Flow induces dilatation in the femoral artery of uraemic rats but constriction in control rats

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Abstract

Background. Pressure and flow are recognized as important modulators of vascular tone. In mildly uraemic rats, myogenic tone is increased in the femoral artery in the absence of hypertension compared with healthy control rats, but the effect of flow in the same experimental model remains unknown.

Subjects and methods. Twelve male Wistar rats were rendered uraemic (U) by 5/6th nephrectomy or were concurrently sham operated as controls (C). After 8 weeks, isolated femoral arteries were mounted on a flow myograph, pressurized at 80 mmHg, and constricted by 40–50% of the lumen internal diameter (i.d.) by l-phenylephrine (1–10 μmol/l). Flow was initiated (0–207 μl/min) in six steps every 5 min and changes in i.d. recorded. N-nitro-l-arginine methyl ester hydrochloride (l-NNAME) (0.1 mmol/l) and 1H-[1,2,4] oxadiazolo-[4,3-a]quinonoxalin-1-one (ODQ) (1 μmol/l) were applied extraluminally and the flow protocol repeated.

Results. The baseline pre-constricted at 80 mmHg i.d. was significantly smaller in the U (U 255 ± 21 μm vs C 365 ± 36 μm, P < 0.03). At all steps, flow elicited a dilatation in the U and a constriction in the C (U + 24 ± 8% vs C −17 ± 5%, P < 0.01). When l-NNAME and ODQ were applied, a significant basal reduction in i.d. was observed in the C only (C 365 ± 36 μm vs C + l-NNAME & ODQ 182 ± 18 μm, P < 0.01; U 255 ± 21 μm vs U + l-NNAME & ODQ 240 ± 11 μm, P = n.s.). Furthermore, in the U there was no significant blunting to dilatation during flow (+ 9 ± 4%).

Conclusions. Flow elicited a constriction in controls, but a marked dilatation in uraemic roots which was not entirely nitric oxide dependent. These results suggest that other mediators such as prostacyclin or endothelium-dependent hyperpolarizing factor, or changes in the vascular smooth muscle may contribute to flow-induced dilatation in mild experimental uraemia.

Keywords: femoral artery, flow; myography; nitric oxide; uraemia

Introduction

Cardiovascular disease remains the leading cause of mortality in end-stage renal disease (ESRD) patients [1] and parallel changes in both the structure and function of large arteries and the development of left ventricular hypertrophy in this population have been documented [2]. Recently we have demonstrated that in mild experimental uraemia, the femoral artery has a reduced basal internal diameter and increased myogenic tone compared with control rats, indicating alterations in vascular smooth muscle function [3]. Whilst pressure is widely accepted as an important modulator of vascular tone, another important haemodynamic factor, first recognized over 60 years ago, is flow [4].

Flow-dependent dilatation has been observed both in human fetoplacental arteries [5] and in several animal vessels such as the rat basilar artery [6], gracilis arterioles [7], cremaster arterioles [8], mesenteric arteries from pregnant rats [9] and rabbit iliac arteries [10]. However, the response to blood flow is not the same in all vascular beds. Vasodilatation has been observed in the rabbit both in the ear resistance artery [11] and femoral artery [12] and in the rabbit cerebral pial artery, Garcia-Roldan and Bevan [13] observed flow-dependent dilatation at a low intravascular pressure of 30 mmHg but sustained constriction at 90 mmHg with flow rates comparable with those in other vascular beds. Moreover, a similar biphasic response was seen in rat intracerebral arteries in response to a maintained intravascular pressure of 60 mmHg but with variable flow rates between 5 and 25 μl/min [14].

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Changes in flow-dependent dilatation have been observed in some disease states. For example, in streptozotocin-diabetic rats, resistance mesenteric arteries constricted to flow [15] and a reduced dilatation to flow has been observed both in SHRs [16] and in small arteries from pregnant women with pre-eclampsia [17].

To date, no studies have been performed to investigate the effects of blood flow in either humans or animal models of uraemia. However, in dialysis patients there is limited data suggesting that resting forearm blood flow is higher, but dilatation following reactive hyperaemia is reduced compared with control subjects [18]. Moreover, in a previous pilot study [19], flow through unconstricted femoral arteries of rats induced dilatation in uremic vessels and none in controls. However, as we have previously observed little myogenic tone in unconstricted control femoral arteries [3], it is possible that the control arteries failed to dilate due to a lack of vascular tone.

Therefore in this study, the aim was to impose vascular tone on both uremic and control femoral arteries by pre-constricting the basal lumen diameter by 40–50% as described by others [9,12,15] pressurized at 80 mmHg, to see whether uremic vessels have a genuinely different response to flow from control vessels. A further aim was to assess the role of shear stress and the relative contribution of nitric oxide (NO) to flow-dependent dilatation in both groups.

Subjects and methods

Animals

Male Wistar rats (180–200 g) were housed in the on-site Biological Services Unit individually in holding rooms with a constant temperature of 21±2°C and humidity of 40%. The 24-h day was fixed at a 12-h light, 12-h dark cycle. All procedures had prior approval from the UK Home Office (Project Licence: 70/3619) and were performed in accordance with the Animals Scientific Procedures Act (1986).

Induction of uraemia

Pairs of animals underwent two surgical procedures a week apart. Anaesthesia was induced initially by an intramuscular (i.m.) injection into a hind leg of 0.18 ml Hypnorm (fentanyl citrate 0.315 mg/ml and fluanisone 10 mg/ml, Janssen-Cilag Ltd, Sanderton, High Wycombe, Bucks) followed by 0.06 ml Diazepam (Phoenix Pharmaceuticals Ltd, Gloucester) which was given intraperitoneally (i.p.).

The rat was then shaved in the abdominal area for the first stage of surgery which involved decapsulation and removal of two-thirds of the left kidney for the uremic group (n = 6) and decapsulation of the left kidney for the sham operated control group (n = 6). The following week the rats were shaved over the area covering the right flank and the uremic group underwent a total right nephrectomy and the control group was sham operated as described above. For 8 weeks, the rats were pair fed to control for the suppression of appetite associated with uraemia.

Terminal procedure

On each study day one rat was studied. The rat was given 0.25 ml Hypnorm i.m. into a rear thigh muscle and a further 1.6 ml diazepam was then given i.p. to induce deep anaesthesia which was tested by lifting the rat’s head and checking that its neck was truly relaxed, and then sharply pinching its claw. If there was no physical reaction, it was assumed that the rat was sufficiently anaesthetized to proceed, which was usually 5–10 min later. As concurrent experiments were being performed by colleagues on cardiac myocytes, the rat was killed following the opening of the thoracic cavity and rapid removal of the whole heart.

Urinary creatinine clearance and bloods

The day before each study, each rat was weighed and placed in an individual metabolic cage which had a floor with holes in it to facilitate easy collection of urine. Twenty four hours later, the rat was removed and weighed, and the volume of urine was recorded and a sample sent to the Chemical Pathology Laboratory for biochemical analysis. Blood was obtained from the chest cavity for urea and electrolytes (U&Es) and a full blood count at the time of termination.

Dissection of the femoral artery

The femoral artery and surrounding muscle was excised from both legs immediately following killing and pinned onto a silastic Petri dish containing cold physiological salt solution (PSS) and left to equilibrate for about 15 min. Two segments of the femoral artery (approximately 5 mm) were dissected under a microscope (Stemi SV6, Zeiss, Germany) using microscissors and fine forceps.

Flow myography

The technique employed for studying the femoral artery was flow myography, which has been described extensively elsewhere [20]. Briefly, the vessel was mounted in the myograph chamber composed of two opposing microglass cannulae (tips ~ 70 µm) matched for resistance, and secured at each end with two sutures. The vessel was then perfused with PSS both intraluminally and extraluminally. On either side of the chamber was a series of three-way taps with wind-kessels to dampen pulsatile flow and solid state ‘in line’ pressure transducers. These proximal and distal pressure transducers monitored the respective pressures at each end of the vessel and the mean intraluminal pressure was calculated and maintained by the pressure servo control pump. The internal diameter (i.d.) was measured continuously by the video dimension analyser and the vessel displayed on the video monitor which was connected to a CCD camera positioned on the inverted microscope (×10).

Chemicals and solutions

All other chemicals were purchased from Sigma-Aldrich Company Ltd (Poole, Dorset) and all solutions were made up on the day of each experiment. Physiological salt solution (PSS) consisted of 5L Analar water to which, in mmol/l, 119 NaCl, 4.7 KCl, 1.17 MgSO4, 25 NaHCO3, 1.18 NaH2PO4, 0.026 EDTA, 5.5 glucose, and 2.5 molar CaCl2 were added and kept refrigerated until use. Vessel viability was tested
using L-phenylephrine 1 μmol/l in 124 mmol/l potassium PSS (KPSS) which was the same as PSS but the sodium chloride was substituted by potassium chloride. For assessment of myogenic tone, the vessel was perfused with calcium (Ca)-free PSS to obtain passive diameters. This was made up as PSS described above but without CaCl₂, and instead 0.38 g/l of the calcium chelator EGTA was added. Functional integrity of the endothelium was checked by subsequent relaxation to extraluminal application of acetylcholine 1 μmol/l. Prior to initiating the flow protocol the i.d. was reduced by 40–50% using L-phenylephrine (1–10 μmol/l). Both the nitric oxide synthase inhibitor L-NAME (0.1 mmol/l) and the selective soluble guanylyl cyclase inhibitor 1H-[1,2,4] oxadiazolo[4,3-d]quinoxalin-1-one (ODQ) (1 μmol/l) were added to the perfusion bath to block all NO production and any residual guanosine-3’,5’-cyclic monophosphate (cGMP).

**Experimental protocol**

At the start of the experiment, intraluminal perfusion of the vessel was stopped and the intraluminal pressure was raised to 80 mmHg and left to equilibrate in PSS, which constantly perfused the vessel extraluminally at a rate of 19 ml/min for 40 min. The PSS was maintained at 37°C and gassed continuously with 95% oxygen and 5% carbon dioxide to yield a pH of 7.4. The ability of the vessel to vasoconstrict and subsequently relax was then tested in a standard procedure [15] by L-phenylephrine (1 μmol/l) in KPSS and acetylcholine (1 μmol/l) as described above. Criteria for a suitable vessel was dilatation to 90% or more of baseline i.d. If this did not occur, then the vessel was discarded, another vessel from the same rat was mounted, and the procedure repeated.

**1st study**

Following testing of the vessel viability, a baseline i.d. for assessment of myogenic tone was recorded at 40 mmHg and then at 140 mmHg following a 10-min equilibration period at each stage. Maximal dilatation was observed at 140 mmHg in previous experiments in this laboratory [3], therefore this intravascular pressure was additionally selected for assessment of myogenic tone. The intravascular pressure was then raised to 80 mmHg and the vessel left to equilibrate for a further 30 min with no flow. The i.d. was then recorded and used as the baseline measurement. Each vessel was then constricted to 40–50% of this baseline i.d. by extraluminal application of L-phenylephrine in a dose-dependent manner (1–10 μmol/l).

Flow of PSS through the vessel was initiated via the flow pump in six incremental steps from 0 to 207 μl/min. At the end of every 5-min period when the vessel had reached a steady state, changes in i.d. were recorded. Care was taken to maintain the intravascular pressure at 80 mmHg at each flow step by manually adjusting the pressure servo control as required. The maximum flow rate employed was 207 μl/min, as in a separate group of vessels flow data ceased to be reproducible at greater flow rates than this (data not shown). Flow was then stopped and the pressure maintained at 80 mmHg. In order to assess the contribution of nitric oxide to flow-dependent changes, L-NAME (100 μmol/l) and ODQ (1 μmol/l) were applied to perfuse the vessel extraluminally and left to equilibrate for 20 min. The baseline i.d. was then recorded and the flow protocol repeated. The intravascular pressure was then reduced to 40 mmHg and PSS applied extraluminally for 30 min to wash out the L-NAME and ODQ. Then the vessel was perfused with Ca-free PSS and the i.d. recorded at 40 mmHg and 140 mmHg respectively.

Prior to this study and in two separate femoral arteries, a timed control experiment was conducted to confirm that the baseline i.d. remained stable when pressurized at 80 mmHg both before and after flow was initiated (data not shown).

**2nd study**

This was an additional small study conducted on vessels from control rats (n=6) to assess flow in pre-constricted arteries. The rats were the same age as those used in the above experiment but these were allowed to eat *ad libitum*.

**Calculations**

Shear stress (τ) was calculated as follows: \( \tau = 4 \eta Q \pi r^3 \times 10^5 \), where \( \eta \) is viscosity of the perfusate (assumed as 0.007 poise at 37°C), \( Q \) is the perfuse flow, and \( r \) is the vessel radius. As the unit for measurement of shear stress is in dynes/cm², a correction factor of \( 10^3 \) was used in the calculation to allow for the vessel radius being measured in micrometres.

Myogenic tone was calculated as: Percentage (%) myogenic tone = calcium-free PSS i.d.–PSS i.d./Ca-free PSS i.d. \times 100 at intravascular pressures of 40 and 140 mmHg.

**Statistical analysis**

Data are expressed as mean ± SEM. For each vessel a summary score representing the mean percentage change in i.d. from baseline in response to the flow steps for each group was calculated; and the mean of these and the other parameters in both the control and uraemic groups were compared using the Student t-test for paired and unpaired data. As the results showed that changes in i.d. were minimal response following the initial flow step from 0–28 μl/min and that the SEMs at each stage were also similar, the difference in mean response only, rather than ANOVA for repeated measures, was used for analysis [21]. Although the model of uraemia was designed to include paired animals, as it was not known that the rats all came from the same litter, unpaired analysis was used for comparison of uraemic vs control rats. Significance was assumed when \( P \leq 0.05 \).

**Results**

**General data**

For the first study, data were collected from six uraemic (U) and six control (C) rats and for the 2nd study from five of the six control rats. Data were not obtained from the 6th rat because several vessels leaked when pressurized. The response of uraemic and control arteries to acetylcholine (1 μmol/l) expressed as a percentage of the initial baseline i.d. was the same in both groups (U 98 ±1% vs C 97 ±1%, \( P = \) n.s.).

Serum urea and creatinine and creatinine clearance were significantly raised in the uraemic group compared with controls and weight did not differ between the two groups (Table 1). Following the equilibration period when the vessel was pressurized at 40 mmHg,
Table 1. Baseline characteristics (mean ± SEM) of uraemic (n = 6) vs control (n = 6) rats

<table>
<thead>
<tr>
<th></th>
<th>Uraemic (n = 6)</th>
<th>Control (n = 6)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (g)</td>
<td>406 ± 13</td>
<td>384 ± 12</td>
<td>n.s.</td>
</tr>
<tr>
<td>Serum urea (mmol/l)</td>
<td>11.9 ± 0.9</td>
<td>6.4 ± 0.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>96.8 ± 3</td>
<td>77 ± 2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Plasma haemoglobin (g/dl)</td>
<td>12.4 ± 0.4</td>
<td>12.7 ± 0.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Serum sodium (mmol/l)</td>
<td>139 ± 2.3</td>
<td>144 ± 0.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Serum potassium (mmol/l)</td>
<td>4 ± 0.4</td>
<td>3.7 ± 0.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Serum calcium (mmol/l)</td>
<td>2.4 ± 0.1</td>
<td>2.6 ± 0.03</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Serum phosphate (mmol/l)</td>
<td>1.9 ± 0.1</td>
<td>2.1 ± 0.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Serum albumin (g/l)</td>
<td>29.3 ± 0.7</td>
<td>28.3 ± 0.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>0.0059 ± 0.001</td>
<td>0.0086 ± 0.001</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>(ml/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine volume (ml/day)</td>
<td>20.2 ± 2.5</td>
<td>12.3 ± 1.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Internal diameter (µm)</td>
<td>387 ± 35</td>
<td>463 ± 22</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

40 mmHg

the i.d. in the uraemic vessels was significantly smaller compared with controls (U 387 ± 25 µm vs C 463 ± 22 µm, P < 0.05) and myogenic tone higher (U 14.6 ± 4% vs C 4.8 ± 2%, P < 0.05) in keeping with previous results [3]. Furthermore, when the arteries were pre-constricted and pressurized at 80 mmHg, the difference in i.d. between the uraemic and control arteries persisted (C 365 ± 36 µm vs U 255 ± 21 µm, P < 0.03). At the intravascular pressure of 140 mmHg, when maximal dilatation was observed in an earlier study [3], the i.d. of uraemic and control vessels in Ca-free PSS was the same (U 581 ± 31 µm vs C 672 ± 38 µm, P = n.s.).

The effect of flow on pre-constricted control and uraemic vessels

At all incremental steps flow elicited a sustained dilatation in uraemic vessels and a sustained constriction in the control vessels (mean change: U + 23.8 ± 8% vs C −17.3 ± 5%, P < 0.01) as shown in Figure 1. As can be seen, in the uraemic vessels there is an initial large dilatation at 28 µl in immediate response to flow, and thereafter, a minimal steady increase with corresponding increases in flow rate. The same pattern was observed in the control vessels but the behaviour was the converse of that in the uraemic vessels, in that there was an initial marked constriction to flow followed by corresponding minimal declines in i.d. with each flow step.

The effect of L-NAME and ODQ on pre-constricted vessels

Addition of L-NAME and ODQ to the perfusion bath when the vessel was pressurized at 80 mmHg prior to flow, resulted in further significant constriction in the i.d. of the control vessels (C 365 ± 36 µm vs C + L-NAME & ODQ 182 ± 18 µm, P < 0.01) but only a minimal reduction in the uraemic vessels (U 255 ± 21 µm vs U + L-NAME & ODQ 240 ± 11 µm, P = n.s.). Figure 2 also shows that the difference in i.d. in control compared with uraemic vessels persists when pre-constricted and maintained at a constant pressure of 80 mmHg.

In response to flow, the control arteries significantly dilated at all flow rates (Figure 3a) which contrasted sharply to the constriction observed earlier (mean change +25.6 ± 12%, P < 0.03). In uraemic vessels there was no significant change in flow-induced dilatation (Figure 3b).

The effect of flow on shear stress

In the pre-constricted vessels the mean shear stress generated by flow was the same in both groups (U 31.5 ± 4 dynes/cm² vs C 30.6 ± 6 dynes/cm², P = n.s.). Figure 4a shows the amount of shear stress in each group at each flow step, and as can be seen, shear stress is of similar magnitude in both groups once flow was initiated. In the control group, shear stress increased with each flow step in a graded linear manner. In the uraemic group, in immediate response to flow, shear stress increased sharply and to a greater degree than observed in the control (U 26.3 ± 9 dynes/cm² vs C 3.3 ± 0.4 dynes/cm², P < 0.05). This difference from zero to 28 µl/min was not apparent following application of L-NAME and ODQ (Figure 4b).
Fig. 3. Effect of l-NAME (0.1 mmol/l) and ODQ (1 μmol/l) on flow in pre-constricted (a) control (C) (n = 6) femoral arteries (**P < 0.001), and (b) uraemic (U) (n = 6) femoral arteries (P = n.s.).

2nd study

As the controls used in the above study were pair-fed for 8 weeks with the uraemic rats and uraemia tends to suppress appetite, it seemed possible that the unexpected results observed in the control group might be subsequent to some degree of malnourishment. Therefore we repeated the experiments in the femoral arteries control rats (n = 6) of the same age who were allowed to eat ad libitum. The mean starting diameter was 273 ± 20 μm. Each vessel was constricted by the desired amount with the same concentration of l-phenylephrine (1 μmol/l) and in all vessels the response to flow was a sustained constriction (mean change -9.5 ± 4%) with minimal change after the first flow step as previously observed.

Discussion

The principal findings of this study are that in response to flow, uraemic femoral arteries dilate, whereas control vessels constrict; and NO does not appear to be an important mediator in initiating these changes to flow. Furthermore, by performing further studies on control rats in whom food intake had not been restricted, the observation that the pre-constricted femoral artery constricts to flow was found to be reproducible.

Although serum creatinine and urea was significantly raised in the uraemic group, the degree of uraemia induced was very mild and therefore uraemia per se is unlikely to account entirely for the different responses observed. However, urine volume was significantly greater in the uraemic group (P < 0.05), indicating initial changes associated with early renal failure, so subsequent changes in circulating volume may have played a role. Blood pressure was not measured in this group of rats, because in the previous two studies using exactly the same experimental model of uraemia and at the same time point, systolic blood pressure was the same and normal in both groups [3,29].

The response to acetylcholine prior to initiating flow was the same in uraemic and control arteries, which suggests that agonist-induced NO release was not impaired in uraemic femoral arteries. This has previously been reported in 8-week-old uraemic rat mesenteric arterioles using the same experimental model and the technique of wire myography [22].

However, basal control of tone appears to differ between the two groups. When the vessels were perfused with l-NAME and ODQ, the pressurized control vessels constricted significantly, suggesting that NO is an important contributor to basal tone, whereas there was virtually no response in uraemic vessels (Figure 2), which suggests that basal control of tone in these vessels was insensitive to NO. This observed difference may relate to very early changes due to uraemia.

The constriction to flow in the control vessels has consistently been observed in femoral arteries of
rabbits [12]. It has been suggested that this constriction to flow operates as a mechanism to prevent overperfusion of vascular beds further downstream [17]. This suggests that there is likely to be a physiological ‘set point’ at which this mechanism operates. The fact that the control vessels have very little myogenic tone means that to prevent overperfusion downstream, it is logical to constrict to flow to meet the set point. In contrast, in this study and as previously observed [3], the starting pressurized diameter of the uremic arteries has been significantly smaller and myogenic tone greater and therefore in response to flow, the uremic arteries have to dilate to meet the set point.

Although the starting diameter of uremic rats was smaller than that of the control arteries when preconstricted and pressurized at 80 mmHg, it was the same in Ca-free PSS, indicating a functional difference rather than structural difference between the two groups. Therefore another approach would have been to pre-constrict the control arteries to the same absolute diameter of the uremic arteries. However, this would have involved simultaneously studying a uremic and control vessel on two myographs with two investigators, to ensure correct timing of the protocol, which on a practical basis would have been very difficult to achieve. In addition, similar uremic and control starting diameters within groups using pre-constriction would be difficult to ensure with certainty during a series of experiments. As marked differences in response to flow were observed in the unpreconstricted uremic and control arteries, it seems likely that the results of this study reflect genuine differences in the response to flow in uremic and control arteries. Furthermore, when flow was repeated in preconstricted femoral arteries from healthy control rats of the same age who were allowed an unrestricted food intake, again flow was shown to elicit a constriction in starting diameter.

Irrespective of the differences in starting diameter and responses to flow, flow-induced dilatation was different in uremic and control vessels. In the absence of NO (when perfused with L-NAME and ODQ) there was some blunting of dilatation in the uremic group (Figure 3b), although this was not significant. Therefore uremic vessels were not entirely NO insensitive. In contrast, a 25% dilatation to flow was observed in the control vessels, indicating an insensitivity to NO. Similar observations have been made in the femoral artery of cats, when inhibition of NO by L-NAME and L-NMMA not only failed to suppress dilatation to flow, but actually enhanced the dilatation in four of nine cats treated with L-NAME and all five cats treated with L-NMMA [23]. It has been suggested that in large conducting arteries, endothelium-dependent hyperpolarizing factor (EDHF) may usually act in parallel with NO, but if production is impaired, EDHF may be potentiated and behave as a secondary ‘back-up’ system [24].

The vessel radius cubed is used in the calculation of shear stress (see above) and therefore for a small reduction in the vessel diameter and thus radius, there will be increased generation of shear stress. Shear stress has been reported as an effective stimulus for the release of endogenous endothelial vasodilators such as NO and prostacyclin (PGI2) by several authors [7,8,25]. In the femoral artery of cats, dilatation to flow was greater in those with a smaller starting diameter [25]. Moreover, Hecker et al. [26] have shown that in the femoral arteries of rabbits, endothelial release of the vasodilators NO and PGI2 was increased 5–7-fold and 11–12-fold respectively by both increasing shear stress by vasoconstriction at a constant flow rate, and by increasing flow rate at a constant diameter. In support of this, in the initial response to flow from 0–28 µl/min, not only was there significantly increased shear stress generated in the uremic vessels compared with the control vessels ($P < 0.01$) (Figure 4a) but in the absence of NO, there was a marked reduction in shear stress generated in immediate response to flow (Figure 4b).

The differences in basal control of tone and responses to flow observed in such mild uremia may herald the initiation of arterial remodelling and associated arterial stiffness well documented in ESRD patients. Hypertrophy of large conduit artery walls, dilatation of the arterial lumen, and subsequent arterial stiffening of the aorta and other major arteries have partially been attributed to chronic increases in blood flow and shear stress [27].

In diabetic microangiopathy definite progressive stages have been identified with early insulin-dependent diabetes being characterized by increased microvascular flow and subsequent shear stress which later impairs vasodilatory capacity due to structural changes [28]. Such stages of progression may occur in uremia, as our observations suggest increased blood flow through the uremic femoral artery of rats.

To summarize, we have shown that in the femoral artery of mildly uremic rats flow elicited a sustained dilatation, but induced a sustained constriction in control rats.

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References

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