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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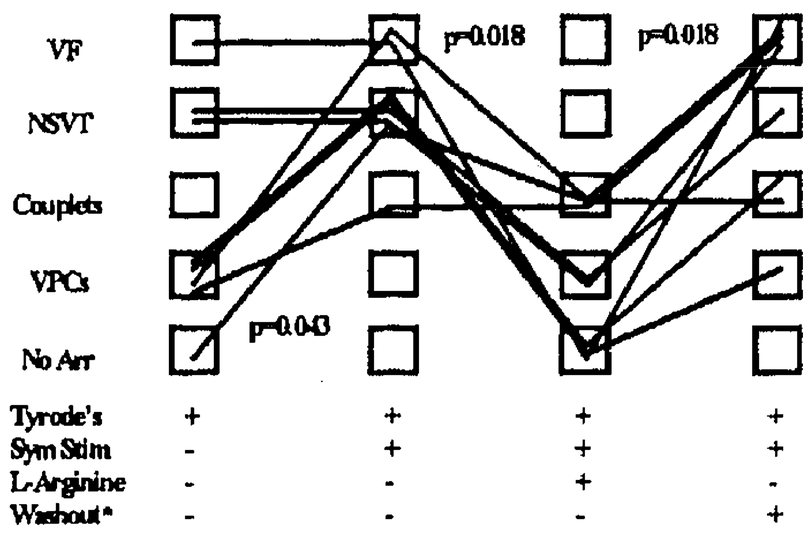
Nitric oxide (NO) modulates autonomic effects on mechanical and electrophysiologic function of the heart. Whether NO influences the prevalence of ventricular arrhythmias (VA) enhanced by sympathetic stimulation (SS) is unknown. We studied the influence of the NO precursor, L-arginine (LA), on the incidence of spontaneous VA during SS in 15 autonomically 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 superfused 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 aortic 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 μ g/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 μ g/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%), LER (16 ± 3%) 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 (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, sympathetictonesandrenin-angiotensin systems. This coronary selective new ATP-sensitive K^+ channel openers, JT-506, may be promising for the treatment of ischemic heart disease.

988-101 Co-Localization of C-Reactive Protein and Complement in Human Hearts during Acute Myocardial Infarction

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C-reactive protein (CRP) plasma levels correlate with clinical outcome in patients with myocardial ischemia and infarction. We hypothesized that these correlations might reflect active participation of CRP in the local inflammatory response ensuing in the jeopardized myocardium, since upon binding to a ligand CRP is able to activate the classical pathway of complement. In addition, complement activation has been shown to occur locally in human infarcted myocardium. To verify our hypothesis, we investigated immunohistochemical localization of CRP, in relation to deposition of complement, in tissue specimens of infarcted and normal heart tissues obtained from 17 patients, who had died following acute myocardial infarction (AMI). CRP was found to be deposited only in infarcted regions and not in normal appearing areas of human myocardium, being co-localized with depositions of C4- and C3-activation fragments of the complement system. Deposition of CRP and complement in infarcted myocardium appeared to be time-dependent since it was found in all infarctions except for one of very short duration (<12 hours) and two of long duration (>1 year).

Conclusion: CRP may localize in infarcted human heart tissue. As CRP was found co-localized with complement, we suggest that this acute phase protein promotes local complement activation, and hence tissue damage in AMI.

988-102 Early Refractoriness of Platelet GPIIb–IIIa in Myocardial Infarction Survivors

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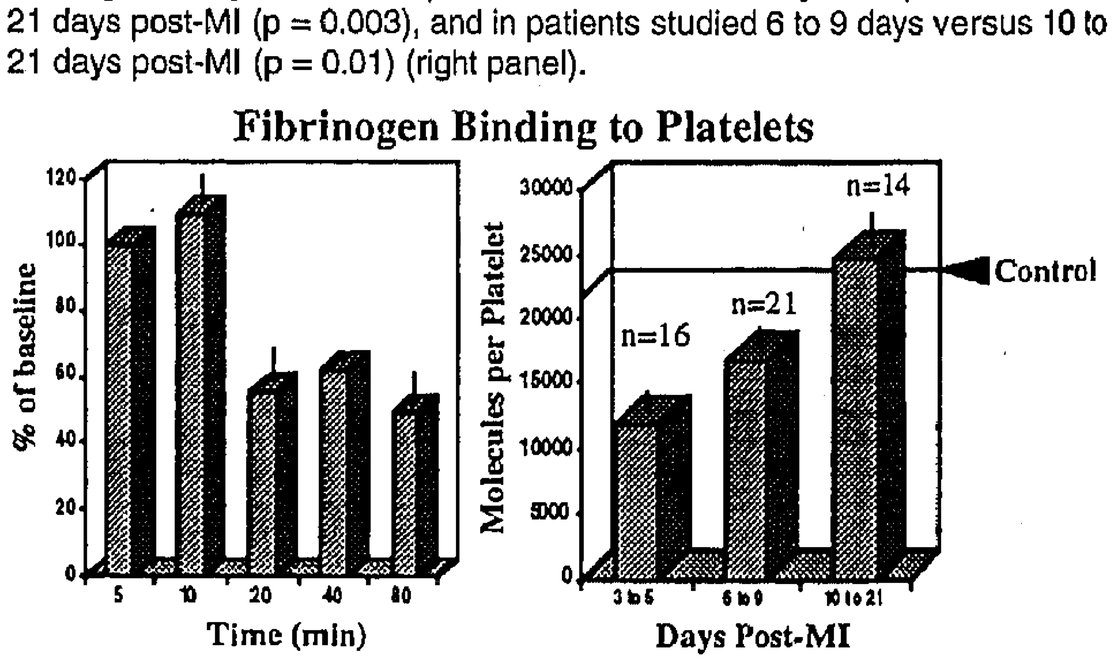
Aggregation of platelets is mediated by the binding of fibrinogen to the activated conformation of integrin αIIb-β3 (GPIIb–IIIa) on the platelet surface. With time after exposure of normal platelets to a stimulus (TRAP, 50 μM), platelets lose the capacity to bind fibrinogen (left panel). Others have shown that this refractoriness of GPIIb–IIIa is due to internalization of the receptor and is associated with loss of platelet aggregability. Platelet aggregation within a coronary vessel corresponds to the triggering step in the development of myocardial infarction (MI). We hypothesized that in survivors of myocardial infarction, GPIIb–IIIa refractoriness might occur. To test this hypothesis, we analyzed the platelets of 51 post-MI patients, 3 to 21 days after their events. Binding of fibrinogen to activated platelets ex vivo (1 μM ADP) was significantly reduced in patients studied 3 to 5 days compared to 10 to 21 days post-MI ($p = 0.003$), and in patients studied 6 to 9 days versus 10 to 21 days post-MI ($p = 0.01$) (right panel).



Based on these data, it is tempting to speculate that platelets from MI-survivors undergo a period of refractoriness that might play an important role in limiting the thrombotic process affecting the coronary vessels of these patients.