Endothelin-1 has haemodynamic effects at pathophysiological concentrations in patients with left ventricular dysfunction

Peter J. Cowburn, John G.F. Cleland, John D. McArthur, Margaret R. MacLean, Henry J. Dargie, John J.V. McMurray, James J. Morton

Abstract

Objectives: Plasma levels of immunoreactive endothelin-1 (ET-1) are raised in chronic heart failure. Whether plasma ET-1 contributes to the haemodynamic derangement found in chronic heart failure is not known. We investigated the effects of exogenous ET-1 on the pulmonary and systemic vasculature in patients with left ventricular systolic dysfunction (LVD), with or without overt heart failure.

Methods: ET-1 was infused at 1, 5 and 15 pmol/min into a distal pulmonary artery of ten patients with LVD to achieve plasma concentrations of ET-1 similar to those found in patients with heart failure and pulmonary hypertension. Haemodynamics were measured using a pulmonary thermodilution catheter and an arterial line. Intravascular Doppler and local pulmonary angiography were used to assess local pulmonary blood flow in the first four patients.

Results: Systemic haemodynamic changes occurred with ET-1 infusion: mean arterial pressure (100 ± 3 [standard error of the mean]) to 107 ± 3 mmHg; p < 0.01) and systemic vascular resistance (1699 ± 118 to 5203 ± 135 dynes s/cm; p < 0.001) rose, while the cardiac index fell from 2.43 ± 0.17 to 2.20 ± 0.16 l/min/m² (p < 0.002). Mean pulmonary artery pressure (21 ± 2 mmHg) and pulmonary vascular resistance (151 ± 14 to 147 ± 14 dynes s/cm³) did not change however.

Conclusions: Exogenous ET-1, when infused to achieve plasma concentrations similar to those in severe heart failure and pulmonary hypertension, causes systemic but not pulmonary vasoconstriction.

Keywords: Endothelin; Heart failure; Left ventricular dysfunction

1. Introduction

The endothelins are a family of potent vasoconstrictor peptides [1,2]. Endothelin-1 (ET-1) is the predominant isoform expressed in the human vasculature [3]. ET-1, together with the C-terminal fragment, are formed by cleavage of big ET-1, a biologically inactive propeptide, a process catalysed by one or more ET converting enzymes [4]. ET-1 acts via at least two receptor subtypes, denoted ET₁A and ET₁B [5,6]. ET₁A receptors have selective affinity for ET-1 and are expressed primarily on vascular smooth muscle cells and cardiac myocytes. ET₁B receptors, which have equal affinity for each ET isoform, are expressed on both endothelial cells and vascular smooth muscle. Whilst both receptors have been shown to mediate vasoconstriction, the endothelial ET₁B receptor may also mediate vasodilatation via nitric oxide and/or prostaglandins [7].

Plasma concentrations of ET-1 have been measured by extraction-based radioimmunoassays with variable cross-reactivity to big ET-1 and the C-terminal fragment and have consistently been shown to be elevated in patients with moderate or severe heart failure [8–13]. Plasma concentrations of ET-1 are increased in proportion to the symptomatic and haemodynamic severity of chronic heart failure (CHF) [14]. Several authors have noted a positive relationship between plasma immunoreactive ET-1 (irET) and pulmonary haemodynamics measurements, in particular pulmonary vascular resistance (PVR) and the ratio of pulmonary to systemic vascular resistance (the resistance
It is difficult to characterise pulmonary artery responses to ET-1 in vivo, as pulmonary haemodynamic indices closely reflect changes in systemic haemodynamics. One possible approach is to infuse ET-1 locally to achieve high local concentrations of ET-1 in the pulmonary vascular bed without increasing concentrations in the systemic vasculature. Therefore we infused ET-1 in a range of concentrations directly into the distal pulmonary artery of patients with left ventricular dysfunction with or without overt heart failure and used intravascular Doppler ultrasound and local pulmonary angiography to study local vascular effects.

2. Methods

2.1. Patient selection

Patients with chronic left ventricular systolic dysfunction (LVD) were eligible for study. LVD was defined as a left ventricular ejection fraction (LVEF) of $<40\%$, LVEF was measured by echocardiography using Simpson’s biplane method (except in one case where radionuclide ventriculogram was used). Patients with severe coronary disease, valvar heart disease, atrial fibrillation, insulin dependent diabetes, uncontrolled hypertension and chronic renal impairment (creatinine $>200\; \mu$mol/ml) were excluded.

2.2. Patient characteristics

Ten patients aged 51–74 (mean 62) years took part in the study. Their mean LVEF was 27±6 (S.D.). One patient had a history of hypertension and one patient had non-insulin dependent diabetes. Further characteristics are given in Table 1.

2.3. Study protocols

Studies were conducted with the approval of the local ethics committee and with the written, informed consent of each patient. Cardiac medications were withheld for a minimum of 24 h before the study. Patients were fasted for 4 h prior to the study. Studies took place in the cardiac catheterisation laboratory. A 7F thermodilution catheter was positioned in a distal pulmonary artery percutaneously via a femoral vein under fluoroscopic control. In the first four patients a 6F multipurpose catheter was also passed to the same pulmonary artery to allow intravascular Doppler studies. A 4F femoral arterial line was also placed to allow continuous intraarterial blood pressure monitoring. Heparin (2500 units) was given as standard prophylaxis against thrombus formation.

An outline of the study protocol is shown in Fig. 1.

<table>
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<th>Table 1</th>
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<td>Patient characteristics</td>
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* NIDDM patient; * hypertensive patient.

M=male, F=female, Age (years), NYHA=New York Heart Association, LVEF=left ventricular ejection fraction, MAP=mean arterial blood pressure (mmHg), MPAP=mean pulmonary artery pressure (mmHg), PCWP=pulmonary wedge pressure (mmHg), CI=cardiac index ($1/min/m^2$), SVR=systemic vascular resistance (dyes $s/cm$), PVR=pulmonary vascular resistance (dyes $s/cm$), IHD=ischaeic heart disease, DCM=dilated cardiomyopathy. Medication: A=ACE-I, B=beta blocker, C=calcium antagonist, D=duretic, DIG=digoxin, N=nitrate, ASP=asprin, LL=lipid lowering therapy.
Baseline haemodynamic measurements were obtained at a minimum of 15 min postinstrumentation. Heart rate (HR, beats per min) was recorded from a precordial electrocardiographic lead. Systemic arterial, right atrial, pulmonary arterial and pulmonary capillary wedge pressure (PCWP) measurements were made simultaneously (mmHg). Cardiac output was measured (in triplicate) at each time point (see Fig. 1) by thermodilution and cardiac index derived (CI, l/min/m²). Systemic vascular resistance (SVR) and PVR were calculated from standard formula [19]. Both resistance values were expressed as dynes s/cm⁵.

After baseline values were established sodium nitroprusside (SNP) was infused into the pulmonary artery under study at 0.56 and 1.12 µg/kg/min to assess vasodilator reserve. Five patients also received 1.68 µg/kg/min. After 5 min of each dose a complete set of haemodynamic measurements were taken.

Time was allowed for haemodynamic values to return to baseline (approximately 30 min). ET-1 (Clinalfa, Switzerland) was then infused at 1, 5 and 15 pmol/min into the same pulmonary artery. Each dose was infused for 20 min with haemodynamic measurements being made at 5 and 15 min. Further measurements were taken 5 and 15 min after the infusion was complete.

2.4. Intravascular Doppler studies

Intravascular Doppler studies were performed in the first four patients in an attempt to identify marked vasoconstriction associated with a high local concentration of infused ET-1. A 0.018 inch Doppler guide wire (Flowire, Cardiomedics) was passed down the multipurpose catheter and positioned in a distal pulmonary artery under fluoroscopic control. Velocity data were recorded on videotape (Flomap, Cardiomedics) and analysed using a computer software system (Tomtek Imaging). Peak instantaneous velocities were analysed, with the formula, (average peak velocity)/2, used to calculate mean velocity in cm/s. The velocity signals for ten consecutive sinuses beats were averaged. This method of determining pulmonary arterial segmental flow velocities has previously been described in man [20]. The technique has been validated ex vivo and demonstrates excellent linear correlation to volumetric flow with $R^2$ values between 0.98 and 1.00 [21,22].

The guide wire was positioned distal to the tip of the thermodilution catheter through which the SNP and ET-1 were infused. Recordings were made at baseline and at each dose of SNP and ET-1. Local pulmonary angiography was performed at baseline and at peak dose via the multipurpose catheter to allow estimation of the diameter of the pulmonary artery under study.

2.5. Measurement of plasma ET concentrations

2.5.1. ET-1 infusion group

Blood samples were obtained from all patients from a peripheral vein after 30 min of supine rest 2 h prior to the study. In six patients samples were also taken from the femoral artery at baseline prior to SNP infusion, after reestablishment of a baseline prior to ET-1 infusion, at the end of each dose of ET-1, and at 5 and 15 min of recovery (see Fig. 1).

2.5.2. Control subjects and patients with LVD

Blood samples were also taken from a peripheral vein from a further 17 patients with LVD undergoing haemodynamic evaluation (cardiac medications were withheld for 24 h). Eight of these patients had a mean pulmonary artery pressure of >30 mmHg. A total of 21 control subjects were also studied: 11 subjects with no history of cardiac disease, a normal electrocardiogram, and taking no medications and a further ten patients with chronic stable angina, on standard antianginal therapy, shown to have normal left ventricular function at cardiac catheterisation.

Blood was collected into chilled tubes containing 4% EDTA. Samples were kept on ice and were then centrifuged at 4°C. Separated plasma samples were immediately stored at −20°C. ET-1 and big ET-1 were assayed directly (and separately) using enzyme immunoassays (Biomedica). The kits incorporate an immunoaffinity purified polyclonal capture antibody and a monoclonal detection antibody, both highly specific for ET (1–21) or big ET (1–38). Samples were assayed in duplicate and averaged.

2.5.3. ET (1–28) assay characteristics

Measuring range 0.1 to 15.6 fmol/ml; crossreactivity ET-1: 100%, ET-2: 100%, ET-3: <5%, big ET (1–38): <1%, big ET (22–38): <1%.

2.5.4. Big ET (1–38) assay characteristics

Measuring range: 0.025–6.25 fmol/ml; crossreactivity big ET (1–38): 100%, big ET (22–38): <1%, ET-1: <1%, ET-2: <1%, ET-3: <1%.

2.6. Statistical analysis

Baseline values are reported as mean±S.D., values relating to an intervention are reported as mean±standard error of the mean (S.E.M.). The primary endpoint of the study were the changes in PVR and SVR from baseline to the maximum achieved dose of ET-1. Student’s paired $t$-test (two-tailed) was used to compare baseline and peak haemodynamic measurements in the SNP and ET-1 infusion study. Students unpaired $t$-test (two-tailed) was used to compare plasma ET-1 and big ET-1 in patient and control groups. Values were considered significantly different if $p<0.05$. 

The guide wire was positioned distal to the tip of the thermodilution catheter through which the SNP and ET-1 were infused. Recordings were made at baseline and at each dose of SNP and ET-1. Local pulmonary angiography was performed at baseline and at peak dose via the multipurpose catheter to allow estimation of the diameter of the pulmonary artery under study.
Table 2
SNP haemodynamic data

<table>
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<th>Baseline</th>
<th>SNP peak</th>
<th>Mean change</th>
<th>p</th>
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<tr>
<td>HR</td>
<td>75±17</td>
<td>88±6</td>
<td>12±2</td>
<td>&lt;0.001</td>
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<tr>
<td>MAP</td>
<td>99±9</td>
<td>76±3</td>
<td>−24±3</td>
<td>&lt;0.0001</td>
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<tr>
<td>RAP</td>
<td>4.8±1.4</td>
<td>4.5±0.6</td>
<td>−0.3±0.5</td>
<td>ns</td>
</tr>
<tr>
<td>MPAP</td>
<td>19±5</td>
<td>11±1</td>
<td>−8±1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PCWP</td>
<td>11±4</td>
<td>4±1</td>
<td>−7±1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CI</td>
<td>7.5±1.8</td>
<td>6.2±1.0</td>
<td>−1.3±1.0</td>
<td>ns</td>
</tr>
<tr>
<td>MPAP</td>
<td>5.8±1.5</td>
<td>5.0±0.8</td>
<td>−0.8±0.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CI</td>
<td>2.6±0.8</td>
<td>2.4±0.6</td>
<td>−0.2±0.6</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>SVR</td>
<td>1575±287</td>
<td>1112±86</td>
<td>−464±54</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PVR</td>
<td>124±30</td>
<td>94±13</td>
<td>−30±14</td>
<td>ns (p=0.06)</td>
</tr>
</tbody>
</table>

Baseline values: mean±S.D; SNP and mean change given as mean±S.E.M. SNP=sodium nitroprusside, HR=heart rate (beats/min), RAP=right atrial pressure (mmHg), TPG= transpulmonary gradient (mmHg); other haemodynamic indices (units) as described in Table 1.

3. Results

3.1. SNP infusion

Table 2 demonstrates the haemodynamic effects of SNP in these patients. As reported in previous studies SNP reduced mean arterial pressure (MAP), mean pulmonary pressure (MPAP), PCWP and SVR whilst increasing HR and cardiac output (CO). The fall in PVR did not reach statistical significance (p=0.06). Mild flushing was reported by a minority of patients.

3.2. ET-1 infusion

No symptomatic adverse effects were noted during the infusion of ET-1. Two patients did not receive the 15 pmol/min infusion due to a fall in cardiac output of >15% in one patient and a 20 mmHg systolic blood pressure rise in the other. Figs. 2 and 3 show the responses of SVR and PVR to ET-1. No haemodynamic change was observed with ET-1 at 1 pmol/min and only trends to increased SVR at 5 pmol/min. Table 3 demonstrates the peak haemodynamic effects of ET-1 infusion in these patients compared to the baseline taken after SNP infusion. At 15 pmol/min of ET-1 the HR remained unchanged, MAP rose by 7%, CO fell by 9% and, consequently, SVR rose by 20%. MPAP was unchanged, there were trends to a rise in PCWP (and hence trends to a fall in transpulmonary gradient) and therefore PVR remained unchanged despite the fall in CO.

3.3. Intravascular Doppler and local pulmonary angiography

Mean velocity did not change with infusion of SNP or ET-1: baseline 0.41±0.07, SNP 0.39±0.02, baseline 0.35±0.04 m/s, ET-1 0.36±0.03 m/s. No change could be observed in the diameter of the pulmonary conduit artery under study: baseline 0.36±0.11 cm, SNP 0.38±0.06 cm, ET-1 0.36±0.06 cm.

Fig. 2. Changes in systemic (SVR) vascular resistance in response to graded infusion of endothelin-1 (ET-1). The increase in SVR was statistically significant at the highest concentrations of ET-1 (p<0.001). Data shown as mean±S.E.M.
Fig. 3. Changes in pulmonary vascular resistance (PVR) in response to graded infusion of endothelin-1 (ET-1). No significant change in PVR occurred. Data shown as mean ± S.E.M.

3.4. Plasma ET concentrations

3.4.1. ET-1 infusion group

The mean venous plasma concentrations of ET-1 and big ET-1 were 0.15±0.17 fmol/ml and 0.62±0.26 fmol/ml respectively (mean±S.D.). During ET-1 infusion (six patients) the peak mean femoral arterial plasma ET-1 concentration rose from 0.17±0.17 fmol/ml at baseline (postSNP) to 1.13±0.40 fmol/ml (15 pmol/min dose) (p<0.003). The plasma concentrations during 1 and 5 pmol/min infusions (of 0.18±0.05 and 0.25±0.04 fmol/ml respectively) were not statistically different from baseline values. Big ET-1 plasma concentration did not change. Fig. 4 illustrates the mean femoral arterial plasma ET-1 and big ET-1 concentrations during the study.

3.4.2. Control subjects and patients with LVD

Results are demonstrated graphically in Fig. 5. ET-1 and big ET-1 were higher in LVD patients than controls (0.40±0.59 vs. 0.15±0.12 fmol/ml, p=0.02 and 1.13±1.01 vs. 0.56±0.27 fmol/ml, p=0.004 respectively). Patients with MPAP >30 mmHg had higher ET-1 and big ET-1 levels than patients with LVD and MPAP <30 mmHg (1.07±0.76 vs. 0.20±0.34 fmol/ml, p<0.02 and 2.42±1.47 vs. 0.73±0.26 fmol/ml, p<0.02 respectively). Big ET-1 was elevated in patients with LVD and MPAP <30 mmHg compared with controls (0.73±0.26 vs. 0.56±0.27 fmol/ml, p<0.04), whereas ET-1 was not (0.20±0.34 vs. 0.15±0.12 fmol/ml, p=0.49).

4. Discussion

This study shows that infusions of ET-1, that achieve plasma concentrations similar to those observed in patients with severe heart failure and pulmonary hypertension, cause systemic vasoconstriction in patients with LVD. This suggests that ET-1 can act as a circulating hormone, at least in the systemic circulation, in advanced CHF. However, we observed little or no change in MPAP or PVR.

Table 3

<table>
<thead>
<tr>
<th>Endothelin-1 haemodynamic data</th>
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<tbody>
<tr>
<td><strong>Baseline</strong></td>
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<tr>
<td>HR 73±17</td>
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<tr>
<td>MAP 100±8</td>
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<tr>
<td>RAP 5.8±1.4</td>
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<tr>
<td>MPAP 21±7</td>
</tr>
<tr>
<td>PCWP 12±6</td>
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<tr>
<td>TPG 8.6±2.5</td>
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<tr>
<td>CI 2.43±0.53</td>
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<tr>
<td>SVR 1699±375</td>
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<td>PVR 151±43</td>
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Baseline values: mean±S.D.; ET-1 and mean change given as mean±S.E.M. Haemodynamic indices (units) as described in Tables 1 and 2.
Fig. 4. Plasma femoral arterial concentrations of endothelin-1 (ET-1) and big endothelin (big ET-1) during graded infusions of ET-1 into the pulmonary artery (mean±S.E.M.). SNP = sodium nitroprusside.

during ET-1 infusion. Even administration of ET-1 to produce very high local concentrations of ET-1 failed to cause local pulmonary vasoconstriction, as measured by intravascular Doppler ultrasound.

Three studies have reported the effects of exogenous ET-1 in healthy volunteers. Wagner et al. [23] infused ET-1 peripherally at approximately 1 ng/kg/min (we gave up to approximately 0.5 ng/kg/min) to achieve a 4.5-fold increment in pulmonary arterial plasma concentrations, achieving levels compatible with those found in heart failure. They reported a small fall in MPAP though PVR did not change. Weitzberg et al. [24] infused approximately 10 ng/kg/min to achieve a 20-fold increase in pulmonary arterial plasma concentrations of ET-1, well above the pathophysiological range, and reported a 2 mmHg increase in MPAP, with a greater rise in PVR than SVR. PCWP was unchanged. Kiely et al. [25] infused approximately 7 ng/kg/min of ET-1 and reported rises in systemic and total pulmonary vascular resistance. However they used noninvasive techniques to estimate haemodynamic change, and could not report changes in PVR as they did not measure PCWP. Plasma concentrations of ET-1 were not measured during ET-1 infusion. In our study, the plasma concentration of ET-1 obtained after infusion of ET-1 at 15 pmol/min was 1.13 fmol/ml which was comparable to the plasma concentrations of ET-1 found in patients with a raised MPAP (1.07±0.76 fmol/ml).

Administration of bosentan, a nonselective ET antagonist, led to a fall in both SVR and PVR in patients with CHF when administered acutely [18] and over a 2 week period [26]. It is possible that the fall in PVR observed during administration of bosentan was passive, secondary to an improvement in cardiac and systemic haemodynamics, rather than due to inhibition of a direct and selective pulmonary vasoconstrictor effect of ET-1. Therefore the studies of bosentan do not prove that ET antagonists specifically reduce PVR.

The lack of an effect of ET-1 in the pulmonary circulation in patients with LVD requires explanation given the in vitro effects of ET-1 in pulmonary arteries and the close correlation between plasma concentrations of ET-1 and pulmonary vascular resistance [10,17,18,27]. ET-1 is secreted abluminally and has been thought to act in a paracrine fashion [28,29]. Tissue rather than plasma concentrations of ET-1 could be the more important determinant of PVR. Infusion of ET-1 to achieve much higher concentrations of ET-1 in the plasma than we did might be
required to raise tissue concentrations to pathophysiological levels and to cause pulmonary vasoconstriction, as reported in studies of healthy volunteers [24,25]. Nonetheless, we did observe systemic vasoconstriction at pathophysiological plasma concentrations of ET-1. One explanation for a differential effect on the systemic and pulmonary circulations may be that concentrations of ET-1 at the pulmonary vascular smooth muscle cell are already high and exogenous ET-1 in the doses that we gave may not have resulted in a further substantial increase in tissue ET-1 concentrations. Alternatively, there may be differential regulation of $E_{\text{T}_{A}}$ and $E_{\text{T}_{B}}$ mediated responses in the pulmonary and systemic circulations in heart failure. For instance impaired systemic or enhanced pulmonary endothelial $E_{\text{T}_{B}}$ mediated vasodilation may occur.

ET-1 does cause pulmonary vasoconstriction in vitro at the plasma concentrations we observed, but in this preparation vessels are bathed in ET-1, and ET-1 may act predominantly and directly on vascular smooth muscle $E_{\text{T}_{A}}$ and $E_{\text{T}_{B}}$ receptors [27]. In contrast, exogenously administered ET-1 may have a more prominent effect on endothelial $E_{\text{T}_{B}}$ receptors, leading to vasodilation via nitric oxide and/or prostacyclin [7], balancing any vasoconstrictor effect mediated via smooth muscle $E_{\text{T}_{A}}$ and $E_{\text{T}_{B}}$ receptors [30].

If plasma ET-1 is not causing pulmonary vasoconstriction, what then is the explanation for the relationship between plasma ET-1 and PVR? Elevated plasma ET-1 concentrations could merely be a marker of endothelial dysfunction. There is considerable evidence for endothelial dysfunction in patients with heart failure, and in many respects this dysfunction reflects endothelial hyperactivity. In CHF patients von Willebrand factor, a glycoprotein released from endothelial cells, is elevated and correlates directly not only with PVR [31] but also with plasma concentrations of ET [32]. Habib et al. showed an enhanced response to N$^{\text{G}}$-monomethyl-L-arginine in patients with heart failure suggesting enhanced basal nitric oxide production in heart failure [33]. Endothelial derived vasodilator prostaglandins are also increased in heart failure [34].

Alternatively, the association between high plasma ET-1 concentrations and pulmonary haemodynamic measurements may be explained by the postulated role of the pulmonary circulation in ET-1 clearance. The pulmonary vasculature has been reported to be a major site of synthesis [17,35] and of clearance of ET-1 in many [23,24,35] but not all [36,37] studies. Increased plasma ET-1 could reflect reduced clearance and/or increased synthesis of ET-1 in severe CHF. A recent report suggested that the pulmonary clearance of ET-1 in heart failure is inversely related to the severity of pulmonary hypertension [38]. The authors concluded that elevated plasma ET-1 concentrations are a marker of pulmonary hypertension and reflect pulmonary endothelial dysfunction.

Finally, there was one other important finding in this study. We have been able to explore the relationship between plasma concentrations of ET-1 and big ET-1 in patients with heart failure and normal controls. True plasma concentrations of ET-1, as opposed to measurements of irET-1 that include big ET-1, have not often been measured in patients with heart failure [10,16,17]. Wei et al. measured ET-1 and big ET-1 separately in four healthy volunteers and four patients with severe heart failure [12]. Big ET-1 was not detected in the plasma of healthy volunteers but accounted for over 60% of irET-1 in patients with severe heart failure. In a larger population we could detect big ET-1 even in healthy volunteers. In patients with heart failure and normal pulmonary artery pressures only big ET-1 was raised compared to controls. However, in patients with severe heart failure and raised pulmonary artery pressures (MPAP >30 mmHg), both ET-1 and big ET-1 were elevated, the increase in ET-1 being relatively greater than the increase in big ET-1 (see Fig. 5). Whether the increase in the ratio of ET-1 to big ET-1 in patients with higher pulmonary artery pressures reflects differential clearance or increased ET converting enzyme activity remains speculative.

4.1. Study limitations

After a period of rest to achieve stable baseline haemodynamics each study began with an infusion of SNP to assess pulmonary vascular responsiveness. Despite a 30 min wash out period during which mean systemic and pulmonary arterial pressures were noted to have returned to normal some rebound increase in PVR and SVR was noted. This could have obscured a small increase in PVR during infusion of ET-1. Even if this were the case any rise in PVR was no greater than the increase in SVR and a preferential vasoconstrictor effect in the pulmonary circulation can be excluded.

As we were unable to demonstrate changes in local pulmonary blood flow, whilst observing systemic changes in response to ET-1 infusion, we discontinued the intravascular Doppler studies after only four patients. It is possible that we could have missed small changes in local pulmonary vascular resistance that could have been detected with a much larger number of patients. However, any major local pulmonary vascular effect of ET-1 is effectively excluded even with this small number of observations.

5. Conclusion

ET-1, when infused into patients with LVD to achieve plasma concentrations in keeping with patients with severe heart failure and pulmonary hypertension, causes systemic vasoconstriction with little or no effect on the pulmonary vasculature. ET-1, in addition to having paracrine effects,
acts as a circulating hormone with haemodynamic effects in advanced heart failure. Further studies of selective ET antagonists are required to determine the importance of endogenous ET-1 production in the control of pulmonary vascular tone.

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References