Glomerular Hemodynamics in Persistent Renovascular Hypertension in the Rat

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SUMMARY We studied the glomerular hemodynamics and activity of the tubuloglomerular feedback system (TGFS) in Wistar rats with persistent hypertension 60 days after removal of the clipped kidney in the Goldblatt (two-kidney, one clip) hypertension model. Ten hypertensive rats (HBP) were compared with 12 normotensive ones (NBP). Micropuncture studies revealed that values for the single nephron glomerular filtration rate (SNGFR), glomerular plasma flow (Q_G), and afferent oncotic pressure (P_A) were similar in both groups, whereas glomerular capillary pressure (P_G) and effective filtration pressure (EFP) were higher in the HBP group (p < 0.05). A slight but insignificant increase in afferent resistance was present in the HBP group. A positive correlation was found between mean arterial pressure and stop flow pressure (SFP) (r = 0.64, p < 0.05) but not with SNGFR, suggesting a reduction in the ultrafiltration coefficient in hypertensive rats. This was further supported by studies of the activity of the TGFS, which demonstrated that interrupting flow to the macula densa was followed by a smaller increment in SNGFR in HBP, in spite of a similar rise in SFP. The mechanism responsible for decreasing glomerular permeability is unknown but could be related to structural changes in glomerular capillary or to an increase in intrarenal angiotensin II, as has been demonstrated previously in this model. It is suggested that these adaptations occurring in the kidney exposed to hypertension can contribute to the maintenance of elevated arterial pressure after removing the stenotic kidney. (Hypertension 5 (supp V): V-110-V-114, 1983)

KEY WORDS • persistent renovascular hypertension • afferent resistance • Kf • tubuloglomerular feedback sensitivity • contralateral kidney resetting

RENOSVASCULAR hypertension frequently persists after arterial stenosis has been corrected. This is usually the case in patients with long-standing hypertension in whom nephrosclerosis is present in the contralateral kidney.¹ In rats with Goldblatt hypertension (two-kidney, one clip), a similar situation has been described, characterized by persistence of elevated blood pressure after removal of the clipped kidney. This has been related to alterations in the contralateral kidney, because blood pressure becomes normal when the stenotic kidney is revascularized and the contralateral kidney is removed.²

The nature of these alterations is unknown. However, various functional changes have been described in the contralateral kidney during earlier stages of hypertension, before removal of the stenotic kidney. These include increased afferent resistance, reduced glomerular capillary permeability coefficient (Kf),³ ⁴ as well as impaired tubuloglomerular feedback activity⁵ with concomitant loss of autoregulation.⁶ At least from a theoretical point of view, these functional adaptations could also contribute to the maintenance of hypertension if they persist after nephrectomy of the clipped kidney.

We undertook the present study to evaluate the hemodynamic determinants of single nephron glomerular filtration rate (SNGFR) and the sensitivity of the tubuloglomerular feedback system (TGFS) in rats with persistent renovascular hypertension.

**Methods**

**Production of the Experimental Model**

Systemic hypertension was produced in 22 male Wistar rats weighing 150 g, by applying a silver clip (0.2 mm i.d.) to the left renal artery. Sixty days later, the left kidney was removed. Blood pressure was mea-
sured before the clip was placed and before nephrec-
tomy. Micropuncture studies were performed 60 days
after nephrectomy of the clipped kidney.

Systolic blood pressure was measured in the tail
with the rats awake, using a programmed electro-
sphygmomanometer and an MK-IV physiograph from
Narco Bio Systems (Houston, Texas). Rats were al-
lowed free access to water and received a standard rat
pellet diet throughout the experiments.

Micropuncture
Anesthesia was induced with Inactin (100 mg/kg
i.p.). Following tracheostomy, rats were prepared in
routine fashion for micropuncture, as described pre-
viously. Briefly, the jugular vein, femoral artery, and
bladder were catheterized with PE-50 tubing; the right
kidney was exposed through a flank incision, placed in
a lucite holder, and packed with thin-flowing silicone
(Xantoprene, Bayer) and the surface covered with Ringer’s solution. The femoral artery catheter was used for
periodic blood sampling and monitoring of the mean
arterial pressure (MAP) with a transducer (Model P23
Db, Statham Instruments, Gould Division Inc. Hato
Rey, Puerto Rico) connected to a direct writing record-
er (Model 7712, Hewlett Packard, Waltham, Massa-
chusetts). During the operation, rats received a con-
tinuous infusion of plasma (1% of body weight)
through the jugular catheter. A bolus injection of 100
mg of inulin in 1 ml of Ringer’s solution was given,
and immediately afterward an infusion of 4% inulin in
Ringer’s solution was started at a rate of 3.2 ml/hr.
After operation, a period of 60 minutes was allowed
before tubular collections.

In all experiments, glomerular hemodynamics were
measured as follows: exactly timed (3-minute) sam-
ple of fluid were collected from the proximal tubules
after inserting an oil block in six nephrons for determi-
nating flow rate, inulin concentration, and calculation of SNGFR. Coincident with these tubular fluid collec-
tions, three or four samples of femoral arterial blood
were obtained in each period for determination of sys-
temic arterial hematocrit (Hct) and inulin concentra-
tion in plasma. In addition, two or three samples of femoral arterial blood plasmas, usually in duplicate, using the fluorometric method of Viets et al.13

Results are expressed as means ± standard error.
Student’s t test was used for statistical analysis.
Results

Renal artery stenosis produced sustained hypertension after a few days in all rats. Systolic blood pressure rose from 101 ± 4 to 171 ± 6 mm Hg at 2 months. Nephrectomy of the clipped kidney normalized blood pressure in 12 rats (NBP), and 10 remained hypertensive (HBP). During the hypertensive stage, there was no difference in systolic pressure between HBP and NBP (173 ± 10 vs 170 ± 7 mm Hg).

Values for SNGFR, Qa, and \( \Pi_a \) were similar in both groups (table 1). SNGFR and Qa were elevated as expected 2 months after unilateral nephrectomy. Persistence of high blood pressure was associated with an increment in SFP, glomerular capillary pressure (PC), and mean effective glomerular filtration pressure (EPFP). All these differences were statistically significant (\( p < 0.05 \)).

Afferent resistance was increased in most of the rats of the HBP group. However, the difference between mean values (2.11 ± 0.24 vs 1.53 ± .26 dyn-sec-cm\(^{-3}\)) did not reach statistical significance (\( p < 0.0625 \)) because of individual variability.

The values for Kf showed no difference between groups, even though in the HBP group, similar values of SNGFR were associated with higher levels of PC and SFP, suggesting that glomerular permeability was actually reduced.

To further evaluate the relationship between SFP and SNGFR and possible alterations in Kf in the hypertensive rats, values of MAP, SNGFR, and SFP were analyzed individually for each rat from both groups. As shown in figure 1, SNGFR did not rise in rats with a higher MAP despite an increasing stop flow pressure \( (r = 0.64, p < 0.05) \). These data suggest that persistence of hypertension after nephrectomy of the clipped kidney is associated with a decrease in glomerular permeability, which is more apparent with greater degrees of hypertension.

The tubuloglomerular feedback system (TGFS) was studied in nine of 12 NBP and seven of 10 HBP rats. The activity of this system was evaluated by the changes in SFP and SNGFR induced by interrupting tubular flow to the macula densa. The magnitude of these changes reflected the activity of the system which is directly influenced by the level of systemic MAP. Results are shown in table 2.

Stop flow pressure increased when perfusion to the macula densa was stopped in both groups. All increments were significant, and no difference in the magnitude of the changes was apparent between groups. Similarly, SNGFR measured in the distal tubule was decreased compared to estimates based on collections of fluid made from the proximal tubule when the flow distal to the collection site was interrupted. However, the magnitude of the changes was strikingly different between the groups. In the NBP group, in which MAP was 105.8 ± 2.8 mm Hg, a marked increment in SNGFR \( (23.4 \pm 5.6 \text{ nl/min}, p < 0.01) \) was observed.

The tubuloglomerular feedback system (TGFS) was analyzed in rats with normal blood pressure (NBP) and high blood pressure (HBP) after nephrectomy of the clipped kidney.
In contrast, the HBP group, the rise in SNGFR was considerably smaller (11.0 ± 3.8), in spite of a much higher level of systemic MAP (135.9 ± 2.9 mm Hg), indicating a decreased sensitivity of the tubuloglomerular feedback system.

**Discussion**

The aim of our study was to characterize the glomerular hemodynamics in a model of persistent renovascular hypertension after nephrectomy of the clipped kidney. A slight increase in the afferent resistance, normal GFR in spite of increased stop flow pressure (SFP), and a decrease in the TGFS sensitivity were associated with this form of hypertension. Increased afferent resistance has previously been shown in the earlier stages of this model and in other models of experimental hypertension except those that are salt-dependent. The increase in afferent resistance with elevated MAP suggests that it occurs in response to autoregulation. However, this could also be secondary to structural damage associated with a reduction in the arterial lumen, as has been previously described by different methods (microspheres, scanning microscopy) in other experimental models.

The finding in the hypertensive group that the rise in SFP was not followed by a concomitant increase in SNGFR suggests a reduction in glomerular permeability. However, the difference in Kf values between groups did not reach statistical significance, but the observed correlation between individual values of MAP and SFP indicates that, at least in the more hypertensive rats, a decreased glomerular permeability could be present. On the other hand, when we analyzed the response to interruption of flow to the macula densa, the increase in SNGFR in the hypertensive rats was significantly less, in spite of a similar increase in SFP, further supporting a coexistent reduction in glomerular capillary permeability. The reduced Kf could be due to structural alterations in the capillary wall that diminish permeability. In different forms of hypertension, including human, thickening of the basal membrane has been demonstrated in early stages, Steiner et al. and Schweitzer et al. have suggested that the increase in capillary pressure that appears early in the course of hypertension could be the cause of this change in capillary permeability. However, in other models of hypertension in which capillary pressure increases even more, Kf is reported to be normal or even increased.

A reduction in Kf could also result from mesangial contraction by reducing the effective filtration area. Recently, Schor et al. have suggested that angiotensin II is the final pathway by which vasoactive substances regulate Kf through mesangial contraction. Our model has been characterized as associated with activation of the renin-angiotensin system (RAS), and decreased values of Kf in early stages. In late stages, as in our study, plasma values of angiotensin II are normal but hypertension responds to inhibition of the RAS with converting enzyme inhibitor. Moreover, Mendelsohn has recently shown that the contralateral kidney has a normal or increased concentration of angiotensin II in spite of concomitant renal depletes. These data would suggest that the decrease and maintenance of low values of Kf could be secondary to a persistent generation of local angiotensin II.

Independent of its mechanism, this alteration becomes particularly important because in conditions of filtration pressure disequilibrium, as occurred in our rats, SNGFR is highly dependent on Kf and rather independent of flow rate or transcapillary hydraulic pressure. Under such conditions, a high filtration pressure is required to overcome the reduction in Kf in order to maintain GFR at normal levels.

In our study, the sensitivity of the TGFS was evaluated by the changes induced in SNGFR by interrupting flow to the macula densa (proximal vs distal SNGFR). However, the differences observed in the NBP group (23.4 nl/min, 63%) and HBP group (11 nl/min, 29%) appear to be considerably greater than those previously reported in normal two-kidney rats (6 nl/min, 24%). One possible explanation for this discrepancy is that, in our rats there was considerable hypertrophy of the remaining kidney that resulted in a 65% increase of basal (distal) SNGFR; under these conditions it is possible that the same changes in pressure and flow could lead to greater changes in filtration rate.

Independent of absolute values, our results demonstrated a clear difference between the NBP and HBP groups, indicating that persistent hypertension was associated with diminished sensitivity of the tubuloglomerular feedback system. This finding has been shown previously in earlier stages of Goldblatt II hypertension. The mechanism responsible is unknown, but it has been proposed that lack of angiotensin II and/or vascular damage of the afferent arteriole could be the causal factor. Recent studies by Mendelsohn and Ploth et al. would tend to discard the first possibility. On the other hand, demonstration that structural alterations in the afferent arteriole were not associated with a loss of TGFS sensitivity in other experimental mod-
els\textsuperscript{15} militates against the second one. An additional possibility is that this alteration resulted from a decreased glomerular capillary permeability coefficient. Previous studies by Ichikawa et al.,\textsuperscript{23} have demonstrated that the response to TGFS is partly mediated by modifications in Kf. Accordingly, if Kf is reduced, the same change in filtration pressure will induce a smaller change in SNGFR. In our study, interrupting flow to the macula densa in the HBP group was followed by a smaller rise in SNGFR, in spite of a similar increment in stop flow pressure.

In summary, persistent renovascular hypertension was associated with slightly increased afferent resistance, diminished glomerular capillary permeability, and hyporesponsiveness of TGFS. All these alterations seem to reset the kidney in such a way that increased filtration pressure is required to maintain the GFR at normal levels. At the same time, these adaptations of renal function can contribute to perpetuate elevated systemic arterial pressure.

References

23. Ichikawa I, Brenner BM: Critical analysis of the effector limb of the tubulo-glomerular (TG) feedback mechanism. 8th Int Congress of Nephrology 8: 12, 1981
Glomerular hemodynamics in persistent renovascular hypertension in the rat.
J Herrera-Acosta, F Gabbai, M Franco, E Tapia, G Linfa, L Díaz and J Campos

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