Transmural ablation of all the pulmonary veins: is it the Holy Grail for cure of atrial fibrillation?

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This editorial refers to ‘Atrial fibrillation following lung transplantation: double but not single lung transplant is associated with long-term freedom from paroxysmal atrial fibrillation†, by G. Lee et al., on page 2774

Atrial fibrillation (AF) is a complex disease most probably due to multiple aetiopathogenic mechanisms. This arrhythmia usually requires a trigger for initiation and a vulnerable electrophysiological and/or anatomic substrate for maintenance. It is still unclear whether the trigger mechanisms for AF initiation include focal enhanced automaticity, triggered activity, or microre-entry from myocardial tissue inside the pulmonary vein (PV). In spite of an incomplete understanding of the anatomo-functional basis for the initiation and maintenance of AF, various catheter and surgical ablation techniques have been shown to modify the substrate of this arrhythmia, achieving a stable sinus rhythm, free from AF, in a high proportion of cases.

In the past 10 years, catheter ablation techniques in patients with AF have evolved from an initial approach focused on the PVs and their junctions with the left atrium (LA), to a more extensive intervention, mainly, but not exclusively, on the LA myocardium and its neurovegetative innervation (Figure 1). It is now recognized that the cornerstone of most catheter and surgical ablation approaches is to isolate the PVs electrically from the LA wall. Despite more or less substantial differences among the various catheter techniques that are currently utilized worldwide, results seem to be uniformly similar, with success rates in the range from 50% to 80% in patients with long-standing, persistent, or paroxysmal AF. Notably, a median of two AF ablation procedures are usually necessary for a successful outcome.1,2

Using single (SLT) and double lung transplantation (DLT) surgery, the study of Lee et al.3 constitutes a model for unilateral and bilateral isolation of the pulmonary venous antral region. With a remarkable number of patients and 5.4 ± 2.9 years of follow-up, the study provides evidence to support the importance of a complete and ‘durable’ electrical isolation of all the PVs in order to achieve long-term freedom from AF.

Early and late post-procedural AF

Acute AF is a common complication following thoracic surgery in the early post-operative stage. In the study by Lee et al.,3 early AF was more frequent in patients after SLT (28%) and DLT (29%) compared with a control group of patients undergoing non-transplant thoracic surgery (14%). Mechanisms underlying post-operative AF may include changes of atrial electrophysiological properties induced by surgical manipulation, pericardial inflammation, oedema, and/or neurohormonal imbalance.4,5 It is interesting to note that the episodes of early post-operative AF did not predict the subsequent development of ‘late AF’ in the DLT group as no DLT patient developed recurrent AF during long-term follow-up, compared with 33% in the SLT group and 53% in the non-transplant group.

Acute return of PV conduction is also common after successful catheter-based PV isolation. The delayed effect of radiofrequency ablation lesions and transient inflammatory or autonomic disturbances have been suggested as possible causes. Drawing an analogy with catheter ablation techniques, a 3 month ‘blanking period’ is recommended, and recurrences of AF or atrial flutter are not considered as failures of the procedure.6 Therefore, both scenarios (early post-surgical appearance of AF and acute post-ablation AF recurrences) appear to be less dependent on triggers originating from the PVs than AF occurring in other contexts. Still, the topic of early recurrences of AF after catheter ablation is far from being settled.

As previously reported, late recurrences after AF ablation may be due to a variety of factors including late recovery of conduction of previously electrically isolated PVs and, in some cases, emergence of non-PV triggers or foci not properly identified at the initial ablation session.1,2 The time between PV reconnection and AF recurrences is unknown. Progression of atrial fibrosis or clinical factors such as hypertension may also contribute to the development of electrophysiological abnormalities promoting recurrences of AF. In the study by Lee et al., the incidence of late AF following...
DLT was significantly lower (0.5%) compared with SLT (12.6%) and non-transplant thoracic surgery (11.4%). Surprisingly, although it is known that patients receiving DLT are more prone to other atrial arrhythmias such as atrial flutter and atrial tachycardia, a low incidence of these incisional arrhythmias was found in this study. As stated by the authors, an important point in the interpretation of their results is the baseline differences in age, LA dimensions, and the underlying diagnosis among the three groups.

Recurrence of PV conduction after catheter ablation is also more likely to occur in older patients with non-paroxysmal AF, hypertension, and a large LA. The major limitation of the present study is how AF was detected during follow-up. In this observational and retrospective study the predominant assessment of AF following hospital discharge was determined by symptoms, or if the arrhythmia was suspected based on routine clinical evaluation. It is well known how a substantial proportion of AF episodes may be asymptomatic and therefore the true incidence of AF can be underestimated. As outlined in the Heart Rhythm Society consensus document on AF ablation, ‘success’ should be defined as freedom from symptomatic or ‘asymptomatic’ AF, atrial tachycardia, or atrial flutter lasting 30 s or longer 12 months following AF ablation. The true incidence of AF recurrences remains a limitation for many clinical studies conducted over long follow-up periods.

Transmurality as the key for success

In our opinion, the most important question that arises from this study is whether transmural or complete lesions of all right and left PVs are important or necessary for achieving stable long-term sinus rhythm. Some investigators have suggested that complete electrical isolation of the PVs may not be crucial for a successful outcome. As Lee et al. describe in their article, the surgical technique used in the DLT patients leads to antral isolation of the PVs, analogous to catheter-based PV isolation. Recovery of PV conduction and atrial tachyarrhythmias is a dominant finding after continuous circular lesion around the ipsilateral PVs in patients with AF. With the use of a pure
anatomical approach, it is possible to prevent AF in a significant proportion of patients undergoing catheter ablation. The ability to create a full-thickness lesion that completely disconnects PV varies depending on the catheter technique or energy used. Different contributing architectural factors for catheter-based treatment of AF can determine the success of the procedure. These factors may include (i) the complex LA endocardial structure; (ii) a non-uniform myocardial thickness; (iii) a flow-mediated cooling effect by the intramyocardial atrial arteries; and (iv) the epicardially located inter-PV muscular connections. The need for transmural lesions to achieve complete disconnection of individual PVs is unclear. Residual myocardial continuity leads to conduction gaps, possibly causing the failure of the procedure. Although it can be debated, the study of Lee et al. provides the first clinical validation that complete and transmural isolation of all the PVs may be necessary to increase long-term success rates.

Transmural PV isolation is a shared consequence of DLT and cardiac transplantation operations. However, cardiac transplantation also involves posterior LA isolation and a more complete cardiac denervation, providing added benefit in preventing AF. Despite recent studies showing no clear benefit, additional linear lesions targeting the posterior LA wall have been demonstrated to increase the success rate of catheter ablation in persistent and long-standing AF. Different atrial regions contribute to the fibrillatory process and to the maintenance of AF, emphasizing the role of structural discontinuities and heterogeneous fibre orientation favouring anatomic re-entry or anchoring rotors. Abrupt changes in muscular thickness and fibre orientation transmurally along the myocardial bundles of the posterior atrial wall are a substrate for slowing conduction and seem to play an important role in maintaining AF.

Experimental studies have shown that initiation and maintenance of AF can be favoured by both parasympathetic and sympathetic stimulation. A non-uniform regional distribution of the cardiac nerves and differential patterns of innervation have been observed in human hearts. Complete vein denervation seems to be an additional predictor of long-term benefit after circumferential PV ablation of AF. As can be seen in Figure 2, during lung transplantation surgical anastomoses 2–3 cm proximal to the PV orifice involve nerves and ganglia of the autonomic nervous system present at the veno-atrial junction and thus have the potential to improve outcome.

The presence of atrial innervation within the myocardium of the LA suggests that non-transmural lesions could have a clinical impact during catheter ablation. However, the autonomic nervous system elements are mainly present in the fat pads on the epicardial surface of the left atrial wall and therefore transmural lesions are needed to denervate the atria. The contribution of the neural inputs to the ablation areas points to a complex interplay of anatomical and electrophysiological substrates for the genesis and recurrence of AF.

The study of Lee et al. demonstrates the importance of ‘durable’ electrical isolation of all right and left PVs as the cornerstone in catheter and surgical strategies for the long-term prevention of AF. Their findings represent an additional piece of the complex and still unassembled puzzle that is the pathophysiology

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**Figure 2** (A) Dissection showing the subepicardial myocardial fibres viewed from the superior–posterior aspect. The myocardial tissue encircles the veno-atrial junction. (B) Cross-section in a specimen of a 65-year-old subject stained with the van Gieson technique to show the myoarchitecture along the entire thickness of the PVs and LA walls. The LA musculature lies external to the venous wall between the adventitia and the venous media in a fine matrix composed of collagen, elastic fibres, and blood vessels. Note the abrupt changes in muscular thickness and fibre orientation transmurally along the PV antrum and posterior atrial wall. Surgical antral isolation of the PVs may partially involve the autonomic ganglia and nerves (dotted line). (C) Cross-section along the left superior PV to show the mixed arrangement of myocardial fibres making up the wall of the LA and the vein. Note the presence of collagenous septa between the myocardial fibres and the autonomic nervous system elements mainly located in the fat pads on the epicardium. Epi and Endo mark the orientation for epicardial and endocardial surfaces, respectively. LAA, LA appendage; SVC, superior vena cava.
of AF recurrences after catheter ablation, and reinforce the need of a better understanding of the anatomo-functional substrate of the arrhythmia.

Conflict of interest: none declared.

References