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SELECTIVE LATE INa INHIBITION BY GS967 EXERTS POTENT SUPPRESSION OF CATECHOLAMINE-INDUCED VENTRICULAR TACHYCARDIA

Poster Contributions

Poster Hall B1

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Background: Catecholamines can elicit early and delayed afterdepolarizations (EADs and DADs), resulting in ventricular tachyarrhythmias. As late sodium current (INa) inhibition suppresses EADs and DADs, we examined whether GS967, a selective inhibitor of late INa that is devoid of beta-adrenergic blocking action, can prevent VT induction in an intact porcine model of epinephrine infusion following bilateral vagotomy.

Methods: In 6 closed-chest anesthetized Yorkshire pigs, spontaneous VT was induced by epinephrine administration (2.0 µg/kg, i.v., bolus over 1 min). Effects of GS967 (0.4 mg/kg, i.v., infused over 30 min) on VT incidence were investigated using intraventricular electrocardiogram recordings. A decapolar electrode catheter was positioned on left ventricle to monitor T-wave alternans (TWA) measured by modified moving average method.

Results: Epinephrine elicited spontaneous VT in 6 of 6 pigs and significantly elevated T-wave alternans (TWA) by 29-fold compared to baseline ($p < 0.001$). GS967 reduced TWA level by 55% (from 139.83 ± 13.17 to 62.17 ± 12.13 µV, $p < 0.01$) at 30 min after GS967; by 62% (53.33 ± 8.33 µV, $p < 0.01$) at 60 min, and by 50% (to 69 ± 14 µV, $p < 0.01$) at 90 min (mean \pm SEM). GS967 reduced 3- to 7-beat VT occurrence by 55% (from 9.5 ± 2.72 to 4.28 ± 0.76 beats/2 min, $p = 0.020$), and ≥ 8 -beat VT by 58% (from 1.6 ± 0.47 to 0.67 ± 0.42 beats/2 min, $p = 0.033$).

Conclusion: Selective late INa inhibition with GS967 confers significant protection against catecholamine-induced TWA and VT.

