Thoracic Vein Arrhythmias

Yi-Jen Chen, MD, PhD; Shih-Ann Chen, MD*

The thoracic veins are important foci for the genesis of ectopic atrial tachycardia and play a critical role in the pathophysiology of paroxysmal and permanent atrial fibrillation. The pulmonary veins have the highest arrhythmogenic activity and other venous structures (eg, superior vena cava, coronary sinus and ligament of Marshall) have also been shown arrhythmogenic potential. Thoracic veins contain cardiomyocytes with distinct electrical activities and complex anatomical structures. This review summarizes the current understanding of the basic and clinical electrophysiology of thoracic vein arrhythmias. (Circ J 2007; Suppl A: A-20–A-25)

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Radiofrequency ablation of the thoracic veins has become a potential way of curing atrial fibrillation (AF), since premature electrical activity in the pulmonary veins (PVs) was shown in 1998 to initiate AF! The superior vena cava (SVC), coronary sinus (CS) and ligament of Marshall (LOM) are the other thoracic veins that have also arrhythmogenic potential to induce AF, to a lesser extent.2–6 The arrhythmogenic potential of the thoracic veins has been proposed because of the connection of the myocardium in the thoracic veins with the atrium.7,8 The thoracic veins not only initiate paroxysmal AF, but also induce ectopic atrial tachycardia and maintain AF.9–11 Mechanistic information about thoracic vein arrhythmias has improved through clinical and basic studies, and this review summarizes the updated understanding of thoracic vein arrhythmias.

PV Arrhythmia

The PVs are the most important of the thoracic veins, causing almost more than 70% of cases of AF (Fig 1A).1,2 PVs have multilayered muscles spreading from the left atrium (LA) into the proximal PVs, with a complex and 3-dimensional (3-D) organization.12–16 The distal PVs have disseminated myocardial clusters bordered by fibrous tissue. These cardiomyocytes induce repeated depolarizations that initiate AF, and also produce PV tachycardia with rapid electrical activity.17 In addition, rapid focal discharges in the PVs may represent the so-called “focally driven” AF.18 Arentz et al studied human PVs and found that single or double focal ectopic discharge initiated 39% of AF and stable focal tachycardia produced 14% of cases.19 Similarly, our previous study also found that PVs may induce AF through cycle length oscillated electrical activity or from constant electrical activity.

Radiofrequency ablation in the PVs can terminate persistent AF and prevent AF recurrence10–11 which suggests that PVs play a role in generating persistent AF. Even though the mechanisms are not clear, reducing the AF substrate and decreasing atrial remodeling from PV firings should be a reasonable strategy. Moreover, rapid atrial pacing enhances PV arrhythmogenesis,21,22 so PV isolation not only stops these focal discharges from reaching the LA, but also prevents PV remodeling caused by AF. All of these effects may reduce PV arrhythmogenesis.

Mechanisms of PV Arrhythmogenesis

Enhanced triggered activity/automaticity and reentry have been suggested as contributing to PV arrhythmogenesis. The known fractionated electrograms (caused by anisotropy conduction and degenerative fibrosis) and shorter refractory time enhances the genesis of reentry in the PVs. Kumagai et al used a basket catheter to identify the pathophysiology of PV arrhythmogenesis in humans.23 They suggested that reentry may be the possible mechanism, because of the existence of PV or PV–LA re-entrant activation fronts initiated by focal discharge in the PVs. In contrast, a recent study using high-density 3-D mapping of human PVs has found that PV arrhythmogenic activity is more likely caused by discrete focal activity.19 Our previous pharmacological study showed that ß-blockers and calcium-channel blockers decrease the PV ectopic activity.24 Those results also suggest that abnormal automaticity and triggered activity play a role in PV arrhythmogenesis.

Previous histology studies have shown that human and rat PVs contain specialized conduction cells.24–27 Electrical recordings in single cells and tissue specimens also identified spontaneous diastolic depolarization in PV cardiomyocytes.28–30 The shorter action potential duration, reduced resting membrane potential and smaller inward rectified potassium currents show distinct electrical characteristics in the PVs.30 However, the question as to why the PV becomes arrhythmogenic is not fully elucidated. Increased evidence supports abnormal calcium regulation having a role. Our previous studies have shown that both the L-type and T-type calcium currents have a role in PV triggered activity and automaticity (Fig 2A).31,32 Honjo et al showed that a low concentration of ryanodine induced phase 4 depolarization in the PVs, but not in the atrium,33 which suggested that ryanodine receptor dysfunction has a role in PV arrhythmogenesis. Patterson et al have shown that the sodium-calcium exchanger may induce early after-depolarization and result in high PV arrhythmogenesis.34

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*National Yang-Ming University, School of Medicine. **Division of Cardiology and Cardiovascular Research Center, Veterans General Hospital-Taipei. †Division of Cardiovascular Medicine, Taipei Medical University-Wan-Fang Hospital and School of Medicine, Taipei Medical University, Taipei, Taiwan

Mailing address: Shih-Ann Chen, MD, Division of Cardiology, Taipei Veterans General Hospital, 201, Sec 2, Shih-Pai Road, Taipei, Taiwan. E-mail: epsachen@ms41.hinet.net
Additionally, administration of a preferential reverse mode of a sodium–calcium exchanger inhibitor (KB-R7943) reduces PV electrical activity (Fig 2B) and also prevents ouabain-induced PV arrhythmogenesis. We have also found that the angiotensin II receptor blocker, losartan, may directly reduce the sodium–calcium exchanger to create its anti-AF effect (Fig 2C). All those findings suggest the potential role of the sodium–calcium exchanger in PV arrhythmogenesis.

The sarcoplasmic reticulum Ca\(^{2+}\) content may determine spontaneous diastolic Ca\(^{2+}\) release, and may alter the beating rate or triggered activity of cardiomyocytes. Couto et al have shown that atrial cardiomyocytes and PV non-pacemaker cardiomyocytes have similar Ca\(^{2+}\) stores and responses to isoproterenol. However, the calcium regulation in PV pacemaker cells is unclear. From optical mapping, it was found that calcium-mediated triggered activity from delayed afterdepolarization induced PV ectopy. Because PV cardiomyocytes have less negative resting membrane potentials, abnormal calcium regulation can

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**Fig 1.** Spontaneous ectopic beats from the thoracic veins initiate atrial fibrillation (AF). (Panel A) Ectopic beat from the left superior pulmonary vein (LSPV). Rapid activation can be seen in LSPV-2 or LSPV-3, conducting to left atrium with 2:1 block. (Panel B) Ectopic beat from the superior vena cava (SVC)-3 (arrow) initiates AF (Reproduced with permission from references 2 and 3).
Fig 2. Calcium regulation of pulmonary vein (PV) electrical activity. (Panel A) T-type calcium current blocker (nickel, 40μmol/L) prolongs the cycle length of spontaneous beating and decreases the later phase of diastolic depolarization in an isolated single PV cardiomyocyte. Action potentials are superimposed before (∧) an after (˝) nickel administration. (Panel B) Preferential reverse mode of the sodium–calcium exchanger inhibitor (KB-R7943) reduces the PV firing rates in an isolated tissue preparation. (Panel C) Losartan (1, 10μmol/L) decreases PV spontaneous activity (Reproduced with permission from references 32, 35, 36).

Fig 3. Effects of precipitating factors on pulmonary vein (PV) electrical activity. (Panel A) Rapid atrial pacing increases PV spontaneous activity and induces early afterdepolarization. (Panels B–D) Mechanical stretch induces PV spontaneous activity (B) and early afterdepolarization (C) or increases PV firing rates (D) (Reproduced with permission from references 30 and 42).
easily trigger PV arrhythmogenesis because of the reduced depolarizing threshold.

**Factors Determining PV Arrhythmogenesis**

Even though the PVs have the potential to induce AF, the existence of precipitating factors plays a critical role in PV arrhythmogenesis. Histological studies in humans have found that AF patients have severely discontinuous, hypertrophic and fibrotic PVs, changes that would enhance automaticity/triggered activity because of poorly coupled cells and would induce local reentry caused by conduction block. Rapid atrial pacing can increase PV automaticity/triggered activity (Fig 3A) with increased transient inward currents.21,22 Similarly, thyroxine also increases PV arrhythmogenic activity.39 All these results may underline the mechanism of the occurrence of thyrotoxicosis-related AF.

Dilated PVs have been shown to cause greater arrhythmogenesis. Kalifa et al found that atrial pressure modulated PV electrical activity.40 Our previous study also found that the PV diameter has a role in human PV arrhythmogenesis.41 In isolated PV specimens, we also demonstrated that mechanical stretch increases automaticity and triggered activity in the PVs and those effects are suppressed by stretch channel blockers (Figs 3B–D).42 Therefore, mechano-electrical feedback plays an important role in PV pathophysiology. Moreover, we compared the PV electrical activity in adult and aged PVs and found that the aged PVs had larger delayed afterdepolarization, which may be caused by calcium leak via ryanodine receptor dysfunc-

tion.43 Those results may explain the high incidence of AF in the aged, at least in part.

### SVC Arrhythmia

Our previous study was the first to indicate the potential of the SVC in the genesis of AF.3 In addition, radiofrequency ablation of the SVC can cure SVC-related AF. The SVC is the second-most important thoracic vein, causing approximately 10% of AF (Fig 1B). The SVC has multilayered muscles on the outer side of the venous adventitia, with lots of degenerative changes and less myocardial tissue in the posterior wall.44,45 Similar to in the PVs, SVC cardiomyocytes may induce repeated depolarizations to initiate AF and also can produce SVC tachycardia and “focal AF”.3,46 In addition, macroreentry in the SVC may induce atypical atrial flutter.47 Compared with the PVs, SVC ectopy has a higher incidence of intravenous conduction block and a shorter interval preceding ectopic P waves. Moreover, the left SVC (the embryological precursor of the LOM) can also be the arrhythmogenic source of AF.48

Are there useful ways of predicting SVC arrhythmia? We found that comparisons of the endocardial atrial activation sequences from the high right atrium and His-bundle during sinus rhythm and atrial premature capture may predict arrhythmogenic foci in the SVC.49 The female gender is associated with a higher incidence of SVC arrhythmia.50

### Mechanisms of SVC Arrhythmogenesis

Enhanced triggered activity/automaticity and reentry have been proposed as explanation for SVC arrhythmogenesis. Atypical atrial flutter suggests that reentry is a possible mechanism. The rapid and irregular activity in the SVC in some cases suggests that triggered activity/automaticity may be the underlying mechanism. We studied the mor-

### LOM Arrhythmia

LOM is the development remnant of the left SVC and induces AF with an incidence of 1–2%.45,50 The LOM extends from the CS to the orifice of the left superior PV. Because the LOM may connect to the left superior PVs, it not only induces AF but may also enhance the arrhythmogenesis of the left superior PV, inducing AF. Ablation of the LOM insertion site can cure LOM-initiating AF.56 Those findings also relate to the relatively higher arrhythmogenesis of the left superior PVs.57 Moreover, LOM may
also cause persistent AF through rapid focal discharges.

Mechanisms of LOM Arrhythmogenesis

Scherlag et al discovered electrical activity in the LOM in 1972 and proposed the potential of LOM arrhythmogenesis.66 The LOM is richly innervated by sympathetic nerves.55 Previous studies have shown that isoproterenol is needed to induce LOM AF and Doshi et al further demonstrated that isoproterenol infusion enhances the automaticity in the LOM, which degenerates into fibrillatory activity.26 The shorter reentrant cycle length recorded around the LOM will facilitate AF maintenance.60 However, knowledge about the ionic currents and cellular electrophysiology is limited, because isolated single LOM cardiomyocytes are not available.

CS Arrhythmia

The CS is lined by layers of cardiomyocytes connected to the LA to a variable degree and which may also link to the LOM. The CS has been shown to generate repeated depolarizations to initiate less than 1% of AF. The CS also induces tachycardia or “focal AF”.61,62 In addition, the CS cells have less negative resting potential and depolarizations to initiate less than 1% of AF. The CS also induces tachycardia originating from the musculature of the coronary sinus.64 CS abnormalities are also related to the existence of accessory pathways that induce atrioventricular reentrant tachycardia.

Mechanisms of CS Arrhythmogenesis

The CS cells have less negative resting potential and easily develop delayed afterdepolarization.67 Patch-clamp experiments in CS preparations suggest that transient inward currents play a major role in generating delayed afterdepolarization.68 However, studies of isolated single CS cardiomyocytes are still not available. The muscular structure and double potentials found in the CS may serve as reentrant circuits from conduction delay.

Conclusions

The thoracic veins contain cardiomyocytes with high arrhythmogenic activity. Catheter ablation of the PV, SVC, LOM or CS can successfully eliminate paroxysmal and nonparoxysmal AF, suggesting the crucial role of thoracic veins in AF. Accurate identification of the arrhythmogenic thoracic veins is pivotal to successful elimination of AF through ablation. Increasing knowledge of cellular electrophysiology may assist in developing target drugs for treating thoracic vein arrhythmias.

References


