

Impairment of Endothelial Thromboprotective Function by Haemodynamic and Inflammatory Stress

Implications for hypertensive disease

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This thesis is based on the following papers:

- I Ridderstråle W, Ulfhammer E, Jern S, Hrafnkelsdóttir T. Impaired capacity for stimulated fibrinolysis in essential hypertension is restored by antihypertensive therapy.
Hypertension 2006;47:686-91.
- II Ulfhammer, E, Ridderstråle W, Andersson M, Karlsson L, Hrafnkelsdóttir T, Jern S. Prolonged cyclic strain impairs the fibrinolytic system in cultured vascular endothelial cells.
Journal of Hypertension 2005;23:1551-7.
- III Ulfhammer E, Carlström M, Bergh N, Larsson P, Karlsson L, Jern, S. Steady laminar shear stress suppresses tissue-type plasminogen activator expression in vascular endothelial cells.
Submitted for publication.
- IV Ulfhammer E, Larsson P, Karlsson L, Hrafnkelsdóttir T, Bokarewa M, Tarkowski A, Jern S. TNF-alpha mediated suppression of tissue type plasminogen activator expression in vascular endothelial cells is NF-kappaB- and p38 MAPK-dependent.
Journal of Thrombosis and Haemostasis 2006;4:1781-9.



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Impairment of Endothelial Thromboprotective Function by Haemodynamic and Inflammatory Stress

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Abstract

The physiologically most important activator of intravascular fibrinolysis is tissue-type plasminogen activator (t-PA). The endothelium synthesizes and stores t-PA and regulated release of the enzyme is an important local protective response to prevent thrombus extension. Previous work by our group has shown that both patients with primary and secondary hypertension have a reduced capacity to release t-PA upon stimulation, a defect that is likely to contribute to the enhanced risk for arterial occlusion and tissue infarction in these subjects. The mechanism of this impairment is unclear although our experimental studies have indicated that it could be a direct effect of the elevated blood pressure.

In order to investigate if the impairment could be reversed by lowering the blood pressure, we used the perfused-forearm model to examine hypertensive subjects for stimulated t-PA release before and after antihypertensive treatment. The findings show that the capacity for stimulated t-PA release can be significantly improved by blood pressure lowering. Treatment increased the amount of t-PA released and also improved the rapidity of the response. The changes were of similar magnitude regardless of treatment with the angiotensin converting enzyme inhibitor lisinopril or the calcium antagonist felodipine, suggesting that the improvement was related to the blood pressure effect *per se*.

To examine the underlying mechanism of blood pressure-induced suppression of t-PA, we explored the potential involvement of the two main haemodynamic forces tensile stress and shear stress. Using *in vitro* biomechanical experimental models and cultured endothelial cells we observed suppressed t-PA gene expression and protein secretion in response to prolonged cyclic strain stimulation and a magnitude dependent suppression of t-PA transcript with prolonged laminar shear stress. Moreover, all reductions of t-PA were consistently followed by inductions of the main inhibitor of t-PA, plasminogen activator inhibitor type 1 (PAI-1).

Further, as hypertension is often associated with a low-grade inflammation, we investigated the impact of the prototypic proinflammatory cytokine tumor necrosis factor- α (TNF- α) on t-PA expression. Prolonged stimulation of cultured endothelial cells was observed to suppress t-PA gene and protein expression. Mechanistic experiments with pharmacologic inhibitors showed that the inhibitory effect was nuclear factor- κ B (NF- κ B) and p38 mitogen-activated protein kinase (p38 MAPK) dependent and indicated that potential effector molecules might be the transcription factors NF- κ B and CREB interacting with the t-PA κ B and CRE promoter elements, respectively.

In conclusion, these findings show that the impaired capacity to release t-PA in hypertensive subjects is directly related to the elevated blood pressure. Data from experimental studies indicate that this impaired fibrinolytic response could be an effect of an enhanced tensile, shear and inflammatory stress acting on the endothelium.

Key words: tissue-type plasminogen activator, endothelium, fibrinolysis, hypertension, shear stress, strain, antihypertensive agents, inflammation, TNF- α , NF- κ B, MAPK