Role of Kinins in the Control of Renal Papillary Blood Flow, Pressure Natriuresis, and Arterial Pressure

Jerónimo Tornel, María Isabel Madrid, Miguel García-Salom, Klaus J. Wirth, Francisco J. Fenoy

Abstract—The present study evaluated the effects of blocking kinins with the bradykinin B2 receptor antagonist Hoe140 on the relationship between renal perfusion pressure, papillary blood flow (PBF), and sodium excretion. To determine the relevance of renal kinins in the long-term control of arterial pressure, the effect of a chronic intrarenal infusion of Hoe140 on arterial pressure and sodium balance was also studied. PBF was not autoregulated in volume-expanded rats, and the administration of Hoe140 reduced PBF (~30%) and improved PBF autoregulation. The kinin antagonist also decreased sodium excretion (~35%) and blunted pressure natriuresis with no whole-kidney renal hemodynamic changes. These effects may be mediated through nitric oxide (NO), because in rats pretreated with N\(^{-}\)-nitro-L-arginine methyl ester, Hoe140 had no additional effects on PBF or pressure natriuresis. A role for NO in mediating the renal response to Hoe140 is also supported by the finding that Hoe140 reduced basal urinary NO\(_3^{−}\)/NO\(_2^{−}\) excretion (~33%), and it blunted the arterial pressure–induced increase in NO\(_3^{−}\)/NO\(_2^{−}\) excretion, which is compatible with the idea that the pressure-natriuresis response may be mediated through kinins and NO. The importance of kinins in long-term regulation of arterial pressure is demonstrated by the severe arterial hypertension (172±6 mm Hg) induced during the chronic intrarenal infusion of Hoe140 associated with sodium and volume retention. These data suggest that renal kinins and NO may be a part of the renal mechanism coupling changes in arterial pressure with modifications in PBF and sodium excretion, therefore contributing to the long-term control of arterial pressure. (Circ Res. 2000;86:589-595.)

Key Words: bradykinin ■ nitric oxide ■ renal medulla ■ kidney ■ renal hemodynamics

Although in the past few decades many studies have indicated that renal kallikreins and kinins seem to be important in regulating renal sodium excretion, the role of this hormonal system in the long-term control of renal function and arterial pressure remains to be established.1,2

In recent years, considerable advances have been made in our understanding of the role of the renal medulla controlling sodium excretion in normal condition and in hypertension.6 Although cortical blood flow (CBF) and glomerular filtration change very little within a broad range of renal perfusion pressure (RPP), papillary blood flow (PBF) is not autoregulated, and it has been hypothesized that as arterial pressure rises, medullary blood flow, vasa recta capillary pressure, and renal interstitial pressure increase, leading to a fall in tubular sodium reabsorption. This mechanism is thought to be non-adaptive and responsible for the long-term control of arterial pressure.6 According to this hypothesis, arterial pressure is dependent on humoral factors regulating the renal medullary circulation, such as NO and kinins. Blockade of B2 kinin receptors selectively lowers PBF and blunts the natriuretic response to volume expansion without affecting CBF or glomerular filtration,7 whereas the local infusion of bradykinin into the renal medullary interstitium increases PBF and sodium and water excretion,8 with no whole-kidney hemodynamic effects. The renal medullary vasodilatation produced by kinins seems to be mainly due to NO production.8 A role for NO in pressure natriuresis is likely because NO synthesis blockade blunts pressure natriuresis and improves medullary blood flow autoregulation.9,10 Because the preglomerular autoregulatory vasoconstriction should increase endothelial shear stress as arterial pressure rises, it has been postulated that the vascular endothelium may be the sensor, and NO may be one of the mediators coupling preglomerular elevations in arterial pressure with reductions in tubular sodium and water reabsorption, by increasing medullary blood flow.9

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kinins may be a part of this mechanism because they can be released by the endothelium in response to increased shear stress\(^1\) and also because their renal medullary actions are due to NO release.\(^8,11,12\) Therefore, to test the hypothesis that kinins and NO are a cascade of endothelium-derived mediators coupling preglobular changes in arterial pressure to modifications in renal medullary blood flow and tubular sodium reabsorption, in the present study the effect of the long-acting and potent bradykinin B2 antagonist Hoe140 on pressure natriuresis and PBF autoregulation was evaluated. The role of NO in mediating the renal effects of Hoe140 was also studied. Finally, to demonstrate that the effect of kinin receptor blockade on pressure natriuresis is not a transient phenomenon but a long-term control mechanism of arterial pressure, the effects of a chronic Hoe140 intrarenal infusion due to NO release.\(^8,13\) Therefore, to test the hypothesis that the role of NO, vehicle (group 7), NAME (groups 8 and 10), or Hoe140 (groups 9 and 11) was administered intravenously, and later, either Hoe140 (experiment 1) and Hoe140 + NAME (experiment 2, group 3), or indomethacin (INDO, experiment 1) and indomethacin + Hoe140 (experiment 2, group 4). Bottom, Reversal of the effects of Hoe140 by intrarenal interstitial medullary infusion of bradykinin (BK, 0.1 and 1 \(\mu\)g/min). *Significant difference from the control value of the same group. †Significant difference from the previous value of the same group.

RPP were determined 3 consecutive times in groups 1 (control, Hoe140, and Hoe140 + N\(^\text{-nitro-L-arginine methyl ester [NAME]})\), 2 (control, NAME, and NAME + Hoe140), and 3 (saline, time control). The dose of Hoe140 (35 nmol \(\cdot\) kg \(^{-1}\) \cdot min \(^{-1}\) IV) was the minimum that lowered sodium excretion acutely and abolished the hypotension after a 100-ng IV bolus of bradykinin. The dose of NAME (37 nmol \(\cdot\) kg \(^{-1}\) \cdot min \(^{-1}\) IV) was the minimum that blunted pressure natriuresis.\(^9\) The finding that there was no additive effect between Hoe140 and NAME on PBF was interpreted as if Hoe140 reduced PBF by lowering NO, assuming that PBF did not reach the minimum after Hoe140 and can be lowered further. To show this, PBF was measured in groups 4 (Hoe140 and Hoe140 + indomethacin, 5 mg/kg IV) and 5 (indomethacin and indomethacin + Hoe140). In group 6, the specificity of Hoe140 was tested by locally infusing bradykinin (0.1 and 1 \(\mu\)g/min) into the renal medullary interstitium\(^8\) after Hoe140.

To examine the effects of Hoe140 on pressure natriuresis and the role of NO, vehicle (group 7), NAME (groups 8 and 10), or Hoe140 (groups 9 and 11) was administered intravenously, and later, either Hoe140 (group 10) or NAME (group 11) was added to the infusion in anesthetized, volume-expanded rats. Urinary nitrate/nitrite (NO\(_x\)) excretion was measured in groups 12 (saline, n=6), 13 (NAME), and 14 (Hoe140) using a Griess-based kit (Boehringer).

### Materials and Methods

Laser-Doppler blood flow experiments were performed in volume-expanded, thiobutabarbital-anesthetized Munich-Wistar rats\(^6,10,14\) to study the effect of Hoe140 on PBF autoregulation and the role of NO in mediating these effects. The relationships between CBF, PBF, and

### Effects of NAME and Hoe140 on MAP, RBF, GFR, UF, Sodium Excretion (UNaV), and Fractional Sodium Excretion (FNa)

<table>
<thead>
<tr>
<th>Group</th>
<th>MAP, mm Hg</th>
<th>RBF, mL \cdot min \cdot g(^{-1})</th>
<th>GFR, (\mu)L \cdot min \cdot g(^{-1})</th>
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<tr>
<td></td>
<td>Control</td>
<td>Exp 1</td>
<td>Exp 2</td>
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<tr>
<td>7, control</td>
<td>136 ± 4</td>
<td>133 ± 3</td>
<td>135 ± 2</td>
</tr>
<tr>
<td>8, NAME</td>
<td>137 ± 5</td>
<td>145 ± 4*</td>
<td>147 ± 5*</td>
</tr>
<tr>
<td>9, Hoe140</td>
<td>140 ± 3</td>
<td>138 ± 4</td>
<td>141 ± 5</td>
</tr>
<tr>
<td>10, NAME + Hoe140</td>
<td>142 ± 2</td>
<td>153 ± 3*</td>
<td>155 ± 4*</td>
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<td>11, Hoe140 + NAME</td>
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<td>138 ± 3</td>
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<td>147 ± 3*</td>
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Data are mean ± 1 SEM. Rats in group 7 were infused with saline throughout the experiment. Rats in group 8 were treated with NAME (37 nmol \(\cdot\) kg \(^{-1}\) \cdot min \(^{-1}\)) in experimental periods (Exp 1 and 2. Rats in group 9 were infused with Hoe140 (35 nmol \(\cdot\) kg \(^{-1}\) \cdot min \(^{-1}\) during experimental periods 1 and 2. Rats in group 10 were infused with NAME in experimental period 1 and with NAME + Hoe140 in experimental period 2. Rats in group 11 were infused with Hoe140 in experimental period 1 and with Hoe140 + NAME in experimental period 2.

*Significant difference from the control value of the same group.

\(\text{Hoe140} (35 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1})\) and \(\text{Hoe140} + \text{NAME} (37 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1})\)
Chronic intrarenal and intravenous infusions were undertaken to evaluate the long-term effects of Hoe140 on arterial pressure. Two weeks after a left nephrectomy, catheters were inserted into the femoral artery for mean arterial pressure (MAP) measurements, and in groups 17 and 19, also into the femoral vein for infusions. The rats in groups 15, 16, and 18 underwent catheterization of the right suprarenal artery.\textsuperscript{15} These lines were threaded through a flexible spring connected to a swivel, and free access to standard rat chow (0.4\% sodium; sodium intake of 2.87 mmol/day) was allowed for 4 days. Then, an infusion of saline (group 15, 5 mL every 24 hours intrarenally), NAME (185 pmol \cdot kg\textsuperscript{-1} \cdot min\textsuperscript{-1} intrarenally in group 16 or intravenously in group 17), or Hoe140 (185 pmol \cdot kg\textsuperscript{-1} \cdot min\textsuperscript{-1} intrarenally in group 18 or intravenously in group 19) was then started and continued for 10 days. The doses of NAME and Hoe140 were the minimum intrarenal doses that increased arterial pressure. Sodium and volume balances were measured in uninephrectomized rats (group 20) with right suprarenal and femoral artery catheters.\textsuperscript{16} Because Hoe140-induced hypertension was hypothesized to be caused by sodium retention, these rats were maintained on high sodium intake (7 mmol/day, 50 mL/day of saline). When balance was achieved (5 days after surgery), MAP and sodium and water balances were determined during 4 control days and later (5 days after surgery), MAP and sodium retention was associated with significant sodium and volume retention. However, no significant changes were observed in hematocrit (42.8±0.3\% on day 0 and 38.6±1.8\% on day 10) or in creatinine clearance (0.60±0.05 on day 0 and 0.52±0.08 mL/min×g\textsuperscript{-1} on day 10) after 10 days of intrarenal Hoe140. A 10 mg/kg dose of losartan did not normalize MAP in these rats (from 165±2 to 145±2 mm Hg on day 10 of intrarenal Hoe140 infusion).

**Results**

Hoe140 had no effect on CBF, but it lowered basal PBF and also shifted the RPP-PBF relationship by reducing PBF in the range of 120 to 140 mm Hg of RPP, increasing the PBF autoregulation index (from 0.1±0.4 to 0.56±0.14). The subsequent addition of NAME to the infusion reduced CBF by ≈10\%, but it had no further effects on PBF (Figures 1A and 2B).

NAME alone reduced CBF by ≈10\% at all RPPs studied, lowered basal PBF, and also shifted the RPP-PBF toward higher pressures, increasing the papillary autoregulation index (from 0.20±0.04 to 0.56±0.14). The subsequent addition of Hoe140 to the infusion solution containing NAME had no further effects on CBF and PBF (Figures 1B and 2B).

Hoe140 reduced basal PBF (∼31\%), and the subsequent addition of indomethacin to the infusion reduced PBF further (∼36\%). Indomethacin alone lowered PBF (∼42\%); the succeeding addition of Hoe140 to the infusion reduced PBF additionally (∼38\%, Figure 2B).

Hoe140 reduced PBF (∼28\%), and the subsequent renal medullary interstitial infusion of bradykinin (0.1 and 1 µg/min) increased PBF to 86\% and 104\% of control, respectively (Figure 2B).

NAME increased MAP (Table) and reduced renal blood flow (RBF), sodium excretion, and urine flow (UF). Hoe140 had no effects on RPP or renal hemodynamics. However, Hoe140 lowered UF, sodium excretion, and fractional sodium excretion. In rats pretreated with NAME, Hoe140 had no effects on renal function. In addition, in rats pretreated with Hoe140, NAME increased MAP and lowered RBF, but it had no additional renal effects.

The administration of either NAME or Hoe140 severely blunted pressure natriuresis (Figure 3). In rats given NAME, this effect was associated with reductions in RBF (∼24\%, Figure 4) and glomerular filtration rate (GFR) (∼17\%). In contrast, Hoe140 blunted pressure natriuresis with no hemodynamic effects. In rats pretreated with NAME, Hoe140 had no further effects on pressure natriuresis. Also, in rats pretreated with Hoe140, NAME had no additional effects on pressure natriuresis. Both NAME and Hoe140 lowered urinary NOx excretion (∼31\% and ∼34\%, respectively, Figure 5). Increasing arterial pressure from 100 to 140 mm Hg produced an elevation in urinary NOx excretion (212\%) that was blunted by pretreatment with either NAME or Hoe140.

The chronic intrarenal infusion of saline (Figure 6) had no effects on MAP, whereas intrarenal NAME elevated arterial pressure by 34 mm Hg. However, the same dose of NAME infused intravenously had no significant effects on MAP. The intrarenal infusion of Hoe140 raised MAP from a control value of 108.7±4.3 to 171.8±6.6 mm Hg after 10 days. The same dose of Hoe140 had no effect on MAP when administered intravenously.

In sodium balance experiments (Figure 7), arterial hypertension was associated with significant sodium and volume retention. However, no significant changes were observed in hematocrit (42.8±0.3\% on day 0 and 38.6±1.8\% on day 10) or in creatinine clearance (0.60±0.05 on day 0 and 0.52±0.08 mL/min×g\textsuperscript{-1} on day 10) after 10 days of intrarenal Hoe140. A 10 mg/kg dose of losartan did not normalize MAP in these rats (from 165±2 to 145±2 mm Hg on day 10 of intrarenal Hoe140 infusion).
However, the hypotension after losartan was greater in rats given Hoe140 than in control rats (−20.4 ± 1.2 mm Hg in rats given Hoe140 versus −8.0 ± 2.2 mm Hg in control rats).

**Discussion**

In the present study, Hoe140 reduced renal PBF at high RPP and improved PBF autoregulation, without any effects on the renal cortical circulation. This is consistent with previous reports showing that other B2 antagonists lowered PBF. The source of renal medullary kinins is unknown, because most of the renal kallikrein is produced in the connecting tubule, within the renal cortex. The effects of Hoe140 on PBF are compatible with a vascular source from which kinins can reach the renal interstitial fluid, where bradykinin is present. Interestingly, kinins can be synthesized and released by endothelial cells and mediate part of the endothelial shear stress–induced changes in blood flow. It has been previously reported that NO synthesis blockade abolishes the pressure-induced increases in medullary blood flow, and it has been hypothesized that as arterial pressure rises, endothelial shear stress increases in the preglomerular vasculature, releasing NO and originating the intrarenal redistribution of blood flow toward the renal medulla that causes the pressure natriuresis response. The results in the present study demonstrating that kinin blockade produces the same effect, increasing PBF autoregulation, are compatible with the hypothesis that kinins may be part of the mechanism that mediates the lack of blood flow autoregulation in the renal medulla. This effect may be mediated through NO, the main mediator of the renal medullary actions of bradykinin, because Hoe140 has no additional effects on PBF in rats pretreated with NAME. Interestingly, the renal medulla is especially rich in NO synthase, and medullary NO levels are higher than in the cortex. Also, bradykinin has been shown to stimulate endothelial B2 receptors in descending vasa recta, increasing endothelial intracellular calcium, a well-known stimulus for NO release. This hypothesis is compatible with the fact that both Hoe140 and NAME blunt pressure natriuresis. Therefore, kinins and NO could act sequentially as the mediators leading to increased PBF and natriuresis when arterial pressure is elevated.

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**Figure 3.** Comparison of the relationship between RPP and UF (top), sodium excretion (UNa V, middle), and fractional sodium excretion (FNa, bottom) of control rats (group 6) and also of rats treated with NAME (group 7), Hoe140 (group 8), NAME + Hoe140 (group 9), or Hoe140 + NAME (group 10). †Significant difference from the same value of the control group.

**Figure 4.** Comparison of the relationship between RPP and RBF (top) and GFR (bottom) of control rats (group 6) and also of rats treated with NAME (group 7), Hoe140 (group 8), NAME + Hoe140 (group 9), or Hoe140 + NAME (group 10). †Significant difference from corresponding value of control group.
Renal kinins inhibit sodium transport in the distal nephron directly, through activation of B₂ receptors and the subsequent increase in eicosanoids and NO. Blocking either B₂ receptors with Hoe140 or kallikrein with Fab fragments of monoclonal antibodies lowers sodium and water excretion, which is associated with a fall in urinary prostaglandin E₂ (PGE₂) and interstitial levels of PGE₂ and cGMP. This indicates that both NO and PGE₂ mediate the renal effects of kinins. Nevertheless, the results of the present study, which show that NAME and Hoe140 have no additive effects on PBF, whereas Hoe140 reduced PBF after indomethacin, indicate that the renal medullary hemodynamic response to B₂ receptor blockade seems to be mainly dependent on NO. This conclusion is in agreement with a previous report that the medullary vasodilation produced by bradykinin is abolished by NAME.

The acute administration of Hoe140 lowered sodium excretion, with no effects on renal blood flow or glomerular filtration. This is in agreement with a previous study, showing that Fab fragments of monoclonal antibodies to rat urinary kallikrein reduced sodium and water excretion in conscious, volume-expanded rats. However, these data are in contradiction with other reports indicating that kinin receptor blockade does not alter sodium excretion in rats or dogs maintained on a high-sodium diet, but it lowers natriuresis in sodium-depleted animals. The reasons explaining these discrepancies are unknown, but they may be related to the use of kinin antagonists with a lower receptor affinity than Hoe140, and in other cases the lack of effect of Hoe140 on sodium excretion and arterial pressure may be due to the low dose used (from 20 to 80 pmol·kg⁻¹·min⁻¹ SC to 150 pmol·kg⁻¹·min⁻¹ SC of Hoe140), which is insufficient to induce sodium retention and hypertension when given systemically. Nevertheless, it seems clear that the renal sensitivity to kinin receptor blockade is greater under sodium depletion, and this is consistent with the previous finding that in rats fed a high-sodium diet, renal interstitial fluid kinin decreased 100-fold compared with levels in rats with normal sodium intake. However, although renal interstitial levels of kinins are very low in rats fed a high-sodium diet, it appears that even in these conditions, kinins are of importance in sodium balance and arterial pressure regulation, because the administration of an adequate dose of Hoe140 or antibodies to kallikrein reduces sodium excretion and induces arterial hypertension in normotensive, sodium-loaded rats.

The importance of this local renal medullary effect of Hoe140 improving PBF autoregulation is demonstrated by the finding that the compound also blunted pressure natriuresis because of increased tubular reabsorption, with no effects on RBF or GFR. These results are consistent with previous studies showing that interstitial medullary infusion of bradykinin increases medullary blood flow and sodium excretion with no whole-kidney hemodynamic changes. These medullary effects of kinins seem to be mainly due to increased NO production, because they are abolished by the administration of NAME. However, the data of the present study are in contradiction with a previous report that a kinin receptor antagonist did not affect basal sodium excretion or pressure natriuresis in dogs. The lack of effect of the earlier kinin analogs on renal function is probably due to the lower
receptor affinity binding and higher agonistic activity compared with Hoe140, which is up to 10^7 times more potent as a B2 antagonist than the previous peptidic blockers. The less potent peptidic antagonists lower sodium excretion only in sodium-depleted animals, which are more sensitive to kinin blockade.

A role for NO in mediating the effects of Hoe140 is likely, because NAME had no further effects on pressure natriuresis when given after Hoe140. To test this hypothesis, the effect of Hoe140 on the urinary excretion of NOX^-/NO_2^-, a marker for NO production within the kidney, was determined. Raising arterial pressure from 100 to 140 mm Hg increased the excretion of NOX >3-fold; also, NO synthesis blockade lowered baseline NOX excretion and abolished the arterial pressure–induced increase in NOX excretion, as previously reported. Interestingly, the administration of Hoe140 also lowered basal NOX excretion and blocked the pressure–induced increase in urinary NOX excretion, indicating that the effects of Hoe140 on pressure natriuresis are mediated through NO.

The hypothesis that renal kinins are important in the control of arterial pressure is based on studies showing that genetic alterations affecting this hormonal system produce arterial hypertension. However, this idea is in apparent contradiction with the finding that the chronic systemic infusion of Hoe140 has little effect on arterial pressure, even when administered with a high-sodium diet, unless the kinin antagonist is given with deoxycorticosterone acetate or angiotensin II. Consistent with those reports, in the present study the intravenous long-term administration of Hoe140 did not affect arterial pressure in rats fed a normal sodium diet, but the intrarenal infusion of the same dose of Hoe140 produced severe arterial hypertension (172 mm Hg after 10 days). In a previous study, a high dose of Hoe140 (5 mg/kg per day, ∼10-fold the dose used intrarenally in the present study) was given subcutaneously to normal brown Norway rats maintained on a 2% NaCl diet, producing arterial hypertension (166 mm Hg) and sodium and water retention. This indicates that the chronic systemic administration of lower doses of the antagonist does not achieve the intrarenal concentrations necessary to effectively block B2 kinin receptors. This may be due to the fact that Hoe140 is metabolized in the liver, and after the systemic administration of the B2 blocker, only a small fraction of the total dose (from 3.7% to 5.6%) is excreted as the intact, active compound in the urine, and the rest as an inactive metabolite.

The hypertensive effect of the intrarenal infusion of Hoe140 is in apparent contradiction with the fact that deficiencies in the kallikrein-kinin system originate salt sensitivity, rather than hypertension. Although the rats in the present study were not on a high-sodium diet, their daily sodium intake (∼2.8 mmol/day) may have been enough to induce sodium retention and elevate arterial pressure after intrarenal B2 receptor blockade. Nevertheless, the previous finding that transgenic mice lacking B2 receptors are not hypertensive unless they are given a high-sodium diet appears to be more compatible with a role for kinins as modulators of pressure natriuresis rather than as mediators of this response, as proposed in the present study. Recently, Mattson and Krauski reported that the administration of captopril to conscious mice for 5 days lowered arterial pressure from 114 to 58 mm Hg, which was associated with a significant sodium loss. In addition, it has been recently shown that plasma renin is as high as 1323 ng angiotensin I/mL per hour in normal mice and 620 ng angiotensin I/mL per hour in mice lacking the B2 receptor gene. Thus, it appears that in mice, arterial pressure is primarily controlled by the renin-angiotensin system and also that transgenic mice compensate for the B2 receptor deficiency by partially suppressing renin release. This extreme angiotensin dependence of arterial pressure in mice is unique and indicates that the mechanisms of regulation are different from other species studied, thus suggesting that the interpretation of data obtained in mice cannot be easily extrapolated and should be interpreted with caution.

In the present study, the hypertension produced by the intrarenal kinin antagonist is associated with significant sodium and volume retention. Most of this volume expansion seems to be extravascular, as indicated by the fact that hematocrit did not change. Also, the hypertension cannot be attributed to activation of the renin-angiotensin system, because losartan did not normalize arterial pressure in those
hypertensive rats. The macroscopic postmortem examination of the kidneys did not reveal any gross abnormality, and the creatinine clearances measured demonstrate that those rats were not in renal failure and that the infusion of Hoe140 did not affect glomerular filtration. Although the mechanism responsible for this volume retention remains to be established, it may be due to the renal medullary hemodynamic and tubular effects of Hoe140, blunting pressure natriuresis. This is compatible with the hypothesis that renal kinins are important mediators that contribute to the normal control of renal sodium excretion and arterial pressure.

In summary, the results of the present study indicate that renal kinins are an important control system of renal sodium excretion and arterial pressure. Also, the present study suggests that kinins and NO may be involved in coupling changes in arterial pressure with modifications in renal medullary blood flow and sodium excretion, thus mediating the pressure-diuresis and -natriuresis response.

Acknowledgments

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References

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