

Direct comparison of selective endothelin A and non-selective endothelin A/B receptor blockade in chronic heart failure

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Heart 2005;91:914–919. doi: 10.1136/hrt.2004.040386

Objective: To investigate the potential differential effects of selective endothelin (ET) A and dual ET-A/B receptor blockade in patients with chronic heart failure.

Methods: Nine patients with chronic heart failure (New York Heart Association class II–III) each received intravenous infusions of BQ-123 alone (selective ET-A blockade) and combined BQ-123 and BQ-788 (dual ET-A/B blockade) in a randomised, placebo controlled, three way crossover study.

Results: Selective ET-A blockade increased cardiac output (maximum mean (SEM) 33 (12)%, $p < 0.001$) and reduced mean arterial pressure (maximum -13 (4)%, $p < 0.001$) and systemic vascular resistance (maximum -26 (8)%, $p < 0.001$), without changing heart rate ($p = 0.38$). Dual ET-A/B blockade significantly reduced the changes in all these haemodynamic variables compared with selective ET-A blockade ($p < 0.05$). Selective ET-A blockade reduced pulmonary artery pressure (maximum 25 (7)%, $p = 0.01$) and pulmonary vascular resistance (maximum 72 (39)%, $p < 0.001$). However, there was no difference between these effects and those seen with dual ET-A/B blockade. Unlike selective ET-A blockade, dual ET-A/B blockade increased plasma ET-1 concentrations (by 47 (4)% with low dose and 61 (8)% with high dose, both $p < 0.05$).

Conclusions: While there appeared to be similar reductions in pulmonary pressures with selective ET-A and dual ET-A/B blockade, selective ET-A blockade caused greater systemic vasodilatation and did not affect ET-1 clearance. In conclusion, there are significant haemodynamic differences between selective ET-A and dual ET-A/B blockade, which may determine responses in individual patients.

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Accepted 18 August 2004

Endothelin (ET) 1 is a potent endogenous vasoconstrictor in humans and contributes to the maintenance of basal vascular tone¹ and blood pressure² in healthy people and patients with systemic arterial hypertension.^{3,4} It acts through two receptor subtypes: the ET-A and ET-B receptors. While both receptors are expressed on vascular smooth muscle cells and mediate vasoconstriction, only the ET-B receptor is located on the endothelium, where it produces a prostanoid and nitric oxide mediated vasodilatation. Thus, ET-B receptor mediated effects are complex and include vasoconstriction, endothelium dependent vasodilatation, and a role in the clearance of ET-1.⁵ In healthy people, in contrast to the vasodilator and vasodepressor effects of ET-A receptor blockade,^{6,7} systemic ET-B receptor blockade has vasoconstrictor and pressor effects,⁸ suggesting that the vascular balance of basal ET-B receptor activation favours vasodilatation.

Chronic heart failure is associated with neurohumoral activation as a consequence of reductions in cardiac reserve, systemic blood pressure, and renal perfusion. This leads to peripheral vasoconstriction, increased systemic vascular resistance, and sodium and water retention, which together increase cardiac work and further compromise cardiac performance. Many regulatory mechanisms are involved in this maladaptive response, including the renin–angiotensin, sympathetic nervous, and vasopressin systems. The ET system also appears to contribute to the pathophysiology of heart failure, which is associated with increased plasma ET-1 concentrations^{9,10} that correlate with haemodynamic changes,^{11,12} reduced exercise capacity,¹³ and a poor prognosis.¹⁴

In patients with chronic heart failure, systemic administration of both selective ET-A^{15–17} and non-selective ET-A/B

blockade^{18–21} reduces systemic vascular resistance and increases cardiac output. In patients with acute decompensated heart failure systemic administration of non-selective ET-A/B blockade has been shown to have beneficial effects.²² However, systemic ET-B blockade increases systemic vascular resistance and has potentially detrimental effects in patients with chronic heart failure.²³ Therefore, the question arises as to whether differences between selective ET-A and non-selective ET-A/B blockade can influence haemodynamic responses to ET blockade, which in turn might have contributed to the recent failure of ET blockade as a treatment approach for patients with chronic heart failure.^{24,25} However, to date, there have been no direct studies comparing these two approaches.

The objectives of this placebo controlled study, in patients with stable chronic heart failure, were to compare in a head to head manner the effects of selective ET-A blockade with non-selective ET-A/B blockade on systemic and pulmonary haemodynamic function.

METHODS

Patient selection

Nine patients with chronic heart failure (New York Heart Association (NYHA) class II–III) caused by left ventricular dysfunction were recruited if they had an ejection fraction $\leq 35\%$ (by echocardiography with the biplanar Simpson's rule) and had been stable with treatment, including angiotensin converting enzyme inhibitor or angiotensin receptor antagonist, for at least three months. Patients were all in sinus rhythm and no patient had a pacemaker or implantable cardiac defibrillator. Patients were excluded if they had insulin dependent diabetes mellitus, abnormal liver function, renal impairment (creatinine $> 200 \mu\text{mol/l}$ for

men; > 180 µmol/l for women) or a systolic blood pressure > 190 or < 90 mm Hg, or within three months had undergone coronary artery bypass graft surgery or percutaneous coronary intervention or had an acute coronary syndrome, myocardial infarction, or cerebrovascular accident.

The study was undertaken with the approval of the local research ethics committee and in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient before entry into the study.

Measurements

Blood pressure and heart rate were measured non-invasively with a Dynamap compact TS (Critikon LLC, Ascot, UK). Cardiac output, mean pulmonary artery pressure, pulmonary artery wedge pressure, and central venous pressure were measured continuously with a single multilumen thermodilution cardiac output pulmonary artery catheter (Swan-Ganz CCOMbo—CCO/SVO2; Edwards Lifesciences, Irvine, California, USA). Cardiac output was calculated automatically (Vigilence, Edwards Critical Care, Baxter's Healthcare Corporation, Irvine, California, USA) and, at each time point, the cardiac output was taken as the mean of three measurements.

Protocol

All patients attended fasted at 7.30 am on three occasions at least one week apart. Patients were asked to omit their regular medications on the morning of the study. The studies were conducted in a quiet, draught-free room maintained at a constant temperature (22–24°C). A pulmonary artery catheter was inserted through a 9 French femoral venous sheath into the right pulmonary artery and was flushed with 0.9% heparinised saline. Before starting drug administration, patients underwent an equilibration period of > 90 minutes until blood pressure, heart rate, and cardiac output were stable, with three consecutive measurements within 10%. Study drugs were administered by 15 minute infusion in two incremental doses 60 minutes apart.

Drug administration

A venous cannula for drug administration was inserted under local anaesthesia. Pharmaceutical grade BQ-123 and BQ-788 (Clinalfa AG, Läuelfingen, Switzerland) were dissolved in 0.9% saline (Baxter Healthcare Ltd, Thetford, UK). On each study day, patients received a low dose infusion at $t = 0$ for 15 minutes followed by a high dose infusion at $t = 60$ minutes for 15 minutes. On different study days and in

random order, patients received saline placebo, BQ-123 (low dose, 1.5 µmol; high dose, 15 µmol) alone or the co-infusion of BQ-123 (low dose, 1.5 µmol; high dose, 15 µmol) and BQ-788 (low dose, 0.45 µmol; high dose, 4.5 µmol). These doses were selected following studies in healthy volunteers given BQ-123 and BQ-788. This dose of BQ-123 was sufficient to reduce systemic vascular resistance and block the effects of local infusion of ET-1 into the forearm.⁷ This dose of BQ-788 was sufficient to reduce systemic vascular resistance.⁸ The detailed rationale for these doses has been discussed elsewhere.²⁶

Blood sampling and plasma assays

Venous blood for ET-1 and big ET-1 (the 38 amino acid precursor of ET-1) assay was taken from the femoral vein. Blood was collected into 0.16% EDTA (Sarstedt, Aktiengesellschaft & Co, Numbrecht, Germany) and immediately separated by centrifugation (2500 g for 20 minutes at 4°C) and stored at –80°C until analysis. Following extraction in Bond Elut columns (Varian, Harbor City, California, USA), ET-1 (Peninsula Laboratories Europe Ltd, St Helens, UK) and big ET-1 (Peninsula Laboratories Europe Ltd) concentrations were determined by radioimmunoassay as previously described.²⁷ The intra-assay coefficients of variability were 7.0 and 7.2%, respectively, and the interassay coefficients of variability were 9.0 and 9.3%, respectively.

Table 2 Baseline parameters

Parameter	Placebo (n = 9)	BQ-123 (n = 9)	BQ-123 + BQ-788 (n = 9)
HR (beats/min)	64 (5)	62 (4)	63 (5)
MAP (mm Hg)	91 (7)	87 (6)	90 (7)
SBP (mm Hg)	106 (8)	104 (9)	106 (9)
DBP (mm Hg)	69 (4)	68 (6)	71 (4)
CVP (mm Hg)	5 (1)	5 (1)	3 (2)
CO (l/min)	5.0 (0.3)	5.5 (0.4)	5.3 (0.3)
SVR (dyn.s/cm ⁻⁵)	1462 (150)	1266 (138)	1344 (138)
MPAP (mm Hg)	16 (1)	16 (1)	17 (2)
PAWP (mm Hg)	11 (2)	11 (1)	12 (3)
PVR (dyn.s/cm ⁻⁵)	83 (12)	91 (14)	78 (18)

Data are mean (SEM).

CO, cardiac output; CVP, central venous pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PVR, pulmonary vascular resistance; SBP, systolic blood pressure; SVR, systemic vascular resistance.

Table 1 Patient characteristics and medications

Patient	Age (years)	BMI (kg/m ²)	BP (mm Hg)	HR (beats/min)	MPAP (mm Hg)	PAWP (mm Hg)	Cause of HF	NYHA	Drugs and dose*
1	75	26	186/79	52	20	11	Ischaemic	III	ASA75, En20, Bu1, Sim20
2	63	23	120/74	64	13	6	Idiopathic	II	ASA75, En20
3	60	27	122/58	62	17	12	Ischaemic	III	Val80, Frus40
4	43	30	98/64	77	12	8	Ischaemic	II	ASA75, Lis10, Frus40
5	56	29	139/88	96	11	6	Ischaemic	III	ASA75, Lis20, Frus40, Car12.5, Dig250, Sim20
6	61	26	136/77	66	16	12	Ischaemic	III	ASA75, Lis10, Frus40, Spir25, Dig125, Sim20
7	52	36	184/106	94	25	23	Ischaemic	III	Lis15, Frus20, Aten100
8	74	33	143/75	58	14	10	Ischaemic	III	ASA75, Lis10, Frus40, Bis10, Sim10
9	67	21	154/78	65	14	10	Ischaemic	II	ASA75, Lis10, Aten50, Pra20
Average	61	28	142/78	70	16	11			
SEM	3	1	9/4	5	1	2			

*Doses in mg except for digoxin (µg).

ASA, aspirin; Aten, atenolol; Bis, bisoprolol; BMI, body mass index; BP, blood pressure; Bu, bumetanide; Car, carvedilol; Dig, digoxin; En, enalapril; Frus, furosemide; HF, heart failure; HR, heart rate; Lis, lisinopril; MPAP, mean pulmonary artery pressure; NYHA, New York Heart Association; PAWP, pulmonary artery wedge pressure; Pra, pravastatin; Sim, simvastatin; Spir, spironolactone; Val, valsartan.

Data and statistical analyses

Data are expressed as mean (SEM) change from baseline or mean (SEM) area under the curve (AUC) unless otherwise specified. Data were examined by analysis of variance with repeated measures over time and Student's *t* test with correction for multiple measures where appropriate (Excel version 5.0, Microsoft, Redmond, Washington, USA). Significance was taken at the 5% level.

RESULTS

Table 1 shows baseline patient characteristics and medications. There were no adverse events and the study was well tolerated by all patients. There were no significant differences in baseline haemodynamic variables between study visits (table 2). Placebo administration caused no significant changes in haemodynamic variables throughout the course of the study (analysis of variance $p > 0.9$).

Cardiac output and heart rate

In comparison with placebo, BQ-123 alone (AUC $p < 0.001$), but not BQ-123/788 (AUC $p = 0.08$), increased cardiac output with a maximum increase of 33 (12)% at 75 minutes. Infusion of BQ-123 alone increased cardiac output compared with BQ-123/788 (AUC $p < 0.001$) (fig 1C, fig 2). There was no significant change in heart rate with either BQ-123 alone (AUC $p = 0.38$) or BQ-123/788 (AUC $p = 0.39$) (fig 1A, fig 2).

Left ventricular filling pressure and systemic haemodynamic variables

In comparison with placebo, BQ-123 alone (AUC $p = 0.01$) and BQ-123/788 (AUC $p < 0.01$) reduced pulmonary artery wedge pressure by a maximum of 19 (7)% at 150 minutes and 26 (7)% at 105 minutes, respectively (fig 2, fig 3C). There was no difference between the magnitude of reduction in

pulmonary artery wedge pressure between BQ-123 alone and BQ-123/788 (AUC $p = 0.47$). BQ-123 alone (AUC $p < 0.001$) and BQ-123/788 (AUC $p < 0.05$) reduced mean arterial pressure by a maximum of 14 (5)% and 12 (4)%, respectively, at 150 minutes. BQ-123 alone reduced mean arterial pressure to a greater degree than BQ-123/788 (AUC $p < 0.05$) (fig 1B, fig 2).

BQ-123 alone (AUC $p < 0.001$) and BQ-123/788 (AUC $p < 0.05$) reduced systemic vascular resistance by a maximum of 26 (8)% and 16 (5)%, respectively, at 75 minutes in comparison with placebo. BQ-123 alone reduced systemic vascular resistance to a greater degree than BQ-123/788 (AUC $p < 0.05$) (fig 1D, figs 2 and 3).

Right ventricular filling pressure and pulmonary haemodynamic variables

In comparison with placebo, neither BQ-123 alone (AUC $p = 0.17$) nor BQ-123/788 (AUC $p = 0.69$) changed central venous pressure (fig 2, fig 3A). BQ-123 alone (AUC $p = 0.01$) and BQ-123/788 (AUC $p = 0.02$) reduced mean pulmonary arterial pressure by a maximum of 25 (7)% and 26 (6)%, respectively, at 90 minutes. There was no significant difference between these responses (AUC $p = 0.98$) (fig 2, fig 3B).

In comparison with placebo, both BQ-123 alone and BQ-123/788 (AUC both $p < 0.001$) reduced pulmonary vascular resistance by a maximum of 72 (39)% and 40 (16)%, respectively, at 75 minutes. There was no significant difference between these responses (AUC $p = 0.49$) (fig 2, fig 3D).

Plasma ET-1 and big ET-1

There was no change in plasma concentrations of big ET-1 with placebo, BQ-123 alone, or BQ-123/788. There was no significant change in plasma ET-1 concentrations with

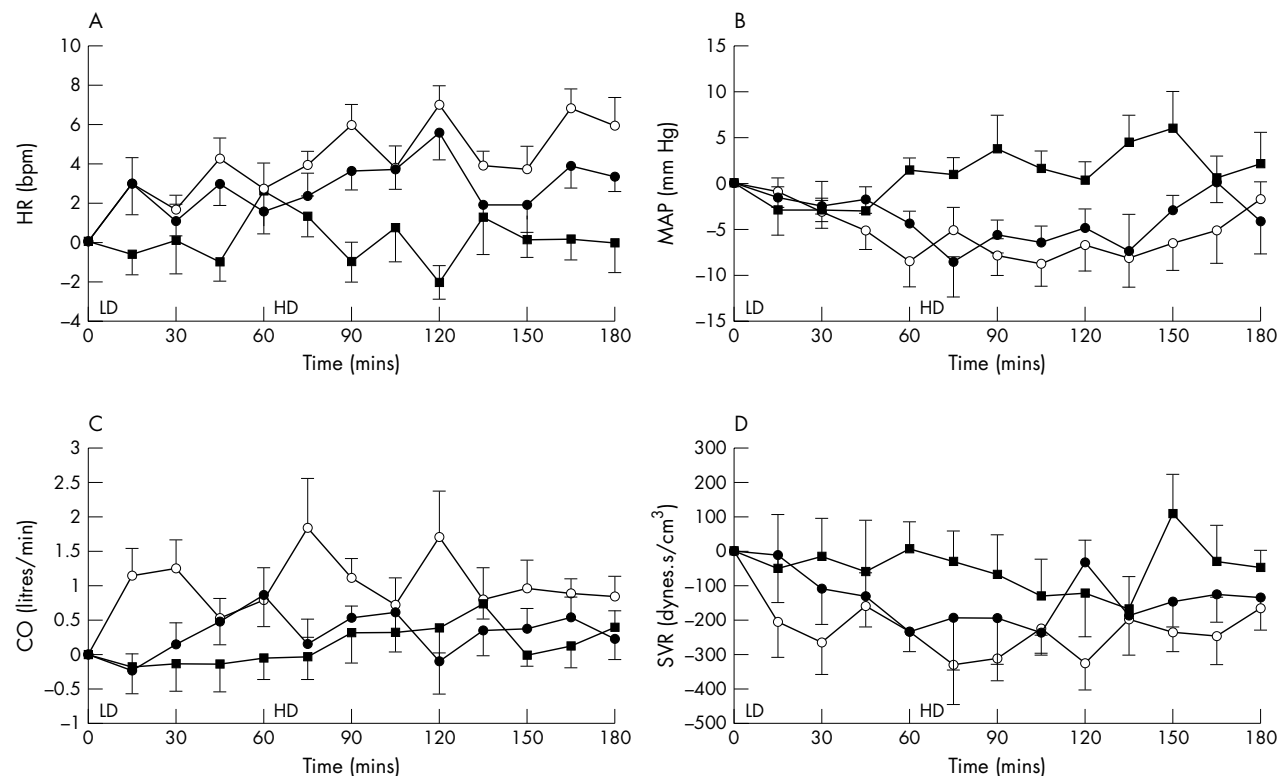


Figure 1 Effect of selective endothelin (ET) A blockade (open circles), dual ET-A/B blockade (solid circles), and placebo (solid squares) on (A) heart rate (HR), (B) mean arterial pressure (MAP), (C) cardiac output (CO), and (D) systemic vascular resistance (SVR) at low dose (LD) and high dose (HD).

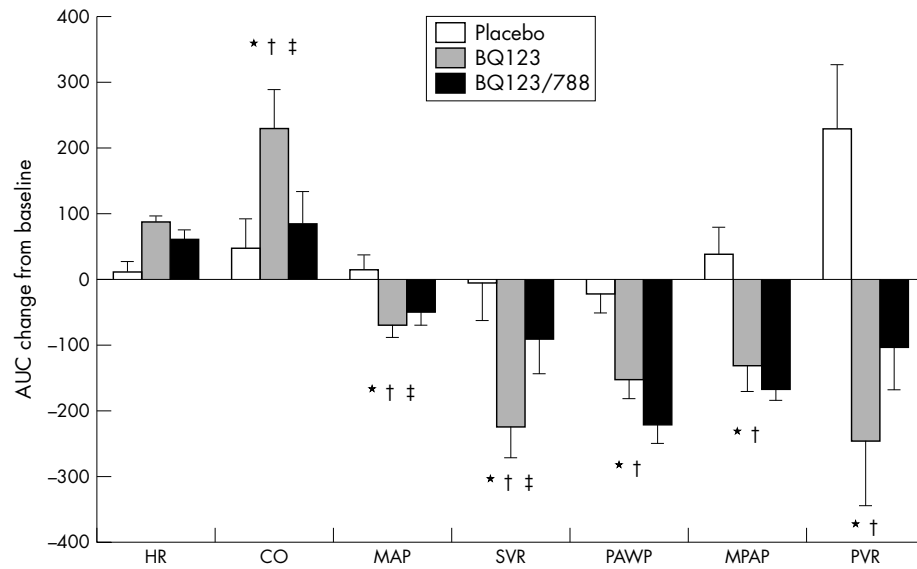


Figure 2 Comparison of the haemodynamic effects of placebo (white), selective ET-A blockade (grey), and dual ET-A/B blockade (black) on HR, CO, MAP, SVR, pulmonary arterial wedge pressure (PAWP), mean pulmonary artery pressure (MPAP) and pulmonary vascular resistance (PVR). AUC, area under the curve. *p < 0.05 BQ-123 v placebo; †p < 0.05 BQ-123/788 v placebo; ‡p < 0.05 BQ-123 v BQ-123/788.

placebo or BQ-123 alone, whereas BQ-123/788 caused an increase in plasma ET-1 concentrations (47% with low dose and 61% with high dose, both p < 0.05) (fig 4).

DISCUSSION

In this randomised placebo controlled crossover study, we have shown, for the first time, that there are small but significant haemodynamic differences between the responses to selective ET-A and non-selective ET-A/B receptor blockade in patients with chronic heart failure. Both selective ET-A and non-selective ET-A/B receptor blockade increased cardiac

output and reduced mean arterial pressure and systemic vascular resistance. However, selective ET-A receptor blockade caused a greater increase in cardiac output and reduction in systemic vascular resistance than non-selective ET-A/B receptor blockade. In contrast, selective ET-A and non-selective ET-A/B blockade caused similar reductions in both pulmonary artery pressure and pulmonary vascular resistance. There was a greater reduction in pulmonary artery pressure with non-selective blockade than with selective ET-A blockade after low dose infusion, although this difference was not apparent after high dose infusion.

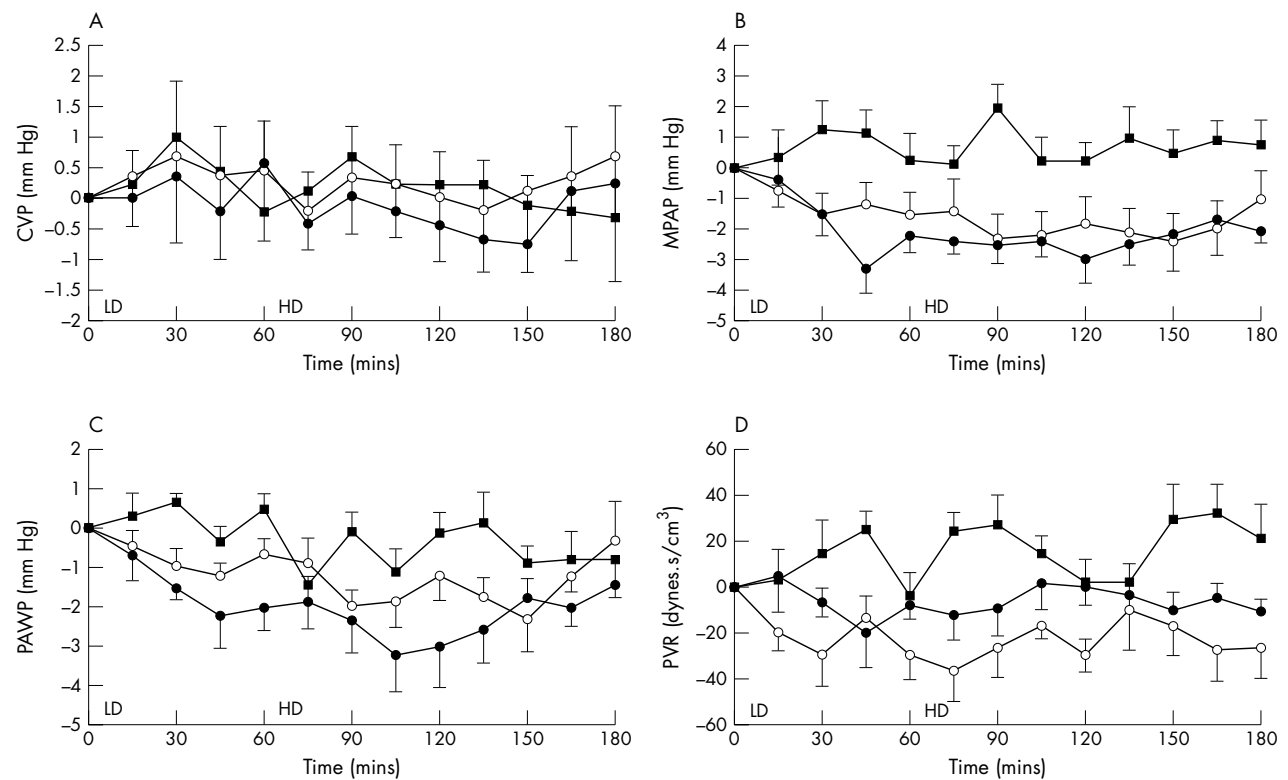


Figure 3 Effect of selective ET-A blockade (open circles), dual ET-A/B blockade (solid circles), and placebo (solid squares) on (A) central venous pressure (CVP), (B) MPAP, (C) PAWP, and (D) PVR at low dose (LD) and high dose (HD).

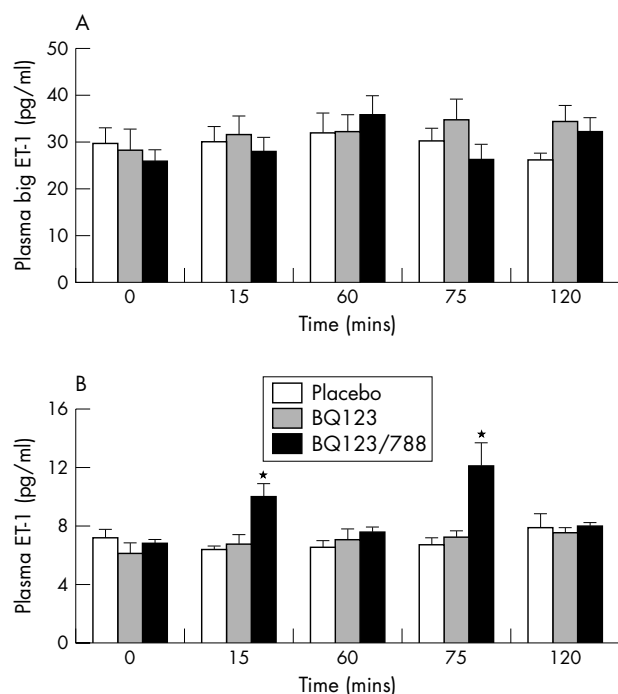


Figure 4 Effects of placebo (white), selective ET-A blockade (grey), and combined ET-A/B blockade (black) on plasma concentration of (A) big ET-1 and (B) ET-1. * $p < 0.05$ v baseline.

This is the first study to directly compare systemic selective ET-A and non-selective ET-A/B blockade in patients with heart failure. Our findings are consistent with other short term studies, which have shown that both selective ET-A¹⁷ and non-selective ET-A/B^{20–22} blockade increase cardiac output and reduce systemic vascular resistance, importantly with no change in heart rate, and that both selective ET-A^{16–17} and non-selective ET-A/B^{20–22} blockade reduce pulmonary vascular resistance and pulmonary artery wedge pressure. Comparing magnitude of response between different ET antagonists in different patient populations is difficult but we have shown in this head to head study that selective ET blockade had greater effects than non-selective ET antagonism on the systemic vasculature.

There is increasing evidence that the ET-B receptor has a role in the clearance of plasma ET-1. Plasma ET-1 concentration increases after systemic selective ET-B blockade in healthy people⁵ and after non-selective ET-A/B blockade in healthy people²⁸ and in patients with hypertension⁴ and with chronic heart failure.^{18–20} However, the effects of systemic ET-A blockade alone are less consistent with little, if any, increase in plasma ET-1 concentrations in most studies,^{6–15–16} although one study did report an increase at higher degrees of ET-A blockade.¹⁷ These results are confirmed in our study, in which selective ET-A receptor blockade had no effect, whereas plasma ET-1 concentrations were increased by non-selective blockade. Because there was no change in plasma big ET-1 concentration, increased plasma ET-1 is likely to reflect interference with its clearance rather than an increase in its synthesis and release. Thus, selective ET-A blockade has a theoretical benefit of leaving the ET clearance receptor (ET-B) functional. Nevertheless, if the ET-A receptor is also effectively blocked during ET-B receptor blockade then the high circulating concentrations of ET-1 may not be of clinical importance.

Although selective ET-A receptor blockade had greater effects on systemic vascular resistance, there may be clinical situations in which blockade of the ET-B receptor is desirable.

There is a higher density of ET-B receptors in the pulmonary vasculature and these may be upregulated in pulmonary arterial hypertension,²⁹ though selective ET-A and non-selective ET-A/B receptor blockade have not yet been compared head to head in this condition. Also, ET-1 release across the pulmonary vascular bed correlates strongly with the pulmonary vascular resistance in chronic heart failure.³⁰ Raised pulmonary artery pressure is an independent risk factor in chronic heart failure and responds poorly to conventional treatments. Here, we showed that both selective ET-A and non-selective ET-A/B receptor blockade reduce pulmonary artery pressures.

These observations suggest that ET antagonism may benefit patients with heart failure who also have raised pulmonary artery pressures, although we did not directly address this condition in our study. Indeed, the non-selective antagonist bosentan has recently been approved to treat primary pulmonary arterial hypertension based on its effectiveness in this situation.³¹ The long term clinical effects of ET receptor blockade in patients with pulmonary hypertension secondary to chronic heart failure are unknown, but it is tempting to speculate that ET receptor blockade may also be more effective in this setting. We have failed to show convincingly whether there are true haemodynamic differences between selective ET-A and non-selective ET-A/B receptor antagonism in the pulmonary circulation. However, none of the patients in the present study had significant pulmonary hypertension. We believe that the role of ET antagonism now warrants further careful assessment in a much larger trial of patients with both heart failure and a significant degree of pulmonary hypertension.

Many studies use agents that, while termed “selective” or “dual” inhibitors of ET-A and ET-B receptors, have a range of receptor selectivities, mostly inhibiting the ET-A receptor at much lower concentrations than at the ET-B receptor.²⁶ In this study we have used two receptor antagonists, BQ-123 and BQ-788, given separately and with selectivity for the ET-A and ET-B receptor, respectively. Therefore, it is important to recognise that we have examined mechanistically the influence of major blockade of the ET-B receptor on responses to full ET-A blockade. This may not exactly represent the clinical situation that exists with non-selective antagonists, such as bosentan, which are relatively selective for the ET-A receptor (ET-A:ET-B selectivity > 10). The doses of BQ-123 given here have been shown to produce maximum systemic haemodynamic effects and to block responses to forearm artery infusion of ET-1, but not to increase plasma ET-1 concentrations. Given that BQ-123 caused greater systemic vasodilatation than the combination with BQ-788, the overall haemodynamic effect of ET-B blockade in patients with heart failure is likely to be vasoconstriction, a finding consistent with other work.^{23–32}

As a limitation, this was an acute haemodynamic study and we have not assessed whether these effects are sustained in the long term. Nevertheless, previous haemodynamic studies indicate that the acute effects of both selective ET-A²⁴ and non-selective³² ET receptor blockade are maintained, or even enhanced, over several weeks and therefore likely to be sustained. The clinical impact of these haemodynamic changes is, of course, uncertain and can only be clarified in the context of large scale clinical outcome studies. We have shown that selective ET-A blockade causes more major systemic vasodilatation than non-selective ET-A/B receptor blockade in New York Heart Association (NYHA) class II–III patients with heart failure. To date, there have been only two as yet unpublished large scale, randomised controlled trials of ET receptor blockade in patients with heart failure (NYHA class III–IV), both of which observed no major clinical benefit of either bosentan (ET-A:ET-B selectivity

~10)²⁵ or darusentan (ET-A:ET-B selectivity > 500).²⁴ The results of these longer term studies were disappointing, although perhaps it is not surprising that two agents with 10 to > 500 selectivity for the ET-A receptor yielded similar results given the small haemodynamic differences found in the current study, when much greater relative ET-B receptor blockade was achieved. Nevertheless, bosentan has found utility in the treatment of primary pulmonary hypertension and whether it may have utility in a subset of patients with CHF with secondary pulmonary hypertension remains to be seen.

Conclusions

In this study both selective ET-A and non-selective ET-A/B blockade cause acute systemic and pulmonary haemodynamic changes in patients with heart failure. However, differences exist and selective ET-A blockade causes greater systemic haemodynamic effects than non-selective ET-A/B blockade.

ACKNOWLEDGEMENTS

This project was funded by the British Heart Foundation (PG/99043 and FS/98040, SJL). This study was also supported by the Wellcome Trust Clinical Research Facility. DJW was supported by a Research Leave Fellowship from the Wellcome Trust (WT/0526330).

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Grant Support British Heart Foundation (PG/99043 and FS/98040)

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