This paper reviews some of the major advances made in experimental and clinical studies that provided insights into the mechanisms of sustained and stable atrial flutter in man (AFL).

**Early Experimental Findings**

John Alexander MacWilliam in 1887 was probably the first to describe the abnormal atrial rhythm known as atrial flutter. His work opened the way of correlating clinical electrocardiography with the actual visualization of the abnormal beating in the hearts of experimental animals. In his 1887 article in the *Journal of Physiology* he described the electrically-induced atria arrhythmias this way:

"The application of the current sets the auricles into a rapid flutter, the rapidity of which largely depends upon the excitability of the auricular tissue and the strength of the current employed. The movements are regular; they seem to consist of a series of contraction originating in the stimulated areas and then spreading over the rest of the tissues. The movement does not show any distinct sign of inco-ordination, it looks like a rapid series of contraction waves passing over the auricular walls." [1]

McWilliam also tested the influence of vagal stimulation on AFL and found that "the fluctuating movement of the auricles can be checked or arrested by the influence of the vagus nerve." [1]

Most interestingly, McWilliam was perhaps the first to observe an association between cardiac mechanical and electrical activity in the maintenance of an arrhythmia: "The vagus influence appears to act by weakening the individual contractions [of the atria] to the point of invisibility." [1]

It was clear from the MacWilliam’s work that AFL was a rapid (~300 to 400 beats/min) yet a regular rhythm that could be sustained over the atria causing rapid and regular series of contractions. When Einthoven first introduced the ECG recording technique in man in 1906, he made an actual electrocardiographic recording of AFL. [2] However, it was Sir Thomas Lewis 1909 who recorded a case in a dog of AFL alternating with atrial fibrillation (AF) that he called "auricular paroxysmal tachycardia." [3] It was only in 1911, that Jolly and Ritchie applied the term "auricular flutter" to the clinical arrhythmia in man and described the characteristic "sawtooth waves" in the inferior ECG leads. [4] Two years later, Sir Thomas Lewis established the diagnostic criteria of electrocardiographic of AFL as "the restless, sawtooth baseline" now known as the F waves, which today are recognized as the principal criterion for the diagnosis of AFL in man. [5]

The recognition and the electrocardiographic description of this arrhythmia led to intense efforts to determine the mechanism of the AFL that still continues today. It was in 1920 that Lewis and his colleagues provided the first mechanistic insight into the reentrant excitation pattern causing AFL that in many ways is still valid today. Lewis’ original description of the AFL reads as follows: "A main excitation wave is propagated through the fluttering auricles via a narrow circular pathway embracing..."
the two venae cavae; the main wave pursues a unidirectional course and re-enters the original pathway upon the completion of each circuit.”7,8) However, the AFL that Lewis and his colleagues induced was short-lived and the number of recording electrodes limited, this necessitated much extrapolation for the full and complete reconstruction of the reentrant pathway in the atria.

Further insight into the potential mechanisms of AFL was later provided by the important experiments of Brams and Katz in 1932 who have caused surgical separation of the dog’s right and left atria and demonstrated that AFL could still be induced either in the isolated right or the isolated left atrium.9) These studies were aimed at determining if a single and unique right or left atrial focus (reentry or otherwise) was responsible for causing AFL. These authors concluded that: “Such results are obviously incompatible with any theory that flutter or fibrillation in heart is due to a single focus or a single circus ring sending centrifugal waves into the other auricles.”9)

In all of these previous experiments AFL was induced by Faradic shocks in otherwise normal atria. AFL induced in this way was short lived. This clearly limited investigators because detailed studies of the arrhythmia requires long periods of stable AFL to allow detailed activation mapping to be made. This necessitated efforts to develop animal models that promote long lasting and stable AFL. Motivated by the desire of maintaining the AFL for longer duration and better characterization of the mechanism and sequence of activation during the AFL, Rosenblueth and Garcia Ramos created a surgical lesion between the SVC and IVC. They showed that there was no need for the obstacle to be anatomic. They created functional conduction block between the IVC and the SVC by topical application of the local anesthetic, cocaine and showed that the circus movement activation around either the functional site of block (local cocaine-induced) or crush injury (surgical incision) could still induce AFL.10) They concluded that all that was required to initiate AFL was the presence of conduction block of the activation front across the crista terminalis, perpendicular to the IVC-SVC axis, which could then propagate by either clockwise or counterclockwise direction around the crista causing AFL. These authors also demonstrated that the AFL could be entrained or terminated by electrical pacing and also could be terminated by crushing the isthmus over the tricuspid valve (TV) annulus.10) In addition these authors presented evidence that a portion of the pathway extended along the crista at the caval junction with the right atrial free wall, by showing that extending the lesion across this region increased the flutter cycle length. In other experiments, when they made an incision extending from the intercaval lesion across the crista all the way to the AV ring, AFL stopped and could not be reinitiated. Finally, these authors showed that the AFL cycle decreased by the administration of adrenaline and to a lesser extent during vagal stimulation.10) Clearly, the slight acceleration of the flutter rate with vagal stimulation, was an argument against automatic mechanism for the AFL because vagal activation is known to slow and inhibit all forms of automatic activity. However, the portion of the presumed reentry pathway over the posterior wall of the left atrium was not observed by later similar experiments by Kimura et al. (1954), Takaysau et al. (1958) and Hayden et al. (1967). These authors demonstrated progressive delay of activation times over the left epicardial surface, a finding that does not prove that this activation sequence represents wave propagation in a portion of the primary reentrant circuit.11)

The issue of a focal perhaps an automatic mechanism as a cause of AFL was rigorously promoted by Prinzmetal and associates in 1950. These authors using high speed cinematography (up to 2,000 frames per second), cathode-ray oscilloscope and multiple-channel electrocardiography insisted that AFL occurs from one ectopic focus and dismissed circus movement reentry as a mechanism of AFL.12) A major cause of this seeming discrepancy (focal vs. circus movement) stems from the fact that Prinzmetal and associates used local injection of aconitine to induce AFL. Aconitine is a drug that prevents sodium channel inactivation causing repetitive depolarizations of the kind of early afterdepolarization-induced triggered activity. According to their original description: “When auricular flutter is produced by applying aconitine locally at the center of the wall of the right auricle, the contraction waves are seen to originate at the ectopic focus in a perfectly rhythmic manner, and to spread over the
auricles in all directions at once. It thus appears clear that the mechanism of auricular flutter is not a circus movement; for if it were, the contraction wave would have to pursue a unidirectional path around the cavae. The films show that this is not the case; each contraction wave takes its origin at an ectopic focus, and, instead of traversing the auricles in a single direction, actually spreads from the focus simultaneously in all directions. The visual observations disprove the circus movement theory of auricular flutter and establish the tree nature of the auricular tachycardia.”12) While it is possible that aconitine-induced AFL may be focal it is however unlikely that this AFL model is the clinical counterpart of all forms of AFL in man.

Recent Findings

A case can be made for focal mechanism for some types of human AFL as increasing evidence supports the idea that the myocardial cells in the atrial venous system manifest increased susceptibility to afterpotentials and triggered activity. In such cases rapid focal activity may conceivably cause AFL-like activity should triggered activity remain stable and supported by a single wavefront. The work of Rosen and his associates in 1969 demonstrated that pacing from the coronary sinus at rates similar to the AFL rate mimicked AFL in man.13) This isolated finding was of some interest because of the later demonstration by Wit and associates14) that the cardiac fibers in the canine coronary sinus may initiate triggered activity at rates that might drive the atria rapidly simulating clinical AFL. It is therefore possible that under certain conditions focal activity, such as triggered activity in the coronary sinus, might be a mechanism for at some types of AFL in man.

The mechanism of AFL in humans was studied more extensively by Puech and his collaborators in 1970 at Montpelier Clinic in France. Using esophageal and atrial endocardial activation mapping with multipolar (ten) electrode catheters, this pioneering study, reporting experience on 55 patients over a 15 year period (1955 to 1970) provided much insight into the mechanisms of AFL in man.15) These authors defined AFL as an atrial rhythm at rates ranging between 230 beat/min to 330 beat/min (atrial cycle lengths of 260 ms to 180 ms) and associated with 2:1 or higher degrees of AV block.15) These authors first dismissed Prinzmetal’s focal theory of AFL as being of an “extremely simplistic character” and asserted with their mapping data that the most commonly occurring AFL in man resulted from a reentrant waves of excitation in the right atrium that rotated counterclockwise along the crista terminalis.15) These authors also found the less common form of AFL (only one case) in whom the rotation of the reentrant wavefronts was clockwise.15) The occurrence of AFL with a focal mechanisms or reentry located in the left atrium was rather a rare phenomenon in Puech’s report.15) Attempts to terminate AFL with pacing failed in the hands of these French investigators, perhaps due to the application of relatively low current strengths of stimulation.16) Pacing at rates faster than the AFL rate converted the AFL to AF in few cases with subsequent (minutes to hours later) resumption of the original AFL.15) With the report of Puech and associates it became clear that macro-reentry in the right atrium is a common mechanism of AFL in man. More thorough endocardial mapping of human type 1 atrial flutter was carried by Feld and associates.17) These authors using catheter ablation technique, endocardial mapping and entrainment pace mapping during AFL (mean cycle length of 253 ± 39 msec) determined the critical site for the maintenance of AFL in order to ablate it and cure the arrhythmia. The critical site of the reentry circuit consisted of an area of slow conduction, and the exit site from the area of slow conduction. These authors found a counterclockwise reentrant wave during the AFL that originated just inferior or posterior to the coronary sinus ostium, proceeded superiorly in the atrial septum to the right atrial free wall, then inferiorly toward the tricuspid annulus and finally medially between the inferior vena cava and the tricuspid annulus, where low-amplitude fragmented electrical activity was noted. Entrainment pace mapping from this area produced an exact P wave match to atrial flutter on 12-lead ECG with a long (greater than 40 msec) stimulus-to-P interval indicated slow conduction, whereas pacing just inferior or posterior to the coronary sinus ostium produced an exact P wave match with a short stimulus-to-P interval (less than 40 msec), presumably identifying the exit site from the area of slow conduction. Radiofrequency ablation of this critical site terminated and prevented the reinduction of AFL in 70 per cent of the patients. Sites where ablation was successful, were located just inferior or posterior to the coronary sinus ostium and were characterized by discrete electrograms with activation times of −20 to −50 msec before P wave onset and exact entrainment pace maps with a stimulus-to-P interval of 20 to 40 msec, consistent with the exit site from the area of slow conduction.17) These authors concluded that radiofrequency energy applied to a critical area in
AFL reentrant circuit, inferior or posterior to the coronary sinus ostium, terminates and prevents arrhythmia reinduction.17) Similar findings were also observed by Cosio and associates18) who have shown that radiofrequency ablation of the inferior vena cava-tricuspid valve isthmus was an effective procedure in terminating and preventing reinduction of in common AFL in humans.

The Era of Computerized Mapping

Since the 1980s when computer-assisted cardiac mapping technology became available and when newer animal models of AFL were developed, detailed analysis and greater insight of AFL mechanism became possible. A prelude to AFL studies using a large number of electrodes was first made by Boineau and associates in a dog with spontaneous and inducible AFL resembling typical and atypical human AFL. Using up to 96 epicardial atrial bipolar electrodes these authors not only mapped the sequence of activation during AFL but also constructed maps of refractory period distribution of the mapped atrium. These studies concluded that AFL was caused by a circus conduction pattern on the free wall of the right atrium and was the result of a nonuniform bimodal refractory state of the atrium that simultaneously exerted a blocking effect while permitting conduction and complex shaping of the unblocked wave, which was routed back to the its site of origin.19) These authors further concluded that for AFL to occur three interacting factors were necessary: first, an ectopic atrial beat, second, nonuniform distribution of atrial refractory periods characterized by a bimodal distribution with close proximity of the regions of longest and shortest refractory periods, and three, slow conduction of the wave initiated by the ectopic atrial beat.19) According to these authors, the paroxysmal nature of the AFL was related to the changing nature of atrial refactororiness (dynamic heterogeneity) and atrial ectopic activity which in these authors words “are extremely labile and influenced by multiple secondary factors and tertiary factors” like the “autonomic nervous system” and “a particular distribution of the refractory field.”19) Boineau later refined his assessment of AFL mechanism and gave a primal role to the tricuspid annulus in the reentry by stating: “The tricuspid annulus forms an integral anterior component of the circular reentrant surface.”20)

The study by Hoffman’s group at Columbia University of the circular movement during lesion-based stable AFL, confirmed some of Boineau’s findings, i.e., the role of the anterior tricuspid annulus as a component of the reentry circuit. However, perhaps most importantly their study cast a whole new way of interpreting the mechanism and the primary location of reentrant activation by introducing the phenomenon of outward secondary spread of excitation from a primary focus or “rotor” a term later coined by Winfree.21) In this respect Frame et al. in a series of elegant Y-lesion based experiments, originally introduced by Reesebthough and Garcia Ramos, have shown both in intact hearts and in isolated tricuspid ring preparations in vitro that the induced AFL was caused by a reentrant impulse that circulated around the tricuspid valve orifice in either a clockwise or counter-clockwise direction.11,22) The Y-shaped lesion in the Frame et al studies was caused by one incision made between the cava and the second lesion, connected to the first, extended intro a portion of the free wall of the right atrium.22) These authors found no discrete segment of markedly slow conduction in the reentrant circuit around the ring and cutting a portion of the ring terminated the rhythm and prevented its reinduction. Most interestingly the reentry, albeit at slower rate, was also induced in atrial tissue surrounding the tricuspid orifice when this structure was isolated and superfused in vitro.11) This study introduced a new concept of the pattern of reentrant excitation, originally described in chemical reactions by Winfree.23) According to this dynamic scenario rotation around a relatively small core (functional or anatomical) sends an outwardly propagating wave that envelops a larger body of atrial tissue giving the impression of a larger (primary) reentrant circuit than the actual primary size of the reentry (see Figure 1). This scenario is also depicted schematically based on our own observations on reentry in ventricular tissue around a core of functional block which is remarkably similar to Frame’s ring tissue reentry around a core of anatomical block (Figure 2). A variant of Frame’s model was introduced Feld et al.24) who have shown that a single linear incision between the IVC and SVC (“crush injury”) could cause circus movement activation around the obstacle created between the cavae causing AFL in the in situ canine hearts. These authors did not suggest reentry to be sustained around the tricuspid ring as was suggested by Frame et al. A possible explanation of the difference between these two studies, as suggested by Frame et al., may result from the ability of the Y-shaped lesion to provide a “protective barrier” for the impulse to travel around the ring, which these authors insisted was the primary anatomical obstacle around which the wave circulated. The “secondary” lesions caused by the Y-
incision served, according to these authors, as pure protective barriers to prevent short-circuiting and/or premature interruption of the reentrant activation.\(^{11,22}\) A new model of canine AFL was developed in 1986 by Waldo and associates using the method of postpericardiotomy pericarditis.\(^{25}\) Using sterile techniques, the pericardium was opened by way of a right thoracotomy, the atrial surfaces were generously dusted with talcum powder and a single layer of gauze was placed on the free left and right atrial walls. The dogs were allowed to recover and AFL was readily induced in this model in the conscious, nonsedated state. These authors using 372 unipolar electrodes arranged in 186 bipolar pairs concluded that AFL was caused by a reentrant excitation that always included a septal component, did not always require a right atrial free wall reentrant circuit and was associated with a line of functional conduction block in the right atrial free wall.\(^{16,26}\) The tricuspid ring annulus was not the primary site of rotation during AFL in Waldo’s model. These authors further showed that that a positive flutter wave in ECG lead II (counterclockwise circus movement) was associated with early activation of the Bachmann’s bundle and activation of a considerable portion of the left atrium in an inferosuperior direction (clockwise circus movement).\(^{27}\) The studies of Waldo’s group on sterile pericarditis and that of Boineau’s in a dog with naturally occurring AFL emphasized that myocardial discontinuity between the caval orifices and slow conduction form together the principal obstacle around which the flutter wave circulates and were considered by these investigators to play a decisive role in the maintenance of AFL.

The functional reentrant excitation in atrial tissue first described by Allessie et al. known as the “leading circle”\(^{28,29}\) is in line with subsequent developments and elucidation of the mechanism of functional reentry that became also known as “rotor”\(^{21}\) or “spiral wave.”\(^{30}\) We found that functional reentry in atrial tissue is also consistent with the spiral wave mechanism of excitation with an excitable but non-excited core.\(^{31}\) The spiral wave once induced is often unstable and moves from one site to another (meandering)\(^{32}\) with a tendency to anchor to an anatomical obstacles of suitable size (i.e., equal or greater than 10 mm diameter).\(^{33}\) Smaller sized obstacles were ineffective in causing stable spiral attachment.\(^{33}\) In this respect it is possible that in the Frame et al. studies a reentrant wavefront could have been induced in the first place.

Figure 1

A, activation map of a clockwise activation sequence around the tricuspid orifice during one beat of sustained AFL at a cycle length of 158 ms. Note the sequential activation of sites that encircle the tricuspid orifice (TO) shown in wide arrow around the TO. Note the presence of centrifugal spread of activation away from the tricuspid orifice. There was a secondary wavefront that traveled superiorly on the aortic surface (thin arrow at top) and then across the free wall of the right atrium (thin arrow at the bottom) where it encountered another wavefront spreading from the tricuspid ring toward the right atrial appendage. B, map of a counterclockwise activation sequence around the tricuspid orifice during one beat of AFL later in the same experiment as in panel A. A secondary wavefront spread away from tricuspid ring in the right atria free wall toward the appendage near the transverse portion of the y-shaped lesion. It encountered another wavefront that had emerged from the tricuspid ring area on the aortic surface and spread over the superior portion of the right atrium. (from Ref 11)
during programmed stimulation and that such a spiral could have anchored around the tricuspid ring, that is typically larger than 10 mm in diameter,\textsuperscript{11)} causing stable spiral attachment rotation around the ring. When this happened an outward spread of the front from the ring took place giving the impression of a larger macroreentrant circuit. Consequently, it is likely, at least during some of the episode that the AFL model induced in the Y-lesion configuration may cause AFL by reentry around the ring as the primary site of the reentry. Most importantly however and with much clinical impact, whether full rotation occurs around the ring or it occurs fully around the crista, both of these circuits have a common atrial anatomical path located between the IVC and the tricuspid ring, the right atrial isthmus. This isthmus is a critical part of the AFL reentry circuit regardless of the primary location of the reentry (ring vs. crista) as its disruption is associated with termination of AFL and inability to reinitiate it. In the Y-shaped lesion model of canine AFL, a suggested counterpart of the common AFL in man\textsuperscript{34})

\begin{figure}
\centering
\includegraphics[width=\textwidth]{diagram}
\caption{Diagrams showing generation of spiral excitation morphology. A dot in A denotes the earliest activation near the core that propagates tangentially and sequentially around the core and completes a full rotation A to F, to start again as in A. The rest of the tissue is activated secondarily by the rotating front around the core which now propagates in an outward direction (panels B to F). Spiral morphology (curved front) can be visualized by connecting the activation dots (lower panels). (Modified from Ref 61)}
\end{figure}
interruption of the anterior portion of the ring (isthmus) caused termination of the AFL. 34)

Boyden introduced a different model of AFL associated with chronic right atrial enlargement, atrial hypertrophy and increased interstitial atrial fibrosis. These structural abnormalities were induced by surgically creating tricuspid regurgitation and banding of the pulmonary artery in the dog hearts. 35,36) Using 192 pairs of recording electrodes the total endocardial activation of both atria during electrically-induced AFL were determined. Reentrant pattern of activation, in either clockwise or counterclockwise pattern were demonstrated during episodes of induced stable AFL. An area of functional block was found to be necessary as an essential component of reentry in this canine model of inducible AFL with structurally remodeled hearts. 36)

Miyauchi Canine Model of AFL

While most if not all previous experimental AFL relied on surgically creating lesions in order to induce stable, long lasting AFL, much of the mechanisms of AFL in man, perhaps with the exception of AFL in some post-op patients, is functionally based and often does not involve anatomical lesions. We recently developed a new model of AFL that resembles the common type of AFL in man without causing surgical lesions. In this model, using high resolution electrode mapping technique in the in situ hearts we discovered that the “natural” evolution of chronic ventricular myocardial infarction and chronic nicotine administration promotes intense right atrial interstitial fibrosis. This leads to flattening of the atrial electrical restitution curve which leads to stable and sustained reentry around the crista terminalis causing AFL and often requiring electrical shock for termination. Because of the great similarity of AFL in this model to human AFL, both in terms of mechanism and response to pacing and catheter-based RF ablation of the right atrial isthmus, we will describe this model in some detail.

The Rational of the Model

Epidemiological studies have shown that smoking promotes myocardial infarction and is a major cause of chronic obstructive pulmonary disease (COPD) in the U.S. 38) COPD is shown to be an independent predictor of AFL. 39) Since nicotine is a major constituent of tobacco smoke and an agent thought to be the culprit of cardiac arrhythmias, we tested the hypothesis that the combined presence of chronic myocardial infarction (MI) and nicotine promotes AFL in intact canine hearts. MI was created by ligating the left anterior descending coronary artery just distal to the first diagonal branch as described by Miyauchi et al. 41) In the second group after creating an MI, mini osmotic pumps were implanted s.q. to continuously deliver 5 mg/kg/day of nicotine for a one month period. This dose of nicotine corresponds to the daily intake of nicotine by heavy smokers. 42,43) In the third group, thoracotomy was performed and two nicotine loaded pumps implanted s.q. with no MI and finally a fourth group received no surgery and no nicotine.

AFL Characteristics

Vulnerability to AFL was tested by programmed electrical stimulation and the resultant arrhythmia was mapped epicardially using 1,792 bipolar electrodes distributed over four plaques (1.5 by 2.7 cm) with a spatial resolution of 1-mm. 41) The plaques were placed on both atrial epicardial surfaces. Two plaques were sutured side by side on the right atrial free wall (RAFW) and the crista terminalis (CT) region. The third was sutured on the LA free wall (LAFW) and the fourth, in the isthmus area encompassing the inferior vena cava (IVC) and the tricuspid annulus (TA). We also did simultaneous epicardial (1,792 electrodes) and endocardial (Halo catheter with 20 electrodes) mapping during ablation of the AFL with radiofrequency energy (30 W for 30–60 s). Atrial monophasic action potentials and electrical restitution curves were constructed using the dynamic pacing protocol. 37,41) The results have shown that either burst or atrial pacing at CLs of 200–150 ms induces sustained AFL at a mean CL of 134 ± 10 ms in the MI dogs exposed to chronic nicotine administration (Figure 3). The induced AFL had the characteristic sawtooth appearance on ECG lead II (Figure 3). The AFL lasted for more than 30 min requiring electrical cardioversion for termination. Pacing the atria at CLs shorter (114 ± 9 ms) than the CL of the AFL however could also terminate the AFL (Figure 3). Ability to prematurely capture the AFL with subsequent termination indicates the presence of an excitable gap in the AFL circuit. No AFL could be induced in any of the dogs in the remaining 3 groups. Figure 4 shows the dynamic atrial activation pattern: 1) during sinus rhythm, 2) during atrial pacing and 3) during an induced sustained AFL in a dog with MI and exposed to chronic nicotine administration. During sinus rhythm (Figure 4A), the activation propagates from the upper towards the lower RA and fully activates the entire RA without undergoing conduc-
tion block. The IVC-TV isthmus area and the LA are then activated some 25 ms after the onset of the sinus beat. During RA pacing from the left side of the sinus node (Figure 4B), the wavefront after activating the left side in the RAFW (left side pointing arrows in Figure 4B) also propagates in a SVC-IVC direction as is the case during the sinus beat. During AFL however, (Figure 4C) reentrant activation was observed in the RA. The activation first propagated in the SVC-IVC direction with a line of conduction block, along the CT (downward arrows in Figure 4C). The CT is clearly acting as a functional “obstacle” in this case. Propagation then proceeded across the isthmus activating the LA. The wavefront then propagates upward in the IVC-SVC direction through the region of initial block (upward arrows in Figure 4C) completing a reentrant cycle. The reentrant cycle then repeated itself through the exact same pathway during the AFL. Figure 5 illustrates the isochronal activation map shown dynamically in Figure 4 along with selected electrograms. During AFL the activation wavefront in the SVC-IVC direction, blocked across the crista (Figure 5A), then propagated through the isthmus (Figure 5B) and the LA (Figure 5C). Activation then proceeded in the IVC-SVC direction along the crista completing a full rotation. The electrograms around the line of functional conduction block showed double potentials (Figure 5D) consistent with recordings made in the center of the reentrant circuit seen both in dogs and in human common AFL. The double potentials represent sequential activations when the reentrant wavefront passes on either side of the line of conduction block as shown in the electrograms q, r, s, and t in Figure 5D. The mean length of the line of functional conduction block in the six dogs was 1.46 ± 0.5 cm. The induced AFL was clockwise in 20 episodes (60%) with a positive sawtooth and counterclockwise in 14 episodes (40%), with a negative sawtooth on lead II ECG mimicking common type of AFL in humans (Figure 6). Endocardial mapping during the AFL with the Halo catheter during sustained AFL showed both clockwise, with a positive sawtooth on the ECG (Figure 6A) and counterclockwise, with a negative sawtooth on the ECG (Figure 6B) rotations around the CT. This
observation is consistent with functional conduction block across the crista. RF ablation of the isthmus terminated the AFL and AFL could no longer be induced. The maximum slope of the action potential duration restitution curve was significantly higher in both atria in the MI group compared to the remaining three groups. Nicotine exposure in the MI dogs caused a significant flattening of the maximum slope of the MAPD restitution curve of both atria compared to other three groups. No significant differences in the effective refractory of the right or left atrial could be detected amongst the four groups. Nicotine exposure in the MI dogs caused a considerable and highly heterogeneous increase in interstitial fibrosis in both atria (Figure 7). The increase was significantly higher in the right (up to ten fold) than in the left atrium (two fold). Bundles of myofibers in the atria and the isthmus region of dogs isolated from the MI plus nicotine group were packed less tightly than in the atria of the remaining three groups and were separated by thick layers of fibrous tissue, indicating reactive rather than replacement fibrosis. In contrast to normal collagenous structures, which have an “organoid” parallel arrangement of relatively broad bands of collagen fibers, abnormal interstitial fibrosis consisted of haphazardly arranged, disorganized, fine collagen fibers (Figure 7). The mean ventricular infarct size, with no atria involvement in the process of infarction, was 14 ± 6% of the LV mass in the MI group (not significantly different from the MI plus nicotine group). Atrial chamber size was not significantly different in all four groups. These results show for the first time the initiation of typical, isthmus-dependent, reentrant AFL in dogs without causing surgical lesions (Y-shaped of IVC-SVC crush injury) or inflammatory injury (sterile pericarditis). The combined treatment, healed MI and chronic nicotine exposure were sufficient to bring about the necessary pathological substrates for the induction of a stable and sustained AFL that bears three characteristic resemblances to human common AFL. 1) isthmus-
dependency of the single reentrant wavefront in the right atrium that supports the AFL; 2) the presence of an excitable gap (evidenced by electrically capturing and terminating the AFL) and 3) the presence of functional conduction block across the CT. It was of interest to find that nicotine induced considerable increase in atrial interstitial fibrosis in MI dogs but relatively mild increase with nicotine in dogs with no MI despite similar nicotine blood levels in both groups that were within the range seen in smokers.46) Since nicotine could modulate growth factor production in fibroblasts47) and endothelial cells,48) it is suggested that nicotine’s atrial fibrotic effect in MI dogs may be mediated through cardiac fibroblastic growth factors, such as bFGF and the transforming growth factor beta-1 (TGF-β1).49) which are typically elevated during MI.49–51) Collagen deposition may slow conduction thus allowing the presence of an appreciable tempo-spatial excitable gap52) in the AFL circuit causing the reentry to be stable and sustained with interruption. Another mechanism of stability of the AFL in the chronic nicotine model of AFL is the flattening of the MAPD restitution slope (Figure 8). Nicotine exerts multiple effects on atrial ion channels by blocking outward potassium currents53–55) and exerts variable effects on the inward currents (INa and L-type calcium current) depending on its concentration.55) The net effect of nicotine may thus vary, ranging from no net change, shortening or lengthening of the APD depending on the underlying channel profile (density/conductance) in the remodeled atria.56) Alter-

Figure 5  Isochronal activation maps and selected bipolar atrial electrograms during induced sustained AFL in a dog with MI exposed to nicotine.

Two plaques are located side by side on the RAFW (panels A & E), one on the isthmus (B) and the fourth on the LAFW (C). Reentry proceeds in the SVC-IVC direction (sites a–d), blocks across the CT (dark line in D) and then proceeds in the IVC-SVC direction (sites e–h) (arrows in A and D). Electrograms next to panel D are recorded on the CT and show double potentials (downward arrows). These double potentials represent activation on either side of the line of functional block (electrograms q, r, s, and t) and disappear at sites u and v where no conduction block occurs. (From Ref 37)
natively, nicotine’s flattening effect of the MAPD restitution may not result from direct ion channel effect but rather from the inability of the highly fibrotic right atrial tissue (increased stiffness) to distend (i.e., stretch) at short diastolic intervals. Decreased stretch may decrease APD shortening and thus prevent attainment of ultra short diastolic intervals causing a flat electrical restitution curve.57) The absence of atrial fibrosis in the MI group for example, permits stretch to develop during rapid pacing causing shortening of the APD and thus the attainment of ultra short diastolic intervals. Cardiac tissue with a flat electrical restitution curve does not undergo wavebreak58) while the partial electrical uncoupling caused by the considerable increase in right atrial fibrosis promotes slow conduction59) that increases the excitable gap interval during the flutter. The coexistence of these two electrophysiological properties, uncoupling due to fibrosis and flattening of the restitution curve are of considerable impor-

tance in the formation of stable reentry and provide novel insight into the pathogenesis of a stable AFL without its conversion to AF. The nicotine model of AFL might provide insight into the mechanisms and perhaps the pathogenesis of human AFL, as interstitial fibrosis and flattening of APD restitution curve may develop in a broad spectrum of diseases, including smoking, heart failure, myocardial infarction, and cardiac hypertrophy. To the extent that this model may be representative of human AFL, the combined development of increased atrial fibrosis and flattened atrial electrical restitution curve might be important etiological factors in the pathogenesis of common AFL in man that afflicts some 200,000 patients every year in the US.59)

**Summary and Concluding Remarks**

The experimental insights and the availability of increasing and informative human data on AFL led

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**Figure 6** Endocardial mapping during AFL in a dog with MI and nicotine using a Halo catheter positioned around the CT. Panel A, is a clockwise reentrant AFL at a CL of 136 ms and a positive sawtooth pattern on ECG lead II. B, is during AFL with counterclockwise reentry in the same dog showing negative sawtooth pattern on ECG lead II. Next to each set of electrograms (1 to 10) a schematic diagram shows the locations of the Halo electrodes. CS is coronary sinus and RAA is right atrial appendage bipolar electrogram. (From Ref 37)
us to better understand the fundamental mechanisms involved in the genesis, maturation, and stabilization of AFL. The first step in the development of AFL is the formation of a functional reentrant wavefront, also known as a spiral wave. This functionally-based spiral wave has the potential to meander through the atrial myocardium to either extinguish itself or to find a stable site to anchor. Spiral waves are shown to anchor to anatomical and functional obstacles. For example, a spiral wave can anchor around a critically sized anatomic obstacle not different from the size of the tricuspid ring. Alternatively the spiral can anchor to a structure with intense anisotropic propagation properties, such as the crista terminalis, or around an inflamed tissue with poor electrical coupling. Once attached (anchored) around such sites the spiral wave rotates around it causing AFL. The final step in the emergence stable AFL is the stability of the rotating spiral wave. The presence of slowed conduction through the path of the reentrant circuit allows the reentrant wave front to find fully excitable tissue in its wake as it rotates around the obstacle.

**Future Directions**

It is apparent from these experimental studies that the mechanism of a stable AFL is model-dependent. Each model offers its unique insights and usefulness in understanding the mechanisms of human AFL. Important future research should provide insight into the origin of the spiral wave formation which eventually anchors to an obstacle (anatomical or functional) to cause AFL. What causes the first wavebreak in the atrial tissue to “spontaneously” produce a spiral wave? Waldo et al. found in postoperative patients that common type I AFL did not start immediately after a premature atrial beat. AFL in these patients was found to start after a “transitional rhythm” that was often found to be AF. These authors suggested that a transitional rhythm was required for the initiation of type I AFL. It was further speculated that it was during the transitional
rhythm that the requisites for the development of the AFL reentry circuit evolve causing AFL. These findings indicate that the substrates for the AFL are absent prior to the transitional rhythm but evolve dynamically during the rapid activation of the transitional rhythm which is most commonly caused by AF. Clearly more insight is needed on the relationship between AFL and AF. How AFL may or may not degenerate to AF? Is fibrillatory conduction in human AFL to AF conversion related to electrical restitution? The flat APD restitution slope described in Miyauchi’s model of canine AFL provides a likely mechanism, it however remains to be seen if this mechanism is also operative in humans. If this proves to be true in humans, then we envision a true continuum between AFL and AF with the clinical expression (i.e., typical flutter, coarse flutter, fibrillation) being dependent on the number and course of one or more atrial rotors. It may be reasonable to consider the use of prophylactic AF ablation for patients presenting with crista-isthmus-dependent AFL. While catheter ablation has proved to be a most effective therapy for isthmus-dependent AFL, ablative cure of left atrial circuits (particularly post surgical) is still a major challenge. There is little information on genetic causes of AFL. Young patients with AFL who have multiple family members with the same arrhythmia suggest a genetic basis of AFL, to-date however, no specific genetic mutation associated with AFL has been found. Hence, although much has been accomplished in the field of AFL, clearly much more still remains to be done.

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Figure 8 Monophasic action potential duration (MAPD) restitution curves to 90 percent repolarization (MAPD90) of the RA and LA in control, sham-operated plus nicotine, MI, and MI plus nicotine dogs. Note flattening of the slope of the restitution curve in MI dogs exposed to nicotine. DI is diastolic interval in ms. (From Ref 37)
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