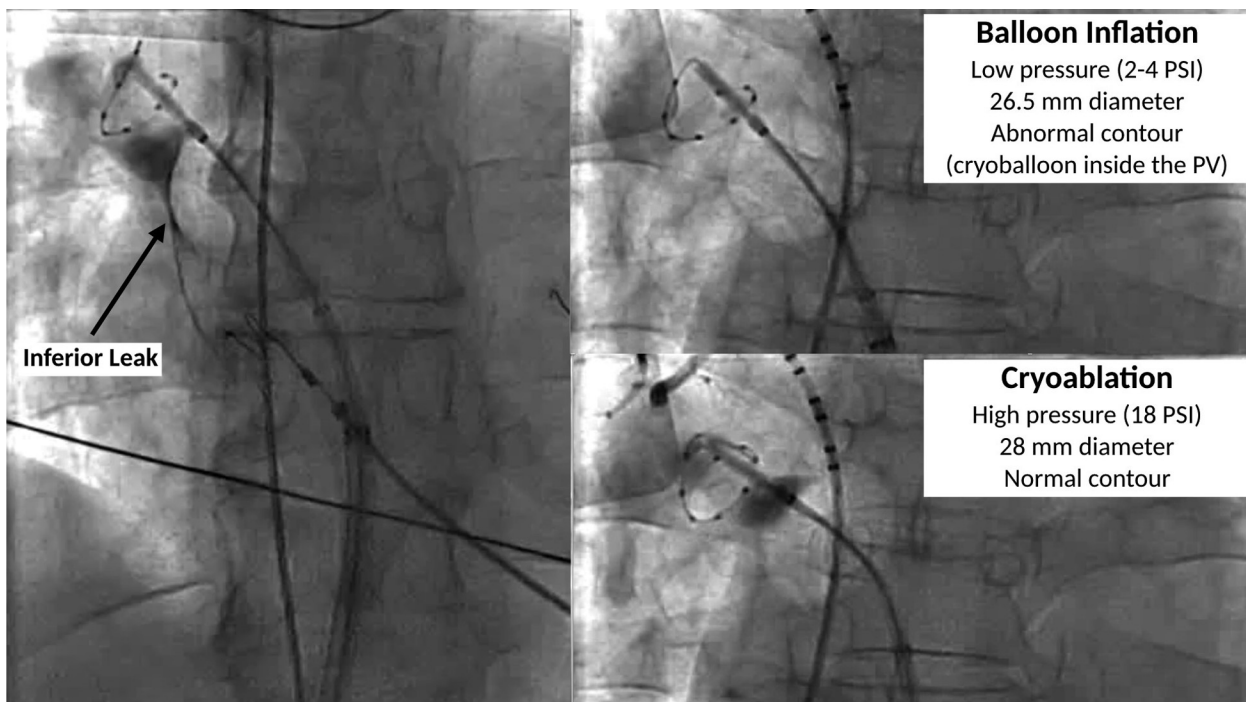
presence of a “sharp” ridge between the left PVs and the appendage, and a more inferior PV angulation can result in impaired circumferential contact, leading to inadequate PV occlusion.<sup>4,5</sup> In these cases, the occlusion can be improved through sheath/catheter rotation, sheath/catheter flexion, and/or repositioning of the guidewire/mapping catheter in order to reorient the balloon’s axis (Figures 2A and 2B).

In general, advancement of the cryoballoon catheter/sheath results in cranial movement of the cryoballoon. For the superior PVs, this can result in improved contact along the LA roof. However, for the inferior veins, this results in a noncentral alignment of the cryoballoon in relation to the PV axis, which favors contact along the

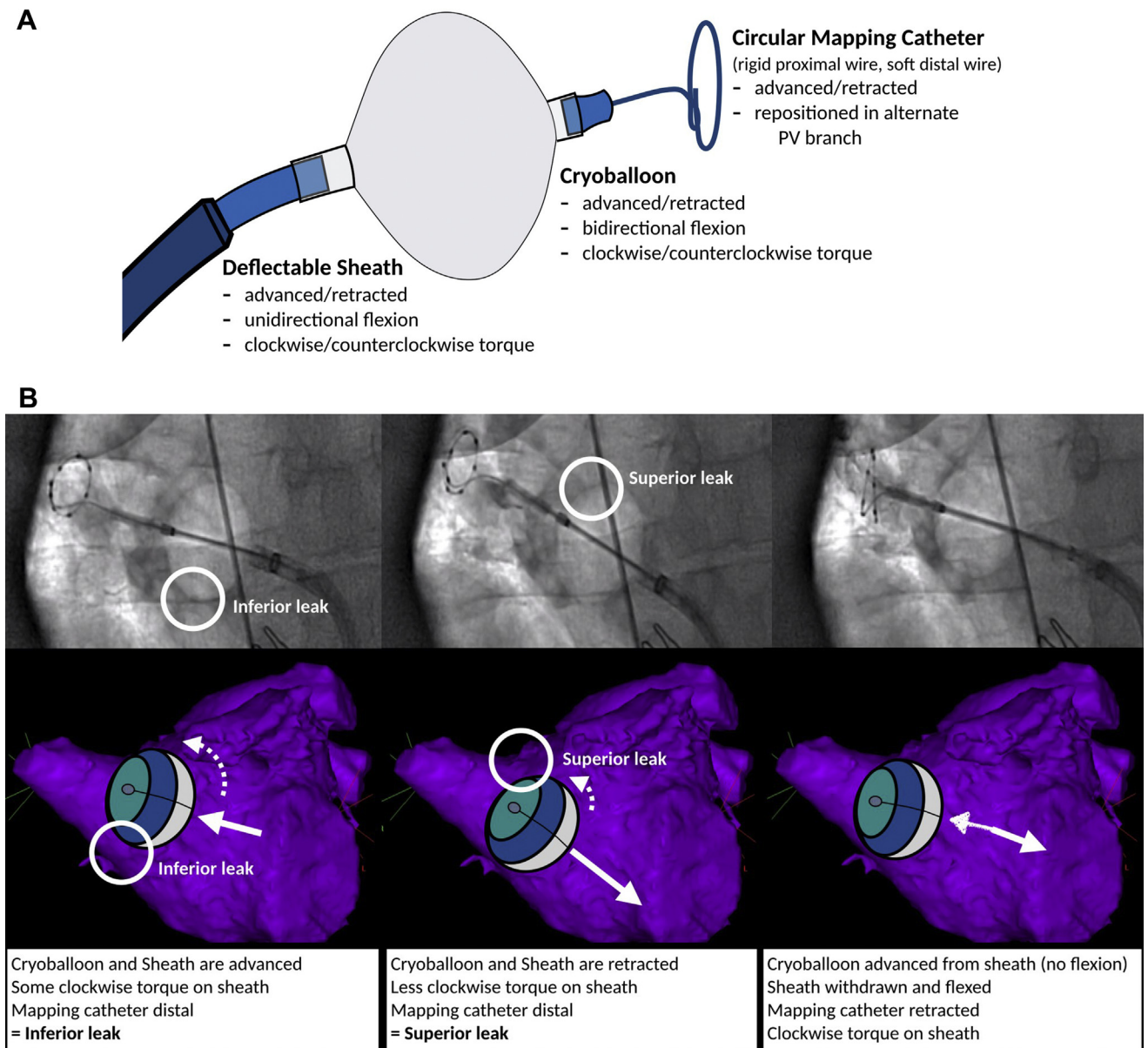
superior (carinal) circumference at the expense of contact inferiorly. If the torsional or angular maneuvers fail to improve the seal, then more sophisticated techniques may be required.<sup>6</sup>

In patients with an early branching inferior PV, the “hockey stick” maneuver can be used to optimize tissue contact along the inferior PV circumference (Figure 2C). This is performed by engaging the early branching inferior PV with the guidewire/mapping catheter. The sheath is then maximally bent and positioned in the superior–posterior LA. Advancement of the balloon results in it being propelled inferiorly to PV antrum/ostium. In patients with a late branching inferior PV, the “pull-down” technique can be used to optimize tissue contact along the inferior PV circumference (Figure 2D). With this technique, the balloon is first placed at the PV ostium in a position to optimize contact along the superior carinal circumference. Cryoablation is then initiated regardless of the presence of an inferior leak (Supplemental Video 3). After the cryoballoon has adhered to the endocardium (approximately 30–60 seconds after initiation of ablation), the balloon and sheath can be gently withdrawn in order to seal the inferior margin of the PV. If the technique is performed properly, the temperature curve will display an abrupt decrease in returning vapor temperature, indicating the inferior leak has been closed (Figure 2D, bottom). Of note, this maneuver must be performed with care, as excessive force has been postulated to result in risk of severe vascular damage.

Although important, these maneuvers were more of a necessity with the first-generation cryoballoons because of the



**Figure 1** Proximal seal technique. **Left:** Leak at the inferior aspect of the right superior PV. **Top right:** With advancement, the inflated cryoballoon advances into the PV, which visibly deforms the contour. The balloon is then withdrawn into the left atrium while the small-caliber circular mapping catheter is left inside the PV for support. **Bottom right:** After initiation of ablation, the balloon is immediately advanced to the left atrial–PV junction but is no longer able to enter into the tubular PV due to the increased balloon pressure and larger diameter after ablation initiation. PV = pulmonary vein.



**Figure 2** Strategies to manage an inadequate seal and improve PV occlusion. **A:** Components of the cryoballoon apparatus and possible manipulations that can be performed by the operator. **B:** Attempted ablation of the right superior PV. **Left:** Direct engagement with the cryoballoon and sheath. The mapping catheter is positioned slightly distal for support. The cryoballoon and sheath are coaxial with the tubular PV, with clockwise torque to push the apparatus anteriorly. The cryoballoon balloon and sheath pressure result in an inferior leak. **Middle:** Withdrawal of the cryoballoon and sheath, with relaxation of the clockwise torque in an effort to close the inferior leak. This results in a superior leak. **Right:** Withdrawal of the mapping catheter, which orients the nose of the balloon more inferiorly. The sheath is withdrawn and flexed such that the orifice is pointing to the middle of the PV in a coaxial alignment. The cryoballoon is then advanced from the sheath with a more horizontal alignment to engage the superior and inferior PV circumference. **C:** “Hockey stick” technique. This technique is best used to close an inferior leak in an early branching PV. After the early branch is engaged with the mapping catheter/guidewire, the maximally bent sheath is advanced, which enables the balloon to be propelled inferiorly to the PV antrum. **D:** “Pull-down” technique. This technique is best used to close an inferior leak. In this case, ablation is initiated with the balloon deviated cranially to ensure adequate carinal contact. After 30–60 seconds (ie, after balloon adherence) the balloon and sheath apparatus are gently withdrawn to close the inferior leak. Closure of the leak results in an abrupt decrease in balloon temperature, as noted by the “step” on the temperature curve. PV = pulmonary vein.

relatively uneven freezing surface associated with the reliance on the 4 anteriorly directed equatorial refrigerant jets. The negative impact of catheter shaft–PV axis misalignment has been minimized by use of advanced-generation catheters with their improved cooling mechanism and greater cryorefrigerant density.

### Don't ablate in the PVs

Ablation within the PV is known to increase the rates of complication without beneficially affecting efficacy outcomes. Specifically, ablation within the tubular PV increases the risk of thermal injury to the vein (eg, pulmonary venous stenosis) by establishing a colder local



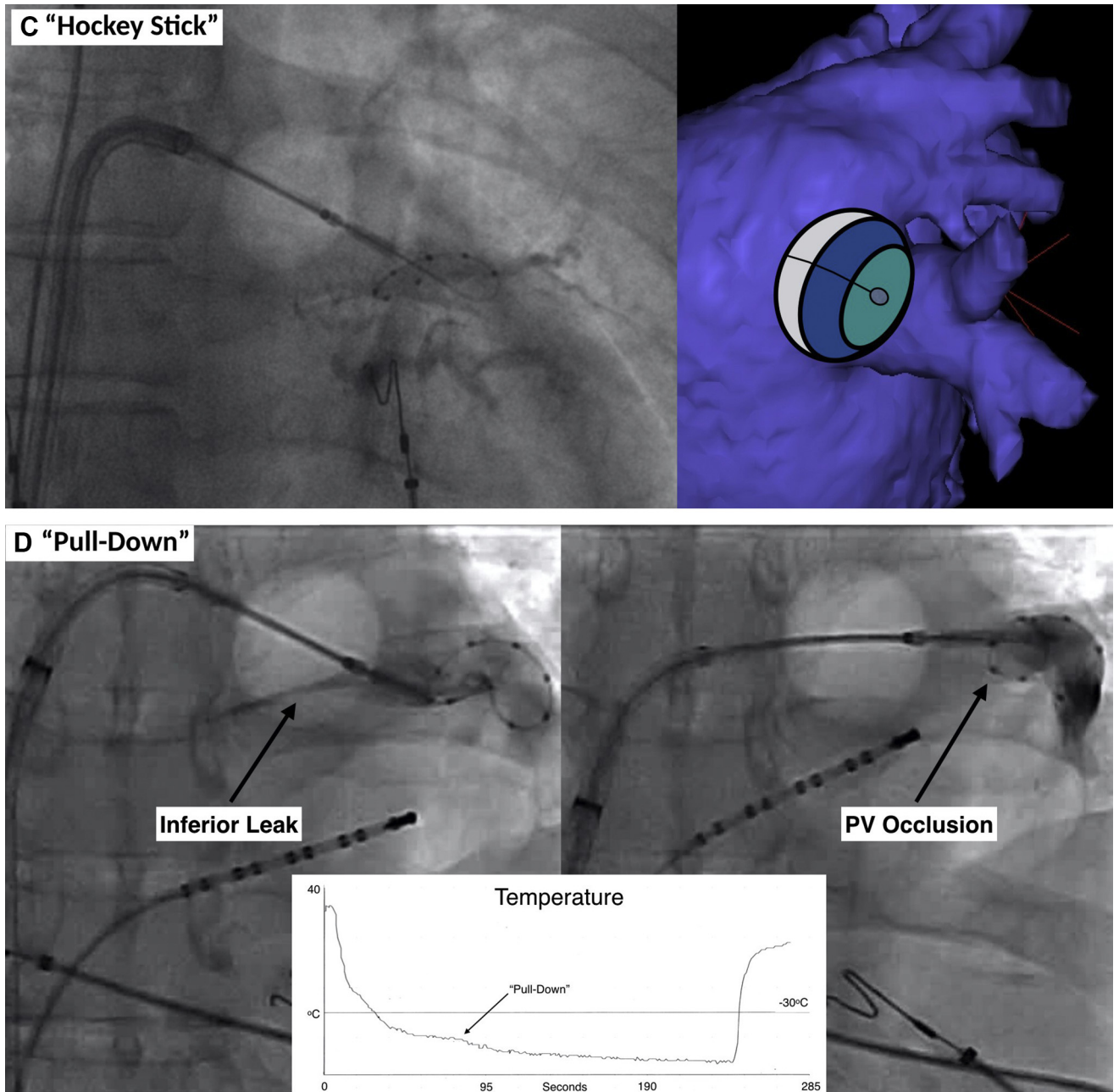


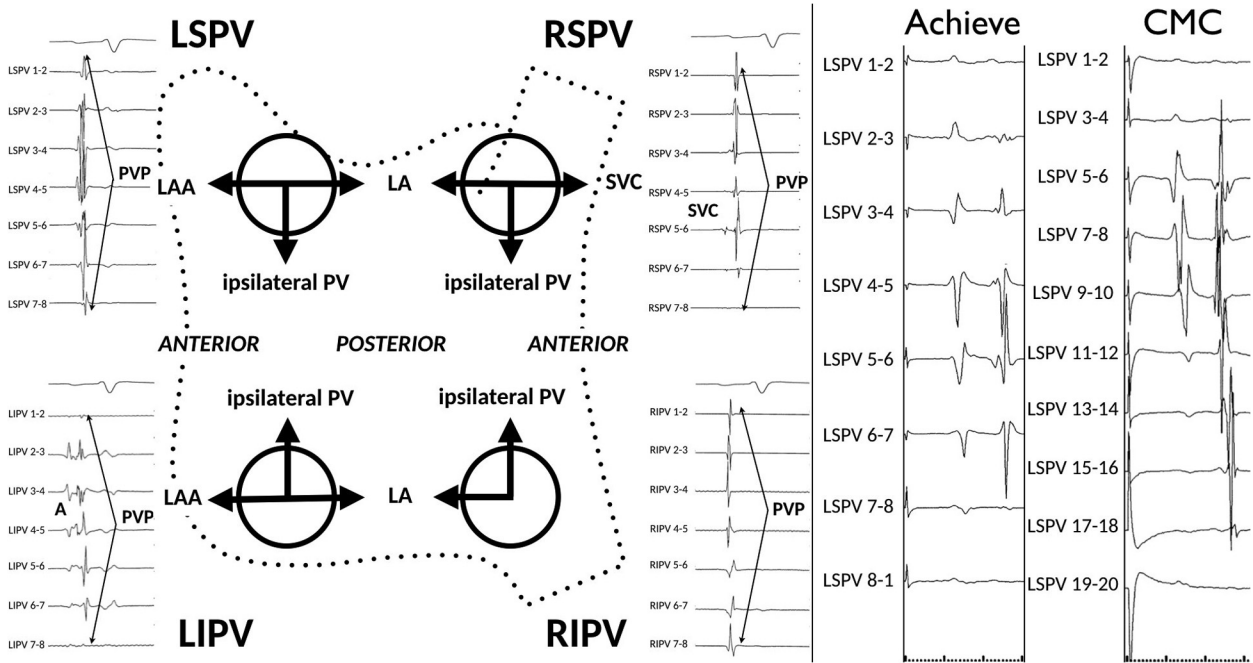
Figure 2 (continued).

environment that is more conducive to heat transfer, as well as leading to deeper lesion penetration into the adjacent tissues (eg, phrenic nerve injury, esophageal injury, or bronchial thermal injury).

Avoidance of ablation within the tubular PVs is most easily achieved using the larger 28-mm cryoballoon. In comparison to the 23-mm cryoballoon, the 28-mm cryoballoon possesses a 1.5 times greater surface area, which facilitates a more proximal (antral) position in the LA. In addition, a more antral position can be assured by using the "proximal seal" technique. This technique takes advantage of the significant pressure differential between the

lower pressure "inflation" and higher pressure "ablation" modes (Figure 1, and Supplemental Videos 4 and 5). To perform this technique, the operator leaves the guidewire/mapping catheter in the distal PV for support. The balloon is then withdrawn into the LA body. Immediately after ablation initiation, the balloon is re-advanced to the LA–PV junction.

Although the proximal seal technique can help ensure that the cryoballoon ablation remains in an antral position, it is important to realize that the lesion may still passively extend 3–4 cm into the PV despite perfect antral positioning and coaxial venous alignment.<sup>7</sup> This is thought to arise from the



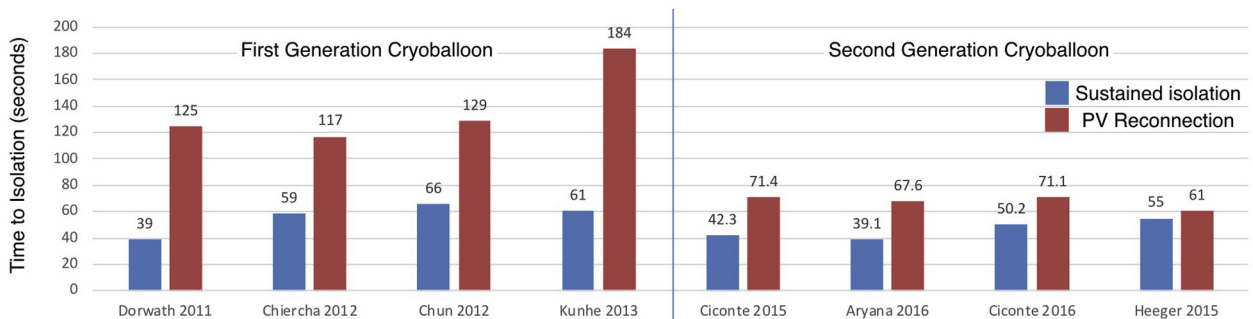
**Figure 3** Left: PV recordings from the Achieve CMC during sinus rhythm and diagrammatic representation of potential far-field electrogram sources. Right: Simultaneous Achieve small-caliber CMC and duodecapolar circular mapping catheter CMC recordings from the LSPV during distal coronary sinus pacing. Note the PV electrogram morphology is less sharp, with more far-field recordings. A = atrial far-field signal; CMC = circular mapping catheter; LA = left atrium; LAA = left atrial appendage; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; PV = pulmonary vein; PVP = pulmonary vein potential; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein; SVC = superior vena cava.

relatively large surface area of ablation that extends from the equatorial region distally to the tip of the cryoballoon catheter. While enhancing lesion creation, this large cooling zone extends beyond the zones of myocardial contact and can result in freezing of stagnant pulmonary venous blood trapped within the PV.

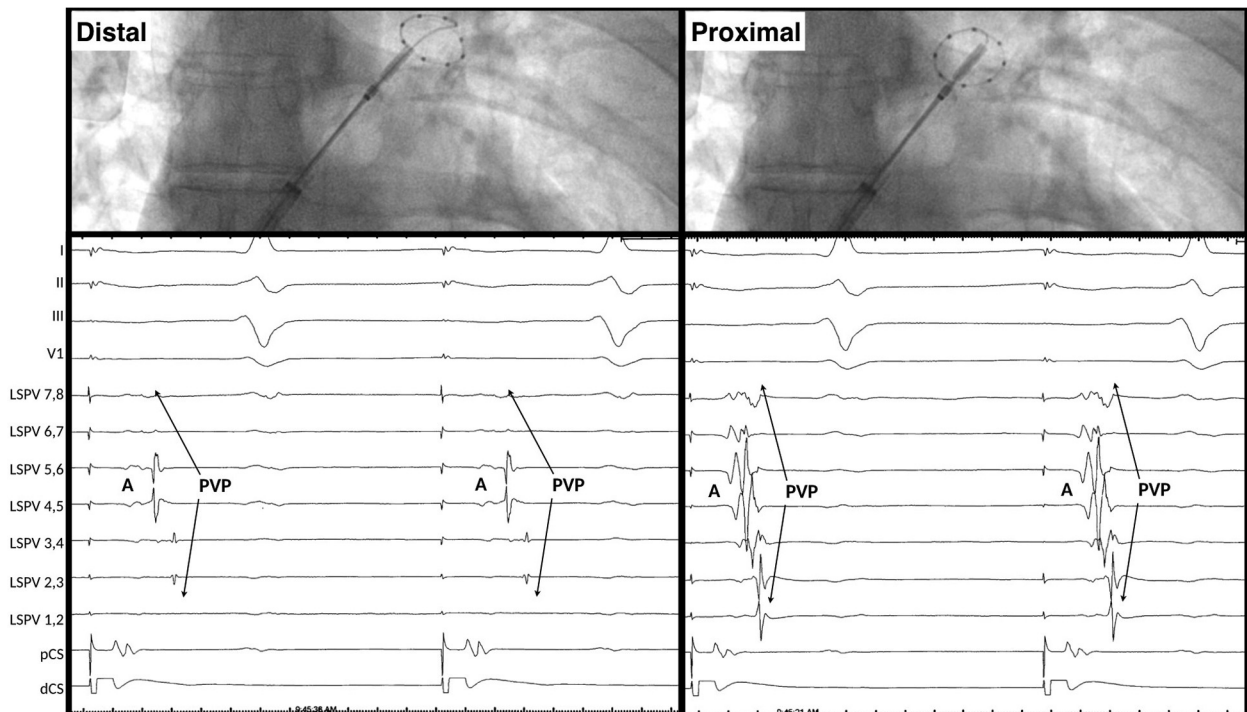
Lastly, it is important to consider the alignment of the PV and cryoballoon. Coaxial alignment of the balloon and PV will result in even contact around the PV antra, which optimizes lesion creation. Conversely, noncoaxial alignment of the cryoballoon–PV axis can result in exposure of the tubular PV tissue to the zone of greatest cryo-refrigerant density (ie, the coldest regions of the cryoballoon surface), which may increase the risk of stenosis or collateral damage.

### PV potentials observed during cryoballoon ablation appear different

The interpretation of pulmonary vein potentials (PVPs) is not always straightforward due to variation in the length and width of the LA myocardium sleeves (ie, they are thickest at the venoatrial junction and longer in the left-sided and superior PVs), as well interference from neighboring (far-field) sources of electrical activity (Figure 3, left).<sup>8</sup> In addition, interpretation of local PVPs with the Achieve mapping catheter (Medtronic) is complicated by the combination of noncircumferential contact (eg, the PVP is only observed on a portion of the bipoles) and the use of widely spaced “unipolar” electrodes (which are more likely to detect far-field structures and confer far-field morphologic characteristics to the near-field PV electrograms) (Figure 3, right).<sup>9</sup> As



**Figure 4** Evidence supporting “time to isolation” as a predictor of pulmonary vein (PV) conduction recovery with the first- and second-generation cryoballoon.



**Figure 5** Representative fluoroscopy images and pulmonary vein (PV) recordings. **Left:** Standard mapping catheter position. **Right:** Proximal mapping catheter position.

such, pacing maneuvers are often required to differentiate local PVPs from far-field potentials.

### Make every effort to record a PVP

Although “real-time” PVP monitoring is not a necessary component of cryoballoon-based PVI, its use has been associated with shorter procedure durations, reduced fluoroscopy exposure, and delivery of fewer cryoapplications. Moreover, documentation of early PV disconnection has been associated with better outcomes after cryoballoon ablation, with shorter time to isolation being associated with sustained PVI (Figure 4).<sup>10–19</sup> Specifically, a “time to isolation” (TTI) cutoff of 83 seconds was shown to predict stable sustained PVI (ie, absent PV conduction recovery) with the first-generation cryoballoon (86% sensitivity, 97% specificity).<sup>15</sup> However, the improved cooling associated with the redesigned refrigerant mechanism has refined this estimate, with TTI <40 seconds shown to predict stable PVI with advanced-generation cryoballoons.<sup>11</sup>

Given that real-time PV electrogram monitoring can help guide PVI, it is important to make every effort to record PVPs before initiating ablation. For the first- and second-generation cryoballoons, real-time PVP recordings could be obtained in approximately two-thirds to three-fourths of PVs. In one-third of cases, the PVP can be recorded from the standard (distal) position, although this is usually restricted to those PVs with the longest myocardial sleeves (eg, the superior PVs). For cases in which stability necessitates a distal mapping catheter position, it may be necessary to interrogate the PV ostia before and

immediately after cryoablation delivery. For cases in which the distal nose of the cryoballoon prevents the Achieve from assuming an adequately ostial position, PVPs often can be recorded by withdrawing and retroflexing the mapping catheter such it resides off the face of the balloon (Figure 5). However, the evolution to shorter-nosed balloons has resulted in improved assessment of real-time PVP (eg, real-time PVP observed in 89.2% of PVs with third-generation cryoballoon vs 60.2% of PVs with second-generation cryoballoon;  $P < .001$ ).<sup>20</sup>

### How do I use TTI if I can't see a PVP?

For cases in which the PVP is not visible, pacing within the PV can be helpful to document real-time isolation during cryoablation.<sup>17,21</sup> In these cases, high-output pacing is performed from the circular mapping catheter. Even in the apparent absence of PVPs exit conduction can be documented. Pacing is continued during cryoablation, with isolation manifesting as progressive PV to LA conduction delay followed by abrupt onset of exit block.<sup>21</sup> Of note, “pseudo-exit block,” or loss of PV capture mimicking loss of exit conduction, is an unlikely observation during cryoballoon ablation, as cryotherapy results in fixation of the catheter to the PV antrum as well as fixation of the mapping catheter within the frozen lumen.

### What if I still can't see a PVP?

In the absence of real-time PVP assessment, it is possible to monitor the efficacy of the ablation lesion through surrogates such as balloon temperature. With the first-generation

**Table 1** Observational and randomized studies evaluating cryoballoon ablation dosing

Study	Dose strategy			Study arm (no. of patients)	Cryo dose (s)	Bonus (s)	Procedure duration (min)	Fluoroscopy duration (min)	Complication	Efficacy outcomes
	Fixed dose	Variable dose	No bonus							
Observational studies										
Ciconte et al <sup>12</sup>	X		X	Standard CBA (80) Short CBA (80)	240 180	240 No	90.6 ± 15.8 vs 75.2 ± 17.1 ( <i>P</i> < .001)	18.3 ± 6.9 vs 13.5 ± 8.7 ( <i>P</i> < .001)	11.3% vs 7.5% ( <i>P</i> = .59)	73.8% vs 75.0% ( <i>P</i> = .92)
Straube et al <sup>32</sup>	X			Standard CBA (57) Short CBA (57)	240 180	240 180	169 ± 52 vs 141 ± 30 ( <i>P</i> = .0001)	28 ± 10 vs 24 ± 9 ( <i>P</i> = .017)	5.3% vs 1.8% ( <i>P</i> = .31)	76.8% vs 83.6% ( <i>P</i> = .27)
Valles et al <sup>41</sup>		X	X	Conventional (69) Variable (88) TTI <60 s + Temp <-50°C TTI <60 s + Temp -40°C to -50°C	180 TTI + 60 180	180 No No	134.6 vs 119.8 ( <i>P</i> = .003)	22.8 vs 20.1 ( <i>P</i> = .036)	11.6% vs 3.4% ( <i>P</i> = .047)	79.7% vs 78.4% ( <i>P</i> = .50)
Aryana et al <sup>40</sup>		X	X	Conventional (400) Variable (355) TTI <60 s TTI 60–90 s TTI > 90 s	180 120–240 TTI + 120 TTI + 120 Abandon	180 Yes/no No 120	145 ± 25 vs 84 ± 23 ( <i>P</i> < .001)	29 ± 13 vs 13 ± 6 ( <i>P</i> < .001)	2.7% vs 2.0% ( <i>P</i> = .48)	78.3% vs 82.5% ( <i>P</i> = .14)
Pott et al <sup>39</sup>		X	X	Conventional (100) Variable (100) TTI <30 s TTI 30–60 s TTI >60 s No PVP visualized	240 240 120 180 180 180	240 240 No No 180 No	115.7 ± 27.1 vs 85.8 ± 27.3 ( <i>P</i> < .001)	22.5 ± 9.8 vs 17.5 ± 6.6 ( <i>P</i> < .001)	12.0% vs 10.0% ( <i>P</i> = NR)	75.7% vs 73.6% ( <i>P</i> = .75)
Tebbenjohanns et al <sup>44</sup>			X	Standard CBA (139) "No bonus" (53)	240 240	240 No	98 ± 16 vs 79 ± 14 ( <i>P</i> < .01)	14 ± 4 vs 14 ± 3 ( <i>P</i> = NS)	5% vs 6% ( <i>P</i> = NS)	79% vs 81% ( <i>P</i> = NS)
Randomized studies										
123 Study <sup>33</sup>	X			Long CBA (74) Medium CBA (74) Short CBA (74)	~220 ~160 ~100	~220 ~160 ~100	92 ± 20 89 ± 27 82 ± 23 ( <i>P</i> = .04)	22 ± 10 23 ± 11 22 ± 10 ( <i>P</i> = .65)	6.8% 6.5% 5% ( <i>P</i> < .01)	NR NR NR
CIRCA-DOSE <sup>34</sup>	X			Standard CBA Short CBA	240 120	240 120	143.0 130.5 ( <i>P</i> = .002)	17.2 19.0 ( <i>P</i> = .63)	5.2% 6.0% ( <i>P</i> = NS)	52.2% 51.7% ( <i>P</i> = .97)



Ferrero-de-Loma-Osorio et al <sup>46</sup>	X	Conventional (70) Variable (70)	180	180	135 ± 35 vs 119 ± 31 ( <i>P</i> < .01)	11.7 ± 4.1 vs 11.3 ± 5.2 ( <i>P</i> = .73)	8.6% vs 7.1% ( <i>P</i> = NS)	79.4% vs 78.3% ( <i>P</i> = .87)
		PVP visualized No PVP visualized Standard CBA (50) "No bonus" (50)	TTI + 60 120 240	120 120 240	89 ± 21 vs 70 ± 20 ( <i>P</i> < .001)	12.7 ± 5.5 vs 10.6 ± 3.9 ( <i>P</i> = .03)	18% vs 6% ( <i>P</i> = .06)	82% vs 88% ( <i>P</i> = .80)
AD-Balloon <sup>47</sup>	X	Standard CBA (55) "No bonus" (55)	180 180	No 240	156 ± 44 vs 146 ± 41 ( <i>P</i> = .25)	40 ± 17 vs 41 ± 14 ( <i>P</i> = .62)	18% vs 15% ( <i>P</i> = .61)	87.3% vs 89.1% ( <i>P</i> = .78)
		TTI < 75 s TTI > 75 s	240 240	No 240	118.4 ± 34.3 vs 99.4 ± 33.3 ( <i>P</i> = .002)	17.9 ± 11.3 vs 16.3 ± 10.3 ( <i>P</i> = .34)	12.9% vs 2.9% ( <i>P</i> = .03)	71.4% vs 73.9% ( <i>P</i> = .74)
Mortzell et al <sup>48</sup>	X	Standard CBA (70) "No bonus" (69)	240 240	240 No				

CBA = cryoballoon ablation; NR = not reported; PVP = pulmonary vein potential; TTI = time to isolation.

balloon, a minimal end-ablation cryoballoon temperature colder than  $-51^{\circ}\text{C}$  was associated with durable PVI (60%–100% specificity).<sup>22,23</sup> However, for prognostication, the reliance on end-ablation temperature makes this unhelpful for assessment of lesion adequacy during ablation. A more useful parameter is the temperature achieved during cryoablation. Using the first-generation cryoballoon, the temperature at 120 seconds after ablation initiation was used to predict lesion durability. In these series, temperatures warmer than  $-36^{\circ}\text{C}$  for superior PVs and warmer than  $-33^{\circ}\text{C}$  for inferior PVs predicted ineffective PVI with >95% specificity (positive predictive value 80% for superior PVs and 82% for inferior PVs).<sup>22,23</sup> As such, we consider lesions that fail to achieve a temperature colder than  $-35^{\circ}\text{C}$  after 60 seconds ineffectual.<sup>24,25</sup>

### How long should I ablate for?

The permanence of cryoablation lesions is a function of tissue temperature and time (ie, freezing duration).<sup>26,27</sup> Historical recommendations to continue the cryoapplication for 240 seconds were based on studies of an early focal cryocatheter. In those studies, the effect of a cryoablation reached a plateau 3 minutes after ablation onset. Thereafter, "prolongation of exposure time... did not result in any further increase in lesion dimension or volume."<sup>28,29</sup> Since then, this focal cryoablation catheter with slow halocarbon R-502-based cooling and a temperature limit of  $-50^{\circ}\text{C}$  has transformed into balloon-based catheters with rapid nitrous oxide-based cooling and temperatures below  $-80^{\circ}\text{C}$ .

In recent years, clinical and preclinical studies have re-evaluated the optimal cryoablation dosing with a focus on determining the shortest effective freezing duration. Conceptually these studies can be divided into 3 different philosophies: (1) fixed-dose cryoablation (eg, 3-minute cryoapplications); (2) variable-dose cryoablation (eg, TTI-based dosing); and (3) "no bonus" cryoablation (Table 1).

### Fixed cryoablation dosing

We recently performed 2 randomized preclinical studies examining shorter cryoablation times. The first study examined a focal cryocatheter.<sup>30</sup> Using 3-dimensional morphometric analyses, this study demonstrated no difference in ablation lesion volume ( $125.7 \pm 69.5 \text{ mm}^3$  vs  $141.0 \pm 83.5 \text{ mm}^3$ ; *P* = .25), surface area ( $167.8 \pm 21.6 \text{ mm}^2$  vs  $194.3 \pm 22.6 \text{ mm}^2$ ; *P* = .40), or maximum depth ( $4.4 \pm 0.2 \text{ mm}$  vs  $4.5 \pm 0.2 \text{ mm}$ ; *P* = .71) between 2- and 4-minute freezes. The second randomized preclinical study examined a single 2-minute vs 4-minute cryoballoon application, with a focus on PVI efficacy.<sup>31</sup> Similarly, no differences were observed between 2- and 4-minute cryoapplications in the rates of procedural PVI or the achievement of complete circumferentially transmural lesions at 30 days (86.2% for 2-minute freezes vs 70% for 4-minute freezes; *P* = .285). The only significant difference was a thicker neointima in the 4-minute group



**Table 2** Suggested approach to tailored cryoballoon ablation dosing

- I. In PVs in which real-time PVP monitoring is feasible, an early TTI (eg, <40–60 s) suggests that the “bonus freeze” may be omitted.<sup>9,22,32,37,39</sup>
- II. In PVs in which real-time PVP monitoring is feasible, a late TTI (eg, >60–90 s) suggests that the lesion be abandoned and the balloon repositioned.<sup>22,32,38</sup>
- III. In PVs in which real-time PVP monitoring is not possible, a balloon temperature warmer than –40°C at 60 s suggests that the lesion be abandoned and the balloon repositioned.<sup>10,22,32,39</sup>
- IV. The minimum cryoablation duration should be 2 min for the right sided-PVs in order to balance clinical efficacy with the risk of phrenic nerve injury.<sup>22,31,32,39,44</sup>
- V. The minimum cryoablation duration should be 3 min (or ideally 4 min) for the left-sided PVs in order to maximize efficacy.<sup>31,47</sup>
- VI. Within these parameters, tailored dosing based on TTI + 120 s seems to be reasonable.<sup>38</sup>
- VII. No more than 1 “bonus freeze” should be delivered.<sup>68</sup>

PV = pulmonary vein; PVP = pulmonary vein potential; TTI = time to isolation.

(223.8  $\mu\text{m}$  vs 135.6  $\mu\text{m}$ ;  $P = .007$ ) and a higher rate of PV strictures (6 strictures in 30 PVs in the 4-minute group vs 0 strictures in 29 PVs in the 2-minute group;  $P = .024$ ). In addition, a separate preclinical series demonstrated that the rates of durable PVI were similar with two 2-minute lesions in comparison to two 4-minute lesions (83% vs 78% isolation at 30 days). However, lesion depth was significantly greater with 4-minute lesions (1510  $\pm$  1093  $\mu\text{m}$  vs 2615  $\pm$  1046  $\mu\text{m}$ ), which likely reflects use of a porcine model in the latter series rather than the canine model employed in the former series.

From a clinical standpoint, there has been a trend toward truncating cryoablation duration. With the first-generation cryoballoon, the usual clinical practice was 240- or 300-second cryoablation durations in North America and Europe, respectively. With the improved refrigerant mechanisms in the advanced-generation cryoballoon, there has been a shift in clinical practice toward using 3-minute cryoablation durations based on thermocouple gel model data and nonrandomized cohort studies.<sup>11,32</sup>

To date, only 2 randomized studies have explored fixed-duration cryolesions, and only 1 of the studies reported efficacy outcomes beyond the index procedure.<sup>33,34</sup> The “123 study” randomized 222 patients to short, medium, or long cryoablation durations, which corresponded to lesion durations of 105 (101–108) seconds, 164 (160–168) seconds, and 224 (219–226) seconds, respectively.<sup>33</sup> The investigators demonstrated that short cryoablation durations were associated with significantly lower rates of phrenic nerve impairment for the right-sided PVs; however, the shorter freezing durations were associated with lower rates of PVI for the left-sided veins. Long-term freedom from arrhythmia was not reported.

The CIRCA-DOSE (Cryoballoon vs. Irrigated Radiofrequency Catheter Ablation: Double Short vs. Standard Exposure Duration) study randomized 346 patients to contact force-guided point-by-point radiofrequency (RF) ablation (CF-RF), 2-minute cryoballoon ablation (CRYO-2), or 4-minute cryoballoon ablation (CRYO-4).<sup>34</sup> At 12 months, there was no difference in the 1-year freedom from any atrial tachyarrhythmia as detected by continuous rhythm monitoring using an implantable loop recorder (53.9% with CF-RF, 52.2% with CRYO-4, and 51.7% with CRYO-2;  $P = .87$ ), the 1-year freedom from symptomatic atrial

tachyarrhythmia (79.1% with CF-RF, 78.2% with CRYO-4, and 73.3% with CRYO-2;  $P = .26$ ), or the median reduction in AF burden (99.3% with CF-RF, 99.9% with CRYO-4, and 98.4% with CRYO-2;  $P = .36$ ). However, the CRYO-2 group required higher rates of AAD therapy 6–12 months postablation, which is postulated to be secondary to the nonsignificantly higher rates of symptomatic AF.

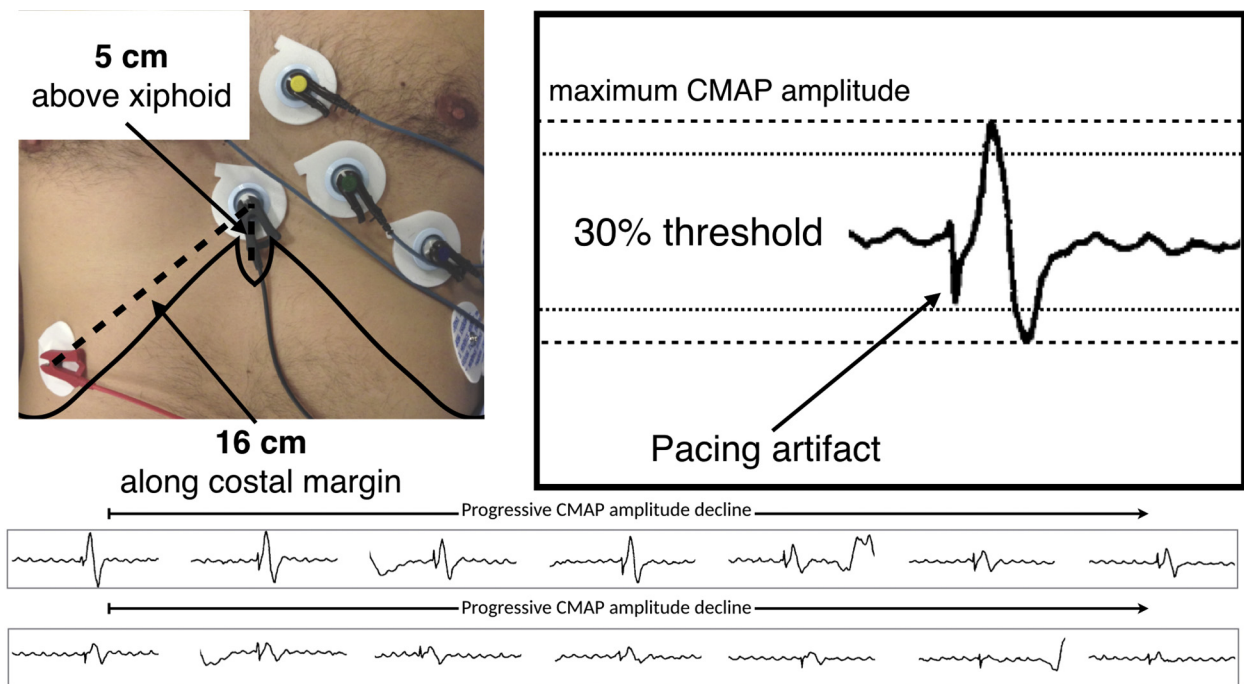
Taken together, these 2 randomized studies support the notion that cryoballoon ablation duration can be decreased from the previous 4-minute standard and support the use of a 3-minute cryolesion; however, 2-minute lesions may not be ideal given concerns regarding lesion efficacy.

### Variable (TTI-based) cryoablation dosing

Given the observation that early TTI has been associated with a greater likelihood of delivering an efficacious lesion, several investigator groups have attempted to incorporate TTI into cryoablation dose-titration algorithms.<sup>35,36</sup> Preclinical randomized data using a canine model has demonstrated that durable PVI could be obtained with doses as low as TTI + 60 seconds (100% electrical isolation with durable PVI in 100% of PVs on gross and histopathologic analysis).<sup>37</sup> Importantly, although no significant differences in efficacy were noted between groups, the only complication (phrenic nerve palsy) occurred in the group with two 3-minute lesions.

These findings of improved safety were also observed in a cohort of 563 consecutive patients, among whom a TTI-guided protocol was associated with a lower incidence of major complications (3.7%) compared with a 4-minute plus bonus freeze (8.5%) and a 4-minute with no bonus freeze (7.9%).<sup>38</sup>

The efficacy of variable-dosing protocols has been evaluated in 3 observational and 1 randomized study (Table 1). All used a variable-dose strategy based on TTI but differing protocols, which limits comparisons between studies. For example, the 3 observational studies with historical comparators used a fixed-dose strategy based on TTI (Pott et al,<sup>39</sup> who performed 2- vs 3-minute cryoapplications based on whether TTI was early [ $<30$  seconds] or not [ $>30$  seconds]); a TTI-plus strategy (Aryana et al,<sup>40</sup> who delivered 120 seconds of cryoapplication beyond the time at isolation, leading to variable exposure within and between patients); or combinations of both (Valles et al<sup>41</sup>). In addition, if TTI was late ( $>60$  seconds), both Pott et al and Aryana et al delivered a



**Figure 6** Phrenic nerve compound motor action potential (CMAP) monitoring. **Top left:** Configuration of surface electrocardiographic (ECG) electrodes for recording the right hemi-diaphragmatic CMAP. **Top right:** Right hemi-diaphragmatic CMAP and far-field QRS complex recorded on the “phrenic” channel. The CMAP is the complex component recorded after the stimulation artifact, with the *dashed line* representing the threshold for termination of ablation (ie, maximal CMAP amplitude on preablation testing minus 30%). **Bottom:** Serial recordings of the diaphragmatic CMAP during right superior pulmonary vein cryoablation. Injury to the phrenic nerve manifests as a progressive decrease in CMAP amplitude, with loss of phrenic capture manifesting ~30 seconds after a 30% decline in maximal CMAP amplitude.

“bonus freeze” (2 or 3 minutes, respectively). However, Valles et al delivered a 3-minute bonus freeze if the balloon temperature was warmer than  $-40^{\circ}\text{C}$ , irrespective of TTI. Lastly, although these 3 observational studies compared variable TTI-based dosing to historical controls, the doses of cryoablation in the control arms were inconsistent: two 3-minute lesions in Valles et al; two 4-minute lesions in Pott et al; and 2- to 4-minute lesions with or without bonus freeze in Aryana et al.

plusONE (A Time-to-effect Based Dosing Strategy in Cryoballoon Ablation of Patients With Paroxysmal Atrial Fibrillation) was the only randomized study of a TTI-based variable-dosing protocol. This study randomized 140 patients to conventional fixed-dose cryoablation using a 3-minute lesion with a single bonus freeze vs a variable-dose strategy using TTI + 60 seconds (or empiric 120-second freezes in the 30% of PVs in which PVP could not be visualized in real time). This study confirmed that dose-limitation strategies could significantly shorten procedure duration and LA time without compromising procedure efficacy. However, the fluoroscopy exposure and complication rates were no different between the variable- and fixed-dosing groups, findings that are in contrast to the observational data.

### Bonus lesions?

It has been proposed that serial cryoapplications may improve outcomes by minimizing PV reconnection. Bonus

freezes have been based on the “freeze–thaw–freeze” principle, and preclinical studies have shown that repetition of the freeze–thaw cycle results in faster and more extensive tissue cooling.<sup>42</sup> Pathophysiologically this process is distinct from the direct cellular damage related to ice crystal formation during active hypothermia. Specifically, the freeze–thaw cycle capitalizes on the microcirculatory failure generated by the index lesion, which limits the amount of heat brought to the periphery of the index ablation area. That is, the tissue at the periphery of the index lesion is less protected by surrounding blood flow during subsequent freezes, which results in extension of the ablation lesion due to faster cooling and a greater depth of freezing. The experimental evidence confirming the increased destructive effect of the second freeze–thaw–freeze cycle is significant enough that most clinicians outside of cardiology adopt routine bonus freezes as a core facet of the technique.<sup>42</sup> However, within the realm of AF ablation procedures, the utility of this bonus freeze is less certain, with several observational series and few randomized studies suggesting that the bonus freeze may not be necessary with the advanced-generation cryoballoon.<sup>9,22,32,37,39</sup>

As with the previously discussed studies of fixed and variable dose limitation, the evidence base for the performance of bonus lesions consists of several observational series and few randomized studies. On the whole, these studies demonstrate that omitting the bonus cryoapplication (either as part of a variable TTI-based dosing protocol or

**Table 3** Strategies to reduce complications during cryoballoon ablation

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Energy-dependent complications (PV stenosis, phrenic nerve injury, thermal bronchial injury, esophageal injury)
<ul style="list-style-type: none"> <li>• Avoid ablation within the tubular portion of the PV (consider proximal seal technique)</li> <li>• Avoid noncoaxial alignment of the cryoballoon to the PV axis (asymmetric balloon position)</li> <li>• Use dose-limitation strategies, including avoidance of unnecessary bonus freezes (Table 2)</li> <li>• Monitor for collateral damage           <ul style="list-style-type: none"> <li>○ Phrenic: Pacing and monitoring of phrenic nerve integrity (eg, CMAP) during ablation of right-sided PVs</li> <li>○ Esophagus: Consider luminal esophageal temperature monitoring</li> </ul> </li> <li>• Consider terminating ablation with extreme cryoballoon temperatures (ie, colder than <math>-55^{\circ}\text{C}</math> to <math>-60^{\circ}\text{C}</math>)</li> <li>• Consider “double-stop” technique to facilitate balloon and collateral tissue rewarming</li> </ul>
Thromboembolic complications
<ul style="list-style-type: none"> <li>• Procedural anticoagulation to target ACT <math>&gt;300\text{--}350</math> s</li> <li>• Strict sheath management</li> <li>• Avoid unnecessary catheter and sheath exchanges</li> </ul>
Access site
<ul style="list-style-type: none"> <li>• Consider ultrasound-guided vascular access</li> <li>• Consider the use of venous closure devices or “figure-of-8” suture</li> </ul>
Pericardial effusion/tamponade
<ul style="list-style-type: none"> <li>• Consider ultrasound-guided transeptal puncture</li> <li>• Always manipulate the cryoballoon/sheath with the guidewire/mapping catheter exposed</li> </ul>

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ACT = activated clotting time; CMAP = compound motor action potential; PV = pulmonary vein.

fixed-dose protocol using 3-, 4-, or 5-minute freezes) results in significantly shorter procedure duration and lower fluoroscopy exposure, with comparable longer-term freedom from recurrent arrhythmia.<sup>11,39–41,43,44</sup>

### Cryodosing: Synthesis and ongoing issues

The ultimate goal of the clinician is to ensure a safe and effective procedure, one that provides sufficient ablation energy to ensure durable isolation without exposing patients to the risk of collateral damage due to unnecessary energy exposure. Although the evidence base is complicated by significant differences in ablation protocols, a synthesis of the observational and randomized studies can provide insight. First, decreasing the cryoablation dose results in significantly shorter ablation procedures and LA dwell times, with reduction in fluoroscopy exposure mostly associated with omission of a bonus freeze.<sup>45</sup> Second, although cryoablation dose-limitation strategies theoretically should reduce the rates of complications directly related to cryoablation (eg, phrenic palsy or atrioesophageal fistula [AEF]), this has not been consistently observed.<sup>33,34,45–48</sup> Third, overreduction in cryoablation dose may compromise efficacy, as higher rates of PV reconnection have been noted in the left-sided PVs where longer freeze durations may be required to penetrate the full thickness of the myocardium in the left atrial appendageal (LAA) ridge.<sup>33,45,49,50</sup> Taken together, these studies suggest an approach to tailored cryoablation dosing that may be reasonable (Table 2).

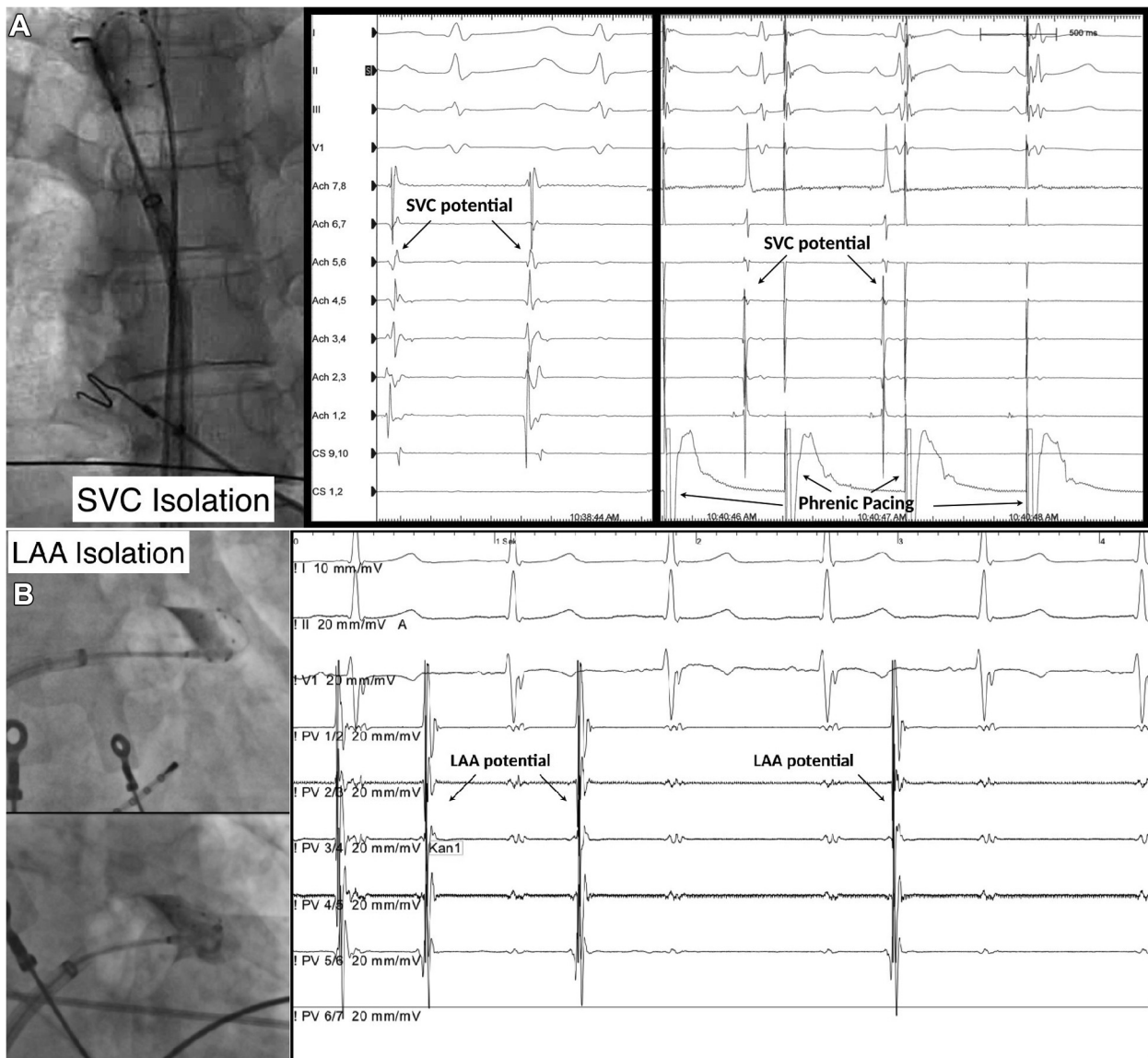
### Monitor for complications

Compared to RF ablation, cryoballoon ablation seems to be associated with a significantly lower incidence of pericardial effusion (odds ratio [OR] 0.44;  $P < .01$ ) and tamponade (OR 0.31;  $P < .01$ ).<sup>51,52</sup> In contrast, cryoballoon ablation is

associated with a significantly greater incidence of transient phrenic nerve injury (OR 7.40;  $P < .01$ ),<sup>52</sup> which is thought to be due to cold-induced large axonal loss.<sup>53</sup> As such, efforts have been made to reduce this complication by use of phrenic nerve pacing with continuous abdominal palpation, continuous diaphragmatic visualization with intracardiac echocardiography, and/or continuous auditory monitoring of diaphragmatic contraction. However, these techniques are reactionary, as they manifest too late in the pathophysiological process to prevent nerve damage. In contrast, real-time monitoring of the diaphragmatic compound motor action potential (CMAP) is a more sensitive technique for detecting early changes to phrenic nerve integrity before it becomes clinically apparent.

In our practice, we record the diaphragmatic CMAP from a standard surface electrode positioned 5 cm above the xiphoid, with the second surface electrode positioned 16 cm along the right costal margin (Figure 6).<sup>53,54</sup> During cryoablation of the right-sided PVs, we pace the right phrenic nerve using a deflectable multielectrode catheter (5–20 mA at 0.5- to 2.0-ms pulse width at cycle length of 1000 ms). During ablation, diaphragmatic CMAP signals are continuously displayed within the electrophysiological recording system and analyzed in real time. We terminate ablation using the “double-stop” technique in the event of a 30% reduction in the maximal diaphragmatic CMAP amplitude or any perceived reduction in the strength of diaphragmatic contraction. Active balloon deflation using the “double stop” technique has been shown to result in more rapid tissue rewarming, which limits the extent of cold-induced phrenic injury due to continued venous occlusion.<sup>55</sup> In addition, we previously demonstrated that active deflation does not induce vascular or endothelial injury.<sup>56</sup>

The second energy-dependent complication to consider is esophageal injury, which is a known complication of all AF



**Figure 7** Cryoballoon ablation of nonpulmonary vein trigger sites. **A:** Superior vena cava (SVC) isolation. **Left:** Cryoballoon position at the right atrial–SVC junction. **Middle:** Premature atrial contraction initiated from the SVC. **Right:** Electrical SVC isolation. Note the phrenic pacing artifact. **B:** Left atrial appendage (LAA) isolation. **Left:** Cryoballoon position at the LAA ostium. **Right:** Electrical LAA isolation. (Images in [Figure 7B](#) are courtesy of Stefano Bordignon.)

ablation procedures. Although the exact rates are difficult to delineate, studies have demonstrated esophageal ulceration in up to 20% of patients after AF ablation, with AEF occurring in <1:1000 after RF ablation and <1:10,000 after cryoballoon ablation. Preclinical evidence suggests that the ablation energy itself may have differential effects on the esophagus, which are thought to be related to the observation that the devitalized cryoablation lesions have preserved ultrastructural integrity, less transmural necrosis of the muscular wall, and preserved tensile strength.<sup>57–59</sup> However, despite the theoretical protective effects of the energy source, occurrence of AEF has been reported after cryoballoon ablation. In particular, AEF has been seen in association with extremely cold ablation temperatures around the left inferior PVs.<sup>60</sup> Strategies to reduce this devastating complication have centered on avoidance of ablation within the

tubular PVs, termination of ablation in the event of extremely cold cryoballoon temperatures (ie, colder than  $-60^{\circ}\text{C}$ ), and luminal esophageal temperature monitoring. Studies evaluating the utility of luminal esophageal temperature monitoring have suggested that ablation should be terminated with esophageal temperatures colder than  $10^{\circ}\text{--}12^{\circ}\text{C}$  (70%–100% sensitivity and 92%–100% specificity for predicting esophageal ulcerations on endoscopy 48 hours post-PVI).<sup>61,62</sup>

Strategies to reduce complications during cryoballoon-based ablation procedures are listed in [Table 3](#).

### Ablation of non-PV sites

Although there is near universal agreement that isolation of the PV triggers is the cornerstone of the invasive



management of paroxysmal AF, ablation beyond the PVs may be necessary for more advanced forms of AF. Depending on the population, non-PV triggers have been documented spontaneously or after isoproterenol infusion in up to 20% of patients. Common sites include the superior vena cava (SVC), LAA, and LA free wall.<sup>63,64</sup> Elimination of these non-PV trigger sites has been suggested to improve long-term outcomes for patients with more persistent forms of AF; however, each of these approaches must be carefully considered given the potential short- and longer-term risks.<sup>63,64</sup>

### SVC isolation

The SVC, like other thoracic veins, contains myocardial sleeves that extend from the atrial myocardium. These SVC myocardial sleeves exhibit automaticity and triggered activity, and in up to 45% of patients they act as non-PV triggers.<sup>65</sup> As such, some have proposed isolation of the SVC as part of the index cryoballoon-based PVI procedure (Figure 7A). If SVC isolation is pursued, it is important to perform ablation at the SVC–right atrial junction in order to avoid complications, as proximal ablation risking direct injury to the sinus node and distal ablation increasing the risk of phrenic nerve injury and SVC stenosis. Key to prevention is avoidance of distal ablation using the proximal seal technique as well as vigilant CMAP monitoring (as outlined in the Monitor for complications section). Given the proximity of the phrenic nerve to the SVC, we have a low threshold for ablation termination with “double stop,” as the time differential between CMAP decrease and clinical palsy is shortened when ablation is performed in the SVC.

### LAA isolation

Similar to the SVC, the LAA is a frequent site of non-PV triggers. Isolation of the LAA has been reported to improve outcomes for patients with recurrent atrial tachyarrhythmias after PVI, as well as for those with more persistent forms of AF. It has been postulated that the cryoballoon may be a better tool for LAA isolation due to the increased stability afforded by freeze-mediated catheter adhesion and the ability to perform simultaneous circumferential isolation (Figure 7B).<sup>66</sup> Potential complications of LAA isolation include injury to the left main and left circumflex arteries (which are located within 3–7 mm of the LAA ostium), left phrenic nerve injury, and LAA perforation. It is recommended that the coronary artery course be delineated by noninvasive cardiac computed tomographic angiography or invasive angiography before ablation in order to avoid ablation-induced coronary vasospasm. Left phrenic nerve injury can be avoided by using CMAP monitoring while pacing from the left subclavian. LAA perforation can be avoided with use of the third- or fourth-generation (short-tip) cryoballoon and by ensuring that the circular mapping catheter remains at the proximal aspect of the LAA. Early reconnections are common after LAA isolation (observed in up to 70% of patients), with some investigator groups

suggesting prolonged postisolation observation periods or use of adenosine testing for dormant conduction.<sup>67</sup> Typically these reconnections are observed at the anterior and superior aspects of the LAA ostial myocardium as a result of the thicker myocardium. In our opinion, the most significant concern of LAA electrical isolation is the long-term risk of thromboembolism due to mechanical LAA dysfunction (eg, a noncontracting LA). Because this risk seems to be persistently elevated despite sinus rhythm maintenance and use of oral anticoagulation, some investigator groups have suggested that percutaneous LAA exclusion/occlusion be performed in all patients after electrical LAA isolation.<sup>68</sup>

### Posterior wall isolation

Posterior wall isolation has been postulated as an adjunct to PVI for patients with more advanced forms of AF because of the common embryologic origins between the PVs and posterior wall. It is postulated that isolation of the posterior wall may specifically target non-PV triggers, AF-perpetuating substrate, and ganglionated plexi. A recent prospective cohort study examined the utility of posterior wall isolation using the cryoballoon.<sup>69</sup> The study demonstrated that posterior wall isolation with the cryoballoon was associated with reduced arrhythmia recurrence at 12 months compared to PVI alone ( $P = .001$ ). However, the addition of posterior wall isolation effectively doubled the procedure duration, requiring an additional 13.7 cryoapplications. In addition, the procedure was technically challenging, which despite specialized balloon maneuvering and extensive ablation still required touchup RF ablation in 32% of patients.

### Conclusion

The contemporary PVI procedure using the cryoballoon can be performed in a safe and effective manner.

### Appendix Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hroo.2020.02.004>.

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