Moderate Intrarenal Vasoconstriction after High Pressor Doses of Norepinephrine in the Rat: Comparison with Effects of Angiotensin II

Bożena Bądryńska Janusz Sadowski

Laboratory of Renal and Body Fluid Physiology, M. Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland

Key Words

Kidney hemodynamics • Laser-Doppler flowmetry • Renal regional perfusion • Norepinephrine • Angiotensin II

Abstract

Aims: Treatment of arterial hypotension with norepinephrine (NE) is associated with renal vasoconstriction and may lead to ischemic kidney injury; the risk involved is still a matter of debate. **Methods:** In anesthetized, acutely uninephrectomized rats, we examined changes in intrarenal hemodynamics induced by intravenous infusion of NE and angiotensin II (Ang II), at doses that increased arterial pressure by ~25 mm Hg (20%). Renal blood flow (RBF) was determined using a Transonic probe, and superficial cortical, outer and inner medullary flows (CBF, OMBF, IMBF) as laser-Doppler fluxes. **Results:** NE decreased regional intrarenal perfusion similarly, by 16, 15 and 16% for RBF, OMBF and IMBF, respectively (all changes significant). The respective decreases after Ang II were significantly greater and clearly differentiated: 45, 32 and 22%, respectively. The renal vascular resistance increased $47 \pm 4\%$ after NE and $131 \pm 11\%$ after Ang II, indicating that the latter drug induces much more pronounced renal vasoconstriction. **Conclusion:** An ~15% decrease of renal perfusion may be taken as an indication of an impairment of renal circulation during antihypotensive NE therapy.

While superiority of NE over Ang II is obvious, a further search for drugs even less harmful to renal perfusion and function is desirable.

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Introduction

Although catecholamines are widely used for treatment of hypotension of diverse origin, e.g. that associated with septic shock, reservations regarding the safety of their use are occasionally re-raised and continue to be debated [1, 2]. A potential risk of catecholamine therapy is that vasoconstriction in the kidney may lead to ischemic renal injury; the most endangered area would be the renal medulla. Its oxygen supply appears to rely on vascular configurations more complex than originally believed [3] and, also under physiological conditions, the medulla appears to be functioning 'at the edge of anoxia' [4]. The actual risk of renal medullary ischemia as a consequence of therapeutic application of catecholamines (especially norepinephrine, NE) has not been satisfactorily evaluated.

We examined the effects of high pressor doses of NE on intrarenal circulation and compared the results with those obtained with angiotensin II (Ang II). For intra-

Fig. 1. Effects of intravenous infusions of NE (—◆—) and Ang II (---◇---), given in equipressor doses which increased MAP by ~25 mm Hg (20%), on the parameters of renal perfusion. RBF denotes renal artery blood flow (Transonic probe), and CBF, OMBF and IMBF denote superficial cortical, and outer and inner medullary laser-Doppler fluxes (PU – perfusion units), respectively. * Significantly different from pre-infusion control (C) by paired Student's t test ($p < 0.001$ – 0.0001). † Change from control significantly different from that measured after Ang II, determined by unpaired Student's t test ($p < 0.003$ – 0.0001).

renal regional hemodynamic measurements, we applied laser-Doppler flowmetry, the technique that seems best established and has been most widely used, also in our laboratory. Given the special interest for the effect of the vasoconstrictors on circulation in the medulla, we increased both the area and 'resolution' of measurements by placing laser-Doppler probes both in the outer and in the inner medullary layer.

Methods

Experimental procedures were approved by the extramural IV Local Ethical Committee, Warsaw. Male Sprague-Dawley rats weighing 280–310 g were anesthetized with intraperitoneal sodium thiopental (Sandoz GmbH, Kundl, Austria), 100 mg/kg body weight. Right-side nephrectomy was performed from a flank

incision; this was done to reduce the disproportionately high contribution of the renal vasculature to the Ang II-induced increase in systemic MAP. Subsequently, experimental procedures were applied enabling aortic blood pressure (MAP) measurement, and exposure and preparation of the left kidney for renal hemodynamic measurements, as described previously [5]. Transonic flowmeter and 1-mm probe (T106; Transonic System Inc., Ithaca, N.Y., USA) were used for measurement of renal artery blood flow (RBF). The blood perfusion of the superficial renal cortex and of the outer and inner medulla (CBF, OMBF, IMBF, respectively) was measured as laser-Doppler fluxes using Periflux 4001 system (Perimed AB, Järfälla, Sweden). The CBF probe was placed on the kidney surface and two needle probes (PF 402), for measurement in the outer and inner medulla, were inserted into the kidney to respective depths of 3 and 5 mm from the surface. After obtaining stable baseline records of MAP and renal perfusion parameters, intravenous infusions of either NE or Ang II in isotonic saline were started and maintained for at least 30 min, to obtain an elevation of MAP to 135–140 mm Hg. The infusion rates of NE and Ang II (both from Sigma, Basel, Switzerland) were, on average, 240 and 150 $\mu\text{g}/\text{h}/\text{kg}$, respectively. Minor adjustments of infusion rates were made to maintain MAP at the desired level.

Student's t test for dependent variables (baseline vs. hormone infusion) or independent variables (NE vs. Ang II), as appropriate, was used to examine the significance of changes.

Results

Intravenous infusion rates of NE or Ang II were adjusted to increase MAP to the same level: 138 ± 2 mm Hg, i.e. ~20%. The responses of intrarenal hemodynamics to NE and Ang II are shown in figure 1. After NE, the decreases of RBF, OMBF and IMBF were quite similar, by 16, 15 and 16%, respectively, with a somewhat lesser decrease in CBF, by 11%. Ang II caused substantially and significantly greater decreases in RBF (–45%) and CBF (–36%). Unlike with NE, Ang II-induced hypoperfusion diminished progressively toward the renal papilla, amounting to 45, 32 and 22% for RBF, OMBF and IMBF.

The baseline renal vascular resistance (RVR) was quite similar in the two drug groups and significantly increased during infusion of either agent, by a modest 47% for NE and an impressive 131% for Ang II (table 1).

Discussion

At doses that increased MAP by a mean of 26 mm Hg (20%), NE reduced renal perfusion ~15%, quite similarly in individual kidney zones. Other studies reported that exogenous NE has less effect on the medulla compared to cortical perfusion [6], an analogy to negligible response of medullary circulation to renal nerve stimula-

tion [7, 8]. Most probably, stimulation of adrenergic α_1 -receptors mediating vasoconstriction is opposed in the medulla by α_2 -mediated release of vasodilator NO [6]. However, this conclusion is largely based on experiments with infusions or bolus injections of subpressor or slight pressor doses of NE into the renal artery, aimed to induce substantial changes in renal perfusion without altering MAP. This approach is necessary to explore mechanisms of complex vascular responses to vasoconstrictors but not suitable for assessment of the risk involved in therapeutic use of NE. Nevertheless, intravenous infusion of NE in anesthetized rats which increased MAP by $\sim 20\%$ was reported to decrease RBF and CBF by almost 20% and MBF by less than 3% [9]. The reason for the discrepancy between this finding and ours is not clear; however, in the quoted study, MBF measurement was restricted to a small area in the inner stripe of the outer medulla, and the polarographic technique used has not been so well validated as laser-Doppler flowmetry. It is evident that in the present study the net result of NE (a resultant of constrictor and dilator effects, both direct and indirect) was a uniform moderate intrarenal vasoconstriction. A similar decrease in the perfusion of the cortex and medulla could reflect similar constriction of inner cortical and juxta-medullary glomerular arterioles.

Compared with NE, Ang II given at equipressor doses provided a much more robust renal vasoconstriction: RVR increased by 131% compared to a 47% increase after NE; the cortical perfusion was significantly more affected than that of the medulla. Remarkably, infusions of subpressor or slight pressor doses of Ang II decreased total renal or cortical blood flow while medullary perfusion usually increased or remained stable [10]. Using laser-Doppler technique identical with that of the present study, we reported an increase [11] or no change [5] in MBF in anesthetized Wistar rats given Ang II at a rate which increased MAP by 2–3%. Our present application of substantially higher doses of Ang II induced a significant decrease in medullary perfusion.

The differential effect of Ang II on intrarenal circulation has been largely clarified. Briefly, the vascular segments which control blood supply to the renal medulla are provided with AT_1 receptors which mediate Ang II-dependent vasoconstriction, however the circulating peptide stimulates a local release and action of vasodilator agents, mostly PGE_2 and NO, which effectively buffer or even overcompensate direct vasoconstriction [5, 10]. The present results indicate that on application of Ang II at high pressor doses, the balance of direct vasoconstriction and secondary indirect vasodilation is shifted to-

Table 1. Comparison of changes in the RVR as affected by equipressor intravenous infusions of NE and Ang II

	RVR, mm Hg/(ml/min)		
	control	experimental	Δ %
NE	13 ± 1	$19 \pm 1^*$	47 ± 4
Ang II	14 ± 1	$31 \pm 1^*$	131 ± 11^a

* Significantly different from pre-infusion control by paired Student's t test ($p < 0.0001$).

^a Change from control significantly different from that measured after Ang II, determined by unpaired Student's t test ($p < 0.0001$).

ward the former. It appears that with increasing Ang II doses, the hormone's direct action further increases, whereas the potential of its secondary vasodilator influence is 'exhausted'. The medullary hypoperfusion is therefore not prevented (or overcompensated) but only attenuated.

In summary, treatment of hypotension of various origins may require application of NE in doses sufficient to increase MAP by 20–30 mm Hg. In our experiments with anesthetized rats, such treatment decreased perfusion of the whole kidney and of the renal medulla by about 15%. This may be a rough indication of the risk for the kidney that is involved in antihypotensive NE therapy. For comparison, similar treatment with Ang II decreased renal perfusion by about 45%. More accurate evaluation of the risk of renal hypoperfusion would require experiments with application of vasoconstrictors in animals with baseline hypotension. Another limitation of this study is the use of anesthesia. Unfortunately, most of techniques applicable for measurement of renal perfusion in conscious animals, also those using radiolabeled microspheres, do not provide full and reliable data for medullary circulation.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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