Endothelin Receptor Antagonists in Congestive Heart Failure: A New Therapeutic Principle for the Future?

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Congestive heart failure (CHF) is characterized by impaired left ventricular function, increased peripheral and pulmonary vascular resistance and reduced exercise tolerance and dyspnea. Thus, mediators involved in the control of myocardial function and vascular tone may be involved in its pathophysiology. The family of endothelins (ET) consists of four closely related peptides, ET-1, ET-2, ET-3 and ET-4, which cause vasoconstriction, cell proliferation and myocardial effects through activation of ETA receptors. In contrast, endothelial ETB receptors mediate vasodilation via release of nitric oxide and prostacyclin. In addition, ET receptors in the lung are a major pathway for the clearance of ET-1 from plasma. Thus, infusion of an ETA-receptor antagonist into the brachial artery in healthy humans leads to vasodilation, whereas infusion of an ETB-receptor antagonist causes vasoconstriction. Endothelin-1 plasma levels are elevated in CHF and correlate both with hemodynamic severity and symptoms. Plasma levels of ET-1 and its precursor, big ET-1, are strong independent predictors of death after myocardial infarction as well as in CHF. Endothelin-1 contributes to increased systemic and pulmonary vascular resistance, vascular dysfunction, myocardial ischemia and renal impairment in CHF. Selective ETA, as well as combined ETA/ETB-receptor antagonists, have been studied in patients with CHF, and their use has shown impressive hemodynamic improvement (i.e., reduced peripheral vascular and pulmonary resistance as well as increased cardiac output). These results indicate that ET-receptor antagonists, indeed, have a potential to improve hemodynamics, symptoms and, potentially, prognosis in patients with CHF, which still carries a high mortality.

Over a decade ago, a novel vasoconstrictor peptide synthesized by vascular endothelial cells was identified (1,2). Since then, knowledge about the role of endothelin (ET) in disease has rapidly accumulated, and the fruits of this research led to the development of specific antagonists of ET receptors. This review will focus on the role of ET and ET-receptor antagonists in the pathophysiology and pharmacotherapy of congestive heart failure (CHF).

Congestive heart failure is a disease process characterized by impaired left ventricular function, increased peripheral and pulmonary vascular resistance and sodium and water retention. Since the prevalence of CHF increases, it will be a major cause of morbidity and mortality in the future (3). Despite progress in pharmacotherapy, CHF still carries a very high mortality (4,5).

ETs. The family of ETs consists of four closely related peptides—ET-1, ET-2, ET-3 and ET-4—which are converted by ET-converting enzymes from “big ETs,” originating from large preproendothelin peptides (6–9). The ET peptides are synthesized by endothelial and smooth muscle cells, as well as neural, renal, pulmonal and inflammatory cells (10,11). Endothelins are structurally closely related to neurotoxins produced by scorpions and snakes (12–14). The major isoform in the cardiovascular system is ET-1. Factors modulating the expression of ET-1 are shear-stress, pulsatile stretch, epinephrine, angiotensin II, cortisol, thrombin, inflammatory cytokines (tumor necrosis factor α, interleukin-1 and -2), transforming growth factor β and hypoxia (Fig. 1) (15–28). In the myocardium, prolonged exercise induces ET-1 expression (29). Endothelin-1 is metabolized by a neutral endopeptidase, which also cleaves natriuretic peptides (30,31).

Endothelin-1 exerts its major vascular effects—vasoconstriction and cell proliferation—through activation of specific ETA and ETB receptors on vascular smooth muscle cells (Fig. 1) (32–40), which leads to increased intracellular calcium concentrations (33,36,41–46). Endothelin-1, most of which is secreted abluminally (47,48), contributes to the maintenance of basal vascular tone (Fig. 2A) (49). Additionally, ET-1 influences myocardial contractility, the central and autonomic nervous system and the baroreflex (43,44,50–61). In the kidney, sodium excretion is modulated (62). Endothelial ETB receptors cause vasodilation via release of nitric oxide (NO) and prostacyclin (Fig. 1 and 2) (63). Additionally, ETA receptors in the lung are a major pathway for the clearance of ET-1 from plasma (64–67). EndothelinB receptors also contribute to the autocrine regulation of ET-1 synthesis (68–71).

These features explain why ET-1—which is essential for
normal embryonic development (72–79)—plays the role of a villain in CHF, which is characterized by increased peripheral resistance and volume retention. Indeed, ET-1 contributes to vasoconstriction, decreased ventricular function and volume retention in CHF. Endothelin-1 plasma levels are elevated in patients with CHF, correlate with symptoms and with the hemodynamic severity and are associated with adverse prognosis (80–84).

**Pathogenetic role of ET. HYPERTENSION.** Arterial hypertension is an important precursor of CHF, even in the absence of myocardial infarction (MI) (85,86). Hypertension is associated with endothelial dysfunction (87,88), a term describing the imbalance of endothelium-derived vasodilating and –constricting substances (89,90). Endothelin-1 acts as the natural counterpart of NO (Fig. 1), which exerts vasodilating, antithrombotic and antiproliferative effects and inhibits leukocyte-adhesion to the vascular wall (15). Besides its blood pressure raising effect in man (91,92), ET-1 induces vascular and myocardial hypertrophy (93–95), which are independent risk factors for cardiovascular morbidity and mortality (96–98).

In fact, ET-1 plays an important role in hypertension. Patients with hypertension exhibit an exaggerated vasodilator response to ET-receptor blockade (99). Plasma levels, however, are not consistently elevated in essential hypertension. Patients with hypertension exhibit an exaggerated vasodilator response to ET-receptor blockade (99). Plasma levels, however, are not consistently elevated in essential hypertension (100–102). Therefore, vascular, rather than plasma, ET-1 levels must be elevated, or the sensitivity to endogenous ET-1 seems to be altered in patients with hypertension. Indeed, in experimental hypertension, vascular ET-1 content is much more increased than are plasma levels of the peptide (28,94,103). Furthermore, there is evidence that certain polymorphisms of the genes coding for ET-1 and ET receptors could be associated with higher blood pressure levels (104–107).

In experimental hypertension, treatment with a selective ET$_A$–receptor antagonist attenuates left ventricular hypertrophy (108), prevents vascular hypertrophy (103) and ameliorates endothelial dysfunction (109,110). Therefore, ET-receptor blockade opens new therapeutic options in hypertension and its clinical sequelae. In essential hypertension, bosentan, a mixed ET$_A$/B–receptor antagonist, decreases arterial blood pressure to a similar degree as an angiotensin-converting enzyme (ACE) inhibitor (111). This effect did not provoke any neurohormonal activation. Further trials are needed to clarify if ET-receptor antagonists offer additional benefits over conventional antihypertensive drugs.

**Atherosclerosis.** Coronary atherosclerosis, and, as a consequence, myocardial ischemia and MI, is the chief etiology of CHF (112). Endothelin-1 essentially contributes to coronary artery disease (CAD) as ET-1 promotes direct vasoconstriction and induces smooth muscle cell proliferation through activation of ET$_A$ receptors (1,35,113–115). Furthermore, ET-1 stimulates neutrophil adhesion and platelet aggregation (Fig. 1) (116,117) and functionally acts as a natural antagonist of NO, a vasodilator with antiproliferative and antithrombotic properties (118–120). An imbalance of NO and ET-1, thus, contributes to atherogenesis (89).

Oxidatively modified low-density lipoprotein cholesterol
induces the production of ET-1 by human macrophages and increases ET-1 release from endothelial cells (Fig. 1) (16). Further risk factors for atherosclerosis, for example, diabetes mellitus and smoking, also enhance endothelial ET-1 secretion (121,122). Indeed, circulating and vascular tissue levels of ET-1 are elevated in patients with atherosclerosis and correlate with the number of anatomic sites involved (123–127). Moreover, tissue ET-1 levels correlate with angina class in patients with CAD and increase as the clinical presentation becomes unstable (128,129). Certain polymorphisms of the prepro-ET-1 and ET-receptor genes may represent a predisposition for vascular diseases (130–134).

Experimentally, ET-receptor blockade prevents endothelial dysfunction and structural vascular changes in atherosclerosis (103,135,136). In patients with CAD, ET-1 is an important determinant of coronary tone (137). Future trials will be required to delineate the role of ET antagonists in the prevention of atherosclerosis. 

**ET in MI.** Endothelin-1 plasma levels are elevated in patients with acute MI and correlate with one-year prognosis (Fig. 3) (125,138–140). Experimentally, treatment with an ET_A-receptor antagonist reduces infarct size and improves survival (141–146).

**ET in heart failure.** Increased peripheral vascular resistance is a key feature of CHF making ET-1 a pathophysiological suspect. Indeed, apart from activation of other neurohormonal systems, ET-1 contributes to vasoconstriction as well (Fig. 4) (147–149).

The production of ET-1 in the heart of rats with CHF is markedly increased (150,151), and in the peripheral circulation, particularly in the lung, ET-1 production is increased (152–154). As a consequence, plasma levels of ET-1 are elevated in experimental CHF (155), as is the density of myocardial ET receptors (154,156).

In patients with CHF, circulating ET-1 is elevated and correlates with hemodynamic severity (Fig. 5) and symptoms (80–83,157–160). Tissue ET-1 levels are also increased in the failing human heart (161,162). Most impressive, plasma levels of the ET-1 precursor, big ET-1, are strong independent predictors of death (84,163–165).

Parallel to ET-1, ET_A receptors are upregulated in the failing human heart (166). In contrast, ET_B receptors seem to be downregulated (162). The vasoconstrictor response to exogenous ET-1 is blunted in CHF as compared with healthy subjects, both in the arterial and venous arms of the circulation (167,168).

The mechanisms leading to increased ET-1 expression in CHF are not completely understood. In CHF, the main source of circulating ET-1 seems to be the pulmonary vascular bed (169). Since there is a correlation between ET-1 plasma levels and cardiac filling pressures and the degree of pulmonary hypertension, respectively, vascular distension may be a stimulus for increased ET-1 production (157). Indeed, ET-1 production is modulated by baroreflexes (170), and baroreceptor function, as well as the normal increase in ET-1 plasma levels in response to postural change, is disturbed in patients with CHF (171,172). Additionally, decreased shear-stress caused by low-cardiac output may also contribute to elevated ET-1 release in CHF (173,174). Downregulation of lung ET_B receptors, which are involved in clearance of ET-1 (Fig. 4), may further contribute to elevated circulating ET-1 levels (175,176). Other neurohormonal systems activated in CHF, such as angiotensin II and catecholamines, may also stimulate ET-1 production (177), as beta-adrenergic blocking agents and certain ACE inhibitors lower circulating ET-1 levels (178,179). In addition, endothelial dysfunction with an imbalance of endothelium-derived substances and decreased NO bioavailability in particular (119,180,181), par-
participates in the activation of the ET-1 pathway (182). As mononuclear cells are capable of ET-1 production, chronic immunologic activation, which occurs in CHF (183,184), could also be implicated in ET-1 activation. Indeed, isolated lymphocytes from patients with CHF, but not healthy controls, show spontaneous ET-1 release (185).

Interestingly, ET-1 seems to exert differential effects on myocardial contractility in the normal and the failing human heart (50,51). In patients with reduced left ventricular function, intracoronary infusion of the selective ETA-receptor antagonist BQ-123 increases contractility, while, in patients with normal ejection fraction, a decrease in contractility occurs. However, ET-1 is not as important as the beta-adrenoceptor pathway is for the regulation of myocardial performance (186).

Renal function in CHF. Sodium and water retention leading to edema is a clinical hallmark of CHF. Renal function in patients with CHF is often impaired because of renal hypoperfusion caused by low cardiac output and neurohormonal activation.

Endothelin-1 has impact on the regulation of normal renal function in addition to its cardiovascular effects (Fig. 3).

ET antagonists in CHF. Given the contribution of ET-1 to the hemodynamic derangement in patients with CHF, specific pharmacotherapy aiming at prevention of the actions of the peptide is a logical approach. As established therapeutic strategies in CHF such as ACE inhibition, and beta-blockade in particular (195–198), proved blockade of activated neurohormonal systems is a promising target. Endothelin-receptor antagonism has already demonstrated the amelioration of the clinical status of patients with CHF and, thus, holds the potential to improve the outcome.

Mixed ET<sub>A/B</sub>-receptor antagonists. Several ET antagonists are under clinical investigation in cardiovascular diseases (Table 1). Administration of the mixed ET<sub>A/B</sub> antagonist bosentan (Ro 47–0203) in rats with CHF after acute MI significantly decreased arterial blood pressure and had in effect additive to that of an ACE inhibitor (199).

Infusion of the mixed ET<sub>A/B</sub> antagonist bosentan improves systemic and pulmonary hemodynamics in patients with CHF, both acutely and chronically (137,200,201). A clinical trial (Research on Endothelin Antagonists in Chronic Heart failure [REACH]-1) investigating the long-term effects of bosentan on clinical events in CHF showed an improvement in symptoms (202). However, the trial had to be stopped prematurely because of elevation of liver transaminases. Bosentan, which was given in large oral dosages, interacts with bile acid excretion. Lower dosages of bosentan are currently being evaluated (ENABLE trial) (Table 2).

Endothelin antagonists may also be of pharmacotherapeutic value in renal failure, which often complicates the pharmacological treatment of CHF. Experimentally, renal vasoconstriction during reperfusion after clamping of the renal artery can be significantly reduced by treatment with an ET antagonist (203). Infusion of a selective ETA antagonist one day after induction of acute renal failure enhanced the tubular reabsorption of sodium, increased glomerular filtration rate and improved survival (204). In rats with experimental CHF, injection of bosentan, a mixed ET antagonist, increased cortical and medullary blood flow but reduced arterial pressure. In rats with compensated CHF and in normal animals, bosentan did not affect blood pressure and cortical perfusion (205).

Selective ET<sub>A</sub>-receptor antagonists. Theoretically, selective ET<sub>A</sub> antagonists may offer advantages over mixed ET<sub>A/B</sub> antagonists. Endothelin-1 causes vasoconstriction through activation of ET<sub>A</sub> and ET<sub>B</sub> receptors on smooth muscle cells (32–37). In contrast, endothelial ET<sub>B</sub> receptors evoke NO-mediated vasodilation and are involved in the clearance of ET-1 (64–67,206,207) (Fig. 1). Reduced pulmonary clearance of ET-1 may contribute to elevated
Figure 4. Pathophysiological role of endothelin-1 (ET-1) in congestive heart failure. In the heart, ET-1 contributes to contractility. In addition to its vasoconstrictive effects in the systemic and pulmonary circulation, ET-1 leads to hypertrophy of myocardial and smooth muscle cells. The pulmonary circulation is an important source of ET-1 but is also involved in the clearance of ET-1. In the kidney, ET-1 regulates sodium and water excretion. ANP = atrial natriuretic peptide.

Figure 5. Hemodynamic severity of congestive heart failure correlates with circulating endothelin-1 (ET-1). There is an inverse relationship between stroke volume and ET-1, whereas pulmonary vascular resistance is positively related to circulating ET-1. (Modified from [223]).
circulating ET-1 levels in CHF (175). Thus, selective ET_A blockers interfere less with the clearance of ET-1 than nonselective ET_A/B antagonists do. Since endothelial ET_B receptors mediate the release of vasodilating NO, their blockade may further deteriorate the balance of endothelium-derived vasoactive substances (208,209). Indeed, infusion of BQ-788, a selective ET_B-receptor antagonist, into the brachial artery caused vasoconstriction in healthy volunteers, suggesting that activation of the vascular ET_B receptor by endogenous ET-1 overall favors vasodilation (63) (Fig. 2A). Correspondingly, systemic infusion of BQ-788 in healthy subjects increased peripheral vascular resistance (Fig. 6) (206). Although BQ-788 had no effect on mean arterial pressure, there was a reduction in stroke volume index, giving further evidence for a theoretical advantage of selective ETA antagonism in CHF. In the human skin circulation, the ET_A-receptor antagonist BQ-123, but not the ET_B blocker BQ-788, prevented ET-1-induced vasoconstriction (210). However, the role of ET_B receptors may differ in healthy subjects and CHF. Whereas ET_B receptors mediate vasodilation in healthy subjects, ET_B receptors cause vasoconstriction, at least in the systemic circulation, in patients with CHF (211).

Congestive heart failure is associated with the development of myocardial hypertrophy as a response to chronic volume overload. Endothelin-1 exerts growth-promoting effects on cardiomyocytes (212), which are potentiated by hypoxia and the renin angiotensin system (213,214). An altered expression of myosin heavy chain (MHC), that is, the switch from \( \alpha \) to \( \beta \)-MHC, is regarded as a molecular marker for heart failure. BQ-123, a selective ETA blocker, prevents the switch of MHC-isoform expression in experimental heart failure (215).

In experimental heart failure, infusion of the selective ETA antagonist, FR139317, improved cardiac performance and renal perfusion, whereas administration of the ET_B blocker RES-701-1 decreased cardiac output and renal plasma flow (207). RES-701-1 lowered circulating aldosterone levels, while FR139317 led to a decrease in plasma atrial natriuretic peptide (ANP) levels, which are elevated in CHF due to atrial distension (216). Compared with the mixed ETA/B antagonist TAK-044, the selective ETA antagonist FR139317 improved hemodynamics to a comparable degree (217). Only TAK-044, however, lowered plasma aldosterone levels, explainable by ET_B-receptor-mediated aldosterone release (Fig. 4). Darusentan, a selective ET_A antagonist, attenuated the deterioration of cardiac function in CHF subjects (218).

### Table 1. Partial Listing of Endothelin Antagonists Under Clinical Testing

<table>
<thead>
<tr>
<th>Substance</th>
<th>Receptor Selectivity</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>BQ-123</td>
<td>A</td>
<td>Transplantation, HF, MI, subarachnoid hemorrhage, renal ischemia</td>
</tr>
<tr>
<td>BQ-788</td>
<td>B</td>
<td>HF</td>
</tr>
<tr>
<td>BMS-193884</td>
<td>A</td>
<td>HF</td>
</tr>
<tr>
<td>J-10432</td>
<td>A</td>
<td>Hypertension</td>
</tr>
<tr>
<td>L-754142</td>
<td>A</td>
<td>Renal ischemia</td>
</tr>
<tr>
<td>LU135252</td>
<td>A</td>
<td>HF, pulmonary hypertension, atherosclerosis, progressive nephropathies (darusentan)</td>
</tr>
<tr>
<td>PD-142893</td>
<td>A/B</td>
<td>Progressive nephropathy</td>
</tr>
<tr>
<td>PD-145065</td>
<td>A/B</td>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>PD-156707</td>
<td>A</td>
<td>HF</td>
</tr>
<tr>
<td>Ro 47-0203</td>
<td>A/B</td>
<td>Transplantation, HF, MI, atherosclerosis, pulmonary hypertension, subarachnoid hemorrhage, renal ischemia, progressive nephropathies (bosentan)</td>
</tr>
<tr>
<td>Ro 61-1790</td>
<td>A</td>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>SB-209670</td>
<td>A/B</td>
<td>Radiocontrast nephropathy</td>
</tr>
<tr>
<td>TA-0115</td>
<td>A</td>
<td>HF</td>
</tr>
<tr>
<td>TAK-044</td>
<td>A/B</td>
<td>Atherosclerosis, subarachnoid hemorrhage, renal transplant rejection</td>
</tr>
<tr>
<td>ZD 1611</td>
<td>A</td>
<td>Obstructive lung disease, pulmonary hypertension</td>
</tr>
</tbody>
</table>

HF = heart failure; MI = myocardial infarction.

### Table 2. Ongoing Clinical Trials With ET Antagonists in CHF or Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Study</th>
<th>Compound</th>
<th>Patients</th>
<th>Primary End Point</th>
<th>Results Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEAT</td>
<td>Darusentan</td>
<td>HF</td>
<td>Chronic hemodynamic efficacy</td>
<td>Abstract (225)</td>
</tr>
<tr>
<td>ET-005</td>
<td>Darusentan</td>
<td>HF</td>
<td>LV mass and function, symptoms</td>
<td></td>
</tr>
<tr>
<td>ENABLE</td>
<td>Bosentan</td>
<td>HF</td>
<td>Combined morbidity and mortality</td>
<td></td>
</tr>
<tr>
<td>ET-005</td>
<td>Bosentan</td>
<td>Pulmonary hypertension</td>
<td>Change in six-minute walk test</td>
<td>Abstract (226)</td>
</tr>
<tr>
<td>Tezosentan</td>
<td>Acute HF</td>
<td></td>
<td>Hemodynamics</td>
<td>Abstract (227, 228)</td>
</tr>
<tr>
<td>BMS-193884</td>
<td>HF</td>
<td></td>
<td>Hemodynamics</td>
<td>Abstract (224)</td>
</tr>
</tbody>
</table>

ENABLE denotes Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure; CHF = congestive heart failure; ET = endothelin; HEAT = Heart Failure ET(A) Receptor Blockade trial; HF = heart failure; LV = left ventricular.
performance and hemodynamics in dogs with pacing-induced CHF (218). In a rat model of heart failure, ventricular function was preserved by selective ETA antagonism (219). A-127722 and PD 156707, two further selective ETA blockers, also improved hemodynamics when given chronically (219,220). There was an accompanying suppression of plasma ANP levels with improved sodium excretion. Most encouraging, long-term survival was improved by selective ETA antagonism in a rat model of CHF (146).

It has been speculated that selective ETA antagonists may be less potent than mixed ETA/B blockers. However, newer selective ETA antagonists are able to achieve similar hemodynamic effects as mixed ETA/B blockers when given to patients with CHF (221). Systemic and pulmonary hemodynamics markedly improved after intravenous infusion of BQ-123, although patients were receiving long-term ACE-inhibitor therapy, which was continued on the study day. Indeed, the vasodilator action of ETA-receptor antagonism is preserved in patients with CHF treated with an ACE inhibitor (222).

Darusentan is a selective ETA-receptor antagonist for oral administration that has been studied both acutely as well as chronically, that is, over a period of three weeks, in patients with moderate CHF (223). Impressive hemodynamic improvements were achieved (Fig. 7). While there was a marked decrease in systemic and pulmonary vascular resistance, cardiac output greatly improved without causing neurohormonal stimulation. Circulating ET-1 increased—most likely due to displacement of ET-1 from the ETA receptor—after administration of the ETA blocker, but the elevation was clearly less pronounced than with the use of the mixed ETA/B-receptor antagonist bosentan (200,201).

With a further selective ETA antagonist BMS-193884 comparable hemodynamic improvements were achieved associated with a trend for improvement of symptoms (224). As is the case for darusentan, the compound was well-tolerated and did not provoke any elevation of liver transaminases. Table 2 summarizes further ongoing clinical trials (225–227).

Taken together, there is evidence for the preferential use of selective ETA blockers for CHF. However, randomized clinical trials are needed to compare the effects of ETA with mixed ETA/B-receptor antagonists on clinical outcome of patients with CHF.

**Conclusions.** Circulating ET-1 levels, which are elevated in CHF, correlate with the hemodynamic severity, with symptoms and with prognosis of the disease. Recent trials with ET blockers, which ameliorate symptoms and hemodynamics in CHF, indicate that ET-receptor antagonism,
indeed, holds the potential to improve the prognosis of CHF, which still carries high morbidity and mortality. Large clinical trials—in part under way—are now required to prove this hypothesis.

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