Endothelin antagonists for chronic heart failure: do they have a role?

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Introduction

Over the last two decades, the vascular endothelium has been shown to produce a variety of vasoactive substances that are crucial for the regulation of vascular tone, both in health and disease. This concept emerged in 1980, with the discovery of endothelium-derived relaxing factor [1], later characterized as nitric oxide [2]. In 1985 Hickey et al. reported the existence of a vasoconstricting factor derived from cultured bovine endothelial cells [3]. Yanagisawa et al. were, however, the first to purify, sequence and clone the 21 amino acid structure of endothelin (ET) and its mRNA from the culture supernatant of porcine aortic endothelial cells in 1988 [4]. The authors stated that ‘endothelin, having a potent, strong and characteristically long-lasting vasoconstrictor activity, may be important in systemic blood pressure and/or local blood flow: disturbances in the control of endothelin production could contribute to the pathogenesis of hypertension and that of pathological vascular spasm’ [4]

Since that original report, remarkable advances have been made in our understanding of the molecular basis of ET biosynthesis and action. ET has been implicated as playing an important physiological role in cardiovascular regulation and a putative pathophysiological role in a wide range of disease states, including chronic heart failure [5,6]. The aim of this review article is to focus on the role of endothelin in chronic heart failure and in particular, the potential therapeutic benefits of ET receptor antagonists for patients with chronic heart failure.

Neuroendocrine blockade: therapeutic promise for patients with chronic heart failure

Neuroendocrine activation occurs early after myocardial infarction and in patients with established heart failure. A lesser degree of neurohormonal activation is present in patients with asymptomatic left ventricular dysfunction, becoming more marked with the worsening of heart failure and/or introduction of diuretic therapy [7,8]. The degree of neurohormonal activation, as assessed by increased plasma levels of noradrenaline, angiotensin II, plasma renin activity, aldosterone and endothelin, has been shown to provide important prognostic information in these patient groups [9,10]. It is, therefore, not surprising that agents which antagonize the effects of these neurohormones, have been shown to confer prognostic benefit to patients with chronic heart failure.

ACE inhibitors, which reduce conversion of angiotensin I to angiotensin II, a potent vasoconstrictor and mitogen, have undoubtedly made the greatest impact so far on our current management of chronic heart failure patients [11,12]. Angiotensin II receptor antagonists have also shown therapeutic promise in chronic heart failure [13,14] but it remains to be seen whether they will have the same clinical impact as ACE inhibitors.

Until recently beta-blockers were considered to be contraindicated in patients with chronic heart failure, but recent clinical trials suggest that appropriate use of beta-blocking agents in stable chronic heart failure can lead to symptomatic and prognostic benefit, similar in magnitude to, or perhaps even greater than, the benefits seen with ACE inhibitors [15–17]. The ESC guidelines [18], and more recently the US Consensus document [19], now recommend the combined use of ACE inhibitors and beta-blockers as standard therapy in the majority of patients with mild to moderate heart failure. Finally, spironolactone, an aldosterone antagonist, has recently been reported to reduce chronic heart failure mortality.
by 30% in the Randomized Aldactone Evaluation Study (RALES)\(^{20}\).

Using the above combination, only about 20 patients with mild to moderate heart failure or 5–10 patients with severe heart failure need to be treated for 1 year to save a life\(^{21,22}\). Despite these benefits, heart failure continues to be a major public health concern, and whilst the results of the above studies are encouraging, it is essential that these agents are actually used in clinical practice. It is also imperative that the search continues for new therapeutic strategies for patients with heart failure. We now know that plasma concentrations of ET-1 are elevated in chronic heart failure, that they correlate with the symptomatic and haemodynamic severity of chronic heart failure, and that they independently predict prognosis on multivariate analysis\(^{32–59}\). Given the beneficial effects of neurohormonal blockade in chronic heart failure, it is not surprising that there is now considerable interest in the therapeutic potential of antiendothelin strategies\(^{29,30}\).

### Endothelin isoforms: structure and synthesis

A family of three structurally and functionally similar ET isopeptides exists (ET-1, -2 and -3), each encoded by distinct genes on chromosomes 6, 1 and 20, respectively\(^{31}\). ET-1 is the predominant isopeptide expressed in the human vasculature and has approximately ten times greater vasoconstrictor potency in vitro than angiotensin II\(^4\). ET-2 is not detectable in human plasma \(^{32,33}\) and while ET-3, the least potent vasoconstrictor in the ET family, is detectable in human plasma, its major source and physiological role remain unclear.

Each member of the ET family is initially synthesized as a larger prepropeptide of approximately 200 amino acid residues\(^9\). These prepropeptides are cleaved at sites containing pairs of dibasic amino acids by furin-like propeptidases to form biologically inactive intermediate propeptides, the ‘big endothelins’. In the case of ET-1, the 21 amino acid mature form of the peptide, and its C-terminal fragment are generated via selective cleavage between positions 21 (tryptophan) and 22 (valine) of the carboxy terminal of big ET-1, a 38 amino acid peptide\(^{4,34}\). This process is catalysed by one of several endopeptidases that are present in the human vasculature. The major physiologically relevant form of the enzyme in the human vasculature is the metalloprotease ECE-1\(^{34}\).

ET-1 is not detectable in human plasma \(^{32,33}\), and it is present in vascular smooth muscle obtained from human aorta, pulmonary artery and coronary artery\(^{34}\). Endothelial ETB receptor stimulation results in vasoconstriction through release of nitric oxide and/or prostacyclin\(^{48–50}\) while vascular smooth muscle ETB receptors mediate vasoconstriction\(^{49,51,52}\). Functional studies have indicated, however, that there is probably a far greater diversity of ET \(A\) and ET \(B\) receptor subtypes than was previously believed. A third postulated ET \(C\) receptor subtype with selective affinity for ET-3 has now been identified in the chicken\(^{53}\), and more recently in the human vasculature\(^{54}\), but has yet to be cloned in human or other mammalian tissues.

### Endothelin receptor subtypes

Two high affinity ET receptor subtypes, ET \(A\) and ET \(B\), belonging to the G-protein coupled family, have been identified by in vitro expression of cloned human cDNA\(^{42,43}\). In humans, ET \(A\) receptor mRNA is expressed primarily in vascular smooth muscle cells (particularly in aortic, cardiac, pulmonary and renal tissues) but not in endothelial cells\(^{46}\). ET \(A\) receptors have selective affinity for ET-1 (binding potency ET-1 > ET-2 > ET-3), with approximately 100-fold greater affinity for ET-1 than ET-3\(^{30}\). ET \(B\) receptors have equal affinity for each ET isoform (binding potency ET-1 = ET-2 = ET-3)\(^{45}\). ET \(B\) receptor mRNA is highly expressed in endothelial cells\(^{46}\), but is also expressed in vascular smooth muscle obtained from human aorta, pulmonary artery and coronary artery\(^{47}\). Endothelial ETB receptor stimulation results in vasoconstriction through release of nitric oxide and/or prostacyclin\(^{48–50}\) while vascular smooth muscle ETB receptors mediate vasoconstriction\(^{49,51,52}\). Functional studies have indicated, however, that there is probably a far greater diversity of ET \(A\) and ET \(B\) receptor subtypes than was previously believed. A third postulated ET \(C\) receptor subtype with selective affinity for ET-3 has now been identified in the chicken\(^{53}\), and more recently in the human vasculature\(^{54}\), but has yet to be cloned in human or other mammalian tissues.

### The biological activity of ET-1

ET-1 has a number of biological effects in vitro\(^{56,57}\) and is a major factor in the regulation of arterial and venous tone\(^{55–57}\). Local endopeptidase- and converting enzyme inhibition and selective ET \(A\) receptor blockade in the forearm vasculature of healthy volunteers substantially increase forearm blood flow, suggesting that endogenous generation of ET contributes to maintenance of basal vascular tone in humans\(^{58}\). This is further supported by the observation that TAK-044, a non-selective ET receptor antagonist, reduces peripheral vascular resistance and blood pressure in healthy volunteers\(^{59}\).

ET-1 has potent inotropic effects in vitro\(^{60}\), although the effect of ET-1 on overall cardiac function is more difficult to assess. Systemic infusion of ET-1 in healthy volunteers and patients with heart failure causes cardiac output to fall\(^{56–63}\). This may be a secondary effect due to potent peripheral and coronary vasoconstriction, rather than a negative inotropic effect of ET-1 on cardiac myocytes. MacCarthy et al. have recently shown...
however, that BQ-123, an ET\textsubscript{A} selective antagonist, reduced left ventricular dP/dt\textsubscript{max} in normal subjects, but had no effect in patients with a dilated cardiomyopathy\textsuperscript{[63]}. This suggests that ET-1 has a positive inotropic effect in normal subjects, but that this effect is lost in the failing human heart. Similarly in an animal model of chronic heart failure, Onishi \textit{et al}. showed that ET-1 slowed left ventricular relaxation and depressed left ventricular contraction\textsuperscript{[65]}, suggesting that elevated levels of plasma ET-1 in chronic heart failure may directly impair cardiac contractility and hence contribute to the functional impairment seen in chronic heart failure.

In addition to its direct arterial and venoconstrictor actions, ET-1 may augment the action of other vasoconstrictor and neuroendocrine systems in health and disease. ET-1 enhances conversion of angiotensin I to angiotensin II\textsuperscript{[60]}, increases adrenal synthesis of both adrenaline\textsuperscript{[67]} and aldosterone\textsuperscript{[68]} and appears to augment plasma renin activity\textsuperscript{[55]}. Angiotensin II increases ET-1 secretion from cultured endothelial cells\textsuperscript{[69]}, and increases tissue ET-1 levels and endothelin-converting enzyme activity in vivo\textsuperscript{[70]}. A synergistic effect between ACE-inhibitors and ET receptor antagonists has been described in animals\textsuperscript{[71]}. Subthreshold concentrations of ET-1 have been shown to potentiate the contractile responses of human arteries in response to catecholamines and serotonin\textsuperscript{[72]}. ET-1 may therefore amplify vasoconstrictor reflexes and be of pathophysiological relevance even when plasma ET-1 concentrations are not clearly elevated. ET-1 also appears to stimulate vascular smooth muscle proliferation and cardiac hypertrophy and is consequently thought to have a role in myocardial and vascular remodelling\textsuperscript{[73,75]}. ET-1 may also play a pathophysiological role in the development of ischaemia/reperfusion injury\textsuperscript{[76]} and may be proarrhythmogenic\textsuperscript{[77,79]}. Given the diversity of actions of ET-1 it appears likely that the peptide plays an important role in the pathophysiology of chronic heart failure.

### Plasma endothelin concentrations in chronic heart failure

Several groups have now reported elevation in plasma ET-1 concentrations in patients with chronic heart failure\textsuperscript{[23,27,63,80–84]}. ET-1 appears to be increased two- to three-fold in chronic heart failure of all aetiologies, in proportion to the symptomatic and haemodynamic severity of the syndrome. Big ET is also elevated in chronic heart failure\textsuperscript{[63,83]}. Plasma ET-1 correlates positively with New York Heart Association (NYHA) clinical class\textsuperscript{[23,27,80,83]} and inversely with left ventricular ejection fraction\textsuperscript{[25,80]}. It is therefore perhaps not surprising that plasma ET-1 and big ET concentrations have also been shown to independently predict clinical deterioration, the need for cardiac transplantation or death in chronic heart failure patients\textsuperscript{[28,56,83]}. On univariate analysis both ET-1 and big ET were more powerful predictors of death than functional class, atrial natriuretic peptide and measurements of left ventricular function\textsuperscript{[28,87]}.

A unique and exciting observation, however, not seen with other plasma markers of neuroendocrine activation, is that plasma ET-1 correlates positively with the severity of pulmonary hypertension in chronic heart failure\textsuperscript{[25,26,83,85,86]} (Fig. 1). A similar correlation has been found in patients with primary pulmonary hypertension and secondary pulmonary hypertension not due to left ventricular dysfunction\textsuperscript{[86]}. Whether the elevation in ET-1 is a marker or mediator of pulmonary hypertension remains speculative. We have, however, shown that exogenous ET-1, when infused into patients with left ventricular dysfunction to achieve plasma concentrations similar to those in severe heart failure and pulmonary hypertension, causes systemic, but not pulmonary, vasoconstriction\textsuperscript{[63]}. Interestingly, we did not see pulmonary vasoconstriction despite infusing ET-1 directly into the pulmonary artery\textsuperscript{[63]}. This does not preclude an important role for ET-1 in governing pulmonary vascular tone, however, as ET-1 has generally been thought to have paracrine effects, and as such, plasma ET-1 concentrations may poorly reflect tissue concentrations.

Increased plasma concentrations of ET-1 may reflect increased synthesis and secretion or reduced clearance. It is possible that some of the elevation in plasma ET-1 seen in patients with heart failure may be a consequence of reduced plasma clearance. Using a radiotracer technique, Dupuis \textit{et al}. have shown that the lung is both an important site of production and clearance of endothelin-1\textsuperscript{[91]}, and that there is reduced pulmonary clearance of ET-1 in pulmonary hypertension\textsuperscript{[92]} and heart failure following myocardial infarction\textsuperscript{[93]}. Tsutamoto and colleagues, by measuring ET-1 in the femoral artery and vein, demonstrated that ET-1 is extracted by the peripheral circulation in severe chronic heart failure and that ET-1 extraction correlated with systemic vascular resistance in these patients\textsuperscript{[94]}. A significant correlation also existed between plasma ET-1 extraction and NYHA class, suggesting that plasma
ET-1 may contribute to the exercise intolerance in chronic heart failure, by limiting the ability of the peripheral vasculature to dilate during exercise.

McMurray et al. reported net uptake of ET-1 in the renal circulation in patients with heart failure\cite{48} while Good et al. reported no difference in ET-1 concentrations across the renal, pulmonary or hepatic circulations in chronic heart failure patients\cite{108}. Stangl et al. have recently reported a net release of both ET-1 and big ET across the pulmonary vascular bed in patients with severe chronic heart failure, whereas there was net consumption of ET-1 and big ET across coronary and peripheral circulations\cite{99}. Interestingly this imbalance was restored with short-term vasodilator therapy\cite{99}.

There is now increasing evidence that ET\(_B\) receptors act as a clearance receptor for circulating ET-1\cite{96-98}. Thus the increased plasma concentrations of ET-1 seen in chronic heart failure could also be due to down-regulation of the ET\(_B\) receptor in chronic heart failure\cite{99}. Several neurohormonal and physical factors probably also contribute to the elevation in plasma ET-1 in chronic heart failure. Catecholamines, angiotensin II, arginine vasopressin, glucocorticoids, cytokines, tumour necrosis factor, free radicals, shear stress and hypoxia have all been shown to increase endothelial cell production of ET-1 in vitro, all of which could be relevant in chronic heart failure\cite{4-6}.

**Studies of endothelin antagonists: animal models**

In view of all the circumstantial evidence implicating ET-1 in the pathophysiology of chronic heart failure, studies with endothelin antagonists were eagerly awaited. The first oral endothelin antagonist to be described was bosentan, a non-selective ET\(_A\)/ET\(_B\) receptor antagonist\cite{110}. Animal studies with bosentan showed haemodynamic promise, but it was a report form Sakai et al. in Nature in 1996 that really stimulated interest in ET receptor antagonists\cite{101}. They reported that long-term administration of BQ-123, an ET\(_A\) selective antagonist, almost halved mortality in a rat coronary ligation model of heart failure (Fig. 2). Since that report, numerous studies have been published describing chronic dosing of endothelin receptor antagonists in animal models of chronic heart failure\cite{101-110}. Three of these studies report the results of non-selective blockades\cite{103,104,110} whilst the remainder studied the effects of ET\(_A\) selective antagonism. Together, these studies suggest that endothelin antagonists may improve left ventricular and myocyte function, cardiac re-modelling, pulmonary and systemic haemodynamics and ultimately prognosis. However, one study suggested the potential for harm with very early introduction of an ET\(_A\) receptor antagonist after myocardial infarction\cite{109}.

**Non-selective endothelin antagonists: human studies**

So what do we actually know about the effects of ET receptor antagonists in human disease states? At present, data exist in the fields of hypertension, where a reduction in blood pressure has been observed\cite{111}, ischaemic heart disease\cite{112,113}, pulmonary hypertension, where beneficial effects on the pulmonary circulation were limited by systemic vasodilatation and hypotension\cite{114}, and heart failure. The majority of studies reported so far have used bosentan, a non-selective antagonist\cite{89,111,112,114,115}.

Bosentan has been shown to improve pulmonary and systemic haemodynamics in patients with heart failure, both in acute and short-term dosing studies\cite{89,115}. Acutely, bosentan reduced pulmonary vascular resistance to a greater extent than systemic vascular resistance (33% vs 17%)\cite{89}. This was associated with a rise in cardiac output and a fall in pulmonary wedge pressure. ET-1 rose acutely, presumably an effect of ET\(_B\) blockade. The differential effect on pulmonary and systemic vascular resistance was not maintained after 2 weeks (20% vs 24%)\cite{115} (see Table 1). The preliminary results of the Research on Endothelin Antagonism in Chronic Heart failure (REACH-1) trial have now been presented\cite{116}. This was a 6 month, multicentre, double-blind, placebo-controlled trial of bosentan in patients with severe symptomatic heart failure on conventional therapy. The trial was stopped prematurely because of abnormal liver function tests in the bosentan group (which were reversible on cessation of the study drug) and in the entire study population there was no difference between bosentan and placebo in terms of clinical improvement. However, the subset of patients followed for the planned 6 months did show benefit with bosentan therapy vs placebo, most notably a 41% reduction in all-cause hospitalization (see Table 2). In a recently published analysis, bosentan demonstrated a trend towards a reduction in total hospitalization days, particularly in patients with impaired left ventricular function\cite{117}.

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reported extension of REACH-1, 86 patients (63 patients had received bosentan during the trial) were enrolled to continue on open label bosentan at a lower dose for a further 6 months\(^{117}\). Deaths and hospitalizations were less frequent with bosentan 125 mg twice daily, than in either the placebo or bosentan arms of REACH-1 and symptom status progressively improved over the 6-month period. In the light of these promising results two large, multicentre, mortality/morbidity studies are now underway using low dose bosentan (ENABLE I and II).

It is interesting to note that in the REACH-1 study, during the first month of therapy, the bosentan group were twice as likely to be admitted to hospital with worsening heart failure, suggesting that care is required with the introduction of endothelin antagonists, a similar picture to that seen with beta-blockers in chronic heart failure\(^{13}\). The explanation for this finding, that has been observed with other non-selective agents (unpublished data), is obscure. Sudden withdrawal of ET-1 mediated inotropic support might occur. Pulmonary capillary distension due to loss of protective pulmonary arteriolar vasoconstriction might lead to shunting\(^{114}\) or increased pulmonary capillary wedge pressure. CI=cardiac index, SVR= systemic vascular resistance, PVR=pulmonary vascular resistance.

### Human studies: ET\(\alpha\) selective antagonists

Whilst there is limited human data with non-selective antagonists, there is even less with the ET\(\alpha\) selective antagonists. Love et al. reported that BQ-123, an ET\(\alpha\) selective antagonist, led to forearm vasodilatation in patients already receiving ACE inhibitors\(^{118}\). We reported the pulmonary and systemic effects of BQ-123 in chronic heart failure patients\(^{119}\). BQ-123 infusion led to systemic vasodilatation with an associated fall in pulmonary artery pressure; however, the fall in pulmonary vascular resistance did not reach statistical significance. It would be premature to conclude that BQ-123 had no pulmonary vasodilator effect, given the small number of patients studied, indeed the % fall in systemic and pulmonary vascular resistance were similar (see Table 1). Importantly, these potentially beneficial effects were seen in patients concurrently treated with an ACE inhibitor\(^{118,119}\).

Recently there have been two larger trials reported with ET\(\alpha\) selective antagonists. Givertz et al. report a double blind, placebo controlled trial with sitaxsentan, an ET\(\alpha\) selective antagonist, in patients with Class III/IV chronic heart failure\(^{120}\). Interestingly, sitaxsentan reduced pulmonary pressures, without having an effect...
on pulmonary capillary wedge pressure, cardiac index, mean arterial pressure or systemic vascular resistance. Cardiac medications were withheld on the day of the study. Plasma ET-1 levels actually fell with sitaxsentan. The authors comment that sitaxsentan may have a specific role in patients with pulmonary hypertension secondary to chronic heart failure. In contrast, Speiker et al. report that LU135252, an ET\textsubscript{A} selective antagonist, reduced both systemic and pulmonary arterial pressures, despite a small increase in plasma ET-1 concentrations, in patients with class II/III heart failure\cite{121}.

The haemodynamic effects of the various ET receptor antagonists are detailed in Table 1. Possible differences between the various agents are difficult to interpret as there may be differences in patient populations. The effects are also dependent on dose and co-administration of other cardiac medications. In our own small study with BQ-123, only a single dose was given and no dose ranging studies were performed\cite{119}. We also gave BQ-123 to patients who had already taken diuretics, ACE inhibitors and/or an AII receptor antagonist on the morning of the study. A synergistic effect between ACE-inhibitors and ET\textsubscript{A} receptor antagonists has been described in animals\cite{73}. It is possible, therefore, that the haemodynamic effects we observed with BQ-123, were enhanced by, as opposed to attenuated by, the co-administration of ACE-inhibitors. The other studies reported in Table 1 withheld ACE-inhibitors prior to study drug administration. Whilst the haemodynamic effects of non-selective and ET\textsubscript{A} selective antagonists agents appear broadly similar, it does appear from the data with sitaxsentan\cite{120} that there may be intrinsic differences between agents in each class.

One potentially very important difference between non-selective and ET\textsubscript{A} selective antagonists is the effect on circulating concentrations of plasma ET-1. Bosentan led to a more than two-fold increase in plasma ET-1 concentrations\cite{98,109}, whereas BQ-123 had no effect\cite{98} and sitaxsentan led to a fall in ET-1 concentrations\cite{98,120}. LU135252, an ET\textsubscript{B} selective antagonist did, however, lead to a small increase in ET-1 concentrations, although this was to a lesser extent than that seen with bosentan\cite{121}. Clearly these are acute responses, we await published data on the effects of ET receptor antagonists on ET-1 concentrations in long-term administration.

Animal studies have previously suggested that ET\textsubscript{B} receptors act as a clearance mechanism for circulating ET-1\cite{96,97}. To explore this further we gave BQ-788, an ET\textsubscript{B} selective antagonist, to patients with chronic heart failure and saw a clear rise in plasma ET-1 concentrations, confirming that the ET\textsubscript{B} receptor does act as a clearance receptor for ET-1 in humans\cite{98}. It is possible therefore, that with chronic administration of a non-selective ET\textsubscript{A}/ET\textsubscript{B} antagonist, increased circulating levels of ET-1 may compete with the receptor antagonist, leading to a reduced therapeutic response. This problem could be circumvented by the use of antagonists selective for the ET\textsubscript{A} receptor.

The haemodynamic effects of ET\textsubscript{B} selective antagonists are also interesting and unexpected from early agonist studies which had suggested enhanced ET\textsubscript{B} mediated vasoconstriction in left ventricular dysfunction/chronic heart failure\cite{118,122}. ET\textsubscript{B} selective antagonists cause vasoconstriction in normal subjects and patients with chronic heart failure\cite{123,126}. Verhaar et al. have shown that the combination of ET\textsubscript{A} and ET\textsubscript{B} selective antagonists causes forearm dilatation in normal subjects, but to a lesser extent than the ET\textsubscript{A} selective antagonist alone\cite{120}. The possible reasons for the discrepancy between the agonist and antagonist studies are discussed elsewhere\cite{122,126}. These data suggest that vasoconstriction in response to selective ET\textsubscript{B} receptor blockade may also reflect a loss of tonic, endogenous vasodilation mediated by endothelial ET\textsubscript{A} receptors. Alternatively, the rise in ET-1 associated with ET\textsubscript{B} receptor blockade could compete with receptor antagonists and attenuate their effects.

### Selective or non-selective antagonists for chronic heart failure?

Debate continues as to which type of ET receptor antagonist will prove therapeutically superior in patients with chronic heart failure, an ET\textsubscript{A} selective or a non-selective antagonist (details of agents currently under investigation are provided in Tables 3 and 4). Promising haemodynamic effects have been observed with non-selective and ET\textsubscript{A}-selective agents, but haemodynamic efficacy does not necessarily translate into long-term benefit in heart failure\cite{127,130}. Theoretically, selective blockade of ET\textsubscript{A} and vascular smooth muscle ET\textsubscript{B} receptors, leaving endothelial ET\textsubscript{B} receptors (which are responsible for ET clearance and enhanced nitric oxide and prostaglandin production) unblocked, would seem preferable. However, it may not be possible to develop a subselective ET\textsubscript{B} antagonist. Early haemodynamic studies appeared to suggest that ET\textsubscript{B} selective antagonists may prove preferable to non-selective agents; however, non-selective agents, through more comprehensive endothelin antagonism, may have more favourable neurohormonal and remodelling effects. Ultimately, the potential benefits of a new therapeutic approach to heart failure can only really be answered by outcome studies. At present we can only speculate as to the relative benefits of each antagonist on the basis of short- and medium-term studies.

### Endothelin antagonists and neurohormonal activation

As discussed earlier, ET-1 tends to rise with non-selective antagonism\cite{59,89,111} and ET\textsubscript{B} selective antagonism\cite{96,98,126,131}, whereas ET\textsubscript{A} selective agents tend to have little or no effect on circulating concentrations of ET-1\cite{96,98,120,131}. However, exceptions to these statements have been observed\cite{105,109,121}.
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In the short-term dosing study with bosentan in patients with chronic heart failure,[119], there was no overall increase in plasma renin activity and angiotensin II concentrations. Indeed the rises in plasma renin activity and angiotensin II following diuretic administration were attenuated in the bosentan group compared with controls. Non-selective agents reduce plasma aldosterone concentrations acutely, whereas ET_A selective agents do not.[132] Sutsch and colleagues have recently confirmed that bosentan reduces plasma aldosterone in patients with chronic heart failure.[133] This could have important prognostic implications, given that administration of spironolactone, an aldosterone antagonist, has been shown to reduce mortality in chronic heart failure.[134] In animal models of chronic heart failure Spinale et al. reported that ET_A selective antagonism has no effect on plasma renin activity.[105]

Norepinephrine levels were unchanged in a short-term study of bosentan in patients with chronic heart failure.[119]. In a longer-term animal study, norepinephrine levels fell with high dose bosentan.[104]. In animal models of chronic heart failure Spinale et al. reported that ET_A selective antagonism has no effect on norepinephrine concentrations[105], whereas Saad et al. reported a fall in plasma norepinephrine concentrations with an alternative ET_A selective antagonist, BMS 193884.[108]. In human studies plasma norepinephrine levels generally remained stable with the ET_A selective agents[108,121], although a small fall in norepinephrine concentrations was noted in some patients[121].

Plasma atrial natriuretic peptide concentration falls with the administration of both ET_A selective and non-selective antagonists[106,122].

### Endothelin antagonists: effects on renal perfusion and function

Wada et al. described the actions of a selective ET_A receptor antagonist, FR139317, and a selective ET_B receptor antagonist, RES-701-1, in a canine model of heart failure.[133] They found that the ET_A selective antagonist increased glomerular filtration rate and renal plasma flow, with an associated increase in urinary flow rate and sodium excretion. In contrast, the ET_B selective antagonist reduced renal plasma flow.

A more recent study by the same group compared TAK-044, a non-selective antagonist, with FR139317, an ET_A selective antagonist, in the same animal model of chronic heart failure. Both agents increased cardiac output and urinary sodium excretion. TAK-044 did not, however, increase urinary flow rate or renal plasma flow, but did increase glomerular filtration rate compared to baseline values.[132]. Hence the renal effects of the ET_A selective antagonist, FR139317, generally appear preferable to the non-selective agent, TAK-044, although it is possible that with long-term administration a reduction in aldosterone levels could favour the latter. To date there are no studies describing the renal effects of ET receptor antagonists in patients with chronic heart failure. There is, in fact, only one study in the current literature which has looked at the renal effects of ET receptor blockade in man.[134]. In this study BQ-123, the ET_A selective antagonist, did not alter renal haemodynamics in normal subjects, but when co-infused with exogenous ET-1, did block the renal vasoconstriction seen with infusion of exogenous ET-1 alone.[134]. This suggests that renal vasoconstriction induced by ET-1 is ET_A mediated in normal subjects. We await further clinical studies with interest.

### Endothelin antagonists: effect on splanchic perfusion

In a canine preparation, ET_A selective antagonism caused an increase, whereas ET_B blockade caused a reduction in small intestinal blood flow during infusion of ET-1.[113]. The effects of combined ET_A/ET_B blockade appeared neutral.

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**Table 4 Endothelin antagonists in pre-clinical and clinical trials for heart failure**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Trial status</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>J 104132</td>
<td>Banyu &amp; Merck &amp; Co</td>
<td>Pre-clinical</td>
<td>Non-selective antagonist</td>
</tr>
<tr>
<td>ABT 627</td>
<td>Abbott</td>
<td>Phase I</td>
<td>Selective ET_A antagonist</td>
</tr>
<tr>
<td>LU 135252</td>
<td>Knoll</td>
<td>Phase II</td>
<td>Selective ET_A antagonist</td>
</tr>
<tr>
<td>Enrasentan/SB 217242</td>
<td>SB</td>
<td>Phase II</td>
<td>Non-selective antagonist</td>
</tr>
<tr>
<td>Bosentan/RO 470203</td>
<td>Roche</td>
<td>Phase III</td>
<td>Non-selective antagonist</td>
</tr>
<tr>
<td>TAK 044</td>
<td>Takeda</td>
<td>Pre-clinical</td>
<td>Non-selective antagonist</td>
</tr>
<tr>
<td>BQ-123</td>
<td>Banyu &amp; Merck &amp; Co</td>
<td>Clinical</td>
<td>Selective ET_A antagonist</td>
</tr>
<tr>
<td>TA 0201</td>
<td>Tanebe Seiyaku</td>
<td>Phase I</td>
<td>Selective ET_A antagonist</td>
</tr>
<tr>
<td>Tezoxentan/RO61612</td>
<td>Roche</td>
<td>Phase II</td>
<td>Non-selective antagonist</td>
</tr>
<tr>
<td>PD 147953</td>
<td>Fujisawa</td>
<td>Pre-clinical</td>
<td>Selective ET_A antagonist</td>
</tr>
<tr>
<td>Sitaxsentan sodium/TBC 11241</td>
<td>Texas Biotechnology</td>
<td>Phase II</td>
<td>Selective ET_A antagonist</td>
</tr>
</tbody>
</table>

Note. The authors have tried to include all ET receptor antagonists undergoing clinical study, but the list may well not be complete or up-to-date in terms of phase of clinical trial.
Endothelin antagonists: effects on vascular remodelling

As discussed earlier both ET$_A$ selective and non-selective antagonists improve left ventricular and myocyte function, cardiac remodelling, pulmonary and systemic haemodynamics and ultimately prognosis in animal models of chronic heart failure. Importantly however, at least one report suggests that non-selective ET receptor blockade may have superior effects on scar healing, and thus potentially more favourable effects on post-infarction left ventricular remodelling\cite{103}. Indeed, an adverse effect on ventricular remodelling post infarction was reported when an ET$_A$ selective antagonist was commenced within 24 h of coronary ligation in rats\cite{109}, contrasting with favourable effects on remodelling and prognosis when either ET$_A$ selective or non-selective antagonists were introduced 7–10 days post coronary ligation\cite{101,104}. This is an important issue, as patients with chronic heart failure are prone to recurrent infarction, and the study reported by Nguyen et al\cite{109} raises the concern that ET$_A$ selective receptor antagonism might prove detrimental in the early post-infarction period. It will be important to clarify the clinical importance of these observations in due course.

Endothelin converting enzyme inhibitors

Endothelin converting enzyme inhibitors offer another possible ‘anti-endothelin strategy’ which may have therapeutic potential for patients with chronic heart failure. Phosphoramidon, a combined endothelin converting enzyme inhibitor and neutral endopeptidase inhibitor has been shown to cause forearm vasodilation in chronic heart failure patients treated with an ACE-inhibitor\cite{119}. A pure endothelin-converting enzyme-inhibitor has now been described\cite{116} and has recently been studied in a dog model of chronic heart failure\cite{117}. The endothelin-converting enzyme-inhibitor decreased mean arterial pressure, mean pulmonary artery pressure, mean pulmonary capillary wedge pressure, systemic and pulmonary vascular resistance and increased cardiac output. It also decreased atrial natriuretic peptide, plasma renin activity, angiotensin II and aldosterone levels and had beneficial renal effects. Whilst the endothelin-converting enzyme-inhibitor was a less potent vasodilator than the ET$_A$ selective antagonist, FR139317, the neurohormonal effects of the endothelin-converting enzyme-inhibitor appear preferable. These results suggest that endothelin-converting enzyme-inhibitors may also have a role in the treatment of chronic heart failure. Human studies will surely follow.

Summary

The development of novel and more effective therapeutic strategies for chronic heart failure is an important priority in cardiovascular medicine. Although much has still to be learned about the role of ET-1 in human physiology, current evidence suggests an important role for the peptide in the pathophysiology of chronic heart failure. It may not be the vasodilatory effect of these agents which provides long-term benefit in chronic heart failure, but the ability of these agents to alter neurohormonal activation, or to delay or regress the adverse left ventricular remodelling and vascular changes that are characteristic of chronic heart failure. We now require long-term clinical trials first to assess the therapeutic potential of ET receptor antagonists compared to placebo in patients with chronic heart failure, and then, if successful, we need to see direct comparison studies with selective ET$_A$ and non-selective receptor antagonists. Only then will we know if endothelin antagonists have fulfilled their potential as new therapeutic agents for the treatment of chronic heart failure.

References


[51] Seo B, Oemar BS, Siebenmann R, Von Segesser L, Luscher TF. Both ET(A) and ET(B) receptors mediate contraction to endothelin-1 in human blood vessels. Circulation 1994; 89: 1203–8.


