Comments on “Effect of Cellular Uncoupling by Heptanol on Conduction in Infarcted Myocardium”  

The recently published study by Spear and colleagues found that in dog ventricles heptanol decreased conduction velocity more readily in infarcted tissue. They conclude that “the abnormality in conduction was due to an abnormality in gap junction distribution and/or function in the infarcted region.” This conclusion rests on the assumption that heptanol is a “relatively selective” blocker of gap junctional conductance (over sodium conductance). Although heptanol has been shown to decrease gap junctional conductance,2 evidence exists to show that it also has an important effect on sodium conductance over the same concentration range.

The evidence that “heptanol does not act primarily by way of depressing the fast inward current” comes from experiments in multicellular tissue in which the maximal upstroke velocity of the action potential (Vmax) was used as an index for sodium current (INa). But Vmax has been shown to be a nonlinear measure of INa in single cells,3 and the relation between Vmax and INa is even less clear during a conducted action potential, especially when internal resistance is changed. An increase in Vmax as internal resistance is increased has been predicted in numerical simulations4,5 and observed in experiments.6 If internal resistance was selectively increased by heptanol, then an increase in Vmax might be expected. The “slight effect (10.7% decrease)” on Vmax that they observed may actually represent a large decrease in INa.

Experimental studies confirm that heptanol has a marked effect on INa. In nerve, heptanol decreases INa for concentrations of 0.5–1.0 mM. Because cardiac sodium channels differ from nerve sodium channels in their susceptibility to block by various agents (e.g., tetrodotoxin), it is important to confirm that heptanol blocks cardiac INa. Subsequent to the publication of the work by Spear et al.,1 we have reported8 that heptanol blocks INa in dog cardiac Purkinje cells with half-block occurring at about 1 mM. Moreover, heptanol shifted the steady-state availability for INa to more negative potentials. This means that heptanol would amplify the effects of ischemia-induced depolarization on INa availability. We conclude the heptanol causes important block of INa in concentrations used in studies on conduction.1,6 and that it cannot be considered even a relatively selective blocker of gap junctions. Conclusions about INa from Vmax measurements must be made carefully, if at all. Infarction may well affect gap junctions, but the possible effects of ischemia on active membrane properties must also be considered.

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References


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Reply to the Preceding Letter

The work of Nelson and Makielski1 that was reported at the last Biophysical Society meeting verifies what others have found in different systems: namely, that heptanol and octanol can reduce sodium current (INa). Taken together, these studies also show the variability in the magnitude of the effect that is species and tissue dependent. The authors also make the well-known points in their letter to the editor that the relation between INa and the maximal upstroke velocity of the action potential (Vmax) is nonlinear and that, because of the complex interaction between active and passive properties, Vmax is influenced by cable properties.

We do not dispute that in a given system at some concentration heptanol’s effect on INa might play a significant role in modifying conduction, and one must be aware of this. However, we are surprised that the authors have chosen to explain our findings of a selective heptanol effect on abnormal conduction in infarcted tissues in terms of an amplification of “ischemia-induced depolarization on INa availability.”

In addition to the hazard of speculating on what might happen to conduction in epicardial strips by extrapolating findings from the effects of heptanol on INa in single Purkinje cells, there are several other issues in our studies that have been misinterpreted or ignored. First, we were studying healed, mottled infarcts, not ischemic tissue. The tissues are not depolarized and the Vmax were normal even in the most abnormally conducting areas. Second, evidence obtained from cells of different species suggests that heptanol is a more potent uncoupler than it is a fast current depressor.1,8 The authors found half-block of peak INa at 1.3 mM in canine Purkinje cells.1 Half-block of junctional conductance in guinea pig ventricular myocyte pairs occurs at the much lower concentration of 0.16 mM.8 Third, seven of our 10 conduction studies in infarcted tissues were performed at 0.2 mM. This concentration has minimal effects on conduction in normal canine epicardium and in normally conducting regions of infarcted epicardium. However, it had profound effects on abnormal conduction. For these reasons, we concluded that the selective effect of
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_Circ Res._ 1990;67:1299-1300
doi: 10.1161/01.RES.67.5.1299

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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