Inhibition of HCN Overexpressed in Failing Heart of Dilated Cardiomyopathy Mouse Model by Ivabradine Prevents Sudden Arrhythmic Death

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Growing evidence demonstrates that the hyperpolarization-activated cyclic nucleotide gated channels (HCNs) is overexpressed in failing hearts and potentially involved in increased arrhythmogenicity. Inhibiting HCN channels could be a promising approach to preventing lethal arrhythmias associated with heart failure. Transgenic mice expressing a dominant-negative mutant of neuron-restrictive silencer factor specifically in the heart (dnNRSF-Tg) exhibit dilated cardiomyopathy and sudden arrhythmic death, accompanied with the increased ventricular HCNs expression. We examined the effects of ivabradine (Iva, 7 mg/kg/d), a specific HCN channel inhibitor on survival and arrhythmogenicity in dnNRSF-Tg and found that Iva significantly improved the survival among dnNRSF-Tg. Iva significantly reduced ventricular arrhythmias in dnNRSF-Tg in ECG telemetry analysis and isoproterenol-induced increase in spontaneous action potentials in ventricular myocardies from dnNRSF-Tg, suggesting that Iva improved the survival by preventing lethal arrhythmias. We also found that transgenic mice overexpressing HCN2 in the heart are highly susceptible to arrhythmias induced by chronic isoproterenol infusion. Our findings demonstrate the contribution of increased ventricular expression of HCNs to the increased arrhythmogenicity and define HCN inhibition by Iva as an useful therapeutic approach to preventing lethal arrhythmias.

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