Head-to-head comparison of acute and chronic pulmonary vein stenosis for cryoballoon versus radiofrequency ablation

Short title: CB vs. RF for PV-stenosis

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Abstract

Background**—**Cryoballoon (CB) applications to pulmonary veins (PVs) can cause stenosis just as radiofrequency (RF) energy deliveries. The goal of the present study was to clarify whether or not there was any difference in the extent of acute or chronic PV narrowing after PV isolation between the 2 different energy sources.

Methods**—**Consecutive patients with paroxysmal atrial fibrillation who were scheduled to undergo a PV isolation were randomized 1:1 to receive CB or RF ablation. The endpoints were any acute PV narrowing assessed with the use of intracardiac ultrasound during the procedure and PV stenosis measured with cardiac computed tomography at the 3-month follow-up.

Results**—**An acute reduction in the luminal area of the left superior PV (mean±standard deviation, -6.8±8.7 vs. -19.9±14.7%; p<0.001) and left inferior PV (-5.1±20.2 vs. -15.3±11.6%; p=0.03) was significantly smaller in the CB arm (N=25) than RF arm (N=25). There was no difference in the extent of PV stenosis 3 months after the ablation between the arms (0-25% stenosis, 90% vs. 88%, 25-50% stenosis, 10% vs. 12%, >50% stenosis, both 0%; P=0.82). A greater acute PV narrowing was likely to lead to chronic stenosis in the RF arm (p=0.004).

Conclusions**—**CB ablation may reduce the acute narrowing of the left-sided PVs as compared to RF ablation.

Key words: acute narrowing, atrial fibrillation ablation, cryoballoon, pulmonary vein stenosis, radiofrequency

Introduction

Pulmonary vein (PV) stenosis is a well-recognized complication of radiofrequency (RF) catheter ablation of atrial fibrillation (AF), with an incident rate of up to 19% [1]. Since the release of the first generation cryoballoon (CB) in 2010, it has rapidly and widely spread as an alternative ablation technology [2,3]. It was initially thought that CB ablation was free from this complication because its mechanism is considerably different from that of RF ablation [4]. Recent publications, however, have indicated that PV stenosis can even occur with the application of cryothermy [2], implying that any thermal injury to the PVs can result in stenosis. So far, there has been no direct comparison regarding the PV stenosis resulting from PV isolation between the 2 different energy sources. We thus in the present randomized study compared the acute PV narrowing and its potential relationship to chronic PV stenosis between CB and RF ablation for the treatment of AF.

Methods

Patients

This study was designed as a randomized and open-label trial, and was conducted in Nagoya Daini Red Cross Hospital from July 2014 to June 2015. The study protocol was approved by the research committee of the institution. Patients ≥18 years old were considered eligible for inclusion if they were scheduled to undergo PV isolation for the treatment of drug refractory paroxysmal AF for the first time. Paroxysmal AF was defined according to the generally accepted guidelines [4]. Patients were excluded if they had renal insufficiency that made it difficult for them to receive contrast agents, or if cardiac computed tomography (CT) revealed that they had a common left PV trunk. All antiarrhythmic drugs (AADs) were discontinued for 5 half-lives before the ablation procedure. Adequate oral anticoagulation therapy was started more than 1 month before the procedure. Prior to the ablation, all the participants underwent transthoracic and transesophageal echocardiography, and also cardiac CT as described later. The eligible patients were enrolled after giving informed consent. Patients were randomly allocated with a 1:1 ratio to be ablated with the use of a CB or by means of RF. The randomization was performed using a block randomization method.

Ablation procedures

All the procedures were performed under conscious sedation using dexmedetomidine with a maintenance dose of 0.6 μg/kg/hour. Intravenous heparin was administered to maintain an activated clotting time of 300–350 seconds throughout the procedure. A decapolar catheter was positioned in the coronary sinus in all patients. They received PV venography following the transseptal catheterization.

In the patients assigned to the CB group, a 28mm size CB (Arctic FrontAdvance™, Medtronic, Minneapolis, MN) was advanced to the PV orifice. The PV occlusion was verified by repeated contrast injections after the balloon inflation. A 180 second-freeze was then delivered to each PV through the CB. A decapolar circular catheter was placed within each PV to confirm the PV isolation. If the PV was not isolated with the single CB application, touch-up freezes with an 8-mm tip cryocatheter (Freezor MAX™, Medtronic) were added to complete the PV isolation. To avoid phrenic nerve injury, cryoenergy applications to the right PVs were given while monitoring the diaphragmatic compound motor action potentials during phrenic nerve pacing. The balloon nadir temperature, defined as the lowest temperature during the CB applications, and total thaw time, defined as time required to rewarm the balloon to 20˚C, were recorded [5].

The patients allocated to the RF group underwent a double Lasso catheter-guided extensive encircling PV antrum isolation. Two decapolar circular catheters were positioned within the ipsilateral superior and inferior PVs. After constructing three dimensional electroanatomical maps using a non-fluoroscopic navigation system (CARTO3™, Biosense-Webster, Diamond Bar, CA), circumferential ablation lines were created around the left- and right-sided ipsilateral PVs using a 3.5-mm tip irrigated catheter (Thermocool SmartTouch™, Biosense-Webster). RF energy was delivered with a maximum power of 30W, and the irrigation flow rate was set at 17ml/minute during the RF applications. Real-time contact force data were used to guide the ablations, with a target force of 10–15 g. The goal of the PV antrum isolation was to achieve both PV entrance and exit block in both groups [4].

Assessment of the PVs during the ablation procedure

The PVs were assessed as described in our previous work [6]. A 9-French intracardiac ultrasound catheter (Ultra ICE™, 9 MHz, Boston Scientific, Natick, MA) was coaxially advanced to the distal PV. The ultrasound catheter was then pulled back so that the transducer was placed just proximal to the PV-left atrial (LA) junction, where the external and internal surfaces of the PV wall were traced to measure the vessel and luminal areas of the PV (Figure 1A and 1B). The PV wall thickness area was calculated by subtracting the PV luminal area from the PV vessel area (Figure 1C). The measurement was carried out in sinus rhythm just before the initial rise in the P wave on the surface electrocardiogram. The left superior, left inferior, and right superior PVs were measured in this order. The right inferior PV, however, was not assessed because an insertion of the ultrasound catheter into it coaxially would be technically-difficult and could potentially increase the risk of any mechanical myocardial injury. Each PV was measured before and immediately after the ablation procedure. The intracardiac ultrasound catheter's transducer was placed as much as possible in the same position before and after the ablation, with the help of the ultrasonic and fluoroscopic images.

Cardiac CT

Cardiac CT imaging was obtained with the use of a multidetector 64-row helical system (Brilliance 64, Philips Medical Systems, The Netherlands) the day before and 3 months after the ablation procedures. Image acquisition was electrogram gated when possible, and the parameters included 70–120 kV, 850mA, 0.6-mm beam collimation, 0.625–1.25-mm thickness, and 20–30-cm field of view. Iodinated contrast material was administered intravenously with a power injection at a rate of 3-4.5 mL/sec for 10 sec. The end-systolic imaging data were used for a 3-dimensional reconstruction. The diameter of each PV was measured at the maximum distance between 2 ostial points before and after the ablation (Figure 2). The wall thickness was also measured at the posterior aspect of each PV ostium, and was compared before and after the procedure. The PV ostium was defined as the point of inflection between the LA wall and PV wall. PV stenosis was categorized as 0-25%, 25%–50%, and >50%.

Follow-up

The AADs that were withdrawn before the ablation procedure were resumed the evening of the procedure in all patients. We scheduled to follow them up 3, 9, and 12 months after the procedure to screen for any AF recurrences [4]. Twelve-lead electrocardiograms were obtained at all clinical visits, and 24-h Holter monitoring was performed at 3-month intervals during the follow-up period. The oral AADs were encouraged to be discontinued in patients who remained free from AF for 3 consecutive months, however, the AADs were continued when they were reluctant to stop them.

Endpoints

The endpoints of the present study were any PV stenosis right after and 3 months after the ablation procedure.

Statistical analysis

The continuous variables were summarized as the means±standard deviations, and categorical variables as proportions. PV stenosis was classified into 3 categories and compared between the groups with the use of a Pearson's Chi-Square test. A Fisher's exact test was used to examine other categorical variables. The changes before and after the ablation in the PV luminal area, PV wall thickness area, and wall thickness of the PV ostium were compared with the use of a Wilcoxon signed-rank test. The comparisons of the other continuous variables were performed by means of a Mann-Whitney U test. All statistical analyses were performed with the use of JMP software version 12.0 (SAS Institute, Cary, NC, USA). A P value of <0.05 was considered significant.

Results

We recruited a total of 52 eligible patients (26 in each arm). We excluded 1 patient in the CB group because he was found to have a common left PV trunk after recruitment. We failed to follow-up 1 patient in the RF arm. We therefore analyzed the data in 25 patients in each arm. No significant difference was noted in the baseline characteristics between the groups (Table 1).

Bidirectional conduction block was achieved in all 200 PVs in the 50 patients. A touch-up freeze was needed in 8 PVs (8%; 3 LSPVs, 2 LIPV, 2 RSPVs, 1 RIPV) among 8 (32%) patients in the CB arm. Intravascular ultrasound assessment revealed a significant reduction in the PV luminal area immediately after the ablation of each PV both in the 2 arms (Figure 3A). The patients in the CB group had a smaller reduction in the luminal area right after the ablation of the LSPV (-6.8±8.7 vs. -19.9±14.7%; p<0.001) and LIPV (-5.1±20.2 vs. -15.3±11.6%; p=0.03) than the patients in the RF group. On the other hand, there was no significant difference in the luminal change immediately after the ablation of the RSPV between the groups (-7.3±12.4 vs. -8.3±9.4%; p=0.75, Figure 3B). In terms of the PV wall thickness area, it significantly increased right after the ablation in both groups (Figure 4A), and the increasing rates were similar (Figure 4B).

No PV stenosis of >50% was noted in either arm at the time of the 3-month cardiac CT assessment. We found a trend toward a more frequent occurrence of 25–50% LSPV stenosis in the RF group (p=0.05). The total number of PVs with 25-50% stenosis, however, did not differ between the groups (10% vs. 12%; p=0.82, Table 2). There was no significant change in the wall thickness of each PV ostium before and 3 months after the ablation in both arms (Figure 5). The change in the PV luminal area right after the ablation was not associated with the extent of the PV stenosis 3 months after the ablation in the CB group (Figure 6A). On the other hand, an analysis including all 3 PVs studied revealed that the PVs with more pronounced acute narrowing had a greater stenosis in the chronic phase in the RF arm (p=0.004, Figure 6B).

No difference between the PVs with and without 25-50% stenosis was noted in the balloon nadir temperature (-48.5±2.2 vs. -49.7±2.1˚C; p=0.1) and total thaw time (47.6±12.3 vs. 54.3±13.1seconds; p=0.12) among the patients in the CB arm, and catheter tip temperature (39.3±2 vs. 38.9±1.4˚C; p=0.39) among the patients in the RF arm.

By 12 months after the procedure, AADs were continued in 7 (28%) and 6 (24%) patients in the CB and RF groups, respectively (p=0.99). In that setting, 20 (80%) patients in each group enjoyed freedom from AF. We did not encounter any serious complications, including phrenic nerve injury, cardiac tamponade, massive bleeding, or strokes, during the study period.

Discussion

The main findings of the present study were as follows. (1) the CB application narrowed the left-sided PVs to a lesser extent in the acute phase than did RF ablation. (2) Although no moderate or severe stenosis was observed in each PV during the chronic phase without regard to the energy source, the PVs with a greater acute narrowing were likely to develop a tighter stenosis in the chronic phase when RF was delivered.

PV stenosis likely results from a combination of endothelial disruption with platelet activation and later neo-intimal proliferation, reversible edema, collagen denaturation, and shrinkage or thermal contracture [7]. Importantly, it is already known that cryothermal applications result in less endothelial disruption [8], maintenance of the extracellular collagen matrix without collagen denaturation [9,10], and no collagen contracture related to the thermal effects [11]. These characteristics may translate into a reduction in the PV stenosis with the use of the CB as compared to RF [7]. The results of the present study may thus highlight the potential superiority of CB ablation over RF ablation for the prevention of PV stenosis by means of comparing the acute morphological response of the PVs to the different energy sources. A study reported that PV reconnections were more common in the right PVs after a radiofrequency-based PV isolation [12]. The authors explained that catheter instability during a right-sided PV isolation was responsible for this finding. Thus, it is possible that a less narrowed RSPV in the RF arm reflected a potential inadequate lesion depth along the right PVs due to catheter instability. Studies including patients treated with RF ablation [1] have reported a higher incidence of PV stenosis in left PVs. A large-scale trial regarding CB ablation [2] reported that the most frequent site of PV stenosis was LIPV. Those findings were consistent with ours, in terms of favorite site of PV stenosis. Interestingly, to the best of our knowledge, we for the first time reported that the thickening of the PV wall was seen with a similar extent immediately after the ablation regardless of the energy source, and it was not observed any more in the remote period. The likely explanation is that cryoablation probably elicited just as much "reversible" edema as RF ablation did. Intramural hemorrhage is another histological alteration observed in acute phase after both cryothermal and RF ablation for atrial myocardium [13]. Although it is highly possible that the intramural hemorrhage also contributed to thickening PV wall immediately after the ablation, we failed to measure its contrition with the use of the ultrasound catheter. Further intensive studies with the use of magnetic resonance imaging or even animal models are warranted.

We in the present study did not encounter any moderate or severe PV stenosis by 3-months of follow-up even in the RF arm. The possible explanations are as follows. (1) We used open irrigated-tip catheters in all patients in the RF arm on the basis of our previous report that it reduced the acute PV narrowing as compared to non-irrigated catheters [6]. (2) Considering the increasing awareness of the risk of PV stenosis [1] and unfavorable outcomes with the use of a segmental PV isolation [14], we tried to create wider continuous circumferential lesions around the PVs.

Clinical implications

To the best of our knowledge, the present study was the first to compare the acute reduction in the PV diameter between CB and RF applications. We showed the clinical importance of assessing the acute change in the PV diameter through the findings observed in the RF arm that a greater acute PV narrowing translated into chronic PV stenosis, though it was not clinically significant stenosis. Therefore, given that PV stenosis is an avoidable complication of AF ablation [1], our findings may provide important information to reduce the complication rate.

Limitations

Once again, no clinically significant PV stenosis was observed in the present study. Therefore, the impact of the present study on the clinical practice was limited. Because of the safety concern, we failed to assess the RIPV. There was a limit to the reproducibility of the ultrasound catheter positioning in each PV to measure the PV luminal area at the same level before and after the ablation. Unlike the other studies [2,3], more than one CB application was not allowed in our study, which could have had a potential favorable impact on the PV morphological change after the ablation in the CB arm. We were unable to deny the possibility that the RF applications could have been unintentionally delivered deep enough inside the PVs to cause mild PV stenosis in a few patients. Finally, this was a single center study with a small number of participants.

Conflict of interest

None declared.

Funding

None declared.

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Figure legends

Figure 1. Intracardiac ultrasound images of the proximal left superior pulmonary vein before (A) and immediately after (B) pulmonary vein (PV) isolation in a patient in the radiofrequency arm. The external (green lines) and internal (red lines) surfaces of the PV were traced to measure the vessel area and luminal area, respectively. The wall thickness area of the PV was calculated by subtracting the luminal area from the vessel area (C). A 32% reduction in the luminal area and 84% increase in the wall thickness area were noted after the radiofrequency application.

Figure 2. Computed tomographic images of the left atrium the day before (A and B) and 3 months after (C and D) the ablation procedure in a patient in the radiofrequency arm. A 28% stenosis was noted at the ostium of the left superior pulmonary vein (red arrows and two-headed arrows).

Figure 3. Luminal area of the pulmonary vein (A) and its %change (B) before and right after the ablation in the cryoballoon and radiofrequency arms. The means and standard deviations are presented. PV=pulmonary vein, LSPV=left superior pulmonary vein, LIPV=left inferior pulmonary vein, RSPV=right superior pulmonary vein, CB=cryoballoon, RF=radiofrequency.

Figure 4. Wall thickness area of the pulmonary vein (A) and its %change (B) before and right after the ablation in the cryoballoon and radiofrequency arms. The means and standard deviations are presented. The abbreviations are the same as in Figure 3.

Figure 5. Wall thickness of the pulmonary vein before and 3 months after the ablation in the cryoballoon and radiofrequency arms. The means and standard deviations are presented. The abbreviations are the same as in Figure 3.

Figure 6. Distribution of the patients with pulmonary vein (PV) stenosis of 0-25% or 25–50% observed 3 months after the ablation according to the change in the luminal area of the PV ostium right after the ablation in the cryoballoon (A) and radiofrequency arms (B). P values are based on the Mann-Whitney U test for the comparison of the acute percentage change in the PV luminal area between the patients with chronic PV stenosis of 0-25% and those with stenosis of 25-50%. The abbreviations are the same as in Figure 3.

Table 1. Baseline characteristics

Variables	Cryoballoon N=25	Radiofrequency N=25	P-value
Age—yrs.	62±12	68±9	0.05
Male	17 (68)	19 (76)	0.53
Body mass index—kg/m^2	23.6±3.5	24.2±3.3	0.54
Hypertension	16 (64)	14 (56)	0.56
Diabetes	3 (12)	5 (20)	0.44
Heart failure	2 (8)	2 (8)	0.99
Previous stroke	1 (4)	2 (8)	0.55
Left atrial diameter—mm	39±6	42±5	0.09
Left ventricular ejection fraction—%	63±5	58±8	0.07

The values are the mean±SD, n (%).

Table 2. PV characteristics 3 months after the ablation

PV	Cryoballoon, N=25			Radiofrequency, N=25			P-value
	Stenosis 0-25%	Stenosis 25-50%	Stenosis >50%	Stenosis 0-25%	Stenosis 25-50%	Stenosis >50%	
LSPV (N=25)	25 (100)	0	0	20 (80)	5 (20)	0	0.05
LIPV (N=25)	15 (60)	10 (40)	0	20 (80)	5 (20)	0	0.22
RSPV (N=25)	25 (100)	0	0	25 (100)	0	0	0.99
RIPV (N=25)	25 (100)	0	0	23 (92)	2 (8)	0	0.49
Overall (N=100)	90 (90)	10 (10)	0	88 (88)	12 (12)	0	0.82

The values are the n (%). PV=pulmonary vein, LS=left superior, LI=left inferior, RS=right superior, RI=right inferior.

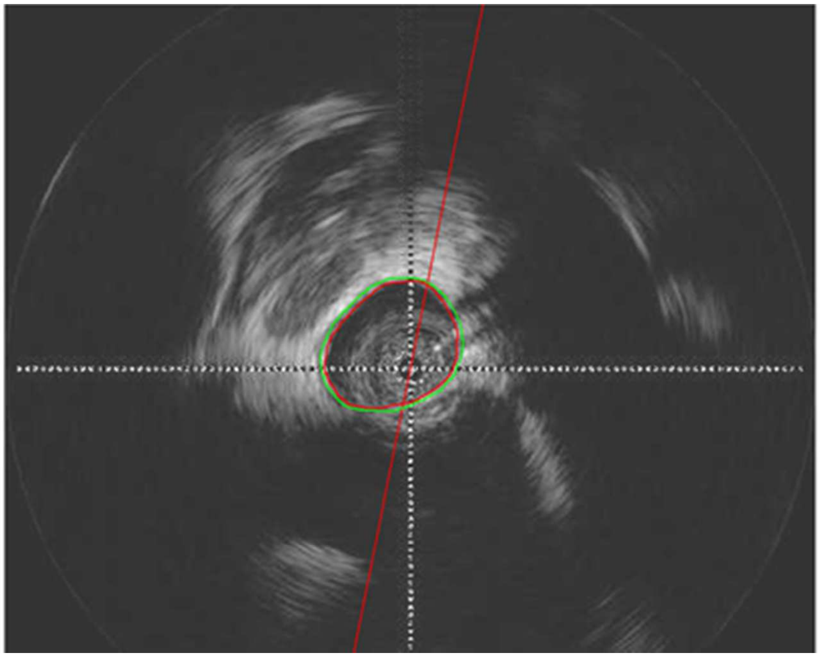

Figure 1A

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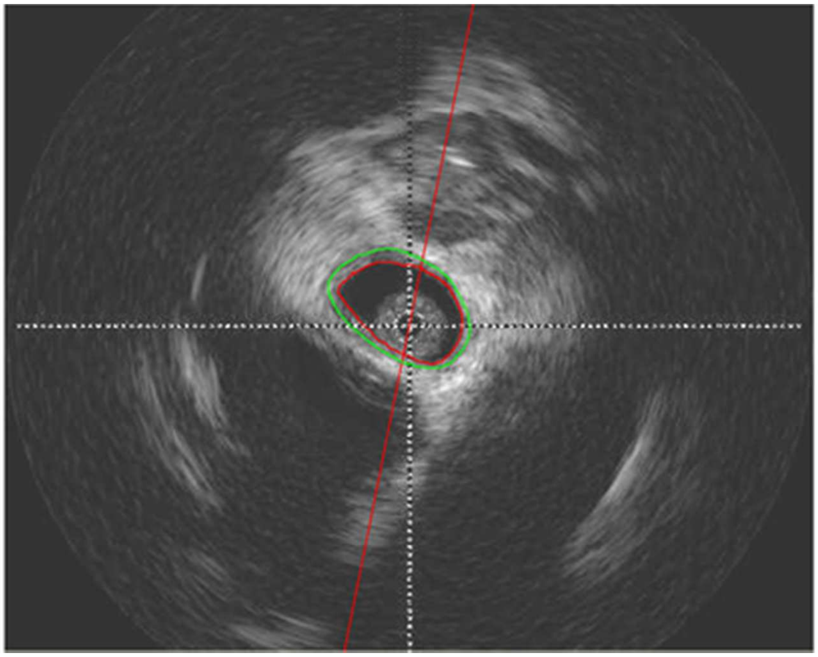

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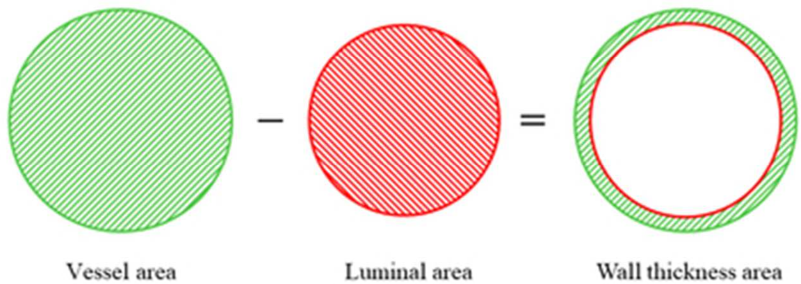

Figure 1C

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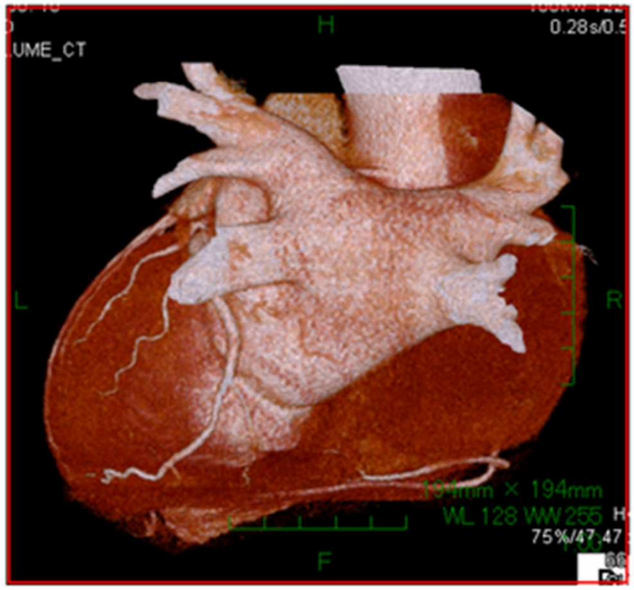

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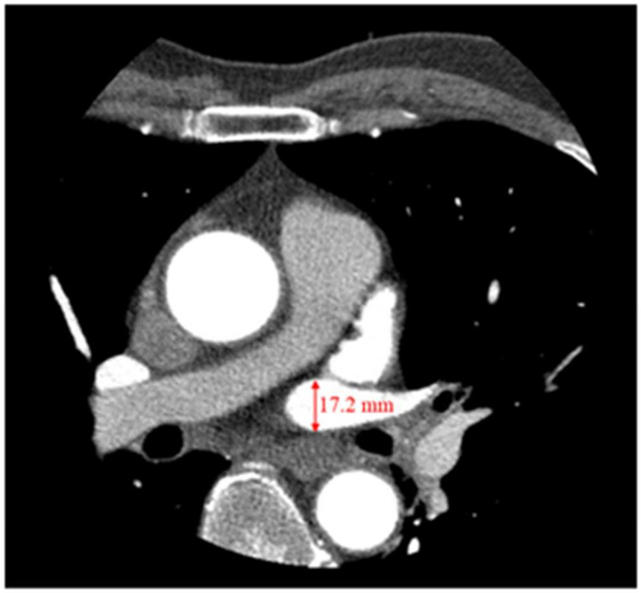

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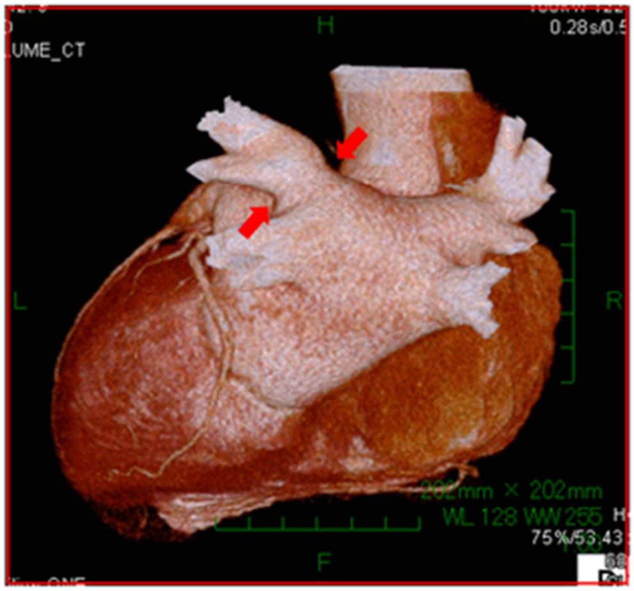

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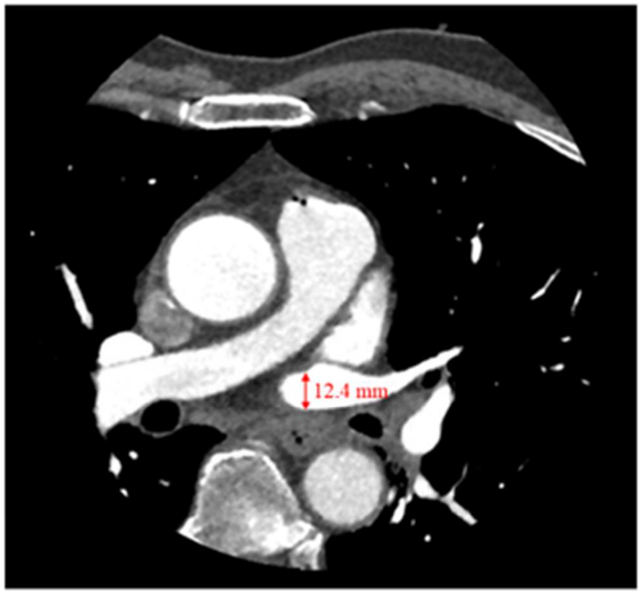

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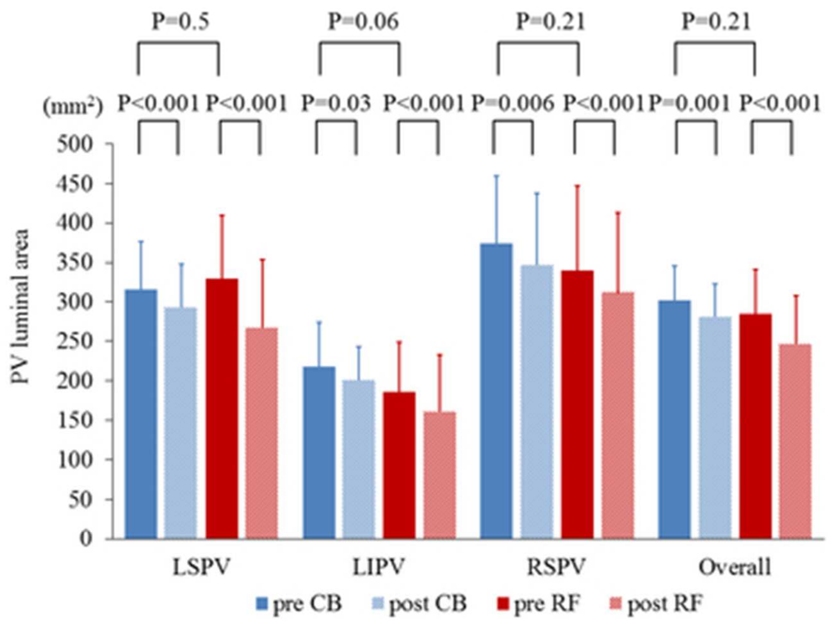

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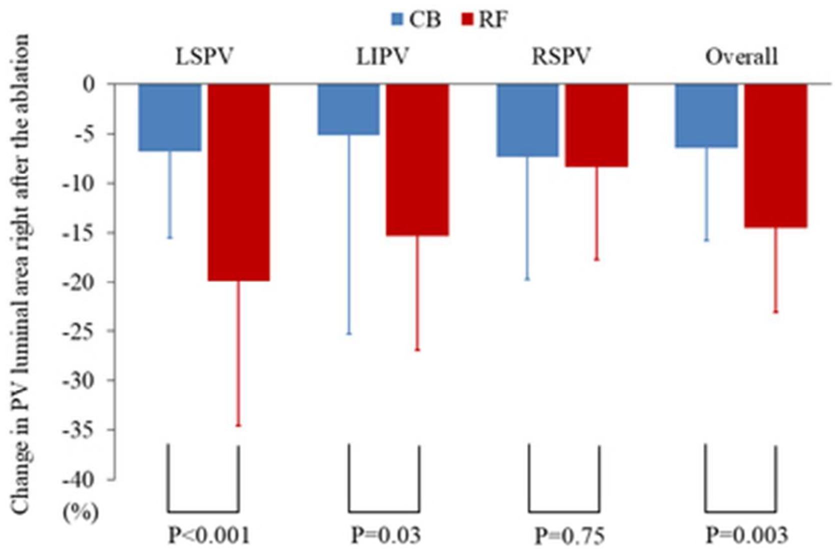

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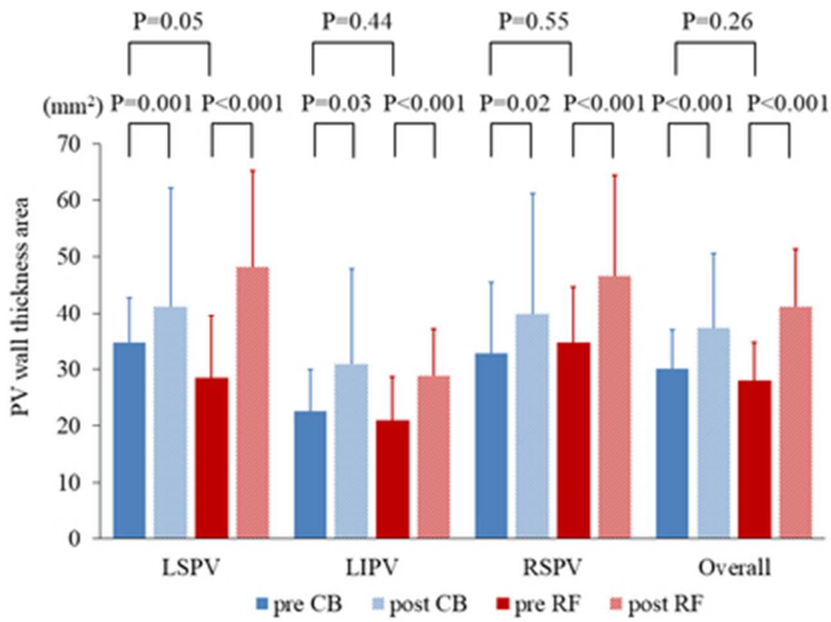

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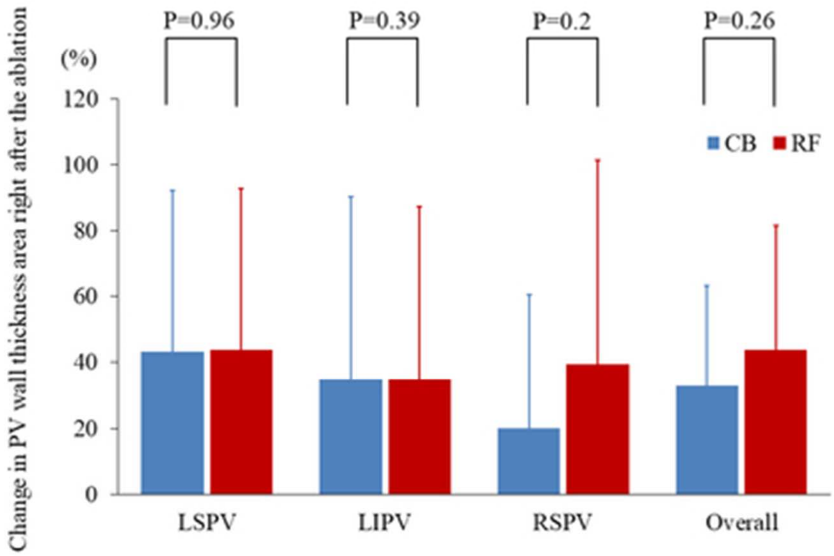

Figure 4B

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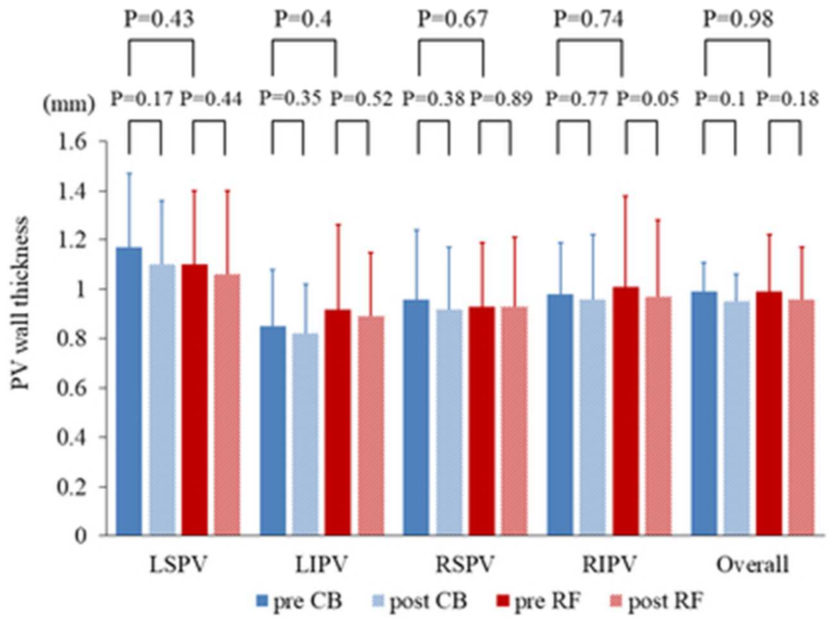

Figure 5

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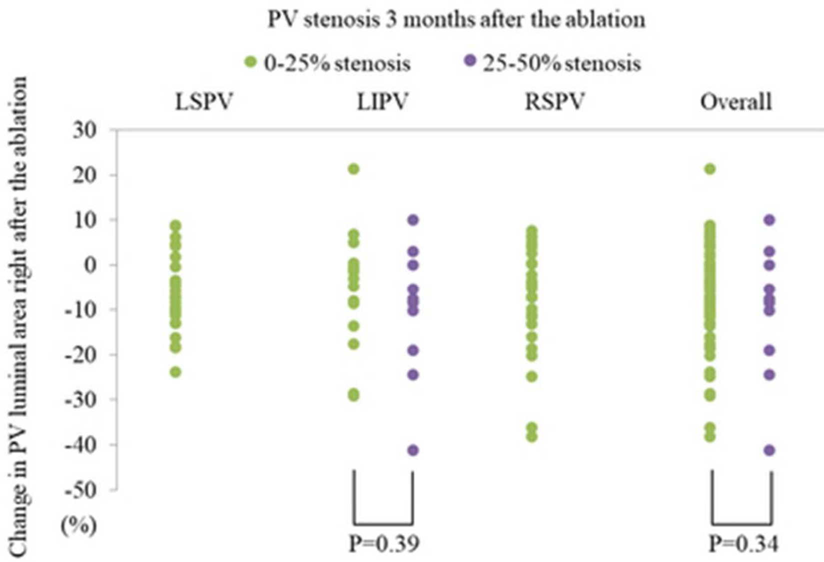

Figure 6A

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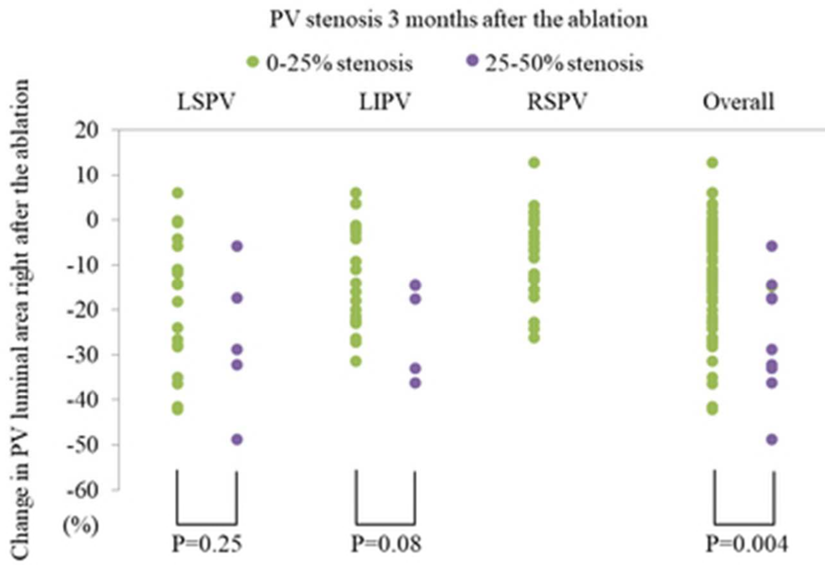

Figure 6B

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