Cardiac ion channels in atrial fibrillation: Disease-related changes and relevance to drug therapy

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Until recently, very little information was available about the properties of cardiac ion channels in atrial fibrillation (AF). We now know that disease entities, like congestive heart failure (CHF), that lead to AF cause characteristic ion channel abnormalities which determine the cellular substrate within which AF arises. AF itself alters ion channel properties (most importantly causing downregulation of L-type Ca2+ channels, which shortens action potential duration) leading to an increased probability of AF initiation and maintenance. This paper reviews the ion channel abnormalities associated with AF and discusses briefly their potential relevance to drug therapy.

I. Introduction
AF is the most commonly-encountered clinical arrhythmia, and is difficult to treat for a variety of reasons. Unlike many other common arrhythmias, such as atrioventricular node and atrioventricular reentrant tachycardias, atrial flutter and ventricular tachyarrhythmias, non-pharmacologic therapy of AF is limited by incomplete efficacy and/or serious adverse consequences. Drug treatment to prevent AF recurrence is also incompletely effective and associated with the possibility of adverse consequences, of which the most serious is potentially lethal ventricular proarrhythmia. For many forms of arrhythmia, an improved understanding of the basic underlying mechanisms has been a key to improved treatment. Much progress has been made in understanding the basic mechanisms of AF over the past 5 years. This paper will review the progress in understanding changes in ion channel function associated with AF. Since ion channels are the keys that control the cardiac action potential, which is the cellular basis of cardiac electrical activity, ion channel alterations are very important in determining the occurrence, mechanisms and manifestations of cardiac arrhythmias.

II. Evidence from animal models
I. Cellular remodeling caused by atrial tachycardia
The now-classical work of Maurits Allessie’s group has shown that simply maintaining AF alters atrial properties in a fashion that makes AF easier to induce and maintain.1 The hallmark functional changes are decreased atrial refractory
period and refractory period accommodation to rate.

There is evidence that the primary factor causing AF-induced remodeling is atrial tachycardia and that atrial conduction velocity may also be reduced by rapid atrial arrhythmias.

In order to evaluate the cellular basis of atrial tachycardia-induced remodeling, we subjected dogs to varying periods of atrial pacing at 400/min, performed a terminal electrophysiological study to evaluate atrial electrophysiology in vivo, and then isolated atrial myocytes for analysis of atrial action potentials and ionic currents with tight-seal, whole-cell patch clamp methods.

Atrial action potential duration (APD) and APD accommodation to rate were reduced in a fashion similar to refractory period in vivo. The density, voltage and time dependent properties of a variety of currents, including inward rectifier (I\(_{\text{K}1}\)), ultrarrapid (I\(_{\text{Kur}}\)), rapid (I\(_{\text{Kr}}\)) and slow (I\(_{\text{Ks}}\)) delayed rectifier, C\(_{\text{a}}\)-dependent Cl\(^-\) and T-type C\(_{\text{a}}\) (I\(_{\text{C,aT}}\)) current were unaffected by atrial tachycardia. However, transient outward K\(^+\) current (I\(_{\text{to}}\)) and L-type C\(_{\text{a}}\) current (I\(_{\text{Ca,L}}\)) densities were progressively decreased over time by atrial tachycardia. Voltage and time dependent properties of I\(_{\text{to}}\) and I\(_{\text{Ca,L}}\) were unaltered. The action potential alterations caused by atrial tachycardia could be mimicked in normal cells by strong pharmacological I\(_{\text{Ca,L}}\) inhibition, and exposure of cells from dogs subjected to long-term atrial tachycardia to an I\(_{\text{Ca,L}}\) agonist returned action potential properties towards normal. On the other hand, selective inhibition of I\(_{\text{to}}\) with 4-aminoopyridine in the presence of C\(_{\text{a}}\) current inhibition had no significant effect on the atrial action potential, suggesting that reduced I\(_{\text{Ca,L}}\) is the primary contributor to action potential alterations caused by atrial tachycardia.

Although changes in I\(_{\text{Ca,L}}\) seem to be the principle determinant of tachycardia-induced abnormalities of atrial repolarization, other ionic processes may also be altered in a significant way. There is evidence for I\(_{\text{Na}}\) downregulation, which is slower to develop and quantitatively less important than I\(_{\text{Ca,L}}\) changes.

I\(_{\text{Na}}\) changes correlate with conduction slowing in the animal model and may be responsible, at least in part, for some of the atrial conduction abnormality typically associated with AF. Besides changes in I\(_{\text{Ca,L}}\) density, atrial myocytes from dogs subjected to chronic atrial tachycardia also show abnormalities in intracellular C\(_{\text{a}}\) handling. The systolic C\(_{\text{a}}\) transient is reduced in a frequency dependent fashion, with abnormalities in C\(_{\text{a}}\) transients paralleling disturbances in cellular contractility.

Abnormal cellular C\(_{\text{a}}\) handling likely explains the transient atrial contractile dysfunction frequently observed after cardioversion of AF, and may also contribute to abnormalities in APD restitution properties associated with AF.

The predominant molecular mechanism for tachycardia-related ion channel alterations in the dog model appears to be downregulation of messenger RNA (mRNA) encoding \(\alpha\)-subunits of I\(_{\text{to}}\), I\(_{\text{Ca,L}}\) and I\(_{\text{Na}}\) channels.

2. Cellular remodeling caused by congestive heart failure (CHF)

CHF is one of the most common clinical causes of AF. Sustained ventricular tachycardia is known to cause clinical CHF and rapid ventricular pacing is often used to cause CHF in experimental animals.

In over 50% of dogs with CHF produced by 5 weeks of ventricular pacing at 220-240 bpm, it is possible to induce sustained AF by atrial burst pacing. The atrial action potential changes caused by CHF are quite different from those resulting from atrial tachycardia, as illustrated in Figure 1.

Whereas atrial tachycardia decreases APD and APD accommodation to rate, CHF produces no change or even an increase in APD. Given the quite different effects of CHF and atrial tachycardia on the action potential, it should not be surprising that the actions of the two pathologies on ionic currents are quite different (Figure 2).

Whereas atrial tachycardia decreases I\(_{\text{Ca,L}}\) density by about 70%, CHF reduces it by about 30%. I\(_{\text{Na}}\) is reduced to a qualitatively similar extent by CHF and atrial tachycardia. The lack of APD reduction...
by CHF is partially explained by the smaller \( I_{Ca} \) decrease produced by CHF compared to atrial tachycardia. Two other changes tend to increase APD in atrial myocytes of dogs with CHF. One is a decrease in atrial \( I_{K_s} \), which is reduced by about 30% in CHF but is unchanged by atrial tachycardia.\(^3,11\) The second is an increased Na\(^+\)-Ca\(^{2+}\)-exchange current (NCX), which contributes depolarizing current by exchanging 3 extracellular Na\(^+\) ions for each intracellular Ca\(^{2+}\) ion removed from the cell during phases 3 and 4 of the action potential.\(^11\) In addition to delaying repolarization, the increased NCX in atrial cells of dogs with CHF carries a transient inward current on repolarization, tending to promote triggered activity via arrhythmogenic delayed afterdepolarizations.\(^11\)

### III. Evidence from studies of clinical samples

#### 1. Ionic current recordings

Ionic current studies in animal models of AF have the limitation that the models themselves are imperfect models of clinical disease. In addition, there may be differences in the nature or regulation of ionic currents between experimental animals and man. On the other hand, studies in human tissues have the limitation that it is virtually impossible to isolate totally single individual factors for analysis. Studies of ion channel properties in patients with AF may be confounded by the presence of concomitant diseases (like CHF or valve disease) and by concomitant drug therapy. Studies of the effects of heart disease can similarly be affected by the presence of atrial arrhythmias and by drug effects.

The data obtained to date with the use of surgical samples from patients in AF confirm the major changes in K\(^+\) and Ca\(^{2+}\) currents seen in the atrial-tachycardia dog model.\(^3\) Transient outward current\(^12,13\) and \( I_{Ca,L} \)\(^13,14\) are decreased by about 70% in patients with AF compared to those in sinus rhythm. Changes reported for other K\(^+\) currents have been more variable. One study has reported increased \( I_{K_1} \) density in the left but not the right atrium of patients with AF\(^12\), whereas another reported increases in both \( I_{K_1} \) and \( I_{K_ACh} \) at hyperpolarizing potentials.\(^13\) One study of AF patients has reported a decrease in the sustained outward current at the end of a depolarizing pulse\(^15\) corresponding to currents carried by the Kv1.5 subunit,\(^10\) along with decreases in Kv1.5 protein.\(^12\) On the other hand, another study reported no change in either the sustained current or Kv1.5 mRNA.\(^15\) The differences may be due to concomitant diseases, since most patients in the Van Wagoner study underwent mitral valve replacement and had significant atrial enlargement,\(^12\) whereas patients in the Grammer study were undergoing coronary artery bypass surgery.\(^15\)

The limited data available for atrial ionic currents in patients with atrial dilatation and/or severe heart failure show decreases in \( I_{to} \)\(^16,17\) and \( I_{Ca} \)\(^17,18\) consistent with results in the dog model of CHF.\(^11\) Cells from patients with dilated atria were found to have normal resting potential values and \( I_{K_1} \) density compared to controls.\(^15\) We are not aware
of data regarding atrial NCX in patients with heart failure.

2. Molecular and biochemical analyses
Most of the data available regarding biochemical and molecular changes in ion channel/transporter expression in patients with AF relates to alterations in the Ca$^{2+}$ handling system. Three papers report reductions of the order of 50% or greater in mRNA for $I_{Ca,L}$ α-subunits in patients with persistent AF.$^{19-21}$ One publication found a statistically significant but small (~20%) decrease in $I_{Ca}$ α-subunit mRNA, with a much larger decrease (~80%) in β-subunit mRNA.$^{22}$ Phospholamban and ryanodine receptor mRNA were reported to be unchanged.$^{19,20}$ Messenger RNA encoding sarcoplasmic reticulum Ca$^{2+}$-ATPase, the main Ca$^{2+}$ uptake mechanism into the sarcoplasmic reticulum, was found to be unchanged in one study$^{21}$ and decreased by varying amounts ranging from 28-43% in three other studies.$^{19,20,23}$

IV. Potential relevance to drug therapy
The ionic remodeling caused by pathological conditions that produce AF obviously has the potential to alter the response to clinically used antiarrhythmic drugs. There is little information available in the literature about the specific alterations in antiarrhythmic drug response in experimental or clinical models of AF. Recent studies have shown that dofetilide is much more effective in terminating sustained AF in the context of experimental CHF-induced remodeling than in the case of remodeling caused by atrial tachycardia.$^{24}$ It is conceivable that the decreased $I_{Kr}$ and increased NCX in atrial myocytes of dogs with CHF increases the dependency on $I_{Kr}$ for repolarization, increasing the sensitivity to $I_{Kr}$ blockers.

The prominent changes in $I_{Ca,L}$ that occur with tachycardia-induced remodeling and other lines of evidence suggest that Ca$^{2+}$ overload may be an important trigger for tachycardia-induced remodeling, with decreased $I_{Ca,L}$ part of the myocytes' protective response to reduce Ca$^{2+}$ loading and minimize the threat to cell viability. There is hope that treatment with Ca$^{2+}$-channel blockers, particularly with drugs that inhibit both T- and L-type currents,$^{25}$ may inhibit remodeling and make AF more responsive to drug therapy and cardioversion.

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References