Drugs 2007; 67 Suppl. 2: 1-2
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Heart rate is a fundamental characteristic of cardiovascular physiology. It is a primary determinant of cardiac output and of myocardial oxygen utilisation. Heart rate slowing was recognised long ago as a useful strategy for preventing angina pectoris in persons whose myocardial oxygen supply is limited by coronary artery occlusive disease, as recognised in current clinical guidelines.[1] When heart rate slowing has been achieved acutely by carotid nerve stimulation, this heart rate slowing also has relieved episodes of angina.[2] More recently, cross-sectional analyses of drug trials for secondary prevention after acute myocardial infarction have suggested a benefit of heart rate slowing in this setting.[3] Similar analyses of trials for heart failure[4] have suggested the benefit of heart rate slowing in this condition as well. Perhaps more importantly, more than 60 years ago, a retrospective study of the records of more than 22 000 US Army officers serving during World War II suggested a direct relation between heart rate and the likelihood of leaving the service for health reasons;[5] when tachycardia was persistent, survival was impacted. These officers had no evidence of heart disease, albeit inferred from the relatively insensitive screening techniques available in that era. Consequently, these data suggested that heart rate may be related in a fundamental manner to processes that determine survival, as a barometer of deleterious health variations and/or, perhaps, as part of the pathogenic process itself. If the latter, then therapeutic heart rate modulation may be useful in mitigating the processes and improving survival. Inferences from this early publication now have been supported by epidemiological and actuarial data collected from more than 100 000 persons in many studies, as noted by Palatini[6] in this issue, together with substantial supporting data suggesting that heart rate truly is a 'risk factor' for cardiovascular disease.

These considerations intrinsically are of scientific interest. However, they assume a particular immediacy since the development of ivabradine, a drug with no apparent cardiovascular effects other than heart rate slowing, enabling exploration of the effects of heart rate slowing divorced from other cardiovascular variations. Heart rate reduction with ivabradine already has evidenced therapeutic benefit: clinical trials indicate clear efficacy of ivabradine in preventing angina pectoris in patients with coronary artery disease.[7] The drug has a very tolerable non-cardiovascular side effect profile comprising transient, reversible ophthalmologic symptoms that seldom lead to drug withdrawal. Ivabradine acts by blocking the sodium- and potassium-mediated I_f current in the myocytes of the sinoatrial node, the only tissue in the heart in which the relevant cyclic adenosine monophosphate-dependant, hyperpolarisation-activated *f*-channels are functionally active. The characteristics of these channels and of the current they mediate, and the basis for the pharmacological effect of the drug, are reviewed in this issue by DiFrancesco,[8] who first identified the I_f current 3 decades ago.

With the availability of a pure heart rate-slowing agent, the effects of isolated heart rate reduction have been explored in preclinical studies, as reviewed by Berdeaux[9] in this issue, to define potential therapeutic

benefits in humans, and in clinical trials and observational studies, to demonstrate and define these benefits, as reviewed by Tardif.[10] The very promising results of these studies not only have supported regulatory approval of ivabradine in Europe for angina prevention, but also have suggested benefit in several other cardiovascular conditions, most prominently including heart failure. The potential future clinical horizons for heart rate slowing with ivabradine are reviewed by Böhm.[11]

The information reviewed in this issue suggests that we have only begun to define the clinical effects of heart rate modulation. Therefore, these articles, in fact, should be considered as a basis for exploring the full range of applications of a powerful tool that promises substantial benefit in mitigating cardiovascular pathophysiology and disease.

Jeffrey S. Borer
New York Presbyterian Hospital–Weill Cornell Center, New York, New York, USA

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