Late sodium current is increased in ventricular myocytes from failing human hearts compared with non-failing hearts

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The action potential duration is prolonged in cells isolated from left ventricles of failing hearts. Studies of ion channel remodeling in heart failure have focussed on K⁺ channel down-regulation to account for this prolongation. Na⁺ current that persists late after the peak has passed has been shown to influence the action potential duration, and animal studies have suggested increased late Na⁺ current in heart failure. In this study we show that late Na⁺ current is significantly increased in ventricular myocytes from failing human hearts when compared to cells from non-failing hearts. This late Na⁺ current may contribute to action potential prolongation and a tendency to arrhythmia in failing human hearts.

Methods
Human heart explants were obtained at the time of surgery; failing hearts were obtained from patients undergoing transplant, and non-failing hearts were obtained from donated hearts that were not transplanted for technical reasons. Left ventricular myocytes were obtained from human hearts by enzymatic isolation techniques involving perfusion a portion of the LAD vascular bed. Sodium currents (I_Na) were studied at 22 °C by whole cell voltage clamp. The pipette (0.5 MΩ) contained (in mM): 20 CsCl, 120 CsF, 10 EGTA, 5 HEPES, 10 TEA-Cl, pH 7.3 for the pipette solution and 5 NaCl, 90 CsCl, 1 CaCl₂, 1.2 MgCl₂, 11 glucose, 5 HEPES, 10 TEA-Cl, pH 7.3 in the bath solution. Reduced Na was necessary to obtain good voltage control. A combination of Ni²⁺ 200 µM, Nifedipine 20 µM, and DIDS 200 µM were added to the bath solution to block contaminating currents. I_Na was elicited by a 750 ms voltage step to -20 mV from a holding potential of -140 mV. Late Na⁺ current (I_NaL) was defined as the mean current at 750 ms after the start of the depolarizing step. Currents were measured after passive leak subtraction.

Results
Representative I_Na traces (Fig. 1) show that the I_Na from the failing myocyte has more late current than non-failing myocyte. Peak I_Na are off scale, and the ordinate is compressed to show the late currents. Figure 2 show summary data for I_NaL. I_NaL was significantly greater for the failing cells. The data shown are means ± SD for 4 cells from 1 non-failing heart, and 7 cells from 2 failing hearts.
Figure 1 – Na⁺ current traces from cells from normal and failing hearts. Depolarization to -0 mV, current scale in pA.

hearts. Notice that the variability of IsNaL (as indicated by the SD of the mean) is greater in heart failure. The currents in this figure were normalized to the peak current obtained in the same cell. We have also analyzed the non-normalized data, and currents normalized to cell capacitance and the differences remain significant and the variability remains increased in the heart failure cells.

Discussion
Sudden cardiac death is a major health problem, and the majority of deaths occur in the setting of structural heart disease such as heart failure. The ion current alterations underlying arrhythmia in heart disease, sometimes called electrical remodeling, are subject to intense investigation¹,². In general, action potential durations are prolonged in heart failure and this may be arrhythmogenic by a number of mecha-

isms. Ion channels affecting action potential duration, therefore, have come under intense scrutiny, particularly outward K⁺ currents that terminate the action potential. Late IsNa also contributes to action potential configuration in heart³ but it is much less studied than K⁺ currents. IsNaL exists in human hearts⁴, and we report here that IsNaL is significantly greater in heart failure cells compared with cells from normal human hearts. Increased IsNaL has also been shown in animal models of heart failure⁵. IsNaL may be modulated by cell signaling pathways⁶,⁷ and these modulators are altered in heart failure⁸. It will be important to determine the mechanisms for this increased IsNa in heart failure, and how it maybe arrhythmogenic.

References