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The role of pulmonary veins in atrial fibrillation: A complex yet simple story

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ABSTRACT

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with increased incidence among the elderly population. The concept that ectopic activity in pulmonary veins (PVs) could be responsible for triggering AF has been put forward, and the inter-relationship between PVs and left atrium has been the subject of many anatomical and physiological investigations. Variable configuration of action potentials among various PV cardiomyocytes has been reported. PV myocytes were shown to have a higher resting membrane potential and a lower action potential amplitude and duration than the left atrium. Much evidence has accumulated to indicate that spontaneous depolarization and/or re-entry from PVs could be the mode by which AF is initiated and/or sustained. Attempts have been made to link AF in certain pathophysiological states, notably, congestive heart failure, valvular disease and hyperthyroidism to PVs. There has been evidence to suggest that an increase in PV diameter may be the trigger for initiating AF. However, there is limited clinical knowledge available on the nature of the antiarrhythmic drugs that act upon PVs to alleviate AF. Most drugs currently employed are the standard agents generally utilized for the treatment of AF. Radiofrequency ablation (RFA) of the PVs and its isolation from the left atrium has become a major curative measure of AF. It is also possible that pharmacotherapy may be more effective or provide extra benefit to patients after a RFA procedure. The trend of the clinical evidence seems to suggest that a hybrid treatment may be beneficial in some population of patients.

Contents

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with increased incidence among the elderly population (Kannel et al., 1982). It seems that the prevalence of AF increases approximately 90-fold from 0.1% among adults <55 years of age to 9.0% in those >80 years of age (Go et al., 2001). In the late 1990s, Haissaguerre et al. (1998) in their seminal discovery, demonstrated that ectopic activity in the pulmonary veins (PVs) may be responsible for triggering AF, in particular, paroxysmal AF (PAF). This landmark finding altered the

Abbreviations: Ar, arrhythmogenic; AF, atrial fibrillation; AP, action potential; CAF, chronic atrial fibrillation; CHF, congestive heart failure; DAD, delayed after depolarization; EAD, early after depolarization; ERP, effective refractory period; LA, left atria; LA–PV, left atrial–pulmonary vein, left ventricle; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; PAF, paroxysmal atrial fibrillation; PV, pulmonary vein; PV–LA, pulmonary vein–left atrial; RA, right atria; RFA, radiofrequency ablation; RCT, randomized clinical trials; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; SR, sarcoplasmic reticulum.

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focus of much of the AF research over the past decade, heightening interest in many areas that had not been given much attention previously. In this review our aim is to summarize the link between AF and PVs, and we have approached the subject in a manner to address issues pertaining to and including (a) the anatomy of the PVs, (b) autonomic innervation of the PVs, (c) the electrophysiology of the PVs, (d) the pathophysiological states predisposing to AF with PV origin, (e) the potential role of volume and pressure changes in the PVs in induction of AF, and (f) the treatment of AF with PV origin.

2. Anatomy of the pulmonary veins — importance to atrial fibrillation

2.1. Gross structure of the pulmonary veins — the myocardial sleeve

A detailed study of PVs and their junctions with the left atrium in human hearts was made over forty years ago (Nathan & Eliakim, 1966). The first observation that provided evidence for the extension of myocardial cells of the left atrium (LA) into PVs (now referred to as 'myocardial sleeves') and historical reference to myocardial sleeves have been made in the publication by Nathan and Eliakim (1966). The discovery that linked PVs and AF by Haissaguerre et al. (1998) has subsequently resulted in numerous studies on the relationship between physiology and pathophysiology of PVs and the myocardium.

While in the earlier study by Nathan and Eliakim (1966), the myocardial sleeves were found to be present in most, but not all, PVs and their absence was usually in the inferior rather than superior veins, it has now been demonstrated that myocardial sleeves are found in up to 97% of PVs (Saito et al., 2000). It was initially established that the fibres of the myocardial sleeves run in a circular, longitudinal, spiral, or oblique manner and that the development of "sleeve" is more prominent in the superior veins than the inferior veins (Nathan & Eliakim, 1966). This basic structure was further elaborated in later studies by Ho et al. (1999, 2001), where it was demonstrated that the fibre bundles were frequently found to blend into each other and form a mesh-like arrangement with several gaps present in the myocardial layer, clearly a more complex picture than was originally described. As well, at the base of the PV, the myocardium was identified in two layers: an outer circular layer which did not always cover the entire circumference of the vein and an inner longitudinal layer which did (Roux et al., 2004).

The measurement of the length of the myocardial sleeves from the left atrial–pulmonary vein (LA–PV) junction in humans showed that the superior veins have longer sleeves than the inferior, and that overall the left superior pulmonary vein (LSPV) has the longest (approx. 1.8 cm) and the right inferior pulmonary vein (RIPV) has the shortest (approx. 0.8 cm) sleeve (Nathan & Eliakim, 1966). These estimates have been confirmed (Ho et al., 1999, 2001; Saito et al., 2000; Hassink et al., 2003; Roux et al., 2004; Steiner et al., 2006) with typical values ranging from 0.4 to 4.8 cm, mostly within 1.0 to 1.3 cm range (Steiner et al., 2006). It was also noted that the myocardial tissue did not extend into the intrapulmonary veins in humans; this was not the case in animals such as mice, rats and other rodent species (Kramer & Marcks, 1965; Nathan & Gloobe, 1970; Paes de Almeida et al., 1975; Mueller-Hoecker et al., 2008). The view that myocardial tissue did extend into the intrapulmonary veins was later established.

An attempt to determine the thickness of the myocardial extensions at various distances from the junction was also made, and it was revealed that the thickest area (approximately 3.7 mm) was at the LA–PV junction of the LSPV, while the thinnest area (approximately 1.2 mm) was 1 cm from the LA–PV junction of the left inferior pulmonary vein (LIPV) (Ho et al., 1999). Moreover, it was demonstrated that, in general, the thickest locations around the circumference of the PV were at the superior wall of the inferior PVs and the inferior wall of the superior PVs (Ho et al., 2001).

2.2. Histology and ultrastructure

Additional information on the structure of the myocardial sleeves of the PV was obtained after many microscopic and histological studies; the myocardial sleeves in humans is always located outside of the adventitial layer, separated from the smooth muscle layer of the PVs by fibro-fatty tissue (Saito et al., 2000; Moubarak et al., 2000; Steiner et al., 2006). Interestingly, the sleeve tapers near its distal end in the PV at which point the myocardial cells are gradually replaced by fibrosis (Saito et al., 2000; Hassink et al., 2003; Steiner et al., 2006). Furthermore, it has been reported that 34% of PVs have some fibrotic changes within the myocardial layer, and this is most commonly found in the +54 age group (Ho et al., 2001).

Earlier ultrastructure studies by electron microscopy of the PV of rats indicated the existence of striated muscle in the PV, which seemed identical to that in the LA myocardium (Policard & Pregermain, 1959; Klavins, 1963). In addition, the presence of intercalated discs with desmosomes was also demonstrated in the sleeve (Ludatscher, 1968). The latter findings suggested that conduction could occur between the cells of the rat myocardial sleeves, a concept that gained momentum later. Subsequently, node-like cells were also discovered in the rat PV (Masani, 1986), suggesting a potential cause of the spontaneous activity that was previously observed (Cheung, 1981a). Similarly, periodic acid Schiff-positive Purkinje-like cells have been identified in canine PVs (Chou et al., 2005). A higher density of such Purkinje-like cells in canine PV has been associated with areas of ectopic activity (Tan et al., 2008).

Similar observations in human PV myocardium have been made in that the 'cardiac' muscle was observed as part of the PV myocardial sleeve (Policard & Pregermain, 1959; Nathan & Eliakim, 1966; Saito et al., 2000; Ho et al., 1999, 2001; Moubarak et al., 2000; Mueller-Hoecker et al., 2008). Later, special conduction cells, namely P cells, Purkinje cells, and transitional cells in the myocardial sleeve were identified (Perez-Lugones et al., 2003), and these cells were only found in patients who had a history of AF (Perez-Lugones et al., 2003). It should be noted however that several others have failed to observe these node-like cells (Ho et al., 1999; Kholová & Kautzner, 2003; Steiner et al., 2006; Mueller-Hoecker et al., 2008). As such, it remains to be determined if these cells are actually functional, and if they can be associated with the occurrence of AF.

2.3. Links between atrial fibrillation and the general structure of the myocardial sleeve

It is recognized that AF can be caused by spontaneous ectopic foci in the cardiac tissue; reportedly among patients with PAF, the PVs exhibit up to 94% of such activity (Haissaguerre et al., 1998). Since this initial suggestion, there have been many hypotheses stipulated and experiments conducted to reveal how AF can be linked to PVs, and how ectopic foci can originate in this vasculature (Fig. 1). Accordingly, as a consequence of such investigations, it has been proposed that the mechanism of initiation of AF could be explained by an alteration in PV anatomy and physiology. While a vast body of evidence has accumulated in support of the pathophysiological modifications of PVs as a source of AF, there is also ample contradictory data against such a concept.

A rather interesting theory is that abnormal fibre length or orientation in the myocardial sleeves can be responsible for AF. It was noted that the longest myocardial sleeves tended to be the ones with the most ectopic foci while the shortest myocardial sleeves had the least of such electrical abnormalities (Nathan & Gloobe, 1970; Haissaguerre et al., 1998; Ho et al., 1999). Essentially, Hassink et al. (2003) found that the sleeves were longer in AF patients than those without AF. In addition, Kholová and Kautzner (2003) reported the PVs were both longer (significantly in the LSPV) and thicker (significantly in right superior PV) in AF patients. These findings are in contrast to those of a previous study where no such relationship