Editorial

The membrane current \( I_f \) in human atrial cells: implications for atrial arrhythmias

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In this issue Uta C. Hoppe and Dirk J. Beuckelmann describe the presence of \( I_f \) channels in human atrial cells [1]. The cells were isolated from small segments of the right atrial appendage obtained at the time of open heart surgery in 96 patients. About 80% of those patients underwent a coronary bypass procedure. The same group recently published a paper on \( I_f \) in human ventricular myocytes. Those cells were isolated from explanted hearts from patients with endstage heart failure and from donor hearts not suitable for transplantation, the latter serving as controls [2]. This Editorial will focus on the implications of the presence of \( I_f \) current in atrial and ventricular muscle in heart failure [3–5].

1. Role of \( I_f \) in normal pacemaking function

The membrane current \( I_f \), often described as `the' pacemaker current, has an interesting history [6,7]. The current was originally considered an outward \( K^+ \) current – labeled as \( I_{Ks} \) – by its decay might contribute to pacemaking. Later, it appeared a mixed \( Na^+ /K^+ \) current, which slowly activates on hyperpolarization [6,7]. This is of interest because both the fast \( Na^+ \) current responsible for the upstroke of the action potential and the \( K^+ \) currents responsible for the onset of repolarization, activate on depolarization. These currents all have equilibrium (reversal) potentials outside the normal voltage range of the cardiac action potential. The reversal potential of \( I_f \) is within the normal range of the action potential (as is the case with \( Cl^- \) currents and the \( Na^+ /Ca^{2+} \) exchanger). Its reversal potential is about −20 mV, depending on the extracellular and intracellular \( Na^+ \) and \( K^+ \) concentrations and on the relative permeabilities for the two ions. Experimental differences in ion concentrations will therefore affect the driving force of the current and thereby, directly, the borderline voltage at which activation of the current may be observed. Obviously, this explains variability between studies.

\( I_f \) plays a prominent role in pacemaking in the sinus node and in Purkinje fibers [8,9]. Its relative role compared to other pacemaker currents has lead to vivid debate [8–12]. Inhibition of the \( I_f \) current, by \( Cs^+ \) [13] and/or by specific \( I_f \) blocking agents [13,14] does not abolish pacemaking in an isolated sinus node, which underscores that membrane currents other than \( I_f \) generate enough current to maintain diastolic depolarization. The \( I_f \) current has been shown to be increased by catecholamines and to be decreased by acetylcholine (see [1] for references). Thus, whatever the role of \( I_f \) for pacemaker function, it apparently is important for the sympathetic modulation of heart rate. Automaticity does not only depend on the presence of pacemaker currents, but also on the absence of the inward rectifier \( (I_{K1}) \), which maintains the stable resting membrane potential in atrial and ventricular muscle [15,16]. The absence of \( I_{K1} \) in the sinus node constitutes the most important condition for pacemaking [16]. An isolated analysis of the pacemaker potency of \( I_f \) in tissue normally not spontaneously active, has a limited significance without analysis of outward – resting membrane potential consolidating – \( I_{K1} \) current. A small upregulation of \( I_f \) due to some pathophysiological stimulus therefore may be arrhythmogenic only with a concomitant downregulation of \( I_{K1} \). This perspective makes the study of Hoppe and Beuckelmann [1] of special interest.

2. Possible role of \( I_f \) in abnormal pacemaker function

The term “abnormal automaticity” is used for automaticity which occurs at depolarized membrane potentials and in tissue that normally is not spontaneously active. Depolarization activates inward \( Ca^{2+} \) current, but at the same time affects the kinetics and inactivation state of the fast inward \( Na^+ \) current, resulting in reduced upstroke
velocity of action potentials and decreased conduction velocity, well known characteristics of acutely ischemic myocardium [17]. Vermeulen et al. [18] have shown that failing ventricular myocardium from rabbits as well as from explanted human hearts develops automaticity in the presence of modified Tyrode’s solution mimicking the extracellular fluid in heart failure. This automaticity started at a maximal diastolic potential of −88 mV and it was absent in control rabbit hearts despite the presence of the modified solution [18]. Obviously, this type of automaticity, although it occurs at normal membrane potential, is also abnormal and it might be associated with \( I_r \). The mere presence of \( I_r \) channels in atrium or ventricle, albeit not activated, potentially allows for automaticity under pathophysiological conditions as pointed out by Carmeliet 14 years ago [19]. This may result from extrinsic factors promoting \( I_r \) current, f.e. a catecholamine induced shift of the activation curve of \( I_r \) current to less negative potentials. Alternatively, the density of the \( I_r \) channels may as well respond to some pathophysiological condition. An increased density of \( I_r \) channels and an increased concentration of an agonist may have the same effect, leading to an increased propensity to automaticity. Due to the long activation kinetics of \( I_r \), it may be anticipated that extrastoles based on \( I_r \) current have long coupling intervals and are promoted by low heart rates.

3. \( I_f \) in human atrial myocytes

There have been previous reports on the occurrence of \( I_f \) in cells derived from human atrium [20–22]. Heidbüchel et al. [20] suggested that the occurrence of \( I_f \) was related to a morphological substrate as in cat atrium [23]. Thus, specialized atrial cells might be involved. Thüringer et al. [21] also suggested the existence of two different cell types with and without \( I_r \). Hoppe and Beuckelmann [1] and also Porciatti et al. [22] describe the overall existence of \( I_f \) in cells from areas that probably do not contain cells from – subsidiary – pacemaker locations.

There are three important technical/experimental limitations in the study of Hoppe and Beuckelmann [1]. These include (i) the presence of 25 mM K⁺ in the extracellular environment, which is incompatible with life and (ii) membrane voltages required for activation of \( I_f \) that are just borderline overlapping with the normal resting membrane potentials in the atrium. Moreover, (iii) the cells were not able to generate action potentials in physiological solution.

It seems justified to increase the extracellular K⁺ concentration in order to show single channel behaviour in isolated patches. However, in a whole cell study one is inclined to consider a current not important if it cannot be demonstrated at physiological K⁺ concentration or if the applied voltage in the clamp protocol has to be far more negative than the resting membrane potential in a normal cell. At 5 mM extracellular K⁺ and at −80 to −90 mV the \( I_f \) current density seems less than −0.1 pA/pF (deduced from figure 2B in Ref. [1]; 100 pF substituted for cell capacitance). Compared to the other current amplitudes either at more negative potentials or at increased extracellular K⁺ concentration (figure 2A–C in Ref. [1]) this seems a very small current indeed. However, in the absence of significant outward current, a depolarizing current density of −0.1 pA/pF may give rise to a diastolic depolarization of 100 mV/s. In a similar study of the same group [2] in ventricular cells the \( I_f \) current density amounted to −0.03 pA/pF at physiological K⁺ concentration. At 25 mM extracellular K⁺ and at −80 mV the authors report current densities of −0.78 pA/pF in the atrium [1] and of −0.15 pA/pF in the ventricle [2]. Current density for \( I_f \) thus seems larger in human atrium than in human ventricle. Moreover, Koumi et al. [5] have shown that the slope conductance of human atrial cells at the reversal potential of \( I_K \) is an order of magnitude smaller (9.7 nS) than the slope conductance of ventricular cells (84 nS) (see also Ref. [24]). In a previous paper the same authors showed that there was a more than 50% reduction of this slope conductance in atrial cells from patients with heart failure compared to control atrial cells from donor hearts [4]. A lower slope conductance at the reversal potential (about the resting membrane potential) implies that less outward current is generated in response to a depolarizing current. Thus the \( I_f \) current density is larger in the atrium than in the ventricle, but the counter-balancing outward current is smaller in the atrium than in the ventricle. Of course, the outward conductances are huge compared to the \( I_f \) current densities both in atrium and ventricle. Nevertheless the basic conditions for an arrhythmogenic role of \( I_f \) before any pathophysiological process may start to affect the existing current balance, seem more prominent in atrium than in ventricle.

4. Pathophysiological changes in \( I_K \) and \( I_f \)

Koumi et al. [4,5] have reported that the density of \( I_K \), can change substantially in human atrium in heart failure and in human ventricle in dilated and in ischemic cardiomyopathy. The decrease in density was more pronounced in dilated compared to ischemic cardiomyopathy [5]. The differences were associated with prolongation of the action potential. Thus, in the pathophysiological process with the largest decrease in \( I_K \), density action potential was more prolonged (491 ms in dilated cardiomyopathy, 421 ms in ischemic cardiomyopathy versus 391 ms in control, all at 1000 ms cycle length), possibly pointing to an important role for dilatation [25–27]. Koumi et al. [5] also showed that the conductance of the individual \( I_K \) channels was similar in human atrial and ventricular cells (control, ischemic and dilated cardiomyopathy) and cat and guinea pig ventricular myocytes. This suggests that changes in current density in heart failure result from changes in
the number of channels rather than from changes in the function of these channels.

$I_f$ has been demonstrated in human ventricle from patients with ischemic [2,28] and dilated cardiomyopathy [2]. There was a tendency to higher density in the pathophysiological states [2]. In the rat the density of $I_f$ is proportional to the severity of hypertrophy in hypertensive rats [29] and the density is even larger in heart failure [30].

No data are available on changes in $I_f$ during a pathophysiological process in the atria. However, specific blockers of $I_f$ prolong cycle length more in failing than in normal rabbit hearts [14], suggestive for a changed expression of $I_f$ in the sinus node of failing hearts.

One problem with the present study [1] is that it is difficult to assess whether the experimental material should be regarded normal or not. The patients were operated for a coronary artery bypass, but this gives little information about the health of their atria. Hoppe and Beuckelmann [1] state in the Discussion of the present study that “$I_f$ is too small to play a physiological role at potentials close to the resting membrane potential and at normal potassium concentration”. In figure 8 of Ref. [1] the authors show a subdivision of their cells into three groups. Type 1 cells have a relative high $I_f$ density and a low $I_K$ density (see also figure 7A of Ref. [1]). Type 2 cells have a relative low $I_f$ density and a high $I_K$ density (see also figure 7B of Ref. [1]). Type 3 cells have low densities for both currents. A caveat should be made: we are looking at current ratios in cells not capable to generate an action potential. From the present study it can therefore not be concluded whether these different cell types may simultaneously occur in the same atrium, or that the transition from type 2 towards type 1 results from a pathophysiological process. It would be of interest to correlate atrial arrhythmias in conscious animals with heart failure with data on action potential parameters. $I_f$ and $I_K$ currents and densities and mRNA for $I_f$ and $I_K$ in tissue and cells from the same animals. This requires an experimental approach from the in vivo towards the molecular level [31].

In summary, the study of Hoppe and Beuckelmann [1] gives food to the hypothesis that $I_f$ is more likely involved in atrial than in ventricular arrhythmias associated with heart failure especially when there is a decreased role for $I_K$ [4,5].

References


