ROSIGLITAZONE ALTERS CHARACTERISTICS OF ISCHEMIC VENTRICULAR FIBRILLATION IN PIGS

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Background: Despite favorable metabolic effects of anti-diabetic thiazolidinedione drugs (TZDs), it is uncertain if TZDs reduce cardiovascular mortality. We previously showed that TZDs exert an off-target effect to block cardiac ATP-sensitive potassium (KATP) channels and may increase propensity for ischemic ventricular fibrillation (VF) in pigs. In this study, we tested the hypothesis that a TZD drug, rosiglitazone (ROSI), alters spectral characteristics of ischemic VF through effects on KATP channels.

Methods: Anesthetized, open-chest pigs underwent occlusion of the left anterior descending coronary artery 90 min after treatment with ROSI (1 mg/kg IV, n=7), the prototypical KATP blocker glyburide (GLY, 1 mg/kg IV, n=7) or inert vehicle (VEH, n=6). As KATP opening is required for ischemic preconditioning (IPC), additional experiments compared effects of ROSI or VEH on VF characteristics (n=12) or success of defibrillation (n=59) when IPC preceded coronary occlusion. Surface ECG power spectrum was computed by fast Fourier transform. Median frequency and edge frequency (below which 95% of power resides) were determined during the initial 30 sec of VF.

Results: Out of a total of 91 pigs, 86 developed ischemic VF. Total spectral energy of VF did not differ among the groups. ROSI, compared to VEH, had higher VF median frequency (10.1±0.4 vs 8.6±0.3 Hz, p=0.02) and edge frequency (11.4±0.4 vs 10.1±0.4 Hz, p=0.02). GLY recapitulated these results, with median and edge frequencies 10.3±0.2 and 12.1±0.2 Hz, both higher than VEH (p<0.01). After IPC, ROSI also increased VF median frequency compared to VEH (10.0±0.3 Hz vs 8.7±0.2 Hz, n=6 each group, p<0.01). Moreover, 74% of pigs were refractory to internal defibrillation after IPC/ROSI, compared with 33% after IPC/VEH (p=0.02).

Conclusions: ROSI shifts the spectrum of ischemic VF to higher frequency. This effect is recapitulated by GLY suggesting that it is due to KATP blockade, and occurs with or without IPC. ROSI also impairs success of defibrillation of ischemic VF after IPC. These findings indicate that ROSI has previously unsuspected potential to alter the characteristics of ischemic VF in a manner that may adversely impact cardiovascular mortality.