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Ionic Remodeling in the Heart Pathophysiological Significance and New Therapeutic Opportunities for Atrial Fibrillation

Stanley Nattel, Danshi Li

Abstract—Heart disease has long been recognized to alter cardiac electrical function. Detailed studies of disease-induced remodeling of ionic transport processes that underlie ventricular electrophysiological alterations have been performed over the past 10 years, but our knowledge of atrial ionic remodeling is more limited and has emerged much more recently. The present review focuses on recent findings regarding ionic remodeling at the atrial level, particularly with respect to two conditions that promote atrial fibrillation (AF) in well-developed clinically relevant animal models: (1) sustained atrial tachycardia and (2) ventricular tachypacing–induced congestive heart failure. Complementary data from experimental models and from observations in atrial tissue samples from patients are examined critically and integrated. Consideration is also given to potential molecular mechanisms underlying remodeling, the relationship between atrial and ventricular ionic remodeling in response to similar stimuli, and the potential relevance of insights into ionic remodeling for understanding the pathophysiology of AF and developing improved therapeutic approaches. (*Circ Res.* 2000;87:440-447.)

Key Words: ion channels ■ heart arrhythmia mechanisms ■ cardiac electrophysiology
■ heart disease ■ congestive heart failure

As early as 1930, it was noted that cardiac K^+ content is altered in patients with congestive heart failure (CHF), pointing to disease-induced changes in ionic transport mechanisms.¹ In 1961, van Dam and Durrer² recorded electrical activity from left atrial appendages of patients with mitral valve disease, noting functional abnormalities in patients with sinus rhythm and an inability to record activity in patients with grossly dilated atria and atrial fibrillation (AF) before surgery. Action potential abnormalities in patients with heart disease were described by Trautwein et al in 1962.³ The first description of action potential abnormalities (including decreased resting potential and dV/dt_{max} and increased action potential duration) in an experimental model of heart failure was provided by Gelband and Bassett in 1973.⁴ The abnormalities in cardiac electrical activity associated with heart disease pointed toward changes in ion channel function, and in the early 1980s, Ten Eick et al^{5,6} described alterations in both outward K^+ currents (decreased inward and delayed rectifiers) and inward Ca^{2+} currents in diseased hearts.

Over the past 10 years, great progress has been made in understanding the ionic remodeling caused by various cardiac pathologies. A particularly large amount of work has been performed to study ionic remodeling in the ventricles, with respect to which the interested reader is invited to consult two recent thorough reviews.^{7,8} Less work has been directed to the

study of atrial ionic remodeling. The ionic properties of the atria play an important role in determining the occurrence and properties of atrial arrhythmias, particularly AF. The present work reviews the information available regarding ionic remodeling in the atria under a variety of pathological conditions. Although ventricular ionic remodeling is not discussed in detail, attempts are made to relate atrial remodeling to that in the ventricles under comparable conditions. Finally, we endeavor to assess the role of atrial ionic remodeling in the pathophysiology of AF and in the context of possible new approaches to treating the arrhythmia.

Ionic Remodeling Induced by AF and Atrial Tachycardia in Experimental Models

The possibility that AF might itself produce ionic remodeling was suggested by the ingenious work of Wijffels et al.⁹ These authors maintained AF in chronically instrumented goats with the use of a computer algorithm that sensed sinus rhythm and then promptly applied a burst of rapid atrial pacing to induce AF. In this fashion, they were able to maintain virtually continuous AF while simultaneously tracking over time the duration that induced AF continued spontaneously until sinus rhythm supervened. AF was found to produce rapid decreases in atrial refractory period (reaching near maximum within 24 hours) and progressive increases in spontaneous AF mainte-

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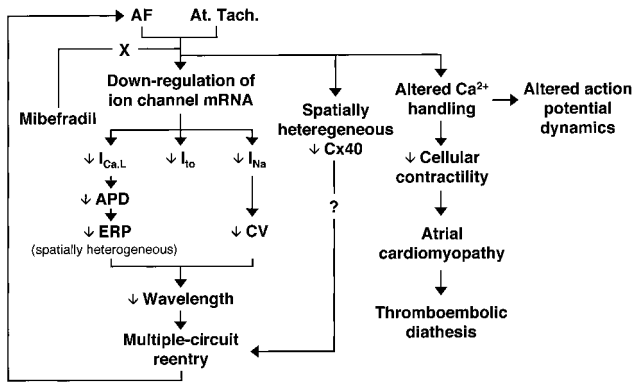


Figure 1. Role of atrial ionic remodeling in AF promotion by atrial tachycardia. Note that mibefradil has been shown to prevent electrophysiological changes (ERP reduction, AF promotion) caused by tachycardia-induced remodeling. The level at which mibefradil acts has not been established. In this Figure, mibefradil action is indicated as proximal to mRNA downregulation, but this remains to be established. At. Tach. indicates atrial tachycardia; ERP, effective refractory period; CV, conduction velocity; and APD, action potential duration.

nance, with AF generally becoming persistent within 1 to 2 weeks. Other studies showed that atrial tachycardia is a sufficient stimulus to induce the changes typical of AF-induced remodeling.^{10–12}

Subsequent work has revealed that many of the AF-promoting effects of atrial tachycardia-induced remodeling are mediated by alterations in ion channel function (as schematically summarized in Figure 1). Rapid atrial pacing (400 bpm) in dogs leads to progressive decreases of Ca^{2+} -independent transient outward current (I_{to}) and L-type Ca^{2+} current ($I_{Ca,L}$) density, by $\approx 70\%$ after 6 weeks of tachycardia.¹³ The dependencies of current on voltage and time are unaffected. A variety of other currents, including the inward rectifier (I_{K1}), ultrarapid ($I_{Kur,d}$), rapid (I_{Kr}) and slow (I_{Ks}) delayed rectifiers, T-type Ca^{2+} current ($I_{Ca,T}$), and Ca^{2+} -dependent Cl^- current, are unaffected by atrial tachycardia.¹³ Inhibiting $I_{Ca,L}$ of a control cell with $10 \mu\text{mol/L}$ nifedipine mimics many of the action potential changes produced by atrial tachycardia, whereas increasing I_{Ca} with Bay K 8644 reverses action potential abnormalities in tachycardia-remodeled myocytes.¹³ Mimicking I_{to} inhibition with 4-aminopyridine fails to reproduce the repolarization abnormalities caused by atrial tachycardia.¹³

The results of pharmacological studies, as well as those provided by mathematical models of the action potential,^{14,15} suggest that $I_{Ca,L}$ suppression is an important determinant of the action potential duration and refractoriness changes observed in response to atrial tachycardia. On the other hand, changes in other ion transport mechanisms have been reported that may be significant in other areas of atrial function.

There is evidence that rapid Na^+ current (I_{Na}) may be downregulated by atrial tachycardia, with changes that are slower to develop and quantitatively less important than those in $I_{Ca,L}$.¹⁶ Alterations in I_{Na} correlate with changes in atrial conduction velocity occurring with maintained atrial tachycardia,¹⁶ and I_{Na} downregulation may therefore contribute to the decreased atrial conduction velocity commonly

associated with AF. By decreasing wavelength, conduction velocity slowing may also favor multiple-circuit reentry.

In addition to a decrease in $I_{Ca,L}$, there is evidence for more extensive abnormalities in cellular Ca^{2+} handling with tachycardia-induced atrial remodeling. Microfluorescent studies with Indo 1-AM show a decrease in the amplitude, as well as a change in the kinetics, of Ca^{2+} transients in atrial myocytes from dogs subjected to long-term (7 days or more) atrial tachycardia.¹⁷ These abnormalities correlate with decreases in cell shortening¹⁷ and likely play a role in the transient hypocontractility (atrial stunning) observed when persistent AF is converted to sinus rhythm. Furthermore, the dynamic behavior of action potential duration in atrial tissues of dogs with atrial tachycardia-induced remodeling is quite different from the behavior of control action potentials, but in the presence of the sarcoplasmic reticulum Ca^{2+} release inhibitor ryanodine, control and remodeled action potentials behave more similarly.¹⁸ These findings suggest that Ca^{2+} handling abnormalities may contribute to abnormal dynamic behaviors of tachycardia-remodeled atrial action potentials.

Connexins are integral membrane ion channel proteins that govern cell-to-cell communication and conduction. There are conflicting data regarding changes in connexins in experimental models of AF. Elvan et al¹⁹ showed upregulation of connexin43 expression in dogs with AF maintained for 10 to 14 weeks by electrical stimulation. van der Velden et al,²⁰ on the other hand, found no change in connexin43 mRNA or protein expression in dogs with AF. Although connexin40 mRNA and protein levels were similarly unchanged, there were patchy areas involving $\approx 25\%$ of the atria in which connexin40 protein expression was substantially decreased.²⁰ The same group subsequently showed evidence for decreases in the ratio between atrial connexin40 and connexin43 protein that correlate with cellular myolysis, without any change in connexin40 mRNA levels.²¹ Transgenic mice completely lacking connexin40 are susceptible to the induction of atrial tachyarrhythmias, but mice heterozygous for connexin40 do not show an increased atrial arrhythmia susceptibility.^{22,23} The notion that alterations in connexins contribute to arrhythmogenic ionic remodeling in AF is thus attractive, but although presently available data are consistent with such a possibility, they are insufficient to establish it.

Ionic Remodeling in Other Experimental Models of Pathology Associated With AF

CHF is one of the clinical conditions most commonly associated with AF. Atrial action potentials are little changed in animals with atrial enlargement due to tricuspid or mitral valve abnormalities causing atrial disease.^{24,25} In cats with cardiomyopathies and atrial arrhythmias, including AF, right atrial action potentials are unaltered, but action potentials tend to be prolonged in tissue from more severely dilated left atria.²⁶ In a recent study of dogs with a substrate for AF produced by ventricular tachypacing-induced CHF, action potential duration in right atrial cells was unchanged at low activation frequencies and increased at higher frequencies.²⁷ Membrane resting potential was unaltered. Several atrial ionic currents were altered by CHF in the latter study: I_{Ks} and $I_{Ca,L}$ were decreased by $\approx 30\%$ and I_{to} by $\approx 50\%$. The density

of $\text{Na}^+-\text{Ca}^{2+}$ exchanger (NCX) current was substantially increased, as was the expression of NCX protein,²⁷ in contrast to the atrial tachycardia-induced substrate in which NCX expression is unchanged.²⁸ A variety of other currents, including I_{K1} , $I_{\text{Kur,d}}$, I_{Kr} , and $I_{\text{Ca,T}}$, were unaltered by ventricular tachypacing-induced CHF.²⁷

Hyperthyroidism is a significant clinical cause of AF, but relatively little is known about the underlying cellular and ionic mechanisms. Atrial action potential duration is decreased by hyperthyroidism,²⁹ a change that would be expected to promote AF. Hyperthyroidism strongly increases I_{to} and enhances its temperature dependence in rabbit ventricle but does not affect rabbit atrial I_{to} .^{30,31} Ventricular I_{Ca} appears to be increased by hyperthyroidism in guinea pigs,^{32,33} and atrial tissue samples from patients with latent hyperthyroidism show increased I_{Ca} due to increased single-channel availability, along with increased α_{1c} subunit protein expression on Western blot.³⁴

Ionic Alterations in Patients With Atrial Disease or Arrhythmias

Data from animal models of heart disease are crucial for understanding the effects of defined cardiac pathologies on atrial cellular and ionic electrophysiology; however, extrapolation to humans must be cautious. Studies on clinical samples are therefore crucial but have the limitation that the results obtained never reflect the effects of any single variable: the contributions of organic heart disease, rhythm disorders, varying age, and concomitant drug therapy all need to be considered. In addition, clinical samples are almost never of the size and quality possible in animal experimentation, and handling conditions (from excision to laboratory processing) are often suboptimal. Thus, experiments with clinical samples and studies with experimental animals provide important complementary information.

Fine-tipped microelectrode action potential recordings in the 1970s showed that diseased human atria have decreased resting membrane potentials.³⁵ Subsequent work indicated that atrial specimens from patients with atrial disease have a reduced resting potential response to $[\text{K}^+]_o$,^{36,37} pointing to decreased resting K^+ conductance as the mechanism of depolarization. The addition of acetylcholine and the reduction of $[\text{Na}^+]_o$ improve the resting potential,³⁷ further pointing to abnormalities in the basal Na^+/K^+ conductance ratio. Koumi et al³⁸ subsequently showed that atrial myocytes of patients with advanced CHF have reduced I_{K1} and acetylcholine-dependent K^+ current (I_{KACh}) densities, confirming the mechanisms inferred previously on the basis of indirect evidence. On the other hand, Le Grand et al³⁹ found that the resting potential and I_{K1} density were not altered in cells from dilated, compared with nondilated, human atria, pointing to variability in the I_{K1} response in different populations of patients with atrial disease. I_{to} is reduced in myocytes of dilated human atria,^{39,40} as is the sustained current (I_{sus}) at the end of a depolarizing pulse³⁹ carried predominantly by $\text{Kv}1.5$ K^+ -channel subunits.^{41,42} Results regarding $I_{\text{Ca,L}}$ changes are discrepant, with two studies

showing a decrease^{39,43} and one no change⁴⁴ in patients with severe CHF and/or atrial dilatation.

A variety of ionic abnormalities have been reported in atrial myocytes from patients with AF. Van Wagoner et al⁴⁵ reported a decrease in atrial I_{to} and I_{sus} (along with $\text{Kv}1.5$ subunit protein) in patients with AF. They also noted an increase in left, but not right, atrial I_{K1} density. Bosch et al⁴⁶ observed a decreased I_{to} and an increase in both I_{K1} and I_{KACh} densities in right atrial myocytes of patients with AF. Two studies have reported that $I_{\text{Ca,L}}$ is decreased by $\approx 70\%$ in atrial myocytes of patients with persistent AF,^{46,47} and that, as in previous experimental work,¹³ action potential duration abnormalities typical of AF can be reproduced by exposing normal myocytes to $I_{\text{Ca,L}}$ blockers. A recent study by Grammer et al⁴⁸ found I_{sus} to be unaltered in patients with AF, with the discrepancy from the earlier study of Van Wagoner et al⁴⁵ possibly attributable to differences in patient populations. (Grammer et al⁴⁸ studied cells from patients undergoing aortocoronary bypass surgery, whereas the patients in the Van Wagoner et al⁴⁵ study were undergoing Maze procedures and mitral valve replacement and generally had quite dilated atria.) In their study of $I_{\text{Ca,L}}$ in human atrium, Van Wagoner et al⁴⁷ also noted that patients in sinus rhythm at the time of surgery who subsequently developed AF had larger I_{Ca} density than those that maintained sinus rhythm throughout their course. This difference could not be explained by discrepancies in patient age or the degree of cellular hypertrophy between groups.

Synthesis of Data Regarding Ionic Remodeling and AF From Studies of Patients and Experimental Animals

As mentioned above, studies of cells isolated from atrial tissues of experimental animals and of patients provide complementary information. Both clinical^{46,47} and experimental¹³ studies consistently point to an important downregulating effect of AF on $I_{\text{Ca,L}}$ and to an important role of $I_{\text{Ca,L}}$ downregulation in arrhythmogenic action potential abnormalities associated with AF. Decreases in I_{to} are also consistently seen,^{13,45,46} although their functional consequences for action potential changes and arrhythmia promotion are unclear. Changes in inward rectifier currents are inconsistent: increased inward rectifier currents in cells from left but not right atrium of patients with AF were seen in one study⁴⁵ and from right atrium in another,⁴⁶ whereas I_{K1} density was unaltered in an experimental study of atrial tachycardia-induced remodeling.¹³ Increased inward rectifier currents could contribute to action potential shortening by AF, so this issue merits resolution by further investigation. Observations regarding ultrarapid delayed rectifier currents and I_{sus} are also inconsistent. One clinical study found a decrease in I_{sus} in AF,⁴⁵ whereas another found no change⁴⁸ and $I_{\text{Kur,d}}$ was not altered in the canine model.¹³ Differences in patient populations and/or in the molecular basis of ultrarapid delayed rectifiers between dogs and humans⁴⁹ may be responsible for the discrepancies noted.

With respect to the effects of CHF and/or atrial dilation, several clinical and experimental studies indicate decreases in $I_{\text{Ca,L}}$ and I_{to} ,^{27,39,40,43} although individual clinical studies report

no change or even an increase.^{44,50} Advanced CHF decreases I_{K1} ,³⁸ but this may not occur with less severe clinical disease³⁹ and is not observed in an animal model of CHF predisposing to AF.²⁷ NCX upregulation is a prominent feature of atrial ionic remodeling in the experimental CHF model²⁷ and is typically observed in failing human hearts,⁵¹ although specific data for atrial NCX expression in patients with heart failure appear to be lacking.

Potential Underlying Molecular Mechanisms

Atrial tachycardia-induced decreases in I_{CaL} , I_{to} , and I_{Na} in the dog model of atrial tachycardia-related AF quantitatively parallel changes in mRNA levels for corresponding pore-forming α subunits,²⁸ suggesting that transcriptional downregulation is a central mechanism of AF-induced ionic remodeling. Clinical studies also show a decrease in α_{1c} Ca^{2+} channel subunit mRNA concentrations in patients with AF, particularly those with long-standing (>6 months) arrhythmia.^{52–55} Substantial decreases in Kv4.3 mRNA, paralleling changes in I_{to} , have also been reported in patients with AF, along with unchanged expression of Kv1.5 mRNA and the corresponding current I_{sus} .⁴⁸ Few data are available regarding other subunits of the L-type Ca^{2+} channel, but one report suggests that mRNA encoding I_{CaL} β subunits may be downregulated to an extent quantitatively greater than that of the α subunit.⁵⁵ Consistent with transcriptional downregulation of channel protein production in AF, decreased quantities of Kv4.3 and Na^+ channel α subunits have been demonstrated in dogs with atrial-tachycardia remodeling by Western blot²⁸ and decreased I_{Ca} channels by dihydropyridine receptor binding assays.⁵⁶ Protein measurements in clinical samples include the demonstration of decreased α_{1c} protein by slot blot assay in the Brundel et al study⁵³ and in the Van Wagoner et al⁴⁵ study of patients undergoing the Maze procedure for AF, decreased Kv1.5 subunit protein expression. There are presently no data available regarding changes in ion channel mRNA or protein expression produced at the atrial level by CHF.

There is very little solid information available about the sequence of signaling events that mediate tachycardia-dependent atrial remodeling. Indirect evidence points to a role for Ca^{2+} overload in short-term (minutes to hours) remodeling.^{57,58} Short-term AF (5 to 15 minutes in humans) is associated with refractoriness abbreviation and promotion of AF induction, effects that can be prevented by the I_{CaL} antagonist verapamil.^{59,60} The changes induced by such short-term AF are too rapid to be due to decreased membrane expression of ion channel proteins and are likely caused by rate-related changes in I_{CaL} availability, largely via Ca^{2+} -induced I_{CaL} inactivation.⁶¹ Verapamil reduces refractory period abbreviation caused by 24 hours of rapid pacing in the goat but has minimal effect on concomitant tachycardia-induced AF promotion.⁶² Remodeling induced by longer-duration tachycardia is not reduced by the L-type Ca^{2+} channel blockers diltiazem⁶³ or verapamil⁶⁴ but is substantially attenuated by mibefradil.^{63,65} Mibefradil blocks T-type Ca^{2+} channels in a relatively selective fashion,⁶⁶ which may indicate that T-type channels play a particularly important signaling role in atrial tachycardia-induced remodeling. On the other hand, the

protection provided by mibefradil could be related in whole or in part to other actions of the drug, such as collateral I_{CaL} blockade,⁶⁶ effects on K^+ channels,⁶⁷ or cytochrome inhibition.⁶⁸ The Na^+ - H^+ exchange inhibitor cariporide,⁶⁹ the angiotensin II receptor antagonist candesartan,⁷⁰ and the angiotensin-converting enzyme inhibitor captopril⁷⁰ reduce short-term atrial tachycardia-induced remodeling, but their precise mechanism of action on remodeling and their effects on longer-term remodeling are unknown.

The effects of drug interventions on tachycardia-induced remodeling are consistent with an important role for Ca^{2+} overload as an early and common signaling mechanism,⁷¹ but this concept remains to be proven. In the dog model of atrial tachycardia-induced remodeling, changes in mRNA expression are slow to develop and parallel changes in ion channel function and protein expression.¹³ A more recent study of tachycardia-induced atrial remodeling in the rat showed rather rapid increases in Kv1.5 mRNA concentration (as early as 30 minutes after the onset of atrial tachycardia), with slightly slower decreases in Kv4.2 and 4.3 expression (substantial after 3 to 4 hours).⁷² Much additional work needs to be performed to establish the precise signaling pathways and the respective roles of changes in transcription, translation, and posttranslational protein modification in the ion channel alterations involved in atrial ionic remodeling.

Relationship of Atrial to Ventricular Ionic Remodeling

One might expect ion channels in the atria and ventricles to respond to corresponding stimuli in comparable fashions. In the case of CHF-related remodeling, there are indeed many similarities. Ventricular I_{to} is strongly reduced by ventricular tachycardia-induced CHF, and I_{K1} density is decreased as well.⁷³ A recent study shows that ventricular I_K is reduced in a rabbit tachycardia-induced heart failure model⁷⁴ but suggests that unlike atrial remodeling in CHF,²⁷ I_{Kr} may be affected as well as I_{Ks} . Changes in ventricular I_{CaL} have been inconsistent across studies, with some investigators finding I_{CaL} to be unchanged in failing ventricles^{73,75} and others reporting a moderate decrease.^{74,76–78} Ventricular NCX overexpression is quite striking in CHF.^{51,79,80} Overall, therefore, the ventricular ionic remodeling caused by CHF is quite similar to that occurring at the atrial level,²⁷ pointing to common underlying mechanisms. Comparison of tachycardia-induced remodeling between atrium and ventricle is greatly limited by the fact that ventricular tachycardia causes substantial CHF, which produces strong ionic remodeling (making it virtually impossible to study the effects of tachycardia alone), whereas atrial tachycardia does not cause CHF unless the ventricular response is extremely rapid.

Pathophysiological Relevance of Ionic Remodeling

The pathophysiological role of ionic remodeling in AF promotion by atrial tachycardia is illustrated in Figure 1. Refractory period changes appear to be central to the AF-promoting properties of atrial tachycardia^{9–12} and are largely

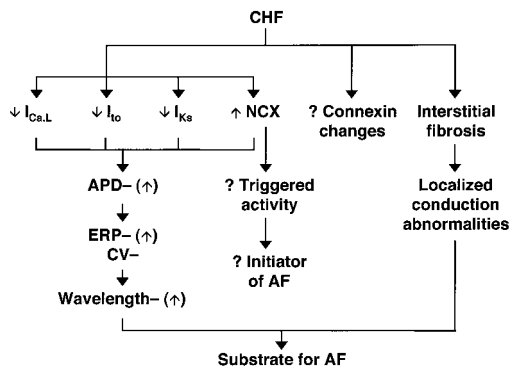


Figure 2. CHF-induced atrial ionic remodeling and the mechanisms by which CHF promotes AF. The net result of ionic remodeling is no change (–) or an increase (↑) in wavelength, which does not promote AF per se but sets the electrophysiological environment for AF initiation and antiarrhythmic drug action.

attributable to downregulation of I_{CaL} .¹³ Spatial heterogeneity of atrial refractoriness changes seem important,⁸¹ pointing to spatially heterogeneous ion channel modifications, but the latter have not been directly evaluated. I_{Na} downregulation may contribute by causing conduction slowing,¹⁶ which reduces the reentrant wavelength and thereby promotes reentry. Spatially heterogeneous connexin40 loss may also contribute to spatially heterogeneous conduction abnormalities.²¹ Thus, ionic remodeling appears to play a very important role in the AF-promoting properties of atrial tachycardia and such clinically important phenomena as the transition from paroxysmal to persistent AF,⁹ the early recurrence of AF after cardioversion,⁸² and the transition from focal atrial tachycardias to AF.⁸³ Changes in cellular Ca^{2+} handling caused by atrial tachycardia likely contribute importantly to the reduced atrial contractility observed after termination of persistent AF,¹⁷ an important determinant of thromboembolic complications after electrical cardioversion.⁸⁴

Experimental CHF clearly promotes AF maintenance,²⁷ but the relationship between CHF-induced AF promotion and ionic remodeling (Figure 2) is much less clear than for atrial tachycardia. Unlike atrial tachycardia, the cellular remodeling in CHF does not reduce action potential duration, atrial refractoriness, or wavelength.^{27,85} The mechanism of AF maintenance in the presence of CHF-induced atrial remodeling appears related to structural remodeling that causes prominent local conduction abnormalities and stabilizes atrial macroreentry.^{85,86} Ionic remodeling sets the conditions under which reentry occurs, without per se facilitating reentry. In addition, the increased atrial NCX current caused by CHF²⁷ may well contribute to atrial tachycardias caused by CHF,⁸⁷ in light of the ability of the NCX to cause arrhythmogenic delayed afterdepolarizations in atrial tissue.⁸⁸ Atrial tachycardias caused by delayed afterdepolarization-related triggered activity may act as initiators in the setting of a vulnerable substrate for AF and could also contribute by causing tachycardia-induced remodeling.

It appears paradoxical that some conditions that promote AF (such as tachycardia-induced remodeling) act by decreasing I_{CaL} ,¹³ whereas others (such as postoperative AF⁴⁷ and

hyperthyroidism³⁴) appear to increase I_{CaL} . This apparent paradox likely reflects the pathophysiological heterogeneity of AF. Increased I_{CaL} could promote AF by increasing Ca^{2+} loading and favoring afterdepolarization-mediated atrial tachyarrhythmias. Decreased I_{CaL} promotes AF by a very different mechanism, the occurrence of multiple-circuit reentry in relation to reduced refractoriness and wavelength. Additional work is needed, however, to determine more precisely the mechanisms of AF in the postoperative setting and in thyrotoxic subjects, as well as to define better the mechanistic role of changes in I_{CaL} in various forms of the arrhythmia.

Potential Therapeutic Significance

The central role of ionic remodeling in atrial tachycardia-induced AF promotion has significant potential relevance for AF therapy. If the signal transduction mechanisms leading to channel downregulation were determined, effective therapy to prevent atrial tachycardia-induced ionic remodeling could be developed, potentially making the arrhythmia much more tractable. At least one drug (mibefradil) has been identified that substantially reduces atrial remodeling caused by long-term tachycardias.^{63,65} Understanding ionic remodeling may also have important implications for improving antiarrhythmic drug therapy. The antiarrhythmic response to the selective I_{Kr} blocker dofetilide is categorically different between the atrial tachycardia and CHF models of AF,⁸⁶ suggesting that differences in ionic remodeling may have a determinant effect in the response to antiarrhythmic drugs. The ionic remodeling that occurs on the ventricular level may explain the proarrhythmic diathesis seen in response to drugs used to treat AF among patients with CHF.⁸⁹ Much more work needs to be done regarding the specific effects of the remodeling of individual ion channels on the response to various categories of antiarrhythmic agents.

An important question relevant to potential therapeutic relevance of manipulating ionic remodeling is whether the latter fulfills an important adaptive function, in which case interfering with remodeling could have negative consequences. For instance, increased NCX expression appears to improve diastolic function in patients with CHF.⁹⁰ K^+ channel downregulation and consequent action potential prolongation increase Ca^{2+} influx and Ca^{2+} transient amplitude after myocardial infarction in rats,⁹¹ potentially helping to maintain contractility. On the other hand, a long-term reduction of I_{to} in transgenic mice may lead to a heart failure phenotype.⁹² Much more work needs to be performed to understand the positive and negative consequences of ionic remodeling and to evaluate the therapeutic implications for the primary disease.

Conclusions

A great deal has recently been learned regarding ionic remodeling. An understanding of the atrial ionic changes caused by AF-promoting pathologies has already provided important new insights into mechanisms of arrhythmogenesis and has opened up interesting new therapeutic avenues. Much more work needs to be done, particularly in the area of understanding the signal transduction mechanisms that lead

from the stimuli to remodeling to the final changes in ion channel function and in the translation of improved mechanistic understanding to new therapeutic approaches.

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