Atrial fibrillation of variable duration precedes the onset of atrial flutter in almost all instances; during atrial fibrillation, the functional components needed to complete the atrial re-entrant circuit, principally a line of block (LoB) between the vena cavae, are formed; if this LoB does not form, classical atrial flutter does not develop. In contrast, there seems to be a spectrum of atrial re-entrant circuits (drivers) of short cycle lengths (CLs) (i.e., atrial flutter). When the CL of the atrial re-entrant circuit is so short that it will only activate portions of the atria in a 1:1 manner, the rest of the atria will be activated rapidly but irregularly (i.e., via fibrillatory conduction), resulting in atrial fibrillation. In short, there are probably several mechanisms of atrial fibrillation, 1 of which is due to a very rapid atrial flutter causing fibrillatory conduction. All of these interactions of atrial fibrillation and atrial flutter have important clinical implications.
The Mechanism of Classical AFL and the Importance of Block Between the Vena Cavae

On the basis of limited mapping studies in normal canine atria (Fig. 1) and vector analysis of electrocardiograms (ECGs) in humans, Lewis (1,2,14) concluded that AFL resulted from re-entry around the great veins. Importantly, these investigators had great difficulty inducing AFL in these normal atria. Subsequently, Rosenblueth and Garcia-Ramos (1,2) appreciated that, to prevent short circuiting of the AFL re-entrant circuit proposed by Lewis (14), an LoB between the superior and inferior vena cavae seemed necessary. They made an LoB between the vena cavae with a crush lesion in otherwise normal canine atria and then reliably induced AFL. Their limited mapping of induced AFL was interpreted as demonstrating re-entry around the great veins.

Years later, Frame et al. produced an intercaval lesion in canine atria similar to that of Rosenblueth and Garcia-Ramos (1,2) but with an extension of the intercaval lesion toward the RA appendage, creating a Y lesion, and showed that induced AFL resulted from re-entry around the tricuspid valve annulus. They recognized that the Y lesion provided boundaries limiting the re-entrant circuit to the tricuspid ring, and also protected the re-entrant circuit from short-circuiting. Clearly, block between the vena cavae had a critical role in the pathogenesis of AFL, and the Y lesion was simply a variant.

A functional LoB in the region between the vena cavae is also necessary in the canine sterile pericarditis model of induced AFL, whether due to single loop (Fig. 2) or
figure-of-eight re-entry (Fig. 2) (5,15). Different than single loop re-entry, the functional LoB is more anterior in figure-of-eight re-entry and does not connect to either vena cava. However, it is still critical to the development of stable AFL and prevents short-circuiting of the re-entrant circuit.

Nevertheless, block in the intercaval region is not critical for development of all types of AFL. Studies by Allesie et al. (1,2) of a canine acetylcholine infusion model showed that re-entrant AFL can occur in either atrium and even in the absence of an anatomic obstacle around which to circulate (Fig. 3). The AFL CLs in this model ranged from 65 to 145 ms but activated the atria in a 1:1 fashion. The absence of fibrillatory conduction almost certainly occurred because the acetylcholine significantly shortened the atrial effective refractory period (ERP). The possible relevance of these studies to AF will be apparent shortly.

There are canine models of AFL in which the re-entrant wave front circulates around a functional LoB that is not necessarily in the region between the vena cavae. They include spontaneous AFL in a dog studied by Boineau et al. (1,2) and an RA enlargement model studied by Boyd and Hoffman (1,2). A canine mitral regurgitation model studied by Cox et al. (1,2) showed several re-entrant circuits, including 1 with no anatomic obstacle.

There are canine models in which an RA lesion creates an LoB around which the re-entrant wave front circulates (1,2,16,17). This AFL mechanism may occur in patients after surgical repair of congenital heart defects that involve 1 or more RA free wall incisions (1,18). However, in approximately two-thirds of such patients, the AFL re-entrant circuit is of the classical type involving the CTI (1,18,19). Why classical AFL would result in these patients was demonstrated by Tomita et al. (17), who showed in normal canine atria that a sufficiently long RA free wall lesion, which often accompanies repair of congenital lesions, may develop a functional extension from the fixed LoB (i.e., the surgical lesion) to 1 or both of the vena cavae (Fig. 4) during induced AF. That LoB permitted development of a re-entrant wave front that traveled up the intraatrial septum and down the RA free wall or vice versa and included the CTI (i.e., the classical AFL re-entrant circuit). When a functional extension of the LoB did not develop, AFL due to lesion re-entry occurred. Thus, this canine model serves as the experimental counterpart of the clinical example and emphasizes again the importance of the LoB between the vena cavae. Lastly, an AFL model due to re-entry around a lesion resulting from detachment and subsequent reanastomosis of the pulmonary veins was shown by Ghandi et al. (1,2) in canine hearts and in patients.
**Further Studies in Patients**

Mapping studies of AFL in humans have further refined our understanding of the usual AFL re-entrant circuit, and have confirmed the importance of an LoB between the vena cavae. The boundaries of the classical AFL re-entrant circuit include either the superior or inferior vena cava or both and an LoB located between them in the region of the crista terminalis (1,2). Cosio et al. (20) first emphasized the presence of an LoB in this area during AFL in patients and considered that the block was functional. One group (21,22) has interpreted their data as showing that this LoB is fixed (anatomic), but other studies have continued to show that block in this region is functional (11,23–25). Nevertheless, block in this region is clearly very important to the pathogenesis of classical AFL (1,2).

**The Role of AF in the Development of AFL**

As demonstrated by studies of induced and spontaneous onset of AFL in animal models and patients (1,2,4–6,15,26), this rhythm most often does not start immediately after a premature beat or burst rapid atrial pacing. Rather, its onset is usually preceded by a transitional rhythm (AF) of variable duration (Fig. 5).

Studies in animal models provide insights into why AF most often precedes the initiation of AFL. As discussed in the preceding text, an LoB is required between the superior and inferior vena cavae to achieve a stable equivalent of classical AFL, but this LoB normally is not present. As shown in the canine sterile pericarditis (2,5,15) and RA enlargement models (2), it is during the induced transitional AF rhythm that the critical functional LoB first develops, completing a necessary boundary between the vena cavae. After development of this boundary, stable AFL may then become established (3,5,15). If this functional component of the AFL re-entrant circuit does not develop, AF either will persist or spontaneously convert back to sinus rhythm. In short, there is no AFL if the functional LoB between the vena cavae doesn’t form. It follows that transitional AF, almost always present before the onset of AFL in patients (1,2,4–6), likely serves the same function shown in animal models. Thus, it is reasonable to conclude that in most instances, without prior AF, there is no AFL.

Further evidence for the necessity of the functional LoB between the vena cavae to permit the maintenance of stable AFL comes from studies during spontaneous and adenosine triphosphate-induced conversion of AFL to AF in the canine sterile pericarditis model (27). In these studies, conversion of AFL to AF was associated with shortening of the length of this functional LoB, resulting in AF. Stable AFL returned when there was reformation of a sufficiently long LoB that re-established the boundary between the vena cavae necessary to permit and protect stable AFL.

Although transitional AF usually precedes onset of induced or spontaneous AFL in patients, it does not always. We suggest that, owing to physiological variability, some patients may already have a very high degree of block or complete block present in the region between the vena cavae (21,22). Another explanation may be that the functional LoB may already have formed in the intercaval region during AF produced by burst atrial pacing of short CL. Studies using high-resolution mapping of the intercaval area during the onset of induced AFL in patients are needed to resolve this issue fully.

**Mechanisms of AF: The Role of Fibrillatory Conduction Secondary to an AFL Driver of Short CL**

Moe and Abildskov (7) proposed the multiple re-entrant wavelet hypothesis as the mechanism of AF. This mechanism was supported by their subsequent computer model (7) and by mapping studies of induced AF in a canine...
acetylcholine infusion model by Allesie et al. (7). Later studies in animal models and patients have found another operative mechanism, fibrillatory conduction in the atria generated by: 1) a single, stable re-entrant circuit of short CL (7,8,13,28); 2) multiple, unstable re-entrant circuits of short CL (7,29); or 3) a single focus firing at a short CL (7,8,30).

Schuessler et al. (7), in an in vitro canine RA preparation superfused with acetylcholine, demonstrated that a single figure-of-eight re-entrant circuit of short CL (approximately 45 ms) drove the rest of the preparation, producing fibrillatory conduction. Subsequent studies in sheep atria by Skanes et al. and Mandapati et al. (7), in the canine sterile pericarditis model by Matsuo et al. (7), and in the canine rapid ventricular pacing-heart-failure model by Ryu et al. (28) have shown that a single, stable, re-entrant circuit, primarily in the left atrium (LA), can drive the atria, producing fibrillatory conduction. Thus, a single re-entrant circuit (if you will, a very fast AFL) can cause AF. Noteworthy in these models, the re-entrant circuit that produced the driver (i.e., the very fast AFL) was induced by burst pacing, which first produced a transitional AF rhythm ostensibly due to random re-entry.

That a fast AFL may be a cause of clinical AF in patients was suggested by a study in post open heart surgical patients (Fig. 6) (6) and during catheter ablation (13). Also, limited simultaneous multisite mapping studies by Cox et al. and Konings et al. (7) during open heart surgery in patients after pacing-induced AF have demonstrated unstable re-entrant circuits of short CL in the RA. This is consistent with studies by Kumagai et al. (7,29), which showed in the canine sterile pericarditis model that unstable re-entrant circuits of short CL can drive the atria, producing fibrillatory conduction and thereby AF. And the recent findings of various LA and RA AFL re-entrant circuits (8–13) suggest that stable re-entry due to a number of mechanisms is possible. Indeed, it is intuitive that a spectrum of AFLs with a range of rates is possible, and that when the rate is sufficiently fast, fibrillatory conduction-producing clinical AF will result. Noteworthy, more than 4 decades ago the group from Mexico City considered that re-entry could occur around 1 of the pulmonary veins or 1 of the vena cavae but that the calculated CL would be too short to explain clinical AFL (31). It is implicit that such re-entrant circuits could act as a driver and cause AF via fibrillatory conduction.

More recent data from patients with AF come from studies using catheter electrode and fast Fourier transform techniques during electrophysiologic studies (30,32–35) and from studies using simultaneous, multisite mapping techniques during open heart surgery (36). The former studies have shown that rhythms of short CL emanating from ≥1 of the pulmonary veins can precipitate AF and perhaps even maintain it (30). The mechanism of such pulmonary vein “firing” is unclear at this time, but it has been shown (29) that the rapid rhythm emanating from the pulmonary veins can be due to re-entry. In mapping studies of chronic AF during open heart surgery (36), 7 of 9 patients had an area of rapid, regular rhythm identified, principally in the LA, which seemed to act as a driver, producing fibrillatory conduction to the rest of the atria. The mechanism of this putative driver is as yet unknown.

In sum, analyses of data from these studies have been interpreted to suggest that there are drivers that generate AF (32–36). Further study is required to clarify the potential relationships between pulmonary vein potentials and the initiation of 1 or possibly more drivers that will generate fibrillatory conduction, and, thereby, maintain AF in patients. The paradigm may be that as AF can evolve to a classical AFL re-entrant circuit with 1:1 conduction to the atria, it may also be capable of evolving to an atrial re-entrant circuit of very short CL (usually in the LA) (i.e., an atrial driver [or drivers] that generates fibrillatory conduction that maintains AF).
Clinical Implications and Applications

Understanding the importance of AF in the genesis of AFL has many clinical implications and applications. For instance, it should be of no surprise that: 1) 3 of every 4 patients with AFL also manifest clinical AF (1); 2) after successful ablation of the CTI to cure AFL, up to 70% of patients subsequently manifest AF, many of whom never manifested AF before the AFL ablation (37)—the explanation we suggest is that, if AF can no longer “evolve” to AFL after ablation because the CTI is no longer available as a critical component of an AFL re-entrant circuit, now AF may simply become clinically manifest; and 3) anti-arrhythmic drugs with sodium channel-blocking properties (i.e., properties that affect conduction in the atria, such as the class IAs, class ICs, and amiodarone) are associated with a significant incidence of “converting” recurrent AF to AFL (1,3), because, we suggest, they make it possible for a functional LoB to form between the vena cavae during the initial AF rhythm, whereas previously it did not form.

An understanding of the relationship of AF to the development of a functional LoB between the vena cavae such that AFL can develop also helps solve a few clinical mysteries and helps us to understand the pathogenesis of some hitherto poorly understood clinical phenomena. Years ago, Interian et al. (38) described a patient cohort that manifested both atrioventricular nodal re-entrant tachycardia (AVNRT) and AFL. In those patients, after ablating the slow AV nodal re-entrant pathway to cure the AVNRT, the AFL was also cured. The supposition was that the re-entrant circuits of AFL and AVNRT shared a common pathway such that ablation of the slow AV nodal re-entrant pathway also cured the AFL (38).

However, invoking both the phenomenon of tachycardia-induced-tachycardia and the relationship of AF to AFL provides a more likely explanation. Thus, AVNRT has been associated with occurrence of AF in many patients (39). The suggested explanation, best understood by the concept of facilitation (40), is that the rate of sustained AVNRT physiologically remodels the atria such that the ERP shortens dramatically (41). This makes the atrial substrate more conducive to initiation of AF by premature atrial beats. Should AF occur, in some patients, an LoB will form between the vena cavae such that AFL may become manifest. Thus, if one ablates the AVNRT re-entrant slow pathway, there will no longer be episodes of sustained tachycardia to remodel the atria. It follows that the atria may no longer be conducive to precipitation of AF by premature atrial beats, presumably generated by pulmonary vein potentials. If AF no longer develops, AFL will not develop either. We find this suggested explanation not only logical but pathophysiologically far more satisfying. Parenthetically, this entire discussion is also applicable to the association of AV re-entrant tachycardia (AVRT) and Wolff-Parkinson-White syndrome with AFL. In fact, it has been recognized for years that either surgical or catheter ablation of the accessory AV connection in patients with AF is associated with a marked reduction (94% and 91%, respectively) in subsequent AF (42,43).

At virtually the same time as the aforementioned study, Kalbfleisch et al. (44) performed a related study. Because of the possibility that AVNRT and AFL may share a common area of perinodal atrium in their re-entrant circuits, they evaluated inducibility of AFL in patients with AVNRT who never had clinically manifest AFL and determined whether this inducibility was altered by ablation of the AV nodal slow pathway. In their study, AFL induction was produced by burst rapid atrial pacing, which first produced AF. They found a strong association between AVNRT and inducible AFL, but found that ablation of the slow pathway did not influence the subsequent inducibility of AFL. These studies indicate that, although AVNRT and AFL may occur in the same patient, successful ablation of the slow pathway does not also cure AFL. Rather, if AF should occur for any reason, AFL may still develop. Because later development of AF still is possible, should it occur, development of AFL would be likely. Thus, in patients with both AVNRT (or AVRT) and classical AFL, ablation to produce bidirectional CTI block seems reasonable.

An additional related clinical example is seen in the study of Wazni et al. (45). They showed that in patients with both AF and CTI-dependent AFL, successful ablation of AF resulted in the subsequent absence of AFL in most of their patient cohort (56 of 59 patients). We would suggest that in the 3 patients with subsequent AFL, subclinical AF likely preceded the AFL.

Another important clinical implication of these concepts relates to the significant incidence of AFL associated with repair of congenital heart lesions. As discussed earlier, the location and length of the surgical incision(s) in the atria used to repair congenital heart lesions are associated with an incidence of late postoperative AFL (1,18,19). An obvious clinical implication is that an attempt to modify the type of incisions and suture lines placed as part of the surgical repair should be made so that a critical LoB between the vena cavae will not develop. Another implication is that, in the presence of incisional re-entry, simply extending the atriotomy lesion to 1 vena cava or both vena cavae may eliminate incisional re-entry only to promote classical AFL that uses the CTI. It is also noteworthy that catheter ablation to cure AF is sometimes associated with subsequent development of AFL. Whereas most of these AFLs are due to lesion re-entry or re-entry around the mitral valve annulus, some are due to CTI-dependent AFL re-entry (46). Once again, the pathophysiology of AFL helps us to understand that in the latter instances an LoB between the vena cavae, perhaps on the LA side as a result of ablation.
lines meant to isolate the right superior and inferior pulmonary veins, may have provided a critical component for a potential AFL re-entrant circuit. Thinking through the nature and location of these lesions may make it possible to avoid this complication or, short of that, placing a prophylactic bidirectional block lesion in the CTI may be worthwhile prophylactically.

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