Heart Rate Slowing by $I_f$ Current Inhibition
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Volume Editors

A. John Camm  London
Michal Tendera  Katowice

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Those animals that live long lives tend to have slower heart rates. Several plausible theories suggest that this may not be a chance association but that the slower heart rate may have a causal relationship to the longer life. Many large population studies have also shown that a slower heart rate is associated with a longer life in the general population, in elderly subjects, and in patients with stable coronary artery disease, hypertension, or myocardial infarction. Similarly, slowing the heart rate with β-blockers in patients after myocardial infarction or when presenting with heart failure extends life in proportion to the degree by which the heart rate is slowed.

The normal heart rate at rest is usually defined as 60–100 beats per minute. Much evidence suggests that the human resting heart rate should certainly be less than 90 beats per minute. However, the optimum has not been defined. A faster heart rate may be a sign of inappropriate autonomic balance with hazardous sympathetic tone outweighing protective parasympathetic effects. Sinus tachycardia is seen in those that are unfit and those that have disease. The arrhythmia may particularly reflect underlying cardiac disease. It may also cause heart disease by damaging atherosclerotic plaques, by provoking myocardial ischemia or by inducing inefficient cardiac hemodynamics.

A variety of medications may be utilized to slow the heart rate for therapeutic purposes. β-Adrenergic blocking agents are the most commonly used, but the nondihydropyridine calcium channel antagonists also slow the pulse. About a decade ago, a new class of potential pharmaceuticals emerged which inhibited the $I_f$ transmembrane current which is specifically responsible for the diastolic depolarization of pacemaker cells within the sinus node. Initial
attempts to develop a medicinal product with this mechanism of action were thwarted by unwanted effects such as hypotension and QT prolongation (due to $I_{Kr}$ blockade). Recently, ivabradine, which selectively inhibits the $I_f$ current and has virtually no other demonstrable effect on the heart, has been successfully developed and approved for clinical use in patients in sinus rhythm who have angina, and in whom β-blockade is contraindicated or poorly tolerated.

The ability to slow the heart rate is a cornerstone therapy for the symptomatic management of angina pectoris since decreased cardiac systole reduces the oxygen demand whilst at the same time longer cardiac diastole increases the supply of oxygenated blood to the myocardium. Titrating the heart rate with an agent which only affects the discharge frequency of the sinus node provides a simple method to mitigate angina without encountering unwanted adverse events. The results of the development program for ivabradine demonstrate impressive antianginal efficacy and only few complications from therapy. Not surprisingly, more new molecules with $I_f$ inhibition activity are now being actively investigated.

As yet, there is no information about the potential prognostic value of pure heart rate reduction such as that which might be achieved with $I_f$ inhibition. However, several studies are now underway to evaluate the effect of ivabradine on the survival of patients with coronary artery disease and poor left ventricular function or significant left ventricular failure. Whether lowering heart rate per se will prolong life is not yet known but it may offer a new and important life saving strategy.

In this volume, experts in the investigation of cardiac pathophysiology and the management of heart disease discuss the new and exciting development of $I_f$ inhibition for the control of angina pectoris and potentially for the prolongation of life.

A. John Camm
Michal Tendera