

## Enhanced Late $\text{Na}^+$ Currents in Atrial Fibrillation

### New Drug Target or Just an Epiphenomenon?\*

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In this issue of the *Journal*, Sossalla et al. (1) present an interesting article on alterations of the  $\text{Na}^+$  current ( $I_{\text{Na}}$ ) in atrial myocytes of patients with persistent atrial fibrillation (AF) and the effects of ranolazine, an orally active piperazine derivative, on these currents. Although peak  $I_{\text{Na}}$  was slightly lower in AF patients compared with patients in sinus rhythm (SR), the late and sustained component of the current ( $I_{\text{NaL}}$ ) was significantly larger (+26%). The inhibitory effect of ranolazine on  $I_{\text{NaL}}$  was stronger in patients with AF compared with SR patients. Ranolazine also suppressed premature atrial contractions in right atrial

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trabeculae and reduced diastolic tension in these preparations. The authors conclude that dysregulation of  $I_{\text{Na}}$  might be a mechanism contributing to AF. They also conclude that ranolazine exerts its antiarrhythmic effect at least partly by inhibition of  $I_{\text{NaL}}$ , thereby suppressing triggered activity and improving diastolic dysfunction. The article touches upon a number of interesting aspects of AF pathophysiology that are relevant for our understanding of ionic remodeling due to AF and its consequences for the identification of drug targets interfering with  $\text{Na}^+$  and  $\text{Ca}^{2+}$  homeostasis.

#### Alterations of $\text{Na}^+$ Handling in AF

Our current knowledge of alterations of  $\text{Na}^+$  homeostasis in AF is largely limited to alterations of  $\text{Na}^+$  ion currents or transporters. For example, there are clear indications for an up-regulation of the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger (NCX) in human AF (2,3). In dogs, inhibition of the reverse mode of NCX ( $\text{Ca}^{2+}$  entry) prevented electrical remodeling during short-term rapid atrial pacing, suggesting that  $\text{Ca}^{2+}$  entry via

reverse-mode NCX contributes to early electrical remodeling (4). Reverse-mode NCX might lead to  $\text{Na}^+$  extrusion and reduced  $[\text{Na}]_i$ . Measurements of  $\text{Na}^+/\text{K}^+$  pump current ( $I_p$ ) in human AF showed no alteration in voltage dependence and sensitivity to external  $[\text{K}^+]$ , but sensitivity to  $[\text{Na}]_i$  and the actual  $[\text{Na}]_i$  was not determined (5). In animal studies, inhibition of the  $\text{Na}^+/\text{H}^+$  exchanger was able to prevent electrical remodeling during short-term rapid atrial pacing (6), suggesting a role of increased  $\text{Na}^+$  loading in early electrical remodeling.  $I_{\text{Na}}$  has been measured by several authors in the setting of AF or rapid atrial pacing. In canine models of AF, peak  $I_{\text{Na}}$  was reduced, whereas a study performed in human atrial myocytes reported no change (7,8).

The study by Sossalla et al. (1) adds new and important pieces to this puzzle. They observe a 20% decrease in peak  $I_{\text{Na}}$  in human AF, while the sustained  $I_{\text{NaL}}$  was enhanced by 26%. In an earlier study, the same group had shown that the  $\text{Ca}^{2+}$ /calmodulin-dependent kinase II activates  $I_{\text{NaL}}$  (9). The previously demonstrated increase in  $\text{Ca}^{2+}$ /calmodulin-dependent kinase II expression and activity in human AF (3) might therefore have contributed to enhancement of  $I_{\text{NaL}}$ . It remains unclear, however, to what extent the 26% increase of  $I_{\text{NaL}}$  would increase  $[\text{Na}]_i$  in atrial myocytes of patients with AF. Shortening of the action potential (electrical remodeling) and reduced peak  $I_{\text{Na}}$  will both tend to reduce  $[\text{Na}]_i$ . Interestingly, the only study to measure  $[\text{Na}]_i$  in an AF model found a 50% reduction of whole-cell and cytosolic  $[\text{Na}]_i$  in dogs subjected to 48 h of rapid atrial pacing (10).

However, should future studies demonstrate enhanced  $[\text{Na}]_i$  in atrial myocytes of patients with AF, the findings of Sossalla et al. (1) might become relevant for our understanding of the alterations in intracellular signaling pathways associated with AF. Enhanced  $\text{Na}^+$  loading of atrial myocytes will tend to increase  $\text{Ca}^{2+}$  loading, which is a crucial step in pathways involved in the electrical remodeling process and in hypertrophic and profibrotic responses. Thus, antagonizing  $\text{Na}^+$  loading might delay or prevent the atrial remodeling process.

In contrast, the implications of the study on direct proarrhythmic effects are much more difficult to appreciate. The authors suggest that enhanced  $I_{\text{NaL}}$  might be an “additional mechanism for AF” by enhancing triggered

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activity in the atria (1). The question arises why the enhanced propensity to triggered activity due to increased  $I_{NaL}$  does not result in proarrhythmic events occurring in the right atrial appendages. Focal discharges initiating AF originate from the sleeves of pulmonary veins, the ostia of the coronary sinus and the caval veins, or the crista terminalis. Ectopy originating from the right atrial appendage is very rare. Thus, one must conclude that enhanced  $I_{NaL}$  currents in atrial myocytes isolated from right atrial appendages of patients with AF are not sufficient to produce focal discharges in vivo. In line with this, the rate of premature atrial contractions was even lower in AF patients compared with patients in SR. However, this does not exclude the possibility that in other regions of the atria, an even stronger enhancement of  $I_{NaL}$  or enhanced  $I_{NaL}$  together with other factors such as impaired intercellular coupling and reduced inward rectifier currents might produce focal discharges, which then contribute to initiation or perpetuation of AF.

### Is the Antiarrhythmic Effect of Ranolazine in the Atria Due to Block of Late $I_{Na}$ ?

Ranolazine has been proposed as an antianginal drug with minimal effects on blood pressure and heart rate. In patients with chronic stable angina, ranolazine decreases the frequency of recurrent ischemia and improves exercise tolerance (11). In the MERLIN-TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes-Thrombolysis In Myocardial Infarction 36) trial, ranolazine did not affect mortality, including sudden cardiac death over a period of 12 months in patients with non-ST-segment elevation myocardial infarction and unstable angina (12). However, ranolazine reduced the incidence of ventricular and supraventricular arrhythmias and caused a trend toward a reduced incidence of new-onset AF ( $p = 0.08$ ) during the first 7 days of treatment.

Ranolazine has a complex profile of electrophysiological and metabolic effects. In normal, healthy hearts, it shifts the balance between fatty acid and glucose oxidation toward glucose metabolism, thereby improving oxygen efficiency, possibly contributing to improved myocardial function (13). Apart from these metabolic effects, ranolazine also inhibits several ionic currents including  $I_{NaL}$  (inhibitory concentration of 50% [IC<sub>50</sub>] 6  $\mu$ M),  $I_{Kr}$  (IC<sub>50</sub> 12  $\mu$ M), the "late"  $I_{Ca}$  (IC<sub>50</sub> 50  $\mu$ M),  $I_{NCX}$  (IC<sub>50</sub> 91  $\mu$ M), peak  $I_{Ca}$  (IC<sub>50</sub> 296  $\mu$ M), and  $I_{Ks}$  (20% inhibition at 30  $\mu$ M), without affecting  $I_{to}$  and  $I_{K1}$  (14). In atrial preparations, ranolazine produced significant post-repolarization refractoriness. It slowed conduction velocity in atrial but not in ventricular preparations (15), especially at high rates. In atrial preparations and intact pigs, ranolazine reduced the stability of acetylcholine-induced AF (15). In myocardial preparations from canine pulmonary veins, it suppressed triggered activity observed in the presence of acetylcholine + isoproterenol (16).

In the current study, Sossalla et al. (1) report an inhibition of the peak  $I_{Na}$  in atrial myocytes from SR patients,

elucidating the earlier findings by Burashnikov et al. (15). However, in myocytes from AF patients, ranolazine did not affect peak  $I_{Na}$ . In contrast, ranolazine reduced  $I_{NaL}$  current to a larger degree in AF than in SR patients. Interestingly, this alteration in sensitivity between SR and AF patients was associated with a shift from Nav1.5 to Nav1.1 subunit expression. In the light of altered Na<sup>+</sup> channel subunit composition in AF patients, it will be important to investigate whether ranolazine retains its particular class I antiarrhythmic effects (the atrium-specific reduction in conduction velocity, prolonged post-repolarization refractoriness, and decreased AF stability) in patients with AF.

Taken together, it remains to be investigated whether the decreased incidence of supraventricular tachycardias and new-onset AF during ranolazine treatment result from direct effects on atrial electrophysiology, from improvement of atrial metabolism, or from improvement of ventricular function, thereby indirectly reducing atrial arrhythmogenesis. Antagonizing enhanced Na<sup>+</sup> loading in atrial myocytes, however, certainly warrants further investigation as a new working principle to prevent atrial remodeling due to structural heart diseases or AF.

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