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 aortic blood pressure, which blunts the cardioprotection of KCO activating sympathetic 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 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/Epi flow ratio increased from 0.73 ± 0.05 to 0.84 ± 0.04, and FS (17 ± 2%) and LER (16 ± 3%) and the pH in coronary venous blood (7.18 ± 0.05 to 7.36 ± 0.02) were also increased. Noradrenaline, renin activity and angiotensin II concentration in the systemic venous blood was not increased due to 8 µg/kg JTV-506 (389 ± 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 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.