Renoprotective effects of nitric oxide in angiotensin II-induced hypertension in the rat

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Chin, So Yeon, Chi-Tarng Wang, Dewan S. A. Majid, and L. Gabriel Navar. Renoprotective effects of nitric oxide in angiotensin II-induced hypertension in the rat. Am. J. Physiol. 274 (Renal Physiol. 43): F876–F882, 1998.—Experiments were performed in anesthetized male Sprague-Dawley rats to determine whether increased nitric oxide (NO) activity during the development of hypertension exerts a protective effect on renal cortical blood flow (CBF) and medullary blood flow (MBF). The effects of acute NO synthase inhibition on renal function and on CBF and MBF, measured by laser-Doppler flow probes, were evaluated in control and ANG II-infused hypertensive rats, prepared by the infusion of ANG II at a rate of 65 ng/min via osmotic minipumps implanted subcutaneously for 13 days. In normotensive rats (n = 8), intravenous infusion of Nω-nitro-L-arginine (NLA; 20 µg·100 g⁻¹·min⁻¹) decreased CBF by 21 ± 4% and MBF by 49 ± 8% and increased blood pressure from 118 ± 1 to 140 ± 2 mmHg. In ANG II-infused rats (n = 7), CBF and MBF decreased by 46 ± 5% and 25 ± 6%, respectively, during infusion of NLA. Arterial pressure increased from 160 ± 5 to 197 ± 7 mmHg, which was a greater absolute increase than in normotensive controls. Basal renal blood flow (RBF), estimated from p-aminohippurate clearance and hematocrit, was similar in both the control (6.0 ± 0.5 ml·min⁻¹·g⁻¹) and hypertensive (6.0 ± 0.6 ml·min⁻¹·g⁻¹) rats. However, NLA-induced reductions in RBF averaged 60 ± 13% in the hypertensive rats, compared with 31 ± 9% observed in control rats. GFR in control (0.97 ± 0.03 ml·min⁻¹·g⁻¹) and hypertensive rats (0.78 ± 0.12 ml·min⁻¹·g⁻¹) decreased to a similar extent during the first 30-min period of NLA infusion. GFR returned toward control levels in control rats; in contrast, GFR remained significantly decreased in the ANG II-infused rats (0.58 ± 0.11 ml·min⁻¹·g⁻¹). Basal urinary sodium excretion (0.2 ± 0.08 µeq·min⁻¹·g⁻¹), fractional excretion of sodium (0.3 ± 0.13%), and urine flow (4.9 ± 0.39 µl·min⁻¹·g⁻¹) in hypertensive rats did not increase significantly after NLA treatment as occurred in normotensive controls. These data suggest that a compensatory increase in nitric oxide activity partially counteracts the vasoconstrictor influence of elevated ANG II levels to regulate renal hemodynamics and maintain cortical perfusion in the renal circulation.

These observations suggest an enhanced modulatory influence of NO on resting renal vascular tone and indicate that this could be a normal counteracting mechanism to maintain adequate RBF during conditions of enhanced vasoconstrictor influences mediating the hypertensive state. In ANG II-infused hypertensive rats, the progressive increases in arterial pressure could cause a greater endothelial shear stress, which is a potent stimulus for endothelial-derived NO synthesis and release (1, 15, 16, 21). Consequently, increased NO formation could partially counteract the ANG II-mediated vasoconstrictor effects and allow maintenance of RBF and GFR.

Several studies have suggested that NO activity may be greater in the medulla than cortex (3, 4, 20). Nakamichi et al. (20) observed that chronic systemic infusion of nitro-L-arginine methyl ester (L-NAME) decreased medullary blood flow (MBF) by 22% without any alterations in renal cortical blood flow (CBF). Similarly, Biondi and Romero (4) showed that the renal medulla has a greater capacity for the formation of cGMP, an index of nitric oxide synthase (NOS) activity, than does the renal cortex in basal and stimulated conditions. Although these studies demonstrate the importance of the renal medullary NO in exerting a tonic influence on the renal circulation, it is unclear to what extent differential changes in regional blood flow participate during the development of ANG II-induced hypertension in response to NO synthesis inhibition.

In view of the greater sensitivity of the renal vasculature to the modulatory influence of NO (11), it is possible that an enhanced NO activity in the cortical and medullary circulations contributes to the maintenance of renal perfusion during ANG II-induced hypertension. Therefore, the primary objective of this study was to determine whether increased NO activity during the development of ANG II-induced hypertension exerts a renoprotective effect on renal CBF and MBF, as well as on overall renal function. Accordingly, the effects of acute NO synthesis inhibition on renal function, including CBF and MBF, measured with laser-
Doppler needle fiber probes, were evaluated in normotensive and ANG II-infused hypertensive rats.

METHODS

Male Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA) were acclimatized in a temperature- and light-controlled room and allowed access to standard rat chow (Ralston-Purina, St. Louis, MO) and water ad libitum. The rats were randomly divided into control (n = 8) and ANG II-infused (n = 7) groups. Rats (180–210 g) were anesthetized with pentobarbital sodium (50 mg/kg ip) to implant minipumps. In one group of rats, synthetic ANG II (Sigma Chemical, St. Louis, MO) was delivered continuously at a rate of 65 ng/min via osmotic minipumps (model 2002; Alza) implanted subcutaneously at the dorsum of the neck. The ANG II was infused into the interstitium to allow slow absorption into the circulation. A sham operation was performed on the normotensive control rats. After recovery, systolic blood pressure (SBP), measured by tail-cuff plethysmography (Harvard Apparatus, South Natick, MA) was followed to monitor the systolic arterial pressures during the course of 13 days.

Renal clearance experiments were performed 13 days after the implantation of minipump or sham operation to assess renal hemodynamics and excretory function before and during acute NO synthesis inhibition. Rats were anesthetized with pentobarbital sodium (50 mg/kg ip) and placed on a thermoregulated surgical table to maintain body temperature at 37°C, monitored rectally. A tracheostomy was performed to maintain a patent airway. The left femoral artery was catheterized with polyethylene tubing (PE-50) filled with heparinized saline (100 U/ml) for arterial blood sampling and monitoring of mean arterial blood pressure via a Statham pressure transducer connected to a Grass polygraph. The left jugular vein was cannulated (PE-50) for continuous infusion of solutions. An isotonic (0.9%) saline solution containing 6% BSA (Sigma) was infused at a rate of 20 µl/min during surgery to replace volume losses. Thereafter, an isotonic saline solution containing 1% BSA, 7.5% Inutest (Laevosan, Linz, Austria), and 1.5% p-aminohippuric acid (PAH; Merck, Sharp & Dohme, West Point, PA) was infused for the duration of the experiment. Supplemental anesthetic was given as required via the tracheal cannula. As previously described (6), the left kidney was exposed through a flank incision and immobilized on a plastic holder. The left ureter was cannulated (PE-10) for urine collection.

Needle flow probes (500 µm diameter) connected to a laser-Doppler flowmeter (PeriFlex 4001; Perimed, Stockholm, Sweden) were used to measure the changes in renal CBF and MBF as demonstrated previously (14, 18). The flowmeter generates a voltage signal proportional to blood flow velocity in ~1 mm² of renal tissue directly under the probe. The flow probes were calibrated with a standard solution comprised of a colloidal suspension of 10-µm latex microspheres to normalize the voltage signals from each probes to the same level. Brownian motion of the standard motility solution provides an absolute value equal to a voltage signal output of 10 mV. The needle fiber probes were inserted directly into the kidney tissue in the cortical and medullary regions through small holes made in the renal capsule with a 27.5-gauge needle. The fiber tips were inserted into the cortex 1 mm beneath the surface of the kidney and 4 mm into the medulla to monitor relative flow changes in these two regions. Although the insertion of the probes is invasive, blood flow is measured in the undisturbed region ~1 mm beneath the tip of the optical fiber. Voltage output was recorded on a Grass polygraph. Zero flow was determined when the renal artery was completely occluded at the end of the experiment. At the end of each experiment, the kidney was excised to confirm the position of the needle probe tips. Animals with incorrectly placed probes were excluded from the study. Although direct validation of the needle laser-Doppler flow probes is a problem due to the absence of an absolute standard, a number of correlation studies indicate that the optical fibers provide reliable measurements of relative change in regional blood flow in the kidney (14, 18). In the present study, the needle laser-Doppler flow probes were shown to reflect parallel and simultaneous changes in CBF and MBF during the administration of bolus doses of vasodilators (acetylcholine and bradykinin) and of a vasoconstrictor (ANG II). The changes in CBF were correlated (r = 0.80, P < 0.01) with the changes in MBF. Figure 1 illustrates an example of the responsiveness of the laser-Doppler flow probes in the renal cortex and medulla during intravenous bolus injections of bradykinin and ANG II.

After completion of the surgical procedures, an equilibrium period of 1.5 h was allowed for the animals to establish steady state before initiating three consecutive 30-min control periods. After the control periods, a continuous intravenous infusion of the NOS inhibitor, N-nitro-L-arginine (NLA; Aldrich Chemicals, Milwaukee, WI), dissolved in an isotonic saline solution containing 1% BSA, 7.5% Inutest, and 1.5% PAH was administered, at a rate of 20 µg·100 g⁻¹·min⁻¹, in both the normotensive and hypertensive rats throughout the remaining three consecutive 30-min experimental clearance periods. The concentration of NLA in the perfusate was adjusted to maintain the same rate of volume infusion (20 µl/min) given during the control period. Previous studies from our laboratory (6) demonstrated that the dose of NLA used in

![Fig. 1. Examples of the responsiveness of the laser-Doppler flow probes in renal cortex (CBF) and medulla (MBF) during intravenous bolus injections of vasoconstrictor ANG II and vasodilator bradykinin (BK). MAP, mean arterial pressure.](http://aprenerophysiology.org/)
this study was the lowest dose eliciting near maximal inhibition of NO synthesis as estimated from attenuation of the hypotensive effects of both acetylcholine and bradykinin.

Urine was collected every 30 min throughout the experiment. At the midpoint of each 1-h clearance period, an arterial blood sample was taken. At the end of each experiment, the left kidney was removed, stripped of surrounding tissue, blotted dry, and weighed, so that we could normalize the data per gram of kidney weight. Microhematocrit measurements were performed on all arterial blood samples collected at the midpoint of each clearance period. The blood cells were then separated by centrifugation, and the plasma was removed. Urine flow was determined gravimetrically. Inulin and PAH concentrations in both plasma and urine were analyzed using colorimetric procedures. Sodium and potassium concentrations in plasma and urine samples were determined by flame photometry. Osmolality was measured with a vapor-pressure osmometer. Standard clearance formulas were used to calculate whole kidney GFR and renal plasma flow. RBF was estimated from the PAH clearance and hematocrit without correction for extraction ratio.

Data are expressed as means ± SE. Analysis of variance for repeated measures, followed by Newman-Keuls was performed for statistical differences within a group. Differences between two separate groups were evaluated by Student's unpaired t-test. Statistical significance was defined as P < 0.05 or exceeding the 95% critical value.

Time controls (n = 4) were performed on the ANG II-infused rats to assess the stability of the preparation following the surgical manipulations. As shown in Table 1, there were no significant changes in the mean arterial pressure, RBF, regional blood flows, GFR, urine flow, or sodium excretion throughout the six consecutive 30-min clearance periods of isotonic saline infusion.

RESULTS

Effect of acute systemic inhibition of NO synthesis by NLA on blood pressure. Before implantation of osmotic minipumps, SBP values in the conscious rats were not statistically different between the experimental groups, averaging 118 ± 4 and 125 ± 2 mmHg as shown in Fig. 2. In accordance with previous studies (29, 30, 32), ANG II-infused rats exhibited progressive increases in SBP over the course of a 12-day period. SBP in ANG II-infused rats increased from a control value of 125 ± 2 to 167 ± 3 mmHg by day 6 and continued to increase gradually to 200 ± 3 mmHg by day 12.

In the anesthetized rats, basal mean arterial blood pressures were significantly greater in the ANG II-infused rats than in normotensive controls (160 ± 5 vs. 118 ± 1 mmHg). The changes in blood pressure in response to NLA are depicted in Fig. 3. NLA infusion progressively increased mean arterial pressure (Fig. 3, bottom) by 37 ± 5 mmHg, from 160 ± 5 to 197 ± 7 mmHg in the ANG II-infused rats, compared with 22 ± 2 mmHg, from 118 ± 1 to 140 ± 2 mmHg in the control rats. The absolute increase in arterial pressure in the ANG II-infused rats was significantly greater than the increase in control rats (Fig. 3, top).

Effects of acute NLA treatment on renal hemodynamics. Acute NLA treatment in both control and ANG II-infused rats led to progressive decreases in CBF and MBF and in the whole kidney blood flow. The changes in CBF and MBF in response to NLA are depicted in top and bottom of Fig. 4, respectively. NLA administration...

Table 1. Time control studies in ANG II-infused rats

<table>
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<tr>
<th>Parameters</th>
<th>30</th>
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<th>90</th>
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<td>MAP, mmHg</td>
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<td>171±4</td>
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<td>RBF, ml·min⁻¹·g⁻¹</td>
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<td>103±5</td>
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<tr>
<td>(U_{Na})V, µg·min⁻¹·g⁻¹</td>
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<tr>
<td>Urine flow, µl·min⁻¹·g⁻¹</td>
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Values are means ± SE; n = 4 rats. For cortical and medullary blood flows, values are expressed as a percent of the overall mean calculated for all periods. Arterial pressure, renal hemodynamics, and excretory function were assessed during continuous infusion of isotonic saline for six consecutive 30-min clearance periods. No statistically significant differences were observed in any of the parameters examined during the clearance periods. MAP, mean arterial pressure; RBF, renal blood flow; CBF and MBF, cortical and medullary blood flows, respectively; \(U_{Na}\)V, urinary sodium excretion; GFR, glomerular filtration rate.
reduced CBF by 46 ± 5% in the ANG II-infused rats, which was greater than the decrease of 21 ± 4% in control rats. In contrast, the decrease in MBF of 49 ± 8% in the control rats was greater than the decrease of 23 ± 7% in the hypertensive rats. Thus, compared with the normotensive controls, CBF was reduced to a greater extent in the ANG II-infused rats. In contrast, the relative decrease in MBF caused by NLA was less in the ANG II-infused rats than in the control rats.

The RBF and GFR responses to NLA infusion are shown in the top and bottom of Fig. 5, respectively. Absolute basal RBF, estimated from PAH clearance and hematocrit, was similar in both groups. NLA administration reduced RBF by 60 ± 5%, from 6.0 ± 0.6 to 2.5 ± 0.5 ml·min⁻¹·g⁻¹ in the ANG II-infused rats; this decrease was greater than the decrease in RBF of 31 ± 9%, from 6.0 ± 0.5 to 4.0 ± 0.4 ml·min⁻¹·g⁻¹ observed in control rats. GFR values in normotensive control rats (0.97 ± 0.03 ml·min⁻¹·g⁻¹) and hypertensive rats (0.78 ± 0.12 ml·min⁻¹·g⁻¹) were decreased to a similar extent to 0.71 ± 0.03 and 0.56 ± 0.09 ml·min⁻¹·g⁻¹, respectively, during the first 30-min period of NLA infusion. However, GFR returned toward control levels during subsequent periods of NLA infusion in the control rats but remained significantly decreased throughout the remainder of the experimental period in the ANG II-infused rats.

**DISCUSSION**

The objective of the present study was to determine whether increased NO activity in the renal cortical and medullary circulatory beds contributes to the maintenance of RBF during the development of ANG II-induced hypertension. Accordingly, the effects of acute systemic inhibition of NO synthesis on total RBF, on regional blood flow in the cortex and medulla, measured with laser-Doppler fiber probes, and on GFR and sodium excretion were evaluated in normotensive and ANG II-infused hypertensive rats.
Previous studies in normotensive rats (2, 11, 25) and dogs (8, 13) as well as in isolated perfused kidneys (22, 31) have shown that NOS inhibition reduces basal RBF by 20–35%. Outer CBF, measured with laser-Doppler flowmetry (6, 13), and blood flow in single cortical capillaries, measured with fluorescence videomicroscopy (12), decreased to about the same extent as the total RBF. However, the GFR responses have been less consistent, either showing no change (12, 13) or a relatively smaller reduction than the RBF (9, 19, 25) depending on the dose and duration. In the present study, GFR responses showed an initial decrease but then returned toward basal levels during subsequent experimental periods. Furthermore, systemic infusions of the NOS blockers have consistently caused substantial increases in arterial pressure (2, 8, 9), which was likewise observed in the present study. Although such increases in arterial pressure complicate the interpretation of direct renal effects of NO synthesis inhibition, studies in rats have indicated that the increase in renal arterial pressure during NOS inhibition helps to maintain RPF and GFR, although there is still an increase in renal vascular resistance (31). Thus these studies are consistent with the concept that basal release of NO exerts a tonic vasodilator influence to maintain the relatively low vascular resistance that is characteristic of the kidney (21).

The results of the present study also provide evidence for a differential modulatory influence of NO on the CBF and MBF in the control rats. These data indicate that NO exerts a greater modulatory influence on the medullary circulation compared with its effect on the cortical circulation in normotensive rats. In line with these observations, Nakanishi et al. (20) demonstrated that chronic intravenous infusion of L-NAME decreased MBF by 22% without altering renal CBF. These changes in MBF were associated with concomitant increases in arterial pressure. Similarly, biochemical studies by Biondi and Romero (4) indicate that the renal medulla has a greater capacity for the NO-induced formation of cGMP than does the renal cortex in basal and stimulated conditions.

Chronic infusion of subpressor doses of ANG II over the course of 13 days elicited a similar pressure profile and degree of hypertension as has been previously reported (29, 30, 32). In the present study, we observed that acute inhibition of NOS led to greater increases in arterial pressure in the ANG II-infused hypertensive rats compared with normotensive rats. The increase in arterial pressure during acute NLA treatment was associated with greater reductions in CBF and total RBF in the ANG II-infused hypertensive rats than in
normotensive rats. Despite the greater increases in arterial pressure, RBF was reduced to a greater extent in hypertensive rats than in normotensive rats (60% vs. 31%). These results are consistent with the hypothesis that a compensatory increase in NO activity counteracts the vasoconstrictor influence of elevated circulating ANG II levels and thus helps maintain renal perfusion. These observations are in accordance with those of Sigmon and Beierwaltes (26), who reported that inhibition of NO synthesis with L-NAME decreased RBF in the nondipped kidney by 61% during the early phase (up to 4 wk after clipping) of 2K1C renovascular hypertension and to a greater extent than in control rats. These data indicate that NO exerts a critical vasodilator influence to maintain renal perfusion of the nondipped kidneys during the early phase of 2K1C renovascular hypertension. Dubey et al. (7) reported elevated NO activity during the first 5 wk of 1K1C hypertension, again suggesting that the early increase in NO synthesis blunts the rapid rise in arterial pressure after renal artery clipping. Along similar lines, the L-NAME-induced decreases in RBF and GFR were significantly greater in the transgenic hypertensive rat strain (mRen2) rats (27).

As a result of the greater modulatory influence of NO on the medullary than on the cortical circulation in control rats, we anticipated that this influence would be augmented further in the hypertensive animals. However, we instead found that the decreases in MBF in response to NLA were actually less in the ANG II-infused rats than in the control rats. This suggests the possibility that a differential regional regulation of NOS activity in the renal circulation may be present in the ANG II-infused rats compared with normotensive rats. In line with this observation, it is possible that endogenous vasodilators in addition to NO also help to counteract the vasoconstrictor influence of elevated ANG II levels on the medullary circulation. Studies have shown that ANG II stimulates the release of prostaglandins from the renal tissue both in vivo and in vitro (5, 23, 24). Therefore, the possibility exists that locally produced prostaglandins may also modulate the actions of ANG II on the medullary circulation. Indeed, Mattson and Roman (17) reported that exogenous ANG II reduced papillary blood flow in kidneys pretreated with both captorpl and medofenamate but not after captorpl alone. Another possibility is that the elevated perfusion pressure could cause sufficient increases in the medullary production of vasodilators other than NO to sustain the MBF against the vasoconstrictor influence of elevated ANG II. As already indicated, NLA caused greater increases in arterial pressure in the hypertensive rats than in control rats. It has been reported that MBF autoregulatory efficiency is less than cortical autoregulatory efficiency so that the greater increases in arterial pressure could have blunted the NLA-induced decreases in MBF more in the ANG II-infused rats (18).

With the use of laser-Doppler flowmetry, this study provides functional information regarding the differential influence of NO on the regional blood flows. Specifically, NO redistributes its modulatory influence to the cortical circulation to maintain adequate renal perfusion in response to elevated ANG II levels. Such evidence for an altered differential regulation of regional circulation would not have been gained solely from the whole kidney blood flow data measured by the PAH clearance. Future studies will be needed to measure the enzyme activity level in the different regions of the kidney. Other possibilities cannot be ruled out and need to be examined further.

The renal excretory responses to NOS inhibition were also evaluated. In control rats, NLA infusion initially had no effect on urine flow or urinary sodium excretion, but then we observed a delayed increase during the last two collection periods. Interestingly, the delayed increases in urine flow and sodium excretion observed in normal rats did not occur in the hypertensive rats during ANG II infusion. One possible explanation is that the delayed increases in urine and sodium excretion during inhibition of NO synthesis in the control rats could be influenced by the associated increase in arterial pressure induced by NLA. These data are consistent with previous observations (2, 9, 25) that the responses to NOS inhibition on urine flow and sodium excretion are influenced by the concomitant increases in arterial pressure. Specifically, Takenaka et al. (28) reported that NOS inhibition decreases urine flow and sodium excretion when the increase in arterial pressure is prevented. In contrast to the results obtained in control rats, there were not delayed increases in urine flow and sodium excretion in hypertensive rats, although the associated increases in arterial pressure were even greater. It is possible that the higher ANG II levels in the hypertensive rats prevented the increases in urine flow and sodium excretion observed during NLA administration in normotensive rats. This possibility implies a pivotal role for NO in partially antagonizing the heightened antinatriuretic activity of the augmented intrarenal ANG II level in the hypertensive rats. In support of this observation, the L-NAME-induced reductions in GFR and RBF were significantly greater in transgenic rats due to their higher renal vascular resistance and lower glomerular ultrafiltration coefficient than in control rats (27). It is possible that the delayed natriuretic responses observed in the control rats were due to decreases in intrarenal renin-angiotensin levels caused by prolonged NOS inhibition (23a), coupled with the associated increases in arterial pressure. Thus the renal excretory responses to NO synthesis inhibition appear to be determined, in part, by the balance between the level of the activity of the renin-angiotensin system and the magnitude of the increase in arterial pressure (28).

In summary, the present findings indicate that when intrarenal ANG II levels are chronically elevated and exerting a greater influence on renal vascular tone, NO serves as an important endogenous vasodilator system that helps maintain renal hemodynamics. In control rats, NO exerts a greater relative effect on the medullary circulation than on the cortical circulation. In response to chronic low-dose ANG II infusion, NO
serves to counteract the vasoconstrictor influence of elevated circulating ANG II levels to maintain perfusion in the renal circulation. In contrast to the results obtained in normotensive rats, NO exerts a greater modulatory influence on the cortical circulation than on the medullary circulation in the ANG II-infused rats. This greater modulatory influence of NO on CBF contributes to the maintenance of overall renal perfusion in the face of elevated ANG II levels.

We thank Sophia Omoro, Murrell Godfrey, George Prophet, and Mike Wegmann for technical assistance. This study was supported by National Heart, Lung, and Blood Institute Grants HL-18426 and HL-26371 and by the Louisiana Educational Quality Support Fund. So Yeon Chin is a predoctoral fellow supported by the Louisiana Board of Regents fund. Chi-Tarng Wang is a predoctoral fellow supported by Education Fund of National Defense Medical Center of Taiwan, Republic of China.

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Received 31 July 1997; accepted in final form 7 January 1998.

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