Linköping University Medical Dissertations No. 1270

Vessel wall integrity

influence of genetics and flow

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Akademisk avhandling
som för avläggande av medicine doktorsexamen vid medicinsk fakultet i Linköping kommer att offentligen försvaras i Berzeliussalen, Hälsouniversitetet i Linköping, fredagen den 20 januari 2012 kl 09.15

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Linköping 2012

ISBN 978-91-7393-033-8 ISSN 0345-0082

ABSTRACT

Cardiovascular disease (CVD) is the major cause of death worldwide. Underlying causes, such as atherosclerosis and hypertension, are associated with remodeling of the vessel wall ultimately leading to loss of structural integrity. There are a number of factors that can influence vascular remodeling and hence structural integrity. The overall aim of this thesis was to investigate aortic wall integrity in relation to genetics and blood flow.

The influence of SNPs within the currently strongest and most robust susceptibility locus identified for CVD (chromosome 9p21.3) on abdominal aortic integrity was studied in elderly individuals. In men, risk-variants were associated with a decreased abdominal aortic stiffness, independent of other factors related to arterial stiffness. Impaired mechanical properties of the abdominal aortic wall may explain the association between chromosome 9p21.3 and vascular disease.

Plasminogen activator inhibitor 1 (PAI-1) is the key inhibitor of fibrinolysis, and involved in several processes associated with vascular remodeling. We investigated the impact of the PAI-1 4G/5G polymorphism on central aortic blood pressure as this pressure more strongly relates to cardiovascular morbidity and mortality than the peripheral pressure. Elderly women carrying the 4G/4G genotype had higher central aortic blood pressure than women carrying the 5G/5G genotype. The association was regardless of other risk factors related to hypertension, suggesting that an impaired fibrinolytic potential may play an important role in the development of hypertension in women.

Blood flow is a strong determinant of arterial growth and vascular function. We investigated flow-dependent gene expression and vessel wall morphology in the rat aorta under physiological conditions. Microarray analysis revealed a strong differential gene expression between disturbed and uniform flow pattern regions, particularly associated with transcriptional regulation. Moreover, several genes related to Ca^{2+} signalling were among the most highly differentially expressed. Up-regulation of Ca^{2+}-related genes may be due to endothelial response to disturbed flow and assembly of cilia, consequently leading to functional and structural modifications of the vessel wall.

Bicuspid aortic valve (BAV) is a congenital disorder associated with disturbed ascending aortic blood flow. Using a new strategy to dissect flow-mediated gene expression we identified several novel flow-associated genes, particularly related to angiogenesis, wound healing and mechanosensing, showing differential expression in the ascending aorta between BAV and tricuspid aortic valve patients. Fifty-five percent of the identified genes were confirmed to be flow-responsive in the rat aorta. A disturbed flow, and consequently an altered gene expression, may contribute to the increased aneurysm susceptibility associated with BAV morphology.