# Catheter Ablation Approaches for the Treatment of Arrhythmia Recurrence in Patients with a Durable Pulmonary Vein Isolation

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Catheter ablation has emerged as an effective treatment for atrial arrhythmias, and pulmonary vein isolation (PVI) is the cornerstone of ablation strategies. Significant technological evolution and widespread increase in operator experience have facilitated the effectiveness of catheter ablation to achieve durable PVIs in single or multiple ablation procedures. Nevertheless, arrhythmia recurrence is a common problem even after establishing PVI. Data on catheter ablation in these patients are sparse and repeat ablation in this population is highly challenging. In this review we have summarized the available data as well as potential strategies of catheter ablation following the initial PVI.

Pulmonary vein (PV) isolation (PVI) is the cornerstone of ablation in atrial fibrillation (AF) treatment. Point-by-point radiofrequency ablation or single-shot ablation, such as the cryoballoon (CB) ablation, is the current standard method to obtain complete PVI.[1] Ablation technology and operator experience have evolved over the last 20 years resulting in less frequent PV reconnections following a successful PVI.[2,3] The utilization of contact force-sensing catheters enables reliable and objective measurement of catheter-to-tissue contact.[4-6] Several studies have demonstrated that increased contact force leads to reproducible creation of transmural lesions and may help to avoid intraprocedural complications such as steam pops or cardiac tamponade.[4-6] Furthermore, if contact force is optimized in areas with high reconnection rates, the safety and efficiency of catheter ablation could be improved.[4,6,7] Novel energy settings such high-power and short-duration (HPSD) radiofrequency ablation may further improve ablation efficacy.[8] Recent studies have found that HPSD utilization results in highly effective and timely ablations with favorable mid- and long-term results.[9-13] The introduction of single-shot devices has resulted in simpler approaches for achieving an effective PVI in a broad spectrum of patients.[14-17] CB ablation reportedly results in low PV reconnection rates (55-69%) during repeat ablation procedures.[18-20] CB PVI is also effective in centers with operators that have less experience.[21] Pulsed-field ablation (PFA) is a promising new technique which has recently been introduced.[22] Compared to the standard ablation methods with radiofrequency or cryoenergy, PFA is a nonthermal ablation technique. In PFA, electrical pulses cause electroporation, which damages the membrane integrity of the cardiac cells, resulting in cell death. The use of PFA for PVI in patients with paroxysmal and persistent AF has yielded favorable results.[23,24]

Besides these studies which demonstrate the high efficacy of catheter ablation for achieving PVI with modern approaches, there is a lack of data regarding ablation for patients not responding to PVI. In this review we have summarized the available data on catheter ablation approaches for the treatment of AF besides PVI as well as data for catheter ablation in patients with a proven durable PVI.

## CATHETER ABLATION IN PATIENTS WITH A DURABLE PVI

While the technology for catheter ablation in AF is continually improving, PV reconnection is less often the cause of AF recurrence.[3] The rate of patients with arrhythmia recurrence despite a durable PVI remains unknown because there is no noninvasive imaging

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technique which can reliably identify PV reconnection. There is limited data on cardiac magnetic resonance (CMR) imaging for the assessment of PV reconduction. Furthermore, this method has remained experimental until today.[12,25-27]

Data on catheter ablation in patients with recurrence of arrhythmia despite isolated PVs are sparse. To our knowledge, there are only five studies that have reported on patients with a durable PVI (Table 1). A case series of 26 patients with recurrence of arrhythmia and a durable PVI investigated those who underwent linear ablation and ablation of the complex fractionated atrial electrograms (CFAEs).[28] In this case series, patients presenting with AF at the time of recurrence were associated with more frequent arrhythmia recurrences than those presenting with organized atrial tachycardias (ATs).[28] After a mean follow-up of 17 months, the arrhythmia-free survival rate following AAD therapy was 20% in patients with AF and 67% in patients with AT.[28] In a retrospective study that included 31 patients with a durable PVI and arrhythmia recurrence, left atrial appendage (LAA) isolation and LAA ligation was performed.[29] In this highly selective patient cohort the estimated arrhythmia-free survival rate was 69.7% after 24 months.[29] In a study by Straube et al.,[30] 67 patients with a durable PVI after CB ablation underwent high-density electroanatomical mapping; additionally, a stimulation protocol was followed to induce organized tachycardias. Re-ablation targeted either the AT mechanisms or substrates for the empiric prevention of potential reentrant circuits.[30] The arrhythmia-free survival rate following antiarrhythmic drug therapy was 49% in patients after 12 months.[30] In a study by Sciacca et al.,[29] a total of 74 patients who underwent repeat ablation for arrhythmia recurrence despite the presence of a durable PVI were analyzed in a prospective single-center study. The arrhythmia type at the time of recurrence was AF in 27 patients (36.5%) and organized (AT) in 47 patients (63.5%).[31] Ablation was aimed either at substrate modification based on endocardial voltage mapping or at specific AT mechanisms. The study found that 64.9% of the patients presented with arrhythmia recurrence after a mean follow-up of 565 ± 342 days.[31] Patients who were admitted with organized tachycardias during the follow-up had significantly lower rates of arrhythmia recurrence that those who were admitted with AF.[31] Additionally, the presence of low-voltage areas and a stage of atrial cardiomyopathy were inversely correlated with ablation success.[31] The party PVI study was a retrospective study that included 39 centers and 361 patients who were admitted for repeat ablation procedures and in whom a PVI was identified during the investigations.[32] In this patient cohort catheter ablation was aimed at creating linear lesions (219 patients), electrogram-based ablation, and exclusion of non-PV triggers, or PV-based ablation aiming at antralization of the circumferential lesions. In 37.1% of the patients two techniques were applied, in 6.5% of the patients three techniques were used, and in 1.9% of the patients no ablation was performed.[32] The ablation was performed at the discretion of the operators and the local standards. After a mean follow-up of 22.6 ± 19.6 months, 122 (33.2%) and 159 (43.3%) patients developed atrial arrhythmia recurrence at 12 and 24 months, respectively.[32] There was no significant difference among the different ablation techniques.[32] Till date, there are no randomized studies on ablation techniques in PVI nonresponders. The ASTRO AF study (ClinicalTrials.gov Identifier: NCT04056390) which aimed to identify ablation strategies in patients with AF recurrence and persistent PVI following a prior AF ablation was preliminary stopped.

Based on the existing studies on catheter ablation in PVI nonresponders no clear recommendation for an optimal ablation strategy can be determined. Figure 1 summarizes a potential strategy for the evaluation of patients with arrhythmia recurrence following AF ablation. The authors recommend evaluating the likelihood of PV reconnection based on available evidence of previous ablation procedures and patient characteristics. Additionally, further imaging like CMR may be used to identify pre-existing left atrial lesions. Decisions regarding the need for a repeat ablation should consider the type of arrhythmia recurrence, symptoms, and co-morbidities. Figure 1 displays potential ablation strategies which may be used such as atrial substrate modification based on voltage mapping (Figure 2). The following text will summarize the information available on these ablation approaches.

## CATHETER ABLATION STRATEGIES BEYOND PVI

There are various ablation strategies beyond PVI which are applied when performing AF ablation for the first time. These approaches may be utilized in patients with a durable PVI. Growing clinical evidence suggests that atrial fibrosis is a prevalent common left

**TABLE 1.** Studies on catheter ablation in patients with a durable PVI.

| Author (year) | Number of patients | Ablation strategy | Follow-up duration | Rate of patients without arrhythmia recurrence |
|---|---|---|---|---|
| Baldinger et al.[28] | 26 | Linear lesions, CFAE | 17 months | 48% at 17 months |
| Fink et al.[29] | 31 | Wide-area LAA isolation, LAA ligation | 24 months | 70% at 24 months |
| Straube et al.[30] | 67 | AT induction and ablation or ablation of low-voltage areas | 772 ± 317 days. | 49% at 12 months |
| Sciacca et al.[31] | 74 | Substrate modification (linear lesion deployment aiming at low-voltage areas) or AT ablation | 565 ± 342 days | 36% at 24 months |
| Benali et al.[32] | 367 | Linear-based (n = 219), electrogram-based (n = 168) trigger-based (n = 101), or pulmonary vein-based (n = 56) ablation | 22 ± 19 months | 57% at 24 months |

AT, atrial tachycardia; CFAE, complex fractionated atrial electrograms; LAA, left atrial appendage; PVI, pulmonary vein isolation atrial substrate in patients with AF.[33] Apart from PV ostia, focal driving rotors can also be identified; ablation of these areas can assist in maintaining sinus rhythm in patients with persistent AF.[34] In patients with persistent AF, LAA ablation appears to provide a significant additional benefit over conventional ablation in terms of attaining independence from all atrial arrhythmias without increasing the incidence of acute procedural complications.[35] Ablation of isoproterenol- or adenosine-induced nonPV triggers

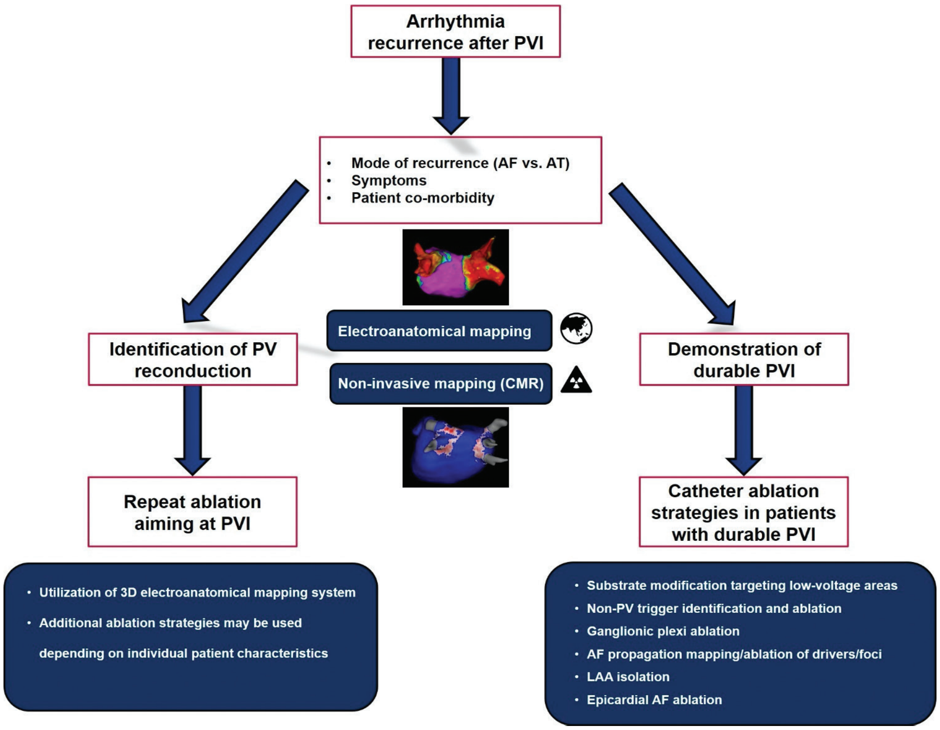


FIG. 1. Ablation strategies in patients presenting with arrhythmia recurrence following AF ablation.

*AF, atrial fibrillation; AT, atrial tachycardia; CMRI: cardiomagnetic resonance imaging; LAA, left atrial appendage; PV, pulmonary vein; PVI, pulmonary vein isolation*

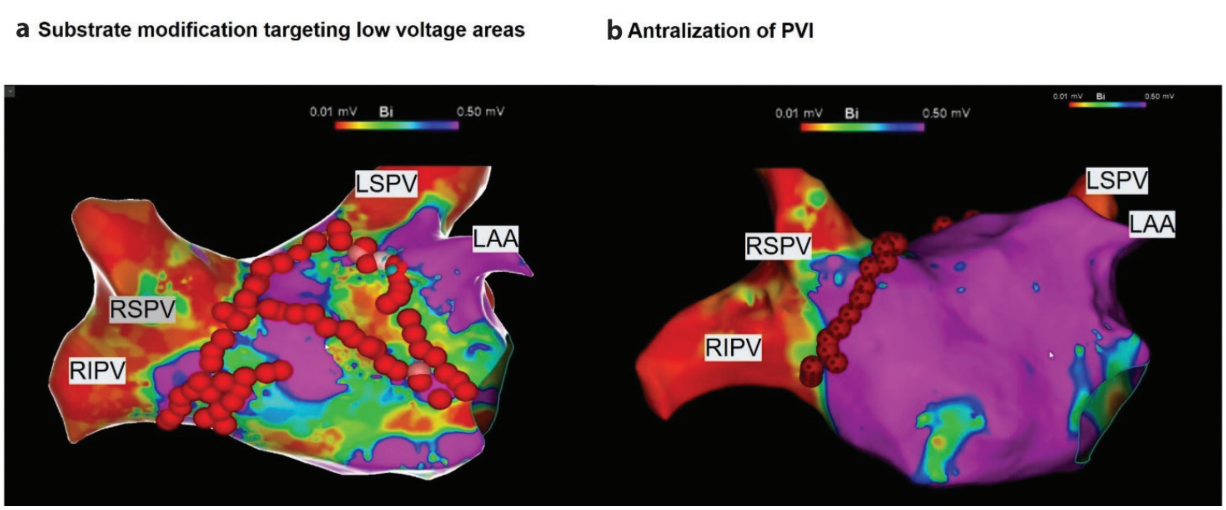


FIG. 2. Ablation methods in patients with a durable PVI.

a) Ablation lesions in a patient with a durable PVI in low-voltage endocardial areas at the LA anterior wall and septum. A linear lesion connecting the anterior mitral anulus, RSPV, and LSPV was created. Additionally, a low-voltage area at the septum inferior to the right PV ostium was targeted. b) The circumferential PV lesion was antralized along the right PV after a previous ablation that utilized pulsed-field ablation.

*LA, ; LAA, left atrial appendage; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; PV, pulmonary vein; PVI, pulmonary vein isolation; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein* such as superior vena cava or coronary sinus have also been used for first-time and repeat AF ablations.[36] Moreover, ganglion plexus ablations or modifications may also decrease AF recurrences.[37,38] CFAE ablation, in addition to PVI, has been investigated.[39] Epicardial or surgical ablation techniques and renal denervation are the other possible strategies for dealing with recurrent AFs.

### Modification of AF substrate

There are several strategies described as "substrate modification" that are aimed at either structural or electrical abnormalities causing AF initiation or maintenance. Thus, this term cannot be used uniformly. In the randomized multicenter Substrate and Trigger Ablation for Reduction of AF (STAR AF-2) trial, two strategies of substrate modification (CFAE ablation or additional linear ablation) were compared between patients with PVI alone and those with PVI and persistent AF.[39] The study could not demonstrate a superior outcome for the additional ablation strategies when compared with PVI.[39] Several smaller trials have investigated various substrate modifications, yielding heterogenous results.[40,41] The so-called "stepwise approach," which aims at AF termination by the sequential application of CFAE ablation and linear ablation, has yielded promising results in single-arm registries.[41,42] The Alster-LOST-AF trial was a randomized, prospective, single-center study which aimed to identify the outcome of initial ablation with PVI alone or with PVI and additional substrate modification, including CFAE ablation and creation of linear lesions aimed at terminating persistent AF.[43] In this study, there was no significant difference in the 1-year clinical outcome between the PVI-only-group and the group with additional substrate modifications as the index procedure.[43] Recent studies have investigated the effect of voltage mapping-guided substrate modification.[44,45] Kircher et al.[46] investigated the ablation of low-voltage areas in addition to PVI in patients with paroxysmal and persistent AF in a single-center randomized trial. They determined that additional substrate modification was associated with significantly lower rates of arrhythmia recurrence than PVI alone.[46] In the randomized multicenter STABLE-SR-II trial, additional ablation of low-voltage areas failed to improve the ablation success rate in a cohort of patients with persistent AF.[47] However, in the subgroup of patients with marked left atrial low-voltage areas, additional substrate modification was associated with reduced arrhythmia recurrence.[47] In the STABLE-SR-III trial, additional voltage map-guided substrate modification in patients aged 65-80 years with paroxysmal AF significantly improved the arrhythmia-free survival rate.[48] In the recent randomized multicenter ERASE-AF study, voltage map-guided additional substrate modification was associated with reduced arrhythmia recurrence.[49] Furthermore, several patients were monitored using implanted event recorders.[49]

Substrate modification may include ablation of electrical phenomena, which are detected during AF propagation mapping (Figure 3). During these procedures, specialized mapping algorithms sought to identify stable electrical activity during AF.[50] There are several systems available for AF propagation mapping. Although initial studies were encouraging,[51,52] the results could not be reproduced.[53]

### LAA isolation

LAA isolation is an ablation strategy aimed either specifically at excluding the LAA as an AF trigger or at modifying the substrate by a special set of linear lesions to isolate the LAA by altering the left atrial electrical properties. The former can be achieved by performing circular ablation around the LAA using radiofrequency or CB ablation (Figure 4).[54-56] Radiofrequency LAA isolation was evaluated in the multicenter randomized BELIEF trial.[57] In this study, LAA isolation in addition to an extensive ablation approach, which consists of PVI, posterior wall ablation, coronary sinus, and SVC isolation, was superior to extensive ablation alone in patients with longstanding persistent AF.[57] In a retrospective study, Yorgun et al.[55] determined that CB LAA isolation was superior to PVI alone in patients with persistent AF. The so-called wide-area LAA isolation by creating a combination of left atrial linear lesions was introduced to suppress AF and organized AT in patients with therapy-refractory arrhythmias.[59] Despite its significant efficacy in suppressing arrhythmias,[29,59-63] LAA isolation reportedly increases the risk for LAA thrombus formation and cardiogenic thromboembolism.[59,64-67] Thus, most groups perform percutaneous

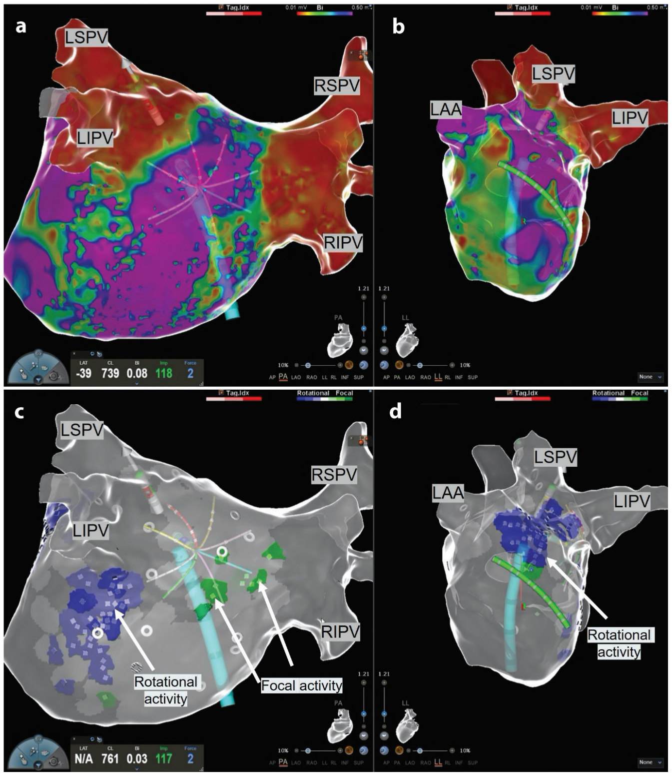


FIG. 3. Mapping of the stable rotational activity and focal sources in a patient with a durable PVI utilizing the CARTO finder module.
Mapping was performed using a high-resolution mapping catheter enabling ultra-density mapping of the LA. a) and b) Endocardial voltage mapping. c) and d) CARTO finder mapping. Rotational activity is depicted by the blue color and focal activity is depicted by the green color.

*LAA, left atrial appendage; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; PVI, pulmonary vein isolation; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein*

LAA closure after a prior isolation to prevent thrombus formation inside the electrically altered LAA.

### Non-PV trigger ablation

PVI continues to be the cornerstone of catheter treatment for AF, regardless of the subtypes. Despite the importance of PVI, AF can be precipitated by extrapulmonary triggers, particularly in the persistent subtypes. From an electrophysiological point of view, AF requires a trigger.[68] PVI is often carried out empirically based on the assumption that the PVs are the primary location of ectopic beats that generate AF.[69] Ectopic beats arising from regions outside the PVs may function as nonPV triggers. These nonPV triggers are frequently found in certain anatomical locations and are responsible for precipitating prolonged or intermittent episodes of atrial tachyarrhythmias and/or premature atrial beats. The most common locations of nonPV triggers of AF include the superior vena cava and coronary sinus, left atrial posterior wall, interatrial septum, and crista terminalis. Additionally, the left superior vena cava or its Marshall ligament remnant may cause AF.

### Left atrial posterior wall isolation

From an anatomical and embryological perspective, the left atrial posterior wall should be viewed as an extension of the PV. The left atrium's dorsal side has four distinct apertures known as the PV, which together with the posterior wall make up the left atrial antrum. Anatomically, the posterior wall has a heterogeneous distribution of fibers that makes it more susceptible to anisotropy and re-entry.[70] In comparison to the other components, the posterior wall has a greater level of fibrous-fatty involvement.[71] Due to the interplay between myofibroblasts and myocytes, this structural component of the left atrial posterior wall also triggers AF episodes.[72] Therefore, the posterior wall is both a perpetuator and source of AF triggers, and its ablation offers a logical method of rhythm management for all AF forms.[13]

### Superior vena cava isolation

Decades ago, animal research established the arrhythmogenic potential of the superior vena cava (Figure 5).[73,74] Patients with and without AF frequently have myocardial sleeves in the superior vena cava, which are mostly diverse and asymmetric.[75] Superior vena cava sleeves may act as a trigger, driver, or a combination of both in patients with AF.[76] Unless provocative actions are taken, the superior vena cava foci typically go undetected in electrophysiological studies. These foci may have longer effective refractory periods, making them more difficult to detect before performing a PVI.[77] Furthermore, as AF progresses, the superior vena cava's function as the AF initiator decreases.[78]

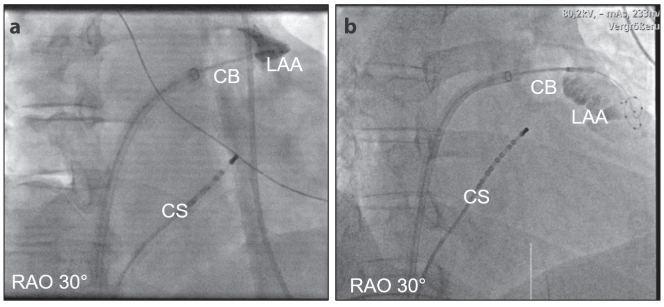


FIG. 4. CB LAA isolation
a) and b) LAA isolation was performed in two patients with a durable PVI. Subsequently, percutaneous LAA closure was performed to prevent cardiogenic thromboembolism.

*CB, cryoballoon; CS, coronary sinus; LAA, left atrial appendage; RAO, right anterior oblique*

### Ligament of Marshall and coronary sinus ablation

The left superior vena cava's anatomic remnant, the Marshall vein, which culminates into the ligament of Marshall, enters into the coronary sinus at the level of the Vieussens valve. The Marshall ligament, which runs at the surface of the epicardial side of the left lateral ridge, contains bundles of autonomic nerves and muscle fibers that bind the Marshall vein to the PV, left atrium, and coronary sinus. Furthermore, atrial activity originating from the Marshall ligament could trigger atrial tachyarrhythmias.[79] The ligament of Marshall has a wide spectrum of frequency triggering AF episodes and its ablation reportedly increases the atrial arrhythmia-free survival rate.[80,81] The entire Marshall Bundle's path, which runs from the mid-to-distal coronary sinus to the LAA, is amenable to ablation. If required, ethanol infusion can be used to precisely ablate the Marshall vein in order to remove the PV components and create a conduction block along the mistral isthmus. A more effective conduction block at the mitral isthmus may be produced by a combination of ethanol ablation and radiofrequency ablation of the Marshall vein rather than by recurrent radiofrequency ablations.[80]

Another source of nonPV AF triggers is the coronary sinus, whose endocardial detachment from the left atrium reportedly reduces AF inducibility in 66% of individuals after PVI.[82] By performing radiofrequency ablation at the coronary sinus' ostium, the AF

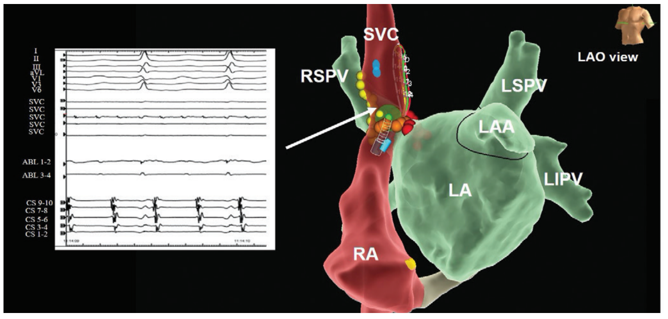


FIG. 5. SVC isolation in a patient with a nonPV trigger
A multi-polar catheter is placed inside the SVC demonstrating faster dissociated electrical activation of the SVC compared to that of the RA (localization of the ablation catheter) and CS. SVC isolation was performed after documentation of AF initiation from this segment.

*ABL, ablation catheter; AF, atrial fibrillation; CS, coronary sinus; IVC, inferior vena cava; LA, left atrium; LAA, left atrial appendage; LAO, left anterior oblique; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RA, right atrium; RSPV, right superior pulmonary vein; SVC, superior vena cava* can be terminated, which electrically isolates the coronary sinus from the atria. Although AF can no longer be precipitated after coronary sinus isolation, episodic bursts may still be detected. Animal models have demonstrated that the coronary sinus has a slow conduction, which favors a block, re-entry, and finally AF. Therefore, to achieve isolation, endocardial and epicardial coronary sinus ablation is strongly advised.[83]

The interatrial septum is a richly vascularized and innervated fibromuscular structure that separates the right atrium from the left atrium. Although atrial cardiomyocytes have a significant conduction velocity, the electrical pathways exist only between the upper and lower halves of the interatrial septum. The interatrial activation pattern usually shows delayed depolarization on the left side in particular.[84] Thus, the interatrial septum could act as a trigger for re-entry, especially in diseased atriums.

In the right atrium, there is a noticeable muscular structure called the crista terminalis. The role of the crista terminalis as a trigger of AF was first described in 2002.[85] In a study with long-term follow-up, AF developed in 3.4% of the individuals with crista terminalis AT. This indicates that the crista terminalis could function as a nonPV trigger.[86]

## Ganglionic plexus ablation

The autonomic nervous system can serve as a trigger for the initiation and maintenance of AF. The role of vagal predominance causing AF attacks, especially in patients with obstructive sleep apnea, has led to the modulation of autonomic nervous systems by electrophysiologists.[87] The vast majority of the ganglia and associated nerve bodies of the cholinergic system are located in the epicardial area. Several studies have performed endocardial mapping, high-frequency stimulation, and spectral analysis of the ganglionated plexi, and the results are favorable for performing ganglion ablation with ease.[88,89] Although ganglionic plexus ablation is not a novel technique, the biggest, randomized, controlled trial investigating the effect of ganglionic plexus ablation in addition to the traditional PVI adopted an anatomical methodology.[37] Ganglionic plexus ablation has previously been compared to PVI; the results were in favor of PVI in terms of freedom from atrial tachyarrhythmias in observational studies.[90] Therefore, the effect of this ablation has been compared as an additive strategy to PVI. According to a comprehensive meta-analysis, individuals with paroxysmal AF benefit more from incorporating ganglionic plexi ablation with PVI than individuals with persistent AF.[91] According to the current data, ganglionic plexi ablation should be considered as an additional strategy in selected patients. The absence of a consistent protocol for performing these ganglionic plexi ablations and the post-ablation phenomena of nerve recovery and restoration are the main drawbacks.

Inputs from the sympathetic and parasympathetic nervous systems are involved in the development and persistence of AF. They are also a component of the complicated ligament of Marshall.[92] The randomized multicenter VENUS trial demonstrated that ablating these neuronal inputs by administering ethanol into the Marshall vein in addition to performing PVI was more effective than PVI alone in treating all varieties of atrial tachyarrhythmias.[93] A low-voltage area may be created around the left inferior PV by administering ethanol in addition to ablating the autonomic and muscular fibers of the Marshall ligament. This may also provide, in part, a rapid and sustained blockade at the mitral isthmus.

## Renal denervation

Renal sympathetic denervation is a neuromodulation technique that has been recently researched for the treatment of AF. The renal sympathetic nerves are located on the surfaces of the renal arteries, and they work closely with the central autonomic nervous system. These neurons significantly influence the onset of AF and resistant hypertension. Ablating these nerves could minimize the frequency of AF events, lower blood pressure, and lessen the sympathetic system's tonus. In the ERADICATE-AF study, renal denervation was performed in addition to PVI in patients with AF, and its effects were studied.[94] Over a period of one year, the recurrences of AF and atrial tachyarrhythmias were considerably reduced in patients who underwent renal denervation in addition to PVI than in those who underwent PVI alone.[94] It was hypothesized that the reduced AF recurrences may have resulted from the lower blood pressure rather than the sympathetic nerve ablation. Further, six months after renal denervation, the blood pressure decreases were far more striking in the SIMPLICITY-HTN 3 study than in the ERADICATE-AF study.[95] Despite these results, the mechanism that lowers the AF attacks remains unknown. Nonetheless, the ERADICATE-AF study indicated that this technique was successful, whether it resulted from the blood pressure management or the nerve denervation.[94] According to a recent meta-analysis that evaluated seven randomized controlled trials, the simultaneous practice of renal denervation and PVI reportedly enhances the systolic arterial pressure, increases the glomerular filtration rate, and lowers the incidence of AF recurrence.[96] However, these findings need to be validated by large long-term trials, which should potentially include studies with a sham control group to further strengthen the findings.

## Surgical ablation

The atrial epicardium can be accessed via thoracoscopy, minithoracotomy, and subxiphoid incision. There are three basic types of lesion sets: posterior box, PVI with a connected roof, and floor lines or posterior left atrial ablation.[97] To be employed in daily practice, the challenges require additional randomized trials because they have been insufficiently recorded. In the last decade, investigations have revealed that a surgical or hybrid approach to AF ablation is successful without increasing the incidence of complications.[98,99] However, surgical ablation has several limitations in terms of availability and invasiveness.

In conclusion, Catheter ablation in patients with arrhythmia recurrence despite having a durable PVI is challenging, and arrhythmia recurrence is common. Several ablation strategies in addition to PVI have been tried in patients undergoing catheter ablation; however, results have been very heterogenous. Future studies are needed to determine the appropriate strategy to suppress arrhythmia recurrences in patients with a failed PVI.

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