“Funny” current: If heart rate slowing is not the best answer, what might be?

Henry Gewirtz, MD

(Department of Medicine, Cardiac Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA)

Contact Information:

Massachusetts General Hospital
Yawkey 5E
55 Fruit St.
Boston, MA 02114
USA
Email: hgewirtz@partners.org
Invited Editorial:

DiFrancesco first described an ion current in the sinoatrial node (SAN) of the rabbit which was thought “funny”, as in unusual, since it was hyperpolarization activated and carried by both sodium and potassium ions \(^1,2\). Hence, its name \(I_f\). The current is active in diastole between roughly -50 and -20 mV when it shuts down and is followed by activation of the T-channel calcium current, which continues the process of diastolic depolarization. Accordingly, \(I_f\) contributes importantly to spontaneous pacemaker activity in the mammalian heart\(^1\). The gene encoding the channel was first discovered in mouse brain\(^3\). Subsequently, in cardiac tissue, four isoforms of the hyperpolarization-activated cyclic nucleotide gating channel protein (HCN 1,2,3,4) were identified\(^1,4\). The channel’s operating range and activity are sensitive to cAMP (second messenger role) and so autonomic tone, both sympathetic and parasympathetic.\(^1\) The distribution of isoforms in the rabbit heart also is variable with HCN4 greater than HCN1 in SAN while much lower levels of HCN2 are found in ventricular myocardium\(^5\), but given the very large mass of myocytes versus SAN tissue, HCN2 likely is the dominant isoform on a mass basis\(^5\). Finally, the \(I_f\) current is active at a threshold of -45 mV in rabbit SAN but is only faint at hyperpolarization to -150 mV in rabbit myocytes\(^5\). However, it is readily apparent at -100mV in adult rat ventricle and even more marked at -65mV in neonatal rat ventricle\(^5\).

In the current issue of the Journal Ceconi and co-workers\(^6\) report a series of experiments conducted in a Langendorff rabbit heart model of ischemia reperfusion in which the hearts were perfused with Krebs-Henseleit buffer at “aerobic flow” (30 min) then low-flow ischemia (75min) followed by reperfusion at aerobic flow (30min). Experiments were conducted comparing ivabradine, a selective blocker of the \(I_f\) current\(^7\), with placebo, given throughout pre-ischemia, ischemia and reperfusion phases and also with ivabradine plus pacing at 180/min during each
phase of the protocol. Experimental parameters measured included left ventricular developed pressure, myocardial CK and norepinephrine release, mitochondrial respiratory control index, myocardial energy metabolism (ATP levels), and redox state (NADPH/NADP⁺). The data obtained demonstrated ivabradine ameliorated ischemia reperfusion injury by all indices measured and that pacing the hearts at 180/min throughout abolished ivabradine’s protective effects. Accordingly, the authors conclude, since the drug has no known negative inotropic effects⁸, that its principal mechanism of action is to reduce heart rate, especially very early in ischemia, and thereby mitigate ischemic damage by favorably impacting the myocardial oxygen supply/demand balance.

The authors consider an alternate mechanism based on reduced sodium influx resulting from Iᵥ current blockade with subsequent enhancement of calcium efflux at the level of the sarcolemmal Na⁺-Ca⁺ exchanger⁹. They note: “This could explain the reduction in the rise in diastolic pressure during ischaemia and reperfusion. Less cytosolic calcium would also facilitate mitochondrial ATP production during reperfusion due to competition for the restored mitochondrial Δψ for calcium accumulation or ATP production¹⁰. This would explain the better energy recovery during reperfusion with ivabradine treatment.” The authors, however, dismiss this explanation as improbable, arguing in effect that the time course of their experiments is too short to permit ischemia-induced “re-expression of Iᵥ channels in the myocyte” in “a major part of the ventricle”. One wonders if the authors may have been a bit too hasty in rejecting their ion flux hypothesis, which is quite BEAUTIFUL¹¹ and deserves additional consideration.
The experimental record demonstrates that low-flow ischemia leads to cardiac arrest within roughly 7.5 min in the presence of ivabradine and approximately 15 min with placebo (see Ceconi et al.⁶, Fig. 4A,B). The corresponding LV systolic pressure (LVSP)-time integral for ivabradine is ~50% that of placebo. For the remaining hour of low-flow ischemia, hearts in both groups are arrested, so any heart rate slowing effect of If current blockade obviously is of no consequence for the vast majority of the ischemic period. It is noteworthy that LV diastolic pressure (LVDP) increases more slowly following cardiac arrest in comparison with placebo though both eventually reach the same level (40 mmHg). Thereafter, upon reperfusion a steep rise in LVDP occurs with placebo but not with ivabradine. Both hearts maintain equal LVSP and so the reduction in developed pressure at reperfusion is accounted for entirely by the increase in LVDP with placebo. Accordingly, the authors are quite correct in calling attention to the beneficial effect of ivabradine on ventricular relaxation and suggesting an elegant ionic mechanism based on If current inhibition which could explain it (editorial, Fig 1) as well as the improved preservation of mitochondrial function and energy production upon reperfusion.

The objection raised by the authors that adult rabbit myocytes do not constitutively express If channels is not correct⁵. Whether the HCN2 channel’s operating characteristics are altered by ischemia in such a way as to open at lesser degrees of myocyte membrane hyperpolarization versus physiological conditions is not known. However, the slower rate of rise of LVDP following cardiac arrest in the presence of ivabradine versus placebo suggests this may occur. Further, abrogation of ivabradine’s protective effects with rapid electrical stimulation of the ventricle throughout the experimental period (Ceconi et al.⁶, Fig. 7) could only be heart rate related for roughly the initial 10% of the entire 75 min ischemic period. The remainder of the
time ivabradine’s failure to mitigate reperfusion injury could reflect ongoing electrical stimulation per se with associated transmembrane ionic flux (and ultimately intracellular calcium accumulation) by mechanisms differing from those more active in the unpaced model and unrelated to the $I_f$ current, ivabradine’s target. Further, as noted by the authors of the current paper, Heusch et al. have previously reported a beneficial effect of ivabradine on infarct size in a porcine ischemia reperfusion model, which at least in part was heart rate independent. Finally, though the results of the BEAUTIFUL trial in patients with CAD and LV contractile failure (LVEF <40%) were largely negative\(^1\), the data presented in the current paper suggest that a clinical trial in patients with diastolic LV failure, particularly related to impaired LV relaxation, may have a positive outcome.

Conflicts of Interest: None
References:


Figure 1 – Legend

Proposed ionic mechanism through which ivabradine inhibition of I_f may facilitate ventricular relaxation (modified after Ceconi et al.6). Reduced entry of Na^+ into the cell ultimately leads to reduced cytosolic calcium levels since calcium access to the Na^+/Ca^{2+} transporter, which is competitive with that of Na^+, is facilitated when Na^+ entry declines. Re-uptake of calcium by the sarcoplasmic reticulum (SR) may also be improved. Additionally, reduced cytosolic calcium helps maintain mitochondrial function and energy production as noted by Ceconi et al. (See text for details.)