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NON-PHARMACOLOGICAL MANAGEMENT OF ATRIAL FIBRILLATION: ROLE OF PULMONARY VEINS AND THE POSTERIOR LEFT ATRIUM

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Abstract

Non pharmacological approaches for the management of atrial fibrillation are rapidly emerging as the mainstay for the definitive management of this arrhythmia. Over the past several years, numerous studies have appeared in the literature that have highlighted various aspects of the pathophysiological mechanisms underlying this arrhythmia. The purpose of this brief review is to place the current approaches being utilized for arrhythmia management in context of what is known about arrhythmia mechanisms.

Atrial fibrillation is an important cause of morbidity and in recent years has received increasing attention in the fields of interventional electrophysiology and cardiac surgery. This is predominantly due to the success of ablative techniques in managing this arrhythmia, and the disappointing results of pharmacologic therapy. This has prompted an expanded use of these techniques in patients with paroxysmal forms of the disease especially in younger patients and those without any structural heart disease¹. From a procedural standpoint, the favorable long-term results of the surgical maze procedure² as well as the recognition that pulmonary veins are critical to the initiation of paroxysmal atrial fibrillation^{3, 4} have also prompted renewed interest in the management of this arrhythmia.

Currently, diverse techniques are being used for the non-pharmacological management of AF. These include: (i) surgical maze and its variants² (ii) catheter-based pulmonary vein (PV) isolation (antral or ostial)^{4, 5} (iii) left atrial ablation⁶ (iv) ablation of complex left atrial (LA) electrograms⁷ and (v) ablation of fat pads (epicardial autonomic ganglia). The purpose of this manuscript is to review the relevant aspects of genesis of arrhythmia especially from the pulmonary veins and attempt to place the current procedures for the management of this arrhythmia in perspective.

At the outset, it would be useful to place the left atrium in its developmental context and review the anatomy of the atria in relation to various structures in its vicinity that have been implicated in the genesis of atrial fibrillation.

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Development and Anatomy of Pulmonary Veins

The anatomy and electrophysiology of the PVs is complex and still incompletely understood. During human embryologic development, the myocardium around the common PV shows expression of an antigen (HNK-1) is associated with the developing conduction system⁸. This raises the possibility that these sites may harbor cells with pacemaker characteristics; indeed, PV myocytes seem to show ion channel expression similar to that of sinoatrial nodal cells, with significant I_f current and lack of I_{K1} current⁹. A recent study has shown that venous tissue is incorporated into the smooth walled body of the LA¹⁰. This is in contrast to the sinus venarum portion of the right atrium and the remaining parts of the left and right atria (Figure 1). The pulmonary vein left atrial junction definition can be difficult to define and the ‘antral regions’ of the pulmonary veins could encompass vast portions of the posterior left atrial wall⁵. Further mapping studies of atrial fibrillation have shown complex patterns of activation in these regions of the atrium (Figure 2). Most catheter based ablative procedures that are being utilized these days tend to target myocardium in this region of the left atrium¹¹. Such lesion sets could affect multiple mechanisms potentially driving this arrhythmia (Figure 3).

Electrophysiology of Pulmonary Veins

Besides having intrinsic pacemaker activity, PV muscle sleeves differ from LA tissue in other important ways. Even in normal controls, effective refractory period (ERP) of PV myocytes is shorter than that of neighboring LA myocytes, favoring reentry or propagation of rapid triggered activity¹². However, in patients with AF, PV ERPs are even shorter than in normal controls¹³, with significant heterogeneity in conduction properties and refractoriness¹⁴. Autonomic stimulation, especially parasympathetic³ but also sympathetic¹⁵, can further shorten PV ERPs. These changes are likely to be arrhythmogenic in patients prone to AF, and may be one reason why vagal denervation seems to improve outcomes in surgical and catheter-based ablation procedures.

Arrhythmia Mechanisms

Thoracic veins, especially the pulmonary veins, are electrically active and have been the subject of several studies^{3, 16–19}. Several mechanisms have been proposed for pulmonary vein arrhythmogenicity. These structures can generate abnormal impulses, and the complex micro-architecture of muscle bundles in this region lead to abnormalities in impulse propagation. These factors set the stage for arrhythmogenesis²⁰. Focal (triggered) activity and reentry have been implicated in mapping studies of PVs^{18, 19}. A detailed review of these mechanisms is beyond the scope of this review. Table 1 summarizes some of the key studies in this field and Figure 2 shows a schematic interpretation the published data²¹.

Triggered activity (early and delayed after depolarizations)

Classically, triggered activity is divided into early after depolarizations (EADs), occurring before the end of the action potential, and delayed after depolarizations (DADs), occurring after the end of the action potential. These have been defined based on single cell recordings and response of cells to stimulation protocols and pharmacological perturbations¹⁹. In the case of PV arrhythmias, triggered activity has been implicated along with reentry^{19, 22}. The data for triggered activity were predominantly generated using pharmacological methods, such as sympathomimetics to initiate PV ectopy^{19, 23}. Electrophysiological characteristics of PVs have also shown to be different from those in the atria. Beta-adrenergic receptor blockers, calcium channel blockers, and sodium channel blockers have been shown to suppress PV ectopy²³. Traditionally, EADs are seen in the setting of a prolonged action potential duration that favors reactivation of inward calcium or sodium currents during the

plateau phase of the action potential. However, recent work has provided a new paradigm for EADs in the atria, resulting from a complex interplay of the autonomic nervous system's effects on action potential duration and calcium current in PV myocytes. In this setting, APD prolongation is not required for EADs. Instead, the PV muscle sleeve is associated with a peak calcium transient that occurs much later in the action potential, a phenomenon augmented by parasympathetic stimulation induced shortening of the APD. The result is increased intracellular calcium at a time that the membrane potential is nearly repolarized, providing the necessary conditions for inward current via the sodium calcium exchange, which can trigger arrhythmias^{24, 25}.

Reentry

Other studies in humans and animal models have suggested reentry as a mechanism of AF arising from the region of the PVs and the PV-LA junction^{18, 26}. The ultra structure of this region is well suited for micro-reentry²⁷. Further, studies analyzing modulation of the action potential during AF and localizing sites of highest dominant frequency also suggest that paroxysmal AF is maintained by reentrant sources that may be located at the PV-LA junction²⁸.

These mechanisms undoubtedly interact with other factors, such as atrial stretch, that profoundly affect the electrical behavior of atrial myocardium. In an animal model (sheep hearts), the rate and organization of fibrillatory waves originating from the superior pulmonary veins increased with elevation of intra-atrial pressures²⁹.

Left Atrial Structures Relevant to Catheter Ablation

i) PV Muscle Sleeves—Atrial myocardial sleeves extend a variable distance onto the epicardial surface of the pulmonary veins, often covering less than the full circumference of the vein³⁰ (Figure 4). These outer circular or spirally arranged myocardial sleeves are formed from either a cardiac or an extra cardiac source. However, there is some level of agreement in the literature that the myocardium in the region of the primitive PV has different characteristics compared to the working myocardium of the LA appendage.

Several studies have shown that the atrial myocardial sleeves in human PVs have a highly variable architecture^{27, 31, 32}. Further, the anatomical distinction between PVs and the LA can be difficult to discern either anatomically or by electrical recordings⁵. It can be argued that the entire posterior LA could constitute the 'antrum' of the pulmonary veins, as it embryologically contains pulmonary venous endothelium. Mapping studies have also shown that the actual conduction of impulses within the PVs can follow a complex course.²⁰

Catheter ablation techniques for paroxysmal AF aim to prevent PV triggers from conducting to the LA by energy delivery at the LA-PV junction or within the 'antral' areas of the LA. Electrical measures using loss/reduction of PV electrogram amplitudes and electrical isolation of the PV's (determined by pacing maneuvers) have been used as end points. In the early years of AF ablation, actual triggers within the PVs were targeted. However, due to reports of PV stenosis, the approach was modified to one that targets PV antra to achieve conduction block between the PVs and the LA³³. It is intriguing that patients benefit from LA ablation even when PV isolation is not achieved, especially in persistent AF³⁴. This highlights the importance of the LA in the genesis of this arrhythmia, and suggests that in chronic forms of the disease, the PVs might be somewhat less important in the pathogenesis.

ii) Left Atrial Substrate and Maintenance of AF—Complex fiber geometry can provide factors such as structural heterogeneity, anisotropy, and slow conduction that favor initiation and maintenance of localized reentry within and around the PV's. Micro-reentry is

made possible by myocardial fibrosis that electrically isolates adjacent muscle bundles, forcing ‘zigzag’ conduction of impulses²⁷. Further several studies have shown that atrial fibrosis can enhance the ability of the atrial myocardium to sustain arrhythmias in animal models³⁵ and humans³⁶. Human studies have also shown that the atrial myocardium may show areas with electrogram morphologies that identify sites from which autonomic responses can be elicited³⁷; these may also serve as catheter ablation targets³⁸.

In addition to the above findings, there are extensive experimental and clinical data showing dynamic electrophysiological changes that occur as soon as atrial fibrillation begins. These changes, collectively termed “atrial remodeling”, increase the likelihood of continued atrial fibrillation³⁹. The mechanisms of these changes are beyond the scope of this review. However, it is important to place these pathophysiological events in perspective in order to develop a framework to understand different ablation procedures.

iii) Autonomic Ganglia and the Ligament of Marshall—There has been a great resurgence of interest in the role of the autonomic nervous system in the genesis of atrial fibrillation⁴⁰. Dedicated articles in this issue of *Heart Rhythm* will deal with the role of the autonomic ganglia, the fat pads and the role of structures such as the ligament of Marshall (LOM). With relevance to the discussion in this article the pulmonary veins have cells with specialized conduction properties: P cells, transitional cells and Purkinje cells have been demonstrated in the pulmonary veins⁴¹. Further epicardial nerves penetrate the PV walls transmurally and form a neural network beneath the endothelium of the PVs⁴². These structures, due to their anatomic location, may be modified during catheter ablation techniques that target the LA in general (Figure 3).

Finally, it should be pointed out that non-pulmonary vein foci can also drive AF⁴³ and their mechanisms are incompletely understood.

PERSPECTIVE

Although several studies appearing in the literature have advanced our understanding of the mechanisms of atrial fibrillation, many questions still remain. Why PVs are arrhythmogenic in some people but benign in those without arrhythmias is an enigma. The mere fact that ectopic beats arising within the PVs can conduct to the atria and drive an atrial fibrillation is itself intriguing, considering the mismatch between a small source (PVs) and a large sink (LA) (Figure 5). Impulses from such sources would be expected to be blocked in tightly coupled tissues⁴⁴. It is intriguing to hypothesize that a certain degree of uncoupling of conduction due to disease may be the responsible for PV to LA conduction. Differences in connexin (Cx40) expression between muscle sleeves and atrial myocardium have been reported in canine studies⁴⁵. Recently, differences in the restitution characteristics and conduction properties of the PV-LV junction have been demonstrated in humans with paroxysmal AF compared to persistent AF⁴⁶. Single PACs were shown to result in extreme APD oscillations and initiation of AF. Future studies will enable us to better understand how tissue excitability and conduction characteristics contribute to the genesis and persistence of AF. It is likely that there are important issues in cell-cell communication/coupling in this area that will shed light on the mechanisms of such electrical activity. Conceptual breakthroughs in understanding this arrhythmia along these lines are likely to have a major impact on our therapeutic strategies.

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FIGURE 1. Development of the pulmonary veins (PV) and left atrium (LA)

Panel A (modified from Blom et al⁸): Three-dimensional reconstructions of an embryonic heart. The HNK-1 pattern is indicated in gray. The panel shows an anterior view looking at the dorsal wall of both atria. The anterior part of the atria, the atrial septum primum (AS) and the upper part of the right and left ventricles (LV, RV) are removed. Right atrium (RA). HNK-1 is present in the base of both venous valves (LVV, RVV) and sinoatrial node (SAN). Anteriorly, it continues in the septum spurium (SS). Posteriorly, the HNK-1 reaction is visible in the base of the atrial septum (BAS), the common pulmonary vein (PV), and coronary sinus (CS). There is no connection to the medioposterior node-like part of the RAVR (PAVN= posterior atrioventricular node). LBB, left bundle branch; RBB, right bundle branch; and RSCV

Panel B: (modified from Douglas et al¹⁰). A Schematic depiction of outer side of atrial chambers with PVs and systemic veins. LA body (LAB) and right atrial body (RAB) covered by myocardium with smooth-walled inner aspect (blue), which stretches out over extra cardiac segments of PV and over small peripheral part of systemic veins (blue area above and below dotted line). LA appendage (LAA) and right atrial appendage (RAA) consist of trabeculated myocardium (brown). Left-sided sinus venosus tissue found at junction of LAB to LAA (blue between dotted lines). (B) Schematic depiction of tissue types found in left and right atria seen from inside of atria. Vessel wall tissue (red), myocardial tissue with smooth-walled inner aspect (blue), primary atrial segment tissue (brown), left-sided sinus venosus tissue (*), which is smooth-walled and lacking vessel wall tissue. SC = coronary sinus; IVC = inferior caval vein; SVC = superior vena cava

FIGURE 2. Atrial Fibrillation Interpretation of Mapping Studies

(reproduced from Eckstein et al²¹)

Cartoons of left (1 and 5) and right atria demonstrating potential mechanisms of atrial fibrillation. Fibrillation waves are displayed in red with arrows indicating the direction of propagation.

FIGURE 3. Pathophysiology Of Atrial Fibrillation: Pulmonary Veins, Antral Regions And The Posterior Left Atrium

Schematic showing the major structures in the pulmonary vein (PV) left atrial (LA) junction and the interplay of structural changes and functional events in the genesis of arrhythmias. The lesions used for the catheter based management of atrial fibrillation (AF) such as WACA (wide-area circumferential ablation) can affect different parts of this framework. Abbreviations: AG= autonomic ganglion, PLA=posterior left atrium, LOM=Ligament of Marshall

FIGURE 4. PV muscle sleeves

(Modified from³⁰) Panels show a MR image of a pulmonary vein (for demonstration purposes) and the cross section of the ultrasonic image and histopathologic images showing sleeves (covering variable parts of the circumference of the pulmonary veins).

FIGURE 5. ‘Focal’ PAC’s initiating AF

Upper panel shows a telemetry strip demonstrates a single PAC initiating AF. The bottom panel shows a single PAC mapped using intracardiac catheters. Abbreviations: I,aVF, Vi,V6+ surface ECG tracings, HRA=high right atrium, proxd,2,3,4,p are recordings from a linear multipolar catheter within the pulmonary vein. LSD,2,3,4, P= left superior pulmonary vein recordings. CS=coronary sinus, 9, 10=ostium and 1,2= distal coronary sinus, His-His bundle catheter, Abl=ablation catheter distal (d) and proximal (p). PAC= premature atrial contractions, AF=atrial fibrillation

Table 1**Mechanisms of Atrial Fibrillation (animal models and human data)**

REENTRY
- Multiple circuits (humans): <i>Moe (1962)</i> ⁴⁷
- <i>Allessie (1994)</i> ⁴⁸
- Functional reentry: <i>Allessie (1977)</i> ⁴⁹
- Spiral waves: <i>Jalife</i> ⁵⁰ , <i>Allessie (1990)</i> ⁵¹
- Mother rotor: <i>Mandapati (2000)</i> ⁵²
'FOCAL'
- Aconitine on RAA: <i>Scherf (1947)</i> ⁵³
- Focal PV ablation site: <i>Jais et al (1997)</i> ⁵⁴

Abbreviations: RAA –Right Atrial Appendage; PV- Pulmonary Vein.