Editorial

Atrial fibrillation-induced electrical remodeling in humans: What is the next step?

Maurits A. Allessie

Department of Physiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, The Netherlands

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See article by Bosch et al. [1] (pages 121–131) in this issue.

In the article elsewhere in this issue, “Ionic mechanisms of electrical remodeling in human atrial fibrillation”, Ralph Bosch and co-workers [1] describe the changes in atrial action potential characteristics and ion-channel densities in 8 patients with chronic atrial fibrillation (AF). The action potentials of single atrial cells isolated from patients in AF, showed a normal resting membrane potential more negative than $-75 \text{ mV}$ and amplitudes higher than $115 \text{ mV}$. However, compared to patients in sinus rhythm the repolarization phase was markedly changed. Both, the early rapid repolarization (phase 1), carried by $I_{\text{to}}$ and the plateau of the action potential mainly carried by $I_{\text{Ca,L}}$ (phase 2), were clearly attenuated or even abolished. As a result, atrial cells in AF patients seemed to repolarize almost exclusively by phase 3 repolarization. The total duration of the action potential was markedly decreased. At a pacing rate of 60 beats/minute, the duration had shortened from a control value of $255 \pm 45 \text{ ms}$ to $104 \pm 9 \text{ ms}$ (a reduction of 60%). In addition, also the physiological rate adaptation was reduced and the atrial action potentials showed almost no shortening anymore when the stimulation frequency was increased ($98 \pm 8 \text{ ms}$ at 240 beats/minute). An important consequence of this loss of the physiological rate adaptation is that chronically fibrillating atria can no longer be expected to prolong their action potentials when sinus rhythm is restored. Since short action potentials (and short refractory periods) facilitate the induction of atrial re-entry, this maladaptation may be the pathophysiological basis for the frequently observed early recurrences after cardioversion of AF [2,3].

Long-term shortening of the atrial refractory period by rapid pacing or atrial fibrillation has first been demon-
Ca\(^{2+}\) current) was studied by Yue et al. in a canine model of atrial fibrillation [8]. In this study, dogs of 27.3±2.4 kg were instrumented with an atrial pacemaker programmed at 400 beats per minute. Atrial myocytes were isolated 1, 7, or 42 days after continuous rapid atrial pacing. After 42 days the APD90 was shortened from 161±11 to 85±5 ms. Voltage clamp studies showed no change in $I_{K1}$, $I_{Kr}$, $I_{Kur}$, $I_{Cas}$, or $I_{CaT}$. In contrast, the density of the transient outward current ($I_{to}$) and the L-type Ca\(^{2+}\) current were markedly reduced. The action potentials and ionic currents in remodeled myocytes actually were similar to those recorded in normal cells subjected to nifedipine (an L-type Ca blocker). The hypothesis that the long-term shortening of the atrial action potential and its reduced rate adaptation was mainly due to a reduction of the L-type Ca\(^{2+}\) current was further supported by the observation that administration of Bay K 8644 (an agonist of the L-type Ca\(^{2+}\) current) largely restored the plateau phase in remodeled cells [8].

The importance of the paper of Bosch et al. [1] is that it completes the picture of the AF-induced changes in ion channels in humans. In their study they established that the shortening of the human atrial action potential by AF was due to a 70% reduction in $I_{Ca,L}$ and $I_{to}$ together with an increase in $I_{K1}$ and $I_{KACH}$. This concerted action of the atrial potassium and calcium channels in response to prolonged atrial pacing offers a good explanation for the observed shortening of the action potential and the perpetuation of the arrhythmia.

At this point one may wonder why the atrial myocytes are responding in this way. There must be a good reason for the atria to give up their protection against reentrant arrhythmias and to ‘choose’ to shorten their action potentials rather than to maintain (or even prolong) the plateau. A likely reason is to prevent calcium overload of the cell. During atrial fibrillation the rate of the atrial action potentials is very high and the cell membrane is depolarized most of the time. As a consequence, the L-type calcium channels are almost always in the open state, causing a constant flux of calcium ions into the cell. Downregulation of the expression of the L-type Ca\(^{2+}\) current counteracts this chronically increased calcium influx and thus may be regarded as part of the calcium-handling system of the cell. Little is yet known about the regulating mechanisms determining the palette of ion-channels involved in repolarization of the cardiac action potential. There exists a wide variation in action potential duration in hearts of different size. In general, there seems to be a direct correlation between the length of the plateau and the cardiac tissue mass, with the atria having a shorter action potential than the ventricles, and the action potentials of the atria as well as the ventricles becoming longer with increasing body weight. It is not clear at this point whether these marked differences in repolarization are solely due to differences in genotype, or whether they are also partly the result of changes in phenotype. The frequency of the normal heart beat amongst different species (from mouse to elephant) varies more than the difference in atrial rate during sinus rhythm and atrial fibrillation. It is tempting to speculate that the different duration of the cardiac action potentials in small and large animals is the result of similar intracellular signalling processes as the ones leading to changes in expression of membrane ion-channels during atrial fibrillation.

Although it now has been firmly established that AF-induced electrical remodeling also takes place in humans, still a number of questions have to be answered before one can tell how important this process is for the natural history of atrial fibrillation. The first thing to determine is the time course of tachycardia-induced electrical remodeling in humans. This knowledge is important to determine the optimal moment for pharmacological or electrical cardioversion of AF. How long can one wait for spontaneous termination without jeopardizing the effectiveness of pharmacological defibrillation or increasing the risk of early recurrences after cardioversion? The second question that should be answered is how long AF-induced electrical remodeling is still completely reversible and whether reverse remodeling follows the same time course as AF-induced remodeling. A third important point is whether electrical remodeling alters the action of class I and class III drugs. Since atrial fibrillation changes the expression of ion-channels involved in atrial repolarization, it is quite likely that the effects of class III drugs are changed (become less effective). Last but not least, knowledge of the intracellular signal-transduction pathways involved in tachycardia-induced remodeling may provide new targets to interrupt the chain of cause and effect leading to ‘domestication’ of atrial fibrillation. Only if we find answers to these questions the role of electrophysiological remodeling in the development of a substrate for sustained atrial fibrillation can be estimated. Although it should not be forgotten that other factors like ageing, atrial dilatation, atrial ischemia and neurohumoral changes may be of greater clinical importance, the work of Bosch et al. [1] has set the stage for basic clinical studies to further elucidate the role of electrical remodeling. The present availability of the implantable atrial cardioverter provides an opportunity for systematic studies in humans which otherwise would have only been possible in animals.

References


