Exciting treatment of reentrant arrhythmias

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This editorial refers to ‘Expression of skeletal muscle sodium channel (Nav1.4) or connexin32 prevents reperfusion arrhythmias in murine heart’ by E.P. Anyukhovsky et al., pp. 41–50, this issue.

Circulating cardiac excitation was first described by George R. Mines in his seminal publication ‘On dynamic equilibrium in the heart’.¹ Mines recognized the importance of his finding and suggested that circulating excitation may be responsible for ‘some cases of paroxysmal tachycardia as observed clinically’, and directly defined the optimal circumstances for circular excitation: ‘The circumstances under which the phenomenon made its appearance were such as to produce the favourable conditions of slow conduction and short refractory period’.

During acute myocardial ischaemia, [K⁺]₀ is increased which leads to a reduced membrane potential and partial inactivation of the cardiac Na⁺ current (Nav1.5). Secondly, ischaemia leads to intracellular acidification,² which in turn leads to electrical uncoupling by closure of pH-sensitive connexin43 (Cx43) gap junction channels.³ Both reduced excitability and reduced electrical coupling may contribute to the observed conduction slowing during acute ischaemia.⁴

Interventions that suppress the reduction of excitability or electrical coupling during acute ischaemia may prevent slow conduction-related arrhythmias. Anyukhovsky et al.⁵ used gene transfer to explore the effect of such interventions. The rat skeletal Na⁺ channel (Nav1.4), which is less sensitive to depolarization-induced inactivation, was overexpressed in the ventricular myocardium. This overexpression increased the upstroke velocity (Vₘₐₓ) and conduction velocity (CV) of the cardiac action potential under control conditions and reduced these parameters to near normal values under circumstances of simulated ischaemia (high [K⁺]₀ and pH 6.0). Similarly, in a second set of experiments, the overexpression of the pH-insensitive gap junction channel protein Cx32 prevented conduction slowing during ischaemia. Both the overexpression of Nav1.4 and Cx32 reduced VT incidence and duration in a mouse model of ischaemia/reperfusion.⁵ Anti-arrhythmic effects of Nav1.4 overexpression were also observed in the epicardial border zone of a canine infarct model, emphasizing the therapeutic possibilities of this sodium channel.⁶ The effects of overexpression of the native Nav1.5 sodium channel were not studied. This may be of particular interest because the relationship between Vₘₐₓ and the resting membrane potential is quite parallel for both in the range between −75 and −60 mV.⁵ The overexpression of Nav1.5 would lead to an upward shift of this relationship, which may have comparable effects. This would open avenues for therapies with enhancers of the endogenous Na⁺ channel.⁷

The overexpression of Cx32, a pH-insensitive connexin that is able to replace the electrical function of Cx43,⁸ seems most delicate under circumstances of ischaemia. Gap junctions tend to close during ischaemia, which is both protective (by limiting infarct size) and pro-arrhythmic. Reduced expression of Cx43 in mice (Cx43 haploinsufficient mice) resulted in smaller infarcts⁹ but higher arrhythmogeneity.¹⁰ However, the balance between beneficial and adverse effects of Cx overexpression may become much more positive in other contexts.

Several non-ischaemic cardiac pathologies are also characterized by changes in factors that determine CV of the cardiac impulse: reduced Cx43 expression,¹¹ reduced Na⁺ channel expression,¹² and increased collagen deposition.¹³ The heart has a high redundancy (conduction reserve) for these parameters, since isolated changes do not lead to reduced CV or increased arrhythmogeneity.¹⁴–¹⁶ Even a 50% reduction in Cx43 expression combined with a 40% reduction in peak Na⁺ current leads to only a moderate change in CV and not to arrhythmias.¹⁷ However, reduced Na⁺ current or reduced Cx43 expression combined with increased fibrosis lead to severe conduction slowing¹⁵ or arrhythmias.¹⁸ The suppression of collagen deposition normalized conduction and strongly reduced the amount of induced arrhythmias.¹⁹ On the other hand, the normalization of the Na⁺ current or gap junction expression on the background of fibrosis is expected to have similar results. In this respect, the approach of Anyukhovsky et al.³ by overexpressing Na⁺ or gap junction channels in the diseased heart may open anti-arrhythmgonic therapeutic avenues far beyond the scope of acute ischaemia.

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References


