Ionic Determinants of Atrial Fibrillation and Ca\textsuperscript{2+}
Channel Abnormalities
Cause, Consequence, or Innocent Bystander?

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Over the past several years, there has been increasing interest in understanding the basic mechanisms underlying atrial fibrillation (AF). The rise in interest is partly related to the prevalence of AF, which is presently the most common arrhythmia in clinical practice, and partly to the fact that the treatment of AF remains inadequate, making new insights into basic mechanisms essential for improving therapy.\textsuperscript{1} Of great importance, as well, has been the development of new, clinically relevant animal models of the arrhythmia\textsuperscript{2,3} and advances in scientific methodology, including high-density mapping, patch-clamp recording, and molecular cloning of ion channels, that have permitted much more sophisticated approaches to defining AF mechanisms at very basic levels. The studies by Van Wagoner et al\textsuperscript{4} reported in this issue of Circulation Research provide important information about the potential role of Ca\textsuperscript{2+} channel abnormalities in clinical AF and at the same time, raise some intriguing questions. To appreciate the results of these findings presented by Van Wagoner et al, it is important to place them in the context of preceding work on the ionic determinants of AF.

Ion Channel Abnormalities in Experimental Models of AF

The discovery by Wijffels et al\textsuperscript{5} that AF alters atrial electrophysiology in ways that promote AF maintenance was a substantial advance in understanding the arrhythmia. Not only did it reveal previously unrecognized fundamental and clinically relevant aspects of the physiology of the arrhythmia, but it also permitted investigators to prepare animals with great susceptibility to AF in a clinically relevant model. It was subsequently shown that the remodeling caused by AF is primarily a function of very rapid atrial activation rates,\textsuperscript{5} and that atrial tachycardia produces a substrate for multiple circuit atrial reentry on the basis of decreased atrial effective refractory period (ERP), slowed conduction, and increased heterogeneity in atrial repolarization.\textsuperscript{6,7} Studies in isolated canine atrial myocytes showed that dogs subjected to chronic atrial tachycardia have important reductions in L-type Ca\textsuperscript{2+} current (\(I_{\text{CaL}}\)) and transient outward K\textsuperscript+ current (\(I_{\text{K1}}\), density, without any change in the inward rectifier (\(I_{\text{Kr}}\)), the rapid or slow delayed rectifiers (\(I_{\text{Ks}}\) or \(I_{\text{Kr}}\)), the Ca\textsuperscript{2+}-dependent Cl\textsuperscript- current, or T-type Ca\textsuperscript{2+} current.\textsuperscript{8} Pharmacological analyses suggested that the refractoriness changes that have become a hallmark of AF-related remodeling, a decrease in ERP and in ERP rate adaptation,\textsuperscript{2,6,9,10} are largely due to the associated decrease in \(I_{\text{CaL}}\). The changes in conduction velocity associated with tachycardia-induced atrial remodeling appear to be due to decreases in Na\textsuperscript+ current density.\textsuperscript{11} Thus, the major electrophysiological changes by which atrial tachycardia promotes AF in animal models are attributable to ion remodeling. Atrial tachycardia causes reductions in the density of specific ion channels by reducing the concentrations of messenger ribonucleic acids encoding the pore-forming \(\alpha\) subunits of \(I_{\text{Na}}, I_{\text{Kr}}, \) and \(I_{\text{CaL}}\) and thereby reducing the concentration of corresponding subunit proteins.\textsuperscript{12-14} It is likely that transcriptional downregulation underlies these changes, although that has not been explicitly shown.

Although much has been learned about the ionic changes in atrial tachycardia-related remodeling, we must be cautious to avoid extrapolating these observations to all substrates for AF and to avoid thinking that we now understand completely the cellular electrophysiological changes caused by atrial tachycardia. Connexins are hemichannel proteins that play a critical role in cell-to-cell coupling. Studies of changes in connexins caused by AF have provided apparently contradictory results, with one study showing an increase in connexin 43,\textsuperscript{15} another a decrease in connexin 43,\textsuperscript{16} and a third a spatially heterogeneous decrease in connexin 40 with no change in connexin 43.\textsuperscript{17} More work needs to be done to clarify the changes in connexins in AF and to understand their electrophysiological significance. Most of the alterations in ion channel properties that have been observed are static changes—current density decreases—but the voltage and time dependence of channel gating are affected little, if at all.\textsuperscript{4,8,11} The dynamic properties of currents in response to tachycardia-induced remodeling have been studied to a very limited extent. The dynamics of Ca\textsuperscript{2+} handling are markedly altered in atrial myocytes from dogs with atrial tachycardia–induced remodeling.\textsuperscript{18} Given that [Ca\textsuperscript{2+}], can affect the properties of many currents, their dynamics might be altered as well, an issue that requires further exploration. Finally, all of the work that has been performed to study ion channel alterations in experimental AF has been performed in...
isolated cells studied in vitro. How these changes affect electrophysiological functioning in the intact atrium, in the context of intact innervation and autonomic influences, cell-to-cell coupling, and complex 3-dimensional geometry, remains to be elaborated more completely.

Congestive heart failure (CHF) is probably the clinical entity most commonly associated with sustained AF. Atrial ionic channel remodeling occurs in association with experimental CHF, along with an increased ability to maintain AF; however, the specific atrial ionic changes caused by CHF are different from those in the atrial tachycardia model. Atrial I_{Ca,L} downregulation, although it occurs in CHF, is much less marked compared with changes after atrial tachycardia. I_{Ca,L} density is not affected by atrial tachycardia but is decreased by experimental CHF. The more balanced effects on inward and outward currents in CHF compared with atrial tachycardia produce no net decrease in atrial action potential duration. The ways in which atrial ionic remodeling affects the likelihood of AF in subjects with CHF remain to be clarified, but the ionic changes do not explain the occurrence of AF in the canine CHF model in the same straightforward way that they do for tachycardia-related remodeling. These results indicate that specific ion channel alterations are likely to be associated with different clinical forms of AF, and that much more research needs to be done in this area. Furthermore, although ion channel abnormalities seem to account for most of the AF promotion caused by atrial tachycardia, other factors, such as structural changes, may play a critical role in other forms of AF.

**Ion Channel Changes in Clinical AF and the Contribution of the Study by Van Wagoner and Coworkers**

To date, there has been very limited knowledge available regarding changes in cardiac ion channel function in patients with AF. In a previous publication, Van Wagoner et al. showed that the transient and sustained current components elicited by depolarization of human atrial myocytes are reduced in patients with AF. The reduction observed in I_{Ca,L} was quite similar to the changes described in the dog model of atrial tachycardia. As pointed out by Van Wagoner et al., it is difficult to conceive how a decrease in outward currents can produce the reductions in ERP and ERP rate adaptation that characterize AF.

In their article in the present issue of *Circulation Research*, Van Wagoner et al. take their analysis of ionic alterations in the atrial myocytes of patients with AF much further. They study changes in I_{Ca,L} and show a 64% reduction in mean I_{Ca,L} density among patients with AF compared with patients with sinus rhythm, a change of a very similar order to the decrease in I_{Ca,L} density noted in dogs with atrial tachycardia–induced remodeling. Furthermore, they show that exposure of atrial myocytes from patients in sinus rhythm to 10 μmol/L nifedipine (to inhibit I_{Ca,L}) reproduces qualitatively the action potential abnormalities associated with AF. These observations are in agreement with recent mathematical modeling studies, which suggest that the I_{Ca,L} reductions reported by Van Wagoner et al. in a preliminary communication are sufficient to account for the lion’s share of the action potential abnormalities observed in patients with AF.

Van Wagoner et al. report an additional set of observations that are quite intriguing. They find that in patients with sinus rhythm at the time of surgery, I_{Ca,L} density is greater in patients who subsequently develop postoperative AF than in patients who maintain sinus rhythm throughout their hospital course. It appears paradoxical that both a decrease in I_{Ca,L} (in patients with chronic AF) and an increase in I_{Ca,L} (in patients who subsequently develop AF in the hospital) should be associated with AF. The mechanisms of postoperative AF remain unknown; however, there is some intriguing information available about the particularities of the pharmacological responses of postoperative AF. β-Adrenergic receptor blockers are particularly effective in postoperative AF, contrasting with their relative inefficacy in other forms of AF. It is therefore likely that β-adrenergic stimulation plays an important role in postoperative AF. In light of the effect of β agonists to increase cellular Ca^{2+} entry and of the observations of Van Wagoner et al., one might postulate that Ca^{2+} overload might be involved in the initiation of postoperative AF. An attractive unifying hypothesis to explain the apparently discrepant observations of Van Wagoner et al. would be that [Ca^{2+}] overload can play an important role in initiating AF, but that when AF is maintained, homeostatic cellular responses act to reduce Ca^{2+} loading by downregulating I_{Ca,L} and I_{Kr}, resulting in the ionic changes seen with maintained atrial tachycardia. What is the evidence to support or refute a role for Ca^{2+} overload in the pathophysiology of AF?

**Evidence Bearing on the Role of Ca^{2+} Overload in AF**

Goette et al. showed histological evidence for Ca^{2+} overload in rapidly paced dog atria. The I_{Ca,L} blocker verapamil attenuated the histological changes and prevented ERP reductions caused by several hours of atrial tachycardia. Tieleman et al. showed that verapamil attenuates ERP changes caused by 24 hours of rapid atrial pacing in dogs; however, the AF promoting effects of atrial tachycardia are barely affected. We have shown that the T-type I_{Ca,L} blocker mibebradil is highly effective in preventing the electrophysiological changes and AF promoting effect of atrial tachycardia in dogs, but we have found in more recent studies that the I_{Ca,L} blocker diltiazem is totally ineffective. Some investigators have shown a beneficial effect of diltiazem in preventing postoperative AF, whereas others found no superiority of diltiazem over digoxin or even inferiority compared with the beta-blocker esmolol in converting postoperative AF.

The evidence is thus somewhat unclear, with some studies pointing to an important role of Ca^{2+} overload in mediating AF-induced remodeling and promoting postoperative AF and others suggesting a potentially more complex picture.

Could the observation of increased I_{Ca,L} in patients with postoperative AF be fortuitous or an association without causal significance? Studies on human tissues are notoriously difficult to analyze, because of major uncontrolled variables such as the nature of drug therapy, possible contaminating effects of the underlying heart disease, and differences in patient age. Van Wagoner et al. exclude age and variations in
cellular hypertrophy as factors accounting for their observations by showing that mean cell capacitance and mean age did not differ in groups with versus without postoperative AF. Drug therapy is more difficult to analyze, but the data presented do not reveal any major discrepancies between groups. Additional work will be needed to confirm these findings and, more importantly, to understand their mechanistic basis. The least one can say is that the observations of Van Wagoner et al provide a significant (perhaps the first truly significant) clue to the mechanism of postoperative AF, an arrhythmia of great clinical importance. An improved understanding of the mechanisms of postoperative AF is likely to be the key to improving the prevention and treatment of this expensive complication.

Are Ca\textsuperscript{2+} Channel Abnormalities a Cause, Consequence, or Innocent Bystander in AF? The observations of Van Wagoner et al contribute significantly to the evolving literature regarding the role of Ca\textsuperscript{2+} channel changes in AF. The downregulation of \(I_{\text{Ca,L}}\) caused by atrial tachycardia is clearly a consequence of the arrhythmia, as shown in the dog model. At the same time, \(I_{\text{Ca}}\) downregulation is a cause of AF perpetuation in the sense that the ERP changes resulting from \(I_{\text{Ca}}\) downregulation contribute importantly to AF maintenance in, and vulnerability to AF recurrence after cardioversion of, persistent AF. The \(I_{\text{Ca,L}}\) increases in patients who developed postoperative AF in the Van Wagoner study could not be a consequence of AF, because patients were in sinus rhythm during surgery when samples for atrial cell isolation were taken. There is no evidence for the alternative that the \(I_{\text{Ca}}\) increases noted were fortuitous, making them an innocent bystander to the “true” pathophysiology, although this possibility is not completely excluded. For the moment, larger \(I_{\text{Ca,L}}\) densities should be considered a possible cause (or at least an important contributing factor) in postoperative AF, pending further research to clarify the matter. Much more work needs to be done to define the signal transduction system leading to \(I_{\text{Ca}}\) downregulation in persistent AF, to establish whether Ca\textsuperscript{2+} overload does, in fact, take place, and to determine the role of cellular Ca\textsuperscript{2+} homeostasis abnormalities in different clinical forms of the arrhythmia.

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References


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