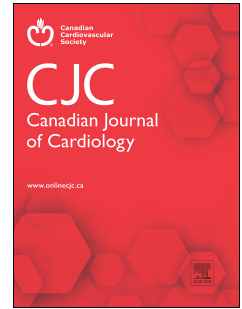


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**Differential remodeling of late  $I_{Na}$  in paroxysmal and persistent AF: another piece in the complex picture of electrical remodeling in AF**

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***Electrical remodeling in paroxysmal and persistent atrial fibrillation***

Atrial fibrillation (AF), the clinically most common form of arrhythmia, is usually classified based on its duration – ranging from paroxysmal AF, consisting of self-terminating episodes lasting typically less than 7 days, to persistent and long-lasting persistent / chronic AF, in which AF fails to self-terminate.<sup>1</sup> In all the different forms, electrical remodeling occurs. This remodeling further increases ectopic triggered activity and provides an electrical substrate even more prone to reentry formation – the two main arrhythmogenic mechanisms in AF – thereby facilitating the occurrence and maintenance of AF, as nicely described in the term “AF begets AF” by the Allesie group already in 1995.<sup>2</sup>

Different – partially contrasting – electrical remodeling processes have been identified in paroxysmal, persistent, and long-lasting persistent AF (reviewed in <sup>3</sup>), suggesting different triggering mechanisms and different substrate characteristics in the different AF entities.

In paroxysmal AF, most studies report an unaltered, normal action potential duration (hence no “electrical substrate” prone to reentry formation), normal L-type  $\text{Ca}^{2+}$ -current and normal  $\text{Na}^+/\text{Ca}^{2+}$ -exchanger function. Triggered activity, e.g., the occurrence of delayed afterdepolarization, however, is usually increased due to a pronounced remodeling of calcium handling with increased  $\text{Ca}^{2+}$ -transient amplitude and sarcoplasmic-reticulum  $\text{Ca}^{2+}$ -load, faster  $\text{Ca}^{2+}$ -transient decay, and increased SERCA2a function,<sup>4</sup> suggesting that an increased propensity for triggered activity is the main driver in this early form of AF. In the following, atrial tachycardia-related  $\text{Ca}^{2+}$  loading activates intracellular signaling pathways, thereby increasing various  $\text{K}^+$  currents (such as the inward-rectifier  $\text{K}^+$  current ( $I_{\text{K1}}$ ), the acetylcholine-dependent inward-rectifier  $\text{K}^+$  current ( $I_{\text{K,ACh}}$ ), and the small-conductance  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  current ( $I_{\text{SK}}$ )) and reducing L-type  $\text{Ca}^{2+}$  current ( $I_{\text{Ca,L}}$ ), which leads to a shortening of action potential duration and creates an “electrical substrate” prone to reentry formation.<sup>3</sup> In addition, also in persistent AF, calcium handling abnormalities occur, but contrast with the remodeling observed in paroxysmal AF: the reduced  $I_{\text{Ca,L}}$  leads to decreased  $\text{Ca}^{2+}$  transient amplitude, reducing atrial

contractility. Similar as in paroxysmal AF, delayed afterdepolarizations (DADs) are frequent in persistent AF, the underlying molecular mechanisms, however, differ:  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase II–dependent hyperphosphorylation of the ryanodine receptor channel type 2 (RyR2) has been identified as major mechanism increasing sarcoplasmic reticulum  $\text{Ca}^{2+}$  leak. In addition, the expression and activity of the  $\text{Na}^+/\text{Ca}^{2+}$ -exchanger are increased in persistent AF, so that the spontaneous  $\text{Ca}^{2+}$  release events produce larger transient-inward currents and thereby DADs.<sup>5</sup>

### ***Electrical remodeling of sodium currents in atrial fibrillation***

Data on remodeling of peak and late sodium currents ( $I_{\text{Na}}$ ) are more sparse. While it has been demonstrated in human cardiomyocytes isolated from right atrial appendages (RAA) of patients with persistent or permanent AF that late  $I_{\text{Na}}$  was increased,<sup>6,7</sup> the data on peak  $I_{\text{Na}}$  were more heterogenous showing either reduced or unchanged currents. Potential changes in peak or late  $I_{\text{Na}}$  in paroxysmal AF had not been investigated.

Casini, Remme and colleagues aimed to close this gap with their study,<sup>8</sup> in which they investigated action potential (AP) characteristics and peak and late  $I_{\text{Na}}$  remodeling in cardiomyocytes isolated from left atrial appendages (LAA) from patients with paroxysmal and persistent AF and compared these to LAA cardiomyocytes from patients in sinus rhythm. They observed shorter AP duration in both paroxysmal and persistent AF LAA-CMs compared to sinus rhythm. Changes in peak  $I_{\text{Na}}$  and late  $I_{\text{Na,L}}$  however differed: Compared to SR, peak  $I_{\text{Na}}$  and SCN5A channel expression were decreased in paroxysmal AF, while they were restored to sinus rhythm levels in persistent AF. In contrast, late  $I_{\text{Na,L}}$  was unchanged in paroxysmal AF as compared to sinus rhythm but was significantly increased in persistent AF.

How can the observed changes in peak  $I_{\text{Na}}$  and  $I_{\text{Na,L}}$  contribute to arrhythmia formation in the different AF states? The reduced peak  $I_{\text{Na}}$  observed in paroxysmal AF can certainly contribute to a slowing of the conduction velocity, which promotes reentry formation – particularly in the

context of the observed APD shortening driven by electrical remodeling mainly in  $K^+$  currents. An increased late  $I_{Na,L}$  in persistent AF may favor DAD formation and triggered activities, particularly by increasing diastolic  $Ca^{2+}$  levels, which may in turn promote spontaneous release from the sarcoplasmic reticulum, which leads to DADs that serve as a trigger for irregular APs and focal arrhythmias.

The fact that AP was shortening both, in paroxysmal and persistent AF despite late  $I_{Na,L}$  being increased in the latter, indicates that a complex interplay of electrical remodeling of different currents – which partially counteract the individual effects on AP shape and duration – determines the AP characteristics. This needs to be considered when trying to understand the arrhythmic consequences of one investigated remodeled electrical feature.

Indeed, in their study,<sup>8</sup> Casini et al. observed not only an increase in late  $I_{Na,L}$  in persistent AF, which may promote arrhythmia formation by the above mentioned mechanism, but also a more negative RMP, which will make it more difficult for an afterdepolarization to reach the threshold for eliciting an AP<sup>9</sup> and will thus counteract the pro-arrhythmic effects of an increased late  $I_{Na,L}$ . In addition, any structural and metabolic remodeling that also simultaneously occurs will also need to be entered into the equation, making the assessment of pro-arrhythmic consequences of remodeling even more complex.

### ***Importance of differential assessment of remodeling mechanisms in right and left atria in atrial fibrillation***

Most studies conducted in human AF samples stem from the right atrial appendages – as these can be easily obtained during surgical procedures, in which the RA is cannulated for the heart-lung machine and the small piece of the right atrial appendage is often considered “surgical tissue waste”. Little is known about differential remodeling in right vs. left atria (RA, LA); which would be particularly important and mechanistically insightful as the LA plays a predominant role

in AF triggering / initiation via the triggered activity originating in the pulmonary vein sleeves. In their study, Casini et al.<sup>8</sup> have taken advantage of a different study protocol, which allowed them to obtain left atrial appendage (LAA) tissue from patients undergoing thoracoscopic procedures. They thus could investigate action potential (AP) characteristics and peak and late  $I_{Na}$  remodeling in LAA cardiomyocytes from patients with paroxysmal and persistent AF compared to patients in sinus rhythm, thus providing important insights into remodeling in the thus far understudied left atrial tissue. Unfortunately, in their study, they did not have the possibility to also obtain RA tissue from the same patients, which would be a particularly valuable combination that could provide insights into potentially differential inter-atrial remodeling of  $I_{Na}$  – but also of other cardiac ion channels that are known to be remodeled in AF. Any regional differences in the electrical remodeling could create regional differences in APD and thus an electrical substrate for reentry formation, similarly as in other arrhythmic diseases such as long QT syndrome.<sup>10</sup>

#### ***Lack of data on sex differences in atrial remodeling***

Pronounced sex differences exist in all age-ranges in the incidence (and mechanisms) of AF (reviewed in <sup>11</sup>). However, little is known, both, on physiological sex differences that may predispose men more to AF development than women, and on potential sex differences in electrical remodeling during different AF states. Indirect evidence indicating that sex may be an important determinant of the degree of electrical remodeling in the left atrium comes from a study on heart failure patients. Analysis of mRNA expression of genes encoding for cardiac ion channel subunits in left atria of explanted human hearts showed differential remodeling between sexes, with lower expression levels in transcripts encoding for Kv4.3, KChIP2, Kv1.5, and Kir3.1 in the failing female left atrium as compared with the male left atrium.<sup>12</sup> Whether similar sex differences also occur in AF-associated remodeling remains to be investigated.

In the study by Casini et al.<sup>8</sup> – similarly to other studies – more tissue was obtained from male patients. Similar results were found in peak and late  $I_{Na}$  remodeling among paroxysmal and persistent AF cardiomyocytes in the complete cohort as when only analyzing male cells. But this is not surprising as only 5% of the sinus rhythm, 17% of the paroxysmal AF and 30% of the persistent AF samples stemmed from female patients so that sex differences in remodeling cannot be excluded. This calls for future studies, which are powered to also investigate sex differences in electrical remodeling of atrial fibrillation – ideally both in the left and right atria – to provide an even more comprehensive insight into the already complex issue of differential electrical remodeling in AF.

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