**988-99**

L-Arginine Reduces the Increased Incidence of Ventricular Arrhythmias During Sympathetic Stimulation in Dogs with Acute Coronary Artery Occlusion

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Nitric oxide (NO) modulates autonomic effects on mechanical and electrophysiologic function of the heart. Whether NO influences the prevalence of ventricular arrhythmias (VA) enhanced by sympathetic stimulation (SS) is unknown. We studied the influence of the NO precursor, L-arginine (LA), on the incidence of spontaneous VA during SS in 15 autonominously denervated dogs undergoing repeated 7 min occlusions of the left descending coronary artery. Bilateral SS (4 Hz, 4 ms, 4–15 volts) was delivered to decentralized stellate ganglia. The effects of LA (100 mM) were assessed by infusing the drug into the pericardial sac for 30 min where it supersedes cardiac vagal and sympathetic nerves. The study protocol and results are shown in the figure. Seven dogs were eliminated because they had no VA during SS. The incidence of VA significantly increased during SS, while LA reduced this increase caused by SS. After washout of LA, the incidence of VA increased to the same degree as before pericardial superfusion with LA (p = 0.600).

Conclusions: Intrapericardial LA reduces the increased incidence of ventricular arrhythmias during SS in dogs with acute coronary occlusion, which may relate to LA-related modulation of sympathetic activity.

**988-100**

A Coronary Selective ATP-sensitive Potassium Channels Opener, JTV-506, Improves Myocardial Ischemia without Alteration of Systemic Hemodynamics in the Canine Hearts

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ATP-sensitive K+ channels opener (KCO) mediates cardioprotective effects. However, an intravenous administration of KCO may acutely reduce blood pressure, which blunts the cardioprotection of KCO activating sympathetic tones and renin-angiotensin systems. Since experiments using coronary vascular rings revealed that JTV-506, a new KCO, is coronary-selective, we tested if intravenous administration of JTV-506 mediates cardioprotection on ischemic hearts without alteration of systemic hemodynamics. In 20 dogs, the left anterior descending coronary artery (LAD) was perfused with blood from the carotid artery. When we administered JTV-506 (1, 2, 4, 6 and 8 μg/kg) into the systemic vein, coronary blood flow (CBF) increased dose-dependently from 92 ± 1 to 110 ± 5 ml/100 g/min without reduction of aortic blood pressure (AoP: 107 ± 2 and 102 ± 4 mmHg). When doses of JTV-506 increased to 16 μg/kg, CBF decreased to 101 ± 3 ml/100 g/min with decreased AoP (87 ± 5 mmHg). In the ischemic heart due to the constant reduction of coronary perfusion pressure (CPP: 52 ± 5 mmHg), CBF (53 ± 1 ml/100 g/min), fractional shortening (FS: 12 ± 1%) and lactate extraction ratio (LER: 0.3 ± 2.1%) decreased. JTV-506 of 4 μg/kg increased CBF from 53 ± 1 to 74 ± 4 ml/100 g/min, while CPP and AoP were unchanged (58 ± 3 and 101 ± 3 mmHg). End-Epil flow ratio increased from 0.73 ± 0.05 to 0.84 ± 0.04, and PS (17 ± 2%) and the pH in coronary venous blood (7.18 ± 0.05 to 7.36 ± 0.02) were also increased. Norepinephrine, renin activity and angiotensin II concentration in the systemic venous blood was not increased due to 8 μg/kg JTV-506 (388 ± 146 vs. 182 ± 85 pmol/ml, 11.1 ± 1.7 vs. 11.8 ± 1.3 ng/ml/min, 653 ± 176 vs. 565 ± 53 pg/ml).

We conclude that JTV-506 can mediate the selective coronary vasodilation and improvements of myocardial ischemia without affecting systemic blood pressure, sympathetic tones and renin-angiotensin systems. This coronary selective new ATP-sensitive K+ channel opener, JTV-506, may be promising for the treatment of ischemic heart disease.