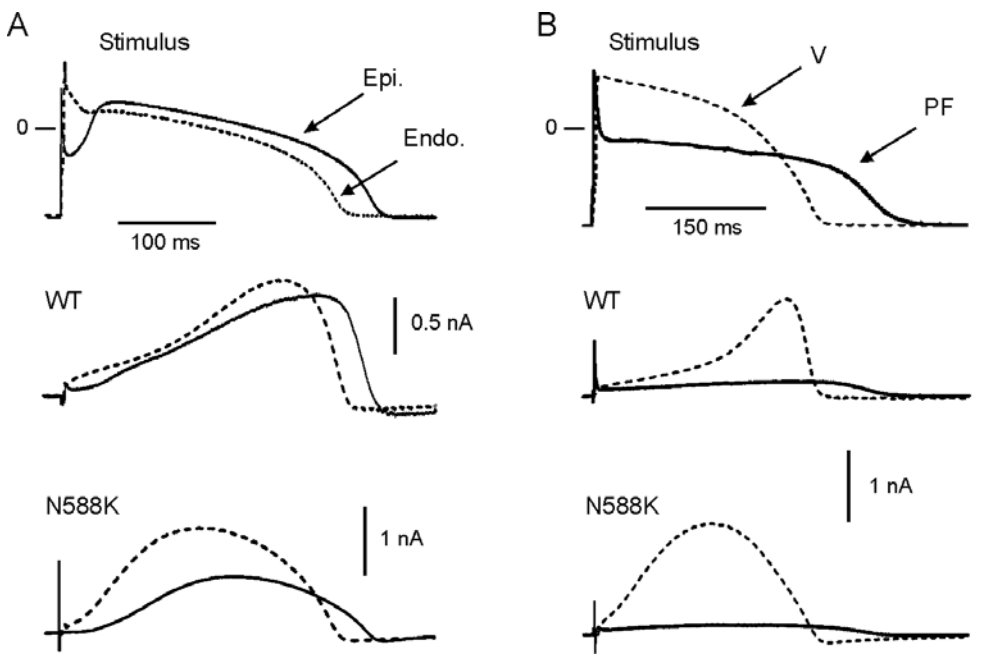

Online figure: The amplitude of N588K currents is more dependent on the early phases of the action potential than that of wild-type (WT) currents. This set of experiments was designed to compare the effects of the epicardium (Epi), endocardium (Endo) and Purkinje fibres (PF) action potential configuration on the amplitude and waveform of WT and N588K currents. A) To test the effects of the deep repolarization during phase 1 of the epicardial action potentials, pre-recorded action potentials from the ventricular epi- and endocardium of dog hearts were used as stimulus to elicit WT (middle panel) and N588K (bottom panel) currents. WT currents activated slowly during phases 1 and 2, buth their amplitude increased more rapidly during phase 3 of both action potentials because the channels recovered rapidly from inactivation and reopened, thus creating the "hump"-like waveform of the current. The configuration of the epi- and endocardial action potentials did not substantially modify the shape and amplitude of WT currents. N588K currents monotonically followed the amplitude of the ventricular action potentials and reached larger amplitudes than WT currents during both stimuli. The lack of inactivation of N588K channels resulted in a dome-shaped current waveform. The more depolarized phase 1 of the endocardial action potential activated more channels early on and increased the amplitude of the currents compared with those of the epicardium. In contrast, phase 1 of the action potentials had little effect on WT current amplitude. These results show that, as opposed to WT, the N588K current is strongly modulated by the amplitude of phase 1 repolarization and thus is likely to create differences in repolarization times (heterogeneity) between the epi- and endocardium layers of the ventricles. B) Representative currents elicited during action potential clamps using pre-recorded action potentials from a ventricular (V) and Purkinje fibre cell. N588K and WT current amplitudes and shapes elicited by the PF action potential were very similar. In sharp contrast, N588K currents elicited by the ventricular action potential had a more rapid onset or activation and larger amplitude than WT. These results suggest that the contribution of the N588K current will be larger than WT in the ventricles but not significantly different in the Purkinje fibres. Thus, N588K-induced shortening of the action potential will be more important in the ventricles than in the Purkinje fibres. The shorter action potentials in the ventricles alongside the longer action potentials in the Purkinje fibres are likely to specifically reduce the ventricular refractory period and create reentrant or tachyarrhythmias triggered by the longer Purkinje fibre action potentials. (Reproduced, with permission, from ref. 8.)