



**Karolinska
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Department of Clinical Science, Intervention & Technology
Division of Obstetrics and Gynecology

SMALL ARTERY DYSFUNCTION: FOCUS ON PREECLAMPSIA AND END-STAGE RENAL DISEASE

AKADEMISK AVHANDLING

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ABSTRACT

Background: End-stage renal disease (ESRD) and preeclampsia (PE) are associated with high risk of cardiovascular events and characterized by endothelial dysfunction. Resistance arteries are actively involved in the control of blood pressure and blood flow to the target organs. The expansion of the current knowledge specific to the structure and function of resistance arteries in subjects with increased risk of cardiovascular events is of importance for clinical practice.

Overall aim: To investigate structure and function of resistance arteries isolated from ESRD patients, women with PE and women at reproductive age with a history of early-onset PE.

Results:

Study I. Reduced flow- and acetylcholine-induced dilatations, but preserve response to NO donor were found in arteries from the ESRD group vs. controls. Deficiency of NO was evident in flow-induced response. Distensibility was reduced in the ESRD group, but vascular structure, myogenic tone and sensitivity to vasoconstrictors remained unchanged. Increased ADMA levels and enhanced expression of nitrotyrosine were found in arteries from the ESRD group. Exclusion of ESRD patients with diabetes and/or cardiovascular diseases from analyses had no influence on the main findings.

Studies II-III. Dilatation to bradykinin (BK) was reduced in myometrial but not in subcutaneous arteries from pregnant women with PE vs. controls. In PE, endothelium-derived hyperpolarizing factor (EDHF)-type responses were impaired in both types of arteries. The contribution of myoendothelial gap junctions (MEGJs), implicated as a common pathway of EDHF-type responses in arteries from normal pregnant women, became reduced in subcutaneous and particularly diminutive in myometrial arteries from women with PE. The reduced contribution of MEGJs in PE was partly compensated by H₂O₂ alone (myometrial) or in combination with cytochrome P450 metabolites of arachidonic acid (subcutaneous arteries).

Study IV. Reduced dilatation to flow due to the lack of NO contribution, increased myogenic tone, higher sensitivity to norepinephrine and reduced distensibility were observed in arteries from women with a history of early-onset PE vs. controls. Responses to BK and NO donor were similar between the groups. Basal tone and arterial structure were preserved in women with a history of PE.

Conclusions: Uraemia primarily targets endothelial function and elastic properties of resistance arteries. The lack of NO contribution to flow-induced dilatation together with enhanced circulating levels of ADMA and enhanced nitrotyrosine staining in the vascular wall support the critical role of NO deficiency in resistance arteries from ESRD patients.

In PE endothelial function of myometrial arteries is primarily targeted. This could significantly contribute to the impaired uteroplacental blood flow. EDHF-type responses through MEGJs are the major compromised pathway of endothelium-dependent dilatation in both myometrial and subcutaneous arteries in PE. The attenuated role of MEGJs in PE is partly compensated through the contribution of H₂O₂ or other endothelium-derived factors.

Functional alterations in subcutaneous arteries from women with a history of early-onset PE might create prerequisites for the increased peripheral resistance with following impact on the long-term cardiovascular health.

Key words: Resistance arteries, preeclampsia, end-stage renal disease, endothelium, nitric oxide, endothelium-derived hyperpolarizing factor, flow-induced dilatation, myogenic tone, distensibility.