Role of the renin-angiotensin system in regulation and autoregulation of renal blood flow

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Autoregulation of renal blood flow (RBF) has been recognized for decades (10, 15, 20). The two intrarenal mechanisms believed to be responsible for this action are the myogenic response and the tubuloglomerular feedback (TGF) mechanism (15). These two mechanisms ensure that RBF is kept fairly constant when acute systemic blood pressure changes occur within 80–180 mmHg (5, 20).

If the change in blood pressure is of longer duration, the RBF adapts to the new blood pressure by regulation to a new level of RBF such that the autoregulating ability is kept intact. This is accompanied by a resetting of the autoregulation limits (2, 7). Thus it is important to distinguish between autoregulation and regulation of RBF. Autoregulation relates to acute changes in perfusion pressure and prevents these changes from affecting RBF, provided they are within the autoregulating limits. Regulation is the process whereby a longstanding change in blood pressure or extracellular fluid volume leads to compensatory changes in RBF. The process of regulation is accompanied by a resetting of autoregulation, implying that RBF is autoregulated at new values during acute changes in the perfusion pressure.

The change in sodium chloride concentration ([NaCl]) at the macula densa that leads to activation of the TGF mechanism and a constriction of the afferent arteriole also affects the release of renin from the juxtaglomerular cells (21). The [NaCl] at the macula densa increases when Henle loop flow rate increases (12, 18). Consequently, the renin release and the local concentration of ANG II ([ANG II]) decrease. Changes in the local [ANG II] are therefore part of the response elicited by a change in distal tubular NaCl delivery.

The role of ANG II in renal autoregulation and regulation is still not fully resolved. It has been shown that renin depletion by salt loading in dogs only affects autoregulation of glomerular filtration rate, and this has been attributed to a more pronounced effect of ANG II on the efferent compared with the afferent arteriole (6). However, it has also been reported that blockade of the angiotensin-converting enzyme (ACE) abolishes the resetting of the lower limit of RBF autoregulation (2, 7).

The aim of the present study was to investigate the hypothesis that RBF autoregulation, resetting of autoregulation, and finally, the regulation of RBF are dependent on an intact renin-angiotensin system (RAS). By clamping the RAS by simultaneous infusion of the ACE inhibitor captopril and ANG II, renal perfusion pressure (RPP) and RBF were maintained at the values observed before captopril infusion. The results indicate that a constant low [ANG II] improves the ability to autoregulate RBF, because the lower auto-
regulation limit was decreased, whereas the ability to regulate RBF and reset autoregulation was abolished. The time frame for resetting autoregulation of RBF to a new level was examined and seems to be on the order of 10 min.

**METHODS**

*Animal Preparation*

The experiments were performed in male Sprague-Dawley rats weighing 250–330 g obtained from Mollegård (Lille Skensved, Denmark). The experimental protocol was approved by the National Research Animal Committee. The rats had free access to food and water until immediately before the experiments and were fed ordinary rat chow (Altromin nr. 1314, Chr. Petersen A/S, Ringsted, Denmark) containing 87 mmol Na+/kg.

Anesthesia was induced with 5% halothane delivered in 35% nitrogen and 65% oxygen. Polyethylene catheters were placed in the right jugular vein (PP-10) for infusion and in the left carotid artery (PP-50) for continuous measurement of the systemic blood pressure by a Statham P23-db pressure transducer (Gould, Oxnard, CA). A tracheostomy was performed, and the rat was placed on a servo-controlled heating table to maintain body temperature at 37°C. The rat was connected to and ventilated by a small animal ventilator, tidal volume 1.7–2.5 ml, depending on body weight and a frequency of 60 breaths/min. The final halothane concentration needed to maintain sufficient anesthesia was ~1%. An intravenous bolus injection of 6 mg gallamine triethiodide (Relaxan, A/S GAE, Denmark) in 0.4 ml 0.9% saline was given followed by continuous intravenous infusion of 12 mg/ml Relaxan at 20 μl/min. Additional saline was given continuously at a rate of 20 μl/min.

The left kidney was exposed after laparotomy extended to the left flank. The left femoral artery was catheterized (PP-25) for measurements of the RPP. The left ureter was catheterized (PP-10 connected to PP-50) to ensure free urine flow. The left renal artery was stripped from any fat or fascias, and a recalibrated electromagnetic perivascular flow sensor (Skalar Medical, model 1401, Holland) was placed around it (lumen diameter 0.6–0.8 mm). The aorta was exposed, and a servo-controlled aortic clamp (RPC-2 controller, Electronic Workshop, McGill University, Canada) was placed above the bifurcation of the renal arteries. The controller of the clamp maintained a constant RPP by comparing the pressure signal from the femoral artery to a reference signal corresponding to a preset pressure.

Blood pressure and RBF were recorded on a stereo video recorder (Sony, Japan) through a frequency modulator (Reditech, Copenhagen). The kidney was superfused with heated saline (37°C) during the experiment. After the experiment, the kidney was removed, drained, and weighed.

*Experimental Protocol*

**Resetting of autoregulation. Intact RAS.** Twenty rats were used. The rat was allowed to equilibrate for at least 30 min after completion of surgery. A blood sample for renin measurement was taken just before the experiment. The blood was replaced by 0.3 ml 0.9% saline. RPP was reduced in steps of 10 mmHg from the spontaneous blood pressure down to 65 mmHg, each step lasting 1 min. The pressure was kept at 65 mmHg for 15 min after which the clamp was released. After 1–2 min at spontaneous blood pressure to allow stabilization of the perfusion pressure and the RBF, the reducing steps were repeated down to 65 mmHg. At the end of the experiment, a second blood sample was collected. Ten microliters of 300 mM EGTA were added to the blood samples to avoid coagulation. The blood samples were centrifuged at 7,000 rpm for 5 min, and the plasma was kept frozen for later renin measurement.

The RBF at a blood pressure of 100 mmHg was set to 100%, and RBF was normalized to this flow. Average pressure and flow values were determined in the last 30 s of a pressure step.

To determine the inflection point on the autoregulation curve for each rat, two straight lines were fitted by eye to the five points on the curve, and the intersection was found. If there was no obvious inflection point, the rat was assigned the lowest possible value (65 mmHg), i.e., perfect autoregulation.

**Clamped RAS.** Sixteen rats were used. To clamp the level of ANG II, 12 μg/min (1.2 mg/ml dissolved in 0.9% saline) of the ACE inhibitor captopril (ICN, Aurora, OH) were infused intravenously as soon as blood pressure and RBF were stable. When new levels of blood pressure and RBF were obtained after ~10–15 min, infusion of ANG II [0.5 μg/ml dissolved in 0.9% saline (Sigma Chemicals)] was started at 3 ng/min and increased until precaptopril levels of blood pressure and RBF were obtained, usually at 4 ng/min. The rat was then allowed to equilibrate for at least 30 min. The protocol was otherwise similar to that of the experiments with an intact RAS, but no blood samples were taken. To prevent overhydration, saline was infused at a reduced rate of 10 μl/min. An additional six rats were used to reduce perfusion pressure in steps down to 50 mmHg.

Inflection points were found as described above.

**ACE inhibitor and methoxamine.** Seven rats were treated as above, but the specific α1-adrenergic agonist methoxamine hydrochloride (Wellcome, London, UK) was used to restore RPP and RBF. Infusion of methoxamine (0.5 mg/ml dissolved in 0.9% saline) was started at 5 μg/min and increased until precaptopril levels of blood pressure and RBF were obtained. After ~10 min, the infusion rate was reduced again to 2.5 μg/min to prevent extensive vascular constriction due to accumulation of the agonist. The rat was then allowed to equilibrate for at least 30 min. The protocol was otherwise similar to that of the experiments with a clamped RAS.

**Regulation of renal blood. Intact RAS.** Eleven rats were used. The experiment was divided into eight 5-min periods. The first two periods were intrinsic controls before reduction of perfusion pressure. RPP was reduced in one step from basal to ~88 mmHg and kept there for 30 min. Blood samples were collected before and after the period of perfusion pressure reduction for measurement of plasma concentrations of renin. The average of RBF in the two control periods was set to 100%. Values in the remaining six periods, where the perfusion pressure was reduced, were normalized compared with the intrinsic control.

**Clamped RAS.** In three rats, the RAS was clamped using the same protocol as above. Otherwise, the protocol was as in the experiments examining regulation of RBF in that the RPP was reduced to 88 mmHg in one step and kept there for 30 min.

**Time-control experiments.** In seven control experiments, the perfusion pressure was left at its basal value.

**Time frame for resetting of autoregulation.** The perfusion pressure was reduced in one step to 88 mmHg. After different time intervals (5 min, 10 min), the clamp was released for 1 min to allow the perfusion pressure to return to the spontaneous value. The perfusion pressure was then reduced again.
for the remainder of the 30-min period. Twelve rats were used for the 10-min experiments, and eight rats were used for the 5-min experiments.

**Analysis**

Plasma renin concentration (PRC) was measured using the protocol of Lykkegaard and Poulsen (13). Aliquots of plasma were diluted 20- to 80-fold with Tris buffer containing human albumin, and 5-µl portions of these samples were incubated for 24 h at 37°C with 20 ml of a reaction mixture that contained purified rat renin substrate (~1,200 ng ANG I equivalents/ml). This incubation was followed by radioimmunoassay of generated ANG I. PRC was measured in reference to renin standards obtained from the National Institute for Biological Standards and Control (Potters Bar, Herts, UK; 1 mgGoldblatt unit (GU) = 160 pg ANG I·ml⁻¹·h⁻¹).

**Statistics**

Results are presented as means ± SE of original or normalized data. RBF changes were compared by ANOVA for repeated measurements on normalized data. If a significant difference between means was found in the ANOVA, points at which there were significant differences from the respective control values were detected using the least-significant difference test for post hoc comparisons.

PRCs before and after the experiment were compared using Student's *t*-test for paired measurements. A *P* value < 0.05 was considered significant.

**RESULTS**

**Resetting of Autoregulation**

Mean arterial pressure and initial RBF are shown in Table 1 for the animals used in the resetting experiments. The animals used in the clamped [ANG II] and the methoxamine experiments had slightly higher arterial pressures than the control rats for reasons not apparent. Otherwise, the rats were of comparable physiological status.

After inhibition of ACE, RPP decreased from 108 ± 2 to 100 ± 2 mmHg (*P* < 0.01) and RBF increased from 7.9 ± 0.4 to 8.5 ± 0.5 ml/min (*P* < 0.01). After subsequent infusion of ANG II, the RPP increased and RBF decreased to the levels observed before infusion of the ACE inhibitor.

Figure 1 shows the RBF autoregulation curves from control rats before and after the RPP had been kept at 65 mmHg for 15 min. The values were normalized to the RBF at 100 mmHg. During the first set of pressure-reduction steps, RBF was autoregulated until RPP was reduced to 80 mmHg (Fig. 1). At this point, RBF had decreased significantly from 100% to 95 ± 1% (*P* < 0.01). The mean inflection point was 85 ± 1 mmHg. When the perfusion pressure was kept at 65 mmHg, a steady decline in RBF was seen. RBF remained at 78% of the initial spontaneous RBF when the aortic clamp was released and the RPP allowed to return to its control value (Table 1 and Fig. 2).

When the stepwise reduction was repeated, autoregulation of the lowered RBF was apparent until RPP was decreased to 70 mmHg (Fig. 1). At 70 mmHg, RBF had decreased from 79 ± 2% to 77 ± 2% (*P* < 0.05). At 65 mmHg, RBF had decreased further to 75 ± 2% of the control RBF (*P* < 0.01). The mean inflection point for the second set of pressure reductions was 73 ± 2 mmHg, which was significantly lower than the value in the first set of reductions. At all perfusion pressures in the second set of pressure reductions, the RBF was significantly lower when compared with the corresponding RBF value in the first set of pressure reductions (*P* < 0.01 at all pressures).

**Table 1. Physiological status of the rats used in the autoregulation experiments**

<table>
<thead>
<tr>
<th></th>
<th>Control Rats (n = 20; 265 ± 7 g)</th>
<th>Clamped [ANG II] (n = 22; 283 ± 3 g)</th>
<th>Methoxamine (n = 7; 286 ± 6 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before reduction</td>
<td>After reduction</td>
<td>Before captopril</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>104 ± 1</td>
<td>111 ± 2†</td>
<td>108 ± 2*</td>
</tr>
<tr>
<td>RBF, ml/min</td>
<td>8.6 ± 0.6</td>
<td>6.9 ± 0.5†</td>
<td>8.0 ± 0.3</td>
</tr>
<tr>
<td>PRC, 10⁻⁶ GU/ml</td>
<td>27.8 ± 10.4</td>
<td>93.7 ± 11.9†</td>
<td>8.0 ± 0.3</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of rats. MAP, mean arterial pressure; PRC, plasma renin concentration; GU, Goldblatt units; RBF, renal blood flow; [ANG II], ANG II concentration. Values after renal perfusion pressure reduction were measured following release of the aortic clamp after 15-min reduction at 65 mmHg. *Significantly higher than control rats (*P* < 0.05). †Significantly different from before value (*P* < 0.01).
The RPP increased from 104 ± 1 to 111 ± 2 mmHg (P < 0.01; Table 1) after the aortic clamp of RPP at 65 mmHg for 15 min. PRC increased from 27.8 ± 10.4 × 10⁻⁵ to 93.7 ± 11.9 × 10⁻⁵ GU/ml (P < 0.01; Table 1) after the induced reduction of the RPP.

Figure 3 shows the RBF autoregulation curves before and after reduction of the RPP to 65 or 50 mmHg for 15 min in rats with a clamped RAS. When reducing the RPP down to 65 mmHg (n = 16), no response was seen in RBF. Therefore, RPP was further reduced to 50 mmHg (n = 6) until a response in RBF was found. As the response to RPP reduction above 65 mmHg was similar in the two groups, the results have been pooled in Fig. 3.

In these experiments, autoregulation of RBF was improved. Not until the RPP was reduced to 60 mmHg or lower did the RBF decrease significantly when compared with the value at 100 mmHg (Fig. 3). Further reduction of RPP caused RBF to decrease significantly at perfusion pressures of 60 and 50 mmHg. Mean inflection point for rats with a clamped [ANG II] was 62 ± 5 mmHg, which was significantly lower than the value in the control rats.

The 15-min reduction in RPP to 65 or 50 mmHg did not induce any steady decline in RBF when the ANG II level was clamped (Fig. 4), and when the aortic clamp was released, the RBF returned to 97 ± 1% of the control value (not significant). Also the autoregulatory curve was unchanged after the 15-min pressure reduction in that the RPP had to be reduced to 60 mmHg or lower before a decrease in RBF could be detected. The mean inflection point was 61 ± 5 mmHg and not significantly different from the inflection point found in the first set of pressure reductions. The RPP did not change after release of the aortic clamp after 15 min of pressure reduction to 65 or 50 mmHg (Table 1).

When RPP and RBF were restored after captopril infusion with methoxamine, there was no apparent autoregulation response and no obvious inflection point (Fig. 5). RBF decreased gradually when RPP was reduced in steps and fell to 92 ± 2% even at 90 mmHg.
No steady decline in RBF was seen when RPP was maintained at 65 mmHg for 15 min and RBF returned to 104 ± 11% of the initial response when the aortic clamp was released.

Repetition of the stepwise reductions did not affect the lacking ability to autoregulate. RBF changed significantly at 80 mmHg to 87 ± 7% from 97 ± 8% at 100 mmHg (P < 0.05). No inflection points were found.

**Regulation of RBF**

Table 2 summarizes the mean values for the various physiological parameters of the rats used in this series of experiments.

Figure 6 shows the RBF in normalized values from the rats with an intact and a clamped RAS when the RPP was reduced to 88 mmHg. Also shown is the RBF for the rats in the time-control group.

When comparing the normalized values of the six 5-min periods in the time controls with the two initial control periods (100%), the change in RBF from 100% to 98 ± 1% was insignificant (Fig. 6). The tendency of the PRC to decrease was insignificant (Table 2).

In the rats with an intact RAS, there was a gradual decline in RBF after a reduction of the RPP to 88 mmHg, a value within the autoregulatory range. To avoid any bias caused by the time frame of the experiments, the normalized values of RBF in the six 5-min periods at an RPP of 88 mmHg were compared with the respective value in the same period in the time-control rats. After 5 min of reduced perfusion pressure, the RBF was significantly decreased to 96 ± 2% (P < 0.05) compared with 100 ± 1% in the time-control rats. RBF decreased steadily down to 89 ± 2% after 30 min of reduced perfusion compared with the time-control value of 98 ± 1% (P < 0.05).

PRC increased significantly from 30.6 ± 7.3 to 55.8 ± 15.5 GU/ml (P < 0.05).

In contrast to the rats with an intact RAS, the rats with a clamped RAS did not show a significant decrease in RBF during the 30-min period in which the RPP was reduced to 88 mmHg (Fig. 6).

**Table 2. Physiological status of the rats used in the regulation experiments**

<table>
<thead>
<tr>
<th></th>
<th>Time Control (n = 7; 261 ± 9 g)</th>
<th>Regulation (n = 11; 265 ± 10 g)</th>
<th>Regulation (Clamped [ANG II]; n = 3; 276 ± 12 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>RPP, mmHg</td>
<td>103 ± 1</td>
<td>102 ± 1</td>
<td>102 ± 2</td>
</tr>
<tr>
<td>RBF, ml/min x g KW</td>
<td>5.0 ± 0.3</td>
<td>4.8 ± 0.3</td>
<td>5.4 ± 0.3</td>
</tr>
<tr>
<td>PRC, 10⁻⁶ GU/ml</td>
<td>20.5 ± 4.5</td>
<td>16.5 ± 6.3</td>
<td>30.6 ± 7.3</td>
</tr>
</tbody>
</table>

Values are means ± SE. KW, kidney weight. *P values are found within the group. Before values are means of the 2 initial control periods. After values are means of the 2 last periods (25 and 30 min). †Significantly different from before value (P < 0.05). *Significantly different from before value (P < 0.01).
**Table 3. Status of the rats used in the time frame experiments**

<table>
<thead>
<tr>
<th>Step 10 min (n = 12; 287 ± 7 g)</th>
<th>Step 5 min (n = 8; 283 ± 3 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before</strong></td>
<td><strong>After</strong></td>
</tr>
<tr>
<td>RPP, mmHg</td>
<td>101 ± 1</td>
</tr>
<tr>
<td>RBF, ml/min × g KW</td>
<td>6.1 ± 0.5</td>
</tr>
<tr>
<td>PRC, 10⁻⁵ GU/ml</td>
<td>27.1 ± 7.3</td>
</tr>
<tr>
<td><strong>Before</strong></td>
<td><strong>After</strong></td>
</tr>
<tr>
<td>RPP, mmHg</td>
<td>88</td>
</tr>
<tr>
<td>RBF, ml/min × g KW</td>
<td>5.6 ± 0.5</td>
</tr>
<tr>
<td>PRC, 10⁻⁵ GU/ml</td>
<td>47.0 ± 11.0</td>
</tr>
</tbody>
</table>

Values are means ± SE. P values are found within the group. Before values are means of the 2 initial control periods. After values are means of the 2 last periods (25 and 30 min). *Significantly different from before value (P < 0.05).

**Time Frame for Resetting of Autoregulation**

Table 3 summarizes the mean values for the various physiological parameters of the rats used in this series of experiments.

Figure 7 shows the response of RBF during a 1-min release of the aortic clamp after 5- or 10-min reduction of the RPP to 88 mmHg. After 5-min reduction of the RPP to 88 mmHg, the RBF had decreased to 92 ± 3% of the control value, which was significantly lower than that of the time-control group (100 ± 1%). When the clamp was released for 1 min, RBF increased to 98 ± 2%, which was not significantly different from the time-control value. However, it was significantly different from the value just before release of the clamp.

After 10-min reduction of the RPP to 88 mmHg, the RBF had decreased to 94 ± 2% of the control value. This was significantly lower than that of the time-control group in which the RBF remained at the control level (99 ± 1%). Releasing the clamp for 1 min caused no increase in RBF, which remained 95 ± 1% of the control value, significantly lower than that of the time-control group.

**DISCUSSION**

The present experiments were conducted to elucidate the relationship between autoregulation and regulation of RBF. The results demonstrate that normotensive rats regulate RBF to a lower level and at the same time reset autoregulation within a time period of 15 min when the RPP is reduced to a value within the autoregulatory range (88 mmHg). The downregulation of RBF and the resetting of autoregulation depended on an intact RAS. When RAS was clamped by simultaneous infusion of an ACE inhibitor and ANG II, the downregulation of RBF was abolished. Both regulation and autoregulation of RBF were abolished when the α₁-adrenergic agonist methoxamine was used to restore RPP and RBF.

A prolonged reduction in the RPP caused a gradual decrease in the RBF that evolved over a period of 10–30 min. We use the term regulation of RBF for this process. The downregulation of RBF occurred irrespectively of whether the prolonged reduction in RPP was set to a value within (88 mmHg) or below the autoregulatory range (65 mmHg). It is important to realize that the present observation is not in conflict with the well-known concept of autoregulation of RBF. The rats in the present study showed excellent maintenance of RBF as the RPP was acutely reduced within the autoregulatory range. However, if the reduced RPP was kept within the autoregulatory range and at the same time maintained at this level for a prolonged period, the initial autoregulatory response was overridden by a gradual decrease in the blood flow. Thus there was a slow adaptation of RBF to the lower perfusion pressure.

Because the RPP was kept constant, this adaptation must represent a gradual increase in renal vascular resistance. In the series in which the RPP was reduced to 65 mmHg, sudden release of the aortic clamp, and thus a restoration of the RPP to the control level, did not significantly increase the RBF. This is in agreement with a previous study by Holm et al. (7). These authors suggested that the maintenance of RBF at the lower level, despite the normalization of the RPP, represented a resetting of the autoregulatory mechanism.
This is indeed the case, as demonstrated by the present study. When the autoregulatory curve was reassessed after the release of the aortic clamp, it was evident that the new level of RBF was autoregulated down to an RPP of \( \approx 73 \pm 2 \) mmHg (Fig. 1). This is 10 mmHg lower than the lower limit found in the first set of pressure reductions and indicates that not only is autoregulation reset to a lower level of blood flow, but the curve is also shifted to the left, i.e., toward lower pressures.

This is in good agreement with the results of Cupples (2), who observed a similar downward and leftward shift of the autoregulatory curve when the RPP was kept below the lower limit of autoregulation for \( \approx 10 \) min. In contrast, Kvam et al. (11) found that a reduction in mean arterial pressure of 20% of the spontaneous pressure for 10 min did not affect the limits of autoregulation in normotensive rats. This corresponds to a decrease in RPP from 100 to 80 mmHg, which is a higher perfusion pressure and a shorter time frame than used both in the present experiments and in the study by Cupples (2). These differences in study design could explain the apparent dissimilarities of the results. Alternatively, but less likely, the differences could be due to the use of different breeds of rats and/or different anesthetics.

Regardless of whether the RPP was reduced to a value within (88 mmHg) or below the autoregulatory range (65 mmHg), the reduction was associated with a significant increase in the PRC (Tables 1 and 2). When the RAS was clamped, the gradual downregulation of RBF after the reduction of RPP was abolished (Figs. 4 and 6). In addition, a further resetting of autoregulation was absent (Fig. 3). This is in agreement with previous studies (2, 7) and shows that both the regulation of RBF and the resetting of autoregulation are mediated by the RAS. This is supported by the experiments in which methoxamine, instead of ANG II, was used to maintain vascular tonus. Methoxamine combined with an ACE inhibitor abolished the ability to autoregulate and regulate RBF.

The activation of the RAS was also evident from the increase in systemic arterial pressure after the decrease in RPP (Table 1). Clamping the RAS abolished this increase in arterial pressure (Table 1). ANG II is a potent renal vasoconstrictor that predominantly affects the efferent arteriole (6). In addition, it may indirectly cause constriction of the afferent arteriole through potentiation of the TGF mechanism (17). Together, these actions could explain the gradual increase in renal vascular resistance seen during the prolonged reduction of the RPP. In addition to increasing the maximum response of TGF, ANG II also shifts the feedback curve toward lower flow rates (17). This could be one mechanism whereby activation of RAS causes the observed leftward shift of the autoregulatory curve. Whether or not ANG II has any effects on the other autoregulatory mechanism, the myogenic response, is unknown.

The relationship between changes in perfusion pressure and renin release has been widely debated. It is generally accepted that renin release at perfusion pressures above the lower limit of autoregulation is low and increases steeply as pressure is reduced below the autoregulatory limit (4, 9). However, renin release may increase during pressure reductions, even at pressures within the autoregulatory range, depending on duration of the reduction of blood pressure, total body sodium (3, 19), and sympathetic nervous activity (10). The observation in the present study that clamping RAS abolished the downregulation of RBF adds further evidence to the fact that there is a physiologically significant increase in renin secretion even when the RPP is kept within the autoregulatory range.

An important question is whether the downregulation of RBF and the resetting of autoregulation represent one and the same process. In the time-frame studies, a significant downregulation of RBF was evident already after 5 min. However, when the clamp was released, the RBF returned to the control value. After 10 min, the RBF remained at the lower level even as the clamp was released. Thus the full resetting of the autoregulatory process occurred somewhat later than the downregulation of the RBF. This difference in the dynamics of the two processes indicates that they are not simply one and the same process, but that some differences exist between them. Clearly, more work is needed in this area.

To our surprise, clamping the RAS resulted in a significant lowering of the lower limit of autoregulation (Fig. 3). With RAS clamped, RBF did not decrease until RPP was reduced below \( 62 \pm 5 \) mmHg. In contrast, in the control rats, the RBF decreased significantly already at an RPP of \( 85 \pm 1 \) mmHg. This could appear to be at variance with previous studies, which have failed to demonstrate an effect of ACE inhibitors on RBF autoregulation (1, 2, 8, 14). The major difference between this study and the previous studies is that we infused ANG II to prevent the renal vasodilatation seen after the administration of an ACE inhibitor. This suggests that the better autoregulation seen in this study was related to the ANG II infusions and possibly a better preservation of tone in the renal vasculature.

However, when using the specific \( \alpha_{1} \)-adrenergic agonist methoxamine to preserve the renal vascular tone after infusion of an ACE inhibitor, we found that the ability to autoregulate and regulate RBF was completely abolished. Thus the response seen when RAS was clamped is not dependent on renal vascular tone alone, but seems to be due to an ANG II specific effect.

In conclusion, a prolonged reduction in RPP within or below the autoregulatory range results in a downregulation of RBF and a resetting of autoregulation to this new level. This is mediated by the RAS and appears to preserve autoregulatory capacity despite prolonged decreases in the arterial pressure.

**Perspectives**

The results of the present study suggest that autoregulation is a short-lived response that guards renal function against short-lived changes in the RPP. If the change in RPP is longer lasting, the RBF will be reset...
to accommodate this new pressure, and, at the same
time, autoregulation will reset to guard this new level of RBF against fluctuations in RPP. If resetting of autoregulation were not to occur when the RPP fell, the result would be a prolonged reduction in autoregulatory capacity with the possibility of severe disruptions in renal function should the pressure decrease further. Therefore, it appears that autoregulation maintains RBF around a certain set point in a fashion similar to how the baroreceptors control the arterial blood pressure. This is supported by the results of Persson et al. (16). Monitoring the blood pressure in conscious dogs for 4 h, they concluded that RBF behaved as if the autoregulatory set point changed between a few distinct values during the 4-h period, RBF being autoregulated around these values. Thus autoregulation does not prevent physiologically relevant changes in RBF, but rather acts to minimize fluctuations in response to short-lived changes in the arterial pressure.

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