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Selective or non-selective endothelin receptor antagonists for chronic heart failure: what do we know so far?

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Endothelin-1 (ET-1) is a potent vasoconstrictor peptide produced by the vascular endothelium [1], which acts as a locally active paracrine factor and probably also as a circulating hormone in the regulation of arterial and venous tone [2–5]. Plasma concentrations of endothelin-1 are elevated in patients with moderate to severe chronic heart failure (CHF) [6–10] and correlate with the symptomatic and haemodynamic severity of CHF [9, 10]. Of particular interest is the noted close correlation of plasma ET-1 with pulmonary haemodynamic indices in this patient group [8, 9, 11, 12]. Given the known poor outlook for CHF patients with pulmonary hypertension [13] it is perhaps not surprising that plasma ET-1 has now also been shown to independently predict prognosis on multivariate analysis [14].

In addition to its direct arterial and venoconstrictor actions, ET-1 has a number of other actions which may play a role in the pathophysiology and progression of chronic heart failure. ET-1 appears to enhance conversion of angiotensin I to angiotensin II [15], to increase adrenal synthesis of both adrenaline [16] and aldosterone [17] and also to augment plasma renin activity [2]. Similarly, angiotensin II increases ET-1 secretion from cultured endothelial cells [18] and increases tissue ET-1 levels and endothelin converting enzyme (ECE) activity *in vivo* [19]. Interestingly, the haemodynamic and proliferative effects of angiotensin II can be prevented by blockade of ET_A receptors [20] and chronic administration of an ACE inhibitor during the evolution of experimental CHF appears to inhibit activation of the endothelin system [21]. A synergistic effect between ACE-inhibitors and ET receptor antagonists has also been described in animals [22]. In patients with chronic heart failure, a significant correlation does exist between plasma levels of angiotensin II and ET-1 [23]. Thus, ET-1 secretion and activation of the renin-angiotensin aldosterone system may potentiate each other and synergistically augment vasoconstriction and sodium retention in CHF. Concentrations of ET-1 that are below the threshold required to produce direct vasoconstriction have been shown to potentiate contractile responses to catecholamines and serotonin [24]. ET-1 may, therefore, amplify vasoconstrictor reflexes and be of pathophysiological relevance even when plasma ET-1 concentrations are not elevated.

There is also further evidence of an interaction between ET and the sympathetic nervous system. Gulati et al. have shown that the systemic and regional vasoconstrictor effects of infused ET-1 are abolished in cervical-sectioned rats and furthermore an ET_A selective antagonist was able to block clonidine-induced hypotension and bradycardia, a mechanism known to be mediated by the sympathetic nervous system [25]. 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 [26–28]. ET-1 may also play a pathophysiological role in the development of ischaemia/reperfusion injury [29] and may be arrhythmogenic [30, 31]. Given the diversity of actions of ET-1 in the pathophysiology of CHF, it is not surprising that there is considerable interest in the therapeutic potential of endothelin receptor antagonists for this patient group [32].

The vasoconstrictor action of ET-1 is mediated through two high affinity endothelin receptor subtypes on smooth muscle, denoted ET_A and ET_B. ET_B receptors are also present on the vascular endothelium where they mediate vasodilatation via nitric oxide and/or prostaglandins [33, 34]. There is growing evidence of altered endothelin receptor function in CHF, and it is not yet established as to whether the net effect of endothelial and smooth muscle ET_B receptor activation is that of vasoconstriction or vasodilation. There is, therefore, much debate as to whether a selective ET_A receptor antagonist or a non-selective ET_A/ET_B receptor antagonist might be the better therapeutic strategy in CHF.

Agonist studies were first used to explore the importance of ET_A and ET_B receptors in CHF. Love et al. demonstrated enhanced forearm vasoconstriction to sarafatoxin S6c (a highly selective ET_B receptor agonist) in CHF patients, but attenuation of the vasoconstrictor response to ET-1, compared to controls [35]. We also have *in vitro* evidence for impaired vasoconstriction to ET-1 in human CHF vessels [36]. Enhanced ET_B-mediated vasoconstriction has been demonstrated in coronary arteries in a canine model of CHF [37]. We have recently reported our results from agonist studies in patients with left ventricular dysfunction (LVD), with or without overt heart failure [38]. We compared the pulmonary and systemic effects of ET-3, a relatively selective ET_B receptor agonist with ET-1, a non-selective ET_A/ET_B receptor agonist, in similar patient groups. ET-3 had previously been shown to vasoconstrict forearm resistance vessels of healthy volunteers, though to a lesser extent than ET-1 [39]. We found that equal molar concentrations of ET-1 and ET-3, caused a similar degree of systemic vasoconstriction in patients with LVD, with or without overt heart failure. There was little or no effect on the pulmonary vasculature. Our data are also consistent with enhanced ET_B mediated vasoconstriction, possibly due to down-regulation of endothelial ET_B receptors [40, 41]. Alternatively, or in addition, there may be attenuated ET_A mediated vasoconstriction in the systemic circulation in LVD/CHF. These agonist studies suggest that a non-selective ET_A/ET_B receptor antagonist may be necessary to fully inhibit the vasoconstrictor effects of endogenous ET-1.

Whilst agonist studies do allow investigation of receptor activity, pharmacologically it is preferable to use antagonists, to inhibit the action of endogenously produced ET-1. As these antagonists have become available, we are now learning more about the actions of ET-1 and the receptor subtypes. 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. They found

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that the ET_A selective antagonist decreased cardiac pressures and atrial natriuretic peptide (ANP) and increased cardiac output, 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 increased cardiac pressures and decreased cardiac output and renal plasma flow. The only possible beneficial effect of the ET_B selective antagonist was that it decreased plasma aldosterone, suggesting that such an antagonist might be more effective at preventing electrolyte disorders and fluid retention in CHF. 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 model of CHF. Both agents reduced cardiac pressures and plasma ANP and increased cardiac output and urinary sodium excretion. TAK-044 did not, however, increase urinary flow rate or RPF, but did increase GFR compared to baseline values [42] . TAK-044 did reduce plasma aldosterone levels acutely as expected. Hence, the renal effects of the ETA selective antagonist do appear preferable to the non-selective agent, though it is possible that with long-term administration a reduction in aldosterone levels may have beneficial effects.

There are now several studies describing chronic dosing of endothelin receptor antagonists in animal models of CHF [43–51]. Two of these studies report the results of non-selective blockade [45, 46], 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. Interestingly, however, Nguyen et al. report that an ET_A selective antagonist commenced early after coronary ligation led to adverse left ventricular remodelling [51], suggesting that the timing of introduction of an endothelin antagonist post-myocardial infarction may be important.

There is more limited data with endothelin antagonists in human CHF. Bosentan, a non-selective antagonist, has been shown to improve pulmonary and systemic haemodynamics in patients with heart failure, both in acute and short-term dosing studies [12, 52]. There appeared to be a greater reduction in pulmonary vascular resistance (PVR) than systemic vascular resistance in the acute dosing study (33 % v. 17 %) [12], but this was not maintained in the two week dosing study (20 % v. 24 %) [52]. The preliminary results of REACH-1 have recently been presented [53]. This was a 6 month, multi-centre, 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. 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 six months did show benefit with bosentan therapy versus placebo (41 % reduction in all-cause hospitalisation). Interestingly during the first month of therapy, the bosentan group was 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 CHF [54].

Whilst there is limited human data with non-selective antagonists, there is even less with the ET_A selective antagonists. Love et al. reported that BQ-123, an ET_A selective antagonist, led to forearm vasodilatation in patients already receiving ACE inhibitors [35]. We have recently reported the pulmonary and systemic effects of BQ-123 in CHF patients [55]. BQ-123 infusion led to systemic vasodilatation with an associated fall in pulmonary artery pressure, however the fall in PVR 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 SVR and PVR were similar (12 % versus 14 % respectively). Importantly, these potentially beneficial effects were seen in patients concurrently treated with an ACE inhibitor [35, 55].

It is not possible to directly compare the haemodynamic effects of bosentan and BQ-123: firstly, because only a single dose of BQ-123 was given and no dose ranging studies were performed (c.f. bosentan – two doses [12]). Secondly, BQ-123 was given to patients who were already taking ACE inhibitors or an AII receptor antagonist [55], whereas bosentan was given to CHF patients in whom ACE inhibitors had been withheld [12, 52]. There is, however, one potentially very important difference between the two studies. Bosentan led to a rise in circulating concentrations of plasma ET-1 [12], whereas plasma ET-1 concentrations did not change with BQ-123 infusion [56]. Animal studies have previously suggested that ET_B receptors act as a clearance mechanism for circulating ET-1 [57, 58]. To explore this further we gave BQ-788, an ET_B selective antagonist, to patients with CHF and saw a clear rise in plasma ET-1 concentrations, confirming that the ET_B receptor does act as a clearance receptor for ET-1 in man [56]. It is possible that with chronic administration of a non-selective ET_A/ET_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_A receptor.

The haemodynamic effects of ET_B selective antagonists are also interesting and unexpected from the agonist studies. ET_B selective antagonists have been shown to cause vasoconstriction in normal subjects and patients with CHF [59–61]. Verhaar et al. have shown that the combination of ET_A and ET_B selective antagonists causes forearm dilatation in normal subjects, but to a lesser extent than an ET_A selective antagonist alone [59]. How do we explain the clear discrepancy between the ET_B agonist and antagonist studies? It is possible that the vasoconstriction observed during ET-3 or sarafatoxin S6c infusion studies (ET_B selective antagonists) is not ET_B mediated. The ET_B receptor agonist may displace ET-1 from the receptor and this may cause unopposed vasoconstriction at the ET_A receptor. Similarly, as the ET_B receptor has been demonstrated to act as a clearance receptor for endothelin, an ET_B receptor agonist could lead to increased ET-1 concentrations by blocking ET-1 clearance, leading to systemic vasoconstriction. Support for these theories come from Haynes and Webb and our own study with BQ-123. Haynes and Webb co-infused BQ-123 and ET-1 into the forearm of healthy volunteers and found that BQ-123 blocked the vasoconstriction seen with ET-1 alone [62]. We administered BQ-123 systemically to CHF patients to achieve vasodilatation and then co-infused ET-1 at a dose which we have previously shown to cause systemic vasoconstriction in CHF [5]. We also saw no vasoconstriction with the addition of ET-1 to BQ-123 [55]. As the ET_A receptor was blocked with BQ-123, ET-1 in this setting should have acted as an ET_B receptor agonist. The fact that vasoconstriction did not occur, suggests that the smooth muscle ET_B receptor is not functionally important in mediating vasoconstriction in CHF. We believe, therefore, that the ET_B selective agonist and antagonist studies have proved misleading, and that the most important role of the ET_B receptor may be its role in ET clearance.

From the evidence so far, endothelin antagonists do appear to have promise as a new approach to the treatment of CHF. We now require long-term clinical trials to assess the thera-

peutic potential of ET receptor antagonists in patients with CHF, and in particular, we need to see direct comparison studies between selective ET_A and non-selective receptor antagonists. While short-term haemodynamic studies cannot readily predict the long-term benefits of treatment, the current evidence suggests that ET_A selective agents may prove preferable to non-selective ET_A/ET_B receptor antagonists in the treatment of chronic heart failure.

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