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## ADRENAL-RENAL PORTAL CIRCULATION CONTRIBUTES TO DECREASE IN RENAL BLOOD FLOW AFTER RENAL ARTERY STENOSIS IN RATS

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The aim of the present study was to investigate a role of adrenal-renal portal circulation (ARPC) in a decrease in renal blood flow due to acute stenosis of the renal artery in rats. Animals were divided into three groups. In the control group (I), in order to eliminate the ARPC tissue between the adrenal gland and the ipsilateral kidney was cut. In the second and the third group (II) (III), left renal artery was stenosed by a silver clip (ID 0.40 mm). Then, in the group II, ARPC was surgically eliminated. In the group III, prior to the elimination of ARPC, alpha-adrenergic receptors blockade was produced by phentolamine administration. In the control group, ARPC elimination did not influence either renal blood flow (RBF) or renal vascular resistance (RVR). In the group II, elimination of ARPC caused increase in RBF and decrease in RVR. In the group III elimination of ARPC influenced neither RBF nor renal vascular resistance (RVR). Results of the present study provide the functional evidence that catecholamines reaching the kidney through ARPC, contribute to the decrease in RBF and increase in RVR during acute renal artery stenosis in the rat.

*Key words: ischemic kidney, adrenal gland, rat, adrenal renal portal circulation*

### INTRODUCTION

Since Goldblatt's demonstration of the development of arterial hypertension following stenosis of the renal arteries in the dog (1), the pathogenesis of renovascular hypertension has been intensively investigated. Many authors

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described a marked increase of preglomerular resistance in clamped kidney in spite of normal perfusion pressure behind the clip, whereas postglomerular resistance remained unchanged (2, 3).

Several lines of evidence seem to prove participation of the sympathetic nervous system, in the maintenance of elevated blood pressure, in a variety of types of hypertension. The efferent renal sympathetic nerves can affect the renal vascularisation, and therefore regulate sodium and water excretion by producing changes in intrarenal hemodynamics (4—6).

Despite the enhanced activity of extrarenal sympathetic nerves (7, 8) in Goldblatt hypertension, there are reports suggesting an attenuation of efferent sympathetic drive to the vasculature of the clipped kidney (9). Barajas *et al.* (10) described marked reduction of monoaminoergic nerves fluorescence and catecholamines tissue content in the kidney with artery stenosis. This reduction of fluorescence may indicate a depletion of catecholamines or reduction in the number of sympathetic nerves in the ischaemic kidney.

On the other hand Więcek *et al.* (11) described in hypertensive patients with unilateral renal artery stenosis a significantly higher level of catecholamines in the venous blood of the kidney with stenosed artery as compared to the respective contralateral renal vein. The adrenaline as well as noradrenaline level in the renal vein with stenosed artery was higher as compared with noradrenaline and adrenaline level in the contralateral renal vein. However the adrenaline concentration was higher by about 600% whereas noradrenaline level was elevated only by 30%. These data indicate that rather adrenal gland, than sympathetic efferent activity as a source of increased concentration of catecholamines in the above study.

Besides efferent sympathetic nerves, kidney function remains under the control of catecholamines reaching it through a direct adrenal-renal portal circulation (ARPC). ARPC was described for the first time in 1914 by Cow (12). Later, other authors confirmed the existence of this rete in the rat (13), dog, rabbit, monkey and in humans (14, 15). Furthermore a role of ARPC in the pathogenesis of arterial hypertension was shown in different animal models of hypertension (16, 17, 18).

The aim of the present study was to investigate a role of adrenal-renal portal circulation (ARPC) in a decrease in renal blood flow due to acute stenosis of the renal artery in rats.

## MATERIALS AND METHODS

Experiments were performed on 24 male Wistar rats weighing 300-400g obtained from Medical Academy animal house (Warsaw, Poland). Rats were kept 4 per standard laboratory cage, at controlled 12 hour dark and light phases, with food and water available *ad libitum*.

Anaesthesia was induced with chloral hydrate (Sigma-Aldrich Chemie GmbH) 0.36 g/kg of b.w. i.p. and maintained by intravenously infusion of 0.005 g/kg/min. The level of anaesthesia was regularly assessed by monitoring of the heart rate and blood pressure. The trachea was cannulated, rats were paralysed with pancuronium (Pavulon, Organon Teknika B.V.) at the dose of 0.005 mg/kg b.w. i.v. and artificially ventilated using Harvard pump (L) for small animals. Ventilation was adjusted under control of arterial blood gasometry (Blood Gas System — AVL 995 Hb) to maintain values of pH, pCO<sub>2</sub>, and pO<sub>2</sub> within normal limits. Mean arterial blood pressure (MAP) was monitored using pressure transducer (MCK-4011) attached to a cannula inserted into the femoral artery. The left femoral vein was cannulated for drug and fluid administration. Rectal temperature was maintained at 37.5°C by means of the thermostatically controlled heating blanket.

After laparotomy, the flow-probe of Doppler-flowmeter (Transonic-System, Ithaca, USA) was placed around the left renal vein for the measurement of renal blood flow (RBF).

Animals were allowed for at least 30 min to get stable circulatory condition. When additional surgery or drug administration were done no measurements were performed for at least 20 min to allow recovery of stability.

Animals were divided into three groups.

In the control group (I, n=8) the left renal artery was exposed but not clipped. Thereafter, in the ipsilateral side ARPC was eliminated by cutting the tissue between the adrenal gland and the kidney.

In both experimental groups (II, n=8 and III, n=8) left artery was stenosed by a silver clip (ID 0.40 mm). Then, in the group II, ARPC was surgically eliminated as described above. In the group III, prior to the elimination of ARPC, phentolamine (Regitin, Ciba-Geigy) administration was started by intravenous injection of a bolus of (0.2 mg/kg b.w. in 0.2 ml of saline) followed by i.v. infusion of phentolamine at the dose 0.005 mg/kg/min b.w. (n=8).

RBF was calculated per 1g of kidney weight (k.w.). Renal vascular resistance (RVR) was calculated as mean arterial pressure (mmHg)/ renal blood flow (ml/min/1g k.w.), and expressed as renal resistance units (RRU).

Student's paired t-test was used to compare subsequent values with the relevant control ones. Statistical comparison between groups were performed by Anova analysis of variance. A value of  $p < 0.05$  was considered to be statistically significant. Values are presented as means  $\pm$  standard error of the mean (SEM).

## RESULTS

In the control group — I ARPC elimination did not influence on RBF ( $5.2 \pm 0.11$  vs.  $5.0 \pm 0.23$  ml/min/1g k.w.), RVR ( $16.9 \pm 1.02$  vs.  $17.0 \pm 1.1$  RRU) and MAP ( $87.2 \pm 3.2$  vs.  $85.3 \pm 2.8$  mmHg).

In the group II stenosis of the renal artery significantly reduced RBF and increased RVR but did not carried any changes in MAP ( $87.6 \pm 4.2$  vs.  $85.2 \pm 3.9$  mmHg). Subsequent elimination of ARPC significantly increased RBF and decreased RVR not affecting MAP ( $85.2 \pm 3.9$  vs.  $83.6 \pm 3.8$  mmHg).

In the group III, similarly to the group II, stenosis of the renal artery significantly reduced RBF, increased RVR and did not cause any changes in MAP ( $88.1 \pm 3.8$  vs.  $84.7 \pm 5.9$  mmHg). Subsequent phentolamine administration significantly increased RBF, decreased RVR and decrease MAP ( $84.7 \pm 5.9$

vs.  $71.2 \pm 4.6$  mmHg). Elimination of ARPC after phentolamine administration neither influenced RBF, RVR nor MAP ( $71.2 \pm 4.6$  vs.  $73.5 \pm 3.9$  mmHg). The values of RBF and RVR in the groups II and III are summarised in the Fig. 1 and Fig. 2.

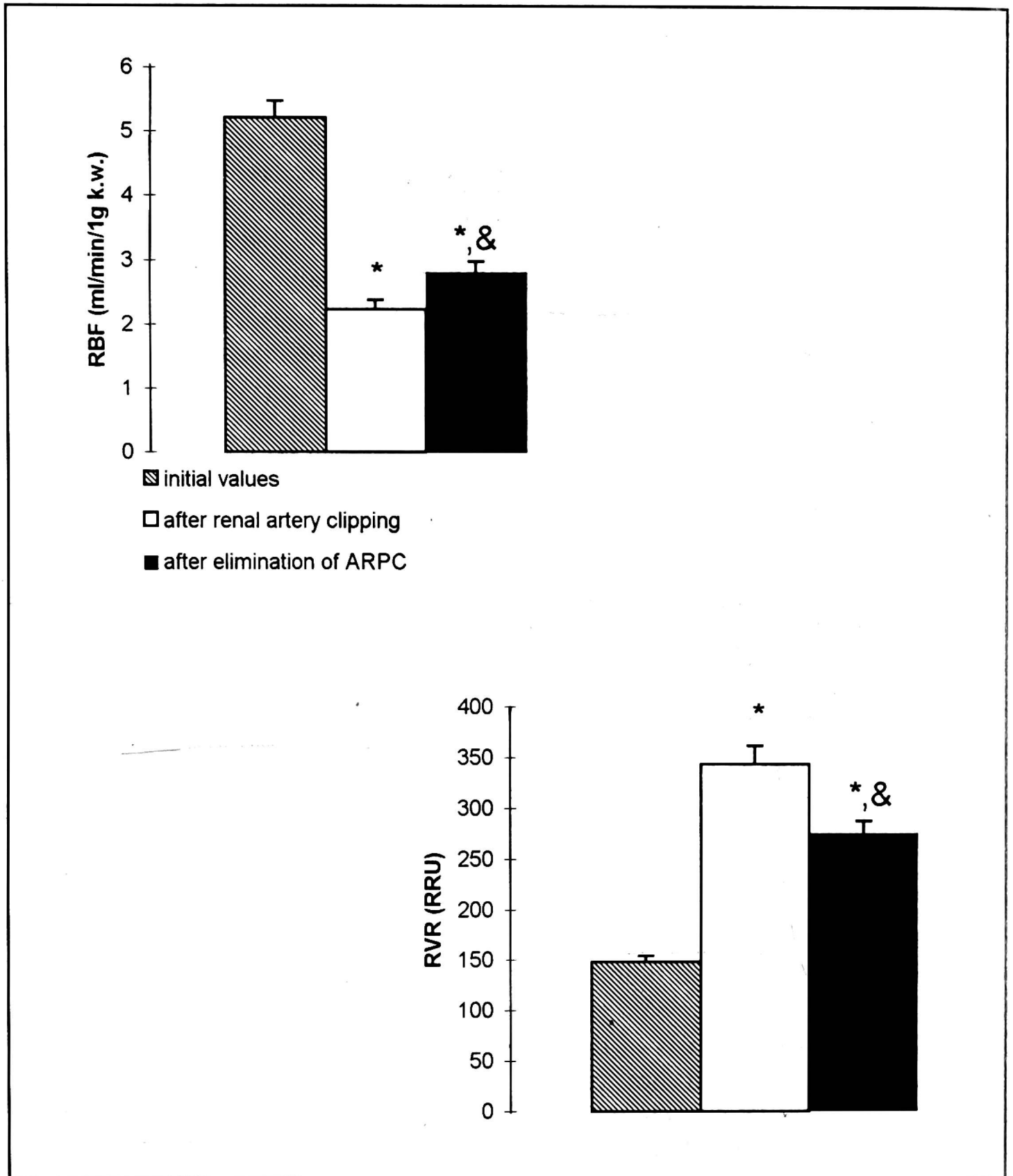


Fig. 1. Influence of elimination of ARPC upon the renal blood flow (RBF) (top panel) and the renal vascular resistance (RVR) (bottom panel) after stenosis of the renal artery. \* $p < 0.01$  vs. initial values, &  $p < 0.01$  vs. values after clipping of the renal artery.

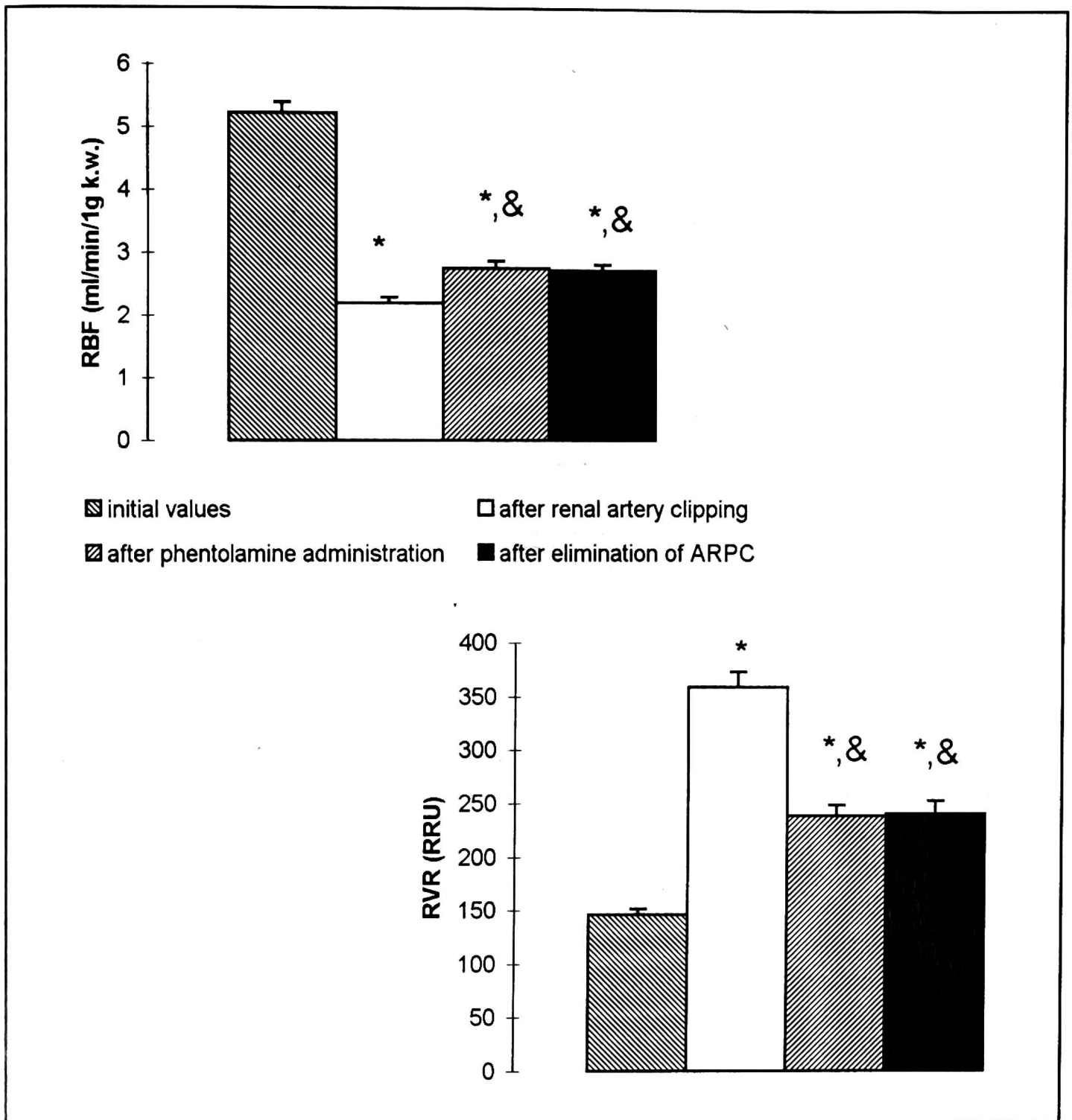


Fig. 2. Influence of elimination of ARPC upon the renal blood flow (RBF) (top panel) and the renal vascular resistance (RVR) (bottom panel) after stenosis of the renal artery and phentolamine administration. \* $p < 0.01$  vs. initial values, &  $p < 0.01$  vs. values after clipping of the renal artery.

## DISCUSSION

In the present study we have selected artery clip of internal diameter of 0.4 mm. This degree of narrowing of renal artery is routinely used to produce renovascular hypertension in the adult rat (19). The observed in the present study decrease in RBF (eg. by about 60%) due to applied clip remains in agreement with other studies.

The physiological meaning of ARPC has been demonstrated for the first time by Katholi *et al.* (20, 21). They showed that elimination of ARPC

markedly reduced renal vasoconstriction caused by decrease in blood pressure due to experimentally induced arrhythmia in the dog. Moreover the above renovascular response to acute adrenal demedullation was comparable to the ARPC elimination (20). The level of catecholamines in plasma collected from these vessels of ARPC was significantly higher than in peripheral blood. Authors concluded that this vascular connection provides a direct route by which adrenal catecholamines can reach the kidney in a higher concentration than judged from their level in peripheral blood.

Results obtained in the present study demonstrate that adrenal-renal vascular connection contributes to decrease in RBF and increase in RVR during acute renal artery stenosis in rats.

Vessels of ARPC have valves permitting only uni-directional flow from adrenal gland to the kidney (22). Stenosis of renal artery decreases blood pressure in small arteries of the kidney. Decline pressure on the renal side of ARPC would increase a driving pressure resulting in higher blood flow through this connection. This suggestion is substantiated by a finding that elimination of ARPC changes RBF and RVR only in the clipped kidney (3).

The above conclusion corresponds well with results described by Abramczyk *et al.* (23). They showed that increase in blood flow through ARPC caused by occlusion of the adrenal vein results in decrease in RBF and increase in RVR in the respective kidney.

Alpha-1 receptors are located on the vasculature of the kidney and they are responsible for renal vasoconstriction (24). In our study alpha adrenergic receptor blockade with phentolamine increased RBF and decreased RVR after renal artery stenosis and prevented changes of these parameters after ARPC elimination. These results indicate that changes of RBF and RVR are elicited by catecholamines reaching the ischaemic kidney directly from adrenal gland by ARPC.

It is well known that catecholamines stimulate renin release. Therefore, the another mechanism which could explain our results is inhibition of renal renin-angiotensin system due to cessation of direct catecholamines inflow to the kidney. However, this is unlikely because of the short latency of the above changes in RVR after the cutting ARPC. Moreover, catecholamines directly stimulate renin release by  $\beta$ , but not  $\alpha$  adrenergic receptors.

Gordon *et al.* (7) showed that in adrenal venous plasma, concentration of noradrenaline and adrenaline was higher in patients with renovascular hypertension than in patients with essential hypertension. Our results provide a link between findings of Gordon *et al.* and described in the introduction study of Więcek *et al.* (11).

The adrenomedullary content of catecholamines is also augmented in experimental Goldblatt hypertension (2K1C) (25). On the other hand it was shown that both noradrenaline content (10) and catecholamine histofluores-

cence (10, 26) are markedly reduced in the kidneys of animals with experimental renal hypertension. It is difficult to interpolate decreased concentration of catecholamines in the tissue to the activity of the postganglionic sympathetic nerves. Decreased catecholamine content in the kidneys in renovascular hypertension may be the result of impaired storage mechanism or enhanced activity of enzymes responsible for their break down.

It was shown that electrical stimulation of sympathetic fibres innervating kidney leads to the lesser vasoconstriction in renovascular hypertensive rats than in control ones (9). This finding points to the impaired synthesis (or uptake) of catecholamines in sympathetic nerves innervating kidney in this model of hypertension. Therefore one can hypothesise that adrenal catecholamines exert more eminent role in regulation of renal resistance than efferent sympathetic drive after renal artery stenosis.

The question if ARPC contributes to the development and maintenance of renovascular hypertension in the rat is the major outcome of the present study.

In conclusion, results of the present study provide evidence that catecholamines reaching the kidney directly from the adrenal gland through the ARPC, significantly contribute to the decrease in RBF and increase in RVR during acute renal artery stenosis in the rat.

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