Renal hemodynamics in renal artery stenosis and angiotensin II-dependent hypertension

Pathophysiological and diagnostic aspects

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av
Aso Saeed

Fakultetsopponent:
Professor Christopher S Wilcox, Georgetown University, Washington DC, USA

Avhandlingen baseras på följande delarbeten:

I. Aso Saeed, Göran Bergström, Karin Zachrisson, Gregor Guron, Elzbieta Nowakowska-Fortuna, Ellen Fredriksen, Lars Lönn, Gert Jensen, Hans Herlitz.
Accuracy of colour duplex sonography for the diagnosis of renal artery stenosis.
Journal of Hypertens. 2009:27(8):1690-6. doi:10.1097/HJH.0b013e32832c417d

II. Aso Saeed, Gerald F. DiBona, Niels Marcussen, Gregor Guron.
High NaCl intake impairs dynamic autoregulation of renal blood flow in angiotensin II infused rats.
American journal of physiology Regulatory, integrative and comparative physiology.2010 Nov;299(5):R1142-9. doi:10.1152/ajpregu.00326.2010

III. Aso Saeed, Hans Herlitz, Elzbieta Nowakowska-Fortuna, Ulf Nilsson, Alaa Alhadad, Gert Jensen, Ingrid Mattiasson, Bengt Lindblad, Anders Gottsäter, and Gregor Guron.
Oxidative stress and endothelin-1 in atherosclerotic renal artery stenosis and effects of renal angioplasty.
(In press, Kidney and Blood Pressure Research)

IV. Aso Saeed, Gerald F. DiBona, and Gregor Guron.
Effects of endothelin receptor antagonists on renal hemodynamics in angiotensin II-infused rats on high NaCl intake.
(Submitted)

UNIVERSITY OF GOTHENBURG

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Aso Saeed, Department of Molecular and Clinical Medicine/Nephrology, Institute of Medicine. The Sahlgrenska Academy at the University of Gothenburg, Sweden, 2011

ABSTRACT

Patients with renovascular hypertension have a poor renal and cardiovascular prognosis. To improve the care of these patients, we need to increase knowledge about the pathophysiological mechanisms involved. Thus, the aims of these studies were to examine: (1) renal hemodynamics and renal blood flow autoregulation (RBFA) in an experimental model of chronic angiotensin (Ang) II-dependent hypertension and the role of superoxide and endothelin (ET)-1; (2) the diagnostic value of intrarenal velocimetric color duplex sonography (CDS) indices in patients with suspected renal artery stenosis (RAS); and (3) biomarkers of oxidative stress (oxs), and ET-1, in hypertensive patients with atherosclerotic RAS (ARAS) and the effect of renal angioplasty.

In chronically Ang II-infused rats, high-NaCl intake (AngII-HNa) resulted in a marked impairment in the myogenic response (MR) of dynamic RBFA. This abnormality was not seen in sham rats on a high-NaCl diet and was significantly more pronounced than in Ang II-infused rats on a normal-NaCl diet. Chronic treatment with tempol, a superoxide dismutase mimetic, attenuated the abnormality in dynamic RBFA in AngII-HNa, whereas acute treatment with ET_A and/or ET_B receptor antagonists had no effect on this abnormality. In AngII-HNa, ET_A antagonism reduced arterial pressure (AP) and specifically increased outer medullary perfusion. These effects were attenuated or abolished by co-administration of ET_B receptor antagonist.

In a retrospective cohort of patients undergoing renal angiography for suspected RAS, acceleration indices of CDS; maximal systolic acceleration (ACCmax) and maximal acceleration index (AImax= ACCmax/peak systolic velocity) provided comparable, good diagnostic accuracy in detecting a hemodynamically significant RAS even in patients with markedly reduced kidney function, in contrast to pulsatility index which correlated significantly to age, renal function and pulse pressure, but not the degree of RAS.

In a prospective cohort of patients undergoing renal angiography for suspected ARAS (significant ARAS; n=83, and non-RAS; n=59) baseline (prior to angiography) inflammatory, but not oxs, biomarkers were significantly elevated in group ARAS vs. both group non-RAS and healthy matched controls (n=20). Plasma ET-1 at baseline was significantly increased in group ARAS vs. healthy controls and was significantly reduced compared to baseline 4 weeks after angioplasty. Angioplasty had no significant effects on AP, biomarkers of oxs, inflammation or serum creatinine.

In conclusion, in a rat model of AngII-dependent hypertension, high-NaCl intake produced a marked impairment in the MR of dynamic RBFA. Tempol attenuated this abnormality, whereas ET-1 receptor antagonists did not, indicating a role for superoxide in the impaired autoregulatory response. In the same animal model, acute ET_A antagonism reduced AP and selectively increased outer medullary perfusion. Our results suggest that selective ET_A antagonists are more effective than combined ET_{A+B} antagonists in this model. Acceleration indices ACCmax and AImax are superior to pulsatility index, and provide a similar, good, diagnostic accuracy in detecting a hemodynamically significant RAS, even in patients with markedly reduced kidney function. Biomarkers of inflammation, but not oxs, are elevated in patients with ARAS. Angioplasty did not decrease inflammatory biomarkers but reduced plasma levels of ET-1 4 weeks after intervention.

Key words: angiotensin II, autoregulation of renal blood flow, color duplex sonography, endothelin-1, oxidative stress, renal artery stenosis, renal hemodynamics, renovascular hypertension,

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