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ORIGINAL ARTICLE
Catheter Ablation

Incidence and Characteristics of Coronary Artery Spasms Related to Atrial Fibrillation Ablation Procedures

— Large-Scale Multicenter Analysis —

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Background: Coronary artery spasms (CASs), which can cause angina attacks and sudden death, have been recently reported during catheter ablation. The aim of the present study was to report the incidence, characteristics, and prognosis of CASs related to atrial fibrillation (AF) ablation procedures.

Methods and Results: The AF ablation records of 22,232 patients treated in 15 Japanese hospitals were reviewed. CASs associated with AF ablation occurred in 42 of 22,232 patients (0.19%). CASs occurred during ablation energy applications in 21 patients (50%). CASs also occurred before ablation in 9 patients (21%) and after ablation in 12 patients (29%). The initial change in the electrocardiogram was ST-segment elevation in the inferior leads in 33 patients (79%). Emergency coronary angiography revealed coronary artery stenosis and occlusions, which were relieved by nitrate administration. No air bubbles were observed. A comparison of the incidence of CASs during pulmonary vein isolation between the different ablation energy sources revealed a significantly higher incidence with cryoballoon ablation (11/3,288; 0.34%) than with radiofrequency catheter, hot balloon, or laser balloon ablation (8/18,596 [0.04%], 0/237 [0%], and 0/111 [0%], respectively; P<0.001). CASs most often occurred during ablation of the left superior pulmonary vein. All patients recovered without sequelae.

Conclusions: CASs related to AF ablation are rare, but should be considered as a dangerous complication that can occur anytime during the periprocedural period.

Key Words: Atrial fibrillation; Catheter ablation; Coronary artery spasm; Cryoballoon; Radiofrequency

Atrial fibrillation (AF) ablation procedures are generally effective and safe; however, devastating complications occasionally occur. Coronary artery spasms (CASs) have recently been reported as a complication of AF ablation, and some patients develop serious conditions (ventricular fibrillation [VF] and/or cardiopulmonary arrest [CPA]).[1,2] However, the rare occurrence of

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a CAS makes it a difficult entity to study in terms of its physiopathology and risk factors. For this reason, effective preventive measures and appropriate therapeutic strategies are currently lacking, and CASs related to AF ablation are not well recognized among electrophysiology physicians and medical professionals. The aim of the present study was to screen a large-scale multicenter retrospective registry to provide a systematic report on the incidence, characteristics, and prognosis of CASs related to AF ablation procedures.

Methods

Study Design

This study used data from a retrospective descriptive registry of cases of CAS associated with AF ablation procedures. Electronic forms, which included diagnostic criteria for CASs related to AF ablation, were distributed to 15 Japanese hospitals. The coinvestigators reviewed the AF ablation records between January 2011 and December 2019 at their hospitals and reported CAS cases that met the study's diagnostic criteria. The electronic forms collected information about patient characteristics, preoperative preparation, details of the ablation procedures, timing of the onset of and the diagnostic process for CASs, patient severity, the treatment adopted, and final outcomes. In addition, we investigated the characteristics associated with the occurrence of CAS during the pulmonary vein (PV) isolation with different ablation energy sources.

The protocol for this research project was approved by a suitably constituted Ethics Committee of Kobe University Hospital (Committee of 1 March, 2019; Approval no. 190017), and the study conformed to the provisions of the Declaration of Helsinki. Patients consented to the use of their anonymized clinical data for research purposes by the opt-out method.

Diagnostic Criteria

CASs related to AF ablation were defined as the incidence of a CAS occurring before, during, or after the ablation procedure. "Before ablation" was defined as the procedure time before the ablation energy application (e.g., anesthetic administration, sheath or catheter insertion, and transseptal puncture). "During ablation" was defined as the time during ablation energy application (e.g., radiofrequency [RF], cryoballoon [Arctic Front Advance; Medtronic, Minneapolis, MN, USA], hot balloon [SATAKE HotBalloon; Toray Industries, Tokyo, Japan], laser balloon [HeartLight; CardioFocus, Marlborough, MA, USA]) or the time between each ablation energy application. "After ablation" was defined as the procedure time after application of the ablation energy (e.g., cardioversion, isoproterenol administration, and compression of the femoral vessels) or within 24 h after the ablation procedure. Based on Japanese Circulation Society (JCS) 2013 guidelines,[3] CASs were diagnosed by ischemic electrocardiogram (ECG) changes that returned to normal quickly after the administration of a nitrate. CASs could be diagnosed without performing coronary angiography (CAG). Because patients are sedated during the ablation procedure, the presence of chest symptoms was not necessary for a diagnosis of a CAS in the present study. Coronary air embolisms were the most important differential diagnosis. Coronary air embolisms we excluded as follows. First, we confirmed that there were no air bubbles in the coronary artery in patients who underwent emergency CAG and that there were no air bubbles in the left atrium, left atrial appendage, and left ventricle in all patients using fluoroscopic imaging. Second, patients in whom ischemic ECG changes spontaneously returned to normal before nitrate administration were excluded from the study because it was difficult to differentiate between a CAS and a coronary air embolism in those patients.

Table 1. Clinical Characteristic of Patients With Coronary Artery Spasms (n=42)

Male sex	41 (98)
Age (years)	66±18
Weight (kg)	66.5±20.6
BMI (kg/m²)	22.7±2.9
Serum creatinine (mg/dL)	0.92±0.36
Medical history	
Paroxysmal AF	24 (57)
Persistent AF	14 (33)
Long-standing persistent AF	4 (10)
Initial AF ablation	35 (83)
LAD (mm)	39.9±7.2
LVEF (%)	61.1±8.2
Diabetes	4 (10)
Hypertension	15 (38)
Dyslipidemia	9 (21)
Smoking	30 (71)
History of vasospastic angina	3 (7)
History of coronary intervention	3 (7)
Medications before ablation	
β-blocker	16 (38)
Calcium channel blocker	9 (21)
Nitrate	3 (7)

Data are presented as the mean±SD or as n (%). AF, atrial fibrillation; BMI, body mass index; LAD, left atrial dimension; LVEF, left ventricular ejection fraction.

Statistical Analysis

Data are expressed as percentages for discrete variables and as the mean±SD for continuous variables. Discrete variables were compared using the Chi-squared or Fisher exact test, as appropriate. If continuous variables were normally distributed, they were analyzed using unpaired t-tests or the Welch test. Two-tailed $P<0.05$ was considered significant. All statistical analyses were performed using SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline Patient Characteristics

The AF ablation records for 22,232 patients from 15

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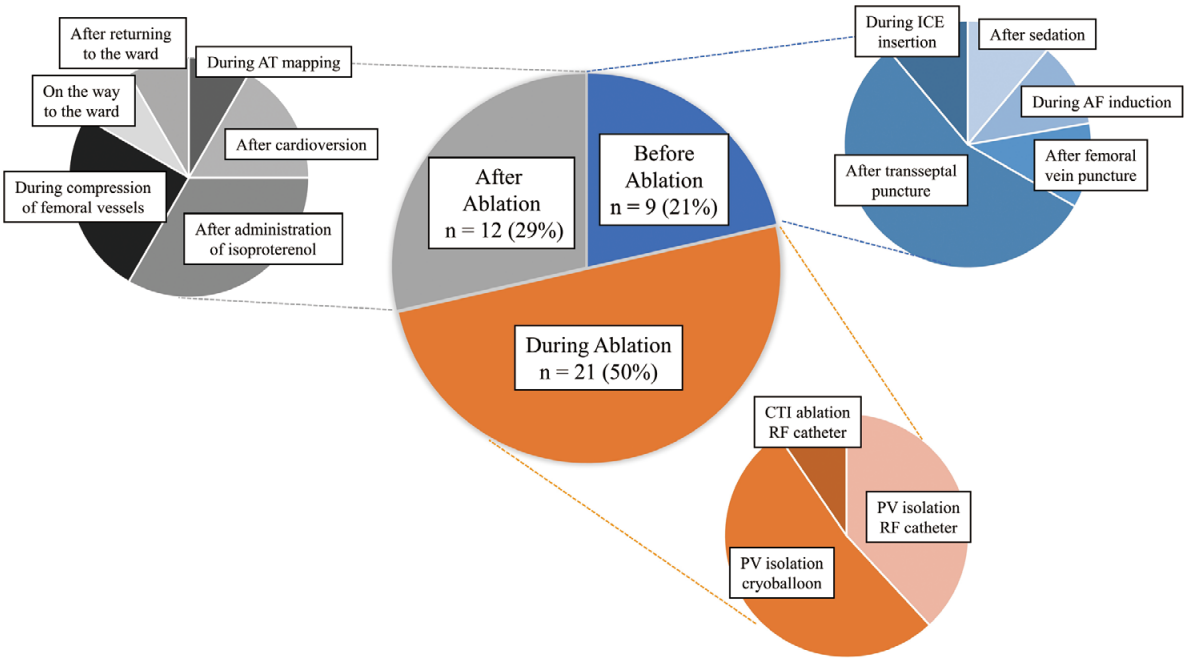

Figure 1. Incidence of coronary artery spasms (CASs) related to atrial fibrillation (AF) ablation and the timing of CAS onset. The large central pie chart shows the timing of the onset of CASs. Half the CASs occurred during the ablation procedure and the others occurred before and after ablation. The 3 small pie charts illustrate the Details of the procedures at the time of CAS occurrence before, during, and after the ablation procedure are shown in the 3 smaller pie charts. AT, atrial tachycardia; CTI, cavotricuspid isthmus; ICE, intracardiac echocardiography; PV, pulmonary vein; RF, radiofrequency.

Japanese institutions were reviewed. CASs associated with AF ablation occurred in 42 of 22,232 patients (0.19%). The baseline characteristics of the patients with CASs are summarized in **Table 1**. Mean patient age was 66±18 years, and 41 of 42 patients (98%) were male. In all, 24 of 42 patients (57%) had paroxysmal AF. Thirty patients (71%) had a history of smoking. Only 3 patients (7%) had a history of a CAS and another 3 (7%) had a history of coronary artery intervention. All patients were administered some type of intravenous anesthetic during the AF ablation procedure. Dexmedetomidine was used in 36 patients (86%), propofol was used in 17 (40%), and thiopental was used in 24 (57%).

Timing of CAS Onset

The timing of CAS onset is shown in **Figure 1**. CASs were most often seen during the delivery of ablation energy (in 21 of 42 patients [50%]). CASs also occurred before the ablation in 9 patients (21%) and after the ablation procedure in 12 (29%). **Figure 2** shows a representative case of a CAS. Just after the administration of intravenous thiopental, the 12-lead ECG revealed ST elevation in the inferior and precordial leads. VF then occurred, cardioversion was performed, and cardiopulmonary resuscitation was initiated. Emergency CAG revealed CAS in the right coronary artery. Intracoronary nitroglycerin was injected, and the spasms were relieved. The ST-segment elevation normalized immediately.

Initial ECG Changes

Overall, 33 of 42 patients (79%) had ST-segment elevation in the inferior leads (II, III, and aVF) of the ECG. In the remaining patients, ST-segment elevation was noted in the precordial leads in 5 patients, in the inferior/lateral leads in 2 patients, in the inferior/precordial leads in 1 patient, and in the precordial/lateral leads in 1 patient.

Emergency CAG Findings and Treatment

Emergency CAG was performed in 37 of 42 patients (88%). No air bubbles were observed in the coronary arteries in any of the 37 patients. In these 37 patients, 42 spastic lesions were observed in the coronary arteries. CAG of the right coronary artery revealed total occlusion in 2 patients, focal severe (90–99%) stenosis in 14 patients, and moderate stenosis or slow flow in 7 patients. CAG of the left coronary artery revealed total occlusion in 1 patient, focal severe stenosis in 2 patients, and moderate stenosis or slow flow in 8 patients. No significant stenosis was observed on the CAG of 8 patients who had received an immediate intravenous injection of nitroglycerin before the CAG. All abnormal CAG findings were relieved by intravenous or intracoronary injection of nitroglycerin, and emergency percutaneous coronary interventions was not needed in any patient. Five of the 42 patients did not undergo CAG at the time of CAS occurrence. In these patients, the ischemic ECG changes returned to normal quickly after the administration of a nitrate.

Patient Severity

VF and/or CPA requiring cardiopulmonary resuscitation occurred in 7 of 42 patients (17%). **Table 2** compares the characteristics of patients with and without a serious

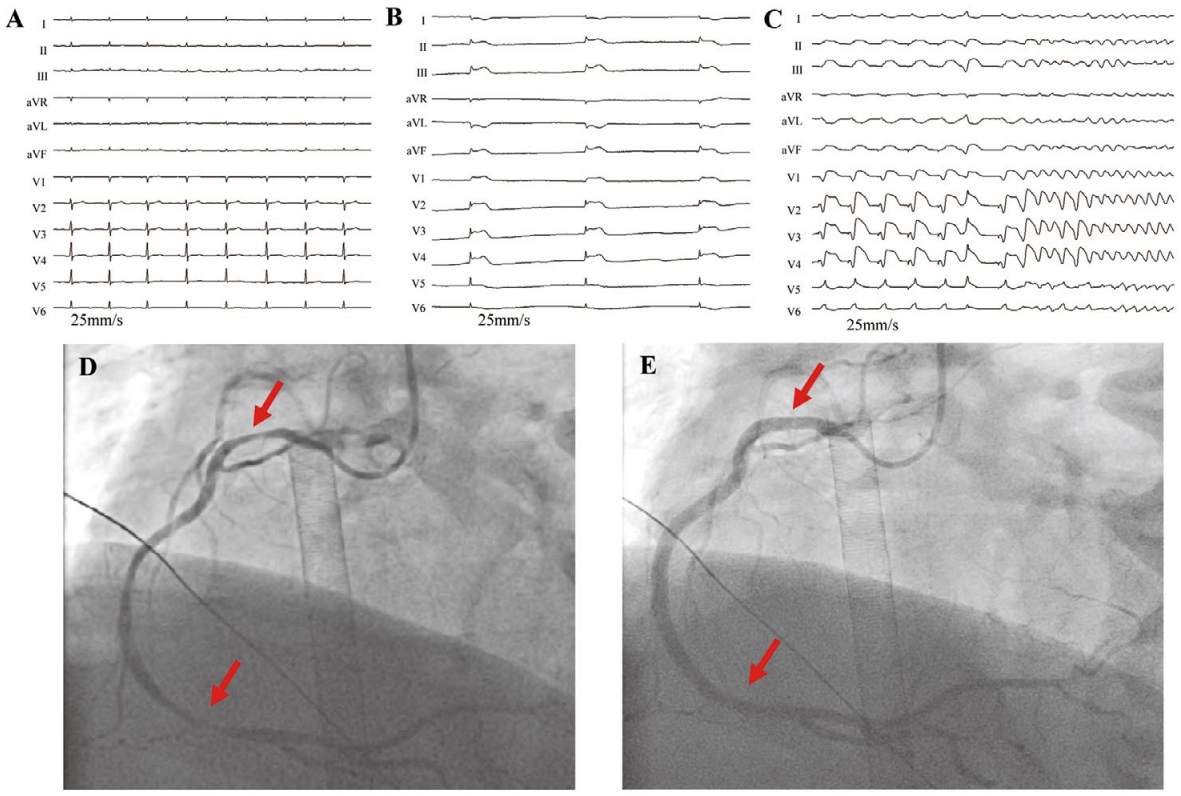

Figure 2. Representative case of a coronary artery spasm (CAS). (**A**) Twelve-lead electrocardiogram (ECG) at the start of the ablation procedure. (**B**) Just after the administration of intravenous thiopental, the 12-lead ECG revealed ST-segment elevation in the inferior and precordial leads. The P wave disappeared, and significant bradycardia was seen. (**C**) Repetitive ventricular fibrillation occurred. Cardiopulmonary resuscitation was started. (**D**) Coronary angiography revealed right coronary artery spasms (red arrows). (**E**) Intracoronary injection of nitroglycerin resolved the coronary artery narrowing completely. Left coronary angiography revealed no stenosis due to the administration of nitroglycerin in the right coronary artery.

condition (VF or CPA). Episodes of persistent or long-standing persistent AF were significantly more numerous in patients with than without a serious condition. Thiopental was more often used in patients with a serious condition.

CAS Characteristics During PV isolation

Energy Source Comparisons between the different ablation energy sources revealed a significantly higher incidence of CAS during PV isolation with cryoballoon ablation (11/3,288; 0.34%) than with RF catheter, hot balloon, or laser balloon ablation (8/18,596 [0.04%], 0/237 [0%], and 0/111 [0%], respectively; P<0.001; **Figure 3**).

PV Sites of CASs **Figure 4** shows the PVs where the ablation energy was delivered at the time of CAS occurrence. In 17 of 19 patients who experienced a CAS during application of ablation energy, left PV isolation was initially performed, followed by right PV isolation. The CASs most often occurred during left superior PV (LSPV) ablation than during ablation of the other PVs (P<0.0001). **Figure 4** also shows the relationship between the PV sites and ECG leads that showed ST-segment elevation. Regardless of the PV site where the RF or cryoballoon application was delivered, ST-segment elevation was most often observed in the inferior leads.

Prognosis

All patients recovered without any sequelae after the treatment. Prophylactic drugs (e.g., calcium channel blockers or nitrates) for CASs were started after the procedure in 24 of 42 patients (57%). Over a mean 28 months of follow-up (range 1–105 months) after CAS occurrence, 3 patients (7%) experienced CAS recurrence. One patient who was treated with a calcium channel blocker experienced 2 CAS episodes related to the AF ablation. In that patient, the first CAS episode occurred during PV isolation using RF energy during the first ablation procedure. During the second AF ablation procedure, CAS recurred during compression of the femoral vessels. The remaining 2 patients were treated with calcium channel blockers or nicorandil and experienced chest symptoms during the follow-up period.

Discussion

To the best of our knowledge, this is the largest series report regarding CASs associated with AF ablation procedures. The main findings of this study are that: (1) the incidence of CASs related to AF ablation was 0.19% and one-sixth of patients with CASs developed a serious condition (VF or CPA); (2) half the CASs occurred during ablation, but

Table 2. Comparison of Characteristics Between CAS Patients With and Without VF and/or Cardiopulmonary Arrest

	CAS with VF and/or CPA (n=7)	CAS without VF and/or CPA (n=35)	P value
Male sex	7 (100)	34 (97)	1.00
Age (years)	64±9	67±9	0.78
Weight (kg)	69.7±12.7	65.9±9.8	0.94
BMI (kg/m^2)	23.6±3.8	22.5±2.7	0.40
Serum creatinine (mg/dL)	0.93±0.17	0.91±0.19	0.70
Medical history			
Paroxysmal AF	1 (14)	23 (68)	0.027
Persistent AF	5 (71)	9 (26)	
Long-standing persistent AF	1 (14)	3 (9)	
Initial AF ablation	5 (71)	30 (86)	0.58
LAD (mm)	47.5±5.0	37.6±6.1	0.17
LVEF (%)	58.1±7.9	60.1±8.2	0.78
Diabetes	2 (29)	2 (6)	0.12
Hypertension	2 (29)	13 (37)	1.00
Dyslipidemia	1 (14)	8 (23)	1.00
Smoking	5 (71)	25 (71)	1.00
History of vasospastic angina	1 (14)	2 (6)	0.43
History of coronary intervention	1 (14)	2 (6)	0.43
Medications before ablation			
β-blocker	4 (57)	12 (34)	0.40
Calcium channel blocker	2 (29)	7 (20)	0.63
Nitrate	1 (14)	2 (6)	0.43
Time of CAS onset			
Before ablation	1 (14)	8 (23)	0.06
During ablation	1 (14)	18 (51)	
After ablation	5 (71)	9 (26)	
CAG findings			
Total occlusion	1 (14)	2 (6)	0.027
Severe stenosis	6 (86)	10 (29)	
Slow flow	0 (0)	10 (29)	
No stenosis	0 (0)	8 (23)	
Sedative agents			
Dexmedetomidine	7 (100)	29 (83)	0.57
Propofol	1 (14)	16 (46)	0.21
Thiopental	7 (100)	17 (49)	0.014
Fentanyl	4 (57)	19 (54)	1.00
Pentazocine	3 (43)	9 (26)	0.39
Buprenorphine	0 (0)	4 (11)	1.00
Prognosis			
Introduction of a prophylactic drug	5 (71)	19 (54)	0.40
CAS recurrence	0 (0)	3 (9)	0.57
AF recurrence	3 (43)	8 (23)	0.35

Unless indicated otherwise, data are presented as the mean±SD or as n (%). AF, atrial fibrillation; BMI, body mass index; CAG, coronary angiography; CAS, coronary artery spasm; CPA, cardiopulmonary arrest; LAD, left atrial dimension; LVEF, left ventricular ejection fraction; VF, ventricular fibrillation.

CASs also occurred before and after the ablation procedure; and (3) CASs often occurred during LSPV ablation, and the incidence of CAS was significantly higher during cryoballoon ablation than ablation using the other energy sources.

Incidence of CAS and Patient Characteristics

The incidence of CASs (0.19%) in the present study was twice as high as the incidence of coronary artery thrombus and embolus formation due to direct thermal injury from RF energy close to the coronary artery reported in previous studies.[4,5]

Coronary atherosclerosis, implantation of drug-eluting stents, and habitual smoking are recognized predisposing factors for CASs.[6,7] In the present study, most patients with CASs were male; however, many of those patients had no coronary risk factors. Therefore, it would be difficult to predict the occurrence of CAS related to AF ablation

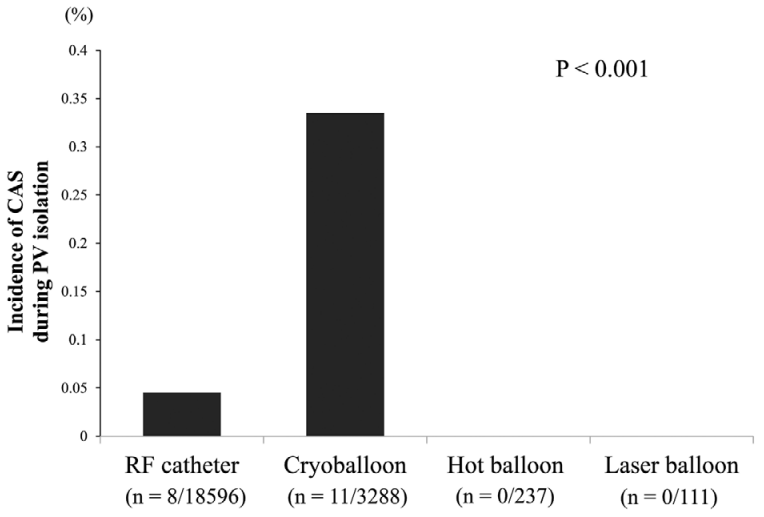

Figure 3. Comparison of the incidence of coronary artery spasms (CASs) during delivery of ablation energy using different ablation energy sources. PV, pulmonary vein. RF, radiofrequency.

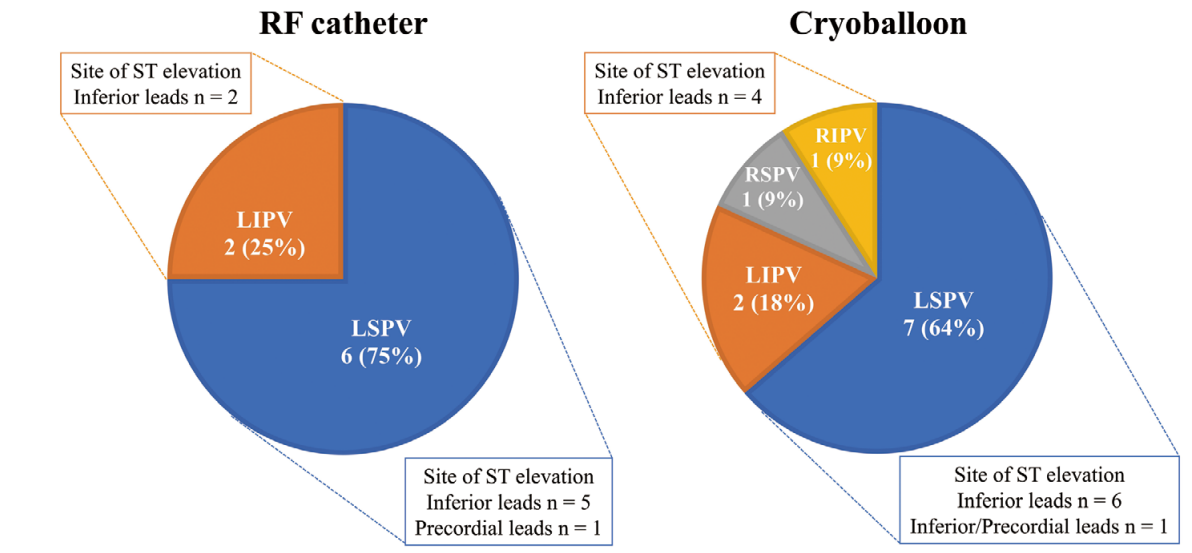

Figure 4. Distribution of the pulmonary vein (PV) sites and electrocardiogram (ECG) changes in patients experiencing coronary artery spasms (CASs) during PV isolation. LIPV, left inferior PV; LSPV, left superior PV; RF, radiofrequency; RIPV, right inferior PV; RSPV, right superior PV.

based only on baseline patient characteristics.

Presumed Mechanism Underlying CASs

Changes in Autonomic Tone CASs tended to occur in association with specific steps during the ablation procedure: just after trans-septal puncture, during PV isolation, after isoproterenol administration, or during compression of the femoral vessels. Notably, these steps can all affect the activity of the autonomic nervous system.[8] Therefore, we speculate that a major trigger of CASs could have been a change in autonomic tone. Endocardial catheter ablation may affect the epicardial ganglionated plexi (GP), which could cause a sudden increase in sympathetic or vagal tone and trigger CAS.[9] In a previous high-frequency stimulation study, we demonstrated a larger number of GP-positive sites around the left PVs (Marshall tract GP and superior left GP) than around the right PVs (anterior right GP).[10] This uneven distribution of GP would result in a higher incidence of CASs during left PV ablation.

The GP also have an interactive effect on the other GP and the extrinsic autonomic nervous system.[11] The anterior right GP serves as the integration center for both the right and left vagosympathetic trunks. Miyazaki et al[12] found that cryoballoon ablation of the right before left PVs significantly reduced the incidence of a vagal response. In the present study, left PV isolation was initially performed

in most patients with CASs during ablation energy application. Consequently, the imbalance in autonomic tone induced by GP ablation around the left PV would spread through the anterior right GP, which was not ablated.

In addition, the incidence of a vagal response is higher during cryoballoon than RF ablation.[12,13] A stronger effect on the sympathetic and parasympathetic nervous system during cryoballoon ablation would explain the higher incidence of CAS. The cold pressor test is also a well-known procedure for provoking CASs.[14] The spread of cryothermal conduction from the balloon may lead to the occurrence of CAS.

Anesthetics Another cause of CASs related to AF ablation could be the use of dexmedetomidine during catheter ablation. Dexmedetomidine hydrochloride stimulates α_2-adrenergic receptors, and strained vagal tone has been reported to induce CASs.[15] In the present study showed, dexmedetomidine was used in 86% of patients with CASs.

Severity of CAS

Most patients with a serious condition during the CAS had persistent or long-standing persistent AF. An investigation of postmortem isolated hearts demonstrated a higher density of nerves containing adrenergic components in subjects with AF than in subjects with sinus rhythm.[16] In addition, the vagal response elicited by high-frequency stimulation of the left atrial GP increased stepwise from the response occurring in non-AF patients to that occurring in paroxysmal AF patients and then to that occurring among persistent AF patients.[17] The higher sympathetic and parasympathetic nerve activity in patients with persistent AF would cause more severe CAS.

Thiopental was used significantly more often in patients with a serious condition. A study that compared autonomic tone variables between thiopental and propofol infusions indicated that vagal activity declined more significantly than sympathetic activity after thiopental infusion, thereby causing a marked autonomic imbalance.[18] Differences in the autonomic nervous system effects of each anesthetic could have led to differences in the severity of the CAS.

Preventive Strategy and Treatment

We must remain aware of the possible occurrence of a CAS at any time during the perioperative period of an AF ablation procedure. Intravenous nitroglycerin or nicorandil infusion during the catheter ablation may be an option to prevent CASs in patients with a history of vasospastic angina or in those undergoing cryoballoon ablation. Another possible strategy may be to switch from dexmedetomidine or thiopental to propofol for any further sedation requirements during the procedure. Moreover, continuous monitoring with a 12-lead ECG, focusing particularly on ST-T changes in the inferior leads, would be necessary during left PV isolation. One-sixth of patients with CASs in this study had a serious condition, and so when significant ST-segment elevation occurs during the ablation procedure, immediate transvenous administration of nitrates would be recommended before an emergency CAG. Continuing prophylactic drugs (e.g., calcium channel blockers or nitrates) for CASs after the acute management is controversial. Further follow-up is needed in patients with CASs related to AF ablation procedures.

Study Limitations

The present study was a retrospective compilation of cases with CASs, and some important information regarding patients' clinical history and procedures may be missing. We did not perform the CAS provocation test after the acute management of CAS related to the ablation procedure. Another essential point to recognize is the racial heterogeneity in the prevalence of CASs. Previous studies have reported a more frequent reactivity to CASs in Asian countries, with multivessel CASs being especially more frequent, as well as a higher inducibility of CASs with a drug provocation test than in Western populations.[19] The nationwide Japanese Catheter Ablation Registry is currently ongoing to document real-world data regarding the acute success and complications in Japan;[20] this will also provide information about the racial differences in catheter ablation.

Conclusions

The present large-scale retrospective multicenter study found an incidence of CASs related to AF ablation of 0.19%, and that one-sixth of patients with CASs had a serious condition. We must pay attention to CASs not only during the application of ablation energy, but also before and after the ablation procedure. The characteristics of the CASs presented in this study provide practical information for dealing with this high-risk complication.

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IRB Information

The protocol for this research project was approved by a suitably constituted Ethics Committee of Kobe University Hospital (Committee of March 1, 2019; Approval no. 190017), and the study conformed to the provisions of the Declaration of Helsinki.

Data Availability

The deidentified participant data will not be shared.

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