Editorial

Does the Na⁺,K⁺ pump current undergo remodeling in atrial fibrillation?

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See article by Workman et al. [1] (pages 593–602) in this issue.

The sodium pump current has been the subject of many studies, but information on human cardiac tissue is lacking. This gap has been filled by a paper published in this issue in which Workman, Kane and Rankin [1] describe the maximal capacity and functional characteristics of the Na⁺,K⁺ pump current (Iₚ) in atrial cells from patients with and without chronic atrial fibrillation (AF). The main conclusions are that the pump current contributes to the resting potential and the duration of the action potential. Sensitivity to the external K⁺ concentration, [K⁺], and the voltage dependence of the pump do not change in AF. The authors conclude that Iₚ is not involved in AF-induced electrophysiological remodeling in patients. Before discussing these interesting findings it seems worthwhile to provide some general information on the characteristics of the Na⁺,K⁺ pump [2].

The Na⁺,K⁺ pump is essential to cell survival. (1) By producing K⁺ and Na⁺ gradients between the intra- and extracellular medium the pump is of primordial importance in the generation of the resting membrane potential and the action potential upstroke. Since the number of Na⁺ and K⁺ ions transported is three to two, the pump also generates an outward current. Its contribution as a current to the resting potential is minor, but it modulates pacemaker activity and action potential duration. The effect on the repolarization process is related to the high electrical resistance during the plateau of the cardiac action potential. Block of the pump causes action potential lengthening and symptoms comparable to the LQT syndrome. (2) By generating a Na⁺ gradient the pump provides potential energy to transporters that do not use ATP as an energy source, such as the Na⁺,Ca²⁺ exchanger, the Na⁺,H⁺ exchanger, the Na⁺,K⁺,2Cl⁻ cotransporter, the Na⁺,HCO₃⁻ cotransporter, and the Na⁺,glucose and Na⁺,amino acid cotransporters [3].

Important biophysical characteristics of the Na⁺ pump are its maximum capacity, the sensitivity to [K⁺]₀ and [Na⁺]₀, its voltage dependence and its sensitivity to cardiac glycosides. These properties differ among species, among tissues and among regions in the same tissue. In guinea pig atrial cells, the maximum hydrolytic activity of Na⁺,K⁺ ATPase is only 33% of that of ventricular cells [4]. This lower density of pump sites in atrial cells has been confirmed in a study of protein expression and has been suggested to be the reason for the lower resting membrane potential and the higher sensitivity to pump blockade in atrial cells [4,5].

The sensitivity to ions and drugs depends on the constitution of the isoforms [6]. The sodium pump is a heterodimer consisting of a catalytic α-subunit and an associated glycoprotein, the β-subunit. Three α-isoforms have been described. In the human heart the pump consists of 55% α₁, 18% α₂ and 27% α₃, and β₁. The sensitivity of these isoforms to ions and drugs can be expressed by the affinity or the half maximum (K₀.₅) constants. In the human heart the affinity for [K⁺]₀ is 0.9, 1.3 and 0.9 mM, respectively, for the three isoforms; the sensitivity to [Na⁺]₀ is 8.2, 12.8 and 24.7 mM and to ouabain 5.1 x 10⁻⁸, 37 x 10⁻⁹ and 14 x 10⁻⁹ M. The affinity values demonstrate that [Na⁺]₀ is the main regulator of the Na⁺ pump, since the actual values of [Na⁺]₀ are close to the K₀.₅ of ATPase. For external K⁺, the K₀.₅ value is much smaller than the concentration encountered in the extracellular medium, indicating that the K⁺ sensitive site is practically saturated. The isoform constitution is important in de-
remains constant \[12\]. The inactivation curve was slightly myocytes isolated from patients in AF has been found to properties of the pump remain normal and constant, this finding \[12\] Bosch RF, Nattel S. Cellular electrophysiology of atrial fibrillation. 48 h of stimulation. Assuming that the functional prop- Cardiovasc Res 2002;54:405–415.

and other ions were measured in left atrial preparations Circulation 2003;107:1810–1815.

rate is dramatically increased in AF, an increase in Circulation 2002;105:2543–2548.

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mNa influx will be greater for \(a_1\) than for \(a_1\) Furthermore, even with no change in the \([Na^+]\) dependency, the Na pump current will change when \([Na^+]\), is altered. In a rabbit heart failure model, such a situation seems to be present; an increase in \([Na^+]\), caused by enhanced Na influx has been found to result in an increased pump current, whereas the functional properties of the pump did not change \[7\]. A similar situation occurs when the frequency of contraction is increased (see Ref. \[8\] for references). When the stimulus rate is suddenly increased, the cell is loaded with Na+ through influx via the fast Na+ channel and the Na+ ,Ca++ exchanger. The amount of Na+ entering the cell during an action potential has been estimated to be 8 \(\mu\)M via the fast Na+ channel and 32 \(\mu\)M via the exchanger, corresponding to an increase of 2.4 mMM/min \[3\]. Such an increase in Na+ influx activates the pump. The enhanced outward current is generally assumed to be one of the factors responsible for the second slow phase of shortening of the action potential after an increase of stimulus rate \[8\]. Since the rate is dramatically increased in AF, an increase in \([Na^+]\), may therefore be expected to occur.

Does \([Na^+]\) increase in AF? A search of the literature revealed only one publication \[9\] where the total sodium and other ions were measured in left atrial preparations applying the electron probe method. Whereas a small but insignificant increase in sodium was observed during short time (3 and 30 min) pacing at 640/min, contrary to expectation cytosolic sodium was seen to fall by 51% after 48 h of stimulation. Assuming that the functional properties of the pump remain normal and constant, this finding presumes a drop in Na+ influx. For the fast Na+ channel, a fall in iNa has been measured in the dog pacing model \[10,11\]. In humans, however, the maximum iNa in atrial myocytes isolated from patients in AF has been found to remain constant \[12\]. The inactivation curve was slightly shifted in the positive direction, indicating that activation from the resting potential might even result in greater iNa.

The second component of importance for Na+ influx, the Na+ ,Ca++ exchanger, has not been measured directly, but the expression of mRNA did not change \[12\] and the expression of the protein was even increased by 67% \[13\]. The reported changes of inward currents in humans would normally result in a rise of \([Na^+]\), the opposite of what has been found by direct electron probe analysis in dogs \[9\]. The question of whether \([Na^+]\), is increased or decreased in AF thus remains open.

Based on the available findings in AF \[1,12\] it is unlikely that the pump shows dramatic changes in maximal capacity or in kinetic behaviour. In the future, our attention should therefore be focussed on short-term modulation, such as caused by changes in \([Na^+]\), neurotransmitters, autocrine and paracrine factors and hormones.

References


\[6\] Verdonck F, Volders PGA, Vos MA, Sipido KR. Intracellular Na influx activates the pump. The enhanced outward current is generally assumed to be one of the factors responsible for the second slow phase of shortening of the action potential after an increase of stimulus rate \[8\]. Since the rate is dramatically increased in AF, an increase in \([Na^+]\), may therefore be expected to occur.


