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The Remodeling of Connexins Localized at Pulmonary Vein – Left Atria in Triggering and Maintenance of Atrial Fibrillation

Guo-qiang Zhong¹, Ri-xin Xiong², Hong-xing Song,
Yun Ling, Jing-chang Zhang and Zhe Wei

¹*The Department of Cardiology, The First Affiliated Hospital
of Guangxi Medical University,*

²*The Department of Cardiology, The People's Hospital
of Guangxi Zhuang Autonomous Region,
China*

1. Introduction

Atrial fibrillation is the most common sustained arrhythmia and the major cardiac cause of stroke (Sellers & Newby, 2011). Recent studies in patients and animals with paroxysmal atrial fibrillation had shown that the arrhythmia was triggered by focal sources from muscular sleeves originated in the left atria extending into pulmonary veins (Date et al., 2007; Chen et al., 2001; Patterson et al., 2007; Honjo et al., 2003). What is more, the autonomic nervous system has a crucial role in the genesis, maintenance and abruption of atrial fibrillation (Duffy & Wit, 2008; Sandres et al., 2004), and there is a fat pad localized in superior vena cava and the root of aorta as the origin of cardiac nerve, being called SVC-Ao fat pad (Kapa et al., 2010; Volders, 2010; Ji et al., 2010). The mechanism of atrial fibrillation involves multiple effects (Chiou et al., 1997; Tsuboi et al., 2000; Hoffmann et al., 2006; Haissaguerre et al., 1998; Wit & Boyden, 2007), the expression of connexins is changed and is associated with increased propensity for arrhythmias (Kanagaratnam et al., 2002; Herve et al., 2007; Stergiopoulos et al., 1999; Verheule S et al., 2002; Kanagaratnam et al., 2007; Valiunas et al., 2001; Valiunas et al., 2000; Cottrell et al., 2002; Elenes et al., 1999). Pulmonary veins and left atria are the primary structure of genesis, persistence of atrial fibrillation. Vagus nerve plays a key role in the initiation and maintenance of atrial fibrillation, it can mediate the electrical remodeling of atria and pulmonary vein, enhance the maintenance and stability of atrial fibrillation. However, these effects can be inhibited by avianizing vagus nerve.

2. Overview of gap junction structure

The name “gap junction” was coined from their appearance in electron micrographs in the 60s (Revel & Karnovsky, 1967). They are specialized at cell-cell contact regions that contain tens to thousands of intercellular channels that link two apposed cells. These channels facilitate a form of intercellular communication by permitting the regulated passage of ions and small molecules from one cell to another (Bennett & Goodenough, 1978). The gap junction

membrane channel is composed of macular aggregations of intercellular channels permitting the direct intercellular transfer of ions and small molecules. Each intercellular channel is formed by the apposition of two hexameric transmembrane channels (connexons), one from each cell (Yeager & Gilula, 1992). Each intercellular channel is composed of two oligomers with each of two adjacent tissue cells contributing one oligomer. Each connexon is built from six copies of one or more members of a protein family called the connexins (Unger et al., 1999; Perkins et al., 1998). The functional cell-cell channel is formed by the end-to-end docking of the extracellular domains of the two connexons. Therefore, the gap junction membrane channel can be thought of as a dimer of two hexamers joined together in the gap region. In this manner, the membrane channel extends across both cell membranes.

Vertebrate gap junction channels are assembled to form multimers of one or more different proteins from a multigene family of homologous protein, which are composed of an entirely different gene family but the sequences predict a similar folding pattern. Up to now, more than 20 different connexin genes have been identified in the mouse genome and at least 6 others have been identified in other vertebrates. Connexins are highly homologous proteins with 50%-80% identity between amino acid sequences and display considerable amino acid sequences conservation between species. The distribution and developmental regulation of connexins are tissue specific. The predicted molecular mass of the connexin protein family ranges from ~26 to ~60KDa, and the proteins are named "connexin" followed by their predicted molecular mass. The connexin family can be subdivided into two classifications called α and β based on similarities in certain regions of the primary sequence. The x-ray diffraction analysis by Tibbitts et al. (1990) indicated that there was more α -helical content that could be accounted for by four transmembrane helices. The E1 and E2 loops are thought to be as rigid as the transmembrane domain (Hoh et al., 1993; Sosinsky, 1992). Hence, the extracellular region is visible with the crystallographic averaging used. Each extracellular protrusion may therefore include an extension of the intramembrane α -helical structure (Tibbitts et al., 1990). Mutagenesis studies have suggested that the extracellular loops contain disulfide-bonded β -sheet conformation (Foote & Nicholson, 1997), which would be expected to act as a rigid domain, for instance, connexin43 (isolated from heart tissue, Yeager & Gilula, 1992), connexin32 and connexin 26 (isolated from liver tissue, Fallon & Goodenough, 1981; Hertzberg, 1984) would be seen for the same structure. In the human heart, 4 main isoforms are expressed. Connexin43 is expressed in all chambers of the heart, but predominantly in the ventricles. Connexin45 is found in the conduction system of the heart and at low levels in the atrial and ventricular working myocardium and connexin37 is located in the endothelial gap junctions in many vessels. Finally, connexin40 is expressed mainly in the atrial working myocardium, the conduction system, and the vasculature. Connexin40 was first described in a range of animal species and subsequently mapped to human chromosome. It became apparent that connexin40 was expressed in the atrioventricular conduction system and abundantly expressed in the atrial but not in the ventricular gap junctions. Recently, a new connexin was described in the mouse heart, i.e. connexin30.2 (the human equivalent is connexin31.9), which in mice seems responsible for slowing of impulse conduction in the atrioventricular node. However, the role of connexin31.9 in the human heart is unclear, for it is not detectable in the human cardiac conduction system. Connexons formed the functional intercellular channel, which is defined as homotypic when the connexin composition of the contributing connexons is identical or heterotypic when different. The ability of connexins to form homomeric/ heterotypic channels has been examined in the *Xenopus* oocyte and HeLa

cell expression systems as well as in other settings. Connexin43 and connexin40 are co-expressed in several tissues, including cardiac atrial and ventricular myocytes and vascular smooth muscle. It has been shown that these connexins form functional homomeric/homotypic channels with distinct permeability and gating properties.

3. Connexon and the heart development

In the vertebrate embryo, a single outflow vessel initially develops from the common ventricles undergo septation to form the four-chamber heart (Kirby & Waldo, 1995). The four-chambered heart develops from a single straight tube composed of three layers: an inner endocardium and outer myocardium separated by a thick extracellular matrix called cardiac jelly. The growing tube loops, with the convexity of the loop demarcating a functional inflow from an outflow portion of the looped tube. This original convexity forms the two ventricles by expansion and septation, and as the ventricular septum forms, the inflow and outflow must be redefined. Initially, all of the inflow is through the atrioventricular canal connecting a common atrium to the presumptive left ventricle; the entire outflow is from the presumptive right ventricle into the aortic sac via the conotruncus. Several septa are formed simultaneously, making a rearrangement of inflow and outflow critical. The atrioventricular canal is divided into left and right channels, the nascent right and left ventricles are separated by the ventricular septum, the conotruncus is converted into aortic vestibule and semilunar valve continuous with the left ventricle, and the pulmonary infundibulum and semilunar valve originating from the right ventricle (see Fig1.). Concomitantly, the outflow tract septates and rotates to generate the pulmonary and

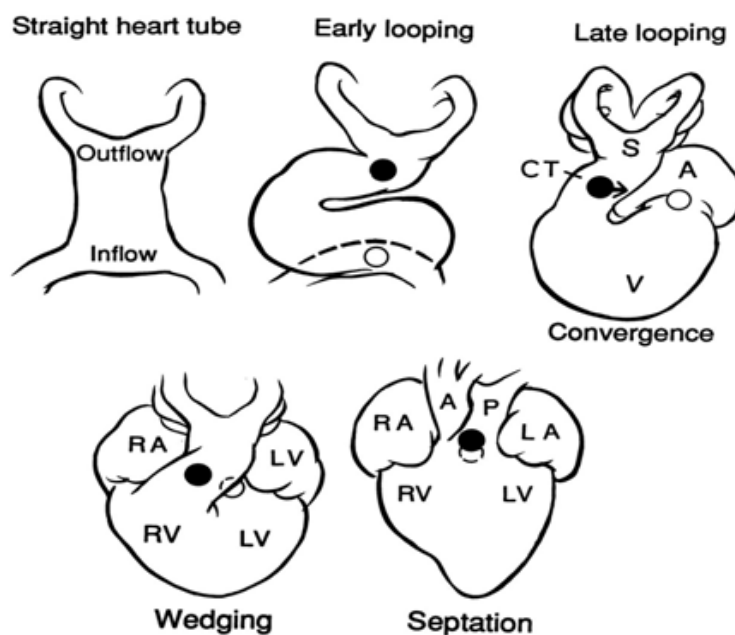


Fig. 1. Major events in development of the heart from a single straight tube. Early looping is probably a function of the myocardium. Convergence of the outflow and inflow tracts occurs during late looping and is critical for normal wedging. Wedging produces alignment of the three components that complete outflow septation. A, aorta; V, ventricle; P, pulmonary trunk; RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle.

aortic outflow tracts, becoming connected to the right and left ventricular chambers, respectively. This morphogenetic sequence is significantly affected by the activity of neural crest cells. With the development of heart, the co-expression of multiple connexins in diverse tissues support the idea that communication between cells does not depend on just one type of connexin, which results in forming heterotypic channels with properties different from those homotypic parental connexons.

Pluripotent mammalian embryonic stem cells, which are derived from the inner cell mass of preimplantation blastocysts, have the capacity to differentiate into cells of all three germ layers. Under suitable conditions, embryonic stem cells remain pluripotent through repeated rounds of cell division in culture. The recent isolation of human embryonic stem cells has spurred great interest in their potential use for therapeutic tissue repair because appropriate manipulation of the culture environment can induce both mouse and human embryonic stem cells to differentiate in vitro into specific somatic cell types, and the result shows human embryonic stem cells express RNA encoding most of the known human connexin genes. The mRNA of Cx25, Cx26, Cx30.3, Cx31, Cx31.1, Cx31.9, Cx37, Cx40, Cx43, Cx45, and Cx46 for all of the undifferentiated human embryonic stem cultures that were detected. The remaining connexins (Cx30, Cx30.2, Cx32, Cx36, Cx47, Cx59, and Cx62) were also reliably detected (Rackauskas et al., 2010).

4. Cardiac electrical properties of connexins and the methods for detection

For effective cardiac output, it is essential that electrical excitation spread rapidly throughout the atria and ventricles. This is effected by electrical coupling through gap junction channels at contact sites between myocytes (Danik et al., 2008; Harris, 2001; Söhl & Willecke, 2004; Moreno, 2004). These channels form a low-resistance pathway between adjacent myocytes and consist of connexin proteins. The connexin family is a large multigene family, and the channels formed by different members of this family have distinct electrical and regulatory properties (Reisner et al., 2009; Gros & Jongsma, 1996; Verheijck et al., 2001; Valiunas et al., 2002). Voltage sensitivity is particularly important in regulating the intercellular coupling between excitable cells. Cx43 channels are relatively insensitive to changes in transjunctional voltage compared with channels composed of Cx45 (Rackauskas et al., 2007; Bruzzone et al., 1993; Haubrich et al., 1996). Each gap junction composing hemichannel contains two Vj sensitive gates. The fast gate is located at the cytoplasmic entrance of hemichannels and operates from open to residual state. The slow, or “loop” gate is located toward extracellular ends of hemichannels and exhibits slow gating transition to the fully closed state. Cx26, Cx30, Cx50 close at positive voltages, and Cx31, Cx32, Cx37, Cx40, Cx43, Cx45, Cx57 at negative. Interestingly, Cx46 hemichannels close at both, positive and negative voltages. Besides, each type of connexon has a certain sensitivity to H⁺, it is showed the order of decreasing sensitivity to pH: Cx50>Cx46>Cx45>Cx26>Cx37>Cx43>Cx40>Cx32, anyway, it is not completely clear whether H⁺ acts directly on GJ channels. Cytoplasmic C-tail of connexins contains multiple serine, threonine, and tyrosine residues that may be phosphorylated by various protein kinases (Valiunas et al., 2000; Haubrich et al., 1996). Phosphorylation modifies electrical and metabolic communication between contiguous cells by changing channel molecular structure that affects channel unitary conductance, mean open time, or open probability. Moreover, phosphorylation alters the net charge of C-terminus that in turn may modulate voltage or pH sensitivity of the connexins (Kirchhoff et al., 2000, 1998; Bukauskas et al., 2004).

From the gene level to protein expression, novel methods of detection of gap junctions can lead us to realize the therapeutic potential, including morphological diversities, ultrastructure and spatial heterogeneity. The authors induced rapid persistent atrial pacing dogs and did a comparison between removal and retention of cardiac vagus nerve in dogs (superior vena cava and aorta root fat pad, SVC-Ao fat pad), then recorded the effective refractory period and the dispersion of effective refractory period, analyzed the expression of atrial and pulmonary vein connexin40, connexin43 and the heterogeneity of its spatial distribution and the changes of atrial collagen volume fraction, tried to illuminate the correlation of atrial fibrillation with connexin40, connexin43 remodeling and the function of vagus nerve. There was obvious shortness of effective refractory period in atrial fibrillation animal models, while the removal of vagus nerve could attenuate this effect, meanwhile, the quantity and distribution of connexin40 and connexin43 changed at different locations and the deposit of collagen fibers, which might explain the mechanism of electrical heterogeneity and the structural remodeling originated from the pulmonary vein and left atria for the atrial fibrillation.

5. The distribution of connexins in heart and the relationship with arrhythmia

Gap junction remodeling is a common response to many forms of heart disease (Strom et al., 2010; Burstein et al., 2009; Kieken et al., 2009; Qu et al., 2009; Yamada et al., 2008). Previous studies have demonstrated that loss of cell-cell coupling is highly arrhythmic (Chaldoupi et al., 2009), however, a detailed understanding of arrhythmia dynamics has been lacking. With respect to mechanistically link a primary perturbation of gap junction function with arrhythmia, conduction properties, arrhythmia dynamics, and cellular electrophysiological characteristics have been detected (Zhou et al., 2008; Severs et al., 2008; Gutstein et al., 2001). Accumulative evidences showed that ventricular gap junctions contain at least 20 times more connexin43 than connexin40, while atrial gap junctions contain much more connexin40 than connexin43 (Kontogeorgis et al., 2008; Lin et al., 2010). In the ventricle, the heterogeneous loss of connexin43 gap junctions in a murine conditional cardiac connexin43 knockout model best exemplified how the focal loss of cardiac gap junctions lead to significant dispersion of conduction, increased incidence of spontaneous arrhythmias, and loss of ventricular systolic function with only minor reductions in overall connexin43 expression. The gating of connexin43-containing ventricular gap junctions during the action potential is also proposed to promote cardiac arrhythmias via inactivation and recovery that depends on transjunctional voltage (V_j) and contributes to conduction slowing or block and the formation of reentrant arrhythmias. In the atria, targeted gene deletion of connexin40 in mice produced multiple aberrations: P wave and PQ interval prolongation, prolonged sinus-node-recovery time, prolonged Wenckebach period, burst-pacing induced atrial tachyarrhythmias, reduced atrial, A-V node, and left bundle branch conduction velocity, right bundle branch block, and reduced interatrial conduction heterogeneity (Leaf et al., 2008; Gutstein et al., 2005). There are close correlation between electrical properties and the anatomy of pulmonary veins and left atria. In animal studies, data showed that segmental muscle disconnection and differential muscle narrowing at pulmonary vein and left atria junctions and complex fiber orientations within the pulmonary vein provide robust anatomical bases for conduction disturbance at the pulmonary vein and left atria junction and complex intra pulmonary vein conduction patterns (Date et al., 2007).

6. The anatomy and electrical activation in pulmonary vein and left atria

Catheter radiofrequency ablation of triggers originated from the pulmonary veins may successfully terminate paroxysmal atrial fibrillation (Jais et al., 1994). Because ablation within the pulmonary veins may result in stenosis of the pulmonary veins, the junctions between the pulmonary veins and the left atria have become new ablation targets for achieving electrical pulmonary vein isolation (Haissaguerre et al., 1998, 2000). Segmental ablation can successfully isolate the pulmonary vein by placing radiofrequency lesions in only 21% to 59% of the circumference of the pulmonary veins ostia (Pappone et al., 2000; Oral et al., 2002). Previous studies showed that ectopic beats originated from the pulmonary vein propagated to the left atria with characteristically long conduction time, often with conduction delay or block within the pulmonary vein or at the pulmonary vein and left atria junction (Nathan & Eliakim, 1966). The complex arrangement of myocardial fibers in the pulmonary vein and/or in the pulmonary vein and left atria junction is a possible reason for conduction delay or block in the pulmonary vein and left atria junction and within the pulmonary vein (Saito et al., 2000). Ho et al reported that a differential thickness of muscle sleeves could also account for a variable safety factor of propagation across the pulmonary vein and left atria junction (Ho et al., 2001). Hocini reported that zones of activation delay were observed in canine pulmonary veins and correlated with abrupt changes in fascicle orientation (Hocini et al., 2002). Hamabe identified that segmental muscle disconnection and differential muscle narrowing at pulmonary vein and left atria junctions and complex fiber orientations within the pulmonary vein provide robust anatomical bases for conduction disturbance at the pulmonary vein and left atria junction and complex intra pulmonary vein conduction patterns (Hamabe et al., 2003, see Fig2. and Fig3).

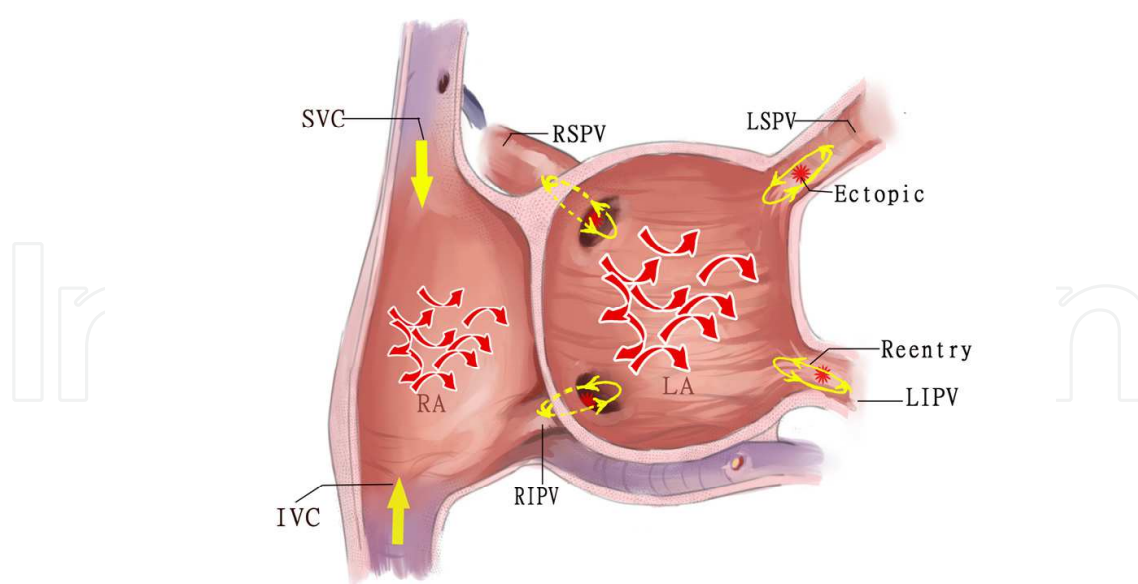


Fig. 2. Ectopic excitement exiting in pulmonary veins and left atria conjunction, propagating into atria and forming reentry, which is so called "Atrial fibrillation begets Atrial fibrillation". SVC, superior vena cava; IVC, inferior vena cava; LIPV, left inferior pulmonary vein; RIPV, right inferior pulmonary vein; LSPV: left superior pulmonary vein; RSPV: right superior pulmonary vein. LA: left atria; RA: right atria.

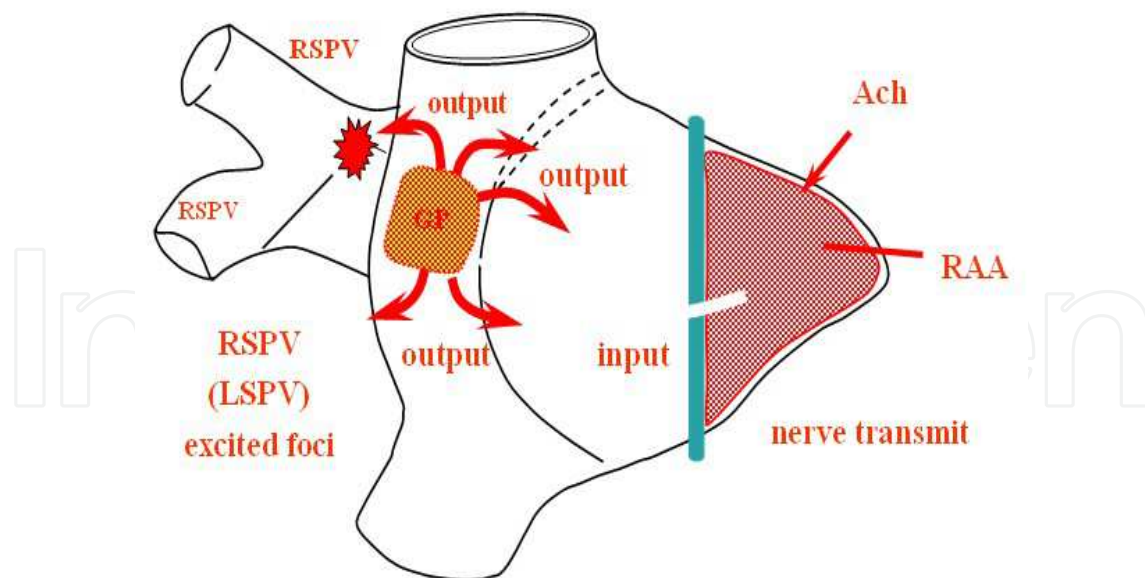


Fig. 3. Electrical remodeling of atria, Acetylcholine injecting at RAA activates ganglion to output impulse and effects on the excited foci in pulmanory veins, therefore, the arrhythmia perpetuates. Ach, acetylcholine; RAA: right atrial appendage; RSPV: right superior pulmanory vein; LSPV: left superior pulmanory vein. (Lu et al. 2008)

The autopsied heart showed that myocardial cells were localized to pulmonary vein between 9 and 38 mm from the pulmonary vein and left atria junction (Roux et al., 2004). The sleeve was composed of circularly and longitudinally oriented bundles of cardiomyocytes. The peripheral end of the myocardial sleeve was irregular. The longest myocardial sleeves were found in the superior veins and were longitudinally oriented. At the pulmonary vein and left atria junction, the circular bundles were not often circumferential. Pulmonary vein myocardial architecture confirmed the possibility of initiating atrial fibrillation. Tan (Tan et al., 2006) examined 192 sections in 32 veins obtained from 8 healthy human heart, each segment included between 7 and 20 mm of the adjoining left atria, and found 1) pulmonary vein and left atria muscular discontinuities and abrupt 90° changes in myofiber orientation were present in the pulmonary vein and left atria junction in over half of all segments examined; 2) These anisotropic features were found more frequently in the anterosuperior than posteroinferior junctions; 3) Adrenergic and cholinergic nerve densities were highest in the left atria within 5 mm from the pulmonary vein and left atria junction, higher in the superior aspect of left superior pulmanory vein, anterosuperior aspect of right superior pulmanory vein, and inferior aspects of the both inferior pulmanory veins than diametrically opposite, and higher in the epicardial than endocardial half of the tissue; 4) adrenergic and cholinergic nerves were highly co-located at tissue and cellular levels of spatial organization. Tan suggest that: 1) the pulmonary vein and left atria junction contains anatomical substrates (muscular discontinuities and abrupt fiber orientation changes) to support reentry; 2) there are no good empiric targets for segmental pulmonary vein isolation because of the widespread distributions of pulmonary vein and left atria muscular discontinuities; 3) the left atria region close to the pulmonary vein and left atria junction rather than farther away in the left atria or pulmonary vein would be the most appropriate target for autonomic modulation procedures; 4) it is not possible to selectively ablate either adrenergic or cholinergic nerves in this location because

both nerve types are highly co-located in this region. Steiner found that pulmanory vein myocardial sleeves frequently harbour pathological lesions, particularly senile atrial amyloid, and scarring in atrial fibrillation (Steiner et al., 2005). The degree of scarring of the sleeves did not correlate with the degree of coronary atherosclerosis, and inferred the genesis of the scarring is not post necrotic but degenerative, due to diffuse hypoxia of the sleeve myocardium. Amyloidosis and particularly scarring of pulmanory vein myocardial sleeves appear generally in the elderly population as an arrhythmogenic substrate for atrial fibrillation.

In animal studies, pacing had different effects on connexin40 and connexin43 gap junctions, collagen content increased as well (Yeh et al., 2006). They found there was a 98% increase in connexin43 in pacing 2 weeks, and a 74% increase in pacing 6-8weeks animals. In contrast, connexin40 decreased 47% in pacing 2 weeks but increased 44% in pacing 6-8weeks animals. Our studies also found the moderate to severe deposit of collagen fibers in canine atria after persistent rapid atrial pacing (XIONG et al., 2010, see Fig4. and Fig5.), connexin40 mRNA expression decreased in left atria and right atria, but increased in left atria appendage, right atria appendage and atrial septum; connexin43 mRNA expression was reduced in left atria, right atria, left atrial appendage and right atrial appendage while increased in atiral septum (see Fig6., Fig7. and Fig8.). The pacing induced collagen remodeling and modulation on connexin40 mRNA and connexin43 mRNA expressions could be partially attenuated by removing SVC-Ao fat pad suggesting vagal nervation plays a key role in the initiation and preservation of atrial fibrillation .

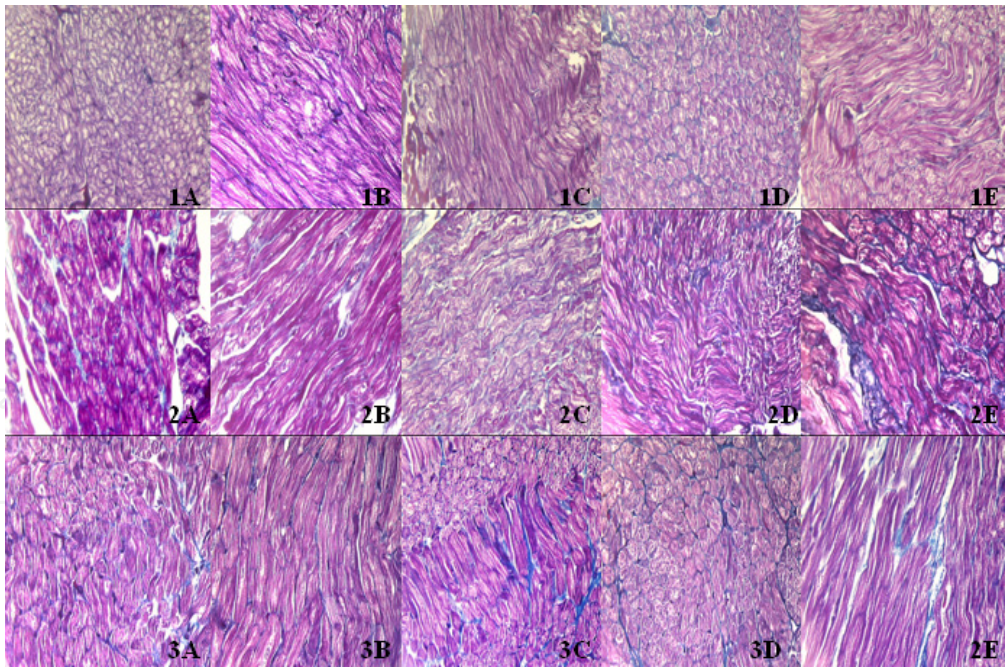


Fig. 4. Different degree of collagen fibers deposits at intercellular substance.1A to 1E: normal distribution of collagen fibers in the whole atria; 2A to 2E: severe degree of collagen fibers deposits at different locations of atria after persistent atrial pacing; 3A to 3E: moderate degree of collagen fibers deposits at different locations of atria after persistent atrial pacing without SVC-Ao fat pad.A: left atria; B: right atria; C: left atrial appendage; D: right atrial appendage; E: atrial septum; SVC-Ao fat pad: superior vena cava and aorto root fat pad.

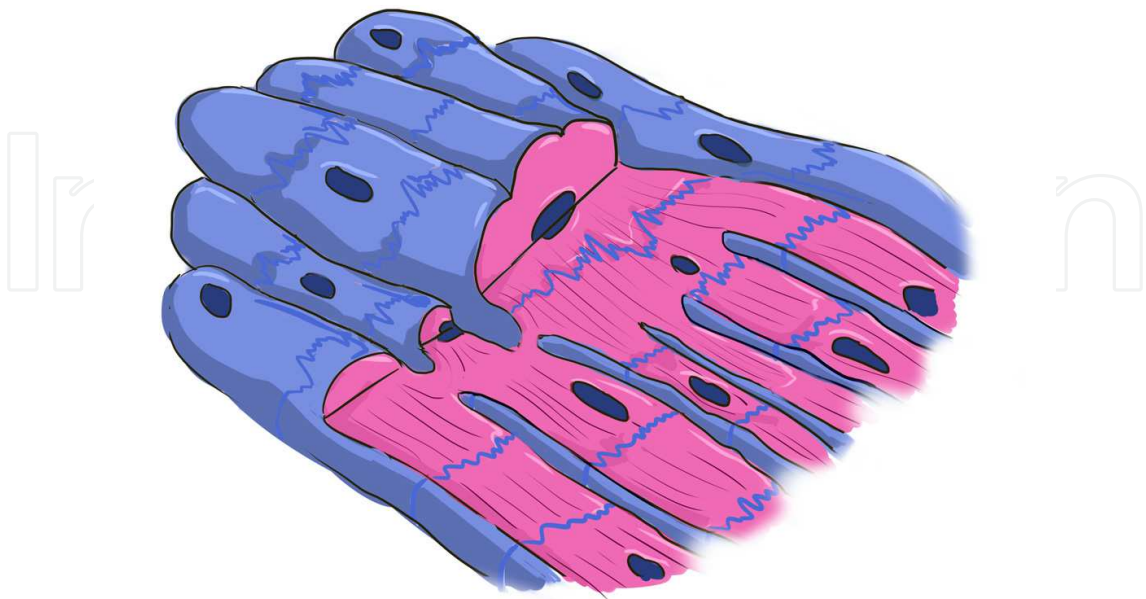


Fig. 5. Collagen fibers wrap the cardiac muscle cells and interrupt the normal intercellular electrical and signal conduction.

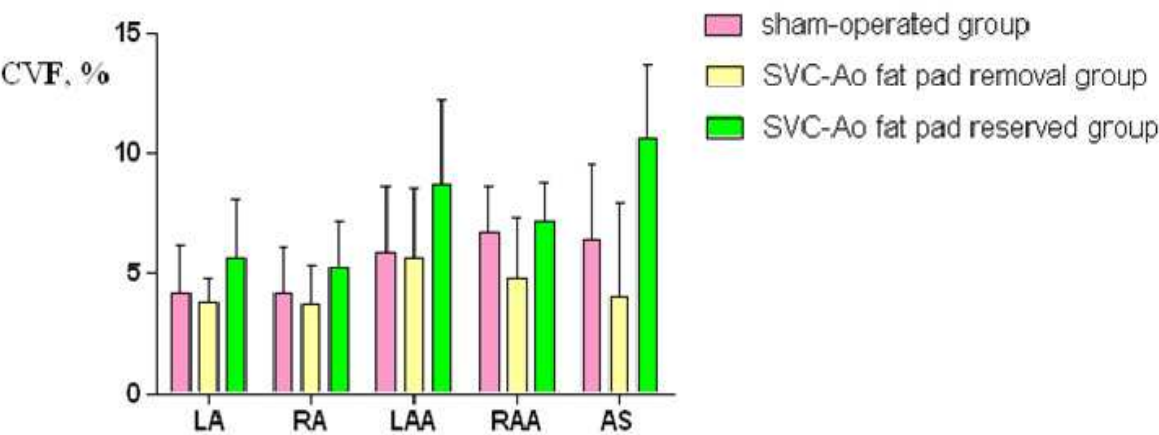


Fig. 6. Collagen Volume Fraction compared among three different groups. There was no significant spatial difference on collagen distribution in sham operated group and SVC-Ao fat pad removal group, while significant spatial difference on collagen distribution in SVC-Ao fat pad reserved group. CVF: collagen volume fraction; SVC-Ao fat pad: superior vena cava and aorto root fat pad; LA: left atria; RA: right atria; LAA: left atrial appendage; RAA: right atrial appendage; AS: atrial septum.

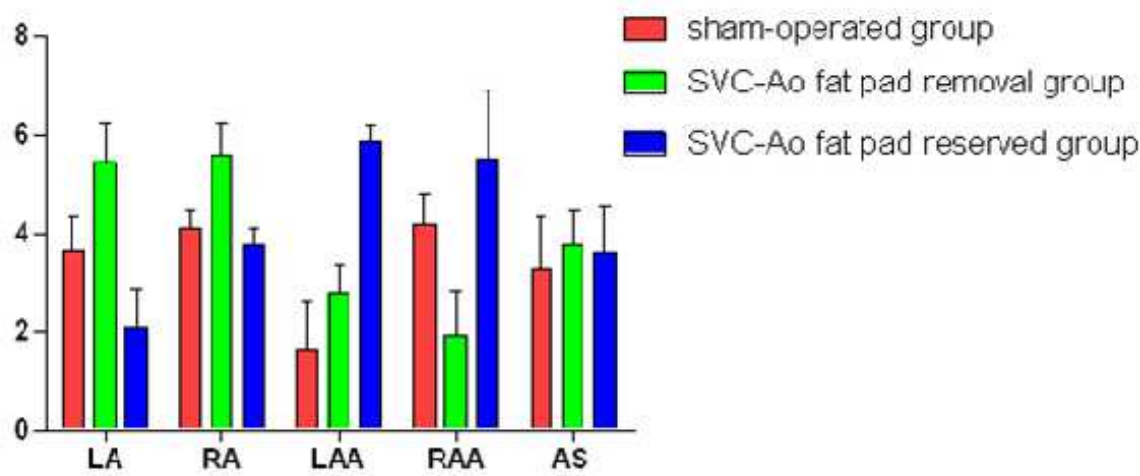


Fig. 7. Expression of Cx40 mRNA compared among three different groups. There was significant difference of increased Cx40 mRNA expression after persistent atrial pacing, the expression at atria in SVC-Ao fat pad removal group but that at atrial appendage in SVC-Ao fat pad reserved group are the significant difference. SVC-Ao fat pad: superior vena cava and aorto root fat pad; LA: left atria; RA: right atria; LAA: left atrial appendage; RAA: right atrial appendage; AS: atrial septum; Cx40: connexin 40.

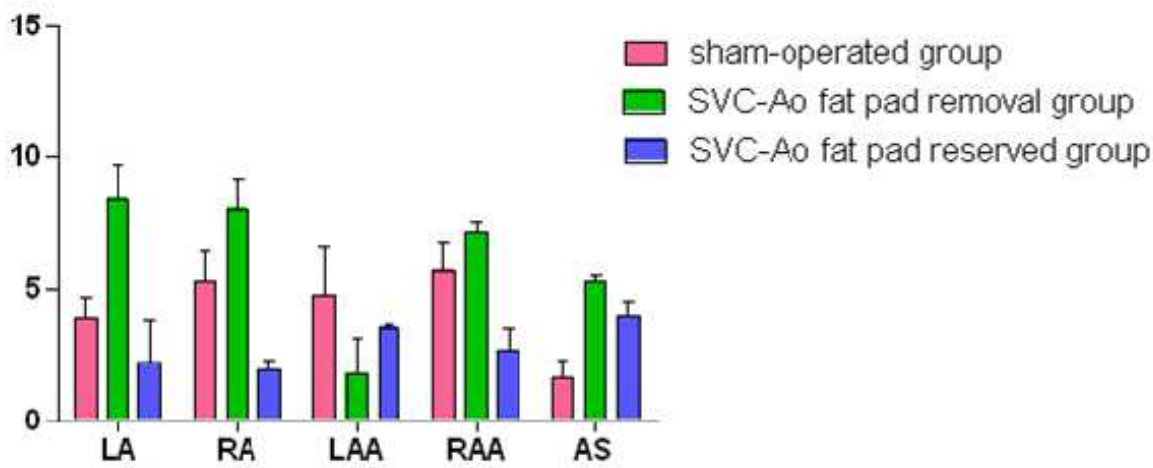


Fig. 8. Expression of Cx43 mRNA compared among three different groups. There was significant difference of increased Cx43 mRNA expression in SVC-Ao fat pad removal group but decreased Cx43 mRNA expression in SVC-Ao fat pad reserved group. The most interesting locations are left and right atria. SVC-Ao fat pad: superior vena cava and aorto root fat pad; LA: left atria; RA: right atria; LAA: left atrial appendage; RAA: right atrial appendage; AS: atrial septum; Cx43: connexin 43.

7. Acknowledgment

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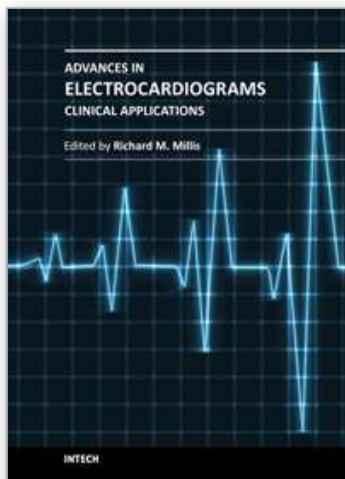
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Electrocardiograms have become one of the most important, and widely used medical tools for diagnosing diseases such as cardiac arrhythmias, conduction disorders, electrolyte imbalances, hypertension, coronary artery disease and myocardial infarction. This book reviews recent advancements in electrocardiography. The four sections of this volume, Cardiac Arrhythmias, Myocardial Infarction, Autonomic Dysregulation and Cardiotoxicology, provide comprehensive reviews of advancements in the clinical applications of electrocardiograms. This book is replete with diagrams, recordings, flow diagrams and algorithms which demonstrate the possible future direction for applying electrocardiography to evaluating the development and progression of cardiac diseases. The chapters in this book describe a number of unique features of electrocardiograms in adult and pediatric patient populations with predilections for cardiac arrhythmias and other electrical abnormalities associated with hypertension, coronary artery disease, myocardial infarction, sleep apnea syndromes, pericarditides, cardiomyopathies and cardiotoxicities, as well as innovative interpretations of electrocardiograms during exercise testing and electrical pacing.

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Phone: +86-21-62489820
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