Original Article

Reduced venous responsiveness to endothelin-1 but not noradrenaline in hypertensive chronic renal failure

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Abstract

Background. Endothelin-1 (ET-1), acting mainly through the ET_A receptor, is a potent endothelium-derived vasoconstrictor peptide. Circulating concentrations of ET-1 are increased in chronic renal failure (CRF) and may influence vascular tone.

Methods. We investigated dorsal hand vein responsiveness to local infusion of ET-1 and noradrenaline in 12 hypertensive and 12 normotensive CRF patients and in 12 age and sex matched control subjects. We also investigated dorsal hand vein responses to the ET_A receptor antagonist, BQ-123, and the endothelium-independent vasodilator glyceryl trinitrate (GTN), in six patients with CRF.

Results. The dose of noradrenaline causing a 50% of maximal vasoconstriction was similar in the hypertensive (32±11 pmol/min) and normotensive (26±7 pmol/min) CRF patients and control subjects (21±6 pmol/min). Vasoconstriction to ET-1 (5 pmol/min) was similar in CRF patients as a whole (AUC 35±5%) and controls (32±4%; P = 0.70). However, vasoconstriction was significantly less in hypertensive (23±6%) than in normotensive CRF patients (48±8%; P = 0.01). Overall, vasoconstriction to ET-1 correlated inversely with mean arterial blood pressure in the CRF patients (R = −0.43, P = 0.04). In addition, basal vein size was smaller, and plasma endothelin concentrations greater, in the hypertensive CRF group. However, infusion of BQ-123 or GTN did not cause venodilatation in these subjects.

Conclusions. These studies are consistent with the hypothesis that elevated plasma ET-1 contributes to vascular tone, and elevated blood pressure, in hypertensive CRF patients, and is associated with vascular receptor downregulation consequent on the increased exposure to ET-1. The reduced vein size in CRF patients appears to be structural rather than functional in nature. Further long-term studies with endothelin antagonists are required to determine the pathophysiological role of ET-1 in the altered structure and function of blood vessels in patients with CRF.

Keywords: chronic renal failure; endothelin-1; hypertension; noradrenaline; vein structure; vasoconstriction

Introduction

The endothelins are a family of 21-amino-acid peptides with potent and sustained vasoconstrictor and vasopressor actions [1]. Plasma concentrations of immunoreactive endothelin are elevated in chronic renal failure (CRF) [2] and although endothelin-1 (ET-1) is generally considered to be a locally active peptide, secreted predominantly abuminally [3], plasma concentrations of endothelin may be high enough in some patients with CRF to influence vascular tone [4]. Indeed, blood pressure correlates positively with plasma ET-1 concentrations in haemodialysis patients [5]. In addition, patients with essential hypertension and normal renal function have increased venous vascular sensitivity to ET-1 [6]. However, although responsiveness of the forearm vascular resistance bed to ET-1 does not appear to be increased in patients with CRF [7,8], little is known concerning the in vivo sensitivity of the capacitance system to ET-1 in this condition. Endothelin-1 might contribute to the increased venous tone found in hypertensive patients with CRF [9] and so indirectly contribute to the hypertension, and consequently to the increased cardiovascular mortality and morbidity, associated with this condition.

Cutaneous limb veins are under sympathetic vennmotor control and should broadly reflect responses found in those vessels that control venous capacitance and cardiac preload [6,10]. Moreover, investigation of hand veins generally avoids the confounding effects.
associated with vascular hypertrophy and other structural changes that may occur in the resistance vessels of patients with hypertension [6]. Therefore we examined the effect of local intravenous infusion of ET-1 and a comparator constrictor, noradrenaline, on dorsal hand vein diameter in hypertensive and normotensive subjects with CRF, who were dialysis independent, and in healthy age- and sex-matched control subjects. In a small subgroup of subjects with CRF we also observed the effect of local intravenous infusion of the vasodilator glyceryl trinitrate (GTN) [11] and the specific ETA receptor antagonist BQ-123 on basal vein size [12].

Subjects and methods

Subjects

We studied 24 patients with established CRF (creatinine \(\geq 200 \text{ mmol/l}\)) of whom 12 were hypertensive (BP \(\geq 160/100\) or taking anti-hypertensive medication for hypertension at the time of recruitment) and 12 were normotensive (BP \(\leq 160/90\) and not taking any antihypertensive medication at the time of recruitment) (Table 1). Causes of renal failure in the hypertensive group were: IgA nephropathy (n = 5), hypertensive nephropathy (n = 3), nephrocalcinosis (n = 1), interstitial nephritis (n = 1), crescentic nephritis (n = 1) and unknown aetiology (n = 1); and in the normotensive group were: obstructive uropathy (n = 4), IgA nephropathy (n = 2), adult polycystic kidney disease (n = 2), nephrocalcinosis (n = 1), myeloma kidney (n = 1) and unknown aetiology (n = 1). We also recruited twelve age- and sex-matched normotensive subjects (BP \(\leq 160/90\) and not taking any antihypertensive medication at time of recruitment) for the study (Table 1). Subjects were excluded if they had a diagnosis of diabetes mellitus or were taking nitrovasodilator drugs. All studies were conducted with the approval of the local Research Ethics Committee and all subjects gave their written informed consent to participate. Anti-hypertensive medication was withdrawn 1 month before each study and blood pressure was monitored weekly. Subjects avoided caffeine-containing drinks or cigarettes on the day of each study.

In addition, subjects were fasted for at least 3 h before each study.

Drugs

Locally, but not systemically, active doses of noradrenaline (1-192 pmol/min; Sterling–Winthrop, Guildford, UK) [6]. ET-1 (5 pmol/min: Climaffa AG, Läufelfingen, Switzerland) [6], the nitric oxide donor, glyceryl trinitrate (GTN: 2 nmol/min; Schwarz Pharma Ltd, Chesham, UK) [13] and the selective endothelin A-type receptor antagonist, BQ-123 (0.3 and 30 nmol/min: American Peptide Co.) [14] were given. All drugs were dissolved in physiological (0.9%) saline. Ascorbic acid (Evans Medical, Horsham, UK) was added to the noradrenaline solutions, at a final concentration of 100 \(\mu\)g/ml, to prevent degradation by oxidation [6,11].

Intravenous administration

A selected dorsal hand vein of the non-dominant arm was cannulated in the direction of flow with a 23 SWG cannula (Abbott, Sligo, Republic of Ireland), without the use of local anaesthesia, for the purpose of intravenous infusion of drugs. The rate of infusion was maintained constant throughout each study at 0.25 ml/min.

Measurements

Dorsal hand vein size

The infused arm was supported above the level of the heart by means of an arm rest. Internal diameter of the dorsal hand vein, distended by inflation of an upper arm cuff to 30 mmHg, was measured by a displacement technique [10]. In brief, a lightweight magnetized rod rested on the summit of the infused vein \(\sim 1\) cm downstream from the tip of the infusion cannula. This rod passed through the core of a linear variable differential transformer (LVDT: Lucas Control Systems Products, Slough, UK) supported above the hand by means of a small tripod, the legs of which rested on areas of the dorsum of the hand free of veins. Local venoconstriction results in a downward displacement of the rod, causing a linear change in the voltage generated by the

Table 1. Patient data

<table>
<thead>
<tr>
<th>Controls</th>
<th>Patients with renal failure</th>
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<tbody>
<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td>Number (n)</td>
<td>12</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>8:4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55 ± 3</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>122 ± 3</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>77 ± 2</td>
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<tr>
<td>Mean arterial blood pressure (mmHg)</td>
<td>92 ± 2</td>
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<tr>
<td>Pulse pressure (mmHg)</td>
<td>45 ± 3</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>82 ± 3</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>13.8 ± 0.4</td>
</tr>
<tr>
<td>Plasma endothelin (pg/ml)</td>
<td>5.2 ± 0.8</td>
</tr>
<tr>
<td>Basal vein size (mm)</td>
<td>0.9 ± 0.2</td>
</tr>
</tbody>
</table>

*ªP < 0.05 when compared to control subjects; *ªP < 0.01 when compared to control subjects; *ªP < 0.001 when compared to normotensive CRF subjects.
LVDT, and allowing the determination of the internal diameter of the vein. Voltage output from the LVDT was transferred to a Macintosh personal computer file using a MacLab analogue/digital converter and Chart software (v. 3.2.8; both from AD Instruments, Castle Hill, NSW, Australia).

Blood pressure

Blood pressure was measured in the non-infused arm using a well-validated semi-automatic oscillometric method (Takeda UA751) [6].

Endothelin and haemoglobin assays

Plasma immunoreactive endothelin was measured by an established technique using a previously validated assay [6]. The recovery of added ET-1 was 84%. The sensitivity of the assay was 2 pg/ml endothelin and the mean intra- and inter-assay coefficient of variations in our laboratory are 2.4 and 4.2% respectively. Cross-reactivity of the assay with ET-1, ET-2, ET-3, and proendothelin-1 is 100, 52, 96 and 7% respectively. Haemoglobin was measured using a Coulter STKS analyser (Coulter Electronics Ltd, UK).

Design

During each phase of the study subjects rested semi-recumbent in a quiet room which was maintained at a constant temperature of between 23 and 25°C. An intravenous cannula was placed in the non-infused arm under local anaesthesia for blood sampling, the dorsal hand vein was cannulated, and the LVDT sited. Saline was infused for 30 min to allow the establishment of basal vein size during which time vein size and blood pressure were measured every 5 min. Venous blood was then taken from the non-infused arm for assay of plasma endothelin concentration, haemoglobin and creatinine. Noradrenaline was then infused at incremental doubling doses of 3–192 pmol/min, with each dose given for 10 min, to define individual full dose response relationships. Vein size was measured 5 and 10 min after starting each dose of noradrenaline. Blood pressure was measured 10 min after starting each dose of noradrenaline. Once a maximal response to noradrenaline was achieved, saline was infused for 30 min to allow vein size to return to basal values. Endothelin-1 was then infused at 5 pmol/min for 90 min with vein size measured every 5 min and blood pressure every 30 min [6]. Venoconstriction to ET-1 is sustained whereas that to noradrenaline is short-lasting [6,7]. Therefore it was necessary to give noradrenaline first rather than to randomize the order of infusions.

Six subjects with CRF underwent further investigation with local infusion of GTN and BQ-123. In this subgroup, after saline had been infused for 30 min to allow the establishment of basal vein size, GTN was infused at 2 nmol/min for 10 min. Vein size was measured 5 and 10 min after starting the GTN. Blood pressure was measured 10 min after starting the GTN. Saline was then infused for 15 min to allow time for the vein size to return to basal values. BQ-123 was then infused either at 0.3 or 30 nmol/min for 90 min with vein size measured every 5 min and blood pressure every 30 min. These doses of BQ-123, based on an estimated dorsal hand vein flow of 1 ml/min [11] would be expected to achieve local concentrations, within the vein, similar to those previous intra-arterial studies demonstrating maximal inhibition of the ET_{A} receptor [15]. Vasodilatation to BQ-123 is sustained [14] whereas that to GTN is short-lasting [11]. Therefore, it was necessary to give GTN first rather than randomize the order of infusions.

Data presentation and statistics

Vein size was measured in arbitrary units and was converted to millimetres after calibration at the end of each experiment. Basal vein size was calculated by taking the mean of the last three measurements before the start of the noradrenaline or GTN infusion as appropriate and expressed in millimetres. Venoconstriction to noradrenaline and ET-1 is expressed as per cent constriction (100×(vein size with infusion–resting vein size)/resting vein size). Individual noradrenaline dose response curves were analysed by calculating the dose producing the half-maximal response (ED_{50}) which is a measure inversely proportional to sensitivity [6]. Because serial measurements were made in each subject, following infusion of ET-1 and BQ-123 the response to ET-1 and BQ-123 is given as the area under the curve (AUC) for each individual.

All results are expressed as the mean±the standard error of the mean. Data were analysed using Student’s unpaired t-test, simple regression analysis, or by two-way ANOVA as appropriate, using STATVIEW 512+™ software (Brain-power Inc., Calabasas, California, USA) for the Apple Macintosh microcomputer. Values of P≤0.05 were considered statistically significant. Simple regression analysis was used primarily for hypothesis generation and the P values accepted for statistical significance were therefore not corrected for multiple comparisons.

Results

All patients who were previously on antihypertensive therapy remained off treatment until completion of their studies. There were no differences between CRF patients and control subjects in distribution of age and sex (Table 1). However, plasma creatinine and endothelin concentrations; and systolic, diastolic, mean arterial blood pressure and pulse pressure were higher, whereas resting vein size and haemoglobin concentration were lower, in the patients with CRF (Table 1). When comparing the hypertensive with the normotensive CRF patients there were no differences with respect to age, sex, creatinine, haemoglobin or resting vein size. As anticipated, systolic, diastolic and mean arterial blood pressure were higher in the hypertensive patients although there was no statistical difference in pulse pressure (Table 1). In addition, plasma ET-1 was higher in the hypertensive than the normotensive patients with CRF. Within the renal failure group there were no significant relationships between the plasma ET-1 concentration and age (R=0.24, P=0.28), creatinine (R=0.11, P=0.63), haemoglobin (R=0.22, P=0.30), pulse pressure (R=0.32, P=0.13) or basal vein size (R=−0.11, P=0.61), although there was a trend with mean arterial pressure (R=0.40, P=0.06).

Maximal venoconstriction to noradrenaline was similar between controls (84±4%), normotensive
CRF patients (89 ± 4%; \(P = 0.91\) vs controls) and hypertensive CRF patients (90 ± 4%; \(P = 0.66\) vs controls, \(P = 0.75\) vs normotensive patients). Responsiveness to noradrenaline, as measured by the ED\(_{50}\), was similar between patients with CRF and control subjects (Figure 1) and also between hypertensive and normotensive patients (Figure 1). Within the renal failure group there were no significant relationships between the sensitivity of the vessels to noradrenaline and age (\(R = 0.14\), \(P = 0.52\)), creatinine (\(R = 0.24\), \(P = 0.27\)), haemoglobin (\(R = 0.19\), \(P = 0.38\)), plasma ET-1 (\(R = 0.20\), \(P = 0.36\)), mean arterial pressure (\(R = 0.05\), \(P = 0.83\)), pulse pressure (\(R = 0.02\), \(P = 0.92\)) or basal vein size (\(R = -0.35\), \(P = 0.11\)).

Endothelin-1 caused a slow onset venuconstriction, which was similar between patients with CRF (AUC \(-36 ± 6\%\); \(P = 0.67\); Figure 2) and control subjects (AUC \(-32 ± 4\%;\ P = 0.67\); Figure 2). Responsiveness to ET-1 was similar when comparing control subjects to hypertensive (AUC \(-23 ± 6\%;\ P = 0.23\)) or normotensive (AUC \(-48 ± 8\%;\ P = 0.07\)) CRF patients. However, responses to ET-1 in the hypertensive patients with CRF were significantly blunted when compared with responses in normotensive patients (\(P = 0.01\); Figure 3). Within the control group there were no significant relationships between the response to ET-1 and systolic (\(R = -0.18\), \(P = 0.58\)), diastolic (\(R = -0.44\), \(P = 0.15\)) or mean arterial pressure (\(R = -0.36\), \(P = 0.25\)). Within the renal failure group there were no significant relationships between the responses to ET-1 infusion and age (\(R = 0.16\), \(P = 0.46\)), creatinine (\(R = 0.21\), \(P = 0.33\)), haemoglobin (\(R = 0.13\), \(P = 0.56\)), plasma ET-1 (\(R = 0.05\), \(P = 0.83\)), response to noradrenaline (\(R = 0.40\), \(P = 0.06\)), pulse pressure (\(R = 0.32\), \(P = 0.13\)) or basal vein size (\(R = -0.27\), \(P = 0.21\)). However, the response to ET-1 did correlate inversely with systolic (\(R = -0.43\), \(P = 0.04\)), diastolic (\(R = -0.41\), \(P = 0.05\)), and mean arterial pressures (\(R = -0.43\), \(P = 0.04\)).

Infusion of GTN did not cause a significant change in basal vein size in the CRF patients (9 ± 5%; \(n = 6\)). Also, infusion of BQ-123 did not cause a significant change in basal vein size in the CRF patients (AUC \(-10 ± 5\%\); \(n = 6\)) and the effect was similar when infused at either 0.3 nmol/h (AUC \(-7 ± 4\%\); \(n = 3\)) or 30 nmol/h (AUC \(-12 ± 10\%\); \(n = 3\)).

**Discussion**

In these studies we have shown that hypertensive CRF patients, despite having similar responses to noradrenaline, have impaired vasoconstriction to ET-1 compared to normotensive patients with a similar degree of CRF. In addition, we have found increased plasma concentrations of immunoreactive endothelin in hypertensive renal failure patients compared with both normotensive CRF patients and control subjects with
normal renal function. Furthermore, we have demonstrated that patients with CRF have a smaller basal vein size than control subjects but that resting vein size is not increased by infusion of the endothelium-independent nitric oxide donor and potent venodilator, GTN, or the specific ETA receptor antagonist, BQ-123.

These studies show that the responsiveness of capacitance vessel to noradrenaline is normal in normotensive and hypertensive patients with CRF, as it is in patients with end-stage renal failure requiring maintenance haemodialysis [16] and in patients with hypertension and normal renal function [6]. These studies suggest that the functional response of capacitance vessels to noradrenaline is maintained in renal failure but they are not designed to address the potential pathophysiological role for increased noradrenergic tone in either the establishment or maintenance of hypertension in patients with renal failure.

Plasma concentrations of big ET-1, the precursor of the mature ET-1 peptide, are reported as normal in patients with CRF [12]. Also, intra-arterial studies with the ETA receptor antagonist BQ-123 and the endothelin converting enzyme inhibitor phosphoramidon suggest that vascular generation of ET-1 may be decreased in CRF [8]. Therefore, it is likely that the elevated concentrations of immunoreactive ET-1 observed in our CRF patients occur mainly as a consequence of decreased clearance of ET-1 [12]. However, although the degree of renal impairment was similar in the hypertensive and normotensive CRF patients, the concentrations of plasma endothelin were further elevated in the hypertensive CRF patients. Therefore, reduced clearance of ET-1 in CRF does not adequately account for all of the elevated plasma endothelin concentrations observed in the hypertensive CRF patients. Increased plasma endothelin concentrations have been described in some states of essential hypertension with tissue injury, such as atherosclerosis [17]. Also, there is a relationship between the presence of atherosclerotic plaques and plasma ET-1 in CRF [18] which may further explain the higher endothelin concentrations in the hypertensive CRF patients, although it is not known whether this is a causal relationship or whether the raised endothelin concentrations reflect atherosclerotic endothelial injury. In addition, some evidence suggests that increased generation of ET-1 in the vascular wall may be associated with hypertension and vascular change [19]. Increased concentrations of plasma endothelin may also occur in association with a generalized endothelial dysfunction [18], similar to that observed in dialysis dependent CRF [16]. However, it remains possible that the elevated concentrations of immunoreactive endothelin may occur because generation of big ET-1 degradation products in these patients cross-reacts with the ET-1 antibody used in our assay.

Venoconstriction to ET-1 was similar between control subjects and the combined group of hypertensive and normotensive CRF patients. However, hypertensive CRF patients generated substantially less venoconstriction in response to ET-1 than the normotensive patients and there was an inverse relationship between the response to ET-1 and blood pressure in these patients. An inverse relationship between the response to ET-1 and blood pressure has also been reported in healthy subjects [6] although it could not be confirmed in this study. Also, an inverse relationship between the response of forearm resistance vessels to ET-1 and blood pressure has been described in patients with end-stage renal failure undergoing haemodialysis and treatment with human recombinant erythropoietin [7]. These findings are in contrast to those observed in subjects of a similar age and sex to our renal failure patients but with hypertension and normal renal function, who underwent a similar experimental protocol and who show an increased venoconstriction in response to ET-1, compared to control subjects, which correlates positively with blood pressure [6]. The differing vascular responsiveness to ET-1 for hypertensive subjects with and without renal impairment suggests that the pathophysiological role of ET-1 in these two hypertensive states may be different.

Plasma ET-1 concentrations were higher in the hypertensive CRF patients compared to normotensive patients. Therefore the reduced venoconstriction to ET-1 in the hypertensive patients may be due to increased receptor occupancy and/or receptor down-regulation as a consequence of the higher plasma endothelin concentrations and is consistent with the hypothesis that plasma endothelin contributes to hypertension in these patients. Interestingly, reduced sensitivity to endothelin is also found both in the forearm resistance and capacitance vessels of patients with chronic heart failure [20]. These patients also have raised plasma concentrations of ET-1, although in association with raised plasma big ET-1, and here increased vascular generation of ET-1 probably contributes to the elevated peripheral resistance described in this condition [20]. However, evidence in the forearm resistance bed of patients with CRF suggests that ET-1 generation and the contribution of ET-1 to resistance vessel tone may be reduced in CRF [8]. Therefore our results are also compatible with a reduced functional contribution of ET-1 to venous compliance in CRF.

Basal vein size was substantially less in patients with renal failure than in control subjects, raising the possibility that these vessels are under the influence of an additional tonic agent or have undergone structural change. However, infusion of the ETA receptor antagonist, BQ-123, at a concentration well above the EC50 [15], and given for a time previously shown to allow a maximal effect [8], did not cause venodilatation. Therefore the veins studied are unlikely to be reduced in diameter as a consequence of increased venomotor tone caused by ET-1 acting through the ETA receptor. Venomotor tone mediated through the ETB receptor is not addressed by these experiments. Furthermore, infusion of the nitric oxide donor GTN, at a dose
previously demonstrated to reverse vеноconstriction to exogenous ET-1 [13] and other vеноconstrictor agents [11,16], did not cause significant venodilatation of these vessels. Although the responses to GTN and BQ-123 were assessed in relatively small numbers of patients and the results should therefore be interpreted with caution, the absence of a response to GTN makes the explanation for the reduced basal vein size as a consequence of a functional ET-1-mediated vеноconstriction or secondary to another vеноconstrictor agent unlikely. Indeed, unlike muscle capacitance vessels, hand veins at rest and in a warm environment do not generally exhibit basal tone [11]. However, failure of the hand veins under study to dilate with BQ-123 and GTN does not exclude a functional role for ET-1 in the reduced venous compliance affecting larger veins in hypertensive CRF [9].

Altered structure of both veins and arteries has been observed in animal models of renal failure [21] and the high plasma endothelin concentrations observed in the hypertensive CRF patients may be sufficient to cause structural vessel changes through mitogenic [22] and atherogenic [17] effects and may even contribute to the very high cardiovascular mortality in patients with this condition. Indeed, high plasma endothelin concentrations are associated with left ventricular hypertrophy, arterial intima–media thickening and the prevalence of atherosclerotic plaques in end-stage renal failure [18]. However, it is not known whether they are causal, a consequence of endothelial cell injury, or linked by a third factor. Previous studies have linked increased pulse pressure in CRF to high plasma ET-1 and vascular change [18]. However, a significant relationship between pulse pressure and plasma endothelin concentration was not observed in our study. Interestingly, the trend for the hypertensive CRF patients to have smaller veins and higher plasma ET-1 concentrations at rest supports a role for ET-1 in causing a structural change within the veins which is unlikely to be influenced by the brief infusion of BQ-123 used in our study. Therefore, if altered vein structure in CRF is confirmed, it would be valuable to explore the longer-term effects of endothelin receptor antagonists, which could have a beneficial effect in this situation. However, the hypothesized alteration of venous structure did not affect vеноconstriction to noradrenaline in the CRF patients, where maximal vеноconstriction was similar to that in control subjects, but greater than the venoconstriction to ET-1. Therefore, altered venous structure per se does not account for the reduced responsiveness of the veins in the hypertensive CRF patients to ET-1. In addition, the CRF patient groups differed in aetiologies of their renal failure because it was not feasible to match for age, sex, blood pressure, and aetiology of CRF. Therefore, although unlikely, these differences may account for some of the effects seen on plasma endothelin and vein size.

In summary, functional responses to infusion of noradrenaline were similar between healthy control subjects and either normotensive or hypertensive patients with CRF. In contrast, vеноconstriction to ET-1 was reduced in hypertensive patients when compared to normotensive patients with CRF. Also, the hypertensive CRF patients had the highest plasma endothelin concentrations. ET-1 may therefore contribute by functional mechanisms to the development of reduced venous compliance which may, in turn, contribute to the raised cardiac preload and cardiac output observed in CRF-associated hypertension. However, given the inverse relationship between the venous response to ET-1 and blood pressure in the CRF patients, a decreased contribution of endogenous ET-1 to venomotor tone may be an alternative explanation. We also observed that basal vein size was reduced in patients with CRF through an apparently structural effect, although this requires confirmation by histological studies. Therefore, structural alteration mediated via ET-1 may also be of importance in the pathophysiology of hypertension associated with CRF. Further long-term studies with endothelin antagonists are required to determine the pathophysiological importance of ET-1 in the regulation of vascular tone, blood vessel structure, and atherogenesis in patients with CRF. In addition, inhibition of the endothelin system may potentially reduce the high cardiovascular mortality and morbidity in patients with hypertension and CRF.

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