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SPOTLIGHT

Spatiotemporal incremental change of radiofrequency catheter ablation-associated pulmonary vein calcifications

Yasunobu Yamagishi MD, PhD | Yasushi Oginosawa MD, PhD | Yuki Nakamura MD | Keishiro Yagyu MD | Taro Miyamoto MD

The Second Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

Correspondence
Yasushi Oginosawa, The Second Department of Internal Medicine, University of Occupational and Environmental Health, Japan, 1-1 Iseigaoka, Yahatanish, Kitakyushu 807-8555, Japan.
Email: y-ogi@med.uoeh-u.ac.jp

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A 52-year-old Japanese man was admitted to our center for a fourth PV isolation for recurrence of symptomatic paroxysmal atrial fibrillation (AF). His medical history included hypertension, left nephrectomy for renal cancer, and hemodialysis for chronic glomerulonephritis since the age of 27 years. The patient underwent cavotricuspid isthmus (CTI) ablation without warfarinization 16 years prior.

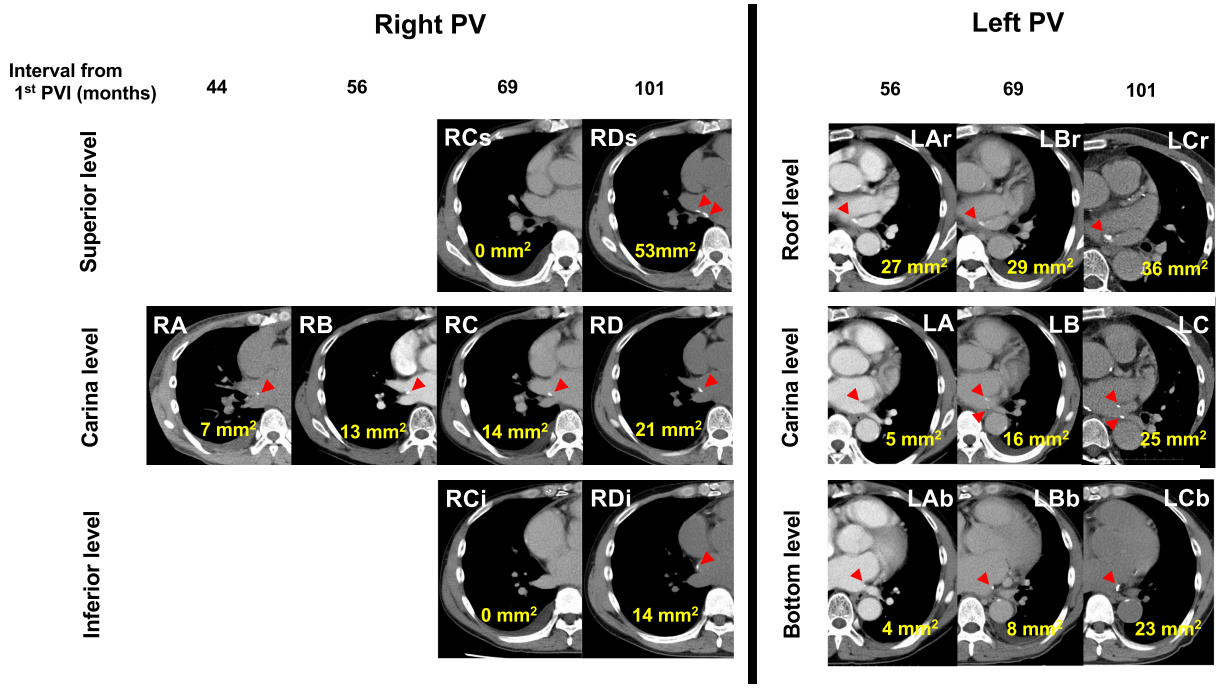

FIGURE 1 Follow-up of right and left PV calcification by CT. Each of these CTs was obtained 44 months after the first session, 56, 69, and 101 months. Red triangles meant PV calcifications. The calcification of the right PV carina progressed over time (RA, RB, RC, and RD) and spread to both superior and inferior (RDs and RDi) levels. The calcification at both the LSPV roof level (LAr, LBr, and LCr) and the LIPV bottom level (LAb, LBb, and LCb) progressed over time. PV calcification was also advanced at the level of the left PV carina (LA, LB, and LC). The calcification area at each slice level was measured and was noted in the figure (in yellow). CT, computed tomography; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; PV, pulmonary vein; PVI, pulmonary vein isolation.

PV isolation was performed under the guidance of three-dimensional (3D) electroanatomic mapping (CARTO 3; Biosense Webster Inc.). The patient was administered warfarin during the perioperative period of PV isolation. The radiofrequency (RF) energy was applied using a quadripolar 3.5-mm-tip irrigation catheter (Thermocool, Biosense Webster, Diamond Bar, CA, USA). Basically, the RF energy was 25–30 W in the right PVs, anterior of the left PVs, and carina line and 20–25 W at the posterior of the left PVs (near the esophagus). In the first session, we achieved right PV isolation; however, left PV isolation was abandoned because of ridge connection, despite linear ablation of the left PV carina.

In the second session 12 months after the first session, we confirmed reconnection of the right PV. Re-isolation of the right PV, including linear ablation of the right PV carina and left PV isolation was performed, and all four PVs were isolated.

In the third session 44 months after the first session, we solely confirmed the reconnection of the right inferior PV, while the right inferior PV could not be isolated, even with a maximum of 35 W. Since the area of ablation was extensive, we decided to abandon isolating the right inferior PV in consideration of the risk of PV stenosis. Preoperative computed tomography (CT) for the third session showed PV calcification for the first time in the right PV carina (Figure 1-RA).

Fifty-six months after the first session, a CT scan for follow-up of renal cancer showed calcifications in the roof of the left superior PV and the bottom of the left inferior PV (Figure 1-LAr, LAb).

In the fourth session 101 months after the first session, preoperative CT showed that the bilateral PV calcification had obviously progressed (Figure 1-RDs, RDi, LCr, LC, LCb). The preoperative 3D CT showed a calcified area around the left PV and in the right PV carina (Figure 2A'–C'; white part). All calcification sites were located along

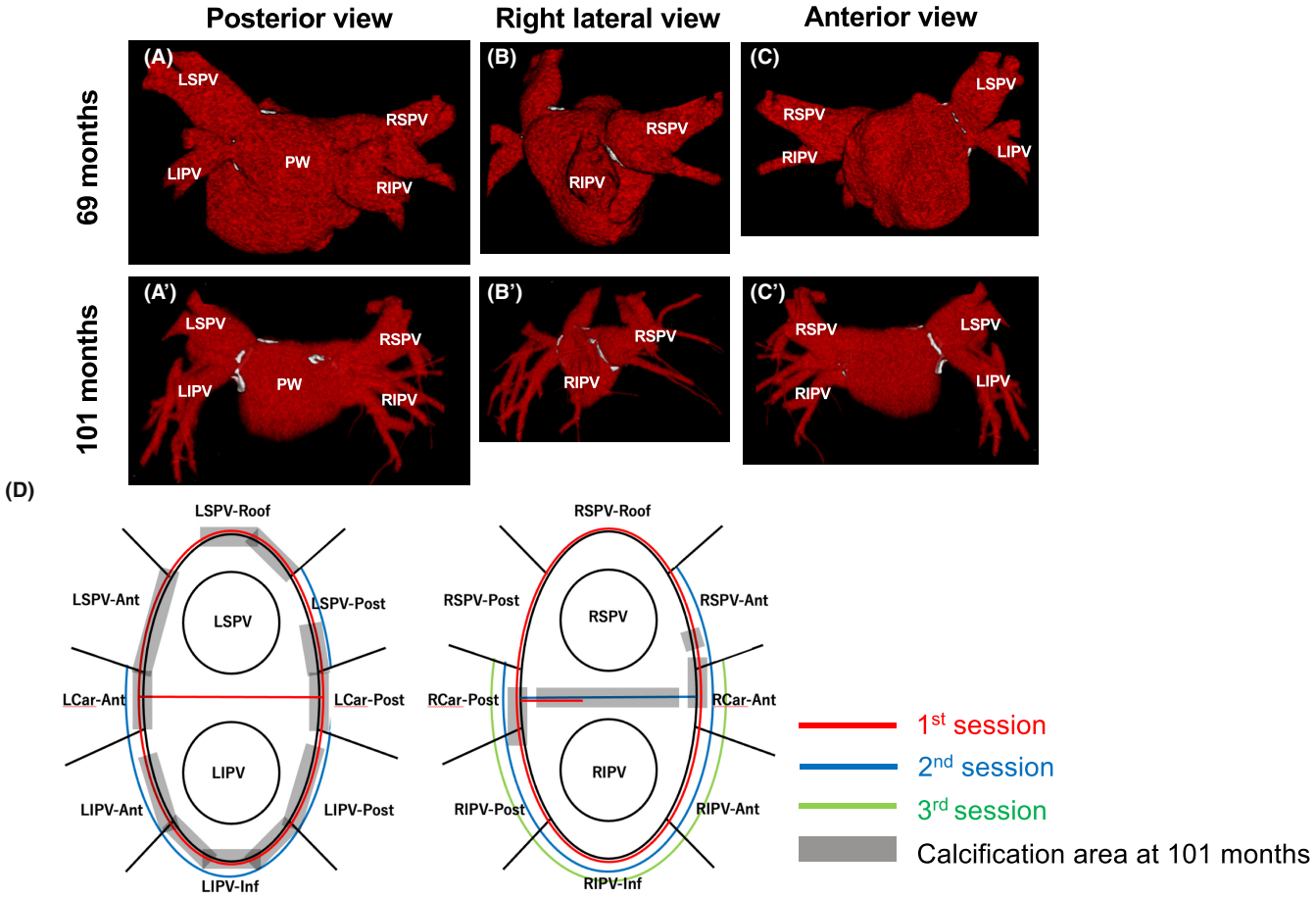

FIGURE 2 Three-dimensional CT at 69 and 101 months, and the schema showing previous ablation sites and the distribution of PV calcification. The three-dimensional CT at 101 months showed the calcified area (A'–C'; the white part); PV calcification was seen around the left PV, and in the right PV carina. These calcifications were obviously advanced compared to the three-dimensional CT at 69 months (A–C; the white part). All of the calcification sites were along the past ablation lines. The left atrial appendage is removed to reveal calcification around the left PV. Schema D showed that RFCA-associated PV calcification was not fully explained by neither the time since initial ablation, the frequency of ablations, nor the ablation energy: the first session or multiple session sites were not correlated with calcification. Moreover, we applied a lower energy at the posterior site of left PV, which was near the esophagus, however it was calcified as well as other sites. Ant, anterior; CT, computed tomography; Inf, inferior; LCar, left carina; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; Post, posterior; PV, pulmonary vein; PW, posterior wall; RCar, right carina; RFCA, radiofrequency catheter ablation; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

past ablation lines. However, no calcification was observed in the previous CTI ablation line. We solely confirmed the reconnection of the right inferior PV and successfully isolated it by ablating the posterior wall of the right inferior PV with 30W (non-calcified lesions). Since AF initiation was reproducibly observed from the posterior left atrium (LA), LA posterior wall isolation was additionally performed. No other non-PV foci were observed with drug or pacing. There was neither recurrence of AF nor heart failure at 4 months after discharge.

Reports of RFCA-associated PV calcifications were limited[1] and the detailed time course of calcification process has not been determined. It took a relatively long time (44 months) from the initial PV isolation to the first finding of PV calcification (Figure 3). During the observation period, the total amount of calcification increased over time, whereas echocardiography showed no consistent changes in E/e', which is an indicator of LA diastolic dysfunction, or in systolic pulmonary artery pressure (Figure S1).

We have shown that RFCA-associated PV calcification was not fully explained by the time since the initial ablation, the frequency of ablations, or the ablation energy (Figure 2D). A recent paper reported that multiple ablation procedures were independent risk factors for calcification.[1] Unlike previous studies, we analyzed the relationship between the ablation site of multiple sessions and the site of calcification over time and semiquantitatively. Although the overall calcification increased with each session after the second procedure, the number of ablation sessions per site did not correlate with calcification. Hence calcification may progress over time even with a single ablation.

These results, which cannot be explained by ablation factors, suggest that RFCA-associated calcification may also be influenced by factors on the myocardial side. A recent paper speculated that the presence of consistently high wall stresses cause calcification at the site, and wall stresses in PV ostia is high.[1] However, it has also been reported that the distribution of high wall stresses in the LA varies among subjects, hence there was a possibility that wall stresses was low in some areas of the LA, which are non-calcified in this case. Moreover, there have been no reports of RFCA-associated CTI calcification including in our case. One speculation is that in addition to the differences in wall stresses associated with structural differences between PV ostia and CTI, wall stresses is known to correlate with intracardiac pressure, so calcification may not have appeared in CTI in the right atrium, where pressure is lower than in the LA.

There are several possible mechanisms underlying calcification. Ectopic calcification deposits because of disturbances in calcium and phosphorus metabolism caused by chronic renal disease or hyperparathyroidism, and calcification deposits on necrotic tissues are thought to be responsible.[2] In patients with rheumatism, chronic inflammation is thought to cause calcification of the LA.[2] Oral vitamin K antagonists (VKA), such as warfarin, have the potential to decrease the activity of matrix-γ-carboxyglutamic acid protein, a strong inhibitor of soft tissue calcification.[3]

Although this patient was on dialysis, the serum calcium and phosphorus levels were only mildly elevated, at 10.5 and 4.9 mg/dL, respectively. An animal study demonstrated that RF energy causes inflammation, coagulation necrosis, and edema in the acute phase, and fibrosis, fatty degeneration, and sometimes calcification in the chronic phase.[4] This has the potential to explain the relatively long time required for calcification after RFCA. It has been reported that the longer the VKA is used, the higher the coronary calcium scores.[3] However, the period of warfarin use in the present case was only the perioperative period of PV isolation (1 month before and 3 months after RFCA, Figure 3), and furthermore, the site of PV calcification was clearly along the previous ablation line. Hence, calcification could not be explained by metabolic disorders alone. These results suggested

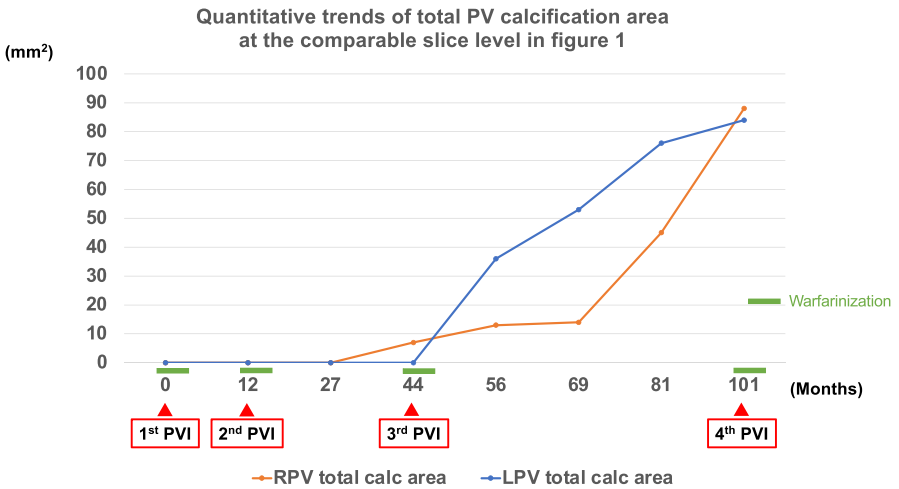

FIGURE 3 Quantitative trends of total PV calcification area at the comparable slice level in Figure 1. PV calcification area in CT at the comparable slice level was summed. Comparable slice level was the height of Figure 1 (superior, carina, inferior level in RPV, and LSPV roof, carina, LIPV bottom level in LPV). There was no calcification until at least 27 months after initial PVI. CT, computed tomography; LIPV, left inferior pulmonary vein; LPV, left pulmonary vein; LSPV, left superior pulmonary vein; PV, pulmonary vein; PVI, pulmonary vein isolation; RPV, right pulmonary vein.

that the main mechanism of PV calcification in this case was calcification deposits in catheter ablation-associated necrotic tissues.

Here, we present a detailed time course of RFCA-associated PV calcification process for the first time. It is known that progressive calcification has the potential to reduce the function of the LA as a reservoir or booster pump.[5] Because RFCA-associated PV calcification may progress over time even with a single ablation, long-term caution should be paid in cases of especially extensive ablation and/or patients with stiff LA syndrome.

CONFLICT OF INTEREST STATEMENT

Authors declare no conflict of interests for this article.

PATIENT CONSENT STATEMENT

Informed consent was obtained from the patient.

ORCID

Yasunobu Yamagishi https://orcid.org/0000-0001-8257-7468
Yasushi Oginosawa https://orcid.org/0000-0002-0955-7791

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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