Atrial fibrillation: more than just an arrhythmia

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Atrial Fibrillation: More than just an Arrhythmia

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Dedication

I would like to take this opportunity to thank my husband, Nick, for all of his love and support. He has always shown me that I can do anything I put my mind to and he continues to give me the opportunity to show it.
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I would also like to thank Dr. Carlos Baptista for his guidance and knowledge throughout the duration of this project. His delightful attitude was extremely motivating during this extensive process and helped me to understand his passion for this particular topic.
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Introduction

According to the American Heart Association, atrial fibrillation (AFib) is the most common sustained cardiac rhythm disturbance, increasing in prevalence with age (Fuster et al., 2006). Up to 11% of patients above the age of 80 years suffer from this arrhythmia and, it is estimated that over 2.2 million people are affected each year in the United States alone (Chen, Wasmund, & Hamdan, 2006). It is understood that AFib has multiple etiologies, but it is becoming widely known that AFib is also triggered by ectopic electrical activity originating from muscle sleeves of the pulmonary veins. Most recent research reveals that the myocardial fibers that surround and extend over the pulmonary veins are the trigger for initiating AFib, but the exact origin and configuration of these fibers is still not completely understood.

The common pattern in the collection of the superficial myocardial fibers that surround the pulmonary veins was studied by Nathan and Eliakim in 1966. Their study showed a main circular fascicle of fibers that runs around the openings of the pulmonary veins in the left atrium. The upper part of this fascicle runs above the right and left superior pulmonary veins with fibers running in a horizontal fashion. This fascicle is made up of many types of fibers (see Figure 1); fibers descending from the right atrial appendage, fibers descending from the wall of the superior caval vein, fibers ascending from the right atrium, and fibers to the right of the same main circular fascicle. Fibers running down from the right atrial appendage to the left atrial appendage form a broad interauricular fascicle, which unites with the upper portion of the main center fascicle. Other fibers descend from the left atrium to the left of the main center fascicle, which all end in the atrioventricular fibrotic rings, where new fibers also arise. A sphincter-like
structure is formed by muscle fibers that leave the main fascicle and turn around the opening of the pulmonary veins; these circular fibers contribute to the formation of the myocardial sleeves that cover the venous walls. Another set of fibers, leaves the main fascicle and runs on the posterior surface of the left atrium towards the pulmonary veins. Another layer of fibers, beneath the circular fascicle on the posterior side, has two counterparts. The fibers that are situated between the right and left inferior pulmonary veins run vertically and the fibers that are between the superior and inferior right and left pulmonary veins run in a horizontal fashion (Nathan & Eliakim, 1966).

Multiple treatments for AFib exist and include: rate and rhythm control through antiarrhythmic medications, catheter ablation, surgery, and device implants. Treatment with antiarrhythmic drugs has been considered the first line of therapy in patients with symptomatic AFib. However, because of the inconsistent efficacy and potential toxicities of these drugs, alternative surgical approaches for the treatment of AF have been established (Wudel, Chaudhuri, & Hiller, 2008). This review focuses on catheter ablation and surgical methods, therefore, medications and implant devices will not be discussed.

In 1991, the Cox-Maze procedure was the first surgical approach to the treatment of AFib. This procedure involves a cut-and-sew technique with several full-thickness incisions in both atria to block reentrant circuits and has proven to have success rates exceeding 90%. This approach, however, is technically challenging, requires bypass support, and is associated with prolonged operative time and bleeding complications (Rahmanian, Castillo, Mehta, Adams, & Filsoufi, 2008).

Catheter ablation techniques aiming at electrical isolation of the pulmonary veins and/or at circumferential ablation around the pulmonary ostia have been developed to
treat AFib (Haissaguerre et al., 2000; Kholova & Kautzner, 2004). This technique was
developed as a less invasive, safer alternative to the Cox-Maze procedure.

Literature shows that ablation is the most effective and most successful
technique used in the treatment of this cardiac arrhythmia. The purpose of this review is
to present the available information and data regarding the basic anatomy of the heart,
in particular the morphology of the left atrium, and how it relates to the mechanisms and
electrophysiology of AFib, and the roles of ablative and surgical approaches in the
treatment of atrial fibrillation.

Purpose

The purpose of this review is to compare and contrast the literature available
regarding the basic anatomy of the left atrium of the heart, and how it relates to the
etiology of AFib. The morphological, and electrophysiological aspects of the
mechanisms in the genesis of AFib, are discussed. The roles that ablative and surgical
approaches have in the treatment of atrial fibrillation are presented.

Background

Substantial work on AFib mechanisms was performed in animal models in the
late 1800’s and early 1900’s. With simple observation and the use of primitive
instruments, scientists were able to acquire remarkable insights into the basic
knowledge of arrhythmias (Nattel, Shirotshi-Takeshita, Brundel, & Rivard, 2005). The
literature shows that AFib frequently originates from myocardial fibers that extend into
the pulmonary veins (PVs). However, controversy still exists about the role of other foci
for triggering AFib (Kholova & Kautzner, 2004). Further research is still needed for complete understanding of the origin and configuration of the myocardial fibers that surround the pulmonary veins and exactly how they contribute to AFib. Understanding the gross structure and the composition of the atria is essential to investigations into the substrates and therapy of AFib (Ho, Anderson, & Sanchez-Quintana, 2002a).

Despite the extensive literature concerning atrial arrhythmias, there are relatively few articles on the anatomy of the atrial chambers, in particular the left atrium (Ho, Anderson, & Sanchez-Quintana, 2002b). As the atrial walls expand during early embryologic stages, the smooth tissue of the PVs becomes incorporated into the walls of the left atrium (LA), which later becomes the posterior wall and some of the roof of the LA (Kanj, Wazni, & Natale, 2007). Isolation of this area, known as the PV antra, has proven to successfully treat AFib by eliminating the potential triggers associated with this arrhythmia. Compared with pulmonary vein ostial isolation, this technique offers a higher success rate and a lower complication rate (Kanj et al.) In this review, the anatomy and electrophysiology of the atria will be discussed in order to understand the mechanism of AFib.

Knowledge of the anatomy of the PVs and the PV-LA junction is important to the understanding of the electrical properties of the PVs (Fynn & Kalman, 2004). Studies have shown that muscle fibers in the PVs are excitable and resemble atrial muscle in their action potential characteristics, therefore, allowing electrical activity to spread into the PVs. However, the mechanism of the focal activity leading to AFib is unknown. “The architecture of the PVs may play a role, either by setting up microreentry due to
structural complexity or by facilitating extinction of activation out of a focus” (de Bakker, Ho, & Hocini, 2002, p. 288).

Haïssaguerre and colleagues (1998) were the first to determine that the pulmonary veins may be areas of importance in the generation of AFib; he also proposed the use of pulmonary vein isolation in the treatment of AFib, which is now an accepted method of treatment worldwide. It is currently proposed that ablation strategies can eliminate potential triggers of AFib and serve as a better treatment modality than pulmonary vein isolation alone. Catheter-based ablation and pulmonary vein isolation have gained popularity because of the realization that the pulmonary veins are the source of ectopic foci in most patients with paroxysmal AFib (Haïssaguerre et al., 1998; Wudel et al., 2008). These procedures can be performed using any energy source, but radiofrequency energy tends to be the best method. Radiofrequency (RF) energy is an alternating current that generates heat by causing ions within tissue to follow the direction of the alternating current and in doing so, converts electromagnetic energy to mechanical energy. This energy can be applied to the endocardial and/or epicardial surfaces (Aktas, Daubert, & Hall, 2008). The temperature of the catheter must be monitored throughout the duration of the procedure, as the temperature of the esophagus tends to increase as energy is being delivered to the posterior wall of the atrium.
Literature Review

*Morphological features*

In order to better understand the mechanisms behind AFib, the gross structures, myoarchitecture, and variations in the muscular connections of the heart atria must be considered in any interventional technique that may terminate or treat AFib. The atria, “previously conceptualized as mere reservoirs of systemic and pulmonary venous blood, have functional roles in the dynamics of the cardiac chambers and atrioventricular valves as well as being the substrate for conduction of the cardiac impulse” (Ho & Sanchez-Quintana, 2008, p. 1).

Both the right and left atrial chambers lie posterior to the respective ventricular chambers that they open to. When comparing the orientation of the atria, the cavity of the right atrium is right and anterior, while the left atrial cavity is positioned posterior and slightly left relative to the right atrium. The atrial septum that divides the two atria is oriented in an oblique fashion from anterior to posterior rightward. The posterior aspect of the left atrial wall lies just anterior to the tracheal bifurcation and in close proximity to the esophagus. The PVs enter the posterior portion of the left atrium with the two left PVs positioned more superiorly than the two right PVs. The aortic root arises from the middle of the heart and the anterior walls of both atria form a curve to house this structure (Ho et al., 2002b).

*Morphological Aspects of the Right Atrium*

The right atrium is made up of four components, the appendage, venous portion, and the vestibule. The septum makes up the fourth component and divides the right and
left atria. The dominant characteristic of the right atrium is a structure that extends out from the lateral aspect of the atrial body. This triangular shaped appendage projects anteriorly, with its apex pointing superiorly, and is continuous with the wall of the venous component (Ho et al., 2002a). The right atrium has a terminal crest (crista terminalis), a muscle bundle that defines the border between the smooth wall of the venous component and the rough wall of the appendage (see Figure 2). The crest extends from the entrance of the superior caval vein (superior venae cava), passes in front of the venous orifice and then descends and curves to the right of the entrance of the inferior caval vein (inferior venae cava) to continue as finer bundles that enter the atrial wall (Ho & Sanchez-Quintana, 2008). The crest is arranged in a non-uniform fashion and may be responsible for re-entry due to delay and discontinuities in the spread of the excitatory signal (Sanchez-Quintana et al., 2002). Pectinate muscles (see Figure 3), responsible for the rough texture of the wall of the appendage, stem from the terminal crest and spread entirely over the lateral and inferior walls of the atrium, however, never reach the orifice of the tricuspid valve. The ridges of the pectinate muscles, which can be seen on the internal aspect of the atrial cavity, are separated by areas of thinner walls. Myofibers in the ridges run longitudinally and terminate in the vestibule, a smooth muscular rim surrounding the valvular orifice (Ho et al.).

The opening of the superior venae cava is not guarded by a valve; however, there are sleeve like extensions of right atrial myocardium on the outer aspects of the venous wall (Kholova & Kautzner, 2004). The sinus node of the conduction system lies in the musculature of the terminal crest at the junction with the superior caval vein (Sanchez-Quintana, Cabrera, Farre et al., 2005). The myocardial fibers over the inferior
venae cava, and sometimes the inferior part of the intercaval wall, are significantly less or absent in some cases. The Eustachian valve, a triangular flap of fibrous tissue, guards the entrance of the inferior venae cava (see Figure 4) and inserts in the border between the oval fossa (fossa ovalis) and the coronary sinus (Ho et al., 2002a). This area, called the sinus septum, however, is not a true septum, as it is the atrial wall between the inferior caval vein and the coronary sinus (see Figure 5) (Ho & Sanchez-Quintana, 2008). The orifice of the coronary sinus is guarded by a crescent-shaped flap known as the Thebesian valve that can sometimes be fenestrated and may occasionally cause complications when catheters are inserted into the sinus (Ho & Sanchez-Quintana).

The free border of the Eustachian valve continues as a tendon, the tendon of Todaro, which runs in the musculature of the sinus septum and becomes part of the triangle of Koch (Voboril, 1967).

The triangle of Koch serves as the anatomical marker for the AV node which is located in the apex of the triangle and points superiorly (Ho et al., 2002a). At the base of the triangle, between the coronary sinus and the septal leaflet of the tricuspid valve, is the septal isthmus. The septal isthmus is a common target during ablation procedures to terminate re-entrant arrhythmias. The anterior border of the triangle is formed by the line of leaflet attachment to the tricuspid valve. The triangle’s posterior border is made up of the tendon of Todaro, a continuation of the free border of the Eustachian valve, and runs within the musculature of the sinus septum at the apex of the triangle (Ho & Anderson, 2000). At the most superior portion of the triangle is the central fibrous body, which denotes where the AV node penetrates the AV junctions and forms the bundle of
His (Ho et al.). This serves as the connection point for the AV node and the respective bundle branches, which will be discussed later.

**Morphological Aspects of the Left Atrium**

Like the right atrium, the left atrium has a venous component, a vestibule and an appendage. However, in the left atrium, there is a prominent pulmonary venous component, located posteriorly. The septum in between the atria is shared by both the right and left atria respectively. The atrial appendage of the left atrium is much smaller than that of the right atrium and has a tubular shape (see Figure 6). It has lobes that are potential sites for thrombus formation. The morphology of the left atrial appendage is variable but has a distinct junction with the body of the left atrium. The only rough zone in the left atrium is limited mainly to the left appendage. Like the right atrium, the left atrium also has a complicated network of fine muscular ridges on the internal surface of the endocardial wall, separated by areas of very thin atrial wall musculature (Ho et al., 2002a). The left atrial body, separate from the appendage, unites the vestibule, the atrial septum, and the venous component and has fairly smooth walls (Ho & Sanchez-Quintana, 2008). The left atrium lacks a muscular bundle like that of the terminal crest (crista terminalis); consequently, the division between rough and smooth walls is marked by the orifice of the left atrial appendage (Ho et al.).

The left atrial outlet is marked by the vestibular portion of the left atrium. Since it lacks a prominent atrial appendage, the proximal margin of the vestibule blends with the wall of the smooth atrial body. This vestibular portion forms part of the mitral isthmus, which lies between the opening of the left inferior pulmonary vein and the ring-shaped
attachment of the mitral valve (Wittkampf et al., 2005). The venous component of the left atrium is found on the posterior aspect and receives the pulmonary veins. It lies directly in front of the esophagus, subsequently when performing an ablation, there is potential risk of damaging the esophagus since the posterior wall is not uniform in thickness (Platonov, Ivanov, Ho, & Mitrofanova, 2008; Sanchez-Quintana, Cabrera, Farre et al., 2005). The venous component is described as having four pulmonary veins that enter the left atrium separately, two from the left lung and two from the right lung. Variations exist in the number of venous orifices and their respective arrangements (Kato et al., 2003). The right superior pulmonary vein passes next to the posterior aspect of the right atrium immediately behind the junction with the superior caval vein (superior venae cava), and it is here that its anterior wall is closest to the pathway of the right phrenic nerve (Sanchez-Quintana, Cabrera, Climent, Farre, Weiglein et al., 2005).

The orifices of the right pulmonary veins lie adjacent to the plane of the atrial septum. Musculature of the atrial wall extends into the veins circumferentially and distally, like the caval veins. Near the venous insertions, sleeves are thick and surround the epicardial aspect of the veins completely. However, the distal margins of the sleeves are typically irregular as the musculature fades (Ho et al., 2001; Ho, Sanchez-Quintana, Cabrera, & Anderson, 1999; Nathan & Eliakim, 1966; Saito, Waki, & Becker, 2000). Independent electrical activity in venous sleeves has been well understood (Zipes & Knope, 1972), but within the last decade or so, ectopic foci from within the veins has been linked to spontaneous initiation of atrial fibrillation (Haissaguerre et al., 1998). For this reason, focal ablations or electrical isolation of the pulmonary veins have been included in the treatment of AFib (Ho & Sanchez-Quintana, 2008). The myocardial
sleeves are longest in the superior pulmonary veins, which consequently corresponds to the highest frequency of ectopic focuses reported (Haissaguerre et al.; Ho et al., 1999; Saito et al., 2000).

Along the anterior wall of the atrium a strong external muscle bundle, known as Bachmann’s bundle, extends from the sino-auricular region to the left atrial appendage. This band of muscle fibers lies anterior to the left septopulmonary bundle, which forms the deeper layer of several parallel layers arranged on top of one another. Beneath and inferior to this bundle are myofibers that arise from the anterior rim of the oval fossa (fossa ovalis). These myofibers blend into Bachmann’s bundle, pass to either side of the neck of the atrial appendage and then come together as a broad band encircling around the inferior wall to enter the septal raphe, a ridge that shows the division between the two sides of the heart. On the posterior wall, the septopulmonary bundle, which arises from the septal raphe, runs beneath Bachmann’s bundle, and fans out among the pulmonary veins, often becomes two branches that fuse with the circumferential myofibers coming from the lateral wall. Lying deep to the septopulmonary bundle and forming the subendocardium, the septoatrial bundle has extensions that form loops around the area of the venoatrial junctions and expand to the area of the venous sleeves (Papez, 1920). The venous sleeves are mostly made up of circularly arranged myofibers; however, oblique and longitudinally arranged myofibers intertwine with circular myofibers and may be the substrate for micro-re-entry (de Bakker et al., 2002).

Nathan and Eliakim (1966) performed an anatomic study of human hearts in order to show that the atrial-venous junctions may be of physiological and pathological importance. This study was performed on 16 human hearts obtained from autopsies
from both males and females, whites and blacks, aged 16 to 63 years. The hearts were examined from both the inner and outer aspects and the thickness of the posterior wall of the left atrium was measured. Measurements were taken of the entrances between (1) the right and left superior PVs; (2) the right and left inferior PVs; (3) the right superior and inferior pulmonary veins; (4) the left superior and inferior pulmonary veins. The lengths of the myocardial venous sleeves at the venous walls were also measured. Each of the hearts was stripped of the pericardium, vessels, nerves, and fascia in order to see the myocardial fibers more clearly (Nathan & Eliakim, 1966).

Nathan and Eliakim (1966) found, in most of the specimen examined, that there is a common pattern in the orientation of the superficial myocardial fibers of the atria. This pattern included a main circular fascicle of fibers that runs around the openings of the pulmonary veins in the left atrium. The upper part of this fascicle runs above the right and left superior pulmonary veins with fibers running in a horizontal fashion. This fascicle is made up of many types of fibers; fibers descending from the right atrial appendage, fibers descending from the wall of the superior caval vein, fibers ascending from the right atrium, and fibers to the right of the same main circular fascicle. Fibers running down from the right atrial appendage to the left atrial appendage form a broad interauricular fascicle, which unites with the upper portion of the main center fascicle. Other fibers descend from the left atrium to the left of the main center fascicle, which all end in the atrioventricular fibrotic rings, where new fibers also arise. A sphincter-like structure is formed by muscle fibers that leave the main fascicle and turn around the opening of the pulmonary veins; these circular fibers contribute to the formation of the myocardial sleeves that cover the venous walls. Another set of fibers, forming oblique
fascicles, leaves the main fascicle and runs on the posterior surface of the left atrium towards the pulmonary veins. Another layer of fibers, beneath the circular fascicle on the posterior side, has two counterparts. The fibers that are situated between the right and left inferior pulmonary veins run vertically and the fibers that are between the superior and inferior right and left pulmonary veins run in a horizontal fashion (Nathan & Eliakim, 1966).

The direction of fibers on the posterior surface of the left atrium is unpredictable. The most common patterns seen by Nathan and Eliakim (1966) were the oblique and vertical patterns. After taking measurements of the atrial wall, results show that there is no uniformity in thickness. The upper left atrial wall was consistently thicker than the inferior atrial wall in between the right and left superior and inferior PVs respectively. On average, the upper left atrial wall was 1.8 mm while the lower left atrial wall was 1.0 mm. However, the thickness of the right and left sides of the posterior atrial wall shows no significant differences, 1.0 and 0.8mm respectively. The sphincters surrounding the superior PVs were, to some extent, thicker than those around the inferior PVs. The myocardial sleeves extended to the hilus of the lung in some of the specimen, but had no myocardial extensions in others. Often, the myocardial sleeves had multiple layers of fibers oriented in different directions; circular, longitudinal, oblique, and spiral directions. These fibers, stemming from the atrium, extend out over the venous wall at variable lengths and then wrap back around to the atrial wall. The myocardial sleeves were found to be more extensive and better developed in the superior PVs than the counterpart with average values of; right superior PV, 13 mm; right inferior PV, 8 mm; left superior PV, 18 mm; and left inferior PV, 10 mm (Nathan & Eliakim, 1966).
Another area of study is that of the coronary sinus. Research has focused on this area as another source of AFib due to the link from the inferior right atrium to the left atrial myocardium via the coronary sinus.

Chauvin Shah, Haissaguerre, Marcellin, and Brechenmacher (2000) studied ten necropsied hearts from both male and female patients, aged 27 to 77, who died of unrelated cardiac disease. Measurements were taken of the total length of muscle surrounding the coronary sinus, thickness of the proximal and distal ends, fiber orientation, and connections between the coronary sinus musculature and left atrial myocardium. Results show that in all specimens examined, the coronary sinus was surrounded by a muscle cuff that was “continuous with the ostial right atrial myocardium and extended variably away from the ostium for 25 to 51 mm (mean 40±8 mm)” (Chauvin et al., 2000, p. 648). The muscle cuff ended at the junction of the great cardiac vein and the origin of the coronary sinus or the valve of Vieussens, when this structure was present, at a mean distance of 3.4±3.2 mm. The thickness of the muscle cuff was variable with measurements ranging from 0.3 to 2.5 mm, and in 8 out of the 10 hearts, the area of the ostium had a greater thickness, 1.35±0.7 mm, than the other end, 0.68±0.2 mm. In contrast, adipose tissue separated the left atrial myocardium from the coronary sinus musculature. In every specimen studied, connections extending from the coronary sinus musculature to the adipose tissue were noted. Continuity between the right and left atria is therefore contributed by two parts, a muscular cuff surrounding the wall of the coronary sinus and other fibers extending from this cuff to the left atrial myocardium (Chauvin et al.).
The main area blamed for the initiation of AFib is undoubtedly the PVs; however, the exact substrate responsible for this arrhythmia is unknown. For the first time, Morel, Meyronet, Thivolet-Bejuy, and Chevalier (2008) discovered interstitial Cajal cells (ICC) in the PVs, contributing to abnormal firing of electrical impulses (Morel et al., 2008). These ICCs are normally responsible for peristaltic activity in the gastrointestinal (Khan et al., 2008) tract and any area of decreased concentration results in GI motility disorders. Morel et al. found that out of the eight hearts studied, three hearts had a higher density of ICCs present in sections of the PVs, particularly where the muscular sleeves were thick. Two of the three hearts with previous documented AFib incidents had ICCs in the circumference of the PVs, which supports the theory that these ICCs act as pacemaker cells in the PVs to create abnormal electrical activity. ICCs were found in the external or middle of the muscle wall and were scattered in some areas and found in small groups in other areas. Within these layers, where the ICCs were found, two types of ICCs were seen; multipolar with a pyramidal shape and spindle shaped. The multipolar ICCs were found either in the external side or inside of the muscular layer, while the spindle shaped ICCs were mainly found in the middle of the muscular layer. In the GI tract, these two types of ICCs play different roles. The multipolar cells are in charge of the pacemaker activity, while the spindle shaped cells play a role in neurotransmission (Morel et al.). This study shows that these ICCs can cause electrical signals and take on the role of a pacemaker in smooth muscle cells which can trigger abnormal ectopic firing in the PVs.
Electrophysiology

The primary function of the conduction system is to generate an electrical impulse that is transmitted through the myocardial tissues to ensure synchronized activation of the heart. These conduction tissues must be differentiated from the actual working myocardial cells, which are responsible for the actual contraction of the heart. “The conduction system comprises separate components with distinct functions” (Moorman, de Jong, Denyn, & Lamers, 1998, p. 629). The sinoatrial (SA) node is responsible for the initiation of the electrical impulse; the atrioventricular (AV) node then takes the impulse from the SA node and conducts it through the bundle branches and Purkinje fibers to ensure transmission of the signal through the ventricular myocardial tissues. It is therefore important to understand the location and function of these conduction tissues and their relation to the normal working myocardial cells in order to understand how coordinated activation of the heart occurs (Moorman et al., 1998).

The SA node lies near the junction of the superior vena cava and the right atrial appendage and directly beneath the sulcus terminalis, a groove which marks the separation of the right atrial crista terminalis and pectinate musculature from the embryologic sinus venosus. The sulcus terminalis can be used to designate the location of both the SA and AV nodes, as the superior border marks the transverse plane where the SA node is found, while the inferior border marks the transverse plane where the AV node is found. The AV node lies just anterior to the orifice of the coronary sinus, inferior to the right atrial septal endocardium, and superior to the tricuspid valve (see Figure 5) (James, 2002). Recall that the AV node is also located in the central fibrous body, within the apex of the triangle of Koch (Ho et al., 2002a).
As previously described, the heart is a muscular organ that must work continuously in order to pump the required amount of blood to different areas of the body. To produce a heartbeat, an electrical signal is generated from within the heart muscle. The electrical signal that is transmitted through the hearts cells can be recorded by an ECG, or electrocardiogram. The electrical signal is initiated by the SA node. Once the right atrium fills with blood, the signal spreads across both the right and left atria and causes them to contract. Blood is forced through the valves of the atria into the ventricles. The ECG records a P wave that represents the contraction of the atria. The signal is then transmitted to the AV node where it is delayed in order to allow the atria to finish contracting and for complete filling of the ventricles. The ECG recording that represents this interval is the line segment between the P and Q wave. The signal is further transmitted through the heart to the bundle of His, located in the ventricles of the heart. From here, the signal is transmitted through the septum, where the bundle of His divides into right and left bundle branches; this is represented by a Q wave. After the signal passes through the right and left bundle branches, it is quickly transmitted through the Purkinje fibers that connect the two branches to the cells in the walls of the ventricles. The signal spreads, causing both ventricles to contract, but at different times. The contraction of the left ventricle, represented on the ECG by the R wave, occurs slightly earlier than the contraction of the right ventricle, represented by the S wave. The contraction of the right ventricle pushes blood through the pulmonary valve to the lungs. The contraction of the left ventricle pushes blood through the aortic valve to the rest of the body. Once the signal has completely passed through the heart, the ventricle walls relax, shown by the T wave on ECG, and prepare for the next signal. This pathway
continues repeatedly in order to maintain a normal sinus rhythm, or NSR (Goldberger & Goldberger, 2006).

The term sinus node, instead of SA node, will be used throughout the remainder of this review, as it is a more accurate description of the location of this structure. This umbrella term includes both “sinoauricular” and “sinoatrial” because the sinus node is normally found at both locations, not just one (James, 2002). The sinus node is considered the pacemaker of the heart and initiates a rhythmic electrical signal that causes the heart to beat and creates a NSR. The NSR can be accelerated or slowed in order to provide an optimal rate for the most effective cardiac output. Signals are provided either by the autonomic nervous system, from the vagus or sympathetic nerves, or by humoral substances delivered in the blood stream through the sinus node artery. It was previously unclear about the mechanism of the synchronization of the electrical signal with regards to the many different cell types, pattern of distribution and location of these cells within the sinus node. However, now, there is extensive evidence that shows that the impulse originates in the pacemaker cells, or P cells, surrounding the sinus node. Each set of P cells is surrounded by a basement membrane and, the junctions connecting the P cell clusters are highly undifferentiated. Synchronization between clusters occurs by signal conduction through a dominant pacemaker site, which may shift in response to physiologic stimuli (James, 2003). Michaels, Matyas, and Jalife (1986) have done work to not only understand how each of these separate cells, with their own signal, avoid confusion in the resulting impulse, but also the molecular and mathematical factors that are involved (Michaels et al., 1986). Currently, there are two theories as to how the sinus rhythm is initiated and synchronized. The first theory
involves a regular, repetitive and mechanical pulse that is generated by the sinus node artery, branching from the right coronary artery, and initiation of an electrical impulse in the sinus node (James, 1973). The second theory identifies that, “the transitional cells of the sinus node not only connect between P-cell clusters and ordinary working myocardium of the atria, but some transitional cells actually connect individual P-cell clusters to each other” (James, 2003, p. 337). The sinus node also contains an extracellular matrix that connects directly to the sinus node artery and helps to organize the myocardial cells of the node. This connection to the sinus node artery helps to explain the correlation between contraction of the artery and activation of the sinus node impulse (James).

The blood supplied to the human sinus node comes from two different sources, the right coronary artery, and branching sinus node artery, and the left circumflex artery, which follows the left aspect of the coronary sulcus, separating the atria from the ventricles, and extends roughly to the posterior longitudinal sulcus, separating the ventricles (James, 2002). On the other hand, the blood supply to the AV node has been found to be supplied by multiple different sources. Early studies performed by Van der Hauwaert, Stroobandt and Verhaeghe (1972) found that the ramus septi fibrosi, a branch of the right coronary artery, supplied the dorsal aspect of the AV node, while branches of the left coronary artery supplied the ventral aspect of the AV node and His bundle. Septal arteries of the left anterior descending artery supplied most of the bundle branches but were not responsible for supplying the His bundle. Other anastomoses were also found between the ramus septi fibrosi and other coronary arterioles, in order to create a collateral circulation to feed the AV node and surrounding structures in case
of occlusion (Van der Hauwaert et al.). In 1998, Abuin and Nieponice performed a study, using a new injection and dissection technique, on 20 cadaver hearts aged 15 through 65, with and without coronary artery disease. Results of their study demonstrated that in 14 out of the 20 hearts dissected, the right superior descending artery, originating from the right coronary artery, was responsible for the blood supply to the AV node. Conversely, in 8 out of the 20 hearts, it was found that Kugel's artery, which connects the trunks of the right and left coronary arteries, was the blood source for the AV node (Abuin & Nieponice, 1998). Regardless of the blood supply, it is necessary to understand the collateral circulation to these structures in case of any surgical intervention involving any aspect of the heart, especially the conduction system.

James (2002) performed extensive research regarding the structure and function of the sinus node, AV node and His bundle using canine hearts. Canine hearts were chosen over human hearts because, “gross and microscopic anatomy of the canine heart and its conduction system is more usefully similar to the human heart than almost any other mammalian species” (James, 2002, p. 237). Autonomic influence on the sinus node, as mentioned earlier, comes from either the vagus nerve or the sympathetic nerve and can have enhancing or blocking effects. To show these effects, different test substances were administered directly through the sinus node and into the small veins that drain into the right atrium. The test substances were administered over a period of a few seconds at a volume of two milliliters. In regards to the vagus nerve, results of this study showed that when given in very small amounts, atropine, an anticholinergic, which increases heart rate, will completely block effects of the vagus nerve on the sinus node. Acetylcholine can temporarily reproduce the vagal effect and decrease heart rate, blood
pressure, or both when given in small volumes. However, when given in a more concentrated form over a longer period, acetylcholine can cause transient AFib. If a prolonged vagal effect is desired, a brief administration of eserine, or physostigmine, can be given to block the cholinesterase effect, followed by a dose of acetylcholine to prolong the effects. On the other hand, in order to eliminate these effects, a small amount of atropine can be given (James). In regards to the sympathetic nerve, James and Nadeau (1964) performed another study and found that using other test substances, such as tyramine or catecholamines, had similar varied effects on the sinus node (James & Nadeau). In summation, there are two changes to the rate of the sinus node that occur upon injection of any test substance, which shows that the substance passes directly through the sinus node. A patterned response illustrates an abrupt slowing of the rate during the first seconds of the injection, followed by a brief acceleration for another few seconds, and then a return to stable NSR. This same predictable response can be seen during AV junctional rhythm when test substances are injected into the AV node artery (James).

Clinical and Surgical Applications

As stated previously, AFib is the most common sustained cardiac arrhythmia, affecting millions of adults in the United States every year. The population most affected by this arrhythmia includes those with other comorbidities like diabetes, hypertension, coronary artery disease, excessive alcohol consumption, advanced age, and other such risk factors (Aktas et al., 2008). Morbidity and mortality rates associated with uncontrolled AFib make it an arrhythmia of considerable interest. Although AFib can be
appropriately managed using antiarrhythmic medications in majority of patients, the inconsistent efficacy and potential toxicity of these medications has made surgical and catheter-based solutions a preferred treatment option for those affected by this arrhythmia (Fuster et al., 2006; Wudel et al., 2008).

**Surgical Procedures**

The first successful surgical treatment of AFib was accomplished by the Cox-Maze procedure in 1987. This procedure involves a cut-and-sew technique, creating multiple full-thickness incisions within the atria, blocking re-entrant wavelets from surrounding areas of the atrium. Initially, this procedure was designed for patients undergoing open-heart surgery for repair of other heart abnormalities, requiring a median sternotomy and removal of the left atrial appendage (Cox et al., 2000; Rahmanian et al., 2008). Since 1987, the Cox-Maze procedure has undergone 2 major modifications, allowing a less invasive technique to be used. In this so-called Maze III procedure, transmural atrial lesions are created without cutting atrial tissue, via radiofrequency ablation and photocoagulation, and cardiopulmonary bypass is no longer required (Haghi & Schumacher, 2001; Lee et al., 1999). The procedure itself causes no permanent damage to the sinus node and long term function of the left and right atria is intact in 93% and 99% of patients respectively (Cox et al.). The overall success rate of the Maze III procedure exceeds ninety percent, making it the most successful treatment modality of medically refractory AFib. However, this technique is considered technically challenging and is associated with prolonged operative time and bleeding complications (Rahmanian et al.).
Catheter-based Ablation Procedure

Catheter-based ablation and pulmonary vein isolation have become increasingly popular treatment modalities for AFib due to the technically simple and less invasive nature of the procedures. Haissaguerre et al. (1998) described areas of ectopic foci within the PVs as the primary sites linked to the initiation of AFib. Since then, advances have been made in the ablation strategy to eliminate these potential triggers using two catheters, and various types of energy sources to create areas of conduction block and terminate the arrhythmia. Pulmonary vein antrum isolation (PVAI), described by Kanj et al., and AV node ablation are two procedures that have come to be superior to the pharmacological management of AFib. Although both procedures are options for those who do not find relief through medical therapy, AV node ablation is rarely used. This procedure helps improve symptoms, but does not alleviate the arrhythmia, therefore making it inferior to its counterpart, PVAI (Natale, 2006). The PV antra are funnel-like structures, made up of the junction of the PVs and the walls of the atria. The anterior aspect of the left PV antrum overlaps with the anterior aspect of the PV ostia, where the atria connect to the PVs. In contrast, the right PV antrum includes the right PVs that extend into the interatrial septum. Posteriorly both antrum include and make up a significant portion of the left atrial wall (Kanj et al., 2007). Like other anatomy the arrangement of the PVs is highly variable, therefore making it essential to use pre-procedural 3D imaging to define the anatomy of the PVs and surrounding structures (Stollberger, Schneider, & Finsterer, 2003).

Three-dimensional computed tomography (CT) and magnetic resonance imaging (MRI) have been the mainstay for defining the PV antra. However, these modalities do
not provide real-time images that allow for better visualization of the PV antra and more controlled manipulation of the two catheters involved in the procedure (Kanj et al., 2007; Stollberger et al., 2003). Intracardiac Echocardiography (ICE) provides both 3-D images of the PV antra and surrounding structures, and real-time updates of catheter position along the PV antrum-LA junction (Kanj et al.). When doing procedures using ICE, research has shown an increase in success rates and a significant decrease in complications. ICE allows for a gradual increase of energy delivered avoiding overheating, indicated by microbubbles, and more accurate catheter placement (Stollberger et al.). To aid in the visualization of the catheter location with regards to the PV antra, a mapping technique, known as the CARTO system, is used. The CARTO system creates atrial activation maps that relate an anatomical location to an electrical potential. In the past, mapping was performed using fluoroscopy in combination with analysis of electrograms, but the resolution is limited and requires exposure to radiation. The CARTO system uses a mapping catheter, with a sensor in its tip, which automatically records an electrogram and determines the three-dimensional coordinates. This information is transferred to the mapping system, generating a three dimensional, color coded map of the heart chamber with relevant electrophysiological information in real time (Gonzalez-Torrecilla et al., 2004).

Before any PVAI procedure, careful measures must be taken in regards to individual clotting times. Anticoagulation protocol requires patients to be fully anticoagulated with an INR of 2 to 3.5 prior to the procedure. Before transseptal punctures, a heparin bolus (100-150 units/kg) is given and then the patient is maintained on a heparin infusion rate of 15-20 units/kg to keep clotting time between
350-450 seconds. PVAI is performed through two transseptal punctures, located in the interatrial septum, using two catheters. A circular mapping catheter is placed at the PV antrum-LA junction, using ICE, and an ablation catheter delivers radiofrequency (RF) energy to the potentials targeted by the mapping catheter. The amount and duration of RF energy delivered to the sites is completely dependent upon the potentials being ablated. The mapping catheter is then moved to a different site along the junction and RF energy is again delivered; this process continues until the entire PV antrum-LA junction is ablated. The procedure is considered to be complete when electrical isolation of all PV antra is achieved, which can be determined by entrance or exit block. Entrance block is the lack of surrounding potentials reaching the inside of the PV antrum and exit block is shown by dissociated PV potentials that never reach the surrounding tissues of the LA. If complete isolation is not achieved, conduction gaps along the PV antrum-LA junction are checked for activity and ablated. Other areas ablated during this procedure include the posterior wall and roof of the LA. These sites are of importance, as they connect the remaining portions of the left and right PV antra (Kanj et al., 2007).

Atrial-Esophageal Fistula: A Complication of Catheter-based Ablation Procedures

Although very rare, there are some major complications associated with catheter-based ablation of AFib. One quite serious complication is atrial-esophageal fistula formation, which carries a very high mortality rate. This occurs most often after extensive ablation over the posterior LA, which lies just anterior to the esophagus. Multiple strategies have been implicated in order to avoid esophageal injury, however only a few have proven to decrease the occurrence of esophageal damage.
As described previously, the CARTO mapping system is a superior technique to CT and MRI to display real-time imaging of the LA anatomy during catheter ablation. However, esophageal anatomy should be incorporated into this mapping technique in order to provide a 3-D view of the LA-esophageal relationship (Sherzer et al., 2007). Real-time visualization of the esophagus during catheter-based ablation procedures using barium swallows may help prevent lesions placed near the esophagus (Ripley et al., 2007). In a study performed by Sanchez-Quintana, Cabrera, Climent, Farre, and Mendonca et al. (2005), the esophagus is described as a muscular tube, 23-26 cm long, which runs between the trachea and vertebral column, continues behind and right of the aortic arch and down to the right side of the thoracic aorta. In its inferior course, it bends to the left and crosses in front of the aorta to enter the abdomen through the diaphragm. In regards to the portion of the esophagus closest to the LA, its length was found to be 42±7 mm and width was 13.5±5 mm. The minimal distance measured between the esophagus and the posterior LA wall ranged from 3.3 to 13.5 mm and in 40% of the specimens, this distance was <5 mm. The average thickness of the esophageal wall, closest to the posterior LA, ranged from 1.5 to 4.5 mm (Sanchez-Quintana, Cabrera, Climent, Farre, Mendonca et al.). From these results, it can be understood that imaging that can evaluate the esophagus and posterior atrial wall thickness will significantly decrease the probability of this complication.

Other methods used to prevent esophageal damage include reduction of the RF power settings and alternative posterior wall lesion locations. Because of the anatomic variation of the esophageal course and the assumption that lower power or temperatures are safer and also effective, Cummings et al. (2005) systematically
evaluated the anatomy and temperature change of the esophagus during RF ablation. From their studies, data shows that a more accurate predictor of esophageal temperature is the presence of microbubbles. When power was limited with the appearance of microbubbles, no esophageal damage was seen. Therefore, multiple lesions were made at the highest power (70W) without complications. It has been recommended that lesions made on the mid posterior wall of the LA should, instead, be made near the roof, where the wall is thicker. However, this change may not guarantee avoidance of the esophagus or efficacy of the procedure (Cummings et al.).

With the aforementioned modifications, evidence shows that continuously monitoring the position of the esophagus using the CARTO mapping technique and restricting RF temperatures based on the presence of microbubbles will help to eliminate the potential risk of esophageal fistula formation.

**Future of AFib**

“The frequency with which AFib is reported on death certificates as a contributing cause of death has increased since 1980. To assess the burden of AFib-related deaths and hospitalizations among U.S. residents, CDC analyzed national and state multiple-cause mortality statistics and Medicare hospital claims for persons with AFib in 1999 (the latest year for which data were available) for the 50 states and the District of Columbia. The findings indicate that AFib as a contributing cause of death and hospitalization affects primarily persons aged ≥75 years and that death and hospitalization rates vary by state” ("Atrial fibrillation as a contributing cause of death and Medicare hospitalization--United States, 1999," 2003). Mayo clinic researchers
conducted a recent study that predicts an AFib epidemic. The study found the incidence of AFib increased by more than 12 percent between 1980 and 2000. Based on this data, the study estimates that 5.1 million Americans currently live with AFib. At the current rate, the number of Americans living with AFib will rise to 16 million by 2050 (Miyasaka et al., 2006).

Despite proven pharmaceutical, medical device, and interventional treatments for AFib, we are not effectively treating these patients. A study from Rand institute suggests that up to 75 percent of AFib patients do not receive appropriate care. For example, Warfarin is recommended by the American College of Chest Physicians for people with AFib who are at the greatest risk of stroke. Yet from 1997-1999, 45 percent of hospitalized patients with an irregular heart beat did not receive blood thinning drugs to reduce their risk of having a stroke (Leatherman & McCarthy, 1999; McGlynn et al., 2003). A 2005 survey, conducted by The Heart Rhythm Foundation, of habits of Heart Rhythm Society members and non-member cardiac electrophysiologists was conducted in order to understand their practices concerning the treatment of AFib and their use of ACC/AHA/ESC guidelines. This survey found that while the majority of physicians are aware of and agree with the guidelines, they often do not follow them. In 2006, updated AFib guidelines were released by the American College of Cardiology, the American Heart Association, and the European Society of Cardiology (ACC/AHA/ESC) in order to change practice patterns. Also in effect, The Society proposed The AFib CME Outcomes Campaign, which tracks changes in physician behavior attributed to continuing medical education. This campaign follows participants into their practices to
assess changes in decision-making and patient management and includes the updated AFib guidelines.
Conclusion

Extensive research, performed by many individuals, has shed light on the most important yet least understood areas of AFib. The anatomy of the LA and PVs is very complex, highly variable, and is responsible for initiation of this common arrhythmia. Although there are multiple ways to approach AFib, research has shown that treatment via catheter ablation and surgical maze procedures are far more efficacious methods. Before any ablation procedure, electrophysiology studies need to be obtained in order to identify the exact location of the arrhythmic foci in the heart that needs treatment. RF ablation can provide an important therapeutic option for patients with highly symptomatic and medically refractory AFib. However, the procedure can be complicated by the rare, but serious occurrence of atrial-esophageal fistula. Localization of the esophagus using the CARTO mapping system provides a continuous 3-D view of the atrial-esophageal relationship and therefore significantly lowers the risk of this complication.

Future directions of AFib indicate that there is room for improvement in regards to this common, yet complex arrhythmia. New developments in treatment modalities have already shown significant improvement in the outcomes of AFib and therefore give hope that further research and developments will provide insight into making this arrhythmia a less common occurrence.
References


Figure 1. The common pattern of the superficial myocardial fibers of the left atrium (posterior aspect). Reprinted from “The junction between the left atrium and the pulmonary veins. An anatomic study of human hearts,” by H. Nathan and M. Eliakim, 1966, Circulation, 34, p. 413. Copyright 1966 by Lippincott Williams & Wilkins. Reprinted with permission.

LA= left atrium; RA= right atrium; SVC= superior vena cava; IVC= inferior vena cava; RSPV= right superior pulmonary vein; LSPV= left superior pulmonary vein; RIPV= right inferior pulmonary vein; LIPV= left inferior pulmonary vein.
Figure 2. Image of a trans-illuminated right atrial appendage showing partially the crista terminalis (CT), the pectinate muscles (PM) and the floor of the right atrium (RA).
Figure 3. Magnification of pectinate muscles
Figure 4. Image of the right atrium showing the fossa ovalis (FO), part of the Tricuspid valve (TV) and the valve of the inferior venae cava (IVC).
Figure 5. Image of the right atrium showing the region of the AV node (circle). Observe the fossa ovale (FO), the valve of the inferior venae cava (IVC) and the valve of the coronary sinus (CS).
Figure 6. Image of a trans-illuminated left atrial appendage of a plastinated human heart viewed from the left atrium (LA)
Abstract

**Objective.** This review presents the most recent information regarding the morphology of the human heart, with emphasis on the atria and how it relates to the mechanism, morphology, and electrophysiology of AFib. **Methods.** Articles for this review were accessed through PubMed, Access Medicine, UpToDate, and American Heart Association. **Results.** Fifty six articles were reviewed for morphological and clinical applications of AFib. These articles covered the study of atrial structure, its fiber arrangement and the cardiac conduction system; guidelines for management of AFib patients; complications of surgical procedures, and future directions of AFib management. Various treatment modalities for AFib were also compared on the basis of safety and efficacy. **Conclusion.** Multiple ectopic foci, contributing to AFib, exist in the fibers surrounding the pulmonary veins. Catheter ablation techniques have been created as a safer alternative to the Cox-Maze procedure and are used to isolate the PVs in order to treat AFib.