**RAISING ION CHANNEL CURRENTS TO PREVENT ARRHYTHMIAS**

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*Introduction*: Ion channel blocking drugs are used to treat arrhythmias. Nevertheless, antiarrhythmic drug use is complicated by proarrhythmic risk. We tested whether raising ion channel levels would be an alternative antiarrhythmic strategy with less proarrhythmic risk.

*Methods*: Myocardial infarction (MI) was induced in 12-week-old mice by coronary artery occlusion. MI mice were treated with c-Src inhibitors (PP1 or AZD0530), PP3 (an inactive analogue of PP1), or saline. Nonischemic cardiomyopathy was induced in C57BL/6 mice by hypertension after unilateral nephrectomy, deoxycorticosterone acetate (DOCA) pellet implantation, and salt water substitution. Human explanted hearts were studied using optical mapping.

*Results*: After MI, PP1 raised Cx43 expression by 69% in the scar border (p = 0.048) and by 73% in the distal ventricle (p = 0.043) compared with PP3 mice. PP1-treated mice had restored conduction velocity at the scar border (PP3: 32 cm/s, PP1: 41 cm/s, p<0.05) and lower arrhythmic inducibility (PP3: 71%, PP1: 35%, p<0.05) than PP3 mice. Compared to the sham mice, the ejection fraction of nonischemic cardiomyopathic mice was reduced (37.1±1.8% vs. 49.4±3.7%, P=0.05). Sodium current (INa) was decreased (60±10% of sham, P=0.01). Injection of NAD+ (100 mg/kg) or mitoTEMPO (0.7 mg/kg) twice (at 24 h and 1 h before myocyte isolation) to animals restored INa. Correlating with the mouse model, failing human hearts showed a reduction in conduction velocity that improved with NAD+.

*Conclusions*: In summary, sodium channels and connexins are downregulated in cardiomyopathy. Strategies that raise these ion channel levels reduce arrhythmic risk without apparent proarrhythmic complications.