Ablation of Paroxysmal and Persistent Atrial Fibrillation


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Introduction
Atrial fibrillation (AF) is the most common arrhythmia in humans. Its maintenance is thought to be due to multiple wavelets reentry occurring in both atria [1]. Previous studies have demonstrated the feasibility and efficacy of cryoablation to create lesions in both atria [2] and on the posterior wall of the left atrium [3], connecting the four pulmonary veins and the mitral annulus [4], in patients with chronic AF undergoing valvular heart surgery, as a valid alternative to the Maze procedure. Recently, the pulmonary veins (PVs) have been demonstrated to often play an important role in generating atrial fibrillation [5-7]. Because of their critical role in AF, a variety of surgical and catheter ablation techniques has been used to isolate the PVs from the left atrium [8-10].

Initial attempts at linear ablation
Following the remarkable success of catheter based ablation techniques in curing supraventricular arrhythmias, the attention of the electrophysiological community has turned upon atrial fibrillation based on the assumption that surgical incisions can be duplicated by a catheter based technique that should provide results equivalent to the Maze procedure.

Some studies attempted to intervene in both atria [11-12]; one in a progressive incremental fashion and the other one more directly imitating the surgical Maze with a biatrial approach. Creating continuous linear lesions to duplicate surgical atriotomies was difficult; atrial right lesions alone were safe but usually ineffective; left atrial lesions improved success rates though at a significant morbidity (including proarrhythmic left atrial re-entry) and even mortality cost; and both studies showed the feasibility of cure by catheter based techniques in patients with paroxysmal and persistent atrial fibrillation.

Recognition of initiation of atrial fibrillation from the pulmonary veins
AF initiation has been shown to be due to triggers predominantly clustered within thoracic veins, particularly pulmonary veins (PVs) [5-7] but the reasons for this arrhythmogenic behaviour are unknown.

Anatomic studies have demonstrated that the myocardial sleeves that envelope the PVs are most prominent at the left superior, left inferior, and right superior PVs [13]. Moreover, little is known of the electrophysiological characteristics of these veins, particularly focusing of patients with or without AF. Jais et al [14] have described specific electrophysiological properties of PVs in humans, distinguishing patients with from those without AF. They performed programmed stimulation from multiple sites and showed that in patients with AF, PV effective refractory periods (ERPs) are significantly shorter than LA ERPs, and significantly shorter than venous ERPs of patients without AF. The PV potential (PVP) functional refractory periods (FRPs) of patients with AF were also significantly shorter than those of control patients, whereas the FRPs of the PV-LA junction and the LA ERPs were comparable, demonstrating that the main difference between patients with and without AF were observed in PVs rather than at the junction with the LA or in the LA itself. These short functional refractory periods may explain why rapid high-frequency activity is consistently recorded in the PV area during AF [10,15]. Electrical properties of the thoracic veins have been assessed in animals [16], but currently, there are no animal models of AF spontaneously induced from PVs, and as a result, few experimental data are available to substantiate these findings. However, action potentials at the distal end of PVs were previously reported to be shorter than those of more proximal segments and LA in guinea pigs [17]. The pronounced decremental conduction properties of PVs may probably explain the marked conduction delay in the PVs observed during AF initiation or ectopic beats, as well as the phenomenon of concealed venous ectopies blocked within the vein [18]. The activation delay was correlated with complex fiber arrangement and particularly with abrupt changes in their direction. These decremental conduction properties could therefore be related to anisotropic conduction [19], with the fractionated venous potentials and associated changes in activation sequence and exits probably correlating with the complex arrangement of venous muscular sleeves reported by pathologists.
in humans [23]. In association with long conduction times in PVs, these short refractory periods provide a very favourable "milieu" for arrhythmogenicity, particularly reentry in or around the veins, which may perpetuate the arrhythmia and thus act as a substrate for AF maintenance [14].

The exact mechanism of these isolated or multiple discharges culminating in paroxysms of AF is uncertain, hence, the term "discharges". Activation during the interval between the previous sinus beat and the initial venous discharge which would support a reentrant mechanism has not been documented to date and is suggestive of triggered automaticity. The next phase with repetitive discharges (frequently with continuous activity in the PVs) is followed by apparently random PV activation believed to be related to wandering rotors or fleeting re-reentry. A transitional phase of re-entry within or around the PV of origin is a likely possibility particularly since short refractory periods in the PVs coexisting with long conduction times to the left atrium (at typical short coupling intervals) provide a "milieu" conducive to re-entry.

**Mapping and electrical disconnection of PVs**

The variety of patients with paroxysmal AF (lasting hours to days), however, has frequent involvement of [2-3] PVs as well as additional non-pulmonary vein initiation sources. Therefore, though initiations from multiple PV sources can be documented by trying different provocative manoeuvres or by restudying a patient at another more opportune moment, a practical approach is to systematically ablate and disconnect the myocardial sleeve of at least 3 PVs. The right inferior PV is frequently difficult to map completely, and perhaps, therefore, its arrhythmogenic potential has been underestimated [6].

Pulmonary vein (PV) isolation can be achieved by segmental ostial ablation guided by PVP recorded during sinus rhythm and/or atrial pacing [8,21]. Targets areas are considered those exhibiting the shortest venoatrial conduction time (in sinus rhythm or distal coronary sinus pacing), as measured from the couple of electrodes of the mapping catheter.

De Ponti et al [22] have reported the utility of high-density mapping of the PVs to identify multiple discrete areas of earliest activation along the perimeter of the PV os, which reflect the location of the venoatrial conduction breakthroughs: they also demonstrated different patterns of activation inside the PVs, and that in the majority of the cases, the finding of multiple foci in the PV, in accordance with a prior report by Haïssaguerre et al [23].

Circumferential mapping allows electrophysiological guided disconnection of the PVs to be accomplished with a high success rate. The more proximal the level of ablation for the PVs, the greater the extent of disconnected myocardium, but this requires more extensive ablation because of increasing diameter and myocardial coverage proximally. Electrophysiological sites of preferential "inputs" or "breakthroughs" from the left atrium to the PVs, enable to disconnect at the ostia without circumferential ablation [8]. A circumferential multielectrode catheter (Lasso: Constellation) allows continuous assessment of activation around the complete circumference of the vein in addition to providing a fluoroscopically visible marker for the vein. One of two bipole (s) or electrode (s) typically show earliest activation with later and sequential spread to the rest of the venous circumference. The catheter ablation must be performed proximal to this site. Disappearance of activation in a part of the circumference after proximal ablation suggests the ablation of a fascicle like myocardial extensions. The disappearance of all distal PVs potentials is a clear indicator of conduction block. Electrical disconnection occurs when the PV potentials abruptly disappear or are dissociated from the atrial potentials during RF delivery.

It is important to distinguish PVPs from "far field" atrial potentials so as to avoid unnecessary ablations which could result in vein stenosis or avoidable collateral damage (ex. to the phrenic nerve). In the right sided PVs both right as well as left atrial potentials can be identified (by mapping both sides of the interatrial septum), while in the left PVs, the nearby left atrial appendage is the most common origin of non-PVs potentials. In the latest case, distal coronary sinus pacing by anticipating left atrial appendage activation can distinguish the two. Sometimes, the presence of electrical connections between PVs may imply that treatment of contiguous vessels might be required when PV electrical disconnection procedures are attempted [24].

The use of limited radiofrequency power, minimising the circumferential extent of ablation and targeting the most proximal segments may be important in limiting the frequency of complications.

**Recurrence of AF**

A recurrence of AF after PV isolation must be caused either by the resumption of PV conduction or by the presence of critical foci outside the PVs. In patients who underwent a second procedure, incomplete isolation of a previously isolated PV is frequently found. Recovery of conduction through inadequately ablated muscle fascicles in the muscle sleeves surrounding the PVs may be the most common reason for recurrent AF after PV isolation, at least among patients with paroxysmal AF. Tritto et al [25] have observed that the recurrences
that occurred during the first week after PV isolation are not predictive of an unsuccessful procedure during the follow-up, and may be caused by an irritative or inflammatory process or by the lesion's instability (transient return of atrial-PV conduction that later interrupts spontaneously or by the effect of a previously ineffective antiarrhythmic therapy).

After disconnection of the PVs, provocative manoeuvres (isoprenaline and adenosine infusion, incremental atrial pacing) must be performed [26], in order to know their electrophysiological effects on the residual PV musculature and atrio-venous conduction after successful isolation of different PVs. Non PVs sources are found in up to 30% of patients, and are most frequently located in the posterior left atrium and surrounding the ostia of the PVs. Less commonly, there are extra left atrial sources, and may be located epicardically within the coronary sinus; within the vein or ligament of Marshall, or in the right side of the heart, the junction between the superior vena cava to the right atrium.

Conclusions
Nowadays, pulmonary veins are of major interest as a result of their prominent arrhythmogenic role in AF. In association with long conduction times in PVs, short refractory periods provide a very favourable "milieu" for arrhythmogenicity, particularly reentry in or around the veins, which may perpetuate arrhythmia and thus act as substrate for AF maintenance [14]. De Ponti et al [22] evaluated the activation inside the PVs and identified different patterns, which can be grouped in two fundamental forms: a predominantly longitudinal activation pattern and a predominantly transverse one, that may be correlated with histological data of PVs, reporting the presence of a mesh-like arrangement with a combination of spirally and longitudinally oriented bundles of fibers [27].

Our group [28] have also reported that a subset of patients with AF, even in the absence of an organic heart disease, have an altered atrial conduction on sinus rhythm, as compared to control patients; electroanatomical mapping seems to be able to identify different patterns of altered propagation.

PV isolation can be achieved by segmental ostial ablation guided by PV potentials recorded during sinus rhythm and/or atrial pacing [8], and also during atrial fibrillation [29]. Immediate recurrences of atrial fibrillation are consistently abolished by PV isolation, implying that these recurrences are often initiated by depolarisations originating in the PVs. Also, persistent AF became inducible less often as more PVs are isolated, and demonstrates that the PVs are not only a source of the triggers that initiate AF but also may play an important role in the maintenance of AF.

In previous studies of segmental PV isolation, only the PVs that were found to generate triggers of AF were isolated, and a large percentage of patients required additional ablation procedures [8,23]. Oral et al [30] have reported a segmental isolation approach that targets at least 3 PVs, with a clinically satisfactory result in more than 80% of patients with paroxysmal AF, and showed that, the clinical efficacy of PV isolation is much lower when AF is persistent than when it is paroxysmal. This empiric approach is not based on identification of which PVs were arrhythmogenic. Of note is that the long-term efficacy of these two approaches is very similar, but a second ablation procedure is more frequently performed with the first approach (41% vs. 9%). Therefore, in patients with paroxysmal AF, more reliable results may be obtained with empiric isolation of all pulmonary veins, than with isolation of only the PVs that seem to be arrhythmogenic during the ablation procedure.

These results are similar as the ones reported by our group [31], with 80% of the patients with paroxysmal or persistent AF in sinus rhythm during the follow-up (2.9±3.7 months), with ≲ 33% of patients with antiarrhythmic therapy, after a mean of 2.1 PV isolation/procedure.

Demonstration of elimination of atrial fibrillation frees the patient not only from antiarrhythmic treatment but also from oral anticoagulation. This procedure although does not eliminate paroxysmal AF in about 30% who typically have non-PV focal sources. Resistance to antiarrhythmic drugs should determine when this therapeutic option should be offered to a specific patient with paroxysmal AF.

In conclusion, electrical disconnection of PVs could be performed with clinically satisfactory results, and with a low risk of PV stenosis and thromboembolic complications, which compares favourably with the risk of paroxysmal or persistent atrial fibrillation, and antiarrhythmic or anticoagulant treatment. More than 90% of PVs can be electrically isolated from the left atrium by conventional applications of radiofrequency energy along segments of the ostia, guided by PV potentials. Generally, PVs can be isolated in < 4 hours without creating PV stenosis and with a low risk of other serious complications. A satisfactory clinical outcome, consisting of either complete resolution or marked improvement in symptoms, can be achieved in ≲ 85% of patients with paroxysmal atrial fibrillation. When 3 or 4 PVs are isolated, a satisfactory clinical outcome can be
achieved in most patients with a single procedure and without the need for antiarrhythmic drug therapy. In contrast to paroxysmal AF, persistent AF usually is not eliminated by PV isolation. Electrical disconnection of PVs in patients with drug-refractory paroxysmal AF should not be postponed until AF becomes persistent. Once AF has become persistent, it is likely that PV isolation will have to be supplemented by some other type of ablation procedure directed at the atrial myocardium.

Figure 1: Fluoroscopic image of the left superior pulmonary vein (LSPV) in antero-posterior view. The angiographic catheter is positioned in the vein through transseptal catheterisation.

Figure 2: Fluoroscopic image of the basket catheter positioning in the same vein and patient as in Figure 1 in antero-posterior view before venography.

Figure 3: Fluoroscopic image of the basket catheter and the angiographic catheter both positioned in the LSPV trough transseptal catheterisation in antero-posterior view during angiography. This projection allows us to further assess catheter positioning and contact inside the vein, an homogeneous distribution of all the splines around the vein perimeter and the position of spline A (identified by single radiopaque marker).
**Figure 4:** Fluoroscopic image of the left inferior pulmonary vein (LIPV) in antero-posterior view. The angiographic catheter is positioned in the vein through transseptal catheterisation.

**Figure 5:** Fluoroscopic image of the basket catheter positioning in the same vein and patient as in Figure 4 in antero-posterior view before venography.

**Figure 6:** Fluoroscopic image of the right superior pulmonary vein (RSPV) in antero-posterior view. The angiographic catheter is positioned in the vein through transseptal catheterisation.

**Figure 7:** Fluoroscopic image of the basket catheter positioning in the same vein and patient as in Figure 6 in antero-posterior view before venography.

**Figure 8:** Fluoroscopic image of the basket catheter and the angiographic catheter both positioned in the RSPV through transseptal catheterisation in antero-posterior view during angiography. This projection allows us to further assess catheter positioning and contact inside the vein, an homogeneous distribution of all the splines around the vein perimeter and the position of spline A (identified by...
References

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