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

Marisa Chard, Reza Tabrizchi *

Division of BioMedical Sciences, Faculty of Medicine, Memorial University of Newfoundland, St. John's, NL, Canada A1B 3V6

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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.

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Contents

1. Introduction . . . 207
2. Anatomy of the pulmonary veins — importance to atrial fibrillation . . . 208
3. Autonomic nervous system innervation of pulmonary veins . . . 210
4. Electrophysiology of pulmonary veins — importance to atrial fibrillation . . . 210
5. Pathologies of pulmonary veins promoting atrial fibrillation . . . 212
6. PV Volume and pressure — relevance to atrial fibrillation . . . 213
7. Treatment of atrial fibrillation with pulmonary vein origin . . . 214
8. Concluding remarks . . . 216
Acknowledgments . . . 216
References . . . 216

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.

* Corresponding author. Tel.: 709 777 6864; fax: 709 777 7010.
E-mail address: rtabrizc@mun.ca (R. Tabrizchi).

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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

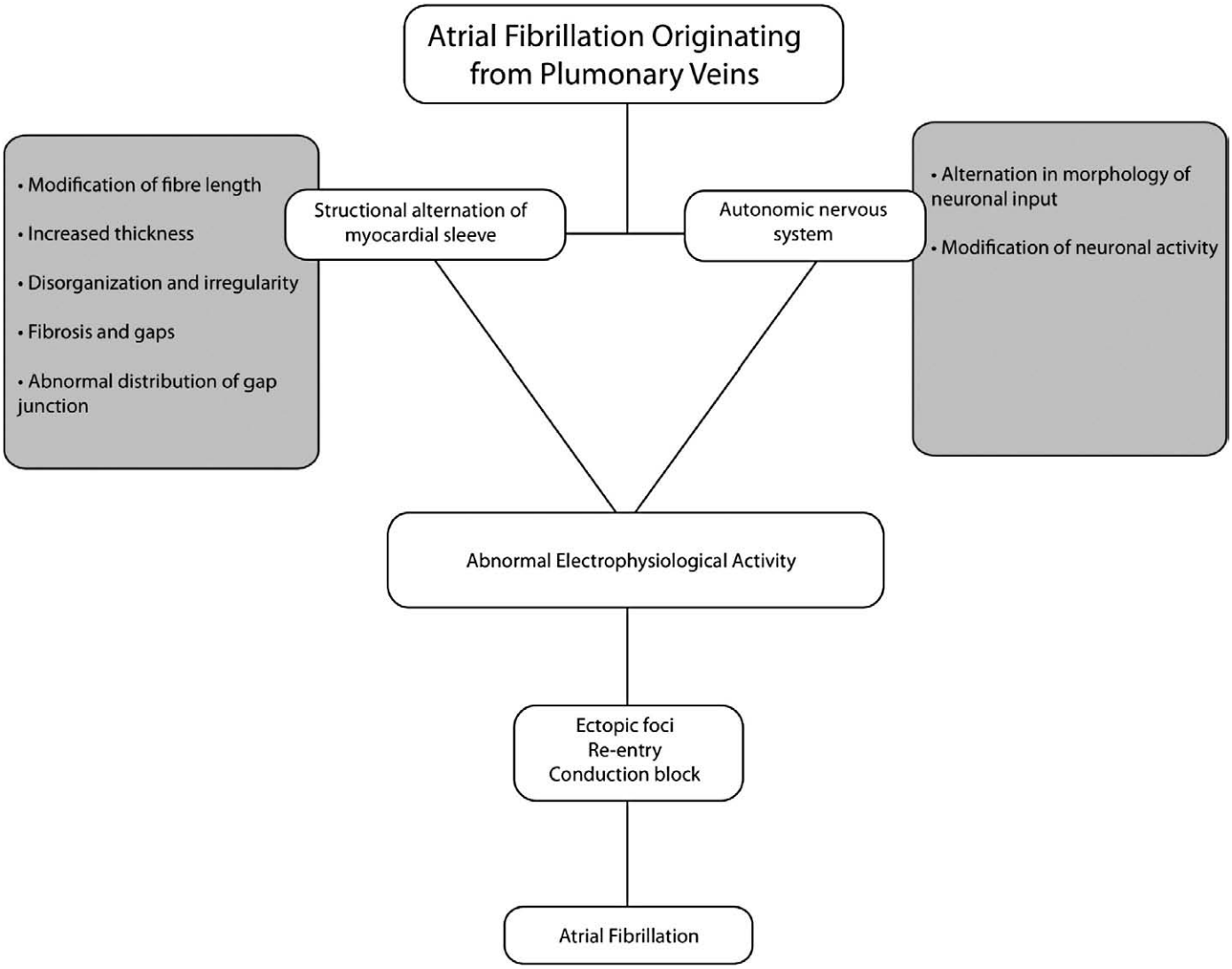

Fig. 1. Schematic of pathophysiological changes in structure and function linking pulmonary veins to the development of atrial fibrillation.

was found to exist between lengths of sleeves and occurrence of AF (Saito et al., 2000), while others have found a positive relationship of AF to changes in fibre length only in the inferior PVs (Tagawa et al., 2001). Inherent structural and morphological differences may account for contrasting findings as to whether fibre length and/or thickness may be among factors causing AF. Based on studies examining alteration in fibre orientation, it has been shown that disorganization and irregularity of the myocardial fibres, complete with fibrosis and gaps (Ho et al., 1999, 2001; Roux et al., 2004), as well as abrupt 90° changes in fibre directionality at the left anterior PV junction (Ludatscher 1968) exist in the human myocardial sleeve. Consequently, this could very well account for micro-re-entry creating foci of ectopic activity leading to AF (Ho et al., 1999, 2001; Roux et al., 2003). Moreover, there has been evidence that the presence of myocardial sleeves is universal in patients with AF, whereas they are present in 85% of patients without AF (Hassink et al., 2003). There is also contrary evidence suggesting that no correlation exists in the feature of the sleeves (i.e. frequency or distribution) in PVs between AF and individuals without AF (Steiner et al., 2006). Nonetheless, it seems that amyloidosis and scarring was more prevalent in myocardial sleeves of the pulmonary veins in the population with AF (Steiner et al. 2006).

Experimentally, in canines it has been demonstrated that disconnections in the myocardial sleeve at the left anterior PV junction exist, and as such it is possible that they could be responsible for conduction block and/or conduction delay within this area (Hamabe et al., 2003). As well, disconnection in the myocardial sleeve at the left anterior PV junction has also been made in humans (Tan et al., 2006). Thus it is plausible that such features can promote re-entry leading to AF initiation.

A higher degree of fibrosis (as well as discontinuity and hypertrophy) has been found in patients with a history of AF when compared to those without AF (Tagawa et al., 2001; Hassink et al., 2003; Steiner et al., 2006). The fact that both fibrosis and ectopic discharges are more commonly found distally in the PV (Haissaguerre et al., 1998; Tagawa et al., 2001; Hassink et al., 2003; Steiner et al., 2006) is a meaningful correlation, and could perhaps be linked to a cause of AF. In addition, by allowing for slowed conduction leading to re-entry, fibrosis in PVs may promote and aid the initiation of AF (Hassink et al., 2003).

2.4. Theories on the embryonic origin of the myocardial sleeve

The embryonic origin of the myocardial sleeve has been the subject of much debate for some time. Fundamental questions that have been lingering are: (a) whether it is the atrial myocardium that extends up to the PVs during development or (b) whether myocardial-like cells are an innate part of the PVs cell-line that develop by differentiation. There has been evidence for the former (Jones et al., 1994; Lyons et al.,

1990; Millino et al., 2000) and the latter (van den Hoff et al., 2004) theories. However, a recent study sheds new light on the issue, indicating that myocardial-like cells are an innate part of the PV cell-line that develop by differentiation (Mommersteeg et al., 2007). By using genetic labelling techniques at different stages of development, it was shown that a biphasic mechanism of myocardial sleeve formation may exist whereby myocardial cells initially originate from PV mesenchymal cells, and then grow by proliferation and expansion to create the myocardial sleeve (Mommersteeg et al., 2007). Thus, it is possible that the PV myocardial sleeve is not derived from atrial myocardium as one would intuitively assume (Mommersteeg et al., 2007). This is further supported by recent evidence concerning a difference in anatomic variability in PV cardiomyocytes (Mueller-Hoecker et al., 2008).

3. Autonomic nervous system innervation of pulmonary veins

It is recognized that the nerve plexus on the PV myocardial sleeve in humans is of cardiac origin (Armour et al., 1997; Pauza et al., 2000; Chevalier et al., 2005; Tan et al., 2006; Vaitkevicius et al., 2008). Cholinergic and adrenergic fibres had earlier been observed in PVs of various animals by light and electron microscopic studies (Fisher 1965; Cech 1969; El Bermani et al., 1970; Paes de Almeida et al., 1975). Armour et al. (1997) found that autonomic nerves in 'ganglionated plexuses' were located around the great vessels of the human heart such as the PVs. Later seven ganglionated subplexuses of the epicardiac neural plexus were identified, and it was demonstrated that three of the seven surrounded the PVs, namely the dorsal right atrial (RA), the left dorsal and the middle dorsal subplexuses (Pauza et al., 2000). A more detailed morphological pattern of these subplexuses in the PVs of the human fetus was further elucidated more recently, showing the common distribution of each subplexus on the various PVs (Vaitkevicius et al., 2008).

It has also been demonstrated that epicardial (location in the PV myocardial sleeve) nerve density was higher at the PV ostium than at more distal locations (Chevalier et al., 2005), but it seems those of the endocardial nerve are less well defined. Tan et al. (2006), employing the technique of immunohistochemical staining, demonstrated that both cholinergic and adrenergic nerves run together in single neural plexuses in PVs. It was also revealed that although the majority of ganglion cells are cholinergic, more than 90% of ganglia are made up of co-localized cholinergic and adrenergic fibres (Tan et al., 2006). It was further reported that nerve densities were highest in the PV antrum within 5 mm of the LA–PV junction rather than further distally in the PV or into the atrium (Tan et al., 2006). More recently, it has been shown that the posterior sides of inferior and the LSPVs are the sites where the ganglion is prominent in human fetal PVs (Vaitkevicius et al., 2008).

4. Electrophysiology of pulmonary veins — importance to atrial fibrillation

4.1. The role of action potentials and ionic currents

Variable configurations of action potentials (APs) among various PV cardiomyocytes have been reported. Cheung (1981a,b) showed, in the guinea pig, the regular-type of cardiomyocyte APs (fast response) generated by stimulation were smaller and shorter in duration at the distal end of the PVs. In addition, the configuration of APs in the more proximal parts of the PVs tended to approach the appearance of atrial cardiomyocyte APs (Cheung, 1981a,b). Moreover, isolated and detached PVs from atria showed spontaneous activity (i.e. pacemaker-like APs) but such APs were not observed when the PV remained attached to the atria (Cheung, 1981a,b). Slow and fast response APs in normal PV tissue have also been observed in canine PVs (Chen et al., 2000). There have also been many observations that distinguish PV cardiomyocyte APs from those in the LA. For instance, PVs were shown to have a higher resting membrane potential and a lower AP amplitude and duration than the LA in canines (Ehrlich et al., 2003).

In the past decade, there has been much interest in the nature of the ionic currents in the PVs cells responsible for the electrical discharge to create ectopic activity. In isolated single canine PV cardiomyocytes, 76% seemed to show pacemaker AP features (Chen et al., 2002a). All PV cardiomyocytes had inward Ca^{2+} currents and transient outward K^+ currents, but the pacemaker-like cells had smaller inward-rectifier K^+ current and a larger delayed-rectifier K^+ current (Chen et al., 2002a; Ehrlich et al., 2003). In the dog, there is a significantly greater expression of the rapid delayed-rectifier and slow delayed-rectifier in PVs versus LA (Melnyk et al., 2005). In addition, in the same study, smaller expression of the inward-rectifier (Kir2.3) but similar levels of Kir2.1, L-type Ca channel ($Ca_v1.2$) and Ca-exchangers were found in PV versus LA (Melnyk et al., 2005). Of interest, there was no I_f current observed in any PV cell and the I_f isoform HCN4 was not expressed in the PV myocardial sleeve (Yamamoto et al., 2006), which differs from cells of the sinoatrial node (Chen et al., 2002a). The same group also found that T-type Ca^{2+} currents exist in canine PV cardiomyocytes, more frequently in the pacemaker-like cells, suggesting that this current may play a role in abnormal automaticity and triggered activity (Chen et al., 2004). Additionally, canine PV cardiomyocytes have a smaller transient outward K^+ current and L-type Ca^{2+} current than LA tissue (Ehrlich et al., 2003). Certainly, the difference in ionic currents between the PV and LA could arguably explain the observed differences in APs, and perhaps even the PVs' preferential generation of ectopic foci in PAF.

Calcium may well play a role in regulating ionic currents in PVs and could be one of the main causes for abnormalities displayed by PV cells. A study using ryanodine in rabbit cardiomyocytes showed pacing-induced spontaneous activity which was thought to be due to activation of a Ca^{2+} dependent current during diastole (Honjo et al., 2003). Spontaneous voltage-independent Ca^{2+} release has been noted to be present in canine PVs, and this in turn may induce triggered activity (Chou et al., 2005). It has also been shown that increased Ca^{2+} transients and increased Na^+–Ca^{2+} exchange current may enhance early after depolarization (EAD) formation in superfused canine PVs (Patterson et al., 2006). More recently Jones et al. (2008) demonstrated that rabbit PV cardiomyocytes have a lower capacity to buffer change in intracellular Ca^{2+} concentration due to a low expression and activity of Na^+–Ca^{2+} exchanger and a lower sarcoplasmic reticulum (SR) capacity. Thus, such inefficiency in Ca^{2+} buffering capacity may predispose the cell to spontaneous activity in Ca^{2+} overloading conditions (Jones et al., 2008). Moreover, it has been reported that rabbit PV cardiomyocytes that exhibit spontaneous activity have enhanced intracellular Ca^{2+} transients, Ca^{2+} sparks, and greater SR Ca^{2+} stores compared to PVs or LA myocytes without such spontaneous activity (Chang et al., 2008).

There has been much debate regarding the mechanisms by which ectopic foci cause PAF. One hypothesis is that they are generated by abnormal automaticity or triggered activity, while another suggestion is that the cause is by re-entry in the PV (Hocini et al., 2002; Arora et al., 2003; Ehrlich et al., 2003; Honjo et al., 2003; Chou et al., 2005). The maintenance of AF has also been thought to be caused by a combination of the mentioned mechanisms (Chen et al., 2000, 2001; Takahashi et al., 2003; Dixit et al., 2004).

Certain electrophysiological characteristics of PVs may be different in patients with AF compared to those without AF. In patients with AF, the effective refractory period (ERP) was found to be significantly shorter in the PV than the LA (Jaïs et al., 2002). In contrast, in the control group, the ERP of PV was found to be significantly longer than those in LA (Jaïs et al., 2002). More specifically, the ERPs in LSPV, right superior pulmonary vein (RSPV) and LIPV were found to be significantly shorter than those measured in LA. Essentially, the ERPs

and the functional refractory periods were significantly shorter in patients with AF in comparison to individuals without AF (Jaïs et al., 2002). In addition, decremental pulmonary vein–left atrial (PV–LA) conduction was found to be significantly more frequent in patients with AF than the control group, and the mean increment in conduction time was significantly higher in AF patients compared to the control group (Jaïs et al., 2002). Collectively, this indicates discrete alteration in the electrophysiogical features of PVs in patients with AF, further supporting the view of (patho)physiological differences between PVs and LA in such patients.

4.2. Enhanced automaticity and triggered activity

While a number of reports suggest that abnormal automaticity and/or triggered activity in PVs is the underlying cause of AF, there are others that dispute such a notion. Prior to the suggestion that ectopic foci originating from PVs could impinge upon cardiac activity, Cheung (1981a) had shown that guinea pig PVs cells could generate independent pacemaker activity which was controlled by inhibitory and excitatory nerves. They also found that digitalis could augment this automaticity causing AF (Cheung, 1981b). Pacemaker activity can be caused by node-like cells which have been identified in rats, canines (Chou et al., 2005; Tan et al., 2008) and humans (Masani 1986; Perez-Lugones et al., 2003). More recently, periodic acid Schiff-positive cells were found at PV focal discharge sites (Chou et al., 2008), and were of a higher density in such regions as opposed to the non-focal discharge sites (Tan et al., 2008). It is possible that such cells may become participants in initiating pacemaker activity in PV.

Spontaneous occurrences of EADs leading to bursts of high-frequency irregular discharge (i.e. triggered activity) in PV sleeves have been demonstrated in dogs (Chen et al., 2000). In experimentally induced AF by chronic rapid atrial pacing, Chen et al. (2000) also observed spontaneous impulses with characteristics of pacemaker cells in PVs. In addition, in PVs during sustained AF but not in non-sustained AF induced by atrial pacing in normal dogs, rapid focal activation has been identified (Zhou et al., 2002). Reportedly, there was no evidence of micro-re-entry within the areas that were mapped, thus implicating abnormal automaticity and/or triggered activity rather than non-re-entrant as the mechanism for initiation of AF. Dixit et al. (2004) also presented evidence that, in human patients, triggered activity, and/or abnormal automaticity are likely to be the mechanisms for sustained PV firing (i.e. repeated, discrete activity from the PV), rather than re-entry, owing to the suppressive effect of overdrive pacing.

Other experimental studies on single PV cardiomyocyte cells from canines have demonstrated that rapid atrial pacing may cause electrophysiological remodelling of the cell, resulting in increased automaticity and triggered activity (i.e. more after depolarizations) which could allow for the maintenance of AF (Chen et al., 2001). This has also focused the debate as to whether triggered activity and abnormal automaticity are the products of pathophysiological changes that may inflict the PV rather than being merely an intrinsic phenomenon associated with the healthy PV tissues. Certainly, there is evidence from canine studies to indicate the existence of spontaneous electrical activity in normal PVs (Chen et al., 2000, 2001) but there are also contrary data (Hocini et al., 2002; Honjo et al., 2003; Wang, 2003; Ehrlich et al., 2003). Wang et al. (2005) recently demonstrated that while abnormal automaticity and triggered activity could be induced by various pharmacological interventions in canine isolated PV sleeves, there was a lack of inherent arrhythmogenic activity in normal healthy PV sleeves without such intervention.

More recently in humans, further evidence was presented in favour of ectopic activity in PVs as the basis for induction of AF as opposed to the re-entrant mode action. Using a basket catheter to map the LA–PV junction in 3D, Arentz et al. (2007) failed to record any re-entrant circuit. Instead, continuous activity (when recorded/observed) showed characteristics of focal activity with decremental or fibrillatory conduction leading to the conclusion that re-entry was not the trigger mechanism here.

4.3. Re-entry

There are numerous studies that support the view that re-entry originating from PV is the cause of AF. The anatomical and electrophysiological features of PVs have been used as a basis in explaining the genesis of re-entry responsible for producing AF. Certainly in canine PVs, there are areas that have been noted to cause activation delays, and these correlated with sudden changes in myocyte arrangement (Hocini et al., 2002). In pathophysiological situations such morphological arrangements may aid in the cause of AF. Also, it is well recognized that AP duration in canine PV cardiomyocytes is shorter than AP duration in atrial tissue (Hocini et al., 2002; Ehrlich et al., 2003). Essentially, the electrophysiological features of the AP of PV cells with slower upstroke and duration compared to the atria leads to a shorter refractory period and a slower conduction velocity (Li et al., 2001; Hocini et al., 2002; Ehrlich et al., 2003). This may facilitate re-entry owing to the resultant reduction in wavelength (Hocini et al., 2002; Arora et al., 2003; Ehrlich et al., 2003).

Re-entry has been visualized in canine PVs using high-resolution optical mapping (Arora et al., 2003). In human, arrhythmias originating from PVs were found to possess decremental conduction properties and short refractory periods, implicating a re-entry mechanism (Takahashi et al., 2003). Human studies, using a multi-electrode basket catheter, identified supporting data in the form of ERP heterogeneity and anisotropic conduction in the PVs, leading to the suggestion that focal discharges from the distal PV could initiate re-entry at the LA–PV junction (Kumagai et al., 2004a). In addition Miyauchi et al. (2005) also found a similar heterogeneity in the PV repolarization in rats as well as intra-PV conduction block implicating re-entry as a mechanism for the generation of ectopic foci in PVs.

A study in canines has revealed re-entry could be responsible for PV tachycardia, and as such could be influenced by the actions of the parasympathetic nervous system which causes a reduction in AP duration and refractoriness in the PV thus promoting re-entry (Po et al., 2005).The latter scenario has been implicated as a method for the maintenance of PAF, and re-entry has been suggested as the mechanism for the maintenance of AF (Atienza & Jalife 2007). In a study investigating the nature of AF originating from PVs, infusion of adenosine was found to accelerate drivers and increased the frequency of AF, but the effect on persistent AF differed from the effect on PAF (Atienza et al., 2006). In patients with PAF, adenosine increased local dominant frequency in pulmonary vein–left atrial junction while in the cohort with persistent AF, it increased dominant frequency at the high right atrium region. The conclusions were that although the source for the maintenance of AF was re-entrant and the location for PAF was PV–LA junction, a non-PV location was the culprit for the persistent AF (Atienza et al., 2006).

4.4. Autonomic nerve stimulation of the pulmonary veins: possible role in atrial fibrillation

Based on an earlier observation that norepinephrine could induce spontaneous APs in guinea pig PVs (Cheung, 1981a), the role of the sympathetic nervous system in ectopic foci generation in PVs has been further scrutinized. It has been demonstrated that high-frequency electrical stimulation of autonomic nerves can create rapid ectopic activity from the PV/superior vena cava in canines leading to AF (Schauerte et al., 2001). Additional evidence has been presented to show that sympathetic and parasympathetic nerves both contribute to the triggered firing in canine PVs (Patterson et al., 2005). Autonomic nerve stimulation was noted to cause a shorter AP and produce rapid firing and EADs in 22 of 28 PVs tested, while either

cholinergic (atropine) or β-adrenergic (atenolol) receptor blockade caused the majority of the triggered firing events to cease (Patterson et al., 2005). Based on the latter evidence, both parasympathetic and sympathetic nerve activations independently and in parallel seem to contribute to the development of AF (Patterson et al., 2005). Furthermore, exposure to acetylcholine (shortens the AP) and norepinephrine (NE) (increases the Ca^{2+} transient), led to a tachycardia-pause phenomenon which was accompanied by a triggered activity in the PV (Patterson et al., 2006). Accordingly, it is certainly possible that autonomic nerve activation near the PV–LA junction could be responsible for the conduction of PV ectopic foci causing AF (Scherlag et al., 2005). Moreover, a hyperactive autonomic ganglia causing the release of a larger quantity of neurotransmitters than normal may be important in focal AF originating in PVs (Po et al., 2006). Collectively, the evidence indicates that both arms of the autonomic nervous system play a role in AF originating from PVs.

It has also been reported that re-entrant activity could be sustained with the β-adrenoceptor agonist isoprenaline (Arora et al., 2003). However, Maupoil et al. (2007) showed that concurrent α_1 and β_1 receptor stimulation (by norepinephrine) was necessary for sympathetically-induced ectopic foci generation in PVs in the rat. More recently, it was demonstrated that in canine PVs, there was a higher density of sympathetic nerves at sites exhibiting ectopic foci than those that did not (i.e. in the same PV) (Tan et al., 2008). Similar observations have been made for parasympathetic nerves (Chou et al., 2008). Interestingly, it was revealed that after removal of sinoatrial nodal dominance, sympathetic nerve stimulation caused ectopic foci to be generated, more often in the PVs than at other sites (Tan et al., 2008). Taken together, the current evidence seems to imply that overactivation of adrenergic and cholinergic systems in PV together or independently induces electrical disturbances (ectopic foci and/or re-entry) that are transmitted to the atria and that can result in manifestation of AF.

5. Pathologies of pulmonary veins promoting atrial fibrillation

5.1. Congestive heart failure

It is known that congestive heart failure (CHF) can predispose to atrial tachyarrhythmias such as AF, resulting in higher morbidity and mortality (Mathew et al., 2000). A number of investigations have explored the link of this phenomenon to the PVs. Okuyama et al. (2003) demonstrated that electrical and anatomical remodelling of the PVs in the CHF state may be important in the maintenance of AF and atrial tachyarrhythmias. Based on histological studies and high-density mapping, it was shown that PVs of canines with CHF had increased fibrosis compared to control animals, and that some AF episodes in CHF could be associated with focal activations and complex fractionated wave fronts within the PVs (Okuyama et al., 2003). These findings led to the suggestion that the occurrence of fibrosis and the concurrent heterogeneous change in conduction velocity precipitated fractionated activity from the PVs which was the cause of AF and its maintenance (Okuyama et al., 2003). In support of such a view, in the same canine model, it has been reported that sustained AF is characterized by single and multiple, stable LA and RA drivers that mainly originated in the PVs and high RA (Ryu et al., 2005).

The concept that vascular pathophysiological changes in the pulmonary circulatory system due to CHF could result in increased triggered activity in PVs requires careful scrutiny both experimentally and clinically. Certainly, it has been shown that PV catheter ablation is a safe and effective treatment for patients with CHF or impaired left ventricular (LV) ejection fraction and AF (Tondo et al., 2006; Lutomsky et al., 2008). However, these studies did not attempt to show that CHF-induced PV changes were responsible for the AF and merely support the notion of existence of AF in patients with CHF and that PV ablation is of some benefit (Tondo et al., 2006; Lutomsky et al., 2008).

5.2. Valvular disease

The exact origin of AF in patients with valvular disease is uncertain. However, Melo et al. (2003) showed that permanent AF in a patient with mitral valve stenosis was potentially the result of the connection between the right PVs and the LA. By isolating the right PVs by ablation followed by recording activity in various epicardial surfaces, it was revealed that the LA remained in sinus rhythm while the PVs showed evidence of self-terminating high-frequency mechanical activity (Melo et al., 2003).

The ultimate outcome of valvular disease on the atria is dilation, which is a product of volume and pressure overloading conditions. There have been many studies on how this dilation can produce structural remodelling in the atria (Sun et al., 2003) which can lead to AF, but there is limited information on how this intertwines with the structural remodelling of the PVs. A link perhaps could be established between valvular disease, expression of gap junctions and possibly electrical disturbances in the PVs. Previously, it has been revealed that lower levels of gap junctions in the cardiomyocytes of PVs could cause electrical decoupling among various types of PV cells (Verheule et al., 2002). This can translate into the dispersions of AP duration leading to electrical instability in PVs which could then manifest as electrical anomalies (i.e. EADs) and be transmitted to the atria precipitating AF. More recently, Sun et al. (2003) reported that in chronic atrial dilation due to mitral regurgitation in a canine model, there were changes in the PVs compared to the controls. Evidence seems to point to a decrease in the expression of gap junctions, connexins 40 and 43, and an increased level of fibrosis in the PVs of the dogs with mitral valve regurgitation versus controls. It was further revealed that the connexin pattern changed from homologous to heterogeneous and that such remodelling in gap junction features was not found in the LA (Sun et al., 2003).

Therefore, the view that the lower levels and abnormal distribution of gap junctions in the cardiomyocytes in the PV may make them become less electrically coupled to other cells leading to a disruption of cell-to-cell communication may have some merit (Polontchouk et al., 2001; Nao et al., 2003). The concept that alteration in gap junction expression in the atria may cause AF has been part of the literature for some time. Polontchouk et al. (2001) had suggested that spatial remodelling of gap junctions could induce changes in functionality of the tissue in AF. Subsequently, reduction of connexin 43 and heterogeneous distribution of connexin 40 in the RA was associated with conduction abnormalities and thus linked to initiation and self-perpetuation of re-entry pathways and the development of AF (Kostin et al., 2002). Other findings have also led to similar conclusions (Nao et al., 2003; Kanagaratnam et al., 2004). In contrast, Wetzel et al. (2005) have argued AF can induce changes in the left atrium with increased expression of connexins 40 and 43. Attempts were made to link such alterations to slow conduction and re-entry that could cause AF (Verheule et al., 2002).

5.3. Hyperthyroidism

Hyperthyroidism is a well known cause of PAF, and its potential effect on the PV myocardial sleeve has been investigated (Chen et al., 2002b). The findings indicated that thyroid hormone increases the spontaneous activity of the PV cells thus enhancing automaticity while also increasing the number of after depolarizations thus facilitating triggered activity. Moreover, the thyroid hormone shortened the AP duration of both PV and atrial cells, a pro-re-entrant effect. The thyroid hormone may achieve this by altering various ionic currents in the PVs (Chen et al., 2002b). A significantly greater transient outward and steady state outward currents in hyperthyroid in comparison to normal PVs and atrial cells was found (Chen et al., 2002b). Certainly, an increase in K current could contribute to shortening of action potential duration and refractory period (i.e.

"gain-in-function"). Both hypothyroid and normal PVs had a slow inward current with behaviour similar to L-type Ca current. Also, peak density of the latter slow inward current was significantly greater in the hyperthyroid compared to normal PVs (Chen et al. 2002b). An increase in L-type Ca current resulting in accumulation of excessive $[Ca^{2+}]_i$ could lead to EADs and delayed after depolarizations (DADs) which could then act as an imputes to causing AF in hyperthyroid state. It was noted that during electrical stimulation, 46% and 92% of hyperthyroid PVs had EADs and DADs, respectively, while none was recorded in normal PVs (Chen et al. 2002b).

Clinically, isolation of PV electrically from the LA has been performed on hyperthyroid AF patients who have since become euthyroid but were refractory to antiarrhythmic therapy (Ma et al., 2007). The beneficial effects of ablation in such a cohort supports the idea that PVs could play a part in generating and/or maintaining AF, although the consequent remodelling of the atria or PVs due to the intrinsic effects of AF rather than the effects of thyroid hormone on these structures is itself a contentious issue here.

5.4. Atrial fibrillation begets atrial fibrillation in pulmonary veins

It is possible that AF itself could be the pathology leading to AF originating in PVs. The mechanism by which AF can remodel the PVs in a way that promotes them to become (further) arrhythmogenic has been alluded to previously in various animal studies, but this concept remains under-explored. The suggestion that remodelling of Ca channels may alter intracellular Ca^{2+} regulation and thus promote PV ectopic foci generation could be associated with AF changing PV physiology (Honjo et al., 2003). Previous ex vivo studies on single canine PV cardiomyocytes from animals with AF induced by chronic atrial pacing revealed arrhythmogenic activity via spontaneous activities and/or high-frequency irregular rhythms where such actions could be suppressed by Na channel blockers, K channel blockers or Mg^{2+} (Chen et al., 2000). Certainly, in dogs, as a consequence of chronic rapid atrial pacing, a widely used procedure that produces sustained AF, various alterations, both anatomically and electrophysiologically, can occur in the myocardial sleeve of the PVs. Thus, it is conceivable that these changes may explain the 'AF begets AF' phenomenon in PVs. For example, Chiu et al. (2005) have reported increased levels of extracellular collagen matrix in PVs after AF was induced (Chiu et al., 2005). This may influence cell-to-cell communications among the myocytes which could promote rapid repetitive activities, leading to further AF (Chiu et al., 2005).

More recently, Rostock et al. (2008) published a study showing that AF can lead specifically to AF in PVs, a phenomenon previously found to exist in non-PV AF. Essentially, electrophysiological parameters (i.e. ERP and conduction velocity) were recorded in PVs and atria before and after induction of short-term AF in patients with a left-sided accessory but without history of AF. Induction of AF caused significant changes in electrophysiological properties of atria and PVs. It became evident that the electrophysiological parameter such as ERP of the PVs and atria decreased (PVs decreasing more significantly than the atria) while conduction slowed in the PVs but not in the atria (Rostock et al., 2008). The findings from the study seem to support the view that susceptibility to AF becomes significantly higher subsequent to exposure to short-term AF, particularly if the source of pacing is originating within the PVs.

6. PV Volume and pressure — relevance to atrial fibrillation

6.1. Pulmonary vein Volume: diameter and atrial fibrillation

While much evidence has accumulated over the years suggesting that increased PV diameter is linked to AF originating in PVs, there is a lack of uniformity among the various findings in the current literature. A morphological study of PVs in patients with PAF with PV foci revealed that the superior veins were more dilated at the ostia and proximal areas than in control patients (Lin et al., 2000). Tsao et al. (2001) using magnetic resonance angiography have demonstrated dilation of both superior PVs and concurrent LA enlargement in patients with both PAF and chronic AF (CAF). However, when compared to a control group, the corrected PV diameters (PV/LA diameter) were similar among the PAF, CAF, and control groups. Nonetheless, while they could not consistently demonstrate that the most dilated PV was the one responsible for the ectopic firing (i.e. dilation was found to be non-specific), they showed that the superior PVs of PAF and CAF patients were larger than the control group.

It has also been demonstrated that arrhythmogenic PVs (ArPVs) were larger than non-ArPVs in the same patient (Yamane et al., 2002). Also, the largest PV was responsible for the generation of the ectopic activity 72% of the time when one or two ArPVs were detected. Knackstedt et al. (2003) have reported that although both PVs and LA are larger in AF patients, there is no correlation between the extent of PV dilation and LA enlargement in AF patients. However, while not statistically significant, they also found a higher corrected PV diameter (PV/LA diameter) in the AF group compared to the control cohort. This is in contrast to the findings of Tsao et al. (2001).

In recent years PV dilation has been related to certain pathologies and this may explain how such conditions can lead to AF. Herweg et al. (2005) showed that the diameters of PVs in hypertensive patients were larger than non-hypertensive patients, and that among the hypertensive patients the ones who had AF displayed larger PV diameters compared to hypertensive individuals without AF. The group also reported that LA dilation was associated with a larger PV diameter (Herweg et al., 2005). More recently, it was shown that aging is an important aetiology for the dilation of PVs, which may help explain why AF is much more common among the older population (Pan et al., 2008).

6.2. Pulmonary vein pressure: stretch and atrial fibrillation

It has been postulated that stretch could be the precipitating factor for AF originating from PVs. Kalifa et al. (2003) demonstrated that an increased intra-atrial pressure in sheep hearts increased the rate and organization of waves coming from the superior PVs. Evidently, a case of bronchogenic cyst that impinged upon the RIPV was thought to be the cause of a patient's AF since the AF resolved upon removal of the mass (Parambil et al., 2006). It seems that stretch could increase ectopic foci from PVs, and the incidence of DADs and EADs (Chang et al., 2007). Putative blockers (gadolinium, streptomycin) of stretch-activated ion channels of cardiac tissue (Gannier et al., 1994; Bode et al., 2000, 2001) have been shown to decrease the spontaneous activity and the firing rate from the PVs (Chang et al., 2007).

Recently, some light was shed on the nature of these supposed stretch-activated ion channels, and the ionic currents they regulate. Seol et al. (2008) characterized currents activated by swelling or mechanical stretching as those that include, (1) a stretch-activated non-selective cationic current and (2) a Cl^- current. It was demonstrated that the type of stretch may lead to the activation of different currents, and that responses to blockers of the stretch-activated ion channel may be dependent on the type of signal generated by the stretch (i.e. swelling versus mechanical stretching) (Seol et al., 2008).

6.3. Pulmonary venous backflow and pulmonary vein stretch

A study of hypertensive patients has shown that an augmented PV backflow contributes to a progression of AF (i.e. from paroxysmal to permanent) (Maruyama et al., 2008). PV backflow occurs in late diastole (i.e. atrial systole) when blood flows forward from the LA into the LV and simultaneously backward into the PVs. Pulmonary venous flow (PVF) is pulsatile in nature (Tabata et al., 2003), thus it was

suggested that PV stretch may be involved in perpetuating the AF (Maruyama et al., 2008), but the evidence is difficult to interpret. Moreover, the data in favour of PV backflow induced AF is in contrast to an earlier study that had determined that PV backflow cannot predict AF progression (Lindgren et al., 2003).

Alterations in PV flow are noted in many pathological states such as aging, preload dysfunction, LV dysfunction, atrioventricular conduction abnormalities, and variation in heart rate (Gentile et al., 1997; Tabata et al., 2003). Mitral valve stenosis/regurgitation and ventricular diastolic dysfunction, in particular, have abnormal PV flow values (Tabata et al., 2003). Whether these variations in PV flow have any correlation with increased pressure or volume on the PVs resulting in stretch or dilation, or if this could be an intrinsic cause of AF, has not been directly determined so far. This is an area for future direction of research in this field.

7. Treatment of atrial fibrillation with pulmonary vein origin

7.1. Pharmacotherapy

There seems to be very limited clinical knowledge available on the nature of the antiarrhythmic drugs that act upon PV myocardial sleeves to alleviate AF. Even though it is recognized that PV is the most common origin for PAF (Haissaguerre et al., 1998), most drugs currently employed are the standard agents generally utilized for the treatment of AF. Current drug therapy directed at AF utilizes Class I and Class III antiarrhythmic agents. The risk of *torsade de pointes* does preclude the use of Class IA and some class III agents in patients with left ventricular hypertrophy. There is evidence from clinical trials that seem to indicate that a combination of quinidine (Class 1A) and verapamil (Class IV) is equally effective as sotalol (Class III) in management of AF (Fetsch et al., 2004; Patten et al., 2004). In one of the trials a higher risk of death, syncope and ventricular tachycardia was noted with quinidine and verapamil combination in comparison to placebo group (Patten et al., 2004). More recently, attempts have been made to specially direct treatment of AF at specific ion channels exclusive to the atrial muscle. For example, the chemical vernakalant (RDS1235) has been suggested to block some Na channels, and a number of K channels predominantly expressed in the atria (Fedida, 2007). As well, some attempts have also been made to direct drugs for treatment of AF with PVs as the target.

Chen et al. (1999) demonstrated that in patients with frequent episodes of PAF, infusions of propranolol (Class II antiarrhythmic), verapamil (Class IV antiarrhythmic) or procainamide (IA antiarrhythmic) reduced significantly the frequency of premature beats and burst AF originating in the PVs compared to baseline. Moreover, in-hospital diagnostic induction of sustained AF by infusion of isoprenaline (β-agonist) could be prevented by pre-treatment with propranolol, verapamil or procainamide in these patients (Chen et al., 1999). Experimentally in dogs, it has been demonstrated that procainamide suppresses focal discharges from thoracic veins (including PVs) and the LA appendage, and reduces communication of wave fronts between the LA and PVs (Chou et al., 2004). However, it was reported that such focal discharges in the PVs are more resistant to the effects of procainamide than focal discharge in the atria (Chou et al., 2004).

Pilsicainide (Class IC antiarrhythmic), a Na channel blocker, reportedly is capable of producing use-dependent prolongation of interatrial conduction time in humans (Sakai et al., 1995). Pilsicainide has been found to more effectively terminate vagally induced AF in canines compared to propafenone (Class IC antiarrhythmic) (Iwasa et al., 1998). Na channel blockers are capable of inhibiting focal discharge in canine PVs (Chen et al., 2000; Chou et al., 2004). Kumagai et al. (2004b) investigated the electrophysiological properties of pilsicainide on PVs in patients with AF using basket catheter mapping. Treatment with pilsicainide was found to prolong ERP and shortened ERP dispersion (estimated from the difference between minimum and maximum ERP within the same PV) in the PVs, as well as causing prolongation of conduction time within the PV. This has led to the suggestion that the unique location of action of this drug on the PVs and the PV–LA junction is the mode by which this compound prevented the development and inhibition of re-entrant circuits and thus was capable of terminating AF (Kumagai et al., 2004b; Hirose et al., 2007). However, it seems premature to suggest the only mechanism of action of pilsicainide is the PVs and PV–LA junction and more evidence is needed to fully establish the clinical actions of this compound.

An attempt has been made to determine how amiodarone (Class III antiarrhythmic) alters the electrophysiology of PVs and potentially prevents initiation of PAF (Rostock et al., 2005). The patients studied were all refractory to more than two antiarrhythmic drugs, and were divided into two groups, a control group not treated with amiodarone, and another that was being treated with amiodarone. PVs were stimulated and electrophysiological features of PVs, LA and RA were assessed. It was noted that the cohort on amiodarone had a significantly longer ERPs in the PVs compared to the control group. However, the impact of amiodarone on PVs, LA and RA was heterogeneous. The ERPs of LSPV, RSPV and RA but not those of LIPV and LA were all significantly increased in the cohort treated with amiodarone. Surprisingly, there were no significant differences between maximal decremental conduction (PV-to-LA) in the two groups studied. Nonetheless, the incidences of sustained AF (>3 min) initiated by the stimulation in RSPV and LIPV were significantly lower in patients on amiodarone as compared to control. Overall, the evidence from this investigation indicates that AF initiation was only partially lowered by amiodarone (Rostock et al., 2005).

Over the recent past, a number of drugs have shown promise in preventing AF originating from PVs, experimentally. Chen et al. (2006) showed that in rabbit PV cardiomyocytes, the angiotensin II receptor antagonist, losartan, could reduce the pro-arrhythmic effects of angiotensin II. Losartan could also inhibit spontaneous activity in PV myocytes in the absence of angiotensin II. Using rabbit PV tissue, it was suggested that the calmodulin kinase II inhibitor, KN-93, might prevent PV arrhythmogenesis caused by adrenergic stimulation (Lo et al., 2007). A preferential ryanodine receptor stabilizer, K201, was shown to have an antiarrhythmic effect on PV electrical activity and Ca^{2+} currents in rabbit PV cardiomyocyte (Chen et al., 2008). The antianginal drug, ranolazine, was reported to produce use-dependent inhibition of Na channel activity causing prolongation of ERP, conduction slowing, and suppression of late phase 3 EAD and DAD-induced triggered activity in canine PV sleeves (Sicouri et al., 2008). These are some of the areas that currently seem to be explored in search of drugs that may have a unique and specific site of action (i.e. PV and/or PV–LA junction) (Fig. 2).

7.2. Radiofrequency ablation

Since the discovery that ectopic foci can originate in PVs and be responsible for AF, radiofrequency ablation (RFA) of the PVs from the LA (electrically isolating the PVs) has become a *major* curative measure of AF (Haissaguerre et al., 1998). Many early studies showed promise for RFA in the treatment of AF. The first study by Haissaguerre et al. (1998) found that RFA at the site of earliest recorded ectopic activity eliminated AF in 62% of PAF patients during an 8 ± 6 month follow-up. Local isolation of specific PV areas showing arrhythmogenic activity in patients with AF proved to eliminate AF in many patients, although 44% had AF reoccurrence after the first procedure (Haissaguerre et al., 2000). Also more than 80% of patients with PAF who underwent 'segmental' RFA of three PVs improved significantly, while a less significant result was seen in patients with persistent AF (Oral et al., 2002). Following these pioneering studies, hundreds more have been conducted to demonstrate the benefit of RFA or to perfect the technique.

In recent years, five randomized clinical trials (RCTs) have been conducted and published which support the use of RFA as a treatment of AF versus pharmacotherapy as a mode of treatment for AF (Krittayaphong et al., 2003; Wazni et al., 2005; Stabile et al., 2006; Oral et al., 2006; Pappone et al., 2006). All of the latter studies have recently been the subject of meta-analysis (Gjesdal et al., 2008). Most RCTs compared RFA therapy to pharmacotherapy in AF patients (Krittayaphong et al., 2003; Wazni et al., 2005; Stabile et al., 2006; Pappone et al., 2006), while one study has compared RFA to no treatment of the AF (Oral et al., 2006). The meta-analysis determined that RFA is superior (lower reoccurrence of AF) to pharmacotherapy in paroxysmal, persistent or permanent AF (Gjesdal et al., 2008). It should be noted that according to international guidelines, the first step to treating AF is pharmacotherapy and RFA should be considered thereafter if drug treatment is unsuccessful (Fuster et al., 2006). Thus most of the RCTs of RFA are for patients' refractory to drugs. It should also be noted that these five studies were based upon a one year follow-up, thus more studies with a longer follow-up are essential to obtain a full picture of the benefit of RFA versus drug therapy, and to verify any potential long-term complications that can arise (Gjesdal et al., 2008). From the RCTs presented in the latter meta-analysis, it seems that RFA could offer patients fewer hospitalizations than pharmacotherapy, at least on the short-term evidence (1 year).

One important complication of RFA at the PV site is pulmonary vein stenosis. This phenomenon was first documented in a different ablation procedure (Robbins et al., 1998). Moreover, it was shown to be a complication of RFA of PVs after a long-term follow-up of patients who underwent the procedure (Yu et al., 2001). This can be a severe side effect of RFA if enough PVs are stenosed to the extent as to cause pulmonary hypertension, but this is rare (Yu et al., 2001). It is estimated that RFA results in PV stenosis 5% of the time (Saad et al., 2003). However, symptomatic severe PV stenosis is a complication of approximately 1–2% of RFA procedures on PVs (Saad et al., 2003; Cappato et al., 2005). As previously stated, the only RCTs available at present are for a one year follow-up period, so sound knowledge of the long-term complications of RFA on PVs is still lacking. It would appear from an international survey that the risk of any major complication following RFA is approximately 6% (Cappato et al., 2005).

There are more RCTs that are currently ongoing. For example, the CACAF-2 Study, expected to be completed by July 2010, aims to determine the benefit of RFA in persistent AF patients who are young to middle-aged and refractory to pharmacotherapy, when compared

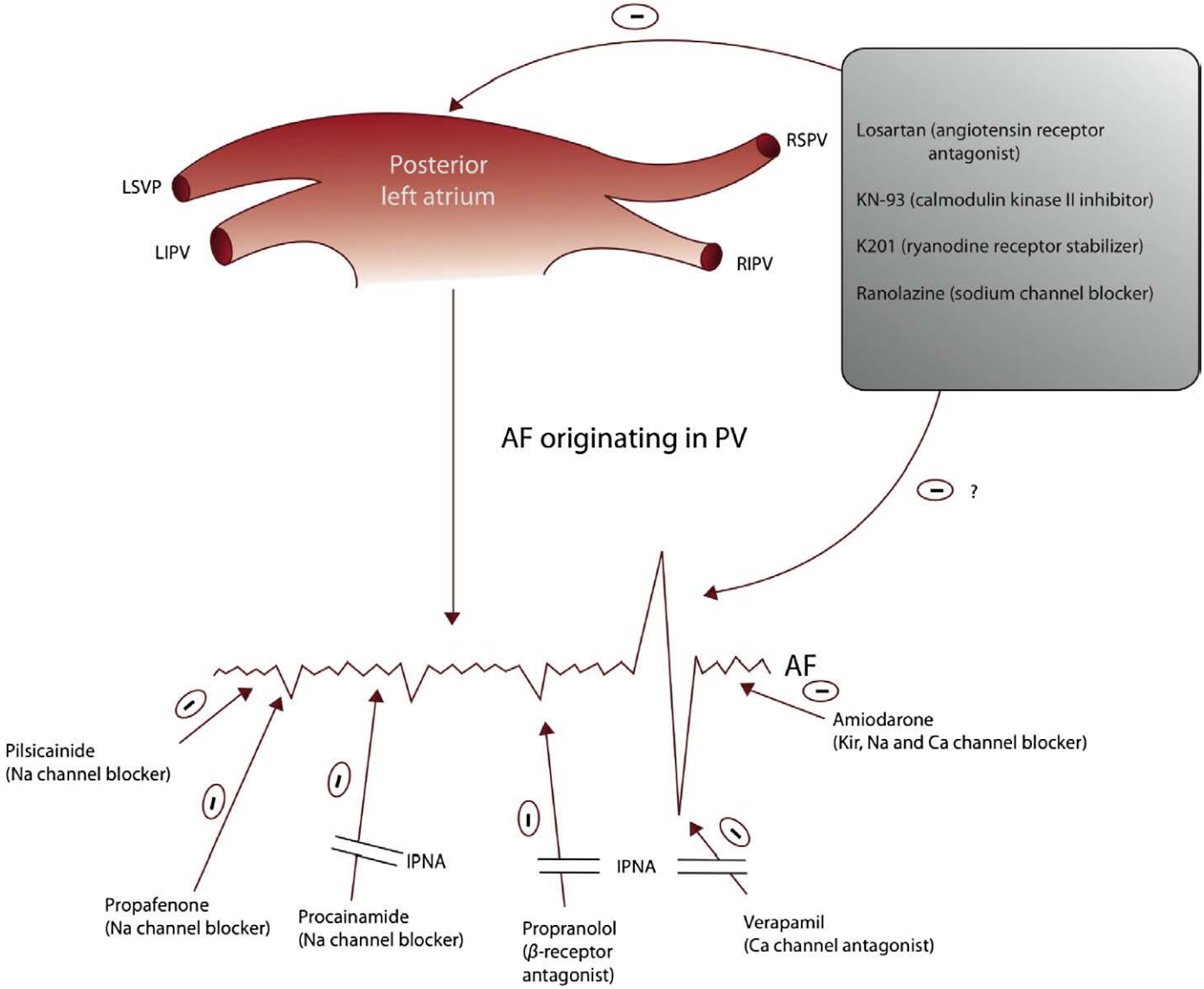

Fig. 2. Examples of some drugs employed to combat atrial fibrillation with possible site of action on pulmonary vein and/or pulmonary vein–atrial junction. AF, atrial fibrillation; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; PV, pulmonary vein; RIPV, right inferior pulmonary vein; right superior pulmonary vein, RSPV.

to pharmacotherapy alone (Bertaglia et al., 2007). This study will have a two year follow-up and will closely monitor complications such as pulmonary stenosis (Bertaglia et al., 2007). RAAFT-2 and CABANA are another two ongoing RCTs in this field (CABANA 2008; RAAFT-2, 2008).

7.3. Hybrid treatment

There has also been evidence that antiarrhythmic drugs may work more effectively or provide extra benefit to the patient after an RFA procedure. For example, pilsicainide was shown to be effective in eliminating re-occurring AF in patients previously refractory to drug therapy, after undergoing RFA but having re-occurring AF (Tojo et al., 2005). An international survey of 8745 patients (most of whom underwent PV RFA specifically) indicated that 2094 of the pool (24%, range among centres 9–50%) became asymptomatic at a one year follow-up, following treatment with previously in-effective AF medication (Cappato et al., 2005). Further, in a randomized, controlled study, it was demonstrated that RFA intervention with drug treatment was superior to drug treatment alone in patients with paroxysmal or persistent AF (Stabile et al., 2006). In yet another randomized, controlled study, it was observed that after one year following RFA of PVs, while patients on antiarrhythmic drugs (amiodarone or a class IC drug) did not have fewer AF reoccurrences on the long-term basis, they did have less symptomatic AF episodes (Turco et al., 2007). In a more recent study, it has been demonstrated that patients for whom drug therapy worked to eliminate reoccurrence of AF after RFA intervention had a lower brain natriuretic peptide level after RFA than patients for whom the drug did not work (Yamada et al., 2008). Based on the evidence provided with the combination of quinidine and verapamil in patients with persistent atrial fibrillation (Fetsch et al., 2004; Patten et al., 2004), a hybrid route may be appropriate for the cohorts that were not responsive to drug therapy alone. Collectively, the trend of the clinical evidence seems to suggest that a hybrid treatment may be beneficial in some populations of patients with AF but more clinical studies seem necessary to arrive at a more definitive answer.

8. Concluding remarks

The discovery that the PVs could be responsible for AF under certain circumstances has been followed by much research to determine how this can occur. Ultimately, it seems that the basis for abnormal activity could be autonomic nerve activity, morphological alteration — congenital or due to various pathological states — increased PV volume, and/or PV pressure, while enhanced automaticity, triggered activity, and/or re-entry could be the cause of the AF induction. As information continues to accumulate, the identification and specification of treatments for AF, especially PAF, can grow. This is a welcomed endeavour, since the number of patients with AF could increase 2.5-fold during the next 50 years (Go et al., 2001).

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