Coronary release of t-PA

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Abstract

Background: Tissue type plasminogen activator (t-PA) is the most important initiator of intravascular fibrinolysis. t-PA is synthesised and stored in endothelial cells. A regulated release of the enzyme from this storage pool is important for removal of intravascular fibrin formations. Plasminogen activator inhibitor type-1 (PAI-1) is the main inhibitor of t-PA. The aim of this thesis was to study the effects of local and general stress activation on the capacity for regulated coronary release of t-PA and to explore the role of β-2 receptor dependent mechanisms in this context. Further, we aimed to study the relation between coronary artery disease (CAD) and coronary t-PA release during cardiac surgery.

Methods: Three studies were performed in an acute pig model. The fourth study was conducted in patients with (n=14) and without CAD (n=8). The net fluxes of t-PA and PAI-1 across the coronary vascular bed was studied during anaesthesia, at baseline and during stimulation by different stressors. Arterial-venous concentration gradients of t-PA (total and active) and PAI-1 were obtained for the coronary vascular bed together with coronary blood flows (retrograde termodilution), from which coronary net release could be derived. Myocardial ischemia-reperfusion (by temporary coronary artery ligation) and sternotomy were chosen to represent stress activation at organ and systemic levels, respectively. Intracoronary infusion of isoprenaline (beta-2 receptor agonist) was used for activation of local adrenergic mechanisms, while atrial pacing was used to provoke changes in heart rate and coronary blood flow.

Results: *In the pig model*, a release of t-PA into the coronary vascular bed was produced by ischemia-reperfusion, intracoronary isoprenaline and sternotomy. A rapid net release of t-PA, returning towards baseline levels in about 10 minutes was observed. *In the clinical study*, CAD patients showed a markedly impaired capacity for regulated coronary t-PA release after sternotomy as compared to non-CAD patients. Increases in heart rate and coronary blood flow (by atrial pacing) did not influence the release of t-PA or PAI-1.

Conclusion: These findings support the hypothesis that stress, at different levels of actions, can initiate a t-PA dependent, adrenergically mediated, fibrinolytic response in the coronary vasculture. One key finding was the that the capacity for regulated coronary t-PA release was reduced in patients with CAD. Atherosclerosis itself can explain the attenuation of regulated t-PA release in the vessels compromised by arteriosclerotic plaque. The decreased endothelial capacity for t-PA release could be a significant mechanism in the high incidence of coronary thrombosis in CAD patients.

Key words*:* tissue-type plasminogen activator, plasminogen activator inhibitor type-1, endothelium, ischemia, beta-stimulation, surgery, heart rate.

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