ORIGINAL RESEARCH ARTICLE

Coronary Arterial Spasm During Pulsed Field Ablation to Treat Atrial Fibrillation

Vivek Y. Reddy, MD; Jan Petru, MD; Moritoshi Funasako, MD; Karel Kopriva, MD; Pavel Hala, MD; Milan Chovanec, MD; Marek Janotka, MD; Stepan Kralovec; Petr Neuzil, MD, PhD

BACKGROUND: Pulsed field ablation (PFA) has a unique safety profile when used to treat atrial fibrillation, largely related to its preferentiality for myocardial tissue ablation, in particular, esophageal sparing. A pentaspline catheter was the first such PFA system studied clinically for atrial fibrillation ablation; in these initial regulatory trials, the catheter was used for pulmonary vein isolation and left atrial posterior wall ablation. Since its regulatory approval in Europe, in clinical practice, physicians have ablated beyond pulmonary vein isolation and left atrial posterior wall ablation to expanded lesion sets in closer proximity to coronary arteries. This is an unstudied important issue because preclinical and clinical data have raised the potential for coronary arterial spasm. Herein, we studied the vasospastic potential of PFA lesion sets, both remote from and adjacent to coronary arteries.

METHODS: During routine atrial fibrillation ablation using the pentaspline PFA catheter, coronary angiography was performed before, during, and after pulsed field applications. The lesion sets studied included: (1) those remote from the coronary arteries such as pulmonary vein isolation (n=25 patients) and left atrial posterior wall ablation (n=5), and (2) ablation of the cavotricuspid isthmus (n=20) that is situated adjacent to the right coronary artery.

RESULTS: During pulmonary vein isolation and left atrial posterior wall ablation, coronary spasm did not occur, but cavotricuspid isthmus ablation provoked severe subtotal vasospasm in 5 of 5 (100%) consecutive patients, and this was relieved by intracoronary nitroglycerin in 5.5±3.5 minutes. ST-segment elevation was not observed. However, no patient (0%, P=0.004) had severe spasm if first administered parenteral nitroglycerin, either intracoronary (n=5) or intravenous (n=10), before treatment.

CONCLUSIONS: Coronary vasospasm was not provoked during PFA at locations remote from coronary arteries, but when the energy is delivered adjacent to a coronary artery, PFA routinely provokes subclinical vasospasm. This phenomenon is attenuated by nitroglycerin, administered either post hoc to treat spasm or as prophylaxis.

Key Words: ablation techniques ■ atrial fibrillation ■ coronary vasospasm ■ electroporation

Since their introduction to treat atrial fibrillation (AF), catheter ablation energy modalities have largely used a thermal approach to tissue destruction: initially radiofrequency energy, followed by cryothermy, and, most recently, laser ablation.1-4 Despite the seeming differences between these various energies, their mechanisms of ablation have important final common similarities: beyond a region of resistive heating or cooling, there is thermal conduction such that tissue that encounters the propagating heat/cold wave is ablated. Accordingly, the degree of tissue damage (both wanted and unwanted) directly correlates to, and is largely predictable by, the magnitude of the propagation of the ablative thermal front. Likewise, the safety of thermal

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Clinical Perspective

What Is New?
- During pulsed field ablation with a pentaspline catheter to treat atrial fibrillation, subclinical coronary vasospasm occurs when the ablation catheter is in proximity to coronary arteries.
- This proximity-related coronary spasm is suppressed by administration of intracoronary or intravenous nitroglycerin before treatment.
- Generalized coronary spasm was not observed when pulsed field applications were delivered to the pulmonary veins or the posterior left atrium, regions remote from the coronary arteries.

What Are the Clinical Implications?
- When delivering pulsed field ablation of lesions in proximity to coronary arteries, physicians should consider whether to administer parenteral nitroglycerin before treatment to avoid coronary arterial spasm.

Nonstandard Abbreviations and Acronyms

| Abbreviation | Description |
|--------------|-------------|
| AF | atrial fibrillation |
| Cohort<sub>IC-NTG</sub> | patients receiving pre-PFA intracoronary nitroglycerin |
| Cohort<sub>IV-NTG</sub> | patients receiving pre-PFA intravenous nitroglycerin |
| Cohort<sub>IC-NTG</sub> | patients receiving no pre-PFA nitroglycerin |
| CTI | cavitricuspid isthmus |
| FFR | fractional flow reserve |
| ICE | intracardiac echocardiography |
| LAPW | left atrial posterior wall |
| PFA | pulsed field ablation |
| PV | pulmonary vein |
| PVI | pulmonary vein isolation |
| RCA | right coronary artery |
| RFA | radiofrequency ablation |

Pulsed field ablation (PFA) is a novel, largely nonthermal energy modality that ablates by the application of brief (micro- to nanosecond duration) high-energy pulses of energy to electroporate the target tissue. Tissue within this pulsed electrical field zone is damaged by a combination of mechanisms, ultimately leading to dielectric breakdown of cell membranes, and some delayed apoptosis, as well. Most strikingly, PFA has demonstrated excellent 1-year freedom from recurrent atrial arrhythmias, with either pulmonary vein isolation (PVI) or PVI plus left atrial posterior wall (LAPW) ablation for persistent AF.

The first clinically tested PFA catheter received regulatory approval in Europe in early to mid-2021. Despite a limited number of European sites to which this pentaspline PFA catheter was released by the manufacturer, there has been rapid clinical uptake with >1700 patients treated before the end of 2021 alone. And entirely consistent with the first-in-human trials, the MANIFEST-PF (Multi-National Survey on the Methods, Efficacy, and Safety on the Post-Approval Clinical Use of Pulsed Field Ablation) survey demonstrated an overall safety profile of PFA to be consistent with preferential tissue ablation: no esophageal damage, persistent phrenic nerve damage, or PV stenosis. On the other hand, one unusual complication was reported: severe coronary arterial spasm with associated ST-segment elevation in a patient undergoing PFA of the mitral isthmus. Furthermore, there are emerging preclinical reports of coronary arterial spasm when PF energy (using the same PF waveform used clinically) is delivered in proximate relationship to the vessel. In an effort to better elucidate the effect of PFA on coronary arteries, we performed coronary angiography during the energy applications during otherwise conventional PFA procedures with the pentaspline catheter. Herein, we report this experience both during traditional lesion sets such as PVI and LAPW ablation and during ablation of the cavitricuspid isthmus, locations that are alternately relatively remote or immediately adjacent to coronary vessels, respectively.

METHODS

Data Availability Statement
The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Rationale
This was a retrospective analysis of a series of patients undergoing PFA for AF. Because of the aforementioned emerging data on the potential for coronary spasm, we decided to perform
coronary angiography at the time of PF applications in consecutive patients planned for routine clinically indicated AF ablation procedures. In the initial PFA cases, only PVI (with or without LAPW ablation) was performed; in later cases, when ablation of the cavotricuspid isthmus (CTI) was included, coronary spasm was routinely observed (see Results), prompting administration of parenteral nitroglycerin before treatment in further cases. Of note, the indication for CTI ablation was not necessarily because of a history of typical atrial flutter, but rather as part of the AF ablation lesion set. Although routine CTI ablation during AF ablation is not performed by all electrophysiologists, and has not been recommended by the Guidelines, it is part of standard practice in some physicians’ practice (including often by the authors). This study was approved by the Ethical Committee at Homolka Hospital, Prague, and all patients provided informed consent.

PFA With the Pentaspline Catheter
All patients underwent ablation using the CE-Mark–approved pentaspline PFA catheter (Farawave, Farapulse-Boston Scientific, Inc) with compatible PFA generator (Farastar, Farapulse-Boston Scientific, Inc). Informed consent was obtained, and, per standard laboratory practice, the procedures were performed with deep sedation (intravenous benzodiazepines, fentanyl, and propofol) without endotracheal intubation. After standard single transeptal puncture, a compatible 13F deflectable transeptal sheath (Faradrive, Farapulse-Boston Scientific, Inc) was used to facilitate positioning of the PFA catheter over-the-wire at each PV ostium. As previously described, the PFA catheter changes shape between fully deployed “flower” and semideployed “basket” configurations. Ablation was then performed by using a proprietary biphasic bipolar waveform, with the following strategy: (1) PVs: typically, 4 applications were delivered in each of the 2 configurations at each vein; (2) LAPW: 2 applications were delivered at each overlapping posterior wall location; and (3) CTI: 3 applications were delivered per site, at a total of 1 to 3 sites as tailored to the patient-specific anatomy (Figure 1). All procedures were performed with an activated clotting time exceeding 350 seconds and with intracardiac echocardiography guidance.

Coronary Angiography
During lesion delivery at either the left or right PVs, the left main or right coronary artery (RCA), respectively, was cannulated; the RCA was also cannulated during CTI or LAPW ablation (Figures 2 and 3). Intracoronary contrast angiography was performed at baseline, either during or after each PF application (using only 1–2 mL of contrast for these injections during and after PFA) and after the end of all applications. If vasospasm was observed, intracoronary nitroglycerin was administered (1–2 mg). For patients receiving nitroglycerin before treatment, either intracoronary (1 mg) or intravenous (1–2 mg) nitroglycerin was administered before CTI ablation, typically 2 minutes before recommencing PF applications. Of note, for all patients who received nitroglycerin before treatment, the drug was administered after PVI had been completed, but before CTI ablation was performed. Spasm was defined as mild (<50%), moderate (50%–90%), or severe (>90%).

Statistics
All values are reported as mean±SD.

RESULTS
Patient Population Characteristics
The patient cohort included 25 consecutive patients, unselected except for being planned for a clinically indicated AF ablation procedure. The cohort was 32% female, with a mean age 65.1±7.7 years, a mean CHA2DS2-VASc score of 2.4 (range, 1–4), with hypertension being the most common risk factor, being present in 72% (Table 1).

Figure 1. Patient flow.
Shown are the number of patients receiving each ablation lesion set and the various CTI ablation cohorts. CTI indicates cavotricuspid isthmus; IC, intracoronary; IV, intravenous; NTG, nitroglycerin; LAPW, left atrial posterior wall; PFA, pulsed field ablation; pts, patients; and PV, pulmonary vein.
Of note, only 1 patient had known coronary artery disease. Ventricular function was overall preserved with a mean left ventricular ejection fraction of 60.5±7.1%, and only 4 patients had an ejection fraction ≤50%. The left atrial anteroposterior dimension was 42.8±5.1 mm (range, 35–53 mm). The cohort included a mix of patients with paroxysmal (n=17) and persistent (n=8) AF, with 68% of the cohort having received treatment with a membrane-active (class I or III) antiarrhythmic drug. Only 2 (8%) patients were taking a calcium channel blocker.

**PFA Procedural Details**

As shown in Table 2, all patients underwent PVI with use of the pentaspline catheter: using a total of 33.2±2.1 PF applications per patient, PVI was successful in all 99 of 99 PVs (100%) in 25 of 25 patients (100%). Ablation of the LAPW was successfully performed in 5 patients, using 17.8±5.8 PF applications per patient. Ablation of the CTI was performed in 20 consecutive patients; using 6.0±0.9 PF applications per patient (range, 3–8 applications), bidirectional conduction block across the CTI was achieved in all 20 of 20 patients (100%). The overall skin-to-skin procedure time was 70.8±15.2 minutes (range, 44–111 minutes), and fluoroscopy time was 12.1±3.5 minutes (range, 6.2–18.1 minutes).

There were no adverse events related to PFA. However, the second patient developed a groin hematoma requiring surgical repair 3 days after ablation. In all subsequent procedures, vascular punctures were performed under direct ultrasound guidance; no further vascular complications occurred.

**Coronary Angiography: Overview**

Coronary angiography was performed using either a femoral or radial arterial approach in 22 (88%) and 3 (12%) patients, respectively. There was baseline evidence of coronary artery disease (eg, coronary calcification or angiographic luminal irregularities) in 5 of 25 patients (20%), including the 1 patient indicated earlier with a known history of coronary artery disease. As shown in Figure 1, all 25 patients underwent PVI and 5 received additional ablation of the LAPW, all without nitroglycerin before treatment. Of the 20 patients receiving CTI ablation, there were 3 patient cohorts: Cohort$_{\text{No-NTG}}$ (n=5) received no nitroglycerin before treatment, Cohort$_{\text{IC-NTG}}$ (n=5) received intracoronary nitroglycerin before treatment, and Cohort$_{\text{IV-NTG}}$ (n=10) received intravenous nitroglycerin (from the femoral vein) before treatment.

**Coronary Effects During PVI**

The PVs were ultimately successfully isolated with PFA in all 25 patients without nitroglycerin before treatment. In all patients (25/25, 100%), the PF applications had no
appreciable effect on the coronary arteries, including no evidence of spasm (Table 3, Figure 2). There were also no ECG changes.

**Coronary Effects During LAPW Ablation**

The LAPW was targeted for ablation with PFA in 5 patients as previously described with overlapping lesions between the PVs along the posterior wall, all without nitroglycerin before treatment (Figure 2G). In all patients (5/5, 100%), the PF applications had no effect on the coronary arteries, and there were no ECG changes.

**Coronary Effects During CTI Ablation**

**Cohort-No-NTG**

Of the 20 patients who underwent CTI ablation, all 5 of 5 (100%) patients in the cohort-\text{No-NTG} group experienced significant subtotal spasm of a large segment of the RCA as a result of the PF applications (Table 3, Figure 4). There was typically a pattern of progressive severity of spasm with successive PF applications: overall, 5.4±1.3 PF applications (range, 3–6) were delivered to each CTI, and the peak level of spasm occurred after 3.8±1.5 PF applications (range, 2–6; Table 4, Figure 5). None of these 5 cohort-\text{No-NTG} patients had any angiographic evidence of coronary artery disease. The angiograms of peak spasm for each of these 5 patients is shown in Figure S1.

In all patients, the spasm was relieved by the intracoronary administration of nitroglycerin (typically 1 mg) in a mean of 5.5 minutes (range, 90 seconds to 10 minutes; Table 4, Figure 4). In 4 of the patients, there were no changes in the surface ECG; but in 1 patient, there was mild ST depression, mild T-wave changes, and QRS widening that normalized after a few minutes (see Figure S2). After the train of PF applications at the CTI, the intracardiac echocardiography catheter was placed directly into the right ventricle to visualize the left ventricle: there was no evidence of systolic wall motion abnormalities in any of these patients. Last, the patients were under propofol sedation, so the patients would not have been able to express any symptoms, if present. Together, these data demonstrated that PF applications delivered immediately adjacent to a coronary artery routinely cause coronary spasm, and this is relieved by intracoronary nitroglycerin treatment.

**Cohort-IC-NTG**

In an effort to determine whether administering nitroglycerin before treatment would prevent spasm, 5 patients (cohort-\text{IC-NTG}) received intracoronary nitroglycerin (1 mg) just before CTI ablation. With the administration of nitrogen before treatment, severe spasm was observed in 0 of 5 patients (0%). However, mild subclinical spasm of the RCA was observed in 1 of 5 patients (20%), situated adjacent to the PFA catheter at the CTI (see Figure S3). The spasm became evident during the last of
the 6 PF applications delivered to this CTI, again without ECG changes. This was one of the patients who did have angiographic liminal irregularities consistent with coronary artery disease, but the location of spasm was not at these grossly visible irregularities, but rather immediately adjacent to the PFA catheter location at the CTI. Another intracoronary dose of nitroglycerin (1 mg) was administered, and the spasm was relieved by 3 minutes (Table 4).

**Cohort IV-NTG**

Given this protective effect of intracoronary nitroglycerin, the effect of intravenous nitroglycerin on attenuating coronary spasm was assessed next. In this group of 10 patients (cohort IV-NTG), most (n=9) received 2 mg IV nitroglycerin, followed 2 minutes later by PFA of the CTI; 1 patient received 1 mg IV nitroglycerin, followed by PFA after 4 to 5 minutes.

Overall, severe spasm was observed in 0 of 10 patients (0%) in cohort IV-NTG, but mild or moderate coronary spasm of the adjacent RCA was observed in 2 of 10 patients (20%; Tables 3 and 4), both without accompanying ECG changes. One of these 2 patients had received the lower 1 mg IV dose of nitroglycerin before treatment with PF lesions commencing after 4 to 5 minutes. Mild spasm was noted with the 6th/final PF application, prompting the administration of another 1 mg IV nitroglycerin (see Figure S3). This spasm resolved in 2 minutes. The second patient had received the standard 2 mg IV dose of nitroglycerin before treatment but developed moderate focal spasm during the last 2 (5th and 6th) PF applications (see Figure S3), again relieved in 2 minutes with additional intravenous nitroglycerin. For both patients, there were no ECG changes.

**DISCUSSION**

In this study of the use of the pentaspline PFA catheter during routine AF ablation cases, the primary findings are: (1) during PVI and ablation of the LAPW, locations at some distance from the coronary arteries, there was no evidence of coronary arterial spasm; (2) during CTI ablation, severe subtotal vasospasm of the right coronary arterial segment adjacent to the PFA catheter location at the CTI. Another intracoronary dose of nitroglycerin (1 mg) was administered, and the spasm was relieved by 3 minutes (Table 4).
Background

Soon after the advent of cardiac ablation procedures, ablation-related coronary vasospastic events were reported. These can be broadly dichotomized into 2 categories: (1) generalized diffuse coronary vasospasm, often after ablation at locations remote from any coronary artery, and (2) regional vasospasm in proximate relationship between the ablation element and coronary artery. The former has been described after both radiofrequency and cryoballoon ablation procedures, frequently in Japanese patients. In a recent meta-analysis of records from 22,232 Japanese patients undergoing AF ablation, diffuse coronary artery spasm occurred in 0.19% of patients, most often during energy applications, but also after either transeptal puncture or a few hours after the end of the procedure. The precise mechanism for this phenomenon is unknown but may be related to (1) an imbalance in the cardiac autonomic nervous system, a sudden surge in adrenergic tone or vagal withdrawal, (2) direct thermal effects from adjacent radiofrequency or cryothermal ablation, and (3) indirect thermal effects of cryoenergy-induced blood cooling.

The second vasospastic phenomenon of proximity-related regional coronary arterial spasm was first described during the initial DC shock experience, in which focal right coronary artery spasm occurred after a DC shock attempt to ablate a right free wall accessory pathway. Because radiofrequency ablation (RFA) then became the dominant energy modality for catheter ablation, there have not been many clinical reports of coronary artery spasm. Accordingly, there are few data as to the mechanism by which any ablative energy induces spasm of adjacent coronary arteries. However, the effect of in vivo electroporation on murine peripheral vessels has been studied. In brief, in a dose-dependent manner, local vascular spasm was reproducibly provoked, and this effect was highly attenuated by administering reserpine before treatment, which depletes nerve terminals of noradrenaline. This indicates that the sympathetic nervous system plays a major role in the local vasospasm induced by PFA.

To our knowledge, systematic coronary angiography during catheter ablation to assess for subclinical spasm has not been previously reported, but there are 3 relevant studies of angiography before and after RFA that bear mentioning. The first 2 (somewhat conflicting) studies evaluate coronary arterial flow in patients undergoing CTI ablation. In the first, 30 patients undergoing posterior mitral isthmus RFA from both the right and left atria were studied. In another study of CTI ablation conducted almost a decade later, 33 patients underwent both coronary angiography before and after ablation. Although there was no reported change on coronary angiography, this was among the first reported uses of saline-irrigated RFA, likely with more conservative titration of energy and without the use of preshaped/deflectable sheaths or force-sensing catheters to optimize catheter-tissue contact. In another study of CTI ablation conducted almost a decade later, 33 patients underwent both coronary angiography before and after ablation and measurement of the fractional flow reserve (FFR) in the vessel before, during, and after ablation. FFR measurement during ablation revealed substantial changes (FFR, 0.75–0.9) in 15.2% and very significant changes (FFR <0.75) in an additional 6%. These FFR changes normalized as the catheter-tip temperature declined to body temperature, so not surprisingly, angiography after the CTI line was complete did not identify any luminal changes.

The third, more recent, study evaluated 54 patients undergoing posterior mitral isthmus RFA from both the

| Patient cohort | Mild spasm* n (%) | Moderate spasm n (%) | Severe spasm* n (%) | Any spasm n (%) |
|----------------|------------------|----------------------|---------------------|---------------|
| Full cohort (no NTG pretreatment), n=25 pts | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Spasm during left atrial posterior wall ablation | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| No NTG pretreatment, n=5 pts | – | – | 5 (100) | 5 (100) |
| Spasm during cavotricuspid isthmus ablation | 2 (13) | 1 (7) | 0 (0) | 3 (20) |
| Any NTG pretreatment, n=15 pts | 1 (20) | 0 (0) | 0 (0) | 1 (20) |
| IC NTG pretreatment (cohort IC-NTG), n=5 pts | 1 (10)*† | 1 (10) | 0 (0) | 2 (20) |

IC indicates intracoronary; IV, intravenous; NTG, nitroglycerin; and pts, patients.
*Mild spasm is defined as any luminal irregularities with overall <50% decrease in vessel diameter. Moderate spasm is defined as an overall 50% to 90% decrease in vessel diameter. Severe spasm is defined as a >90% reduction in the vessel caliber.
†This patient only received 1 mg IV NTG (all other patients received 2 mg IV).
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left atrial endocardium and the coronary sinus. Unlike the preceding 2 studies, a deflectable sheath was used to deliver the saline-irrigated RFA energy, which likely maximized catheter-tissue contact and, hence, lesion quality. Quantitative coronary angiography performed before versus after ablation revealed luminal changes of the left circumflex and obtuse marginal arteries in 28% of the cohort, including significant (50%–84%) narrowing in 9.3% of the cohort, all reversible with intracoronary nitroglycerin. This phenomenon was most evident

![Figure 4](image)

**Figure 4. Provocation and relief of severe coronary spasm in a patient in cohort No-NTG.** The baseline, before ablation angiograms for patient 1 are shown in right (A) and left (B) anterior oblique views. The area of right coronary arterial spasm (arrows) is clearly observed during the third pulsed field application (C), prompting the administration of intracoronary nitroglycerin. Follow-up angiograms are shown at various time points after administration: 2 minutes (D), 5 minutes (E), and 10 minutes (F). Note that the pulsed field spasm appears even tighter at 2 minutes but is then relieved such that it is completely gone by 10 minutes. Corresponding video files for all these images are available (Videos S10–S15). LAO indicates left anterior oblique; NTG, nitroglycerin; PFA, pulsed field ablation; and RAO, right anterior oblique.

| Patient | Severity of spasm | No. of pulsed field lesions | No. of pulsed field lesions with near-peak spasm | Time to resolution after IC NTG, min | ECG changes |
|---------|-------------------|---------------------------|-----------------------------------------------|-----------------------------------|-------------|
| Patient 1 | Severe | 3 | 2 | 10 | None |
| Patient 2 | Severe | 6 | 3 | 3 | None |
| Patient 3 | Severe | 6 | 4 | 1.5 | None |
| Patient 4 | Severe | 6 | 4 | 8 | Mild ST-segment depression, T-wave changes, QRS widening |
| Patient 5 | Severe | 6 | 6 | 5 | None |
| Cohort No-NTG, mean±SD | | 5.4±1.3 | 3.8±1.5 | 5.5±3.5 | |

| Patient | Severity of spasm | No. of pulsed field lesions | No. of pulsed field lesions with near-peak spasm | Time to resolution after IC NTG, min | ECG changes |
|---------|-------------------|---------------------------|-----------------------------------------------|-----------------------------------|-------------|
| Patient 1 | Mild | 6 | 6 | 3 | None |
| Patient 2 | Mild | 6 | 6 | 2 | None |
| Patient 3 | Moderate | 6 | 5 | 3 | None |
| Cohort IC/IV-NTG, mean±SD | | 6.0±0 | 5.7±0.6 | 2.7±0.6 | |

IC indicates intracoronary; IV, intravenous; and NTG, nitroglycerin.
when the left circumflex artery was closer to the coronary sinus. Taken together, these studies indicate that, when thermal energy is delivered within proximity to coronary arteries, focal vasospasm does occur.

**PFA and Coronary Spasm**

**PVI and LAPW Ablation**
Coronary spasm was not observed during PVI or ablation of the LAPW in any patient. As with thermal ablation, this is consistent with the requirement for proximity of the ablation element to the pulsed electrical field. And given the relative distance between the PVs (see Figure S4) and the coronary arteries, it is not terribly surprising that there was no effect on the coronary arteries. In the MANIFEST-PF survey of the first 1758 patients undergoing PFA after regulatory approval in Europe, there was not a single reported case of clinical coronary spasm. On the other hand, it should be remembered that inadvertent air embolism during catheter introduction into the sheath is a possible mechanism producing coronary spasm/occlusion.

**CTI Ablation**
Coronary spasm was invariably provoked in all consecutive patients receiving PFA to the CTI. The magnitude of the arterial segment with spasm varied, but the severity was striking. Severe ECG changes such as ST-segment elevation were not observed in any patient, only milder transient ST-segment depression. But it should be recognized that intracoronary nitroglycerin was instilled immediately at the end of the PF lesions, with subsequent relief of spasm in 5.5±3.5 minutes (Table 4). So, one cannot be certain that spasm would not have persisted longer, with consequent ST-segment elevations, if nitroglycerin had not been administered.

On the other hand, administering intracoronary/intravenous nitroglycerin before treatment was highly effective in attenuating the vasospasm. Of the 15 patients receiving nitroglycerin before treatment, 80% experienced no vasospasm (versus 100% in cohort-NTG, *P*=0.004), and the 20% remaining patients experienced only mild to moderate vasospasm that occurred in a highly focal manner (versus 100% with any spasm in cohort-NTG, *P*=0.09), again all without ECG changes. It was also striking that in all 3 instances, the spasm occurred during the last or next to last PF application (mean PF application number=5.7±0.6; Table 4), consistent with the possibility of the waning of the nitroglycerin effect because of its short (1–3 minutes) half-life. These data would best be interpreted as clear evidence that administering parenteral nitroglycerin before treatment has an ameliorative effect on coronary spasm, but the ideal means to administer nitroglycerin before treatment, nitroglycerin formulation, route of administration, dose, timing, will require additional work to optimize the pharmacodynamics.

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**Figure 5. Progressive coronary spasm during PFA in a patient in cohort-NTG.**

For patient 4, angiography reveals progression right coronary arterial spasm (arrows) with successive pulsed field applications: first (A), second (B), third (C), fourth (D), and sixth (E) applications. The spasm was relieved on administration of intracoronary nitroglycerin (F). Corresponding video files for all these images are available (Videos S16–S21). NTG indicates nitroglycerin; and PFA, pulsed field ablation.
Clinical Implications

During AF ablation procedures, it is useful to think about coronary spasm in the context of the distance between the positioned pentaspline PFA catheter and the coronary arteries. That is, during PVI and LAPW ablation, the primary lesion sets studied in the first-in-human clinical trials with this catheter, the major coronary arteries are remote from the positions of the PFA catheter. According to the kind of proximity-related coronary arterial spasm observed in this study seems highly unlikely, if not impossible.

Of course, physicians should be highly cognizant of the aforementioned phenomenon of Prinzmetal angina-like generalized coronary spasm. Indeed, just as it can occur rarely during thermal ablation, remote coronary arterial spasm has also recently been observed in a patient undergoing conventional PV ablation using the pentaspline PFA catheter (J. Chun and B. Schmidt, unpublished data, June 5, 2022). On the one hand, this is the only proven instance of generalized coronary spasm of the >4000 ablation procedures performed thus far with the pentaspline PFA catheter. So, it is unlikely that there is a unique susceptibility of coronary arteries to pulsed electrical fields. On the other hand, this rare complication can result in complete hemodynamic collapse, culminating in a truly catastrophic outcome. So coronary spasm should not be discounted as 100% avoidable if one simply does not deliver PF energy in proximity to major coronary vessels. Instead, ST-segment elevation, particularly if accompanied by hemodynamic compromise, should raise concern for spasm and prompt immediate coronary angiography, especially if the patient is suspected of having a history of Prinzmetal angina.

Alternatively, the high (perhaps invariable) incidence of proximity-related coronary spasm raises the question of whether PFA should ever be performed close to a coronary artery. On the other hand, it remains possible that the dramatic spasm observed with the pentaspline catheter may not occur with focal PFA catheters. There was no evidence of ST-segment elevation when using a focal PFA catheter to perform CTI ablation in 25 patients in the PersAFOne trial (Feasibility Study of the FARA-PULSE Endocardial Multi Ablation System in the Treatment of Persistent Atrial Fibrillation; with the same PF waveform used by the pentaspline catheter). Whether there really was subclinical spasm in these cases is unknown, although it was certainly plausible given the data regarding RFA at the CTI or mitral isthmus.

The other important related question is whether nitroglycerin should be administered before PFA near a coronary artery, or whether parenteral nitroglycerin should simply be ready for use if ECG changes are observed. Although either approach is probably reasonable, we do believe that administration before treatment will prove more effective than after-the-fact administration. Regardless, it seems quite clear that physicians should be cognizant of this potential for adjacent spasm, and the ameliorative effect of nitroglycerin. This is not a theoretical issue: (1) there have been a number of case reports of PFA with the pentaspline catheter at locations adjacent to coronary arteries, for example, CTI, mitral isthmus, persistent left superior vena cava, and (2) in the MANIFEST-PF survey, approximately one-third of the operators reported that they sometimes performed mitral isthmus ablation.

Authors’ Recommendations

On the basis of these data, we would recommend the following when using the pentaspline PFA catheter. First, during ablation remote from coronary arteries, such as PVI and LAPW ablation, physicians should be cognizant that generalized coronary spasm is a rare, but potentially life-threatening phenomenon of AF ablation (using any ablative energy modality). So, if diffuse ST-segment elevation is observed (even if occurring after the procedure), often with coincident hemodynamic compromise, immediate coronary angiography should be performed with a plan to both acutely instill intracoronary nitroglycerin and provide oral nitroglycerin for at least a few days to prevent recurrent spasm. Second, during PFA with the pentaspline catheter in proximity to a coronary artery, such as CTI or mitral isthmus ablation, we recommend to first consider administering intravenous nitroglycerin before the PF applications.

Limitations

First, this was not a randomized study comparing the various cohorts. However, the uniformly severe spasm observed in the consecutive patients of the cohort group is in stark contrast to the complete absence of severe spasm in the cohort groups, increasing the plausibility of these observations. Second, it is difficult to determine the true effect of coronary atherosclerosis on the propensity of coronary spasm. There were few patients with angiographically visible atherosclerosis, and direct intimal imaging such as optical coherence tomography was not performed.

Last, the effect of pulsed electrical fields on the coronary arteries was studied using the (only) clinically available pentaspline PFA catheter technology. Although other PFA catheters systems and other PF waveforms are likely to similarly cause spasm, this cannot be immediately assumed, but rather should be studied with each PFA technology, both whether coronary spasm is induced and whether the spasm is amenable to nitroglycerin treatment or administration before treatment. It is possible that with other PF waveforms/catheters that create larger/smaller electrical fields, there may be higher/lower rates of vasospasm. It is of note that none
of the published first-in-human clinical studies with other technologies, albeit each including relatively few patients, have reported instances of coronary spasm, including 1 technology that specifically included CTI and mitral isthmus lines.18,46,46

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Affiliations

Homolka Hospital, Prague, Czech Republic (V.Y.R., J.P., MF, KK., PH., MC, MJ, SK, FNJ). Icahn School of Medicine at Mount Sinai, New York (V.Y.R.).

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Disclosures

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Supplemental Material

Figures S1–S4

Legends to Online Videos

Videos S1–S21

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