Commentary

I_{K1} blockade as an antiarrhythmic mechanism

The Controversy articles by Rees and Curtis[1] *I_{K1} blockade is a potentially useful antiarrhythmic mechanism* and Opthof[2] *I_{K1} blockade is unlikely to be a useful antiarrhythmic mechanism* report conflicting views on the potential role of I_{K1} inhibition as an antiarrhythmic principle. Such articles stating different viewpoints are certainly of interest in the light of new strategies for antiarrhythmic drug development. Both articles comment on the role of the potassium current I_{K1} for the resting membrane potential and the terminal phase of repolarisation. It is not so much the difference in opinion about the relative importance of these two effects for preventing or favouring arrhythmias but the entirely different philosophical approach which leads to the different conclusions.

The article by Rees and Curtis starts from experimental observations in whole hearts showing that drugs which are considered as specific inhibitors of I_{K1} lengthen the QT interval (increase of action potential duration) and prevent ischaemia induced arrhythmias in the rat. The speculation about the potential antiarrhythmic action is based on these two observations: refractory period prolongation is expected to decrease the probability of formation of re-entry, and consequently of arrhythmias. The authors are well aware of the potential pitfalls in their argument and carefully list the other known effects of the drug which are not related to I_{K1} inhibition. The article by Opthof starts with the biophysical properties of the I_{K1} channel, projects these properties into the role of I_{K1} in action potential generation, and finishes by rejecting the potential antiarrhythmic role of I_{K1} inhibition. In particular, it is stated that inhibition of I_{K1}, which flows close to resting potentials and is rectified at potentials remote from E_K, is expected to shift resting membrane potential to more positive levels (depolarisation). Such a change is said to be proarrhythmic rather than antiarrhythmic. The effect of lengthening the terminal portion of the action potential, which is at the centre of the Rees/Curtis argument, is considered relatively unimportant. Opthof does not throw doubt on the observation that terikalant and its derivatives can be antiarrhythmic but attributes these effects to actions other than I_{K1} blockade.

The controversy raised by these two articles sheds some light on a situation which is inherent to arrhythmia research. On one hand, drugs are primarily developed in experimental systems which are reduced to single membrane channels. In such systems fascinating results on structure and function of membrane channels are obtained and drugs acting as specific inhibitors can be developed. On the other hand, the analysis of an antiarrhythmic effect necessarily has to involve whole tissue (cell cultures, isolated tissue, whole isolated or in situ hearts) because it is related to disturbances in impulse formation and impulse conduction. Such systems are indefinitely more complex and create a substantial likelihood of additional actions of a channel inhibiting drug. For example, this has been reported from ATP sensitive K^+ channel inhibitors, which are known to have an important influence on glycolysis and lipid metabolism. Furthermore the fact that cardiac cells are coupled by proteins which may also be drug sensitive is rarely taken into account in antiarrhythmic principles.

Personally, I consider the arguments in the article of Rees and Curtis, which is written with caution, to be correct as long as they are used to promote further research, which should include consideration of the pitfalls mentioned by Opthof. In particular, such drugs need to be tested for their effects on electrical cell to cell coupling and metabolism. Experiments have to be carried out at membrane, whole cell, tissue, whole heart, and animal levels, taking into account the advantages and limitations of each model as well as species differences. Only the combined interpretations of all results will eventually lead to a conclusive view.

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1 Rees SA, Curtis MJ. I_{K1} blockade *is* a potentially useful antiarrhythmic mechanism. *Cardiovasc Res* 1994;**28**:421.
2 Opthof T. I_{K1} blockade is *unlikely* to be a useful antiarrhythmic mechanism. *Cardiovasc Res* 1994;**28**:420.

Invited letter to the Editor

Endothelium dependent relaxation in chronic heart failure

The endothelium represents an important cell layer at the interface between the vessel wall and flow blood, subjected to physical forces and neurohumoral stimuli. Changes in blood flow result in adjustments of vessel diameter via vasoactive mechanisms triggered by physical forces.[1] Chronic increases in flow are associated with enhanced release of endothelium dependent relaxing factor (EDRF)[2] and an increase in the vessel diameter.[3] The latter appears to be an endothelium dependent response. Shear stress has been shown to be an important stimulus for the release of EDRF and more recently it has been demonstrated that increases in shear stress causes an upregulation of the expression of the endothelial nitric oxide synthase (cNOS),[4] the enzyme which generates nitric oxide (NO) from its precursor L-arginine. Although NO may primarily account for the biological activity of EDRF, other factors may contribute to the dilator response of the vessel in response to increase flow. While the physiological role of bradykinin for the release of EDRF remains to be fully elucidated, bradykinin is a strong stimulus for the release of EDRF. The local concentration of bradykinin can be modulated by the tissue renin-angiotensin system, since the angiotensin converting enzyme degradates bradykinin. In the face of increased tissue ACE activity, one would expect lower local bradykinin levels.[5] Conceivably, chronically reduced stimulation of release of EDRF (NO) may be associated with downregulation of the nitric oxide synthase. If this hypothesis is true, ACE inhibition should improve endothelial function by upregulating the cNOS. Indeed, preliminary data suggest that ACE inhibitor therapy improves endothelial dysfunction in the aorta of rats with myocardial infarction or aortic banding.[6,7]

In a recent article by Buikema *et al* published in *Cardiovascular Research*,[8] endothelial dysfunction was demonstrated in the aorta proximal to banding whereas endothelial function was normal distal to banding. In rats with myocardial infarction, endothelial function was impaired in all segments of the aorta. The dilator effect of acetylcholine, an