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

Akademisk avhandling
som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs universitet kommer att offentligen försvaras i Hjärtats aula, Blå stråket 5, Sahlgrenska Universitetssjukhuset/Sahlgrenska, Göteborg, torsdagen, den 9 juni 2011, kl. 09:00

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

Avhandlingen baseras på följande delarbeten:

Accuracy of colour duplex sonography for the diagnosis of renal artery stenosis.

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.

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)
Renal hemodynamics in renal artery stenosis and angiotensin II-dependent hypertension
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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\textsubscript{A} and/or ET\textsubscript{B} receptor antagonists had no effect on this abnormality. In AngII-HNa, ET\textsubscript{A} antagonism reduced arterial pressure (AP) and specifically increased outer medullary perfusion. These effects were attenuated or abolished by co-administration of ET\textsubscript{B} receptor antagonist.

In a retrospective cohort of patients undergoing renal angiography for suspected RAS, acceleration indices of CDS; maximal systolic acceleration (ACC\textsubscript{max}) and maximal acceleration index (AImax= ACC\textsubscript{max}/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\textsubscript{A} antagonism reduced AP and selectively increased outer medullary perfusion. Our results suggest that selective ET\textsubscript{A} antagonists are more effective than combined ET\textsubscript{A+B} antagonists in this model. Acceleration indices ACC\textsubscript{max} 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,