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Pathophysiological Mechanisms of Atrial Fibrillation: A Translational Appraisal

ULRICH SCHOTTEN, SANDER VERHEULE, PAULUS KIRCHHOF, AND ANDREAS GOETTE

Department of Physiology, University Maastricht, Maastricht, The Netherlands; Department of Cardiology and Angiology, University Hospital of Münster, Münster; and Department of Cardiology, St. Vincenz Hospital, Paderborn and Institute of Clinical Pharmacology, University Hospital Magdeburg, Magdeburg, Germany

Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological Mechanisms of Atrial Fibrillation: A Translational Appraisal. *Physiol Rev* 91: 265–325, 2011; doi:10.1152/physrev.00031.2009.—Atrial fibrillation (AF) is an arrhythmia that can occur as the result of numerous different pathophysiological processes in the atria. Some aspects of the morphological and electrophysiological alterations promoting AF have been studied extensively in animal models. Atrial tachycardia or AF itself shortens atrial refractoriness and causes loss of atrial contractility. Aging, neurohumoral activation, and chronic atrial stretch due to structural heart disease activate a variety of signaling pathways leading to histological changes in the atria including myocyte hypertrophy, fibroblast proliferation, and complex alterations of the extracellular matrix including tissue fibrosis. These changes in electrical, contractile, and structural properties of the atria have been called "atrial remodeling." The resulting electrophysiological substrate is characterized by shortening of atrial refractoriness and reentrant wavelength or by local conduction heterogeneities caused by disruption of electrical interconnections between muscle bundles. Under

these conditions, ectopic activity originating from the pulmonary veins or other sites is more likely to occur and to trigger longer episodes of AF. Many of these alterations also occur in patients with or at risk for AF, although the direct demonstration of these mechanisms is sometimes challenging. The diversity of etiological factors and electrophysiological mechanisms promoting AF in humans hampers the development of more effective therapy of AF. This review aims to give a translational overview on the biological basis of atrial remodeling and the proarrhythmic mechanisms involved in the fibrillation process. We pay attention to translation of pathophysiological insights gained from in vitro experiments and animal models to patients. Also, suggestions for future research objectives and therapeutical implications are discussed.

I. INTRODUCTION

A. Clinical Relevance: The "AF Burden"

Atrial fibrillation (AF) is the most common sustained arrhythmia in humans, causing an increasing number of complications and deaths (188, 289). Electrocardiogram (ECG)-based surveys suggest that ~1% of the total population is affected (275). The number of patients with AF is likely to double or triple within the next two to three decades (240). The prevalence of AF is clearly age dependent. The growing prevalence of AF can be explained in part by the increasing average age in the human population (85).

AF patients usually seek medical attention because of AF-related symptoms. Treatment of these symptoms has been the main motivation for AF therapy in the past. In epidemiological and other observational studies, AF is associated with excess death (43, 417). The available data suggest that presence of AF approximately doubles death rates in affected individuals, independent of other known cardiovascular conditions. Similarly, AF worsens prognosis in patients with acute myocardial infarction and in patients hospitalized for heart failure. Successful maintenance of sinus rhythm was associated with longer survival in the AFFIRM trial (123). Taken together, the available data clearly suggest that AF increases mortality in affected patients, although death rates in controlled trials (AFFIRM, AF-CHF, RACE) are not affected when ion channel-blocking drugs are needed to maintain sinus rhythm.

Overall, 20–25% of all strokes are caused by AF (384), and AF-related strokes are more severe than strokes of other origin. The importance of cardio-embolic stroke in AF patients is highlighted by the fact that adequate anticoagulation in patients with AF can prevent strokes and reduce mortality in patients at increased risk of stroke (120, 227). Left ventricular function, the best-validated clinical parameter for cardiac prognosis, can be markedly impaired in AF patients and in some trials improved when sinus rhythm is maintained for a longer period of time (254, 284). However, it is worth noting that AF-CHF, a recent large trial of sinus rhythm maintenance in patients with already severely depressed left ventricular (LV) function, and AFFIRM, the first large "rate versus rhythm" trial, did not detect an effect of sinus rhythm on LV function (3, 471).

Apart from antithrombotic therapy, we have so far failed to develop therapeutic interventions that improve prognosis in AF patients (3, 244), underscoring the need for better, possibly earlier and more comprehensive, management of AF, as highlighted by a recent consensus statement (289).

B. The Natural History of AF

Systematic ECG monitoring studies indicate that a substantial portion of AF episodes is asymptomatic (262). Usually, these episodes are self-terminating. Over time, typically over decades, the episodes become longer, and eventually sustained forms of AF develop. This progressive behavior of the arrhythmia has been demonstrated in several large observational studies (283, 542). An example of a patient with progressively longer episodes of AF is depicted in Figure 1*A*. It should be noted, however, that other courses of AF also occur, ranging from frequent paroxysmal AF that never becomes persistent to permanent AF developing as the first episode. As will be discussed in sections **IV–VII**, the progressive nature of AF is partly caused by AF itself, but also reflects progression of underlying structural heart diseases. There is evidence that the time course of AF stabilization in patients with structural heart disease is more rapid than in "lone AF" patients (276).

C. Clinical Factors Associated With AF

Numerous clinical conditions are associated with an increased incidence of AF. Most of them (Fig. 1*B*) contribute to a gradual and progressive process of atrial remodeling characterized by changes in ion channel function, Ca^{2+} homeostasis, and atrial structure such as cellular hypertrophy, activation of fibroblasts, and tissue fibrosis. These alterations may both favor the occurrence of "triggers" for AF that initiate the arrhythmia and enhance the formation of a "substrate for AF" that promotes its perpetuation. The association of clinical factors with AF substrates and triggers will be discussed separately.

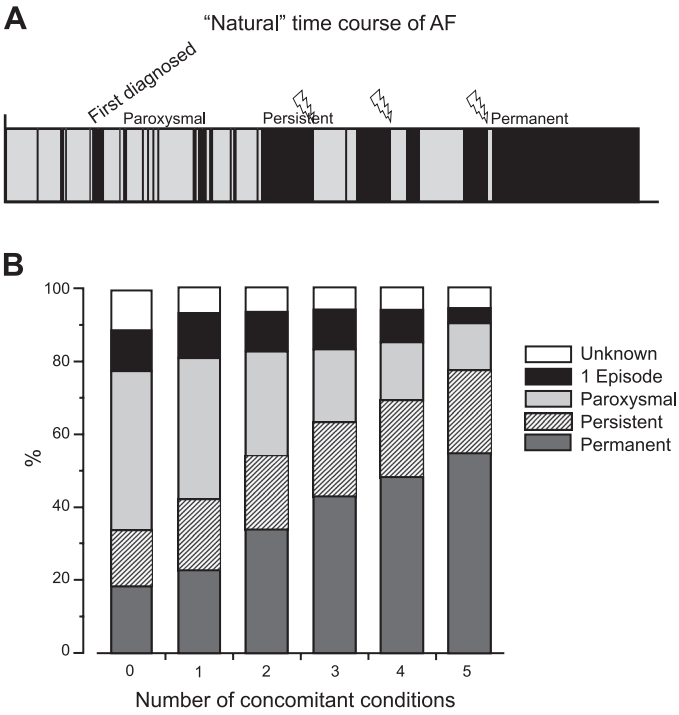


FIG. 1. *A*: example of the "natural" course of the arrhythmia in an atrial fibrillation (AF) patient. Typical pattern of time in AF (black) and sinus rhythm (gray) over time (x-axis). AF progresses from undiagnosed to first diagnosed, paroxysmal, persistent, and permanent. Flashes indicate cardioversions as examples of therapeutic interventions that influence the time course of the arrhythmia. *B*: graph shows the type of AF as a function of the number of "concomitant conditions" at the enrollment visit into the AFNET registry that included 9,582 patients throughout Germany from 2004 to 2006 (396). AF was classified as first episode, paroxysmal, persistent, or permanent. Concomitant conditions were defined as age >75 years, hypertension, diabetes (treated), cardiomyopathy, heart failure, valvular disease, or replacement. The proportion of patients in permanent AF increases while the percentage of patients in paroxysmal AF decreases almost linearly with increasing number of concomitant conditions. The proportion of patients in persistent AF remains relatively constant, suggesting that this is a transitory state between paroxysmal and permanent AF. First episode of AF becomes less likely in the patient population with many conditions.

1. *Clinical conditions associated with the initiation of AF*

Little is known about the mechanisms or clinical conditions that initiate episodes of the arrhythmia. This can be illustrated by the fact that many patients with an accumulation of the above-mentioned AF-causing factors, e.g., patients with advanced heart failure, never experience AF in their lifetime. A sizeable portion of patients with lone AF suffer from "focal AF" that is initiated by triggers that can be localized to preferential sites, mainly the pulmonary veins (PV) (217). Electrical isolation of PVs can prevent recurrence of AF in 70–80% of these lone AF patients during a follow-up period of several years (83). Stretch-activated or catecholamine-dependent automaticity (52), as well as abnormal calcium handling (440), have been suggested as mechanisms causing AF in focal AF patients, but so far these mechanisms have not been shown to be related to specific clinical conditions other than AF itself.

2. *Clinical conditions associated with the development of a substrate for AF*

Hypertension is found in 60–80% of AF patients (396). Hypertension is an independent predictor of AF (581), and it contributes to AF progression. Vascular disease, and most notably coronary artery disease, is found in one-fourth to one-third of AF patients in surveys (396, 416), and may be associated with AF-related complications (255). Heart failure with dyspnea on exertion (NYHA classes II-IV) is found in 30% of AF patients (416), and AF is found in 30–40% of patients with heart failure (115). Heart failure and AF appear to promote each other, with AF compromising LV function, and LV dysfunction causing atrial dilation and pressure overload. Valvular heart disease, especially mitral valve disease, was the most common clinical condition associated with AF 50 years ago. Early antibiotic therapy of streptococcal infections has markedly reduced severe mitral valve disease in more recent surveys (396, 416). These conditions are associated with atrial dilatation, which plays an important causative role in the development of a substrate of AF (sects. **IV** and **V**). Diabetes mellitus is one of the established risk factors for stroke in AF patients (190) and is found in ~20% of all patients with AF (396, 416). The high prevalence of diabetes mellitus in AF populations suggests that diabetes may either cosegregate with AF due to similar conditions that cause both AF and diabetes, or may imply that diabetes mellitus plays a causative role in the occurrence of AF. Thyroid dysfunction, and especially hyperthyroidism, is also associated with AF. Adequate therapy of thyroid disease often terminates AF. Improved clinical management of thyroid disease has rendered thyroid dysfuction relatively rare in current AF populations (416).

It is well worth noting that all these clinical conditions appear to enhance AF susceptibility in an additive manner, as the prevalence of persistent AF increases steadily depending on the number of such conditions present (Fig. 1*B*). As we will discuss in sections **IV–VI**, these conditions will increase AF propensity by many diverse mechanisms. Understanding this diversity of the mechanisms finally leading to AF is one of the unmet challenges in unraveling AF pathophysiology.

II. ATRIAL-SPECIFIC ASPECTS OF CARDIAC PHYSIOLOGY

Before proarrhythmic mechanisms in the atria will be discussed, some atrial specific aspects of cardiac physiology relevant to AF will be reviewed with a focus on differences between atria and ventricles and regional differences in function.

A. Atrial Electrophysiology

The predominant shape of the atrial action potential is triangular with a gradual repolarization phase as shown in the top right inset in Figure 2. If a plateau is present, it is less pronounced than in ventricular myocytes. The left panel of Figure 2 shows a human atrial action potential and its main underlying ionic currents. As in ventricular myocytes, the main depolarizing currents are the rapidly activating and inactivating Na^+-current (I_{Na}) and the L-type Ca^{2+} current (I_{CaL}), which has somewhat slower kinetics. The differences in action potential morphology between atria and ventricles are mainly caused by differences in ion channel current density and kinetics of repolarizing currents. Some types of ion channels are selectively expressed by atrial myocytes. Atrial-specific ion channels represent interesting targets for cardioversion of AF (160), given the risk for ventricular proarrhythmia of traditional class I drugs (reduction of excitability and conduction velocity, mainly by sodium channel blockade) and class III drugs (prolongation of refractoriness, mainly by potassium channel blockade) (465).

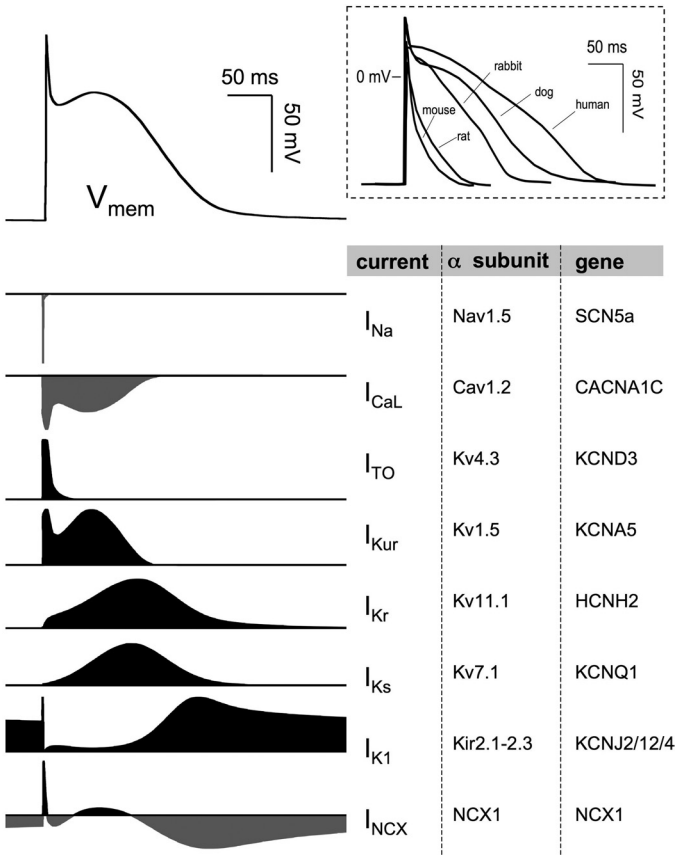


FIG. 2. The atrial action potential. *Top right inset*: comparison of action potentials recorded at 37°C in different species at a pacing cycle length close to the normal sinus cycle length. *Top left*: human atrial action potential simulated using the Courtemanche model (126). The traces below display the time course of the main ionic currents responsible for the action potential. Inward (depolarizing) currents are shaded gray, and outward (repolarizing) currents are black. *Bottom right:* table lists the currents with the channel alpha subunits and the responsible genes.

The ultrarapid delayed rectifier current (I_{Kur}) activates ~100 times more quickly than the rapid delayed rectifier current (I_{Kr}). I_{Kur} significantly contributes to atrial repolarization in most species. Kv1.5, the α-subunit of I_{Kur}, is expressed by atrial myocytes but to a much lower extent in ventricular myocytes (373, 606). Most compounds blocking I_{Kur} also inhibit the transient outward current (I_{to}) and the acetylcholine-activated inward rectifier current (I_{KACh}) (488, 555). These drugs prolong the atrial effective refractory period (AERP) and decrease AF stability, without affecting the QT time (48, 136).

I_{KACh} shortens the atrial action potential duration (APD) during vagal activity. The pore-forming Kir3.x α-subunits are expressed in the atria but not in the ventricles (149). Tertiapin-Q selectively inhibits Kir3.x channels like I_{KACh} without affecting Kir2.x channels (inward rectifier current I_{K1}) (265). In dogs with sustained AF, tertiapin-Q can terminate AF episodes without changing ventricular repolarization (94). Another agent under development, NIP-142, inhibits both Kir3.x and Kv1.5 channels, leading to a atrial-selective prolongation of APD and AERP (369). In dogs, NIP-142 prolonged AERP by 10% and cardioverted vagally induced AF without an effect on ventricular refractoriness (401).

Recently, the presence of apamin-sensitive Ca^{2+}-activated potassium channels (I_{KCa}) in the heart was demonstrated (636). In mouse hearts, the current density of I_{KCa} and its effect on APD are larger in the atria than in the ventricles (636). Of the three genes encoding I_{KCa}, SK1 (KCNN1) and SK2 (KCNN2) are expressed more in the atria than in the ventricles, while the expression of SK3 (KCNN3) is similar (567). The degree of APD shortening mediated by SK channels depends on the cytosolic Ca^{2+} concentration, thus possibly contributing to an interaction of Ca^{2+} handling and repolarization. SK2 channels colocalize with L-type calcium channels through a mutual interaction with α-actinin 2 (349). In some animal models, a role of SK2 channels in the development of atrial remodeling or AF has been suggested. In rabbit PVs, intermittent burst pacing leads to an increased trafficking of SK2 channels to the membrane, resulting in increased apamine-sensitive current and APD shortening (432). In SK2 knockout mice, APD was prolonged and AF inducibility was increased probably due to enhanced triggered activity (333). Furthermore, pharmacological block of I_{KCa} resulted in prolongation of atrial refractoriness and termination of AF in rats, guinea pigs, and rabbits (144). However, another study demonstrated little contribution of SK channels to repolarization in normal rat and dog atrial myocytes (402), and the role of I_{KCa} blockade in large-animal models of AF remains to be determined. Recently, genome-wide association studies demonstrated

an association between lone AF and common gene variants of SK3 (166). It is currently unclear whether this association is related to changes in myocyte repolarization or to effects in other cells types.

The inward rectifier current I_{K1} stabilizes the resting membrane potential and is an important determinant for the initial depolarization and final repolarization of the action potential (346). In atrial myocytes, inward rectification of I_{K1} at depolarized potentials is incomplete, allowing I_{K1} to play a role throughout the repolarization phase (195). In addition, the density of I_{K1} is 5- to 10-fold smaller in atrial myocytes than in ventricular myocytes (195). As a result, the membrane resistance of atrial myocytes at rest is relatively high (205), and thus less depolarizing current is required to reach the action potential threshold, making atrial myocytes inherently more excitable. This is reflected in model simulations that show that the critical size of an ectopic focus required to drive the surrounding myocardium is smaller in the atrium than in the ventricle (269).

In the atria, gap junction channels are formed by connexin (Cx) 40 and Cx43, and these two connexin subtypes may combine to form heteromeric channels (165). In contrast, ventricular myocytes predominantly express Cx43 (575). Manipulation of Cx40 may offer a way to affect atrial but not ventricular conduction, although within the heart, Cx40 is also expressed in the sinoatrial and atrioventricular nodes, the Purkinje system, and endothelial cells (575).

1. Regional variation in atrial electrophysiology

Within the atria, considerable regional variation in action potential morphology exists. As will be discussed in detail in section **II***B*, PV myocytes differ from left atrial myocytes, with a more depolarized resting membrane potential, lower upstroke velocity, and shorter action potential (161, 375). In isolated canine right atrial myocytes, Feng et al. (178) reported relatively long APD with a spike-and-dome morphology for myocytes from the crista terminalis, while myocytes from close to the atrioventricular (AV) groove had shorter action potentials (270 vs. 160 ms at 1-Hz stimulation, respectively). In this study, myocytes from the pectinate muscles and atrial appendage had intermediate durations. Differences in APD between regions correlated to systematic differences in ion channel density. Burashnikov et al. (78) found a similar distribution of action potential morphologies in perfused canine atria, in addition to a long APD in the bundle of Bachmann, the main connection between right and left atria. In some areas, like the crista terminalis, the epicardium has shorter APDs than the endocardium (78, 178), probably due to a relatively high I_{to} current density in epicardial myocytes (178). In older literature, myocytes have been described with a fast action potential upstroke, high conduction velocity, pronounced action potential plateau, and long refractory period. These cells along the caval border of the crista terminalis and in Bachmann's bundle remained excitable at higher potassium concentrations than normal atrial myocytes and may form specialized rapidly conducting tracts within the atrium (243, 579, 596).

B. Electrophysiological Basis of PV Ectopy

In humans, paroxysms of AF often originate in the myocardial sleeves of the PVs. Haissaguerre et al. (217) were the first to demonstrate that repetitive activity with a very short cycle length may occur in the PVs, and that radiofrequency ablation of such drivers can be used to treat AF.

1. Morphology of PV myocytes

In theory, rapid activity in the PV area might result from new impulse formation due to automaticity or triggered activity or from (micro-)reentry due to abnormalities in tissue structure. An argument favoring automaticity is that during embryonic development, some markers, in particular HNK-1 (51, 268), are expressed in areas which will later form the conduction system and nodal tissue as well as in the PV region. However, by all accounts, the PVs in the adult heart consist mainly of myocytes morphologically very similar to normal atrial myocytes. Thus the PVs probably do not harbor large areas of hidden nodal tissue. There are diverging reports about the occurrence of abnormal myocytes scattered throughout the myocardial sleeves. Using electron microscopy, Masani (368) observed small, pale myocytes resembling nodal P cells in normal rat PVs. In normal dog PVs, no evidence for morphologically abnormal myocytes was found in two studies (241, 585), whereas large PAS-positive cells (i.e., cells with a high glycogen content) were found in another (110). In an electron microscopy study on human PVs, Perez-Lugones et al. (447) have reported the presence of nodal-like P cells, transitional cells, and large Purkinje-like myocytes in patients with a history of AF. These cell types were not present in PVs from patients without a history of AF (447). However, this study has engendered criticism of the histological technique itself and of the use of purely histological criteria to classify electrical phenotypes of myocytes (12). Recently, Morel et al. (391) have demonstrated the presence of small Cajal-like cells in the interstitium of human PVs. Similar cells are involved in pacemaking in the intestine, but their role in PV automaticity is unclear, and their presence has also been demonstrated in normal atrial myocardium (235). The contribution of scattered abnormal cell types with possible pacemaking properties remains to be established. In general, a certain critical size

is required for an ectopic focus to act as a driver for the surrounding myocardium (269). Propagation from an ectopic focus is most likely when electrical coupling gradually increases from the focus to the surrounding muscle, because a high degree of electrical coupling would effectively silence the focus (reviewed in Ref. 270). Interestingly, a recent study has indicated that at the PV-left atrial junction, large PAS-positive myocytes expressing the pacemaker channel protein HCN4, are more separated by fibrosis and inflammatory infiltrates in chronic AF patients than in sinus rhythm patients (415).

2. Electrophysiology of isolated PV myocytes

Conflicting evidence about possible differences in cellular electrophysiology between normal atrial myocardium and myocardial sleeves has come from both recordings of isolated myocytes (current and voltage clamp) and multicellular preparations (optical mapping and microelectrode recordings).

Voltage-clamp recordings on isolated PV myocytes from healthy dogs indicate that PV myocytes have a larger density of slow delayed rectifier current (I_{Ks}) and I_{Kr}, a lower density of I_{to} and I_{CaL} than normal atrial myocytes while I_{Na}, the Na^+/Ca^{2+} exchange current (I_{NCX}) and T-type Ca^{2+} current (I_{CaT}) densities were similar to that in normal atrial myocytes (161, 375). These data agree with action potential recordings in myocardial sleeve preparations showing that PV myocytes have a more depolarized resting membrane potential and action potentials with a slower upstroke velocity and shorter duration, without showing spontaneous diastolic depolarizations, afterdepolarizations, or automaticity (161). In combination, the lower upstroke velocity and relatively short APD may contribute to a larger propensity for reentry within the myocardial sleeve. As in the rest of the atria (see section **IV***B*), rapid atrial pacing reduced I_{to} and I_{CaL} in PV myocytes. As a result, differences in APD between the PV and left atrium became smaller (95), arguing against a major role for the PVs in AF maintenance in this model. In addition, Coutu et al. (127) reported that calcium handling and its β-adrenergic response in PV myocytes was very similar to that of left atrial myocytes, both for myocytes isolated from normal dogs and after a week of rapid atrial pacing.

A competing body of evidence has been presented by Chen and co-workers (101, 104). In isolated myocytes from both canine and rabbit PVs, a large proportion of cells showed spontaneous activity (40% resp. 76%), in some cases with unusual action potential morphologies (101, 104). In voltage-clamp recordings, spontaneously active myocytes had a low density of I_{K1}, a larger delayed rectifier amplitude, and sometimes showed a current resembling the hyperpolarization-activated pacemaker (funny) current (I_f) (104). After 6–8 wk of rapid atrial pacing in dogs, the beating rates of spontaneously active PV myocytes had doubled, and a higher incidence of early and delayed afterdepolarizations was observed (101). In this and further studies from the same group, the isolation procedure, in which left atrial cavity (104) or PV lumen (101) were perfused, may have affected the electrical behavior of the resulting myocytes. Also, if normal PV myocytes would have such a pronounced tendency towards automaticity, it is surprising that AF paroxysms or premature atrial beats originating in the PVs are not observed more frequently in healthy animals.

3. Electrical activity of myocardial sleeves

The earliest reports of PV automaticity in atrial preparations far predate the discovery of PV involvement in paroxysmal AF (70, 557). Cheung (106) later described activity of guinea pig PVs as a subsidiary pacemaker with a low, regular intrinsic frequency.

In a study on superfused PVs from normal dogs, Chen et al. (103) reported a large heterogeneity of action potential morphologies in the myocardial sleeves. This was accompanied by a high incidence of high-frequency irregular activity, which was further increased in PVs from dogs after 6–8 wk of rapid atrial pacing (103). However, this high intrinsic arrhythmic tendency of canine PVs was not confirmed in studies by other laboratories, which showed a homogeneous distribution of action potentials throughout the myocardial sleeves without spontaneous activity under baseline conditions (Fig. 3*A*) (95). Rat PVs did not display spontaneous activity, but it was observed during infusion of norepinephrine or a combination of α- and β-agonists (371). Rabbit PVs did not show spontaneous activity under baseline conditions, but PV pacemaker activity with a diastolic depolarization was readily induced by an acceleration in pacing rate in the presence of low concentration of ryanodine (249). Thus most studies on PV preparations indicate that the PVs are not spontaneously active under normal conditions, but that spontaneous and triggered activity can sometimes be induced, particularly during sympathicomimetic treatment (see also sect. **IV***A*). In addition to the PVs, arrhythmic activity may also originate from "myocardial sleeves" in other atrial regions, such as myocardial extensions in the atrioventricular valves and coronary sinus (37, 267, 621–623). Wit and co-workers have amassed an extensive body of data on catecholamine-induced delayed afterdepolarizations (DADs) and triggered activity elicited by fast pacing or extrastimulation in the canine coronary sinus (232, 566, 621). DADs in coronary sinus myocytes involve Ca^{2+} release from the sarcoplasmic reticulum (21) and activation of a transient inward current (565). The contribution of catecholamine-induced triggered activity from the coronary sinus in human AF is unclear at this point (280).

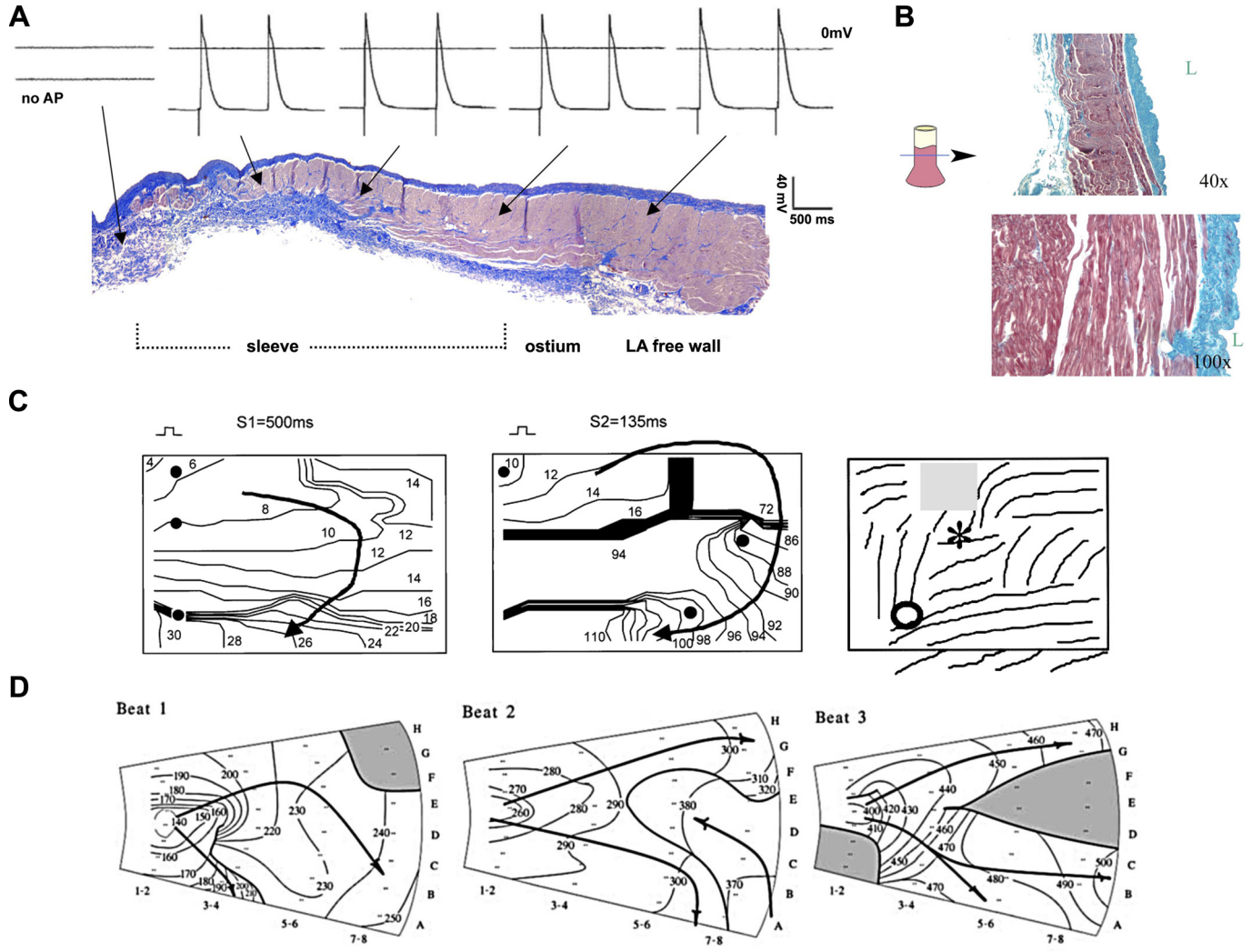


FIG. 3. Electrophysiology of pulmonary veins (PVs). *A*: homogeneous distribution of action potential morphologies along the myocardial sleeve. Photomicrograph shows the muscular layer tapering off from the left atrial ostium to the vein, endocardial side up. [Modified from Wang et al. (602), with permission from Elsevier.] *B*: partial cross section of a canine PV sleeve, Masson's trichrome staining. Within the sleeve, sharp transitions in fiber orientation can be observed. Fibers on the luminal side (indicated by "L") predominantly show a circumferential orientation. [Modified from Verheule et al. (585), with permission from Oxford University Press.] *C*: lines of conduction block within a sleeve correlate with transition in fiber orientation. *Right*: endocardial fiber orientation, with asterisk and circle indicating abrupt changes in fiber orientation. Lines of conduction block, perpendicular to the length axis of the vein, were observed during slow pacing (*left*) and especially when paced with extrastimuli (*middle*). [Modified from Hocini et al. (241), with permission from Wolters Kluwer Health.] *D*: repetitive firing in a human PV. Initial three beats of PV "focal" firing pattern following a normal sinus beat. All three beats originated at the same site, with reentrant conduction into the vein during beat 2 and conduction block at part of the ostium during beat 3. [Modified from Patterson et al. (440), with permission from John Wiley and Sons.]

4. Tissue structure of PVs

Apart from differences in cellular electrophysiology, the PV area also shows salient features in gross anatomy and fiber geometry. The area between the PVs shows a strong preferential superior-inferior fiber orientation on the epicardial side, corresponding with the main propagation direction during sinus rhythm (364). In dog PVs, fiber orientation on the endocardial slide of the sleeves was predominantly circumferential, often with sharp transitions in fiber orientation to the epicardial side at the proximal region of the veins (Fig. 3*B*) (585). After 3–5 mo of rapid atrial pacing, canine PVs showed a heterogeneous increase in extracellular matrix volume, coinciding with rapid repetitive activity originating in the veins (107). In patients, there may be a relation between PV structure and the presence of AF, with a marked variation in PV anatomy between individuals (228, 285). The superior PVs had longer and thicker sleeves in AF patients (285). Guerra et al. (215) specifically linked areas of PV wall thickening to high-frequency potentials and the origin of ectopic beats. PVs in AF patients also showed more fibrosis and discontinuities (228).

5. Conduction patterns in myocardial sleeves

Fractionated electrograms have been reported in the PV-left atrial junction in humans and dogs (261, 528). This

fractionation was explained by slow conduction and/or conduction block between the myocardial sleeves of the PVs and the adjacent atrial myocardium. Zones of conduction delay and fractionated electrograms in normal canine PVs were associated with abrupt changes in fiber orientation (Fig. 3*C*) (241). Using optical mapping on the canine PV area, Arora et al. (23) demonstrated 2:1 conduction block from the proximal to distal part of PVs during fast pacing. Reentry around a functional line of block close to the PV-left atrial junction could be induced by premature stimuli. The core of reentrant circuits were also clustered in a zone of increased anisotropy at the PV-left atrial junction in another study on canine PVs (110). Using monophasic action potentials in AF patients, Narayan et al. (405) described that the slope of the APD restitution curve was larger than 1 in paroxysmal AF patients, which allowed single premature beats to initiate AF. In contrast, in persistent AF patients, the slope was smaller than 1, due to the occurrence of local activation delays (405). While application of acetylcholine flattened the APD restitution curve and reduced APD alternans in canine PVs, the inducibility of rapid reentrant activity was increased (453). In addition, activation of inward rectifier K^+ channels by adenosine increased dominant frequencies at the PV-left atrial transition in paroxysmal AF patients, supporting a reentrant mechanism (25). Indeed, unstable reentry circuits with entry and exit points at the PV-LA junction have been mapped in human PVs, in conjunction with relatively short effective refractory periods and anisotropic conduction (310). Rapid reentrant PV activity and fibrillatory conduction in the rest of the atria may be interdependent, because PV isolation by RF ablation reduced the probability both of bursts of PV tachycardia and of persistent AF (429).

On the other hand, examples of focal spread of activation have also been reported. In normal canine atrial preparation, optical mapping revealed focal activity with a relatively long cycle length near the PV-left atrial junction during isoproterenol infusion (23). Using high-density epicardial mapping, Zhou et al. (653) observed repetitive focal activation patterns with a short cycle length in PVs of dogs after 1 mo of rapid atrial pacing. Focal spread of activation in the PVs, often with block within the myocardial sleeve, was also reported in a canine heart failure model (423) as well as in patients with AF (Fig. 3*D*). The mechanism underlying these focal PV activation patterns was compatible with triggered activity related to increased Ca^{2+} load (440, 441) (see also sections **III** and **V**).

In summary, PVs show differences from the normal atrial myocardium in cellular electrophysiology and fiber geometry. Also, abnormal cell types have been described in some studies. These peculiarities may act in concert to cause arrhythmogenic activity of PVs.

C. Excitation-Contraction Coupling

Research during the past 50 years has revealed that Ca^{2+} ubiquitously mediates excitation-contraction, excitation-secretion, and excitation-transcription coupling. Furthermore, numerous cellular responses are directly or indirectly regulated by this important second messenger.

Mechanisms of excitation coupling in atria and ventricles have been expertly reviewed in great detail elsewhere (46, 55). Basically, excitation-contraction coupling is initiated by depolarization of the cell membrane by an action potential that triggers opening of voltage-dependent L-type Ca^{2+} channels. Influx of Ca^{2+} triggers the release of Ca^{2+} from the sarcoplasmic reticulum through Ca^{2+} release channels or "ryanodine channels" (RYR) in a process called Ca^{2+}-induced Ca^{2+} release. Ca^{2+} binds to troponin C activating the actin-myosin filaments, and the myocyte starts to contract. Relaxation is initiated by a decline of the cytosolic Ca^{2+} concentration mainly by resequestration of Ca^{2+} into the sarcoplasmic reticulum by the sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA), which is tightly controlled by its inhibitory protein phospholamban, and extrusion to the extracellular space by the Na^+/Ca^{2+} exchanger (NCX). In hearts of larger mammals, like dog, rabbit, and human, reuptake into the sarcoplasmic reticulum and elimination by the NCX account for ~70 and 30% of Ca^{2+} removal, respectively (36), while in mice and rats up to 90% of Ca^{2+} is reuptaken into the sarcoplasmic reticulum (see sect. **IV***I*) (36).

Due to the specific ultrastructure of atrial myocytes, the spatiotemporal pattern of Ca^{2+} release and the way Ca^{2+} release is controlled differs from that in ventricular myocytes (55). Most atrial myocytes lack appreciable t tubules or possess only a rudimentary and more irregular transverse t-tubular system (Fig. 4, *A* and *B*) (32, 560). An electron microscopic study in rat atrial myocytes showed a transversely oriented tubular system along the Z-lines which was formed from the membrane of the sarcoplasmic reticulum but not the sarcolemma (639). As in ventricular myocytes, immunostaining of RYRs revealed that most of these receptors are aligned along the Z-lines of the sarcomeres (nonjunctional sarcoplasmic reticulum). In atrial myocytes, an additional population of RYRs embedded in sarcoplasmic reticular membranes is located directly underneath the sarcolemma in close vicinity to the L-type Ca^{2+} channels, thereby forming the junctional sarcoplasmic reticulum (90, 229).

These ultrastructural properties of atrial myocytes have important functional consequences. Upon opening of voltage-dependent L-type Ca^{2+} channels, release of Ca^{2+} starts underneath the sarcolemma at the junctional sarcoplasmic reticulum. From there, Ca^{2+} release spreads towards the center of the cell through Ca^{2+}-induced Ca^{2+} release mechanisms. This centripetal Ca^{2+} "wave propagation" has been documented in atrial myocytes from

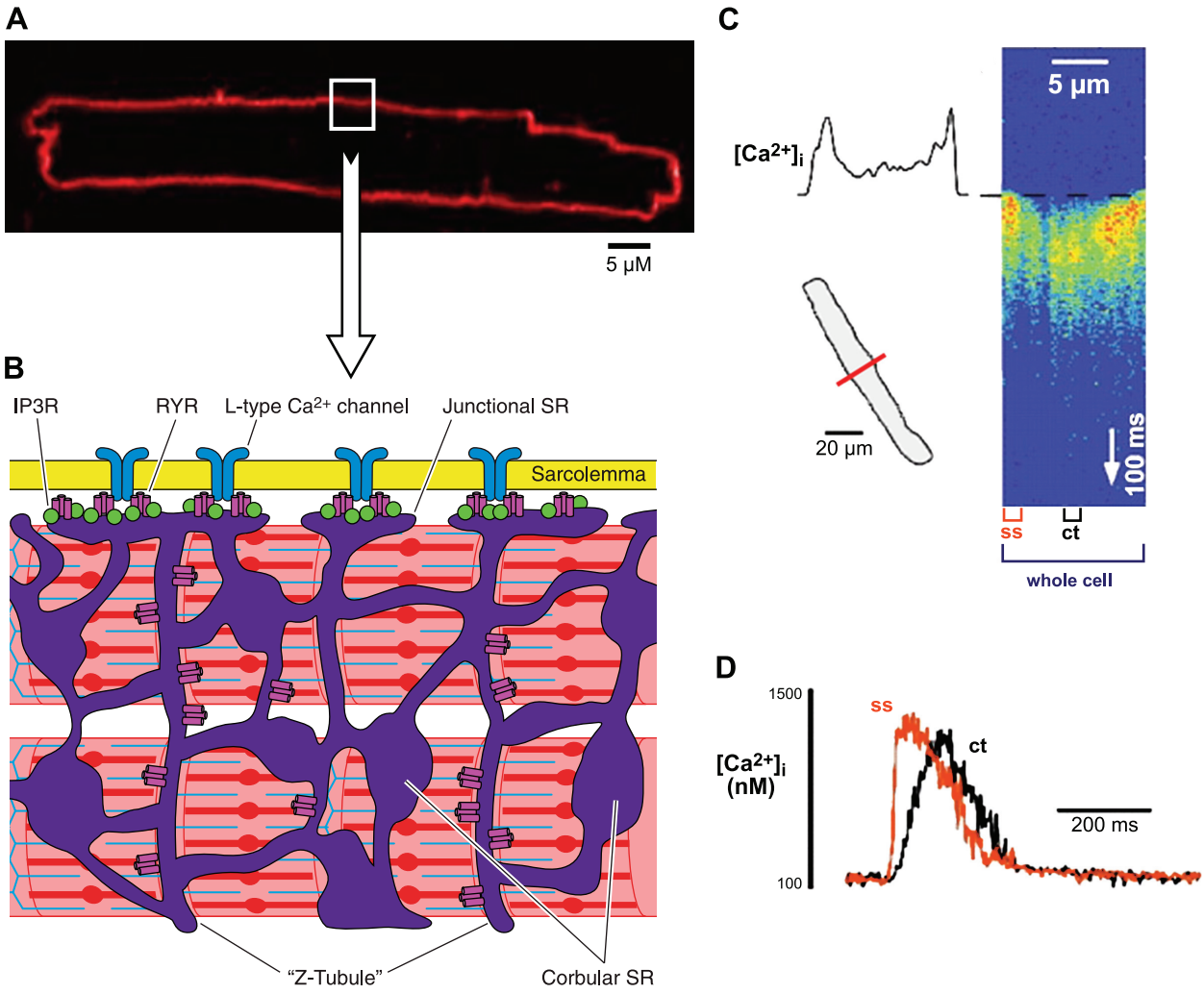


FIG. 4. Excitation-contraction coupling in atrial myocytes. *A*: confocal image of a membrane staining of a rabbit atrial myocyte with di-8-ANNEPS. The myocyte lacks a t-tubular system. *B*: schematic drawing of the ultrastructure of atrial myocytes. Ryanodine receptors (RYR) are located underneath the sarcolemma in close vicinity to the L-type Ca^{2+} channels (junctional SR) or along transverse proportions of the SR oriented along the Z-lines (nonjuntional SR). Inositol 1,4,5-trisphosphate receptors (IP_3R) are located in the junctional SR. Corbular portions of the SR serve as reuptake and storage sites. [Modified from Bootman et al. (55), with permission from *J Cell Sci*.] *C*: confocal line scan of a Ca^{2+} transient in a cat atrial myocyte. The pseudo-color indicates Ca^{2+} concentration (blue represents low, red a high concentration). Ca^{2+} release is initiated underneath the sarcolemma and spreads towards the center of the cell. [Modified from Blatter et al. (50), with permission from John Wiley and Sons.] *D*: the central cellular Ca^{2+} transient (ct) follows the subsarcolemmal (ss) transient with a delay of 10–30 ms but reaches a comparable amplitude. [Modified from Blatter et al. (50), with permission from John Wiley and Sons.]

guinea pigs (342), rats (353), cats (258, 297), and humans (229) (Fig. 4, *C* and *D*). It has been suggested that the regulation of centripetal wave propagation contributes to positive inotropic modulation of excitation-contraction coupling in atrial myocytes (354).

Another consequence of the atrial-specific cellular ultrastructure is that in the junctional sarcoplasmic reticulum, where RYR clusters are located in close vicinity to L-type Ca^{2+} channels, the frequency of elementary Ca^{2+} release events (sparks), which can provoke proarrhythmic Ca^{2+} waves, is higher than in central cellular regions. In addition, L-type Ca^{2+} channel antagonists reduce the spark frequency only in the junctional but only slightly in the nonjunctional regions (515).

III. ELEMENTARY PROARRHYTHMIC MECHANISMS DURING ATRIAL FIBRILLATION

For a long time, reentry of excitation wavefronts was considered the main mechanism of AF. The seminal discovery of localized sources of paroxysmal AF originating from the PVs by Haissaguerre et al. in 1998 (217) has renewed the interest in "focal" sources of AF. Both cellular proarrhythmic mechanisms, like automaticity or triggered activity, and reentrant mechanisms might underlie these phenomena. In the authors' view, the relative contribution of these distinct mechanisms, however, is likely to vary between individual patients and cannot be fully determined at present.

A. Hierarchical and Anarchical Organization of AF

In general, AF can be perpetuated by "hierarchical" or "anarchical" mechanisms. In case of a hierarchical organization of AF, the arrhythmia is driven by a rapid localized source. As the atrial myocardium remote from this site cannot follow the driver in a 1:1 fashion, irregular conduction at a lower frequency ensues. Both focal discharges and reentrant circuits can act as localized sources. Irrespective of its nature, ablation of the source will terminate AF. In the case of anarchical AF, multiple nonlocalized sources act anarchically to sustain AF. As long as a sufficient number of sources is present simultaneously, AF will be sustained. In such a scenario, ablation of a localized driver is not possible, but ablation strategies that restrict the propagation of wavelets may still be successful.

Table 1 gives a few classic examples of hierarchical and anarchical types of AF. Reentrant waves can drive AF in both a hierarchical as well as in an anarchical form of AF. Hierarchical AF can be maintained by multiple forms of reentry. Stable reentry circuits ("mother waves") driving AF can vary in size (430, 509) and are in some cases determined by anatomical structures (73, 370). Even if reentry circuits are unstable, they still might be able to maintain sustained AF as long as they continuously reform and at least one reentry circuit is always present (307). Other examples of hierarchical AF maintained by reentry are rotors that can be either fixed or wandering through the atria (356, 474, 525). Perpetuation of AF by "multiple wavelets" represents an anarchical form of AF with reentrant mechanism.

Cellular proarrhythmic mechanisms (automaticity and triggered activity) can clearly drive AF in a hierarchical manner under certain circumstances (492). However, whether cellular proarrhythmic mechanisms can produce AF in an anarchical type of the arrhythmia is so far hypothetical and technically difficult to determine. Until today, no convincing experiments have been reported supporting "polytopic ectopy" as a cause of AF. This does not mean, however, that disseminated atrial focal discharges cannot occur during AF. In fact, as will be discussed in section **V**, many experimental studies indirectly imply the existence of disseminated atrial ectopy during the fibrillation process as a contributor to the perpetuation of AF.

B. Cellular Proarrhythmic Mechanisms: Automaticity and Triggered Activity

1. Enhanced automaticity

Enhanced automaticity occurs when myocytes possessing pacemaker activity increase their rate of spontaneous discharge. Enhanced automaticity can be due to a lowered threshold of the action potential upstroke (phase 0), a less negative maximal diastolic potential, or an increase in the slope of spontaneous diastolic depolarization (phase 4). A characteristic feature of both normal as well as enhanced automaticity is the phenomenon of overdrive suppression, which is related to intracellular Na^+ accumulation (118, 374). As mentioned in section II *B*, the presence of pacemaker cells in the pulmonary veins or in other regions of the atria outside the sinus node is debatable (391). Over all, there is little evidence for the existence of enhanced automaticity as a proarrhythmic mechanism during AF.

2. Abnormal automaticity

Abnormal automaticity occurs when cells are depolarized by any kind of depolarizing current and the threshold of inward currents is reached (179). In many cases, the degree of depolarization does not allow for complete recovery of Na^+ channels. Thus the upstroke of the action potentials is often mediated by Ca^{2+} inward currents. Abnormal automaticity is less sensitive to overdrive suppression (118) but might be abolished by compounds that shift the membrane potential to more negative values such as activators of inward rectifier currents (acetylcholine and adenosine) (468).

3. Triggered activity

Triggered activity arises from membrane oscillations following normal action potentials (i.e., the trigger). If

TABLE 1. *Examples for hierarchical and anarchical organization of AF*

	Hierarchical AF	Anarchical AF
Reentrant mechanisms	Stable mother wave macroreentrant (73, 370, 430) Stable mother wave microreentrant (356, 509) Unstable reentry circuits (307) Leading circle (5) Rotor (fixed, wandering) (356, 474, 525)	Multiple wavelets (7, 386, 388, 509)
Cellular proarrhythmic mechanisms (automaticity/triggered activity)	Automatic foci (491, 492)	Disseminated atrial focal discharges (hypothetical)

While reentrant mechanisms can underlie both hierarchical and anarchical types of atrial fibrillation (AF), automaticity and triggered activity have so far been demonstrated only in hierarchical forms of AF. Reference numbers are given in parentheses.

such membrane oscillations reach threshold of depolarizing currents, they can provoke new action potentials. Under certain circumstances, such triggered responses can in turn elicit new action potentials, resulting in self-sustaining runs of triggered activity (Fig. 5*A*). Depending on when the membrane oscillation occurs, "early" and "delayed" afterdepolarizations are distinguished.

A) DELAYED AFTERDEPOLARIZATIONS. Delayed afterdepolarizations (DADs) are membrane potential oscillations occurring after full repolarization of the triggering action potential. DADs are favored by conditions producing Ca^{2+} overload, like ischemia, β-adrenergic stimulation, low extracellular K^+ concentration, and tachycardia (117, 277). Excess Ca^{2+} is extruded to the extracellular space by the Na^+/Ca^{2+} exchanger. Due to the 3:1 stochiometry (3 Na^+ are exchanged for 1 Ca^{2+}), the I_{NCX} is electrogenic and produces an inward current that depolarizes the cell. This mechanism forms the basis for the characteristic rate dependence of DADs. The faster the triggering rhythm, the shorter the interval of the triggered response is and the faster self-sustaining episodes of DADs are (277).

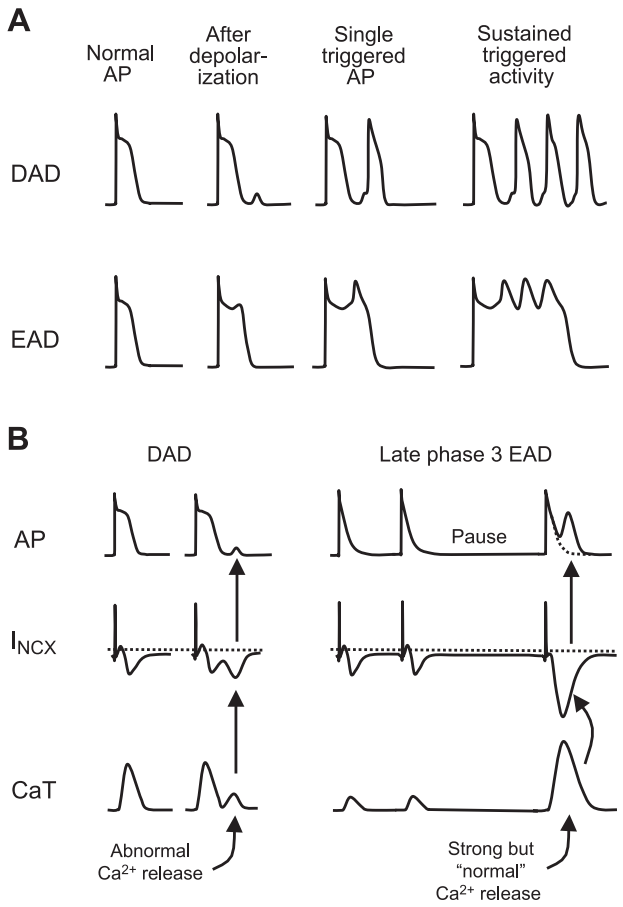


FIG. 5. Cellular proarrhythmic mechanisms in the atria. *A*: schematic illustration of delayed (DAD) and early afterdepolarizations (EAD). Both forms of triggered activity can elicit single or runs of action potentials (AP). *B*: comparison of the mechanism of DAD and late phase 3 EAD. While a DAD is elicited by an abnormal Ca^{2+} release from the sarcoplasmic reticulum, late phase 3 EADs are due to a strong but normal Ca^{2+} release which outlasts the action potential (dotted line). In both cases, the I_{NCX} involved in Ca^{2+} removal depolarizes the cell.

B) EARLY AFTERDEPOLARIZATIONS. Early afterdepolarizations (EADs) are membrane oscillations occurring during phase 2 or 3 of the action potential. They occur in the presence of action potential prolongation. During the prolonged action potentials, "Ca^{2+} window currents" may get activated producing a new action potential upstroke (382). Ca^{2+} window currents occur when the voltage threshold for activation and inactivation overlap, allowing rapid transformational changes from inactivated to closed and open states of the channel (264). Another mechanism likely involved in EADs occurring during β-adrenergic stimulation is spontaneous release of Ca^{2+} from the sarcoplasmic reticulum due to elevated cytosolic Ca^{2+} concentrations (593). In most cases, EADs occur under bradycardic conditions while DADs are more likely to occur during tachycardia or rapid pacing.

More recently, another type of EADs was described by Burashnikov and Antzelevitch (76). In dog atria exposed to combined sympathetic and parasympathetic stimulation, the first action potential occurring after a pause can trigger an EAD during late phase 3 of the action potential ("late phase 3 EADs," see Fig. 5*B*) (76). These EADs exclusively occurred when both a shortening of the action potential (parasympathetic stimulation) and an increase in Ca^{2+} load of the cells (sympathetic stimulation) were present. During the pause, Ca^{2+} is accumulated in the sarcoplasmic reticulum, and the triggering action potential produces a strong release of Ca^{2+} that exceeds the action potential in duration. Because the action potential is short, the high cytosolic Ca^{2+} concentration and the negative membrane potential generate a strong inwardly directed I_{NCX} that will produce the EAD. The important conceptual difference between this type and other sorts of triggered activity lies in the fact that late phase 3 EADs are triggered by a strong but essentially normal Ca^{2+} release from the sarcoplasmic reticulum, while DADs and many forms of EADs are due to abnormal spontaneous Ca^{2+} release from intracellular Ca^{2+} stores. Late phase 3 EADs have been suggested to play a role in the immediate recurrences of AF (77). Interestingly, shortly after cardioversion of AF, ultra-short refractory periods have been reported that might further increase the likelihood for these EADs to occur and to result in reinitiation of AF (155). On the other hand, the occurrence of late phase 3 EADs is strictly limited to the simultaneous presence of agents abbreviating the action potential and enhancing Ca^{2+} load (76, 77, 236, 440). The pharmacological interventions used in these studies (e.g., 1 μM acetylcholine + 1 μM isoproterenol) produce massive shortening of the action potential and provide strong enhancement of Ca^{2+} load. Whether such extreme conditions can occur in patients with or prone to AF is currently unclear.

C. Mechanisms of Reentry

1. Circus movement reentry

Circus movement reentry was first demonstrated in rings prepared from jellyfish (372) and cardiac tissue (381). It is characterized by an activation that can travel along a preformed anatomical structure and reactivate (reexcite) previously excited tissue. A prerequisite for circus movement reentry is recovery of excitability after the previous activation before the next activation reaches the tissue again. As a consequence of this, a short refractory period and a low conduction velocity make circus movement reentry more likely. The minimal pathlength for circus movement reentry can be calculated as the product of conduction velocity and refractory period (wavelength) (613). If the path of the circuit is longer than the wavelength, there is a delay between recovery of the tissue and the moment of reexcitation which is called the "temporal excitable gap." The section of the path which regained excitability before the next excitation is called the "spatial excitable gap," which can be calculated as the product of conduction velocity and temporal excitable gap (Fig. 6*A*).

Initiation of circus movement reentry requires unidirectional conduction block often occurring in regions with long refractory periods. Because of the presence of an excitable gap, circus movement reentry can be entrained (600). External waves can invade the reentrant circuit, causing block and termination of reentry.

2. The leading circle concept

In 1924, Garrey (192) proposed a concept of AF that involved aspects of reentry without a clearly defined anatomical structure. In turtle cardiac muscle, he demonstrated a sustained excitation wave rotating around a stimulation electrode. While in these experiments the stimulus site still might have represented an obstacle for propagation, in 1973, Allessie et al. (6) provided the first evidence that reentry does not necessarily require an anatomical obstacle. In left atrial rabbit atria, tachycardia induced by premature stimulation was due to excitation by rotating waves. Transmembrane electrode recordings demonstrated that the core was not fully activated but instead showed electrotonic depolarizations preventing the tissue from regaining full excitability. According to the "leading circle concept," the size of the reentry circuit adapts to the smallest possible loop in which the wave can continue to propagate (Fig. 6*B*) (5). Excitation wavefronts are propagating through tissue with limited excitability, and the excitable gap is small. Therefore, the arrhythmia is relatively unstable so that small changes in the properties of the tissue can significantly affect the dynamics of the reentry process, the localization of the circuit, and the activation cycle length. Because of the small excitable gap, premature stimulation is less likely (compared with circus movement reentry) but still able to invade the reentry circuit (600). In line with this, entrainment of AF in a limited area around the stimulation electrode (1–4 cm) has been demonstrated in experimental (288) and clinical studies (437).

3. Spiral wave reentry

The theory of spiral wave reentry originally stems from observations of chemical reactions in excitable media (619) and has strongly been influenced by insights obtained from imaging of intracellular Ca^{2+} waves in

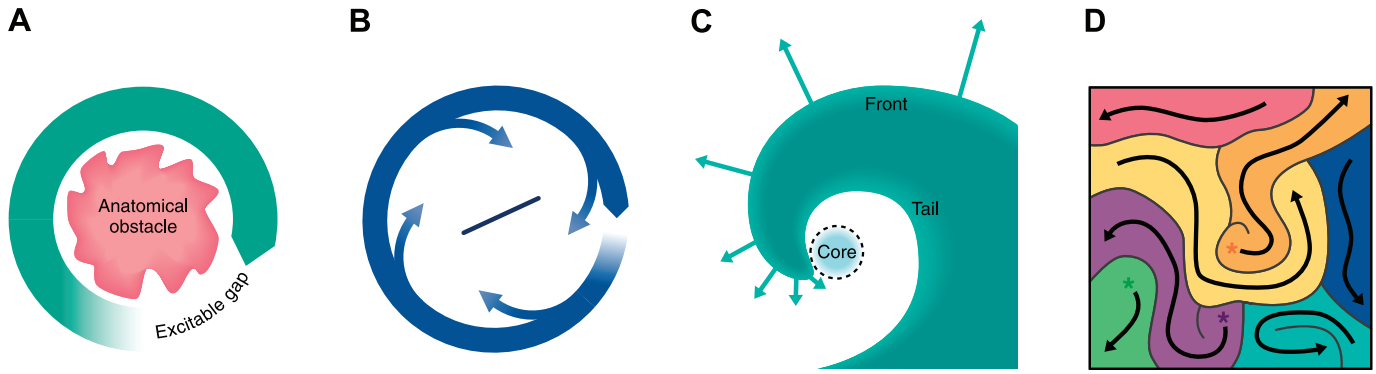


FIG. 6. Mechanisms of reentry. *A*: circus movement reentry. The size of the anatomical obstacle, the conduction velocity, and the refractory period are the main determinants of this kind of reentry. The spatial excitable gap is the section of the path in which full excitability has been regained. *B*: leading circle concept. As no anatomic obstacle exists, the reentry path adopts the minimal possible path length, which depends on conduction velocity and refractory period. The spatial excitable gap is small. The central region is rendered unexcitable by electrotonic depolarization by the circulating fibrillation wave. *C*: rotor theory reentry. The rotor rotates around an excitable yet unexcited core. Lengths of arrows show conduction velocity. *D*: chaotic activation pattern caused by multiple wavelets. Waves are separated by multiple lines of conduction block. Block lines may also occur within waves and form pivot points. Asterisks denote waves appearing within the mapped area presumably due to transmural conduction breakthroughs reflecting a 3-dimensional substrate for AF. See text for further explanation.

Xenopus oocytes (114, 316) and the results of computer simulations (438, 571).

To understand spiral wave reentry, it is important to realize that propagation in the heart depends on a critical balance between the "source" and the "sink" of a depolarizing current. The source of a wavefront is the diffusion current generated by excited tissue tending to depolarize downstream cells, which act as a sink. If the sink is too large, the source current is not sufficient to excite the downstream cells and propagation fails. In convex wavefronts, cells at the leading tip have to activate more cells in front of it, resulting in a relatively small source current and a low conduction velocity. In a concave wavefront, many cells contribute to the activation of a lower number of downstream cells which accelerates conduction (Fig. 7).

The classical protocol to induce spiral wave reentry is to provoke a perpendicular collision of a wavefront with the wavetail of another wave (119). Where the tissue is still refractory, the colliding wave will block while the wave encounters excitable tissue behind the wave tail. The colliding wave will turn towards newly recovered cells and in this way the reentry wave adopts the shape of a rotor (Fig. 6*C*). Importantly, the curvature of the wavefront increases towards the core. Because of increasing source-sink mismatch, the conduction velocity declines towards the core until block occurs (dotted line in Fig. 6*C*). Thus the core, though being excitable, remains unexcited during spiral wave reentry. Also, the core will tend to shorten the action potential duration in its vicinity which together with the low conduction velocity explains the short wavelength (conduction velocity times refractory period) in its proximity.

In general, spiral wave reentry provides a comprehensive concept for reentry during AF. The only, though significant, shortcoming of this concept is that spiral wave reentry has never been documented in AF in humans. More specifically, to the best of the authors' knowledge, there is not a single graphical depiction of sustained spiral waves occurring during AF in patients. A possible explanation might be that in human atria electrophysiological heterogeneity due to structural changes such as fibrosis is much more pronounced than in many animal models, and therefore, more complex propagation patterns occur. Interestingly, structural remodeling resulting in fibrosis of the atrial wall in dogs with heart failure has been shown to reduce the stability of rotors and promote the existence of "multiple unstable rotors" (556), a conduction pattern essentially resembling multiple wavelets.

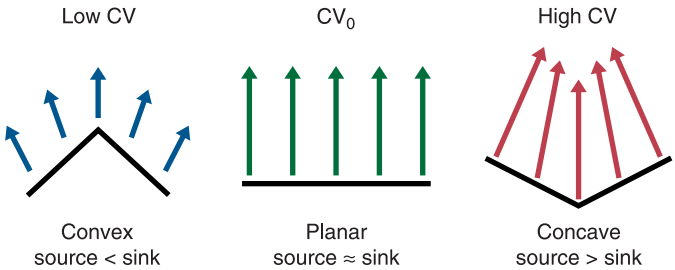


FIG. 7. Effect of wavefront curvature on conduction velocity. In a convex wavefront, cells serve as current source for more than one downstream cell. Because of the relatively strong sink, conduction velocity is low. In contrast, current source of more than one cell adds up in a convex wavefront. As a result, the source is relatively strong and conduction velocity high.

4. The multiple wavelet hypothesis

In the late 1950s, computer models of AF demonstrated that, based on simple assumptions regarding refractoriness and conduction velocity, reentrant wavelets might wander through an excitable medium in a seemingly chaotic pattern (387). According to Moe's "multiple wavelet hypothesis," fibrillation wavefronts continuously undergo wavefront-wavetail interactions resulting in wavebreak and generation of new wavefronts. On the other hand, block, collision, and fusion of wavefronts will tend to reduce their number. As long as the number of wavefronts does not decline below a critical level, multiple wavelets will be capable to sustain the arrhythmia (386, 388). Factors increasing the stability of the fibrillation process include shortening of the refractory period, increased heterogeneity of refractoriness, slowing of conduction, and an increase of the tissue mass. In contrast, prolongation of refractoriness, enhancement of conduction velocity, and reduction of the available substrate will reduce the number of wavefronts until the arrhythmia ceases.

In 1985, Allessie et al. (7) demonstrated for the first time the existence of multiple wavefronts in canine atria exposed to acetylcholine. Numerous experimental and clinical observations could be reconciled with the multiple wavelet hypothesis. For example, during the Maze procedure, the atria are subdivided in multiple electrically independent compartments that are too small to sustain the arrhythmia (128, 129). A comparable mechanism can be postulated for some ablation procedures (see sect. **VI**). Furthermore, prolongation of refractoriness indeed has been shown to reduce AF stability (87, 452).

It has recently been suggested that the multiple wavelet hypothesis would actually not exclude the coexistence of local sources of AF (578). These authors argue that in certain substrates, stable rotors might act as a source of multiple wavelets. As such, this might be true in specific cases (655). Moe's hypothesis, however, goes beyond the simple existence of multiple wavelets. It implies that the fibrillation process is actually driven by them and no localized sources of AF exist ("anarchical" organization of AF). The actual experimental demonstration of multiple wavelets as the mechanism sustaining AF, however, is technically challenging, since fibrillatory conduction

remote from a localized source cannot be distinguished from multiple wavelets with current mapping techniques. Thus the direct demonstration of Moe's multiple wavelet hypothesis would essentially require that all other mechanisms potentially sustaining AF are ruled out. This could only be achieved by recording all electrical activity in the entire atrium, which is not possible with the techniques currently available. As long as it is not possible to identify all local sources of the arrhythmia in AF patients, Moe's multiple wavelet hypothesis will remain an important but hypothetical model for the perpetuation of AF.

IV. EXPERIMENTAL PARADIGMS OF ATRIAL FIBRILLATION

In many patients, AF is associated with some form of underlying heart disease. Congestive heart failure (CHF), hypertension, valvular disease, and aging are all strong clinical predictors of AF (275). To unravel the mechanisms leading to AF, several of these factors have been mimicked in animal models. However, in some patients, AF is observed in the absence of underlying structural heart disease or hypertension ("lone AF"). The analogous animal model is that of rapid atrial pacing (RAP). In some patients, AF episodes may be triggered by increased autonomic activity, which also has been studied in animal models. Postoperative AF has been mimicked in a canine model of sterile pericarditis.

The controlled conditions in animal studies have allowed analysis of separate factors contributing to AF (e.g., rapid activation rates or dilatation). However, in humans, these factors may be present in a mild form over prolonged periods of time, and the final substrate of AF may have evolved very slowly over a period of decades. For practical purposes, stimuli in animal studies are applied in a more intense form, for example, creating acute severe mitral regurgitation to study chronic dilatation (587) and pronounced ventricular tachycardia causing a progression towards decompensating heart failure within a few weeks (326).

In addition, there are further important differences between other animal models and human patient populations. Postoperative AF after open-heart surgery may not be fully represented by sterile paricarditis models, in which the most common arrhythmia is atrial flutter. Several weeks of RAP are required for AF to become self-sustaining, whereas lone AF patients often present with sustained AF episodes. Finally, long-term animal studies in models of aging and long-standing hypertension, two of the most important clinical predictors of AF, are relatively rare. With these caveats, we will give an overview of various animal models and the mechanistic insights gained from them.

A. AF and the Autonomic Nervous System

In paroxysmal AF patients, the onset of AF is frequently preceded by altered autonomic activity (138). One study has indicated that patients with lone AF tend to show a vagal pattern of AF onset, while patients with structural heart disease tend to show a sympathetic pattern (125). However, other studies in lone AF patients have indicated that AF onset is associated with a change in autonomic balance rather than with an increase in vagal or sympathetic drive alone (181, 563). Paroxysms of AF and atrial tachycardia were observed in dog models of both intermittent RAP and CHF induced by rapid ventricular pacing (420, 554). In both models, monitoring of the activities of the left stellate ganglion and vagal nerve in ambulatory dogs revealed that the onset of AF or atrial tachycardia was predominantly associated with simultaneous sympathovagal discharges.

It has long been recognized that cholinergic activity can promote AF (192). Electrophysiological effects are instantaneous upon application of acetylcholine or vagal stimulation. Mainly through an increase in I_{KACh} (and in the presence of β-adrenergic stimulation also by a reduction in $I_{Ca,L}$) APD and AERP are shortened, thereby decreasing the wavelength of reentry circuits (509). The degree of AERP shortening depends on the acetylcholine concentration applied or the intensity of vagal stimulation. At very high concentrations of acetylcholine, AERP may become as short as 30 ms in dogs (509). Although cholinergic AF has been investigated for decades, the exact mechanism is still controversial. In isolated atrial preparations from normal animals, AF can often not be induced. However, in the presence of acetylcholine, prolonged AF episodes are frequently observed after a single premature beat. In isolated canine atrial preparations in the presence of 0.5–2 μM acetylcholine, Allessie et al. (7) described multiple wavelets wandering through the atria in a chaotic pattern, without any single tissue area dominating the activation pattern. In contrast, Jalife and coworkers (360, 525) reported a gradient in activation frequency during AF, with the highest activation frequencies occurring in the left atrium in the presence of acetylcholine. These high frequencies (up to 30 Hz) were proposed to originate from stable microreentrant circuits or "rotors" (356).

The mechanism of cholinergic AF may actually depend on the acetylcholine concentration applied. Schuessler et al. (509) have described conduction in a canine right atrium preparation. Here, a premature stimulus caused multiple wavelet reentry at acetylcholine concentrations up to 1 μM. In this small preparation, multiple wavelet reentry did not sustain for longer than 2 s. Fibrillation was only sustained (>2 min) at very high acetylcholine concentrations (>10 μM), due to the formation of small and localized reentrant circuits with a fast cycle length of

30–50 ms that dominated activation in the entire preparation (Fig. 8*A*). Using a detailed mathematical model, Kneller et al. (296) have demonstrated that ACh can stabilize spiral wave reentry. A heterogeneous distribution of ACh, resulting in dispersion of refractoriness, led to fibrillatory conduction away from the core of the spiral wave.

Adrenergic regulation of atrial electrophysiology is more complex. β-Adrenergic receptor activation increases I_{CaL} (331), I_{Kur} (330, 648), I_{Ks} (479), and I_{KACh}/I_{KH} (641). On the other hand, α-adrenergic stimulation inhibits I_{to} (175), I_{K1} (174), and I_{KACh}/I_{KH} (63, 641). In canine atrial myocytes, the α-adrenergic agonist phenylephrine slightly increases APD, whereas the β-agonist isoproterenol decreases APD (334). As a net result of sympathetic stimulation, the plateau potential of the action potential is increased (527), while the total APD is unaffected or even decreased (654). The resulting increase in sarcoplasmic Ca^{2+} load may enhance triggered activity (620).

The macroscopic innervation of the heart has been described in detail by Kawashima et al. (282). Within the atria, the autonomic nervous system forms an intricate system of ganglionated plexi, especially concentrated in a number of interconnected fat pads (434). Targetted ablation of these fat pads may (490, 493) or may not (131, 421) be a useful adjunct in treating AF in patients. The effect of vagal stimulation on atrial refractoriness is heterogeneous because of heterogeneity in the distribution of parasympathetic nerve endings and/or M_2-cholinoceptors (4, 343). In contrast, the effect of sympathetic stimulation on refractoriness is more homogeneous (343). Enhanced heterogeneity in vagal innervation (by ablation of the right PV fat pad) (237) and in sympathetic innervation (by application of phenol) (424) can both increase AF stability.

The PV region, and the PV-left atrial junction in particular, is rich in both parasympathetic and sympathetic

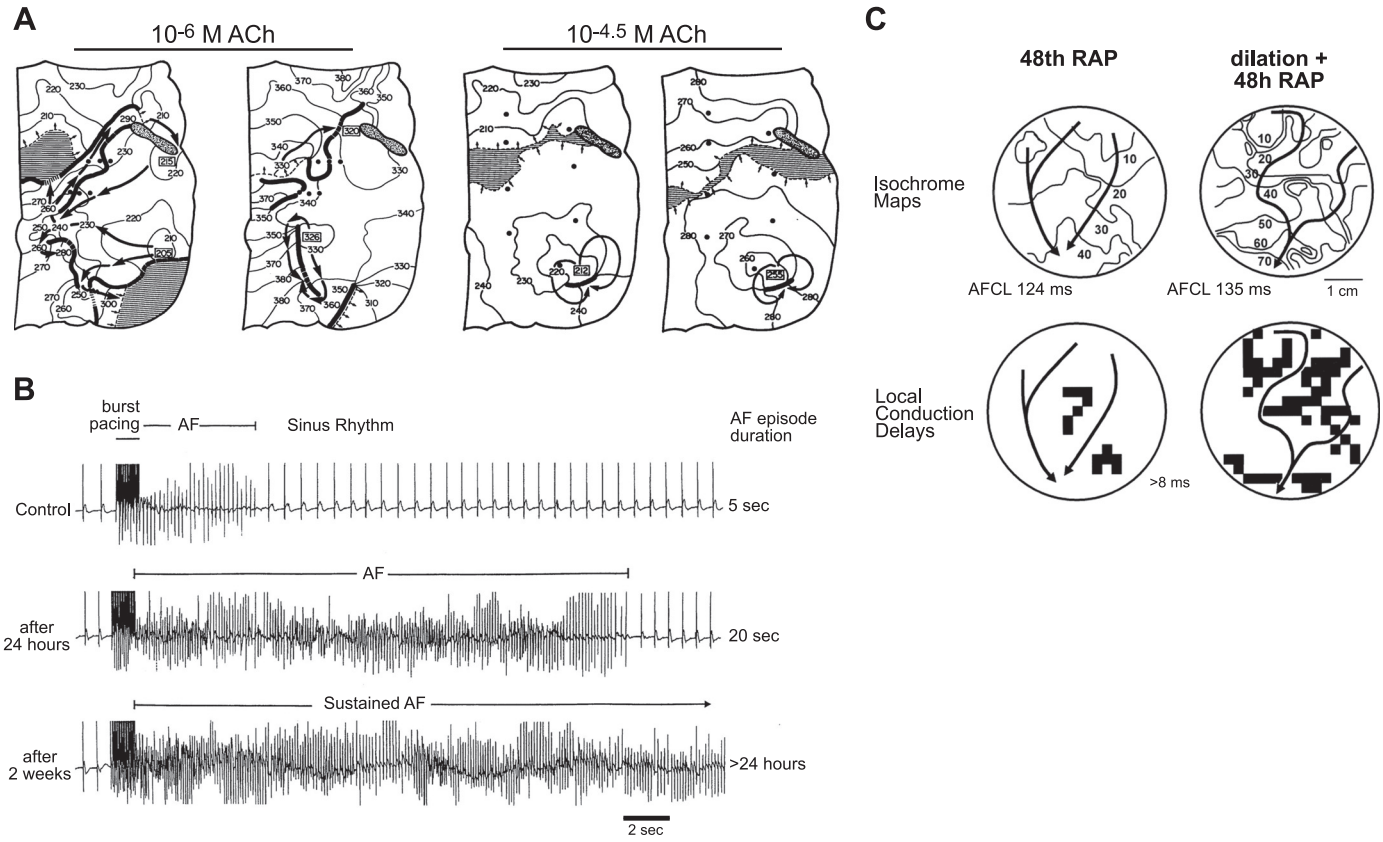


FIG. 8. Mechanism of AF in animal models. *A*: during infusion of acetylcholine (ACh), the mechanism of AF can depend on the applied dose. At 10^{-6} M ACh, multiple wavelet reentry with functional lines of conduction block was observed in a canine right atrial preparation. At a concentration of $10^{-4.5}$ M, a single micro-reentrant circuit became dominant in the same preparation. [Adapted from Schuessler et al. (509), with permission from Wolters Kluwer Health.] *B*: AF begets AF: in control goats, a high-frequency burst evokes only 5 s of AF. After 24 h of artificially maintained AF with a "fibrillation pacemaker," episode length has increased to 20 s. After 2 wk of AF, episodes last for more than 24 h. [Modified from Wijffels et al. (614).] *C*: AF with and without underlying structural heart disease. Fibrillation maps recorded after 48 h of rapid atrial pacing (RAP) from the left atrial free wall of a control goat (*left*) and a goat after 4 wk of atrioventricular block (*right*). In dilated atria, fibrillation waves were less uniform, and local crowding of isochrones occurred more frequently. Local conduction delays of 8 ms between neighboring electrodes are displayed in the lower panels. A higher degree of dissociation of fibrillation waves was observed in dilated atria. [Adapted from Neuberger et al. (410), with permission from Elsevier.]

nerve endings (22, 553). In addition, APD shortening during acetylcholine infusion is relatively large in the posterior left atrium (335), probably due to a relatively high expression of I_{KACh} (487). The normal physiological relevance of the high degree of autonomic innervation and responsiveness of the PV myocardium is unclear. As detailed in section **II***B*, PV myocardial sleeves in healthy animals or preparations probably do not show rapid spontaneous activity, but it can be elicited by both parasympathetic and sympathetic stimulation. As explained in section **III**, the combination of vagal and sympathetic activity may provoke triggered activity (mainly late phase 3 EADs) or promote AF triggered by PV firing (441, 494). This combination can create a state with short APD and increased Ca^{2+} load in atrial myocytes and may explain observations that simultaneous sympathovagal discharge is associated with the onset of AF paroxysms in both patients and animal models (described above).

The autonomic ganglia in the PV area can be activated directly by high-frequency electrical stimulation. In dogs, this led to episodes of AF and atrial tachycardia that could be inhibited by both sympathetic and vagal pharmacological blockade (489). In isolated canine PV preparations, autonomic nerve stimulation decreased APD and increased rapid firing associated with EADs (442). Vagal blockade by atropine prevented APD shortening in these preparations and abolished rapid firing. Sympathetic blockade by atenolol or a high dose of ryanodine (probably reducing sarcoplasmic Ca^{2+} load) also prevented the spontaneous PV activity.

In summary, the local electrophysiological properties of the PV myocardium may play an important role in AF paroxysms triggered by autonomic imbalance. However, as shown recently by Lemola et al. (321), AF due to strong vagal activation is still observed after selective PV isolation, but it disappeared after selective ablation of the autonomic ganglia overlying the PV ostia. Therefore, the current clinical ablation strategies may be effective because they affect both the PV myocardium and the adjacent autonomic ganglia.

B. Chronic Rapid Atrial Pacing

A major advance in the understanding of AF was the observation that AF itself induces atrial changes that promote AF (393, 614). In a goat model, only seconds of AF could be induced by burst pacing in control animals, whereas AF episodes lasting hours were induced after 2 days of pacing. Sustained AF (>24 h) was observed after a week of artificially maintained AF (Fig. 8*B*) (614). In a canine model, continuous RAP (400 beats/min) for 6 wk increased the AF duration from seconds to minutes (194, 393, 647). The increased AF stability was associated with a decrease in AERP to ~55% of baseline values in both goats and dogs (614, 647). In the dog, the spatial heterogeneity of the AERP was increased by RAP, and this seemed to be an independent determinant of enhanced AF vulnerability (172). RAP causes a progressive decrease in the densities of I_{CaL} and I_{to} and an increase in I_{K1} (96, 647). This process of "electrical remodeling" results in a shift towards the repolarizing currents, leading to APD and AERP shortening (see also section **V***B* and Fig. 10). As in atria infused with acetylcholine, AERP shortening can contribute to AF stability.

Interestingly, the time courses of AERP shortening and AF stabilization diverge. In the goat, the AERP was already maximally reduced after 24 h of AF, whereas AF stability continued to increase over the ensuing weeks (614). Moreover, in goats subjected to sequential 4-wk periods of AF separated by 1 wk of sinus rhythm to allow full recovery of the AERP, an acceleration of AF stabilization was observed, independent of alterations in AERP (562). These findings indicate that besides electrical remodeling, at least one other factor contributes to the progression of AF.

Structural remodeling has been proposed as a candidate for this "second factor," since it takes place in a slower time domain of weeks to months. RAP induces structural alterations that develop progressively, including atrial dilatation (517), myocyte hypertrophy, loss of sarcomeres, accumulation of glycogen, and mitochondrial abnormalities (30, 393). In contrast to the rapid recovery of the AERP after restoration of sinus rhythm, recovery of morphological abnormalities is slow and incomplete (29). The contribution of these structural changes to AF stability is unknown at this moment. Overall, fibrosis is not increased in the atria of AF goats and dogs (30, 326). However, the volume of extracellular matrix (ECM) per myocyte in goats increases during months of AF (29). This pattern is similar to interstitial fibrosis or "microfibrosis" observed during aging, which can lead to slow, discontinuous conduction during transverse propagation (529). Indeed, a recent study compared goats with 6 mo of AF to goats with 3 mo of AF, demonstrating a higher degree of dissociation at the later time point, leading to a larger number of smaller fibrillation waves (587a). This increase in complexity of fibrillatory conduction was accompanied by myocyte hypertrophy and increased interstitial fibrosis. In cell cultures, rapid pacing can cause myocytes to release factors that alter the behavior of cultured fibroblasts (81). In vivo, such paracrine factors released by myocytes at high activation rates may modulate fibroblasts function, possibly contributing to ECM remodeling.

Another factor that can directly affect myocardial conduction is electrical coupling between myocytes mediated by gap junctions. In the goat model, no quantitative changes in the total expression of the gap junction proteins Cx40 and Cx43 levels were found, but the distribution of Cx40 became more heterogeneous during persis-

tent AF (572). The significance of Cx40 heterogeneity for AF is unclear; conduction during slow pacing was not affected (572), but the effects during fibrillatory conduction may be more pronounced.

For the interpretation of RAP models, the possible contribution of high and irregular ventricular rates to atrial structural remodeling should be considered. In the dog, most early studies were performed with a single atrial burst pacemaker, leading to a high ventricular rate. Most researchers now combine RAP with complete AV block and a separate low-rate ventricular pacemaker (80–100 beats/min). This distinction among RAP models may explain some of the discrepancies in the literature. For example, dogs with a single atrial pacemaker show a progressive reduction in atrial conduction velocity (194) and an underlying decrease in I_{Na} (193), whereas the double pacemaker/AV block model does not (326, 586). One study in goats has investigated the role of high ventricular rates. Atrial structural abnormalities were observed in a model of RAP alone, but were virtually absent in a model of RAP with a controlled ventricular rate (500). In dogs, 3 mo of RAP increased atrial fibrosis even after AV node ablation, but to a smaller degree than in a group without controlled ventricular rate (31). In sheep, 15 wk of RAP with and without controlled ventricular rate were compared (13). With a controlled ventricular rate, many animals did not develop persistent AF, and no significant increase in fibrosis was observed. In contrast, in the group without AV block, persistent AF developed more rapidly, along with conduction heterogeneity and extensive atrial fibrosis. Thus RAP without a controlled ventricular rate appears to provoke structural changes that increase AF stability. These changes might be caused by a mild form of a ventricular tachycardiomyopathy. RAP models with and without controlled ventricular rate are both relevant to human AF, corresponding to AF without and with effective rate control, respectively.

Taken together, the increased stability of AF in models of RAP involves electrical remodeling by shortening of AERP and contribution of a "second factor," which is likely to involve structural alterations.

C. Heart Failure

To investigate how CHF promotes AF, an experimental model of CHF has been used by Nattel and co-workers (326). Overt heart failure was induced by pacing dogs with a ventricular pacemaker at a high rate (>200 beats/min) for 5 wk. The duration of induced AF episodes was increased from a few seconds in control dogs to several minutes in CHF dogs. Although in this model some ionic currents were altered (see sect. **V** and Fig. 10), CHF did not reduce APD and AERP or increase AERP heterogeneity. In fact, AERP was significantly increased in intact dogs (97, 539). In addition, CHF did not alter the overall conduction velocity during slow pacing (326). Therefore, the mechanisms leading to increased AF stability due to CHF and RAP show important differences.

In contrast to RAP models, atrial fibrosis is dramatically increased in CHF dogs (326), with large areas of connective tissue. These structural abnormalities were accompanied by regional conduction heterogeneity (Fig. 12*C*). Further studies have supported the key role of atrial fibrosis in the promotion of AF in this model (97, 522). When rapid ventricular pacing was followed by a 1-mo period of slow ventricular pacing, ventricular function and atrial dimensions recovered completely (97). At this point, atrial electrophysiology had also normalized, but atrial fibrosis, conduction heterogeneities, and AF stability remained present, indicating that AF stability was determined by structural rather than electrical remodeling (97, 522).

Atrial damage in the CHF model occurs rapidly, with a peak in inflammation, apoptosis, and necrosis within 24 h after activation of the ventricular pacemaker (220). These indicators of tissue injury gradually disappeared in the following 5 wk. In the ventricle, fibrosis developed only slowly over the entire period of ventricular pacing, leading to a modest increase in fibrosis over a 5-wk period. In fact, changes in gene expression were far more extensive in the left atrium than in the left ventricle (89).

The renin-angiotensin system is an important mediator in the development of an AF substrate in CHF. In the atria of CHF dogs, tissue angiotensin II levels were rapidly increased by rapid ventricular pacing and remained elevated thereafter (220). Inhibition of ANG II production by the angiotensin-converting enzyme (ACE) blocker enalapril not only attenuated CHF-induced atrial fibrosis but also reduced conduction heterogeneity and AF stability (328, 518). Atrial fibrosis and increased AF stability in the canine CHF model can also be inhibited by simvastatin (523), pirfenidone (318), polyunsaturated ω3 fatty acids (478), and sprionolactone (640). The PPARα activator fenofibrate was not effective in this model (523), but in rabbits with tachycardiomyopathy-induced CHF, the PPARγ acitvator pioglitazone did reduce atrial structural remodeling and AF stability (519).

The differences in atrial pathology between CHF and RAP models are reflected in gene expression profiles as assessed by microarrays (88). In the canine RAP model, changes entailed mainly downregulation of gene expression. In the CHF model, changes are quantitatively larger and include a strong upregulation of extracellular matrix-related genes.

D. Animal Models of Chronic Atrial Dilatation

Atrial dilatation can be both cause and consequence of AF. In patients, atrial enlargement correlates with the incidence of AF (183, 233), and left atrial size is a strong independent predictor for the development of AF (42). On the other hand, several studies imply that AF also causes atrial enlargement (485), and cardioversion to SR leads to a decrease in atrial dimensions (607).

Chronic atrial dilatation occurs in several animal models with an increased AF vulnerability. In a dog model of RAP with a controlled ventricular rate, the diastolic left atrial surface area increased by 24% (estimated by considering the atrium as a sphere with an area of $4\pi r^2$) (517). In a sheep model of chronic hypertension, left atrial surface area increased by 22% (292), and by an estimated 80% in a canine CHF model (517). However, in these models, the role of atrial dilatation itself in the development of a substrate of AF cannot be established. For this purpose, several models of chronic atrial dilatation without heart failure have been developed. Although most of these models display an increased AF vulnerability, they differ considerably in the structural changes associated with atrial dilatation. Apart from any structural changes, the increase in substrate size inherent to atrial dilatation will also contribute to AF stability, as shown by Zou et al. in a mathematical model (655).

Partial occlusion of the pulmonary artery and partial avulsion of the tricuspid valve in dogs resulted in enlarged right atria with cellular hypertrophy and increased interstitial fibrosis (59). The increased AF stability in this model was not due to electrical remodeling since action potentials were not significantly different from control dogs. In dogs with mitral regurgitation (MR) due to partial mitral valve avulsion, the left atrium dilated within minutes, followed by a gradual increase to 167% of the baseline left atrial area after 3 wk (587). Histological analysis demonstrated areas of inflammatory infiltrates and slightly increased fibrosis, without myocyte hypertrophy (214, 587). Cx40 and Cx43 expression in the atrial free walls did not show marked changes (214). The increased duration of induced AF episodes could not be explained by a decrease in wavelength, because the AERP was homogeneously increased and the overall conduction velocity was unchanged. High-resolution optical mapping revealed heterogeneous left atrial conduction heterogeneity during pacing with short cycle lengths and extrastimulation (see Fig. 12*A*), indicating that the increased AF vulnerability was caused by increased conduction heterogeneity associated with structural changes (586), reminiscent of the canine CHF model. By analyzing activation sequences during AF in a canine MR model, Cox et al. (129) showed that AF was maintained by the presence of multiple unstable reentrant circuits.

In another model of chronic atrial dilatation, the time course of atrial dilatation and AF stabilization was studied (411). Chronic complete AV block in goats resulted in a slow idioventricular rhythm, and volume overload of the ventricles caused a progressive atrial enlargement and myocyte hypertrophy. In a time period of 4 wk of AV block, the right atrial area gradually increased by 29%. Atrial dilatation was paralleled by a gradual increase in AF stability while AERP and dispersion of refractoriness remained constant. During sinus rhythm and slow pacing, atrial conduction velocity was slightly increased. However, atrial mapping showed a higher incidence of areas with slow conduction during fast pacing in dilated atria (see Fig. 12*B*). Interestingly, atrial fibrosis was not increased in this model, suggesting that atrial fibrosis does not form a necessary condition for increased AF vulnerability in dilated atria. Also, the expression of Cx40 and Cx43 did not show marked alterations. The difference in atrial fibrosis between models may be related to the time course of atrial dilatation. In the goat AV block model, the slower time course may allow atrial myocytes to adapt and undergo cellular hypertrophy. In the canine models, partial valvular avulsion causes a sudden onset of dilatation, which may lead to acute damage and subsequent replacement fibrosis.

In a rabbit model, an arteriovenous shunt led to chronic overload with an estimated increase in left atrial surface area of 112% (238). Atrial conduction velocity was significantly decreased by ~30%. The inducibility of AF was increased, and in the majority of cases, the arrhythmias arose from the posterior left atrium, with either a focal pattern of origin or a single reentrant circuit. In this model, the expression levels of both Cx40 and Cx43 protein were significantly reduced (230).

In summary, animal models have demonstrated that chronic atrial dilatation increases AF stability without shortening of refractoriness. The contribution of increased tissue mass is also probably limited. Fibrosis and cellular hypertrophy occur in most but not all models of atrial dilatation. The relationship between these factors and alterations in conduction will be discussed further in section **V***E*.

E. Models of AF Combined With Structural Heart Disease

Some 70–80% of AF patients have some preexisting form of structural heart disease (325). There is evidence that the time course of AF stabilization in patients with structural heart disease is more rapid than in lone AF patients (276, 283). Thus the most common scenario of AF stabilization is that electrical remodeling takes place in atria that are already structurally remodeled. From animal studies, little is known about the process of remodeling

due to AF, AF stabilization, and the efficacy of antiarrhythmic drugs in this setting.

Everett et al. (170) studied a dog model in which atrial dilatation due to mitral avulsion was combined with RAP for 6 wk, leading to sustained AF. After cardioversion, spontaneous AF episodes and a high incidence of atrial premature beats were observed, but these phenomena disappeared within a week. However, atrial structural changes and the vulnerability to induced AF remained. Neuberger et al. (410) created AV block in a goat model, leading to atrial dilatation. After 4 wk, RAP was applied for 48 h. In dilated atria, RAP still led to AERP shortening, but the AF cycle length did not decrease, indicating a longer excitable gap during AF. The duration of AF episodes after 48 h of RAP was significantly prolonged in dilated atria compared with nondilated atria, with an increased incidence of conduction block (Fig. 8*C*).

In dogs, RAP with a preexisting substrate of CHF caused less AERP shortening than RAP alone (521). However, the conduction velocity was decreased by RAP in the presence of CHF but not by either CHF or RAP alone. Atrial fibrosis and AF stability due to CHF was not exacerbated by 1 wk of RAP, but the incidence of sustained AF was increased. Also, RAP in the presence of CHF failed to alter the density of I_{to}, I_{NCX}, and I_{Ks} and had a smaller effect on I_{CaL} and I_{K1} than RAP alone (96). Thus the effects of AF in atria with preexisting structural heart disease, a common clinical scenario, may differ from those of lone AF.

F. Sterile Pericarditis

A clinically highly relevant form of AF occurs in up to 50% of patients in the first days after cardiac surgery (157). This postoperative form of AF has been mimicked in a canine model of sterile pericarditis, in which the atria are dusted with talcum powder and covered with a layer of gauze at the end of open heart surgery (435). The predominant arrhythmia in this model is atrial flutter. However, as in patients (467, 598), the initiation of flutter requires a previous period of AF (520). During this transitional phase of AF, a line of functional block can develop, most often along the crista terminalis between the superior and inferior vena cava (73, 370, 569). If this line of block becomes long enough, a stable reentry circuit can develop and AF converts to flutter. Conversely, if the line of block at the core of the flutter circuit becomes too short, flutter can convert to AF (430, 601). During AF in the sterile pericarditis model, unstable reentrant circuits with a very short cycle length have been observed (307). These unstable circuits often disappear and reform around anatomic obstacles or functional lines of block. Even if only one circuit is present, fibrillatory conduction can be maintained when the circuit is too fast for 1:1 conduction to the rest of the atrium.

Altered connexin expression may be an important contributor to atrial conduction disturbances in sterile pericarditis. Cx40, Cx43, and α-actinin disappeared in the epicardial layer and were reduced in the midmyocardial layer, while the endocardial distribution was normal (472). These changes may lead to transmural heterogeneity in electrical coupling and a disruption of epicardial conduction. The importance of the inflammatory component in arrhythmia vulnerability is underscored by studies showing that anti-inflammatory agents such as atorvastatin (308) and prednisone (202) can prevent AF and atrial flutter in this model.

G. Hypertension

Long-term animal studies in models of hypertension, an important clinical predictor of AF, are relatively rare. In 11-mo-old spontaneously hypertensive rats, the inducibility of atrial tachycardia was increased, accompanied by a decrease in I_{CaL} and an increase in fibrosis (108). In a sheep model of long-standing elevated blood pressure induced by prenatal corticosteroid exposure (mean arterial pressure 94 vs. 71 mmHg in control sheep), 4- to 5-yr-old animals had increased AF stability, reduced conduction velocities, no change in refractoriness, and increased fibrosis with myocyte hypertrophy and myolysis (292). Thus models of elevated blood pressure seem to share some important features of the AF substrate with the more extensively studied models of structural heart disease of CHF and dilatation. Unfortunately, no data are available on the signaling pathways involved in the structural remodeling process induced by hypertension.

H. Aging

Although the clinical prevalence of AF strongly increases with age (176), the intrinsic contribution of aging to AF promotion is difficult to study in humans due to the long time span of senescence and the presence of numerous confounding factors. AF is also quite common in some species of domestic animals during aging, but its pathogenesis has not been studied systematically (71). Several animal models have been used to investigate aging-related AF. Spach et al. (536) studied conduction patterns in canine atria and found an age-dependent slowing of transverse propagation that correlated with the development of extensive collagenous septa that separated small groups of fibers. Similarly, in a comparative study of young and old rats, AF could only be induced in old rats, while the AERP was not different between age groups (231). Instead, conduction slowing and enhanced AF vulnerability were associated with an age-dependent increase in heterogeneous interstitial fibrosis.

In dogs, Koura et al. (304) demonstrated that with age, the amount of interstitial fibrosis and fatty infiltrates increased and that Cx43 became increasingly concentrated at end-to-end connections between myocytes. High-resolution optical mapping of a small tissue area revealed enhanced anisotropy of conduction in old dogs, while the APD was not altered (304). Most notably, extremely slow transverse conduction, sometimes causing a "zig-zag" conduction pattern, was only observed in old atria. Such dissociated conduction between adjacent fibers may become widespread throughout the atria at advanced age.

At the cellular level, a study performed in adult (1–5 yr) and old (>8 yr) dogs showed an age-induced shift in membrane currents that gave rise to a slight (~15%) increase in APD and ERP (Fig. 10) (17). In addition, increased APD heterogeneity and slower conduction of premature beats was observed in aged atrial tissue (16, 17). Despite these changes in atrial electrophysiology, the inducibility of AF was not significantly increased in this study (16). In rabbits, aging increased the tendency toward formation of DADs in the PVs (624, 625).

Taken together, these studies show that even in the absence of any underlying pathology, the senescent heart possesses structural characteristics that predispose to AF. However, in these animal models, the extent of electrical and structural alterations is often not sufficient to lead to the increased AF vulnerability that is associated with aging in humans.

I. Trangenic Mouse Models

It was originally thought that fibrillation required a substrate of a certain size (192, 390, 618). According to this "critical mass" hypothesis, the mouse heart (at 0.0005 times the weight of the adult human heart) would be too small to be able to fibrillate. However, more recent observations of fibrillation in very small hearts represent a challenge to the critical mass hypothesis (570). In a study on mice with selective atrial fibrosis due to overexpression of TGF-β1, the atrial wavelength was ~15 mm (582). With its length of ~5 mm, these atria could probably not accommodate more than one reentrant wavelet, assuming a homogeneous substrate. However, increased atrial fibrosis in this model made the atria a structurally heterogeneous substrate with an increased AF inducibility (Fig. 12*E*).

APD shortening in response to administration of cholinergic agonists can also be sufficient to increase AF vulnerability in normal mice (305, 597), and in one study, AF could be induced in normal mice without pharmacological intervention (508). Thus, at least as a "proof of principle," the mouse heart can be a useful model for AF, even when the underlying mechanism is likely to be reentrant. However, the question remains open to which extent arrhythmias in very small mouse atria with the complete absence or marked overexpression of a single gene can be translated to human pathology.

In recent years, increased AF vulnerability in a number of transgenic mouse models with altered expression of ion channels has been reported. Deletion of the gap junction protein Cx40 leads to decreased atrial conduction velocity and increased AF stability (216, 583). In mice overexpressing Kir2.1, the increase in I_{K1} current was associated with spontaneous AF episodes (332), perhaps through the stabilization of rotors (141). Deletion of KNCE1, an auxiliary subunit for I_{Ks} that normally stabilizes the open state, unexpectedly shortened APD and led to spontaneous AF episodes (558). Deletion of Ca^{2+}-activated SK2 potassium channels also increased APD and AF inducibility (333).

A growing number of transgenic mice display pronounced atrial enlargement and an associated increase in spontaneous or inducible AF: mice overexpressing junctin (247), mice with cardiac-specific overexpression of angiotensin converting enzyme (634), cAMP-response element modulator (395), TNF-α (473), junctate-1 (248), and overexpression of the Gαq protein (239). In these mice, it is difficult to assess to what extent AF vulnerability results directly from the genetic defect or from atrial dilatation and the concomitant alterations in tissue structure.

While mouse models might be useful to study the mechanisms of specific proarrhythmic phenomena as such, translation of these findings to pathophysiology of AF in humans is inherently problematic. The action potential is much shorter so that the currents contributing to atrial repolarization differ between mice and men (Fig. 2). Also, Ca^{2+} handling in mice is characterized by a very rapid Ca^{2+} reuptake and a very pronounced contribution of Ca^{2+} reuptake to diastolic Ca^{2+} elimination (418). Proarrhythmic mechanisms occurring in mice that are related to altered Ca^{2+} handling or ion channel function therefore not necessarily, and in some cases are not likely to, reflect the electrophysiological phenomena that would occur in humans with similar defects in cell function.

V. CONDITIONS AND MECHANISMS CONTRIBUTING TO THE INITIATION AND PERPETUATION OF ATRIAL FIBRILLATION

A. Alterations in Signaling Pathways

The structural and functional adaptations of the atria to underlying heart disease or AF are the result of the regulation by multiple signaling pathways that can occur either as a consequence of AF or before the onset of AF, usually triggered by underlying structural heart disease. Figure 9 summarizes the AF-related changes in atrial signaling.

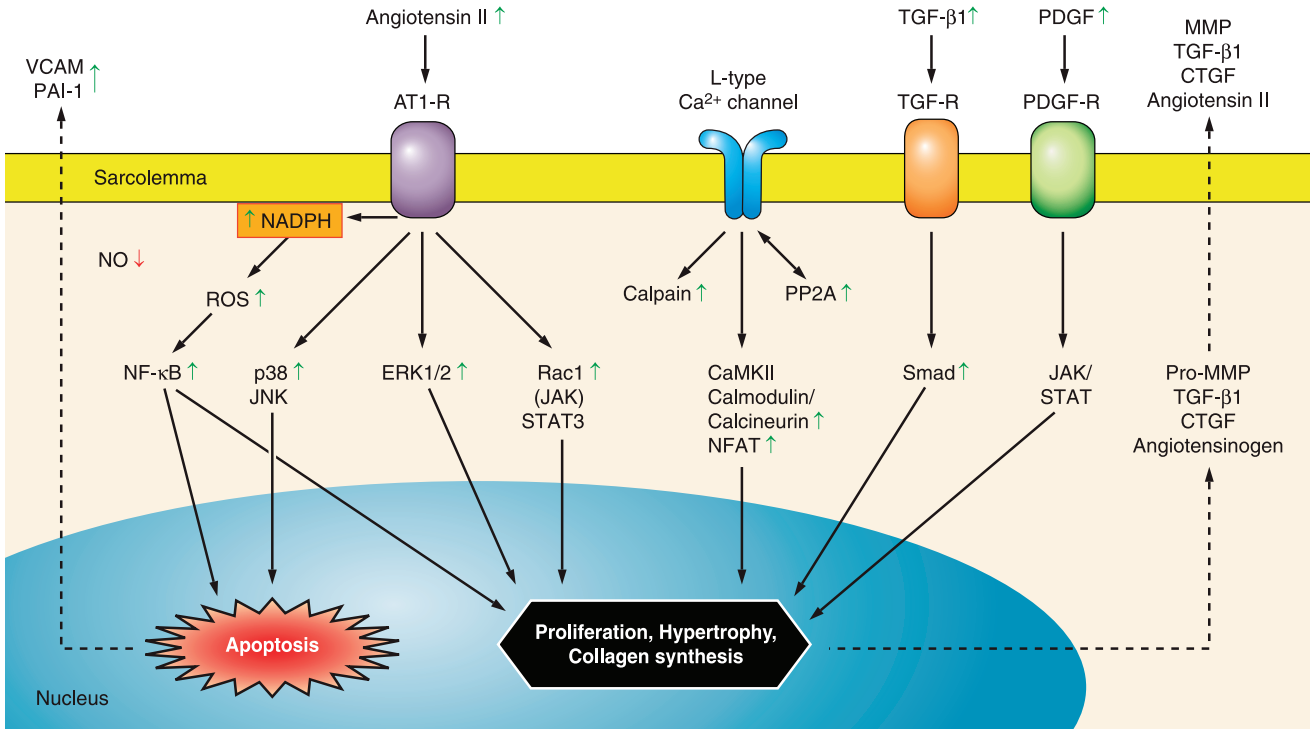


FIG. 9. Atrial signal transduction pathways regulating gene expression in atrial tissue. Signal transduction is induced by several autocrine and paracrine factors. After binding of various ligands (angiotensin II, TGF-β1, PDGF) to cell-surface receptors, numerous intracellular signaling cascades are activated, which regulate essential programs of gene expression responsible for hypertrophy, proliferation, cell survival, and cell death. A central role for redox-signaling is played by NFκB, which is activated after reactive oxygen species (ROS) are generated. One source for ROS is the activated NADPH oxidase. Under baseline conditions, NFκB is retained in the cytosol as an inactive complex with inhibitory IκB proteins. Activation occurs via rapid degradation of the complex and phosphorylation by IκB kinases. Angiotensin signaling encompasses several phosphorylation steps. As a final step, phosphorylated MAP-kinases (ERK, p38, and JNK) induce the cellular response by activation of transcription factors. Cytokines bind to corresponding cytokine receptors, leading to the activation of Janus kinases (JAKs). STAT proteins are the common targets of JAKs. Upon phosphorylation, STATs dimerize and translocate to the nucleus where they bind to interferon response elements or γ-interferon-activated sequences and thereby initiate target gene transcription. AF induces activation of several signal transduction pathways and intracellular signaling molecules. Therefore, structural changes (hypertrophy, fibroblast activation and proliferation, apoptosis) are induced at the cellular and tissue level. These alterations contribute to electrophysiological and morphological alterations of fibrillating atria. After binding of various ligands (angiotensin II, TGF-β1, CTGF, PDGF) to cell-surface receptors or via increased calcium influx, intracellular signaling cascades are activated during AF to induce the development of atrial hypertrophy, proliferation of fibroblast, increased collagen synthesis, increased expression of adhesion molecules (VCAM-1, PAI-1), induction of apoptosis, and increased expression of autocrine and paracrine factors like angiotensin II, TGF, CTGF, and matrix metalloproteases (MMP). AT-1, angiotensin II type 1 receptors; TGF-β, transforming growth factor β; PDGF, platelet-derived growth factor; JNK, c-jun terminal kinase; ERK, extracellular signal regulated kinases; STAT, signal tranducer and activators of transcription; CaMK II, Ca^{2+}/calmodulin-dependent protein kinase II; PAI, plasminogen activator inhibitor; VCAM, vascular cell adhesion molecule.

1. Changes in atrial signaling preceding AF

A) ATRIAL PRESSURE AND VOLUME OVERLOAD. Chronic atrial stretch appears to be one of the most prominent trigger mechanisms for signaling changes involved in the pathogenesis of AF. Interestingly, atria appear to react much faster and more strongly to increased wall stress due to dilatation than ventricular myocardium (221). The induction of heart failure by rapid ventricular pacing induces the development of apoptosis and increased collagen synthesis in the atria within a couple of days, whereas the degree of such changes is substantially smaller and the time course much slower in the ventricles (326). At the molecular level, the development of atrial fibrosis due to pressure and/or volume overload is mediated by both angiotensin II-dependent and angiotensin II-independent mechanism (328, 523). Left ventricular failure increases atrial synthesis of angiotensin II, and thereby atrial fibrosis is induced via activation of mitogen-activated protein kinases (201). Signaling pathways mediated by angiotensin II type 1 receptors (AT1 receptors) are linked to G proteins. Binding of angiotensin II to AT1 receptors leads to tyrosine phosphorylation of receptor tyrosine kinases (656). The activated monomeric G protein Ras interacts with Raf-1 and activated Raf-1 then phosphorylates the kinases MEK-1 and MEK-2. In the final step of this signaling cascade, extracellular signal regulated kinases (ERK-1 and ERK-2) are activated by phosphorylation. ERKs lead to activation of transcription factors, such as Elk-1 and *c-fos*, which are responsible for the effects on gene transcription (545). Studies have shown a linear correlation between angio-

tensin II, ERK1/2 activation, and the degree of atrial fibrosis (328). Another tyrosine kinase that is activated by angiotensin II is janus kinase 2 (JAK2) (367). JAK2 initiates activation of transcription factors STAT-1 and STAT-3. A recent study demonstrated that the angiotensin II/Rac1/STAT3 pathway is an important signaling pathway involved in atrial structural remodeling (564). In addition to angiotensin II, pacing-induced ventricular failure also increased atrial TGF-β and PDGF levels. TGF-β operates predominantly by autocrine and paracrine mechanisms. Binding of a TGF-β homodimer to two TGF-β type II receptors causes phosphorylation of signaling molecules belonging to the family known as SMADs. When phosphorylated, SMADs aggregate and enter the nucleus to induce myocardial fibrosis (61). In addition, TGF-β can redirect protein synthesis to favor expression of fetal genes as described in fibrillating atria (439). A mouse model that overexpresses TGF-β1 develops profound atrial fibrosis and AF, whereas the ventricles are normal (582). Interestingly, atrial fibroblasts are activated significantly faster than ventricular fibroblasts in CHF models, explaining the rapid and more severe degree of interstitial fibrosis in the atria (79). Burstein et al. (79) demonstrated that atrial fibroblasts react more strongly to angiotensin II than ventricular fibroblasts. Importantly, proliferation of atrial fibroblasts was consistently more pronounced than that of ventricular fibroblasts when stimulated with a range of growth factors including angiotensin II and TGF-β1 (79). Connective tissue growth factor (CTGF) is implicated in various fibrotic disorders and is produced by fibroblasts after activation by TGF-β1. Moreover, atrial CTGF was identified as a candidate factor in CHF-induced atrial fibrosis by analysis of gene networks (79).

Several studies clearly suggest that oxidative stress contributes to atrial remodeling in CHF models (98). The peroxisome proliferator-activated receptor-γ (PPAR-γ) activator pioglitazone antagonizes angiotensin II actions and possesses anti-inflammatory and antioxidant properties. Pioglitazone attenuated CHF-induced atrial structural remodeling and AF vulnerability (519). In the same study, both pioglitazone and candesartan reduced TGF-β, TNF-α, and mitogen-activated protein kinase, but neither affected p38-kinase or c-Jun NH_2-terminal kinase activation. In contrast, ω-3 polyunsaturated fatty acids attenuate CHF-related phosphorylation of the mitogen-activated protein kinases ERK and p38 (478).

In failing human myocardium, NADPH oxidase-related ROS production increases, which in turn enhances expression and activity of Rac1. Application of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) like simvastatin downregulate Rac1-GTPase activity by reducing isoprenylation and translocation of Rac1 to the cell membrane (2). Inhibition of Rac1 by statins decreases NADPH oxidase-related reactive oxygen species production in cardiac myocytes and reduces myocardial hypertrophy. Furthermore, simvastatin reduces human atrial myofibroblast proliferation via a RhoA pathway (455). In addition, simvastatin, but not fenofibrate (PPAR-α agonist), inhibits canine atrial fibroblast proliferation, which paralleled collagen-synthetic fibroblast function (449). Thus statins and PPAR-α agonists have very different efficacy in preventing CHF-related atrial structural remodeling.

Chronic atrial stretch is also associated with an altered expression of matrix metalloproteinases (MMP). MMPs are a large group of enzymes that function to break down the extracellular matrix. Patients with persistent AF show decreased atrial expression/activity of MMP-1 and increased tissue inhibitor of metalloproteinase (TIMP)-1 levels (200, 363). In AF patients with congestive heart failure, an increased collagen I fraction appears to be associated with upregulation of MMP-2 and downregulation of TIMP-1 (121, 635). These apparent discrepancies could be explained by temporal changes in MMPs function and the presence of concomitant cardiac diseases (valvular regurgitation, heart failure, etc.), which have a substantial effect on atrial MMP expression (14). In addition to MMPs, ADAMs (a disintegrin and metalloproteinase) also influence interstitial matrix composition and cell-cell and cell-matrix interactions. ADAMs form a large family of membrane-bound glycoproteins that function in proteolysis, signaling, cell adhesion, and cleavage-secretion of membrane-bound proteins (498). Arndt et al. (20) described the effect of AF in patients with concomitant heart diseases on regulation of ADAMs. Atrial tissue of patients with permanent AF shows increased levels of ADAM10 and ADAM15. Membrane expression of ADAM15 is significantly upregulated during AF, whereas most ADAM15 is largely confined to the cytoplasm during sinus rhythm. The ADAM15/β1-integrin ratio is significantly increased in fibrillating tissue and correlates with the left atrial diameter and the duration of fibrillation. Thus regulation of MMPs and ADAMs may influence the composition of interstitial matrix and, furthermore, contributes to geometrical changes and dilatation of the atria and ventricles (257).

B) AGING. Another important factor that influences atrial pathology is aging (199). Both replacement and reactive fibrosis, possibly induced by increased levels of TGF-β are postulated to contribute to structural changes in the elderly. Other profibrotic molecular mechanisms (e.g., angiotensin II, bradykinin, endothelin-1) influencing this process still need to be clarified. In very old myocardium, higher levels of active $p38^{MAPK}$ in atrial trabeculae after ischemia point towards an increased cellular stress, which is even more pronounced after postischemic reperfusion. A recent study showed that aging significantly influences PV anatomy, which may contribute to generate triggers for AF. CT analysis revealed that left atrial ap-

pendages and the four PV trunks become dilated in patients older than 50 years (436).

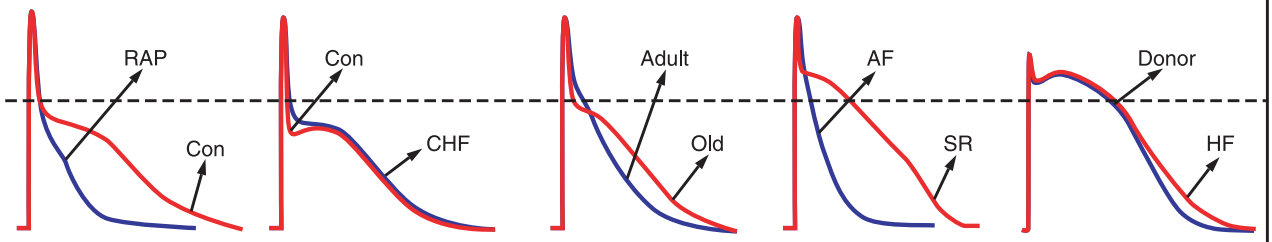
In addition to morphological changes, the aging process is also accompanied by modified cellular Ca^{2+} handling (624). Aging is accompanied by upregulation of $InsP_3Rs$ and transient receptor potential C (TRPC) channels but decreased SERCA activity. Whether these factors contribute to PV arrhythmogenesis is currently unknown.

Another structural change commonly observed with increasing age is isolated atrial amyloidosis (IAA). The incidence of IAA increases with age (466). The formation of amyloid fibrils takes place by a nucleated growth mechanism. As IAA is formed locally at the site where atrial natriuretic peptide (ANP) is synthesized, a high local concentration of the precursor protein and enhanced synthesis of ANP contribute to the formation of amyloid deposits. Apart from an association with AF, the presence of atrial amyloid correlated with age, gender, surface P-wave duration, and valvular diseases. The highest prevalence of atrial amyloid were found in patients undergoing mitral valve replacement (466). Of note, the amount of amyloid is inversely related to the amount of interstitial fibrosis, supporting the concept that amyloid itself produces an arrhythmogenic substrate (466, 644).

2. Changes in atrial singaling as a consequence of AF

A) IMPACT OF AF ON OXIDATIVE STRESS. Several lines of evidence suggest an association between oxidative stress and AF (92, 300, 379). Rapid atrial pacing models showed that AF decreases tissue ascorbate levels and increases protein nitration, a biomarker of oxidative and nitrosative stress (92). Biochemical evidence for oxidation by peroxynitrite and hydroxyl ($^{\bullet}OH$) radicals, both downstream products of $O_2^{\cdot -}$ generation, has also been demonstrated in experimental models. Thus AF itself induces substantial oxidative stress in fibrillating atrial tissue. Recently, it was shown that AF caused left atrial endocardial dysfunction manifested as a 73% decrease in $NO^{\cdot}$ production and a 1.8-fold upregulation of plasminogen activator inhibitor-1 (PAI-1) (82). One possible explanation for the reduction in $NO^{\cdot}$ is increased oxidative degradation by $O_2^{\cdot -}$. Recent studies suggest that increased $O_2^{\cdot -}$ production is at least partly the result of increased NAD(P)H oxidase and xanthine oxidase (XO) activities. Interestingly, the data indicate that the increase in $O_2^{\cdot -}$ production is greater in the left than in the right atrium. Increased NAD(P)H oxidase activity could be explained by an increase in active Rac1 (151). The mechanism of increased NAD(P)H oxidase activity appeared to be increased enzyme activation (486). A membrane-bound $gp91^{phox}$ containing NAD(P)H oxidase in atrial myocytes was the main source of atrial superoxide production in human atrial tissue (82). In contrast to findings in sinus rhythm patients, NO synthases (NOSs) contributed significantly to atrial superoxide production in fibrillating atria, suggesting that increased oxidative stress in AF may lead to NOS "uncoupling" (287). In addition, downregulation of eNOS has also been described in rapid pacing models (75). These findings indicate that a myocardial NAD(P)H oxidase and, to a lesser extent, dysfunctional NOS contribute significantly to superoxide production in the fibrillating human atrial myocardium (287). Rapid pacing of atrial tissue slices in vitro demonstrated that atrial tachycardia is associated with mitochondrial dysfunction and oxidative stress-activated signal transduction (75, 496). Thereby, oxidative stress could contribute to metabolic and structural atrial changes in AF. It has been shown that AF activates the redox-sensitive NF-κB signaling pathway, which causes an elevated expression of target genes, LOX-1 and ICAM-1. Increased expression of these adhesion molecules may contribute to an increased risk for platelet and leukocyte adhesion to the atrial endocardium, which may initiate atrial thrombogenesis (75). However, the true clinical impact of these molecular changes on thrombogenesis remains to be defined.

B) IMPACT OF AF ON CALCIUM-DEPENDENT PROTEASES AND PHOSPHATASES. Ca^{2+}-dependent proteases like calpain and phosphatases are activated during AF (66, 164, 198). Calcineurin (Cn) is a calcium-activated serine-threonine phosphatase composed of a catalytic A-subunit (59–63 kDa) and a regulatory B-subunit (19 kDa) (389). Three catalytic genes (A-subunit) have been identified, of which CnAα and CnAβ are present in the heart (549). The induction of cardiac hypertrophy has been associated with an increase in CnAβ (but not in CnAα) expression (72). An elevation in the intracellular Ca^{2+} concentration leads to calmodulin saturation and the subsequent activation of calcineurin (130). Activated calcineurin dephosphorylates nuclear factor of activated T cells (NFAT), allowing translocation of NFAT into the nucleus. NFATc3 plays a pivotal role in regulating the hypertrophic pathways. Of note, FK506, a Cn inhibitor, abolishes the hypertrophic response induced by electrical pacing of atrial tissue slices (74). Rapid pacing causes an upregulation of CnA activity, leading to increased dephosphorylation of the transcription factor NFATc3. This in turn increases the transcription of genes responsible for the atrial hypertrophic cellular response, characterized by an increased expression of troponin I, ANP, and β-myosin heavy chain (74). The presence of hypertrophied atrial myocytes during AF is a consistent finding of several studies (30, 186). Increased calcineurin enzyme activity was also shown in pigs with AF (337). In this in vivo model, NFAT-c3 and NFAT-c4 were increased in the nuclei in AF tissue (337). In another in vitro study, CnA activity increased during 8 h of rapid pacing, but returned to baseline at 24 h (459). Interestingly, CnA activity was associated with transcriptional downregulation of calcium channel protein.



	RAP, canine	CHF, canine	Aging, canine	Human AF	Human SHD
APD_{90}	0.47 [190 → 90] (647) 0.60 [200 → 120] (95)	↔ (327)	1.08 [188 → 203] (17) 1.14 [167 → 191] (16)	0.51 [203 → 104] (628) 0.74 [202 → 149] (146) 0.84 [239 → 203] (444)	↔ (507) 0.82 (629) 1.14 [301 → 344] (303) 1.28 [289 → 371] (302)
I_{Na}	0.43 (637) 0.48 (193)	na	↔ (33)	↔ (57)	na
I_{CaL}	0.32 (647) 0.39 (96) 0.42 (95)	0.50 (97) 0.68 (96) 0.70 (327)	0.53 (153)	0.27 (57, 526) 0.37 (576, 628) 0.50 (111)	↔ (105, 629) 0.26 (315)
I_{CaT}	↔ (647)	↔ (327)	na	na	na
I_{TO}	0.36 (647) 0.55 (95, 96)	0.35 (97) 0.44 (96) 0.50 (327)	1.31 (153)	0.17 (57, 209) 0.35 (577, 628) 0.56 (62)	0.25 (361) 0.41 (315) 0.66 (629) 2.00 (507)
I_{Kur} /I_{sus}	↔ (647)	↔ (327)	1.27 (153)	↔ (57, 209, 628) 0.45 (62) 0.49 (577)	↔ (361, 507, 629)
I_{Kr}	↔ (95)	↔ (327)	na	na	na
I_{Ks}	↔ (95, 96)	0.53 (96) 0.60 (97) 0.70 (327)	na	na	na
I_{K1}	1.82 (96) 1.85 (95)	↔ (96, 327)	na	1.75 (145, 148, 628) 2.05 (57, 577) 2.37 (146)	0.61 (302)
I_{KACh}	0.65 (162, 642) constitutively active	0.55 (516)	na	0.46 (148) 0.49 (145) 0.53 (146) 1.45 (57) constitutively active	0.64 (302)
I_{KATP}	na	na	na	0.45 (35) 1.42 (631)	↔ (303)
I_{NCX}	1.67 (96)	1.45 (327) 2.04 (96) 2.10 (97)	na	na	na

The histopathology of fibrillating atria is thought to be similar to chronically ischemic ventricular myocardium (30, 186). Ischemia/reperfusion injury is mediated by increased levels of cytosolic Ca^{2+}, which causes activation of the Ca^{2+}-dependent proteases calpain I and calpain II (197). It had been proposed that AF-induced atrial contractile dysfunction is at least partially due to calpain I-dependent degradation of contractile proteins. However, as will be explained in section **V***C*, force generation and Ca^{2+} affinity of myofilaments are only modestly altered in patients with AF. An in vitro study on HL-1 atrial myocytes showed that 24-h electrical field stimulation at 5 Hz reduced plasmalemmal levels of L-type Ca^{2+} channel α_{1C}-subunit by 72% compared with controls, whereas there was no change in amount of the potassium channel subunits Kv4.3 and Kv1.5 (67). In that model, rapid pacing induced marked changes in cellular structure; myolysis and nuclear condensation, paralleled by a 14-fold increase in calpain activity. Interestingly, inhibition of calpain, but not the calcium antagonist verapamil, prevented these ultrastructural changes.

B. Ion Channel Remodeling and Shortening of Refractoriness

In patients, paroxysms of AF often tend to become longer with time, ultimately leading to persistent AF. Animal models of rapid atrial pacing have helped to understand this progressive nature of the arrhythmia. AF itself leads to changes which increase the stability of AF (614). It is widely believed that "electrical remodeling" plays an important role in this process. The rapid rates of AF cause a shortening and a loss of rate adaptation of the AERP (194, 614), as discussed in section **IV***B*. In patients, the existence of electrical remodeling is well established. Several clinical studies have shown that atrial APD in AF patients is shorter than in patients in sinus rhythm (26, 58, 132, 182, 646). In addition to AERP shortening, AF patients show a loss of rate adaptation of the AERP (26, 58, 182). Some studies have also reported an increased AERP dispersion (378, 383).

The molecular mechanisms underlying APD shortening in human AF have been extensively investigated in atrial myocytes isolated from the right atrial appendage of patients undergoing open chest surgery. The properties of these myocytes thus reflect not only adaptations to the rhythm of the patients but also to underlying structural heart disease, medication, and age (189). This shortcoming can partly be overcome by matching respective control populations but remains a potential confounding factor in most of these experimental investigations.

The available data show that the molecular mechanisms of electrical remodeling occur at the level of expression and/or phosphorylation of ion channels (Fig. 10, expertly reviewed in Refs. 408, 626). Of the depolarizing currents, I_{Na} was unaltered (57) while I_{CaL} density was ~70% lower compared with patients in sinus rhythm (57, 68, 526, 576). The mRNA for the L-type channel α-subunit, Cav1.2, shows a corresponding decrease both in RAP animal models and AF patients (56, 68, 69, 573, 649). However, some studies have reported a decrease of L-type Ca^{2+} channel subunit protein expression (68, 69, 649), whereas others have found that protein levels were unchanged (111, 506). Differences in patient populations (underlying heart disease, antiarrhythmic drugs) may be responsible for these discrepancies. Increased activity of protein phosphatase 2A (PP2A) resulting in hypophosphorylation of the Ca^{2+} channel was found to cause I_{CaL} downregulation in one study (111), although in another study, L-type channel open probability was increased, rather pointing towards decreased PP2A activity (294). Finally, increased calpain activity may contribute to increased proteolysis of L-type channel protein (66, 198).

Of the repolarizing potassium currents, I_{to} (57, 209, 577) is strongly reduced in chronic AF. The resulting slowing of phase 1 repolarization of the atrial action potential has been found in human atrial action potentials of patients with AF (112) but was not consistently found in animal models. The inward rectifier potassium current I_{K1} (57, 146, 148, 577) and the corresponding subunits Kir2.1 (mRNA and protein) were found to be increased in AF patients (189). The reported increase in I_{K1} probably has a significant contribution in APD shortening (652).

AF decreases the mRNA and protein for the I_{KACh} subunit Kir 3.1 and 3.4 (68, 69). In myocytes from AF patients, the I_{KACh}-mediated response to acetylcholine is blunted (146), but I_{KACh} is constitutively active due to abnormal channel phosphorylation by protein kinase C (PKC) (94, 145, 592), making this current an interesting target for APD prolongation.

For I_{Kur}, no change (57, 209, 628) or a decrease (62, 577) was reported. Christ et al. (112) recently reported that amplitudes of both rapidly and slowly inactivating components of I_{Kur} were lower in AF patients. No

FIG. 10. Atrial action potentials in models of AF. *Top panel*: superposition of control action potentials with action potentials measured in atrial myocytes from canine models of rapid atrial pacing (RAP), congestive heart failure (CHF), and aging and in myocytes from patients with chronic AF and structural heart disease. The dotted line represents 0 mV. Action potentials are modified from the following references: RAP (647), CHF (327), aging (16), human AF (57), and human SHD (302). Stimulation frequency was 1 Hz in all cases. The table provides an overview of alterations in ionic currents in various animal models of AF and in myocytes from human patients with AF and structural heart disease. Changed are expressed as "fold change." Na, no data available. Note that the reported current changes due to RAP are derived from models of RAP with AV block.

changes in the Na^+/K^+ pump current were found in AF patients (627). Apart from electrical remodeling caused by AF, underlying heart disease in itself can also lead to changes in ionic current that may also increase the likelihood for AF (see Fig. 10 for quantitative details) (626, 629).

Does the process of electrical remodeling explain the progressive nature of AF in patients? Often, AF can be cardioverted by agents that prolong the atrial APD. This indicates that a prolongation of the AERP is antiarrhythmic but does not show to which extent the AERP shortening contributes to AF stability. Importantly, the success rate of chemical cardioversion is relatively high in recent-onset AF, but its efficacy decreases with longer AF duration (15). The exact time course of electrical remodeling during AF in humans is unknown, but in animal models it is complete within at most a few days. The limited efficacy of ion channel blockers in the treatment of chronic AF indicates that other processes occurring more slowly than electrical remodeling contribute to the stability of AF in many patients.

Several studies reported that a short right atrial APD directly after cardioversion was correlated to a higher AF recurrence (124, 426). The question is how long this effect persists. In most patients with recent onset of paroxysmal AF, the time spent in sinus rhythm between two AF episodes may be long enough to completely reverse electrical remodeling. In animal models, complete reversal of electrical remodeling takes place within 2–3 days of sinus rhythm with a gradual prolongation of the AERP and recovery of the rate adaptation response (504, 562, 615). A number of clinical studies have demonstrated that after cardioversion of persistent AF in patients, the AERP also gradually increases and normal refractoriness is restored within several days (357, 460, 646). Interestingly, several other studies showed that increased vulnerability to AF after cardioversion still exists 2–4 wk after reversal of electrical remodeling (561, 568). This discrepancy in time course also indicates that the effect of other processes than just electrical remodeling remain present after cardioversion of AF.

Expression and/or activity of the calmodulin-dependent kinase II (CaMKII) has been shown to be enhanced in fibrillating and dilated atria in animal models and patients with AF (409, 559). The most relevant target proteins of CaMKII are ryanodine receptors, phospholamban, L-type Ca^{2+} channels, and proteins involved in the epigenetic regulation of atrial myocytes (e.g., histone-acetylases). In normal atrial myocytes, CaMKII activation plays an important role in frequency adaptation of cell function. In AF, CaMKII activation might contribute to generation of abnormal impulse formation as will be described in section **V***D*.

C. Loss of Atrial Contractility and Atrial Dilatation

Loss of atrial contractile function after cardioversion of AF was first documented by Logan et al. in 1965 (Fig. 11*A*) (344). Echocardiographic studies showed that this atrial contractile dysfunction correlated with the duration of AF and that it could take months before the atrial transport function was fully recovered (358, 359). While after 2 wk of AF, recovery of atrial contractile function was complete within 24 h of sinus rhythm, it took more than 1 mo to recover from AF lasting more than 6 wk (358). The degree of atrial contractile function appears not to depend on whether AF was cardioverted pharmacologically or by direct-current shock (226). In cases with spontaneous termination of AF, a similar degree of atrial contractile dysfunction was demonstrated (171, 212).

The most important clinical consequence of loss of atrial contractile dysfunction due to AF is the low blood flow velocity in the atria following cardioversion, which significantly contributes to the thromboembolic risk associated with AF (45). Most thromboembolic events occur shortly after cardioversion (>90% within 10 days), which suggests that preformed atrial thrombi are being dislodged from the atrial wall due to restoration of vigorous atrial contractions (49). However, transesophageal echocardiography has shown that new atrial thrombi can be formed after cardioversion (173), stressing a role of prolonged depression of contractility as a factor promoting thrombus formation after cardioversion (49). The loss of atrial contractility also increases the compliance of the fibrillating atria, which may enhance progressive dilatation during AF and may contribute to further stabilization of the arrhythmia (502). In contrast, restoration of sinus rhythm has been shown to reduce atrial size (206, 574). Finally, delayed recovery of atrial contraction after cardioversion might contribute to the delayed recovery of exercise capacity (341).

The mechanisms responsible for atrial contractile dysfunction following cardioversion are not completely understood. In experimental and clinical studies, verapamil was able to largely prevent the atrial dysfunction after short periods of AF, indicating that atrial stunning is mediated by Ca^{2+} overload (133, 319). While the altered atrial function after short paroxysms of AF is likely to be the result of changes in cellular metabolism, long-lasting atrial tachyarrhythmias may induce additional changes causing a more persistent atrial contractile dysfunction.

Some studies point towards an important role of I_{CaL} downregulation as a cause of atrial contractile dysfunction. In dogs with sustained atrial tachycardia (6 wk), the degree of shortening of isolated atrial myocytes was shown to be reduced and associated with a pronounced reduction of the Ca^{2+} transient (295, 547). In this model, I_{CaL} has been reported to be downregulated by 70% (647).

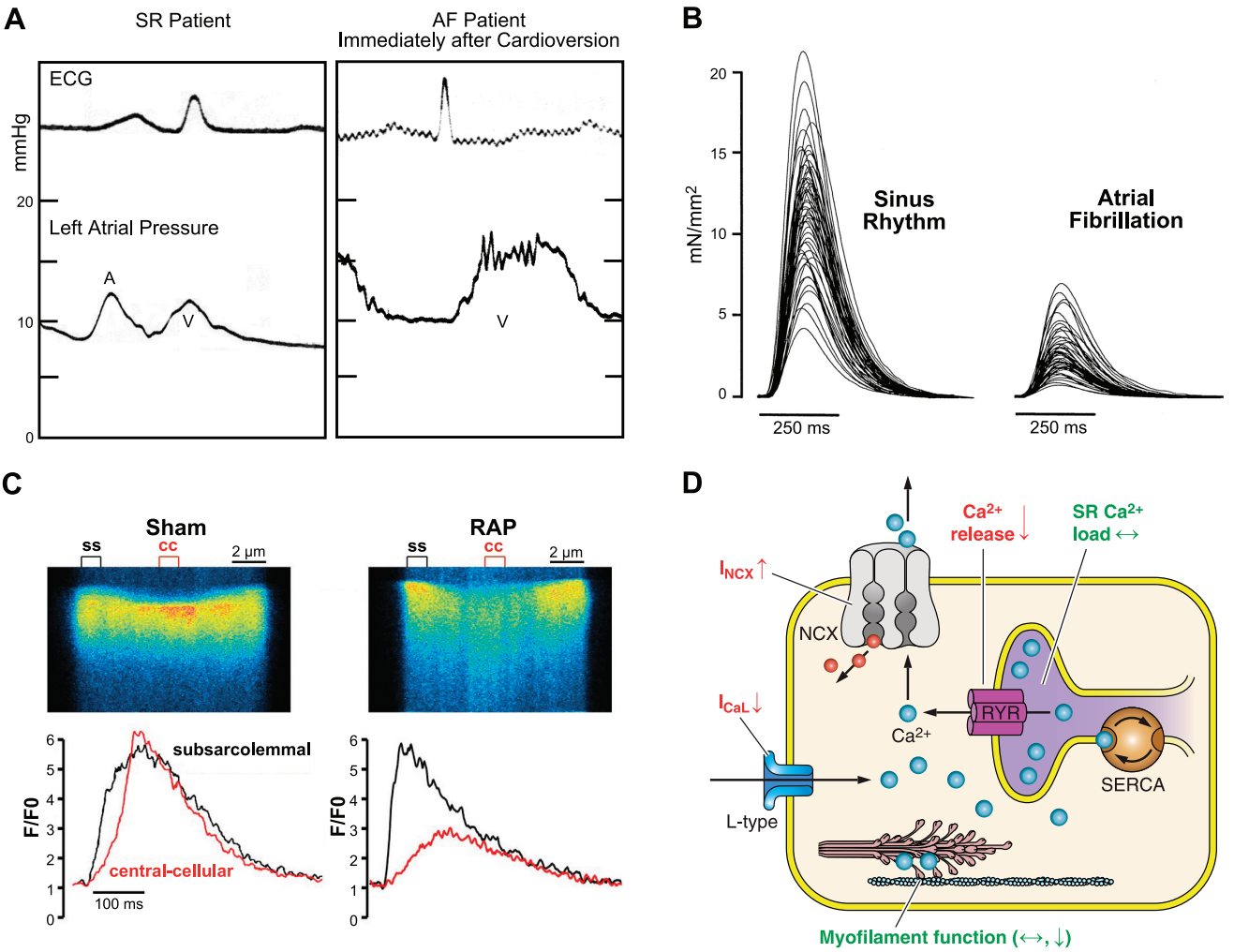


FIG. 11. Mechanisms of atrial contractile dysfunction due to AF. *A*: loss of the a-wave after electrical cardioversion of AF. [Modified from Logan et al. (344), with permission from Elsevier.] *B*: depressed contractility in trabeculae isolated from right atrial appendage of patients undergoing mitral valve surgery. [Modified from Schotten et al. (501).] *C*: confocal line scan of Ca^{2+} release in atrial myocytes isolated from rabbits after rapid atrial pacing for 5 days (RAP) or sham. In RAP cells, central cellular Ca^{2+} release is blunted, indicating failure of intracellular Ca^{2+} wave propagation in tachycardia-induced atrial remodeling. [Modified from Greiser et al. (210).] *D*: schematic illustration of Ca^{2+} handling alterations in AF. Downregulation of I_{CaL}, upregulation of I_{NCX}, and defective release of Ca^{2+} from the sarcoplasmic reticulum are the main mechanisms of atrial contractile dysfunction (dark red labels) while alterations of SR Ca^{2+} load or myofilament function play a minor role (dark green labels).

In goats, the time course of electrical remodeling (presumably related to I_{CaL} downregulation) followed a time course comparable to the progressive loss of atrial contractility during the first days of AF, suggesting that both phenomena are due to the same underlying mechanism (504). Downregulation of I_{CaL} directly reduces Ca^{2+} influx into the cell but also shortens the atrial action potential (211, 647), which further reduces Ca^{2+} entry into the cell. Vice versa, compounds which prolong the atrial action potential but do not directly interfere with I_{CaL} have been shown to enhance Ca^{2+} influx and atrial contractility (136, 503, 608).

There are reasons to assume that in patients with prolonged AF, other mechanisms beyond downregulation of I_{CaL} also contribute to loss of atrial contractility after cardioversion. In such patients, recovery from electrical remodeling occurs within a couple of days after cardioversion, whereas restoration of atrial contraction takes weeks to months. This indicates that I_{CaL} downregulation alone cannot explain the more persistent depression of atrial contractile function after prolonged AF. Additional mechanisms have been studied in right atrial trabeculae prepared from the right atrial appendage of patients undergoing mitral valve repair with and without long-standing AF (Fig. 11*B*) (501, 505). In patients with persistent AF, the contractile force was reduced by ~75%. Interestingly, contractile reserve of these preparations and the sarcomere content were hardly reduced (−18%), indicating that the contribution of myolysis to the loss of atrial contractile function is very limited. Also, the post-rest potentiation was fully maintained, and diastolic properties were preserved, illustrating that the function of the

sarcoplasmic reticulum was not largely altered. In contrast, the positive inotropic effect of isoproterenol was markedly impaired, although the density of the β-adrenoceptors and the expression of the inhibitory and stimulatory G proteins were unaltered (501). The catecholamine-stimulated adenylyl cyclase activity was not reduced, indicating that the β-adrenergic signal transduction was not desensitized (505). Thus, in contrast to ventricular tachycardiomyopathy, which is due to a dysfunction of the sarcoplasmic reticulum and β-adrenergic desensitization, atrial contractile dysfunction after prolonged AF must be due to other mechanisms.

Oxidative injury (379) as well as reduced phosphorylation of myofibrillar proteins (164) have been suggested to reduce the performance of the contractile apparatus in patients with AF. Also, myosin binding protein C was found to be dephosphorylated in patients with AF (164), which would also be in line with reduced contractile performance of the atrial myofibrils. Some studies on skinned fibers showed that both the maximal force generation and also the Ca^{2+} sensitivity of the myofilaments were unaltered (163, 406). A more recent report demonstrated a reduction in maximum tension and the rate of tension development, and an increase in myofilament Ca^{2+} sensitivity in patients with AF (40). The extent to which these changes contribute to loss of atrial contractility due to AF is difficult to assess but might be limited in the light of preserved contractile reserve of intact muscle preparations.

Recently, confocal imaging of Ca^{2+} release from the sarcoplasmic reticulum showed that the centripetal Ca^{2+} wave propagation was significantly impaired in atrial myocytes isolated from dogs (596a) and rabbits (210) undergoing rapid atrial pacing for 5 days (Fig. 11*C*). These studies indicate that impaired release of Ca^{2+} from the sarcoplasmic reticulum might contribute to loss of atrial contractility. The mechanism underlying impaired Ca^{2+} release from the sarcoplasmic reticulum is currently unknown but not related to downregulation of I_{CaL} (210). Instead, impaired coupling between Ca^{2+} channels and RYRs was recently reported in sheep with persistent AF (322). In patients with AF, an upregulation of the Na^+/Ca^{2+} exchanger was reported that potentially reduces Ca^{2+} load of atrial myocytes contributing to contractile dysfunction in AF (505). The main mechanisms causing atrial contractile dysfunction due to AF are summarized in Figure 11*D*.

Atrial dilatation without concomitant AF can also cause an atrial contractile dysfunction. In animal models of heart failure, atrial emptying function is reduced (517), and in patients, loss of atrioventricular synchrony due to single chamber ventricular demand (VVI) pacing increases left atrial diameter while markers of atrial contractility decrease (537). In goats with atrial dilatation due to AV block, atrial dysfunction was related to reduced sarcoplasmic Ca^{2+} load due to phospholamban dephosphorylation and ryanodine receptor hyperphosphorylation (211). Reduced atrial contractile function was associated with disruption of a t-tubular system in atrial myocytes of sheep with heart failure (142). In dogs with congestive heart failure, reduced atrial contractility is associated with prolonged action potential duration, elevated diastolic Ca^{2+} concentrations, and increased amplitude of Ca^{2+} transients (643). These findings point towards reduced force generation or Ca^{2+} sensitivity of the contractile apparatus. Myosin binding protein C phosphorylation was reduced in both goats with atrial dilatation due to AV block and in dogs with CHF. Whether this also contributes to reduced contractile performance in dilated atria is currently unclear.

AF may not only cause contractile dysfunction in the atria but also in the ventricles. Persistent elevation of ventricular rate above 130 beats/min can produce a tachycardiomyopathy of the ventricles (286, 433). Reduction of the heart rate might reverse normal pump function, emphasizing that ventricular rate control might not only prevent deterioration of LV function but also restore pump function that is already compromised (188).

D. Alterations of Atrial Ca^{2+} Handling and Abnormal Impulse Formation

During the past years, alterations of intracellular Ca^{2+} handling in dilated and fibrillating atria have attracted the attention of many research groups. Many of these studies indirectly suggest a role of triggered activity in the generation of fibrillation wavefronts in patients with AF. Vest et al. (589) demonstrated an enhanced open probability of the RYRs in atrial myocardium of dogs undergoing RAP as well as of patients with sustained AF, which in both cases was due to hyperphosphorylation of the RYR channel at the PKA site. The authors conclude that these alterations might facilitate spontaneous Ca^{2+} release events from the sarcoplasmic reticulum, which in turn might induce DADs and possibly trigger action potentials. In agreement with this, Hove-Madson et al. (253) reported an increase of the frequency of Ca^{2+} sparks (elementary Ca^{2+} release events) in atrial myocytes isolated from the right atria of patients with sustained AF. The Ca^{2+} load of the sarcoplasmic reticulum was unaltered, which supports the hypothesis that the increase in spontaneous Ca^{2+} release was due to a change of the intrinsic properties of the RYRs. Recently, increased leak of Ca^{2+} from the sarcoplasmic reticulum and elevated diastolic Ca^{2+} concentrations have indeed been described in right human atrial myocytes (409). In this study, hyperphosphorylation of RYRs was shown to be due to enhanced activity of CaMKII, as mentioned in section **V***A*. This interesting hypothesis, however, raises some impor-

tant questions. For instance, it is unclear why despite the fact that in atrial myocytes isolated from the right atrial appendages of patients with AF the Ca^{2+} spark frequency is enhanced, ectopic activity originating in this region is a rare phenomenon. Similarly, dogs after 2 mo of RAP do not develop atrial ectopy, although the open probability of the atrial ryanodine channels has been reported to be increased (589). Also, increased open probability alone only transiently enhances spontaneous Ca^{2+} release from the sarcoplasmic reticulum, since increased release would reduce the sarcoplasmic Ca^{2+} load and in turn spontaneous Ca^{2+} release (580). However, in ventricular myocytes of dogs with heart failure, enhanced diastolic Ca^{2+} release has been observed even in the presence of reduced Ca^{2+} load of the sarcoplasmic reticulum (306). In this model, reduced Ca^{2+} release during the steady-state Ca^{2+} transients might have prevented progressive emptying of the Ca^{2+} stores. Another possibility is that stimulation of the Ca^{2+} reuptake rate maintains Ca^{2+} load and produces a sustained enhancement of Ca^{2+} release events. Of note, phosphorylation levels of phospholamban, an inhibitory protein controlling the reuptake of Ca^{2+} into the sarcoplasmic reticulum by the sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA), is increased in atrial myocardium of patients with AF (164). Enhanced phosphorylation of phospholamban dissociates the molecule from SERCA and stimulates reuptake of Ca^{2+} into the sarcoplasmic reticulum, possibly increasing Ca^{2+} load and spontaneous Ca^{2+} release from the intracellular Ca^{2+} stores. So far, however, there is no evidence for enhanced reuptake of Ca^{2+} into the sarcoplasmic reticulum in fibrillating atrial myocardium. Rather, experiments with isolated right atrial trabeculae show that at any level of Ca^{2+} load, the diastolic properties of atrial myocardium of patients with AF are unaltered (505). Recently, in mice with a genetic gain-of-function defect in the RYRs, spontaneous AF was absent at rest but could be induced by rapid pacing, which also resulted in increased hyperphosphorylation of RYRs at the CaMKII phosphorylation site (100). Importantly, pharmacological and genetic inhibition of CaMKII prevented AF inducibility. Taken together, these data suggest that enhanced Ca^{2+} leak through hyperphosphorylated or defective RYRs alone might not be sufficient to produce relevant atrial ectopy. It is unknown whether in patients, enhanced sympathetic stimulation or simply the high rate during AF can sufficiently enhance Ca^{2+} load of atrial myocytes to provoke proarrhythmic Ca^{2+} spontaneous leak through hyperphosphorylated RYRs.

The question of whether atrial pathology might enhance spontaneous electrical activity has been addressed by several authors. In cats with atrial dilatation due to spontaneously occurring cardiomyopathy, resting membrane potentials have been reported to be more positive, and action potentials showed lower amplitudes and upstroke velocities (60). In the presence of catecholamines, automaticity and triggered activity were frequently found in atrial preparations from dilated atria but only occasionally occurred in normal atria. In dogs with heart failure induced by rapid ventricular pacing, action potential duration was prolonged, and frequently DADs occurred (539). Left atrial myocytes showed increased diastolic Ca^{2+} concentrations and sarcoplasmic Ca^{2+} loading. Spontaneous action potentials occurred more frequently in heart failure dogs compared with controls and were suppressed by inhibition of SR Ca^{2+} release and the Na^{+}/Ca^{2+} exchanger (643). Of note, in none of the aforementioned studies (60, 539, 643) has ectopic activity or spontaneous onset of atrial tachyarrhythmias been reported.

The response to pacing can provide valuable information about trigger mechanisms of AF. After treatment with ryanodine, rabbit PVs showed pacemaker activity that was enhanced when the preparations were transiently paced at a higher rate (249). In canine PVs exposed to pituitary adenylyl-cyclase activating polypeptide (PACAP), which mimics neurohumoral dysbalance, rapid atrial pacing caused ectopic beats that were coupled with a shorter cycle length when the triggered cycle length was also short (236). In dogs with CHF, rapid pacing induced an atrial tachycardia with repetitive radial spread of activation. The postpacing interval as well as the cycle length of the tachycardia itself were positively correlated with the pacing cycle lengths triggering the tachycardia (539). All these findings are consistent with enhanced Ca^{2+} loading of atrial myocytes causing spontaneous release of Ca^{2+} from the sarcoplasmic reticulum and repetitive DADs. Reentrant mechanisms appear less likely because here a high rate of the triggering impulses results in a longer postpacing interval. It should be noted, however, that DADs do not invariably react on pacing protocols (267) and the specificity of such tests to identify a specific proarrhythmic mechanism might be limited (620).

Mapping of the activation pattern during or at the onset of AF has also been used to support a role of ectopic discharges in initiation and perpetuation of AF. Of note, demonstration of radial spread of activation from a localized area does not allow direct determination of the mechanism of an arrhythmia, but to some degree supports the existence of a localized source of AF. For example, activation mapping has revealed the onset of AF triggered by a spontaneous beat originating from the PVs in dogs during autonomic imbalance (236) or with congestive heart failure (109, 423) and in rats during glycolytic inhibition (427). In patients with paroxysmal AF, endocardial mapping of the PVs demonstrated radial spread of activation of spontaneous beats in the PVs initiating runs of AF (440). It is important to note, however, that radial spread of activation can also be due to "breakthrough" of wavefronts originating from deeper

layers of the atrial wall (159). Therefore, these studies do not prove that in the studies mentioned localized sources have induced episodes of AF.

A higher level of evidence for the presence of a localized driver for AF comes from observations of radial spread of activation occurring repetitively at the same site. This conduction pattern has been described in dogs with CHF and AF-induced by RAP (177, 653). In the study by Fenelon et al. (177), repetitive radial spread of activation was documented in the endocardium and the epicardium primarily at sites along the crista terminalis. Zhou et al. (653) reported repetitive focal spread of activation in the PVs of dogs with AF. Based on these activation patterns, the authors of both studies cannot rule out microreentry as a mechanism of repetitive radial spread of activation. However, they did provide additional arguments in favor of a cellular proarrhythmic mechanism (see below).

Other studies interpreted an increased incidence of radial spread of activation in structurally altered atria as an argument for cellular proarrhythmic mechanisms inducing AF. In dogs with pacing-induced heart failure, acetylcholine increased the rate of "focal discharges" from the PVs by factor 3 (109). Nitta el al. (419) observed multiple "focal activations" with fibrillatory conduction in patients with AF undergoing open chest surgery. The mechanism of these events, however, remains unclear. They might be due to cellular proarrhythmic activity, but they might also be due to an increased incidence of "breakthroughs" due to transmural conduction, which more likely occurs in a complex substrate for AF as explained in section **V***E* (159).

Finally, the response of electrical activity to pharmacological compounds has been used as an argument in favor of the presence of focal discharges during atrial tachyarrhythmias. Spontaneously occurring arrhythmias in PVs of dogs undergoing 6–8 wk of rapid atrial pacing were suppressed by sodium channel blockers or magnesium (103). In canine PV, left atrial preparations exposed to acetylcholine, thapsigargin, and ryanodine eliminated focal discharges from the PVs (109). The atrial tachycardia with repetitive radial spread of activation in dogs with CHF was terminated by compounds reducing Ca^{2+} loading like verapamil, flunarizine, and ryanodine (539). The experiments with verapamil and ryanodine suggest that Ca^{2+} loading might be critical for some forms of spontaneous electrical activity occurring in AF-related atrial pathologies and support the role of DADs as a trigger mechanism for spontaneous activity in the atrium. In contrast, flunarizine has also been shown to terminate reentrant rhythms like atrial flutter in the canine sterile pericarditis model, illustrating that the response to flunarizine cannot be taken as an argument for the existence of Ca^{2+}-related cellular proarrhythmic mechanisms (591). In sheep atria exposed to acute stretch and adrenocholinergic stimulation (perfusion with high concentrations of isoproterenol and acetylcholine), both caffeine and ryanodine inhibited breakthroughs showing radial spread of activation during AF. The sensitivity of these breakthroughs to compounds which empty the sarcoplasmic reticular Ca^{2+} stores might be taken as an argument in favor of focal discharges as the underlying mechanism under these specific conditions (639a).

In summary, the role of altered Ca^{2+} homeostasis for initiation and perpetuation of AF is still obscure, mainly due to technical limitations of existing experimental approaches. As confirmation of Ca^{2+}-dependent AF mechanisms might have consequences for our understanding of the working mechanisms of antiarrhythmic drugs (147), it requires further clarification.

E. Atrial Structural Remodeling and Conduction Disturbances

As explained in sections **IV** and **V***B*, apart from electrical remodeling, other factors must also contribute to the high susceptibility to the arrhythmia in patients with AF. This "second factor" may entail alterations in atrial tissue structure. The relation between structural alterations and AF has been studied in many different clinical entities. Clearly, structural alterations of atria are not exclusively related to AF but at least to the same degree as the existence of structural heart disease present in an individual patient. The kind of structural alterations also shows a high diversity. For example, Frustaci and coworkers (185, 187) have described evidence of occult atrial pathology, such as myocyte necrosis, myocarditis, and fibrosis, in patients with lone AF. However, the majority of chronic AF patients is of advanced age or suffers from structural heart disease. Of the various aspects of atrial structural remodeling in these patients, the consequences of fibrosis, myocyte hypertrophy, and altered connexin distribution have been studied most extensively, as discussed below.

1. Atrial fibrosis

Atrial fibrosis is thought to be one of the most important factors in the formation of a substrate for AF (407, 529). Atrial fibrosis has been observed in biopsies from patients with AF (301) as well as in patients with specific risk factors for AF, such as valvular disease (14), rheumatic heart disease (352, 450), dilated and hypertrophic cardiomyopathy (422), and advanced age (336).

Myocytes are organized in bundles, separated by perimysial fibrous tissue. Within these bundles, strands of myocytes can be separated from each other by endomysial fibrous tissue. Structural remodeling due to heart disease is often associated with fibrosis and an increased transverse fiber separation. In the atria, collagenous septa

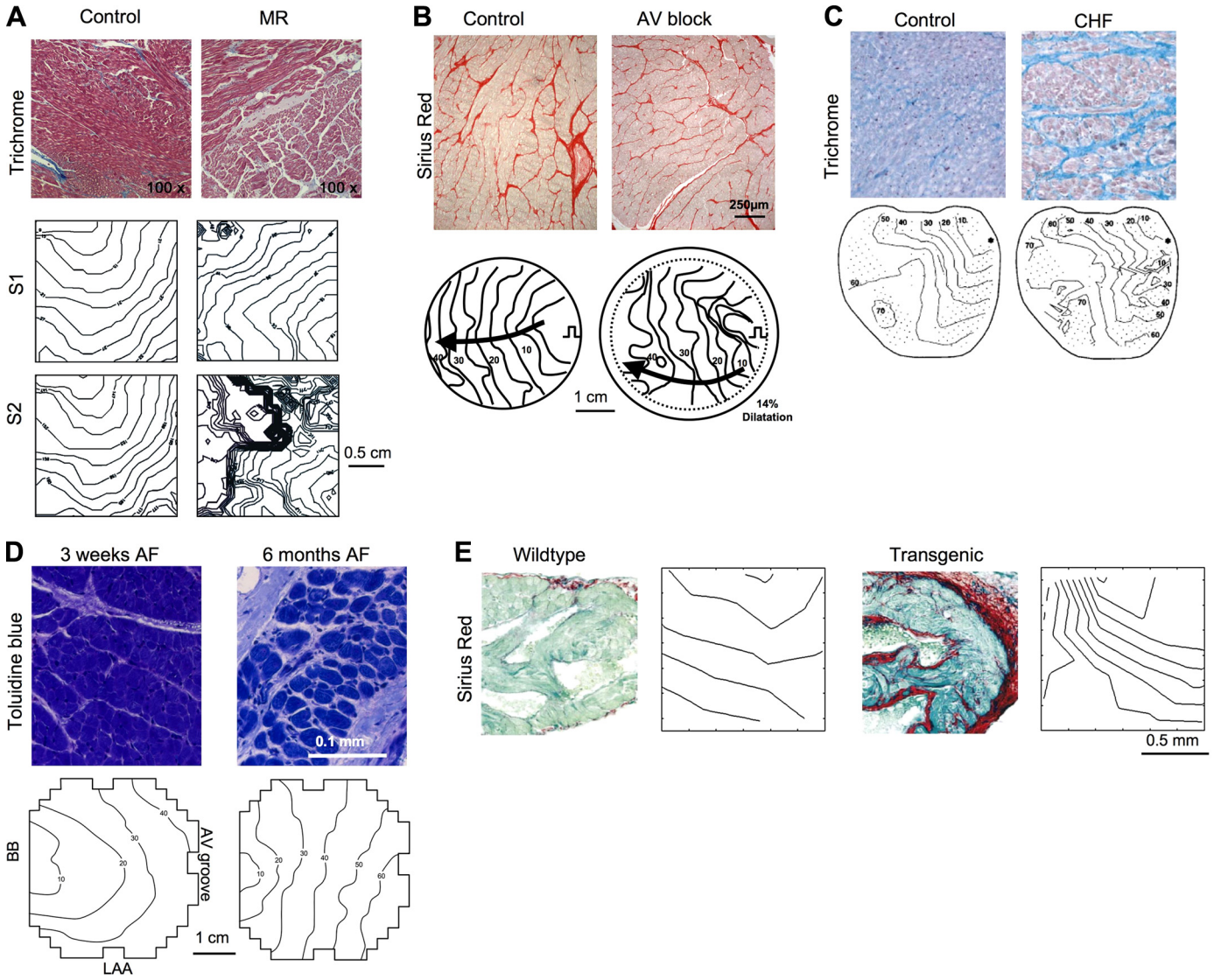


FIG. 12. Relation between structural alterations and changes in conduction in animal models of AF. Fibrosis is stained in blue (Trichrome), red (Sirius red), or light blue (Toluidine Bbue). Myocytes are stained red (Trichrome), green (Sirius red), or dark blue (Toluidine blue). *A*: in a canine model of chronic atrial dilatation due to mitral insufficiency, inflammatory infiltrates and fibrosis were increased. During slow pacing, activation wavefronts spread rapidly and homogeneously, but during extrastimulation, areas of slow conduction were observed. [Adapted from Verheule and co-workers (586, 587).] *B*: cellular hypertrophy without an increase in fibrosis was reported in a goat model of chronic biatrial dilatation due to AV block. Fast pacing (BCL 200 ms) revealed areas of slow conduction. [Adapted from Neuberger et al. (411).] *C*: pronounced increase in fibrosis in a canine model of CHF due to rapid ventricular pacing was associated with areas of conduction heterogeneity in the left atrium. [Adapted from Li et al. (326).] *D*: 6 mo of RAP led to increased interstitial fibrosis in the goat. During slow pacing, the conduction velocity in the left atrium was decreased by 30%. *E*: mouse model of selective atrial fibrosis due to overexpression of TGF-β1. Left atrial activation maps show increased heterogeneity of conduction during pacing at a cycle length of 150 ms (582).

between myofibers increase in volume during normal aging (304, 530). Similarly, the extracellular matrix volume per myocyte increased in the goat of 4 mo of RAP (29). Also in atria of animal models of atrial dilatation (59, 587) and CHF (326), the amount of fibrosis is increased. However, in these models and in particular in the CHF model, larger areas of fibrosis are observed, which are more similar to "replacement fibrosis" secondary to tissue damage and cell death. Various degrees and forms of atrial fibrosis and the resulting conduction disturbances are shown on Figure 12. Atrial fibrosis may in itself be sufficient to increase AF vulnerability, as shown in mice with selective atrial fibrosis due to overexpression of TGF-β1 (582).

Spach and Boineau (529) have demonstrated that the nonuniform anisotropic arrangement in cell-to-cell connections leads to discontinuous conduction at a microscopic scale. While longitudinal propagation may still be fast, transverse propagation may show "discontinuous conduction," i.e., discrete time delays in activation of adjoining myocytes or myocyte bundles (529). During such delays due to poor electrical coupling, propagation

may become increasingly dependent on I_{CaL} rather than I_{Na} (514, 546). Discontinuities in conduction can become more apparent at short cycle lengths or during extrastimulation with short coupling intervals due to incomplete recovery of Na^+ and Ca^{2+} channels (534, 546). This may allow reentry to occur in very small circuits (529, 534, 535). Discontinuous conduction between poorly coupled myocytes forms the basis of "electrical dissociation" during AF that is reflected by fractionated electrograms.

Although there are strong indications from animal models that atrial fibrosis can be proarrhythmic (80, 169), some questions regarding the role of atrial fibrosis in the development of a substrate of AF are so far unresolved.

First, the association between atrial fibrosis and AF is quantitatively not very strong. Some, but not all, human studies have found that atrial fibrosis is more pronounced in chronic AF patients than in patients with sinus rhythm (53, 301, 475). The degree of atrial fibrosis and fibrogenic activity correlates with the persistence of AF (208, 635). However, from these studies it is unclear whether increased fibrosis is caused by underlying structural disease or by AF itself. In some of these studies, the degree of the underlying heart disease is not well documented. From a careful comparison of structural heart disease patients with and without AF, Anné et al. (14) have concluded that AF itself is not associated with atrial fibrosis but is instead related to the underlying structural heart disease.

Second, it is unclear what the quantitative relation between atrial fibrosis and conduction disturbances is. As discussed in section **IV***D*, some animal models of atrial dilation show both atrial fibrosis and conduction disturbances (586). However, other models show similar conduction disturbances in the absence of atrial fibrosis (411).

Another question is how different types of fibrosis, for example, large areas of replacement fibrosis (as in the canine CHF model) or thin strands of interstitial fibrosis (as in models of aging), affect atrial conduction. In ventricular cardiomyopathy, Kawara et al. (281) have demonstrated that conduction abnormalities strongly depend on the pattern of fibrosis. In this study, diffuse fibrosis with short fibrotic strands only marginally affected conduction. However, long fibrotic strands could cause pronounced conduction slowing during extrastimulation, especially during transverse propagation.

Finally, the question remains how important atrial fibrosis is as a causative factor for AF in humans. In patients undergoing open heart surgery, the degree of fibrosis does correlate with the occurrence of postoperative AF (199) and with the recurrence of AF (475). However, both the degree of atrial fibrosis and the occurrence of AF may reflect the severity of underlying heart disease, without a strong, direct causal link between fibrosis and AF. Indeed, a significant degree of atrial fibrosis can be present in patients without a history of AF (199).

Despite the fact that the association between atrial fibrosis and AF is surprisingly weak, experimental and clinical studies show that prevention of atrial fibrosis can delay the development of a substrate of AF. Several compounds (statins, ACE inhibitors, AT_1-receptor blocker, fish oil, and glucocorticoids) have been proven to effectively delay the structural remodeling process and reduce AF stability in a variety of experimental models (309, 318, 328, 380, 477, 478, 523). In patients, several post hoc analyses of clinical trials and small-scale proof-of-principle studies suggest that therapy with ACE inhibitors, AT_1-receptor blocker, statins, and polyunsaturated fatty acids (PUFAs) are useful to prevent the occurrence of AF. The details of these studies are summarized in Tables 2–5. It is tempting to speculate that the beneficial effect reported in these studies is due to an antifibrotic effect in the atria. However, improvement of the patients' hemodynamics with normalization of atrial pressures might also have contributed to the beneficial effects of these compounds. The current ESC guidelines for the management of AF contain recommendations for the use of ACE inhibitors, AT1-receptor blockers, and statins for primary and secondary prevention of AF (see section on upstream therapy) (168a).

Unfortunately, compared with fibrosis, amyloidosis (323, 466, 541) and fatty infiltrates (39), which can occur widely in elderly patients and can potentially have a similar impact on conduction, have received comparatively little attention. Mechanistic studies on the role of these structural changes in AF are so far lacking.

2. Altered connexin expression

Another relevant factor for atrial conduction may be altered connexin expression. In the working myocardium, conduction velocity is higher in the longitudinal than in the transverse direction. In the transverse direction, a propagating wavefront has to cross more cell-to-cell boundaries within a given distance. In addition, the smaller and sparser gap junctional plaques at side-to-side connections represent a higher resistance than the larger intercalated discs at end-to-end connections (531). With age, gap junctions also become increasingly localized at end-to-end connections between myocytes, thus further increasing anisotropy (207, 304, 448).

Several studies have reported alterations in Cx40 and/or Cx43 in patients with AF, but the observations are not consistent (152). In patients with chronic AF, both higher (454) and lower (404, 617) levels of Cx40 were reported. Another study reported lateralization of connexins, with an increased heterogeneity in Cx40 distribution and a reduction of Cx43 (301).

TABLE 2. *Clinical trials of renin-angiotensin system inhibition to prevent new-onset AF in patients with CHF or AMI (primary prevention) and patients with hypertension (primary prevention)*

References	Study Design	Patients	Intervention	Primary Outcome
Pedersen et al. (445)	TRACE study (post hoc analysis)	1,577 Patients with AMI and reduced LVEF	Trandolapril versus placebo Follow-up: 2–4 yr	Reduced incidence of new-onset AF
Pizetti et al. (451)	GISSI-3 study (post hoc analysis)	17,749 Patients with AMI	Lisinopril versus nolisinopril Follow-up: 4 yr	No difference in new-onset AF
Vermes et al. (588)	SOLVD study (post hoc analysis)	347 Patients with LV dysfunction	Enalapril versus placebo Follow-up: 2.9 yr	Reduced incidence of new-onset AF
Alsheikh-Ali et al. (9)	SOLVD study (post hoc analysis)	6,797 Patients with LV dysfunction	Enalapril versus placebo Follow-up: 34 mo	Reduced incidence of hospitalisation with AF
Maggioni et al. (355)	Val-HeFT study (post hoc analysis)	4,395 Patients with chronic symptomatic HF	Valsartan versus placebo Follow-up: 23 mo	Reduced incidence of new-onset AF
Ducharme et al. (150)	CHARM study (prespezified secondary end point)	6,379 Patients with symptomatic CHF	Candesartan versus placebo Follow-up: 37.7 mo	Reduced incidence of new-onset AF
Hansson et al. (224)	CAPPP study randomized, open label (analysis on adverse event reports)	10,985 Patients with hypertension	Captopril versus diuretics ± beta-blocker Follow-up: 6.1 yr	No difference in new-onset AF
Hansson et al. (223)	STOP-2 study (randomized, open label)	6,628 Patients with hypertension	Enalapril/lisinopril versus CCB versus diuretics ± beta-blocker Study duration: 4 yr	No difference in new-onset AF
Lh'Allier et al. (312)	Retrospective longitudinal cohort study (from an administrative database of 8 million people in the USA)	10,926 Patients with hypertension	ACEI versus CCB Average follow-up: 4.5 yr	Reduced incidence of new-onset AF
Wachtell et al. (594)	LIFE study (randomized, double-blind)	8,851 Patients with hypertension+ECG LVH	Losartan versus atenolol Follow-up: 4.8 yr	Reduced incidence of new-onset AF
Salehian et al. (480)	HOPE study (post hoc analysis)	8,835 Patients at high cardiovascular risk without known heart failure or LV systolic dysfunction	Ramipril versus placebo Follow-up: 4.5 yr	No difference in new-onset AF
Schmieder et al. (499)	VALUE study (randomized, double-blind)	13,760 Patients with hypertension at high cardiovascular risk	Valsartan versus amlodipine Follow-up: ≤5 yr	Reduced incidence of new-onset AF

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AMI, acute myocardial infarction; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio; LV, left ventricular; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy.

TABLE 3. *Clinical trials of statins to prevent new-onset and progression of AF (primary and secondary prevention)*

References	Study Design	Patients	Intervention	Primary Outcome
Young-Xu et al. (645)	Prospective observational cohort	449 Patients with chronic stable angina, without CHF	Statins versus no statins Average follow-up: 5 yr	Reduced incidence of new-onset AF
Merckx et al. (377)	Retrospective	218 Patients on statins and 449 matched controls in SR without LV dysfunction	Statins versus no statins Mean follow-up: 6.5 yr	Reduced incidence of new-onset AF
Dernellis et al. (140)	Randomized, single-blind	80 Patients with proven paroxysmal AF and C-reactive protein levels between 0.8 and 13 mg/l	Atorvastatin versus placebo Follow-up: 4–6 mo of therapy	Paroxysmal AF resolved in 65% of statin-treated patients versus 10% with placebo
Amit et al. (11)	Retrospective	264 Patients with permanent pace makers	Statins versus no statins Median follow-up: 359 days	Reduced incidence of new-onset AF
Hanna et al. (219)	Retrospective	25,268 Patients with CHF	Lipid-lowering drug use versus no use	Reduced incidence of new-onset AF
Adabag et al. (1)	Retrospective	13,783 Patients with CHD	Statins versus no statins Average follow-up: 4.8 yr	No difference in new-onset AF
Ramani et al. (463)	Retrospective	1,526 Patients with acute coronary syndrome	Statins versus no statins at time of admission	Reduced incidence of new-onset AF

CHD, coronary heart diseases; CHF, congestive heart failure.

In patients undergoing open-chest surgery, high Cx40 levels correlated with low conduction velocities (274) and an increased incidence of postoperative AF (154). These findings agree with measurements on strands of cultured atrial myocytes from transgenic mice, where a reduction in Cx40 led to an increased conduction velocity (38). However, Kanagaratnam et al. (272) reported that in chronic AF patients, lower relative Cx40 levels detected by immunohistochemistry were associated with an increased complexity of AF conduction patterns.

TABLE 4. *Clinical Trials of statins to prevent recurrence of AF after thoracic surgery*

References	Study Design	Patients	Intervention	Primary Outcome
Auer et al. (28)	SPPAF study (prospective cohort)	253 Patients with no CHF or LV dysfunction undergoing cardiac surgery	Statin use before surgery versus no statin use	Reduced incidence of postoperative AF
Amar et al. (10)	Prospective cohort	131 Patients undergoing major lung or esophageal surgery	Statin use before surgery versus no statin use	Reduced incidence of postoperative AF
Marin et al. (362)	Prospective cohort	234 Patients undergoing CABG	Statin use for median duration of 31 days before surgery versus no statin use	Reduced incidence of postoperative AF
Patti et al. (443)	ARMYDA-3 (randomized, double–blind)	200 Patients undergoing cardiac surgery	Atorvastatin versus placebo starting 7 days before surgery and continued until hospital discharge	Reduced incidence of postoperative AF
Chello et al. (99)	Randomized, double-blind	40 Patients undergoing CABG	Atorvastatin versus placebo started 3 wk before surgery	Reduced incidence of postoperative AF
Ozaydin et al. (431)	Prospective cohort	362 Patients undergoing first elective CABG	Statin use for a mean duration of 2.7 mo before surgery versus no statin use	Reduced incidence of postoperative AF
Lertsburapa et al. (324)	Prospective cohort from the AFIST I, II, and III studies	555 Patients undergoing cardiothoracic surgery	Statin use before surgery versus no statin use	Reduced incidence of postoperative AF
Virani et al. (590)	Retrospective study	4,044 Patients undergoing cardiac surgery	Statin use before surgery versus no statin use	No difference in incidence of postoperative AF

CABG, coronary artery bypass graft; CHF, congestive heart failure; CI, confidence interval; LV, left ventricular.

TABLE 5. *Clinical trials of n-3 (omega-3) polyunsaturated fatty acids to prevent AF*

References	Study Design	Patients	Intervention	Primary Outcome
Mozaffarian et al. (394)	Cardiovascular Health Study (population-based, prospective cohort)	4,815 Patients	Dietary intake assessment Follow-up: 12 yr	Reduced incidence of AF
Calo et al. (84)	Randomized open-label	160 Patients undergoing elective CABG	PUFAs for at least 5 days before surgery and up to discharge versus control	Reduced incidence of postoperative AF
Frost et al. (184)	Danish Diet, Cancer, and Health study (population-based, prospective cohort)	47,949 Patients	Dietary intake assessment Mean follow-up: 5.4 yr	No difference in incidence of AF
Brouwer et al. (64)	Rotterdam study: (population-based, prospective cohort)	5,184 Patients	Dietary intake assessment Follow-up: 6.4 yr	No difference in incidence of AF

CABG, coronary artery bypass graft; PUFA, polyunsaturated fatty acid.

Although altered connexin distribution patterns may play a role in forming a substrate for (micro)-reentry in AF, their exact contribution requires further investigation. Normal atrial myocytes have a high degree of electrical coupling. The extent to which electrical coupling has to decrease to affect wavefront propagation is still a matter of discussion. Some information on the relation between connexin expression and conduction velocity has been obtained in transgenic mouse models. In Cx40 heterozygous mice, atrial conduction velocity was not affected, but in Cx40 knockout mice, atrial conduction velocity was reduced by 30% (583). The effect of reduced electrical coupling on propagation has been investigated in detail in mathematical models. "Coupling clamp" experiments, in which two individual atrial myocytes were coupled via a computer, have demonstrated that a coupling conductance of 0.65 nS is sufficient for action potential transfer between two cells (corresponding to 3–6 gap junction channels) (605). In reality, the average coupling conductance between atrial myocytes is 170 nS or larger (584). Shaw and Rudy (514) have shown that a reduction in gap junctional coupling can cause slow propagation with a high safety factor (i.e., unlikely to block). Spach and Heidlage (531) have presented a model of a two-dimensional sheet of myocytes that incorporated a detailed topology of longitudinal and transverse gap junctions between myocytes. In this model, activation time delays were observed during transverse propagation even with normal coupling conductances. The studies on transgenic mice and mathematical models discussed above have investigated propagation during slow pacing. It is conceivable that reduced connexin expression has a more pronounced effect during the high and irregular activation rates of AF.

In humans, Takeuchi et al. (552) have reported that the levels of Cx40 and Cx43 were not altered in patients with atrial dilatation or AF. However, confocal microscopy showed a redistribution of Cx43, with a shift toward the periphery of intercalated discs in the hypertrophied myocytes of dilated atria. In a modeling study, Wilders and Jongsma (616) showed that the electrostatic interactions between neighboring gap junction channels produces a decrease in the effective junctional conductance in a gap junctional plaque. Thus the conductance of large gap junctional plaques is lower than would be expected based on the number of gap junction channels present.

3. Myocyte hypertrophy

Myocyte hypertrophy has been observed in animal models of RAP (30), atrial dilatation (59, 411), and CHF (326). In these settings, the contribution of cellular hypertrophy to alterations in atrial conduction is difficult to assess. From cable theory, it might be expected that an increase in myocyte width would lead to an increase in conduction velocity. Indeed, in a mathematical model of ventricular hypertrophy, an increase in macroscopic conduction velocity was observed (612). However, using a more detailed model that took the nonuniform distribution of gap junction around myocytes into account, Spach et al. (532, 533) calculated that an increase in cell size would lead to more pronounced propagation delays between myocytes during transverse propagation. In fact, cell size had a larger effect on the anisotropy of conduction in this model than the distribution pattern of gap junctional plaques around the myocyte. This finding may explain how myocyte hypertrophy in the absence of increased fibrosis can also cause conduction disturbances, as in the goat model of chronic AV block (411).

4. Atrial architecture

Some aspects of the atrial architecture itself, apart from pathological structural changes, may play a role in creating a substrate for AF. Based on anatomical and

histological studies of the atria, areas with strong preferential fiber orientation include the crista terminalis, the bundle of Bachmann, and the area in between the PVs (Fig. 13*A*). With the intrinsic anisotropy of these regions, structural remodeling may readily lead to dissociated conduction patterns. Indeed, a high incidence of fractionated electrograms has been reported in these areas (see sect. **V***F*). The bundle of Bachmann forms the major conducting pathway between the right and the left atrium and consists of parallel muscle bundles (Fig. 13*B*). In goats after 1 mo of AF, this structure showed a high incidence of complex fractionated electrograms (513).

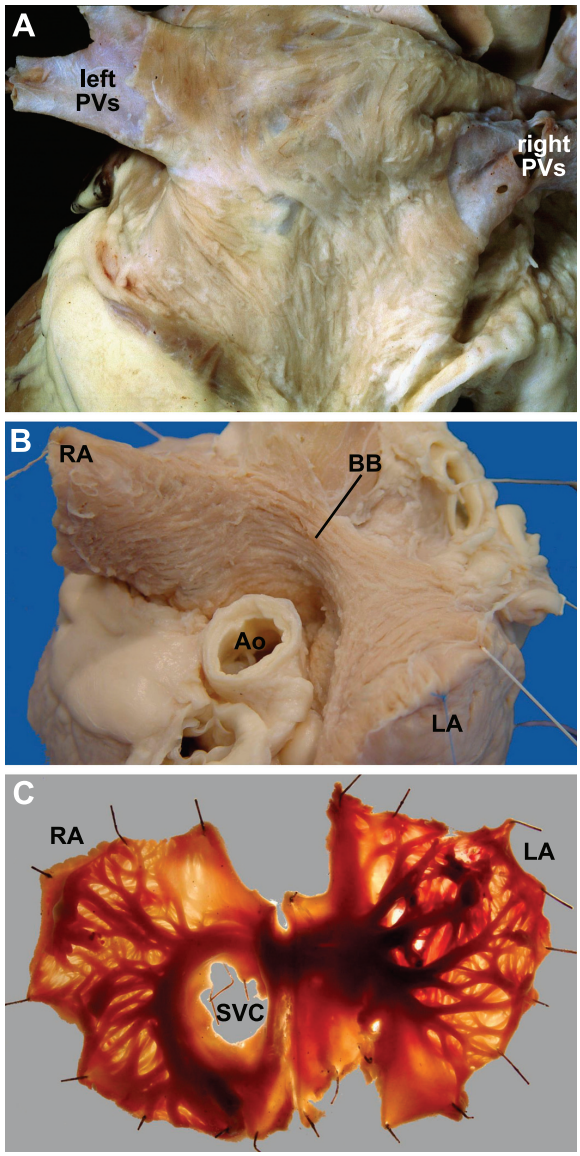


FIG. 13. Aspects of atrial anatomy. *A*: the posterior left atrium, showing the myocardial sleeves of the pulmonary veins in a human heart. In the area between the pulmonary veins, fibers show a preferential inferior-superior orientation. [Photo modified from Saito et al. (476), with permission from John Wiley and Sons.] *B*: epicardial aspect of the bundle of Bachmann (BB) in a goat heart, the main connection between the right and left atrium, consisting of a large number of parallel bundles. Ao, aorta. (Photo by Sander Verheule.) *C*: endocardial aspect anterior part of the left and right atrium in a goat heart, showing the extensive network of endocardial trabeculae underlying the thin epicardial layer. SVC, superior caval vein. (Photo by Sander Verheule.)

Another salient feature of atrial anatomy is the extensive trabecular network underlying a thin epicardial layer in a major part of right and left atria (Fig. 13*C*). Scheussler et al. (510) showed by endo- and epicardial mapping in canine hearts that epicardial and endocardial activation patterns can be markedly different and that the epicardial layer plays a leading role in atrial wave propagation during sinus rhythm. In a study on isolated sheep right atria, Berenfeld et al. (44) have shown how the endocardial network of trabeculae increases the complexity of activation patterns during AF. Recently, Houben et al. (252) have suggested that with a loss of continuity in the thin epicardial layer of the atrial wall, the trabeculated endocardial structure may become dominant, resulting in a more disorganized and stable type of AF (252). Indeed, using simulateneous endo-epicardial high-density mapping, Eckstein et al. (159a) could show that significant electrical dissociation occurs between the thin epicardial layer and the endocardial bundle network, resulting in a complex three-dimensional medium for wavefront propagation. In this study, the degree of endo-epicardial electrical dissociation increased with the complexity of the AF substrate (159a). Also, the majority of "breakthroughs" could be traced back to fibrillation waves propagating on the contralateral side of the atrial wall and therefore are likely to be due to transmural conduction.

One of the challenges ahead is to link the various conduction patterns during AF to the underlying tissue architecture and pathological changes to elucidate the electropathological substrate for perpetuation of AF.

F. Assessment of the AF Substrate by Fibrillation Electrogram Analysis

As described earlier, alterations in myocyte electrophysiology and tissue structure can create a substrate for AF. From animal models and patient studies, it has become clear that different pathological mechanisms with different resulting substrates can cause AF. Thus more specific treatment strategies require diagnostic tools that allow assessment of the nature and severity of the AF substrate in patients. A simple electrocardiographic measure, "coarse" versus "fine" AF, does not correlate well with atrial size (54, 595), heart disease etiology (392), or average AF cycle length (446), but may be indicative of thromboembolic risk (638). However, the dominant atrial cycle length determined from surface lead v1 by Fast Fourier Transform does reflect a spatial average of the AF cycle length in the right atrium (246, 260, 446). In patients with new-onset AF, the dominant atrial cycle length was higher with increasing age, increased

with AF duration, and was lower in patients who cardioverted spontaneously within the subsequent 24 h (259). A new development is the use of tissue Doppler echocardiography to determine the AF cycle length (156) and total atrial conduction time (376). The latter parameter was predictive of new-onset AF (139). At this point, the most extensive information on the AF substrate in humans has come from studies that have investigated atrial electrograms recorded in patients with AF. The distribution of dominant frequencies, fractionation of electrograms, and direct mapping of conduction patterns are the main analysis techniques used, as discussed below.

1. Distribution of dominant frequencies

Dominant frequency analysis is a relatively simple and time-efficient method for determining the AF cycle length. Recorded electrogram signals are broken down by Fast Fourier Transformation into a number of constituent sinusoidal functions. Next, the magnitude of these sine waves is plotted against the frequency in a "power spectrum." The dominant frequency is the highest peak in this power spectrum (412). In principle, a relatively high dominant frequency may be caused by a rapid ectopic focus, dissociated conduction, a rotor, or another form of reentrant circuit or even an artifact. Dominant frequency analysis often correlates well with the AF cycle length, but it is sensitive to the signal quality, recording method (unipolar vs. bipolar), and electrogram fractionation (414). In fact, a recent study indicates that the overall correlation between AF cycle length and dominant frequency can be surprisingly poor, both for unipolar and bipolar electrograms (168). A simulation study has shown that spurious high dominant frequencies can be found when the frequency and amplitude of deflections is variable (413), as often occurs in fibrillation electrograms. Newer forms of signal processing may improve robustness of AF cycle length determination (113, 251).

Lazar et al. (314) reported that in paroxysmal AF patients, dominant frequencies in the PV-left atrial junction were higher than in the coronary sinus and posterior right atrium. Persistent AF patients did not show a consistent dominant frequency gradients between these sites

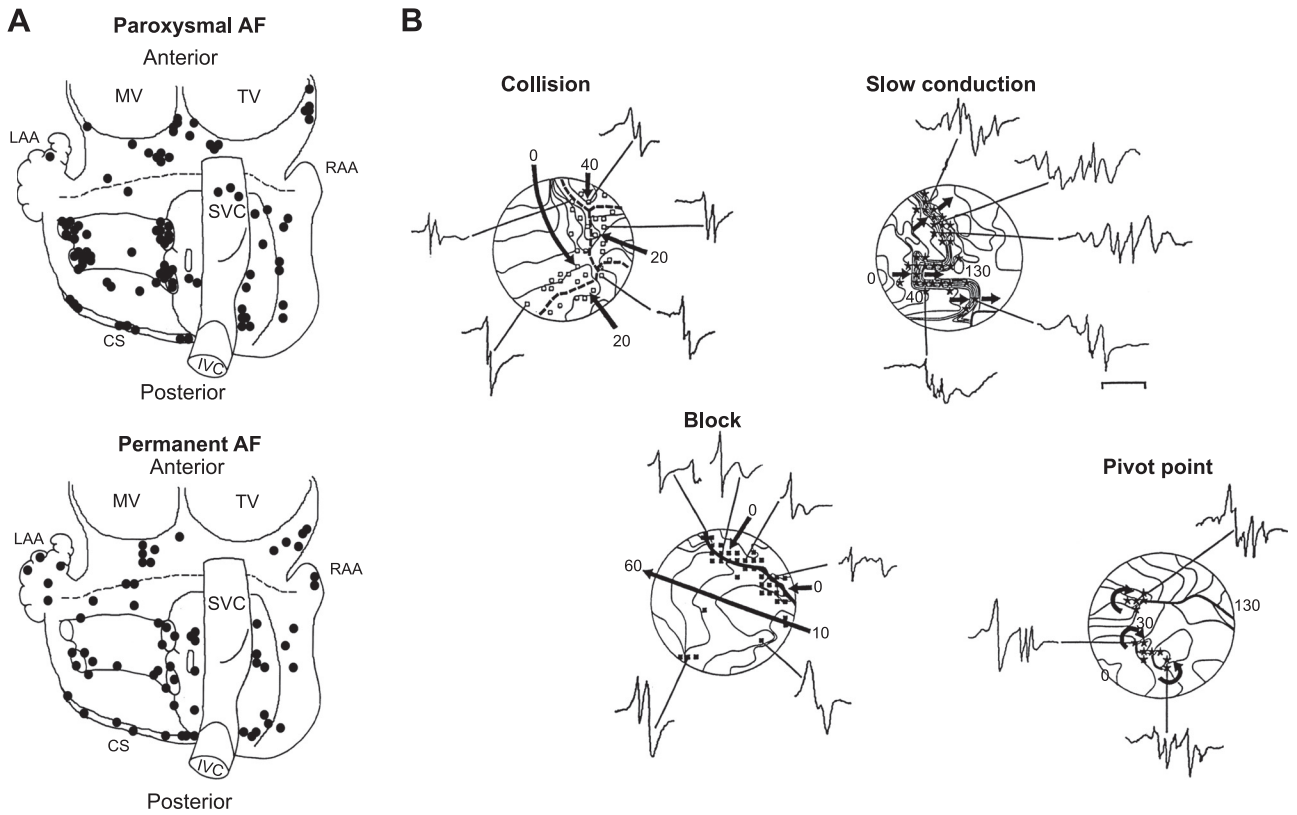


FIG. 14. Substrate of AF in patients. *A*: schematic representation of high dominant frequency sites in patients with paroxysmal AF (*left*) and permanent AF (*right*). Clustering of these sites at PV and PV-left atrial ostial sites was observed in patients with paroxysmal AF. In permanent AF patients, high dominant frequency sites occurred throughout the atria. *B*: unipolar electrograms and underlying activation patterns during acute AF in humans, recorded with a high-density array of electrodes from the right atrial free wall. *Top left*: four wavefronts (arrows) collide at the dashed lines. Fractionated electrograms with short double potentials were recorded at sites of collision. *Bottom left*: long double potentials were recorded along a functional line of block (thick black line). Complex fractionated potentials were recorded at pivot points (curved arrows, *bottom right*) and in regions of slow conduction (crowded isochrones, *top right*). [Adapted from Konings et al. (299).]

(314). PV isolation reduced the left-to-right dominant frequency gradients in paroxysmal AF (313). Similarly, Sanders et al. (482) found in a more detailed analysis that high dominant frequency sites in paroxysmal AF were preferentially clustered around the PVs, whereas persistent AF patients displayed a wider distribution of high dominant frequency sites (Fig. 14*A*). Correspondingly, PV isolation led to a significant decrease in the average atrial dominant frequency in paroxysmal AF patients, but not in persistent AF patients (484). Within another group of paroxysmal AF patients, a higher degree of dominant frequency organization predicted the success of PV isolation (551). Lin et al. (340) reported that a gradient in dominant frequency was present from an arrhythmogenic PV or superior caval vein site to the rest of the atrium in paroxysmal AF. Other studies have indicated that a left to right gradient may also be present in persistent AF patients (143, 474, 633). Lazar et al. (313) have found that PV isolation was more successful in persistent AF patients if a left to right dominant frequency gradient was present. On the other hand, a study by Schuessler et al. (511) has indicated that the location of the area of highest dominant frequency may be unstable, especially in persistent AF, but also in paroxysmal AF. Nevertheless, an ablation strategy specifically targeting high dominant frequency sites was effective in 88% of paroxysmal and 56% of persistent AF patients (24).

2. *Relation between electrogram fractionation and activation pattern*

Structural alterations can disrupt electrical connections between muscle bundles. As a result of this, the muscle bundles become activated out of phase during AF. This dissociation of electrical activity is reflected by fractionated electrograms. An electrogram is fractionated when it shows more than one deflection per activation cycle length. Fractionated electrograms may be relatively simple with two deflections per cycle (short or long double potentials) or more complex, in some cases displaying "continuous electrical activity" throughout the whole cycle. In all cases, fractionation reflects differences in activation time within the area sensed by the electrode. However, the degree of fractionation is not necessarily diagnostic for the severity of the AF substrate: long double potentials can signify the presence of an arrhythmogenic line of block that can cause reentrant conduction, whereas complex fractionation may in many cases only reflect local dyssynchroneities within broad fibrillation waves, without effect on the overall activation pattern.

In recordings of acute AF from right atria in Wolff-Parkinson-White patients, 23% of the fibrillation electrograms were fractionated, compared with 7% during sinus rhythm (299). Of these fractionated electrograms, ~0.2% displayed complex fractionation (>2 deflections) during sinus rhythm, compared with 6% during AF. Fractionation of unipolar fibrillation electrograms was observed in areas of slow conduction, at lines of conduction block, around pivot points and in regions where wavefronts collided (Fig. 14*B*) (299). The observation that during AF, collision and slow conduction were associated with fractionated electrograms indicates that these activation patterns were associated with dyssynchronous activation in the atrial wall. Lines of block can be either anatomical (i.e., also present during slow pacing) or functional (i.e., absent at long cycle lengths, but present during fast pacing). During slow pacing with propagation perpendicular to an anatomical line of block formed by an incision, electrograms displayed double deflections corresponding to the activation time points at either side of the line of block (135). However, fractionated electrograms observed around functional lines of block were often complex, showing numerous deflections. Slow, discontinuous transverse conduction between fibers partially separated by fibrotic tissue may explain why the recorded fractionated electrograms were more complex than in the case of a complete anatomical lesion.

In simulations with an atrial model, Jacquemet et al. (263) showed that fractionated electrograms did not occur in homogeneous tissue, even with a high degree of anisotropy. However, when abrupt changes in conductivity were introduced, fractionated electrograms were observed. Similar to the correlation between activation pattern and electrogram fractionation in patients (299), the morphology and distribution of fractionated electrograms in this model varied from beat to beat, depending on variations in propagation direction. However, fractionation may preferentially occur at certain anatomical locations. In recent clinical studies, the regional distribution of sites with a high degree of electrogram fractionation appeared to be stable over time (398, 470, 495).

3. *Fractionated electrograms as indicators of the AF substrate*

In chronic AF or atria of hearts with underlying heart disease, the slow process of structural remodeling may increase transverse fiber separation and may reduce the number of side-to-side connections throughout the free walls. As a result, fractionated electrograms would become more frequent and more widespread. Several studies indicate that the degree of electrogram fractionation does indeed correlate with AF maintenance. During extrastimulation, electrogram fractionation has a longer duration in paroxysmal AF patients than in healthy control subjects (548), and the prevalence of fractionated electrograms (mainly double potentials) in the coronary sinus musculature (279) and PVs (234) is higher than in patients without AF. In paroxysmal AF patients, a more extensive distribution of fractionated electrograms is predictive for

a transition to persistent AF (403), and fractionation is more localized to the PV region. In contrast, their occurrence is more widespread in persistent AF (339, 632). Some known risk factors for AF are also associated with increased electrogram fractionation. Compared with age-matched controls, CHF patients showed both a higher incidence of double potentials along the crista terminalis and an increased AF vulnerability and stability (483). In addition, the incidence of electrogram fractionation increases with age (93, 293).

A high degree of fractionation may also be a direct result of a high activation rate. Rostock et al. (469) demonstrated that local AF cycle length shortening preceded the development of electrogram fractionation. In paroxysmal AF, fractionated electrograms tend to be clustered at the PVs, which often act as high-frequency drivers of AF in those patients, whereas fractionated electrograms show a wider distribution in chronic AF patients (339, 543, 632). In addition, electrogram fractionation is observed in close proximity to sites with a high dominant frequency (543).

Several studies indicate that fractionation is linked to parasympathetic activity. In paroxysmal AF patients, electrogram fractionation was associated with vagal activity, an effect that could be mimicked by adenosine administration (320). In addition, fractionation preferentially occurred near ganglionated plexi (278). In dogs, acetylcholine injection into ganglionated plexi led to local high activation frequencies with irregular fractionated electrograms (350). As noted above, the occurrence of fractionation may be correlated with the activation frequency. Therefore, the association between vagal activity and electrogram fractionation may be caused by a (local) acceleration of the fibrillatory rate.

4. Ablation of fractionated electrograms

Because of its association with complex activation patterns mapping of electrogram fractionation during AF may allow identification of regions with structural conduction disturbances that are involved in perpetuation of AF. Nademanee and co-workers (398, 399) have studied fractionated electrograms in patients with paroxysmal and chronic AF and frequently localized "complex fractionated atrial electrograms" (CFAE) in the interatrial septum, PVs and the left atrial roof (398, 399). Ablation of areas with these CFAEs resulted in restoration of sinus rhythm in 91% of the patients after a follow-up of 1 yr. Other groups have used similar electrogram characteristics to search for underlying local left atrial parasympathetic innervation ("ganlionated plexus"), and associated the perceived benefit of CFAE ablation with parasympathetic denervation (250, 338). More recent controlled trials have not been able to reproduce the findings of Nademanee, and even suggest that CFAE ablation does not alter the natural time course of AF (428). Also, the benefit of ablation of CFAEs alone or as an adjunct to PV isolation appears to be limited (428). However, more specific electrogram-guided strategies, such as ablation of electrograms with continuous activity or a high gradient in activation rate, may improve efficacy (550). Recent advances of the field of ablation of fractionated electrograms have been expertly reviewed elsewhere (397, 630) and are beyond the focus of this article.

5. Mapping of AF conduction patterns

Although the distribution of dominant frequencies and fractionated electrograms can provide valuable information on the AF substrate, direct mapping of activation patterns using contact electrograms provides the most direct electrophysiological information on the AF substrate. Bipolar electrograms represent a convenient way to reduce noise and far-field (ventricular) potentials, but the morphology of a bipolar electrogram is sensitive to the propagation direction and is more difficult to interpret in case of dissociated or fractionated signals. Unipolar electrograms allow a more accurate determination of local activation times and are therefore preferable for a detailed reconstruction of activation patterns. One of the first studies to describe AF conduction patterns investigated the right atrium during electrically induced AF in patients undergoing surgery for WPW syndrome (298). During sinus rhythm and atrial pacing, right atrial conduction in WPW patients is mostly homogeneous and isotropic (222). During electrically induced AF, right atrial conduction showed varying degrees of complexity (298). With increasing complexity, the number of wavefronts simultaneously present underneath the mapping electrode frequency and irregularity of the AF cycle length increased. Clearly, complex AF was driven by more and narrower waves. Cox et al. (129) studied WPW patients with paroxysmal AF and described conduction of multiple wavefronts around areas of conduction block in both atria, in some cases with a single reentrant circuit between the caval veins in the RA. In chronic AF patients undergoing mitral valve surgery, several studies reported rapid repetitive left atrial activation with more complex fibrillatory conduction in the right atrium, consistent with left atrial driver regions (225, 419, 544). Similar rapid repetitive activation was recorded in the left atrial posterior wall of a varied group of chronic AF patients with structural heart disease, but with more uniform and broader wavefronts in the right atrium (633). Kanagaratnam and co-workers (272, 273) did not detect differences in the complexity (again quantified by the number of wavefronts simultaneously present) of right atrial conduction during acute and chronic AF. However, in another study in patients with persistent AF, a high degree of variability in AF wavefront propagation was observed

throughout the right atrium (464). Recently, Allessie et al. (7a) have described a new, more quantitative, method for analyzing fibrillation waves, showing an increase in longitudinal dissociation between waves in chronic AF compared with acute AF. The PV region showed a higher degree of dissociation than the RA free wall. Longitudinal dissociation resulted in narrower wavefronts and a higher number of simultaneous fibrillation waves. A variety of right atrial activation patterns in chronic AF were reported by Holm et al. (245), with multiple coexisting fibrillation waves in some patients and repetitive focal spread of activation in others, most likely reflecting transmural conduction of fibrillation waves (breakthroughs). De Groot et al. (135a) have recently demonstrated that the incidence of "epicardial breakthroughs" is higher in chronic than in acute AF. The origin of these waves was nonrepetitive in time and widespread throughout the atria. Based on these and other characteristics, the authors have argued that most breakthroughs are caused by transmural conduction.

Several studies have investigated conduction patterns in arrhythmogenic thoracic veins of paroxysmal AF patients. In atrial tachycardia originating in the superior caval vein, Shah et al. (512) observed slow and anisotropic conduction within the myocardial sleeve, compatible with a tendency for local reentry. Similarly, mapping with a 64-electrode basket catheter in the PVs found relatively fast, narrow activation waves along the length axis of the vein and slow conduction perpendicular to it (481). The presence of this dissociated conduction patterns was predictive for the efficacy of ablation at that vein. In contrast, using similar recording methods, Arentz et al. (19) observed predominantly radial spread of activation without indications for local reentrant circuits in the PV myocardial sleeves. However, breakthrough patterns at the PV-left atrial junction, leading to focal spread of activation were also observed during sinus rhythm and atrial pacing (137). In the latter study, mapping during ectopic activity often showed a "multifocal" pattern of activation within the PV area mapped with a basket catheter.

Overall, detailed studies on atrial conduction patterns at various stages of the development of an AF substrate are disappointingly rare, probably due to the limited opportunity for mapping studies in patients and the complexity of the time-consuming techniques involved. Automated and rapid analysis of fibrillation electrograms might enable objective and prompt analysis of activation patterns during AF in the future (251). Another interesting new possibility is the recording of atrial activation patterns by ECG imaging (ECGI). This approach addresses the inverse problem by integrating body surface mapping with detailed anatomical data from magnetic resonance imaging (461). ECGI can delineate atrial activation patterns during sinus rhythm (462), atrial pacing (385), atrial flutter (604), and focal atrial tachycardia (603). Recently, the first study characterizing epicardial activation patterns during AF using ECGI was published (130a). The results show a large variability in the complexity of AF increasing with longer duration of the arrhythmia. It will be important to validate the ability of this technique to image the fibrillation process up to a level of complexity which enables a clinically meaningful classification of AF.

VI. SPECIFIC FORMS OF ATRIAL FIBRILLATION

A. Postoperative AF

In up to 30% of patients who undergo open heart surgery, usually associated with the use of cardiopulmonary bypass, AF occurs during the first days after the operation (538, 609). The most important factor that determines the incidence of postoperative AF is the type of surgery (8, 27). The highest incidence of postoperative AF occurs with mitral valve repair in single cardiac surgery and with coronary artery bypass graft surgery plus mitral valve repair in combined cardiac surgery.

Postoperative AF differs in some respects from other clinical forms of the arrhythmia. The insertion of a cannula in the right atrium and, depending on the type of operation, other cuts in the atrial walls, and compromised hemodynamics are potential external stressors that may promote postoperative AF. Importantly, the use of anti-inflammatory agents may prevent postoperative AF (34, 218, 611), suggesting an important role of systemic or local inflammatory processes. It is known that cardiac surgery causes a biphasic complement activation that is associated with a higher incidence of the arrhythmia (65). Furthermore, during cardiopulmonary bypass, free radicals are produced (116) and atrial ischemia due to inadequate atrial protection during cardiac arrest occurs. However, several studies failed to show a lower incidence of the arrhythmia with off-pump versus on-pump surgery (1, 513, 547, 636), questioning the importance of cardiopulmonary bypass. Finally, sympathetic activation appears to promote postoperative AF. In afflicted patients, norepinephrine levels are elevated, and preoperative and postoperative use of β-adrenoceptor blockers decreases the incidence of postoperative AF (271, 610).

On the other hand, postoperative AF appears to share some pathophysiological mechanisms with other forms of AF. For example, the duration of the preoperative P-wave on the surface ECG does predict the occurrence of postoperative AF (540). Interestingly, the P-wave duration correlates with the amount of interstitial fibrosis, which predicts the occurrence of postoperative AF supporting the concept that fibrosis is also involved in the pathogenesis of this type of AF (199). Advanced age is also a known risk factor for the development of postoperative AF, which can be explained by age-related structural changes like fibrosis and atrial dilatation. Like in other

forms of AF, there is also emerging evidence that oxidative stress contributes to the vulnerability to postoperative AF (91, 248). Also, complex changes in ionic channels and gap junctions might enhance the propensity for postoperative AF (154, 273, 348, 576).

B. Inherited Cardiomyopathies and Genetic Defects Associated With AF

Numerous inherited syndromes associated with AF have been identified during the past years (Table 6). The mechanistic link to AF is not always obvious and sometimes surprising. For example, patients with an inherited prolongation of the atrial action potential carry a risk for AF (41, 266, 351, 651). Most patients show short episodes of paroxysmal AF, and some data may suggest that these arrhythmias can be initiated by EADs (290, 291). Both short and long QT syndromes are associated with AF, indicating that channelopathies can predispose to the arrhythmia by multiple mechanisms. Also the Brugada syndrome is associated with supraventricular arrhythmias, often including AF (158, 311, 497). Whether Na^+ channel mutations, usually loss-of-function mutations, provoke AF in these patients is not known. Because of the large genetic heterogeneity of Brugada syndrome, a clear cause and effect analysis is challenging. Finally, in some, but not all, patients with catecholaminergic polymorphic ventricular tachycardia caused by genetic defects of RYR2, sinus node and AV-nodal dysfunction and AF occur (47).

In addition to these channelopathies, several other inherited cardiomyopathies are strongly associated with AF of early onset (Table 6). Hypertrophic cardiomyopathy is a well-known example for this association. A familial form of ventricular preexcitation and abnormal LV hypertrophy associated with mutations in the PRKAG gene is also often associated with AF. These associations may suggest that abnormal ventricular hypertrophy can promote AF, possibly through cardiomyocyte dysarray, diastolic dysfunction, or metabolic deficiency (345). Other genetic defects associated with AF comprise mutations in the atrial natriuretic peptide and changes in transcription factors (AF in Holt-Oram syndrome and the association of PITX2 and AF) (213, 456). The pathophysiological role of these common genetic variants for the initiation and perpetuation of AF certainly warrants further investigation.

VII. SUMMARY AND FUTURE PERSPECTIVES

A. Summary

Figure 15 provides an overview of the main mechanisms involved in initiation and perpetuation of AF as described in sections **IV–VI**. Figure 15 emphasizes the

TABLE 6. *Genetic abnormalities associated with AF identified in patients with inherited cardiomyopathies carrying a high risk for AF and genetic defects found in association with AF*

Cardiac Abnormality/Type of AF	Genetic Defect	AF Prevalence (Estimate)/Associated With AF In
	Inherited cardiomyopathies (366) associated with AF	
Brugada syndrome	Loss-of-function SCN5A mutations (10–15% of patients)	10–20% (158)
Long QT syndrome	Late gain-of-function SCN5A and loss-of-function K channel mutations, among others	5–10% (266, 290, 291, 651)
Short QT syndrome	Gain-of-function K channel mutations	70% (191, 196)
Catecholaminergic VT	Loss-of-function ryanodine receptor mutation	Rare families (47)
Hypertrophic cardiomyopathy	Sarcomeric proteins	5–15% (317, 347, 365)
Wolff-Parkinson-White syndrome and abnormal LVH	PRKAG mutations	Rare familial forms (18, 204)
Holt-Oram syndrome with AF	TBX5 mutations (regulatory gene)	Family clusters (456)
	Gene defects associated with AF	
"Lone" AF	Loss-of-function SCN5A mutations	5% of "lone" AF patients (134, 167)
AF and heart failure	SCN5A mutation	Rare forms of AF (425)
"Lone" AF	Gain-of-function K channel mutations	Rare families with AF and short QT interval (102)
"Lone" AF	Loss-of-function K channel polymorphisms	Rare families, associated with long QT syndrome (524)
"Lone" AF	Loss-of-function KV1.5 mutation (I_{Kur})	Rare patients (524)
"Lone" AF	Somatic connexin40 mutations	"Lone AF" patients (203) (requires atrial tissue for testing)
"Lone" AF	Frameshift (loss-of-function) ANP mutation	Large families (242)
All types of AF	PITX2 polymorphism (involved in pulmonary and cardiac development)	Populations in Iceland (213)

Reference numbers are given in parentheses. [From Kirchhoff et al. (289).]

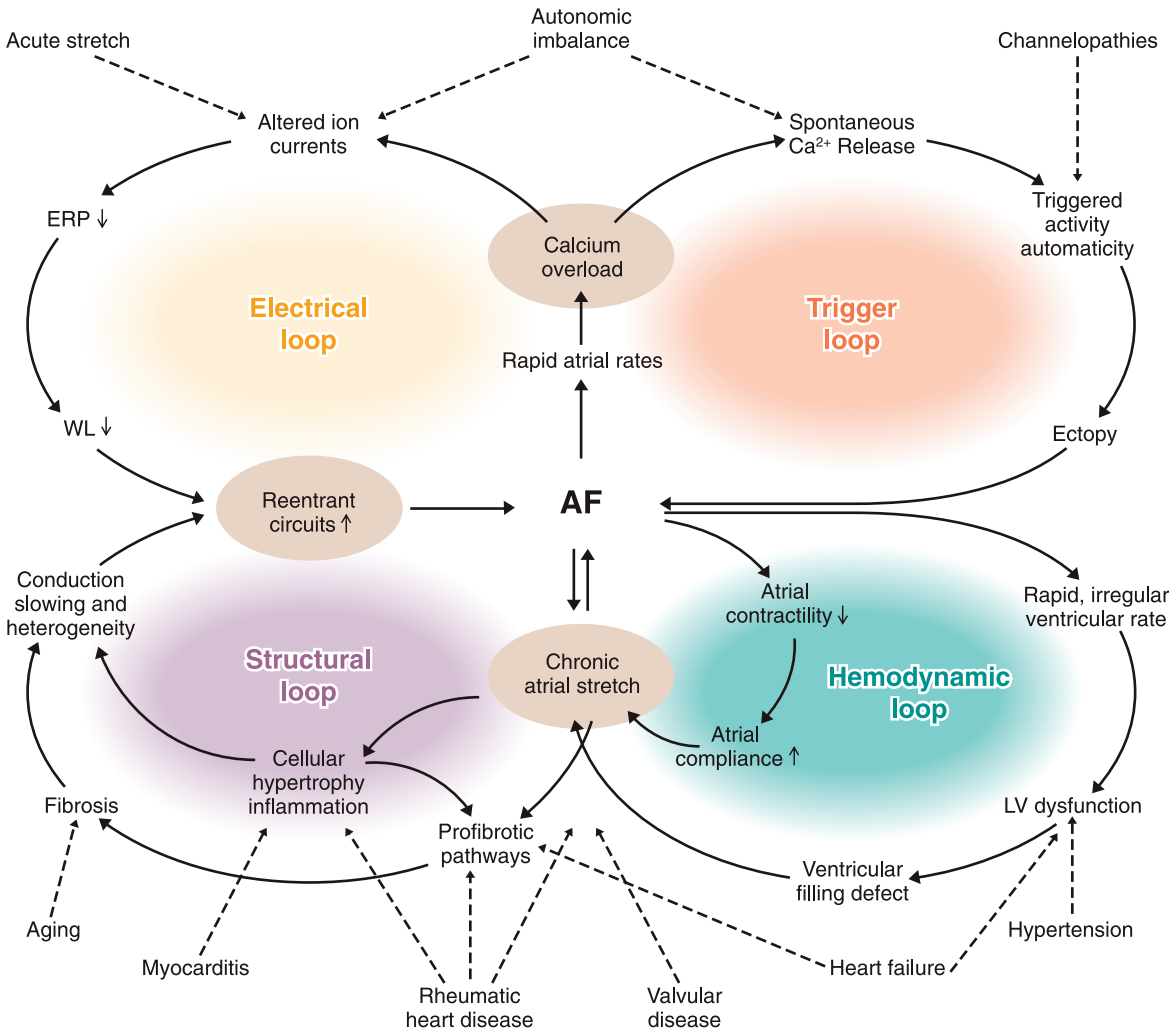


FIG. 15. Overview of mechanisms of AF. Four different positive-feedback loops are proposed as the main driving forces for the atrial remodeling process. Enhanced Ca^{2+} loading during AF is believed to underlie most of the cellular proarrhythmic mechanisms (trigger loop). The main process in the electrical loop is an altered contribution of ion channels to the action potential configuration that protects atrial myocytes against excessive Ca^{2+} loading. Abbreviation of the action potential facilitates reentry and thereby promotes AF. In the structural loop, chronic atrial stretch activates numerous signaling cascades that produce alterations of the extracellular matrix and conduction disturbances, also facilitating reentrant mechanisms. The main changes of the contractile properties of the heart are loss of atrial contractility which increases atrial compliance and the development of a ventricular tachycardiomyopathy, both of which increase stretch in the atrial wall. The circular positive-feedback enhancement of these pathophysiological changes explains the general tendency of AF to become more stable with time. It should be noted that the different loops are interconnected by mechanisms that are part of more than one loop. For example, increased Ca^{2+} loading enhances trigger activity (trigger loop) and also results in a change in the ion channel population and activity (electrical loop). Reentrant mechanisms are promoted by both shortening of refractoriness (electrical loop) as well as by conduction disturbances resulting from tissue fibrosis (structural loop). Like in a system of meshing gear wheels, one loop will drive the other, leading to progression of the arrhythmia. However, the proposed system of gear wheels does not start to move spontaneously. Structural heart diseases, arrhythmias, aging, or inherited diseases are required to initiate movement of one or more of these wheels. When the pathophysiological alterations eventually reach a certain threshold, AF will ensue.

dynamic character of the process and the diversity of the contributors to the atrial remodeling process. The diagram mainly consists of four positive-feedback loops. The central element in all loops is the arrhythmia itself, which at the same time represents both trigger and effect of the four circular processes. The circular positive-feedback enhancement of these pathophysiological changes explains the general tendency of AF to become more stable with time. Also, many of the mechanisms synergistically interact once AF has become manifest in a patient. Since the contribution of these different factors to AF varies from patient to patient, the progression of AF shows a high inter-individual variability. Initially, pathophysiological factors like structural heart diseases, arrhythmias, aging, or inherited diseases are required to drive the positive feedback loops, but once the pathophysiological alterations in the atria have reached a certain threshold, the process will sustain itself and AF will become more stable over time.

B. Current Challenges and Future Perspectives

The increase in life expectancy and recent improvements in treatment of acute heart disease have resulted in

a major increase in number of patients living with heart failure and/or AF. Although the socioeconomic burden of AF is growing steadily and significant progress has been made in understanding the pathophysiology of this arrhythmia, treatment of AF patients is still far from satisfactory. The success rate of pharmacological cardioversion is still limited, and antiarrhythmic drugs are unable to prevent recurrences of AF (86, 122, 488). Prevention of thromboembolic events still requires potentially harmful anticoagulation therapy (256, 599). Radiofrequency ablation, originally developed for treatment of paroxysmal AF, varies in its efficacy to cure persistent AF and is afflicted with a number of potentially serious side effects (180, 400, 457, 458, 650).

In the authors' view, addressing the following research objectives might help to improve therapeutic approaches for AF.

Mechanisms contributing to the initiation and perpetuation of AF show a high diversity and interindividual variability. Functional and structural changes in the atria can promote AF by a variety of processes that may involve ion channel remodeling, atrial fibrosis, inflammation, apoptosis, loss of cell-cell contacts, altered autonomic tone, cellular hypertrophy, and deposition of amyloid. Better understanding of the factors that initiate and maintain AF in specific patients or patient groups will not only allow to chose appropriate therapeutic approaches, but also help to limit therapy duration to periods when these therapies are really beneficial.

To develop individualized therapy for AF, a classification of the arrhythmia based on the pathophysiological changes in the atria needs to be developed. Current therapeutic regimes are most often chosen based on clinical symptoms and the duration of AF (paroxysmal or persistent AF). These categories, though helpful, do not necessarily reflect the nature and degree of electrophysiological changes resulting in AF. New diagnostic tools for AF classification might include invasive and noninvasive electrophysiological measurements, biochemical markers, and imaging techniques.

The structural alterations that progressively increase AF susceptibility occur relatively early during atrial remodeling, in most cases before the first onset of AF, and certainly before the arrhythmia becomes persistent. Identification of patients in early stages of this remodeling process might enable timely and effective preventive therapy.

The development of new upstream therapy targets requires the identification of relevant microstructural determinants of conduction disturbances. Most importantly, the exact qualitative and quantitative relation between atrial fibrosis and conduction disturbances needs to be determined.

The role of ectopic focal discharges in the perpetuation of persistent AF is largely unknown. Clarification of mechanisms and contribution of abnormal impulse formation to the perpetuation of persistent AF might offer the opportunity to identify new pharmacological targets for AF therapy.

Given the complexity of the mechanisms causing AF and the significant contribution of nonmodifiable factors such as aging and genetic predispositions, we believe that even an early, aggressive, and individualized therapy will not prevent or "cure" AF in the foreseeable future. However, addressing the above-mentioned research objectives might allow the postponing of the time point to accept AF in an individual patient. In other cases, we might, based on pathophysiological insights, prefer to refrain from potentially harmful interventions.

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U. Schotten and S. Verheule contributed equally to this work.

Address for reprint requests and other correspondence: U. Schotten, Dept of Physiology, Univ. of Maastricht, PO Box 616, 6200 MD Maastricht, The Netherlands (e-mail: Schotten @maastrichtuniversity.nl).

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Ulrich Schotten, Sander Verheule, Paulus Kirchhof and Andreas Goette

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