ACTIONS OF FLECAINIDE ON PHASE-2 VENTRICULAR ARRHYTHMIAS DURING INFARCT EVOLUTION IN RAT ISOLATED PERFUSED HEARTS

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Flecainide (FL) increased mortality following myocardial infarction (MI) in the Cardiac Arrhythmias Suppression (CAST) trial (Echt *et al.,* 1991) by a mechanism that was not determined, but that has been speculated to involve an exacerbated risk of ventricular arrhythmias (VA) during the early phase of ischemia or, later, during infarct evolution (Greenberg *et al.,* 1995; Hallstrom *et al.,* 1995). Previously we found a weak proarrhythmic effect of FL on the "phase-1" arrhythmias occurring during early ischaemia in a perfused rat heart model (Farkas *et al.,* 2002). Here we examined whether FL can exacerbate the "phase-2" VA that occur during infarct evolution, using a model with low baseline phase-2 VA susceptibility (Clements-Jewery *et al.,* 2005).

Male Wistar rats (180-250g) were anaesthetized with 60 mg kg^{-1} pentobarbitone (i.p.) plus 250 iu heparin. Excised hearts were perfused (Langendorff mode) with Krebs' modified to contain 3 $meql^{-1}$ K^+. The left main coronary artery was ligated for 240 min. Phase-2 VA occur >90 min after the onset of ischaemia (Clements-Jewery *et al.,* 2005), so test solutions were introduced at 90 min. Hearts (n=8/group) received 0.74 or 1.48 μM FL, representing the peak unbound plasma and total blood concentrations, respectively, at therapeutic dosage (Farkas *et al.,* 2002; Woosley *et al.,* 1984), or vehicle (0.018% ethanol in Krebs'). Because it has been speculated that an interaction between catecholamines (CA) and FL contributes to FL's proarrhythmic propensity (Packer *et al.,* 1997), the protocol was repeated in separate hearts with 313 nM norepinephrine plus 75 nM epinephrine co-perfused with FL from 90 min. This CA protocol restores heart rate to levels seen *in vivo*, and increases coronary flow and QT interval, and shortens PR interval, by activation of cardiac β_1 and α_1 receptors (Clements-Jewery *et al.,* 2002). Standard statistical methods were used (Clements-Jewery *et al.,* 2002).

Phase-1 ventricular fibrillation (VF) occurred in 88-100% of hearts in each group ($p>0.05$). FL caused no increase in the incidence of phase-2 VF (0% in all 3 groups), tachycardia (VT; range of incidences 13-25%) or premature beats (VPBs; 50-75%). The high FL concentration slowed heart rate by <10% ($P<0.05$) but had no other vascular or ECG effects. CA had the expected vascular and ECG effects (all $p<0.05$) noted above, and these were not altered by FL co-perfusion. CA caused a weak non-significant increase in phase-2 VF, VT and VPB incidence, but there was no proarrhythmic interaction with FL (incidence ranges, 0-25%, 0-38% and 75-100%, respectively).

In conclusion, FL-induced proarrhythmic activity does not appear to encompass independent facilitation of phase-2 VA, or a phase-2 interaction with CA.

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