JACC: ASIA VOL. 3, NO. 5, 2023


EDITORIAL COMMENT

# Cryoablation

## Nitrogen or Nitrous Oxide? Balloon or Nonballoon?*

Koji Miyamoto, MD, PhD

Cardiac cryolesions are categorized into the following stages: 1) freezing; 2) thawing; and 3) replacement fibrosis. The efficacy of cryoablation is determined by tissue temperature, cooling rate, freezing duration, thawing rate, blood flow, and freeze-thaw cycle.[1]

Liquid nitrogen and nitrous oxide have been utilized for surgical cryoablation. Nitrous oxide used for cryoablation was first introduced in 1977, and it has become a useful method for the surgical treatment of various arrhythmias.[2] The lesions created by cryoablation with nitrous oxide have sharp, well-demarcated boundaries and intact endothelial layers.[1] However, nitrous oxide cryoablation cannot create deep lesions, which sometimes results in failure to reach arrhythmia foci and re-entrant circuit pathways and to create durable and transmural lesions.

The boiling point of nitrogen of -196 °C and critical temperature of -147 °C are lower than the nitrous oxide boiling point of -88.5 °C and critical temperature of 36.5 °C. Ghalili et al[3] compared the cryosurgical lesions created by liquid nitrogen cryoprobes at −196 °C and nitrous oxide cryoprobes at −76 °C with various exposure times on the left ventricular myocardium in the beating canine heart. They described that cryosurgery with liquid nitrogen creates larger lesions than those created by nitrous oxide cryosurgery ($P < 0.05$; 826 ± 163 $mm^3$ vs 493 ± 197 $mm^3$ at 1 minute; 1,356 ± 318 $mm^3$ vs 787 ± 258 $mm^3$ at 3 minutes). Further, cryoablation lesions created with liquid nitrogen have sharply defined borders like the lesions created by nitrous oxide. Subsequently, cryoablation with liquid nitrogen has been increasingly adopted for surgical cryoablation.

For years, cryoablation with liquid nitrogen as an energy source has been exclusively performed during open heart surgery, resulting in the creation of durable, extensive transmural lesions in both the atrium and ventricle. Conversely, cryoablation with nitrous oxide has been the sole option for percutaneous cryoablation due to technical challenges associated with delivering the coolant percutaneously.

However, a recent development in cryoablation technology, known as an ultra low-temperature cryoablation (ULTC), has emerged to address this limitation. ULTC utilizes a high-pressure "near-critical" nitrogen refrigerant, operating close to its boiling point of −196 °C, enabling percutaneous cryoablation with liquid nitrogen.[4,5] The catheter is not a balloon, but its active end of the catheter can be modified with various preshaped endoluminal stylets, facilitating procedures such as pulmonary vein isolation (PVI) in a single shot, posterior wall isolation, and the creation of linear lesions like mitral isthmus and cavotricuspid isthmus ablation lines. The UTLC technology is anticipated to achieve more rapid and deeper freezing of myocardial tissue compared with cryoablation with nitrous oxide. It has already demonstrated excellent results for ablation of atrial flutter, atrial fibrillation, and ventricular tachycardia.[4,5]

Balloon-based PVI has been performed worldwide and has rendered the PVI procedure easier, shorter, and safer. In the current widely utilized cryoballoon ablation (CBA) system (Arctic Front Advance [AFA], Medtronic), nitrous oxide is injected as a cryogen into the inner balloon through 8 injection tubes.

Recently, a liquid nitrogen-based CBA system (Cryofocus Medtech) has been developed for treating atrial fibrillation.[6] Unlike CBA systems using nitrous oxide, which primarily rely on the Joule-Thomson effect for freezing, liquid nitrogen CBA primarily

*Editorials published in *JACC: Asia* reflect the views of the authors and do not necessarily represent the views of *JACC: Asia* or the American College of Cardiology.

From the Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan.

The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2023.08.011

JACC: ASIA, VOL. 3, NO. 5, 2023
OCTOBER 2023:817–818

achieves tissue freezing through vaporization. To facilitate this process, liquid nitrogen CBA is equipped with as many as 18 refrigerant release channels to ensure a uniform release of liquid nitrogen. The potent and rapid freezing capability of liquid nitrogen CBA may enhance the effectiveness of PVI. However, this technology faces challenges related to the potential instability and lack of control over freezing temperature, which can result in inadequate and unsafe ablations. To address this issue, liquid nitrogen CBA incorporates a unique temperature control system. The freezing flow is continuously adjusted based on real-time temperature measurements from the inner cryoballoon, ensuring a consistent freezing distribution while maintaining the appropriate temperature.

An animal experiment was conducted preliminarily using liquid nitrogen CBA to assess its feasibility, safety, and effectiveness for the PVI.[6] In total, 13 dogs underwent PVI: 8 dogs received treatment with liquid nitrogen CBA and 5 dogs received treatment with AFA. The PVI success rate following a single ablation was higher in the liquid nitrogen CBA group compared with the AFA group (92.9% vs 60.0%; $P = 0.05$), although the time to isolation was similar between the groups ($48.1 \pm 29.1$ seconds vs $52.3 \pm 51.2$ seconds). In terms of safety, there was no evidence of thrombus formation, esophageal injury, or pericardial tamponade in any of the dogs. Only 1 case self-limited phrenic nerve paralysis was observed in the AFA group. Pathological findings were comparable between the 2 groups.

In this issue of *JACC: Asia*, Nie et al[7] conducted a prospective, multicenter, single-arm study to evaluate the effectiveness and safety of liquid nitrogen CBA in patients with paroxysmal atrial fibrillation (PAF). The study included a total of 172 patients with PAF, with an average age was $59 \pm 9$ years. The immediate success rate was 97.7% (95% CI: 94.2%-99.4%), and the 12-month freedom from atrial fibrillation was 82.6% (95% CI: 76.9%-88.2%). Phrenic nerve palsy occurred in 6 patients, of whom 5 recovered during the follow-up period.

The safety profile of liquid nitrogen CBA, as presented in this issue with a small sample size, appears to be satisfactory. However, care must be taken to prevent injury to adjacent structures such as the phrenic nerve and esophagus. While a more potent freezing effect may potentially result in larger lesions and improved PVI outcome, it may potentially carry the risk of unintended collateral injuries. Therefore, more rigorous monitoring or preventive measures, such as the use of an esophageal warming balloon, which is employed in conjunction with aforementioned ULTC technology, should be considered.

This prospective, multicenter, single-arm study assessing liquid nitrogen CBA for PAF has demonstrated favorable treatment success rates. Future research involving a larger study population is warranted to further validate the findings in this paper, particularly with regard to safety.

## FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Miyamoto has received grants from Medtronic and Boston Scientific.

**ADDRESS FOR CORRESPONDENCE:** Dr Koji Miyamoto, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, 6-1, Kishibeshimmachi, Suita, Osaka 564-8565, Japan. E-mail: kojimiya@ncvc.go.jp.

## REFERENCES

**1.** Andrade JG, Khairy P, Dubuc M. Catheter cryoablation: biology and clinical uses. *Circ Arrhythm Electrophysiol*. 2013;6:218–227.

**2.** Harrison L, Gallagher JJ, Kasell J, et al. Cryosurgical ablation of the A-V node-His bundle: a new method for producing A-V block. *Circulation*. 1977;55:463–470.

**3.** Ghalili K, Roth JA, Kwan SK, et al. Comparison of left ventricular cryolesions created by liquid nitrogen and nitrous oxide. *J Am Coll Cardiol*. 1992;20:1425–1429.

**4.** De Potter T, Klaver M, Babkin A, et al. Ultra-low temperature cryoablation for atrial fibrillation: primary outcomes for efficacy and safety: the Cryocure-2 study. *J Am Coll Cardiol EP*. 2022;8:1034–1039.

**5.** De Potter T, Balt JC, Boersma L, et al. First-in-human experience with ultra-low temperature cryoablation for monomorphic ventricular tachycardia. *J Am Coll Cardiol EP*. 2023;9:686–691.

**6.** Xie Y, Guo R, Yan M, et al. Effect of pulmonary vein cryoballoon ablation in dogs with coolant-nitrogen. *J Thorac Dis*. 2022;14:1488–1496.

**7.** Nie Z, Zhao D, Ren Z, et al. Liquid nitrogen cryoballoon ablation system for paroxysmal atrial fibrillation: a multicenter, prospective, single-arm clinical trial. *JACC: Asia*. 2023;3:805–816.

**KEY WORDS** cryoballoon ablation, liquid nitrogen, paroxysmal atrial fibrillation, premarketing trial, safety