

# First confirmation of histologic changes in the human heart after cryoballoon ablation



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## Introduction

The second-generation cryoballoon (CB; Arctic Front Advance, Medtronic, Minneapolis, MN) is considered to have the same safety and effectiveness as conventional radio-frequency (RF) catheter ablation for the treatment of paroxysmal atrial fibrillation (AF).<sup>1,2</sup> The advantage of CB ablation is the greater durability of pulmonary vein (PV) isolation because the ablation can form a transmural lesion in the atrium of the heart. However, to date this has only been observed in dogs and has never been confirmed in autopsy cases in humans. Here we describe a human autopsy case performed 6 months after CB ablation was performed for treatment of paroxysmal AF.

## Case report

Informed consent to publish this case was obtained from the patient's family. An 82-year-old woman who had her left kidney removed because of kidney tuberculosis at age 20 years had been undergoing dialysis since age 80 years. She presented with paroxysmal AF. AF occurred once during dialysis and was concomitant with hypotension and tachycardia. She reported feeling uncomfortable and was unable to continue dialysis. Because propafenone treatment failed to terminate the AF, she decided to undergo catheter ablation for paroxysmal AF.

Contrast-enhanced computed tomography of her chest showed no morphological abnormalities of the PVs. Transthoracic and transesophageal echocardiography showed no abnormality other than an atrial septum aneurysm.

PV isolation was completed using only a 28-mm CB (Arctic Front, Medtronic). All PVs, except the right inferior

PV, were isolated using a single application of CB ablation for 180 seconds. During CB ablation of the right inferior PV, the minimum temperature of the CB became  $-69^{\circ}\text{C}$ , so we stopped the procedure at 130 seconds. We also performed cavotricuspid isthmus ablation using an irrigated RF catheter (FlexAbility, Abbott, Chicago, IL) at 30 W for 30 seconds, and we used point-by-point methods for common atrial flutter. No steam pops were observed during the procedure. No AF foci, except the left superior PV, were observed during induction of AF foci using a high-dose isoproterenol drip infusion. Voltage mapping of the left atrium after PV isolation revealed complete isolation of all PVs (Figure 1).

One month after ablation, the patient developed a fever and was diagnosed as having peritoneal dissemination associated with cancer of the small intestine and metastatic liver cancer, as identified by contrast-enhanced computed tomography. She died 6 months after ablation, and an autopsy was performed.

The gross pathologic findings did not show the lesion ablated by the CB in the left atrium initially. However, after carefully review of the findings, we noted that the color around the PVs had changed to a pale beige color (Figure 2A). The RF lesion of the cavotricuspid isthmus was visible and indicated by gray pigmentation of hemosiderin from suspected hemorrhage during the ablation (Figure 2B).

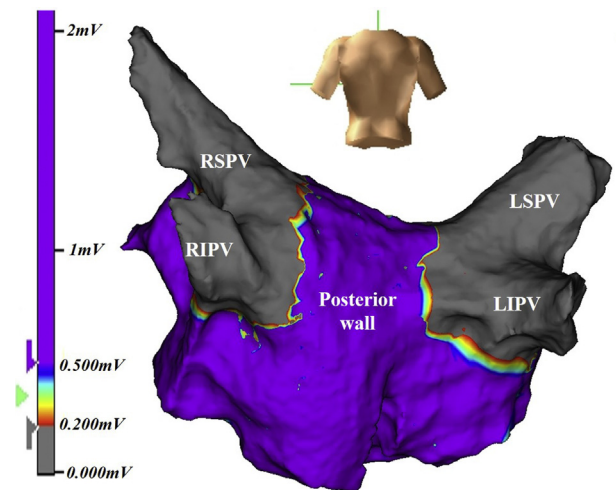
The microscopic pathologic findings clearly delineated the lesion ablated by the CB and showed it had been replaced with enough fibrous tissue to form a transmural lesion (Figure 3A). No thrombus formation was observed in the lesion. Some myocardial tissue was stained red, which was different from the endocardial part, and it seemed that residual atrial muscle existed. However, the tissue stained red was fibrous granulation tissue formation with myocardial destruction, not normal atrial muscle formation. With time, macrophages will phagocytize these tissues and induce fibrosis. Because only 6 months had passed since ablation, the process of fibrosis was not yet complete. The width of the transmural lesion of the atrium and PV was 6 mm (Figure 3B). In

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## KEY TEACHING POINTS

- The histologic changes of the left atrium and pulmonary vein after cryoballoon ablation were observed for the first time in a human autopsy case. The autopsy findings confirmed that the lesion formed after cryoballoon ablation in an 82-year-old woman was similar to those observed in the canine model.
- The radiofrequency lesion at the cavotricuspid isthmus of the right atrium was unclearly demarcated from the normal myocardium. The dense fibrous tissue was thinner, and the lesion was shallower than the cryoballoon lesion.
- The cryoablation lesion had less endocardial bleeding, was more clearly delineated, and had been more uniformly replaced with fibrous tissue than the lesion of the cavotricuspid isthmus.



**Figure 1** Voltage mapping of the left atrium and pulmonary veins after cryoballoon ablation with all pulmonary veins electrically isolated. LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein.

contrast, the RF lesion at the cavotricuspid isthmus of the right atrium was unclearly demarcated from the normal myocardium. The fibrous tissue was thinner, and the lesion was shallower than the lesion after CB ablation (Figure 3C). Moreover, hemosiderin pigmentation was observed on the surface and in the subintimal tissue in the area of right atrium endocarditis (Figure 3D).

## Discussion

The main finding of the autopsy was confirmation that the lesion formed after CB ablation in this 82-year-old woman was similar to those observed in the canine model. To the best of our knowledge, this is the first report on the histologic changes of the PV after CB ablation in humans. This was an early case of ours when we were inexperienced, so we performed the ablation to the RIPV with too low a temperature. Now, we perform CB ablation at about  $-60^{\circ}\text{C}$ . Fortunately, in this case, no adverse events, such as phrenic nerve palsy or histologic abnormality of the right inferior PV, occurred.

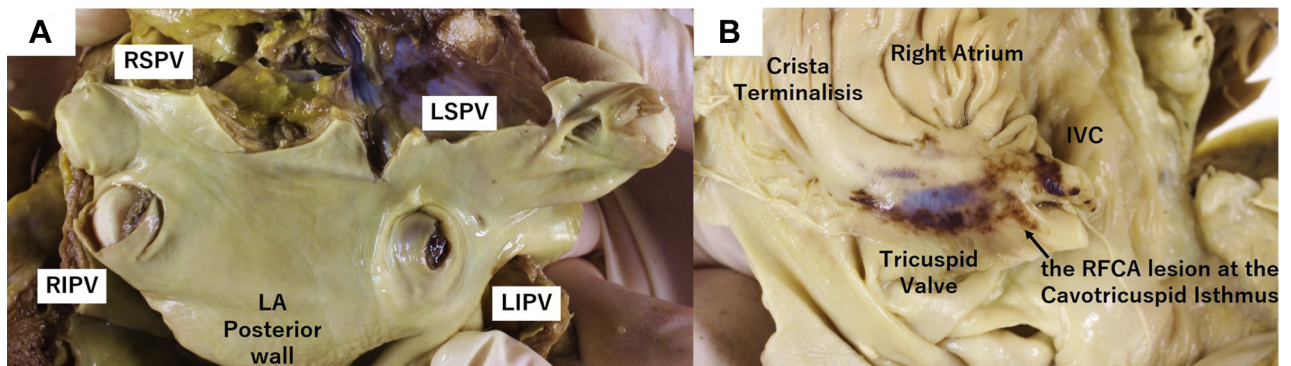
In the study of the canine model, the lesions were also confirmed as transmural circumferential ones in the PV antrum.<sup>3-7</sup> However, the results cannot be applied to humans because the human PV is larger than that of a canine. In a study of cadaver hearts of canines, Takami and colleagues<sup>6</sup> reported that regardless of the size of the CB, PV isolation was completed; however, compared with use of the 23-mm CB, the 28-mm CB caused lesions to be wider. Moreover, it was reported that no lesion gaps around the isolated PV resulted from CB ablation, but a lesion gap around the nonisolated PV was noted macroscopically.<sup>7</sup>

It has been reported that durability of the PV after ablation was greater with the second-generation CB than with nonforce-sensing RF ablation (81.2% vs 65.4%;

$P < .001$ ).<sup>6</sup> The reason for this finding was considered the transmural, wide, continuous lesion located in the PV antrum. With regard to the inflammatory biomarkers of cardiac injury, troponin I and creatine kinase levels were significantly higher after CB ablation than after RF ablation, suggesting that CB ablation damaged a larger amount of atrial muscle.<sup>8,9</sup> Kurose and colleagues<sup>10</sup> reported that the lesion depicted by late gadolinium enhancement magnetic resonance imaging after CB ablation was wider and more continuous than that after RF ablation, but the depth of the lesion could not be confirmed sufficiently. Kowalski and colleagues<sup>11</sup> described the histopathologic and electrophysiological findings of patients with recurrence of AF after PV isolation by RF, who underwent a subsequent surgical maze procedure. In their study, transmural scarring was observed in 50% of specimens by surgical biopsy; the other half showed viable myocardia with or without scarring. The rate of biopsy specimens with transmural scarring without a viable myocardium was considerably greater for the group having PV with conduction block (71%) than for the group having PV with intact conduction (40%). The lesion after RF ablation in humans is not always a transmural lesion, but this has not yet been confirmed after CB ablation. We histologically confirmed the presence of a transmural wide lesion in the PV antrum after the second CB ablation in our case, and this corroborates previous studies that reported wide lesions in the PV antrum after CB ablation and a large amount of cardiac muscle damage by CB ablation.<sup>9,10</sup>

The advantage of RF ablation is that it can make a wide PV isolation area regardless of the size of the PV. For a large PV, the CB occludes the PV at its distal portion, and the PV antrum remains unablated. Nanbu and colleagues<sup>12</sup> reported that with CB ablation, extensive isolation is superior to individual isolation for achieving freedom from AF in the long





**Figure 2** **A:** Developed view of the left atrium (LA). In gross pathologic findings, the lesion after cryoballoon ablation of the LA is unclear, but after careful review, it is evident that the lesion has changed to a pale beige color. **B:** Macroscopic pathology of the radiofrequency lesion of the inferior vena cava (IVC)–tricuspid isthmus. Subintimal hemorrhage in the lesion is observed. LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RFCA = radiofrequency catheter ablation; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein.

term, and the maximal PV diameter is the only predictor of extensive PV isolation. Thus, for a large PV, RF ablation is recommended for achieving extensive PV isolation and better AF-free survival in the long term.

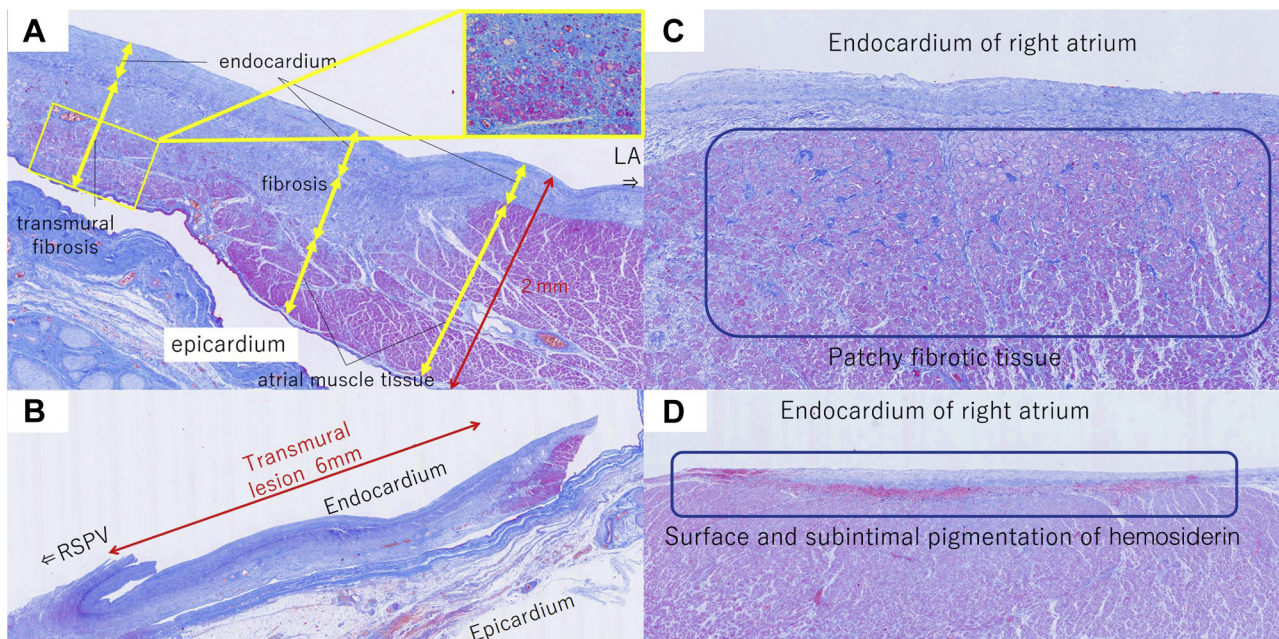
## Conclusion

In this report, the histology of the left atrium and PV after CB ablation was observed for the first time in a human autopsy case. As reported in dogs, the cryoablation lesion in the left atrium and PV in this case was transmural, and the width

of the lesion was 6 mm, which was wider than that of the lesion caused by RF ablation. Compared to the cavotricuspid isthmus lesion that was ablated in this case, the cryoablation lesion had less endocardial bleeding, was more clearly delineated, and had been more uniformly replaced with fibrous tissue.

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**Figure 3** Histologic samples stained with Azan. Fibrotic tissue is blue, and muscle tissue is red. **A:** Medium-power field of the cryoballoon lesion in the right inferior pulmonary vein antrum. A transmural lesion that had been replaced with fibrotic tissue is observed in the vein. No thrombus formation is observed in the lesion. *Inset (upper right)* shows the high-power field of the yellow square area. The area is not completely replaced with fibrotic tissue like the endocardial part; however, fibrous granulation tissue formation is observed with myocardial destruction, and there is no normal formation of atrial muscle. With time, macrophages will phagocytize these tissues and induce fibrosis, but because only 6 months have passed since ablation, the process of fibrosis is not yet complete. **B:** Low-power field of the cryoballoon lesion of the right superior pulmonary vein (RSPV) antrum. The width of the transmural lesion is 6 mm. **C:** Medium-power field of the radiofrequency lesion of the inferior vena cava–tricuspid isthmus. The patchy fibrotic tissue is stained blue by Azan and not clearly demarcated from the normal myocardium. **D:** Medium-power field of the radiofrequency lesion of the inferior vena cava–tricuspid isthmus with Azan staining. Gray pigmentation of hemosiderin is observed in the subintimal area of the lesion. LA = left atrium.

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