Incidence and Factors Associated With the Occurrence of Pulmonary Vein Narrowing After Cryoballoon Ablation

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Background—In contrast with traditional radiofrequency ablation, little is known about the influence of cryoballoon ablation on the morphology of pulmonary veins (PVs). We evaluated the influence of cryoballoon ablation on the PV dimension (PVD) and investigated the factors associated with a reduction of the PVD.

Methods and Results—Seventy-four patients who underwent cryoballoon ablation for paroxysmal atrial fibrillation were included in the present study. All subjects underwent contrast-enhanced computed tomography both before and at 3 months after the procedure. The PVD (cross-sectional area) was measured using a 3-dimensional electroanatomical mapping system. Each PV was evaluated according to the PVD reduction rate (ΔPVD), which was calculated as follows: (1−post-PVD/pre-PVD)×100 (%). Ninety-two percent of the PVs (271/296) were successfully isolated only by cryoballoon ablation; the remaining 8% of the PVs required touch-up ablation and were excluded from the analysis. Mild (25%–50%), moderate (50%–75%), and severe (≥75%) ΔPVD values were observed in 87, 14, and 3 PVs, respectively, including 1 case with severe left superior PV stenosis (ΔPVD: 94%) in a patient who required PV angioplasty. In multivariable analysis, a larger PV ostium and lower minimum freezing temperature during cryoballoon ablation were independently associated with PV narrowing (odds ratio, 1.773; P=0.01; and odds ratio, 1.137; P<0.001, respectively).

Conclusions—A reduction of the PVD was often observed after cryoballoon ablation for atrial fibrillation. A larger PV ostium and lower minimum freezing temperature during cryoballoon ablation were associated with an increased risk of PVD reduction. (Circ Arrhythm Electrophysiol. 2017;10:e004588. DOI: 10.1161/CIRCEP.116.004588.)

Key Words: atrial fibrillation □ cryoablation □ postoperative complications □ stenosis, pulmonary vein

Atrial fibrillation (AF) is the most common cardiac tachyarrhythmia and is associated with an increased risk of stroke, heart failure, and mortality.1 The pulmonary veins (PVs) play an important role in the pathogenesis and maintenance of AF.2,3 Although PV isolation (PVI) has been established as an effective treatment for AF, it is associated with the development of PV stenosis, which represents a serious complication. In previous studies that were performed during the initial AF ablation era, the prevalence of PV stenosis was reported to be 3% to 42%.4–8 Since then, the prevalence has decreased to 0.3% as the ablation site has shifted toward the left atrium (LA)9 and with the optimization of radiofrequency energy and technical improvements that have been achieved by confirming the catheter position with a 3-dimensional electroanatomical mapping system. Although most cases of PV stenosis are asymptomatic, severe PV stenosis can progress to complete occlusion with potentially life-threatening symptoms of segmental pulmonary hypertension or venous infarction of the corresponding lobe.9–10

PVI using a cryoballoon has emerged as a safe and effective ablation strategy for patients with paroxysmal AF.11 Immediate and midterm follow-up studies have revealed that its efficacy is similar to that of radiofrequency ablation.12–16 Although some cases of PV stenosis after cryoballoon ablation have been reported,17,18 the influence of cryoballoon ablation on the morphology of the PV is unknown. The purpose of this study was to evaluate the influence of cryoballoon ablation on the morphology of the PV and to investigate the factors associated with PV narrowing.

Methods

Study Population

The present study included 74 patients with paroxysmal AF without a PV anomaly (such as a left common PV or a right middle PV)
WHAT IS KNOWN

- Pulmonary vein (PV) isolation using a cryoballoon has been established as safe and effective ablation strategy for paroxysmal atrial fibrillation. Immediate and midterm follow-up studies have revealed that its efficacy is similar to that of radiofrequency ablation. Although it was initially suggested that cryoablation was associated with little or no risk of PV stenosis in humans, a few reports have described cases of PV stenosis after cryoballoon ablation.

WHAT THE STUDY ADDS

- When we evaluated the incidence of PV narrowing by comparing PV dimension before and 3 months after cryoballoon ablation, 36.8% of the PV demonstrated PV narrowing; the mean reduction of the PV dimension was 18%. The PV narrowing was classified as mild (25–50%), moderate (50–75%), and severe (>75%) in 30.6%, 5.2%, and 1.1% of the PVs, respectively.
- A larger PV ostium and a lower minimum freezing temperature during cryoballoon ablation were associated with a higher risk of PV narrowing. A cutoff point of −53.5°C for the minimum freezing temperature had a specificity of 76.5% and a sensitivity of 66.0% in predicting PV narrowing after cryoballoon ablation.

whose first catheter ablation procedure was performed using a second-generation cryoballoon at our institution. In the present study, paroxysmal AF was defined as AF of <7 days in duration. All patients received effective anticoagulation therapy for >3 months before the procedure. All antiarrhythmic drugs were discontinued at least 5 half-lives before the procedure. All patients provided their written informed consent before undergoing the procedure. The study protocol was approved by the ethics committee of the Jikei University School of Medicine.

Electrophysiological Study

A steerable 16-polar 2-site (6-polar for the right atrium and 10-polar for the coronary sinus) mapping catheter (Inquiry Luma-Cath; St Jude Medical, St Paul, MN) was positioned within the coronary sinus at 1 to 2 o’clock along the mitral annulus in the left anterior oblique projection via the right subclavian vein. The LA and PVs were explored either through a patent foramen ovale or via a transseptal catheterization with 2 long sheaths. Direct visualization of all 4 PVs was performed for 120 seconds at the same position according to the previously recommended protocol.19,20 In the cases with either a minimum temperature of <−60°C, an esophageal temperature of <20°C or those in which the PV potential remained after a 100-second application of cryoenergy, cryoballoon ablation was discontinued. If the PV potential did not disappear after the third application at the same PV, touch-up ablation with an 8-mm-tip nonirrigated ablation catheter or an 8-mm-tip conventional cryocatheter (Freezer MX; Medtronic) was added. To avoid phrenic nerve injury, the cryoballoon applications for right PVs were performed with the monitoring of the diaphragmatic compound motor action potentials during phrenic nerve pacing.21 After the cryoballoon ablation of all 4 PVs, a bidirectional block at the PV antrum was confirmed using a variable circular mapping catheter (OPTIMA; St. Jude Medical). Dormant PV conduction was induced by the administration of adenosine triphosphate (20–40 mg) under isoproterenol infusion and was subsequently eliminated with touch-up ablation.

Evaluation of PV Morphology

Contrast-enhanced multidetector computed tomography (Somatom Definition; Siemens Medical Solutions, Forchheim, Germany) was performed before and 3 months after the procedure. Three-dimensional images of the LA and PVs were reconstructed from multidetector computed tomographic images using a 3-dimensional electroanatomical mapping system (EnSite NavX; St. Jude Medical), and the PV dimension (PVD) was measured by 2 independent experts who were unaware of the procedural results. The PVD was measured on the 3-dimensional electroanatomical mapping system by tracing the area within the PV plane at 5-mm intervals from the PV ostium in a distal direction until 15 mm or bifurcation in each PV (Figure 1). The PVD reduction rate was calculated at each segment using the following formula: (1−post-PVD/pre-PVD)×100 (%). The ΔPVD was defined as the maximum PVD reduction rate at each PV. Severe PV narrowing was defined as a reduction of 75% in the cross-sectional area, just as in the previous large randomized trial.15 In the present study, PV narrowing was defined as a ΔPVD value of ≥25%. PV narrowing was classified into 3 groups according to ΔPVD value: mild narrowing (25–50%), moderate narrowing (50–75%), and severe narrowing (>75%), respectively. In the present study, the change in the PVD was evaluated in PVs treated only with the cryoballoon, to examine the influence of cryoballoon ablation. We excluded PVs with additional touch-up ablation from the analysis.

Statistical Analysis

The presence of a normal distribution was assessed by the Shapiro–Wilk test. Continuous variables are expressed as the mean±SD. Data were analyzed by a 1-way ANOVA or Kruskal–Wallis test, with the Tukey or Steel-Dwass post hoc test, as appropriate. Correlations were made with the Spearman rank correlation test, and probabilities were calculated for each correlation coefficient. The categorical variables, expressed as numbers or percentages, were analyzed using the χ² test unless the expected values in any cells were <5, in which case the Fisher exact test was used. The receiver operator characteristic curve was determined to evaluate the performance of the predictor of PV narrowing after cryoballoon ablation. The optimal cutoff point was chosen as the combination with the highest sensitivity and specificity. All of the tests were 2-tailed. P values of <0.05 were considered to indicate statistical significance.

To check the multicollinearity of explanatory variables, we calculated variance inflation factor among explanatory variables. The mixed-effect random-intercept logistic regression was used to consider the clustering of the data coming from the same patients in the analysis.
The statistical analyses were performed using the SPSS software program (version 21.0.0; SPSS, Chicago, IL) and Stata 14 software (StataCorp. 2015; Stata Statistical Software: Release 14; StataCorp LP, College Station, TX).

Results

Patient Characteristics

The baseline patient characteristics are shown in Table 1. The mean age was 58±10 years, and 91% of the patients were male. The mean LA diameter was 36.1±4.5 mm, and the mean left ventricular ejection fraction was 65.1±4.5%. Hypertension was observed in 18 (24%) patients, and 2 (2.7%) patients had evidence of structural heart disease.

Table 1. Characteristics of the Study Population (n=74)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=74</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>58±10</td>
</tr>
<tr>
<td>Sex (male), n (%)</td>
<td>67 (91%)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.5±2.8</td>
</tr>
<tr>
<td>AF history, y</td>
<td>3.7±4.2</td>
</tr>
<tr>
<td>LAD, mm</td>
<td>36.1±4.5</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>65.1±4.5</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>55.8±95.1</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>18 (24%)</td>
</tr>
<tr>
<td>Structural heart disease, n (%)</td>
<td>2 (2.7)</td>
</tr>
</tbody>
</table>

Age, BMI, AF history, LAD, LVEF, and BNP are expressed as mean±SD. AF indicates atrial fibrillation; BMI, body mass index; BNP, brain natriuretic peptide; LAD, left atrial diameter; and LVEF, left ventricular ejection fraction.

Results of Ablation

In total, 296 PVs were isolated from the LA during the procedure. Among these, 271 PVs (92%) were successfully isolated by cryoballoon ablation alone; the remaining 25 PVs (8%) required additional touch-up ablation and were excluded from the analysis. In the 271 PVs that were isolated by cryoballoon ablation alone, the total number and duration of cryoballoon ablations in each PV were 2.3±1.0 and 328±139 seconds, respectively. The minimum freezing temperature (MFT) during cryoballoon ablation was −52.2±7.3°C (Table 2). When we compared the cryoballoon ablation parameters among the 4 PVs, the number of cryoballoon ablations for PVI in the left superior PV (LSPV) was significantly greater than that in the right superior PV (RSPV) (1.7±1.5 versus 1.2±0.6; P=0.013). The total number of applications in the LSPV was significantly greater than that in the left inferior PV (LIPV) and RSPV (2.7±1.5 versus 2.2±0.9, P=0.037, 2.7±1.5 versus 2.2±0.7, P=0.026), and the total cryoballoon ablation time in the LSPV was significantly longer than that in the other 3 PVs (LSPV versus LIPV, 384±192 versus 298±139 seconds, P=0.001; LSPV versus RSPV, 384±192 versus 309±78 seconds, P=0.006; and LSPV versus right inferior PV, 384±192 versus 319±93 seconds, P=0.041; Table 2). The MFT in the RSPV was significantly lower than that in the other 3 PVs, whereas that in the LSPV was significantly lower than that in the LIPV (RSPV versus LIPV, −56.8±5.8 versus −52.9±5.3°C, P=0.001; RSPV versus LIPV, −56.8±5.8 versus −46.4±6.2°C, P<0.001; RSPV versus right inferior PV, −56.8±5.8 versus −52.2±7.8°C, P<0.001; and LSPV versus LIPV, −52.9±5.3 versus −46.4±6.2°C, P=0.001).

Figure 1. A typical example of the pulmonary vein dimension (PVD) measurement and the method of calculating the pulmonary vein dimension reduction rate (ΔPVD) value. The PVD was measured before and after cryoballoon ablation at 5-mm intervals from the pulmonary vein (PV) ostium in a distal direction until 15 mm. The PVD reduction rate was calculated at each point of the PV using the following formula: (1−post-PVD/pre-PVD)×100 (%). The ΔPVD was defined as the maximum PV dimension reduction rate among the 0-mm (1), 5-mm (2), 10-mm (3), and 15-mm points (4) from the ostium. The PVD at the 0-mm point (1) indicates pulmonary vein ostial dimension.
Major complications occurred in 4 (5.4%) patients, 3 (4.1%) of whom experienced transient right-side phrenic nerve palsy during cryoballoon ablation of the RSPV. One case of arteriovenous fistula requiring vascular surgery occurred on the seventh postoperative day. There were no cases of stroke or transient ischemic attack, cardiac tamponade, or any other major complications.

**Dimensions of PVs**

Figure 2 shows a comparison of the PVDs before and after cryoballoon ablation. The baseline PVDs of the LS, LI, RS, and right inferior PV were 2.8±0.9, 1.6±0.5, 3.2±0.9, and 2.3±0.7 cm², respectively. The PVDs of the LS, LI, RS, and right inferior PV after cryoballoon ablation were 2.3±0.9, 1.4±0.5, 2.5±0.9, and 2.0±0.7 cm², respectively. In each of the PVs, the PVD was significantly smaller after cryoballoon ablation than it was at baseline. The mean ΔPVD value in all PVs was 18±22%, whereas PV narrowing (ΔPVD ≥25%) were observed in 36.9% (100/271) of the PVs. Mild (25–50%), moderate (50–75%), and severe (≥75%) narrowing were observed in 83 (30.6%), 14 (5.2%), and 3 (1.1%) PVs, respectively. The ΔPVD value was found to be significantly correlated with the baseline PV ostium dimension (r=0.318; P<0.0001; Figure 3A) and the MFT (r=0.489; P<0.0001; Figure 3D). The results of a detailed analysis of the factors associated with the different degrees of PV narrowing are shown in Table 3. The baseline PV ostial dimension in the PVs with mild narrowing was significantly larger than that in those without narrowing (2.8±1.1 versus 2.4±0.9 cm²; P<0.001). Furthermore, the MFT during cryoballoon ablation in PVs with mild narrowing and moderate to severe narrowing was significantly lower than that in those without narrowing (−54.2±7.4 versus −51.0±7.0°C, P<0.001 and −54.2±7.4 versus −51.0±7.0°C, P<0.001). When we compare PVs with and without PV narrowing (ΔPVD ≥25% versus ΔPVD <25%), the PV ostial dimension before the procedure was significantly larger and the MFT during cryoballoon ablation was significantly lower in PVs with narrowing than in those without (2.9±1.1 versus 2.4±0.9 cm², P<0.001 and −54.2±7.4 versus −51.0±7.0°C, P<0.001).

**Table 2. Results of Ablation in PVs Isolated by Cryoballoon Ablation Alone**

<table>
<thead>
<tr>
<th></th>
<th>All PVs</th>
<th>LSPV</th>
<th>LIPV</th>
<th>RSPV</th>
<th>RIPV</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of applications for PVI, times</td>
<td>1.4±1.0</td>
<td>1.7±1.5†</td>
<td>1.3±0.7*</td>
<td>1.2±0.6†</td>
<td>1.4±0.7</td>
<td>0.016</td>
</tr>
<tr>
<td>Total number of applications, times</td>
<td>2.3±1.0</td>
<td>2.7±1.5†</td>
<td>2.2±0.9*</td>
<td>2.2±0.7†</td>
<td>2.3±0.8</td>
<td>0.017</td>
</tr>
<tr>
<td>Total duration of cryoballoon ablation, s</td>
<td>328±139</td>
<td>384±192†‡</td>
<td>296±139*</td>
<td>309±78‡</td>
<td>319±93†</td>
<td>0.001</td>
</tr>
<tr>
<td>MFT, °C</td>
<td>−52.2±7.3</td>
<td>−52.9±5.3§</td>
<td>−46.4±6.2†‡</td>
<td>−56.8±5.8§</td>
<td>−52.2±7.8†‡</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The number of applications for PV isolation, total number of applications, total duration of cryoballoon ablation, and minimum freezing temperature are expressed as the mean±SD. LIPV indicates left inferior pulmonary vein; LSPV, left superior pulmonary vein; MFT, minimum freezing temperature; PV, pulmonary vein; PVI, pulmonary vein isolation; RIPV, right inferior pulmonary vein; and RSPV, right superior pulmonary vein.

*, †, ‡, §, ‖ indicate a pair with a significant difference (P<0.05) in a post hoc test.

**Figure 2. A–D.** The pulmonary vein (PV) dimensions at baseline and after cryoballoon ablation in each PV. The PV dimension was significantly smaller at baseline than after cryoballoon ablation in each of the PVs. LIPV indicates left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein; and RSPV, right superior pulmonary vein.
The variance inflation factors of number of applications for PVI and total number of applications were >10. Of these 2 variables, the number of applications for PVI was excluded from the mixed-effect logistic regression by considering a clinical importance. After excluding number of applications for PVI, all variance inflation factors were <10. According to a multivariate analysis, the PV ostial dimension before the procedure and the MFT during cryoballoon ablation were found to be independent predictors of PV narrowing (\(P=0.01\) and \(P<0.001\), respectively; Table 4). Residual plots of each explanatory variable versus Pearson residuals identified 1 point, which was thought to be an influential point. However, the model without this point did not almost change compared with the model with this point. Therefore, we used the model with this point. A likelihood ratio test revealed that the mixed-effect model was fitted better than the ordinary logistic model.

Because of the 7 missing values of explanatory variables, 264 observations were used in the calculation of variance inflation factors and Pearson residuals, receiver operator characteristic curve analysis and also the mixed-effect logistic model.

The receiver operator characteristic curve for MFT as a predictor of PV narrowing (\(\Delta PVD \geq 25\%\)) after cryoballoon ablation showed an area under the curve of 0.751 (95% confidence interval, 0.687–0.814; \(P<0.0001\); Figure 4). A cutoff point of –53.5°C for the MFT had a specificity of 76.5% and a sensitivity of 66.0% in predicting PV narrowing after cryoballoon ablation.

In the present study, severe PV narrowing (\(\Delta PVD \geq 75\%\)) was observed in 3 LSPVs in 3 (4.1%) cases (Figure 5). The PV ostial dimension before cryoballoon ablation in these 3 cases was 4.2, 3.4, and 2.1 cm², respectively. Additional cryoballoon ablation was performed in all cases, and the MFT in cases 1, 2, and 3 was –59°C, –63°C, and –48°C, respectively. Although the patient in case 3 remains free from any symptoms because of PV stenosis, Tc-99m macroaggregated albumin lung perfusion scintigraphy revealed diminished blood flow to the left upper lobe in the LSPV. PV angioplasty was performed 9 months after the procedure.

**Discussion**

**Main Findings**

In the present observational study, we evaluated the incidence of PV narrowing after cryoballoon ablation by comparing computed tomographic images obtained before and 3 months
after cryoballoon ablation. In total, 36.8% of the PVs demonstrated PV narrowing; the mean reduction of the PVD (ΔPVD) after cryoballoon ablation was 18%. The PV narrowing was classified as mild, moderate, and severe in 30.6%, 5.2%, and 1.1% of the cases, respectively. There was no significant difference in the mean ΔPVD value among the 4 PVs. However, the baseline PV ostial dimension was larger and the MFT was lower in PVs with narrowing after cryoballoon ablation than in those without. To the best of our knowledge, this is the first report to quantitatively evaluate the impact of cryoballoon ablation on the PV morphology after PVI using multidetector computed tomographic imaging.  

### Predictors of PV Stenosis

The predictors of PV narrowing/stenosis have been proposed previously. Traullé et al reported that the supplementation of cryoballoon ablation of the PV with focal, irrigated ostial radiofrequency ablation may be associated with a higher risk of PV stenosis. We excluded PVs in which touch-up ablation was performed from the analysis and showed that a lower MFT during cryoballoon ablation was associated with a higher PV reduction rate.

Arentz et al previously reported that distal ablation inside smaller PVs was associated with a higher risk of stenosis after radiofrequency catheter ablation. In contrast, a larger baseline PV ostial dimension was related with a higher incidence of PV narrowing in the present study. This discrepancy is likely because of the size of the cryoballoon that was used in this study. Cryoenergy application sites may be located in a more distal portion of PVs with a larger ostial dimension in comparison with those with a smaller ostial dimension because the maximum size of the cryoballoon is currently 28 mm. It is possible that cryoballoon application at a more distal portion in larger PVs may cause a stronger seal and a lower MFT, resulting in the narrowing of the PVDs. In addition, the ability of the second-generation cryoballoon to cool the distal hemisphere as well, and not merely the equatorial belt of the balloon’s surface, may have affected the results.

### Mechanism of PV Stenosis After Cryoballoon Ablation

The mechanism of cellular damage because of freezing by cryoenergy has been shown to be a complex process with 3 primary factors: direct cellular damage, vascular failure, and immunologic effects. It has been reported that cryolesions...
are distinguished from hyperthermic injury by the preservation of the basic underlying tissue architecture with preserved endocardial contours, minimal cartilage formation, and the absence of signs of chronic inflammation or evidence of viable myocytes within the lesions, which can result in minimal tissue shrinkage and PV contraction in comparison with radiofrequency lesions. Although the true mechanism of the PV narrowing that was observed in the present study remains to be elucidated, we found that the baseline PV size and the MFT were significantly associated with the occurrence of PV narrowing in the present system of cryoballoon ablation. At the very least, need to keep in mind that cryoballoon ablation can cause PV narrowing/stenosis in human PVI procedures.

Limitations
The present study is associated with several limitations. First, we regarded a PVD reduction of ≥25% as the definition of PV narrowing. Because mild narrowing of the PVD can occur because of reverse remodeling after AF ablation, the results might reflect both PV narrowing and PV reverse remodeling. In a future analysis of a larger study population, PV narrowing should be defined by a ≥50% reduction, as this would provide more accurate results. Second, we used the twice-freezing method as a standard in this study because it was the recommended strategy at the time of this study. The newer strategy of the single-shot freezing method, which has been widely accepted, might yield different results.

Conclusion
A reduction in the PVD is not a rare occurrence after cryoballoon ablation for PVI in AF patients. A larger PV ostium and a lower MFT during cryoballoon ablation were associated with a higher risk of PVD reduction. Larger-sized PVs are not optimal candidates for cryoballoon ablation under the current system in which balloon catheters with a maximum diameter of 28 mm are used.

Table 4. Factors of the PVs With/Without Narrowing (≥25%) After Cryoballoon Ablation

<table>
<thead>
<tr>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
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<tr>
<td></td>
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<tr>
<td>∆PVD ≥25% (n=100 PVs)</td>
<td>∆PVD &lt;25% (n=171 PVs)</td>
</tr>
<tr>
<td>PV ostial dimension before ablation, cm²</td>
<td>2.9±1.1</td>
</tr>
<tr>
<td>Number of applications for PV isolation</td>
<td>1.4±1.0</td>
</tr>
<tr>
<td>Total number of applications</td>
<td>2.3±1.1</td>
</tr>
<tr>
<td>Total duration of cryoballoon ablation, s</td>
<td>321±145</td>
</tr>
<tr>
<td>MFT, °C</td>
<td>−54.2±7.4</td>
</tr>
<tr>
<td>Constant</td>
<td>...</td>
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</tbody>
</table>

The PV ostium dimension before cryoballoon ablation, the number of applications for PV isolation, the total number of applications, the total duration of cryoballoon ablation, and MFT are expressed as mean±SD. The estimate of variance of the level 2 random term was 3.139 with standard error 1.403. CI indicates confidence interval; MFT, minimum freezing temperature; PV, pulmonary vein; and ∆PVD, maximum pulmonary vein dimension reduction rate.
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Disclosures
None.

References
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