Pharmacological stimulation of endothelial function and long-term impact of hypertension in man

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet, kommer att offentligen försvaras i Jubileumsaulan, Gula Stråket 2B, Sahlgrenska Universitetssjukhuset/Sahlgrenska, Göteborg,
Torsdagen den 26 maj 2016 kl. 13.00

av

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Solna

Avhandlingen baseras på följande arbeten:

Study I — Acute vascular effects of atorvastatin in hypertensive men: a pilot study. Saluveer O, Bergh N, Grote L, Andersson O, Hrafnkelsdottir TJ, Widgren BR.
Scand Cardiovasc J. 2013;47(5)275-80

Study II — The impaired fibrinolytic capacity in hypertension is unaffected by acute blood pressure lowering. Ridderstråle W, Saluveer O, Carlström M, Jern S, Hrafnkelsdottir TJ.
J Thromb Thrombolysis. 2011;32(4):399-404

Study III — Profibrinolytic effect of the epigenetic modifier valproic acid in man. Saluveer O, Larsson P, Ridderstråle W, Hrafnkelsdóttir TJ, Jern S, Bergh N.
PLoS One. 2014 Oct 8;9(10):e107582

Study IV — Hypertension is associated with increased mortality in patients with acute coronary syndromes after revascularization with percutaneous coronary intervention – a report from SCAAR. Ott Saluveer, Björn Redfors, Oskar Angerås, Christian Dworeck, Inger Haraldsson, Petur Petursson, Jacob Odenstedt, Dan Ioanes, Peter Lundgren, Sebastian Völz, Truls Råmunddal, Bert Andersson, Elmir Omerovic, Niklas Bergh.
Submitted

UNIVERSITY OF GOTHENBURG

2016

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ABSTRACT

Background: Ischemic heart disease is a major cause of death globally. Rupture of a coronary atherosclerotic plaque with occluding thrombus formation is the main cause of myocardial ischemia and infarction. A healthy vascular endothelium is pivotal for maintenance of vessel patency and normal blood flow, which is important for prevention of thrombotic events. In the event of an intra-arterial thrombosis formation the endothelium reacts with vasodilation and activation of the endogenous fibrinolytic system. Endothelial dysfunction (ED) is a common denominator in patients with different cardiovascular risk factors including hypertension. ED promotes a vasoconstrictive, prothrombotic, and proinflammatory state. ED in hypertension is associated with impaired endothelium-dependent vasodilation (EDV) and impaired endogenous fibrinolysis measured as acute stimulated t-PA (tissue plasminogen activator) release. Hypertension confers a prothrombotic state and ED could be an important contributor to the increased risk for atherothrombotic events.

Aims: The overall aim of this thesis was to pharmacologically improve endothelial function in hypertension and normotension, and to investigate the long-term prognostic impact of hypertension. The aim of Study I-II was to investigate if pharmacological intervention by atorvastatin (ATV) or sodium nitroprusside (SNP) may improve vascular function in terms of EDV or fibrinolytic capacity, respectively, in hypertensive men. The aim of Study III was to evaluate if histone deacetylase inhibition by valproic acid (VPA) affects the endogenous fibrinolytic system, measured as t-PA release capacity or plasminogen activator inhibitor-1 (PAI-I) levels in a cohort of healthy men. The aim of Study IV was to investigate the long-term prognostic impact of hypertension on the mortality after percutaneous coronary intervention (PCI).

Methods: In the clinical experimental studies, venous occlusion plethysmography and intra-brachial infusion of vasoactive substances were used to assess endothelium-dependent vasodilation (EDV), and endothelium-independent vasodilation (EIDV) or vasoconstriction responses in the forearm (Studies I-III). The perfused forearm model was used to measure stimulated t-PA release capacity (Studies II-III) in the forearm. t-PA Release was stimulated by intra-brachial infusion of Substance P. Long-term prognostic impact of hypertension on total mortality after PCI was investigated in a large register study using the Swedish Coronary Angiography and Angioplasty Register (SCAAR), in which data were analyzed for 175.892 patients.

Results: ATV treatment did not improve EDV acutely in hypertensive men. Forearm vascular resistance in response to SNP was lowered by ATV, and vasoconstriction in response to Angiotensin II (Ang II) was diminished by ATV treatment. Acute blood pressure lowering by SNP did not affect Substance P induced t-PA release capacity in patients with hypertension. VPA treatment resulted in considerably decreased levels of circulating PAI-1 antigen, and the t-PA:PAI-1 antigen ratio increased. Acute t-PA release in response to Substance P was not affected by VPA. The SCAAR-study showed that hypertension is associated with higher mortality risk in patients undergoing PCI in Sweden, and the risk was highest in patients less than 65 years, in smokers and in patients with ST-elevation myocardial infarction (STEMI).

Conclusions: The observed acute statin effects in hypertension seem to be endothelium-independent and related to vascular smooth muscle cell function. Acute blood pressure lowering does not restore the impaired fibrinolytic capacity in hypertension, suggesting a diminished releasable t-PA pool in the endothelium. Intervention by VPA treatment did not affect the acute stimulated t-PA release capacity in healthy man. In contrary, VPA diminished plasma PAI-1 antigen levels and altered the fibrinolytic balance, measured as t-PA:PAI-1 ratio in a profibrinolytic direction. Further studies are needed to confirm fibrinolytic effects of histone deacetylase inhibitors in patients with ED, e.g. established atherosclerosis. A long-term adverse impact of hypertension diagnosis on survival after PCI was demonstrated in a large-scale register study, and the highest risk was found in patients with STEMI. These findings underscore the importance of optimal secondary prevention including blood pressure control in patients with coronary artery disease.

Keywords: t-PA, hypertension, fibrinolysis, endothelial function, valproic acid, histone deacetylase inhibitor, atorvastatin, percutaneous coronary intrervention, acute coronary syndromes

ISBN: 978-91-628-9763-5 (Print) http://hdl.handle.net/2077/41844
ISBN: 978-91-628-9762-8 (PDF)