The cryothermy ablation balloon catheter was developed to facilitate pulmonary vein (PV) isolation to treat atrial fibrillation (AF). The STOP-AF (Study of the Arctic Front Cryoablation Balloon for the Treatment of Paroxysmal Atrial Fibrillation [NCT00523978]) trial reported that ablation with the cryoballoon catheter as an alternative to medical therapy eliminated atrial fibrillation in 69.9% of drug refractory subjects, although adjunctive focal ablation was required in 17% (1). To improve outcomes, a second-generation cryoballoon (CB-A) was developed with an enhanced capacity to freeze target tissue and to do so over the entire distal hemisphere of the balloon rather than over an equatorial band, as with the first-generation device (2). Initial studies comparing the first and second generation devices confirmed improved acute (3,4) and long-term (5) outcomes, consistent with enhanced creation of durable PV isolation (6).

The advantage of the CB-A is that it can ablate large regions of tissue to achieve PV isolation with a “one-shot freeze”; however, it necessarily follows that this device provides very limited capability for operators to direct more or less ablation to specific sectors of the targeted PV ostium. Although the operator can adjust the orientation of the balloon to some extent relative to the PV and, in so doing, alter the balloon-tissue contact pattern and the distribution of heat removal around the circumference of the PV ostium, user-determined location-specific delivery of cryothermy ablation is not possible and “over-ablation” at some sites is likely. Indeed, inadvertent injury of the right phrenic nerve (PN), which courses near the right PV ostia (7,8), has emerged as the most common clinically significant complication of cryoballoon ablation. PN injury had previously been reported in only 0.48% of subjects undergoing radiofrequency ablation (9) but was seen in 11.2% of subjects in STOP-AF (1). Not surprisingly, initial studies comparing the “more powerful” CB-A to the first generation cryoballoon revealed an approximate doubling of acute (from 12.6% to 19.5%) and persistent (from 5.4% to 7.3% [beyond discharge from the index procedure]) PN injury (3,4) and an increase in what had been the rare occurrence of PN injury during ablation at the right inferior PV (10).

Various techniques have been proposed to minimize the risk of PN injury during CB-A ablation. Several case series describe exclusive use of the large 28-mm CB-A, which minimizes the likelihood that the balloon catheter will be advanced into the right superior PV (5,11–15), and more recent reports describe shortening the delivery time to 180 s and avoiding “bonus” ablation after isolation is achieved (5,16). Monitoring diaphragmatic compound motor action potential (CMAP) amplitude has also been reported as a valuable adjunct to palpating diaphragmatic contraction during PN pacing. CMAP can be measured using surface electrocardiography leads placed at the costophrenic angle (17,18) or by intravascular recording from the subdiaphragmatic hepatic vein (19), and may allow for improved sensitivity to identify onset of PN injury and facilitate early discontinuation of cryothermy ablation.
to preserve PN function (20). Another reported technique involves manipulating the CB-A to avoid displacing the catheter into the RSPV by carefully withdrawing the cryoballoon until a small leak around the balloon is evident before initiating cryoablation which then expands the balloon slightly to locate the freezing zone as near to the ostia-left atrium (LA) junction as possible (3,16). Active and rapid deflation of the cryoballoon at the first sign of PN injury (double tap technique) (16,21,22), and terminating cryothermy ablation if there is a particularly rapid decrease in temperature to \(<\sim 38^\circ C\) within the first 40 s (23) are additional reported techniques.

In this issue of JACC: Clinical Electrophysiology, Ichihara et al. (24) report on 100 consecutive subjects who underwent LA ablation for drug refractory paroxysmal AF using the CB-A. They combined exclusive use of the large 28-mm balloon, “single-shot” 3-min freezes with no “bonus” freezes, active balloon deflation, and CMAP monitoring; this combination of techniques has not been previously reported. The authors report a 3% incidence of persistent PN injury, with all patients recovering during follow-up. Interestingly, in the 1 subject with late PN recovery at 10 months post-ablation, there had been a delay in terminating ablation despite a reduction in CMAP. These findings are consistent with a study of CMAP monitoring during CB-A ablation that reported a 24.5% incidence of CMAP changes that prompted early termination of ablation but only a 1.5% incidence of persistent PN injury with all recovering (25). A more recent case series of CMAP monitoring found that 13.6% of subjects had CMAP-defined acute PN injury leading to termination of cryoablation, and none developed persistent injury (20). These outcomes are in contrast to long-term follow-up studies of CB-A ablation in which palpation of diaphragmatic contraction was the primary monitoring strategy. These studies uniformly reported some long-lasting PN injury beyond 1 year (12–14,16,26).

Having the ability to predict a priori which patients are at risk for PN injury and to modify lesion delivery to further minimize risk, although untested as a technique, could theoretically be effective. Although direct visualization of the PN with multidetector computed tomography (MDCT) can be difficult (8), visualization of the neurovascular bundle containing the right PN allows localization in most individuals (7). The authors (24) also reported MDCT measurement of right PV morphology and the distance between the RSPV ostium and PN vascular bundle in those with and without PN injury. Subjects with a measured distance of 12.4 mm or more demonstrated no PN injury. A previous study of PV isolation using a variety of balloon ablation technologies in a smaller number of subjects also reported that PN injury was not seen after right PV isolation when the distance between the PN and PV ostium was above a threshold value, in this report, 10.6 mm (7). Perhaps MDCT plus intra-procedural x-ray findings regarding balloon positioning, another method to identify patients at risk (27), could define a subset of individuals for whom cryotherapy ablation pulse duration or refrigerant flow (as a new ablation variable) be adjusted to prevent PN injury?

How to best prevent PN injury is still uncertain, although it seems likely that some technique or combination of techniques in addition to simple palpation of diaphragmatic contraction during PN pacing will be indicated. As ablation systems are developed or modified to produce larger and deeper lesions that better create durable PV isolation, the capacity to produce “collateral injury” to thoracic structures such as the PN or esophagus (28,29) will increase. Pre-procedural imaging and intraprocedural monitoring to assess proximity of vulnerable structures to any of the PV ostia, and to detect undesired collateral injury during ablation, respectively, will become increasingly important to mitigate risk and improve outcomes of left atrial ablation for AF in general. Specifically, questions remain about what the optimal strategy will be to afford patients the antiarrhythmic efficacy benefits of CB-A ablation while preventing PN injury or other complications. Well-designed prospective studies, ideally with randomization, will be required to establish the best integrative approaches, drawing from available or new techniques to improve outcomes of cryoballoon ablation for AF.

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