Review

Endothelin in chronic heart failure: current position and future prospects

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1. Introduction

Chronic heart failure (CHF) is a major and increasing cause of cardiovascular morbidity and mortality [1], due at least in part to the fact that its various haemodynamic, neuroendocrine and other pathophysiological mechanisms remain incompletely understood. Since in Western countries CHF usually arises secondary to previous myocardial infarction, primary preventive strategies directed at reducing the incidence of coronary artery disease are of crucial and fundamental importance. However, changing population demographics coupled in particular with advances in the medical management of myocardial infarction mean that there are increasing numbers of patients in whom the heart failure syndrome is already established [2]. Vasodilator drugs have clearly been shown to improve symptoms and prolong survival [3], but established CHF still impairs quality of life more than any other common chronic medical illness and carries a poorer prognosis than many malignancies [1]. CHF not surprisingly represents a major economic problem, with recent analyses indicating that it accounts for 1 to 2% of total health care expenditure in Europe and the USA [4,5]. Improved understanding of the complex and almost invariably progressive pathophysiology of CHF is essential if novel therapeutic strategies capable of reducing its considerable human and financial burden are to be developed.

2. Neuroendocrine activation and vasoconstriction in chronic heart failure

Impairment of ventricular contractility in CHF results in activation of multiple neural and humoral vasoconstrictor reflexes aimed principally at preserving cardiac output and maintaining vital organ perfusion [6,7]. This is now regarded as something of a maladaptive response, because maintenance of central haemodynamics and perfusion pressure occurs at the expense of an increase in systemic vascular resistance which further impedes left ventricular ejection and precipitates the classical "vicious cycle" of CHF. Cerebral and coronary perfusion are usually preserved in CHF while skeletal muscle, renal and pulmonary bed vasoconstriction lead to predictable clinical and pathophysiological sequelae. Skeletal muscle vasoconstriction impairs vasodilating capacity during exercise in patients with CHF and appears to be a major mechanism contributing to the cardiac symptoms of fatigue and poor exercise tolerance [8]. Renal vasoconstriction occurs early in the course of CHF and causes a proportionally greater reduction in renal blood flow than to any other vascular bed [9]. Reduced renal perfusion in turn augments sodium and water retention, primarily via activation of the renin-angiotensin-aldosterone system. Chronic pulmonary vasoconstriction contributes to the development of pulmonary hypertension in CHF, an important predictor of morbidity and mortality [10].

The importance of vasoconstriction as a fundamental pathophysiological mechanism in patients with CHF is underscored by the fact that drug therapies which decrease systemic and pulmonary vascular resistance have been shown to improve well-being and prolong survival [3]. Indeed, in terms of symptoms and survival, the most effective treatments for CHF have been drugs which act
directly on systemic and pulmonary resistance vessels to interrupt neuroendocrine vasoconstrictor reflexes and cause vasodilatation. The greatest impact has undoubtedly been made by the angiotensin converting enzyme (ACE) inhibitors which reduce conversion of angiotensin I to angiotensin II, a potent vasoconstrictor and mitogen; ACE inhibitors might also enhance endothelium-dependent vasodilatation via a reduction in bradykinin degradation [11]. Novel angiotensin II receptor antagonists have shown therapeutic promise in CHF [12], but it remains to be seen whether they will have the same clinical impact as ACE inhibitors. Such vasodilator therapies, however, make only a very modest impact on morbidity and mortality in CHF, partly because none can achieve normalisation of vascular resistance or exercise associated vasodilatation. Though structural vascular changes may be partly responsible for the residual elevation in vascular resistance, an important objective in CHF is the development of novel therapeutic strategies capable of restoring vasodilator reserve and achieving a greater reduction in vascular resistance than is currently possible.

3. Endothelial regulation of vasomotor tone

In both health and disease, the vascular endothelium plays a pivotal role in the modulation of vascular tone through local synthesis and release of various vasodilator and vasoconstrictor substances [13]. The increase in arterial and venous vasomotor tone which characterises CHF is presumed to represent the net effect of the interaction of these locally produced factors with the other systemically activated vasoconstrictor reflexes, in particular the sympathetic nervous and renin–angiotensin–aldosterone systems. However, the relative contributions of either diminished endothelial synthesis of relaxing factors or enhanced synthesis of contracting factors to vasoconstriction in CHF is controversial. Stimulated release of endothelium-derived relaxing factor (EDRF) has consistently been shown to be blunted in the peripheral vasculature of patients with CHF [14,15]. The effects of CHF on basal EDRF release are more controversial, different studies suggesting blunting [16], preservation [15], or enhancement [17] of basal EDRF release. Conversely, the characteristic vasoconstriction of CHF may be secondary to enhanced synthesis or activity of some endogenous contracting factor. Endothelin is a peptide hormone with potent and uniquely sustained vasoconstrictor properties which is synthesised predominantly by the vascular endothelium and has been implicated in the pathophysiological vasoconstriction of CHF. In this review we aim to discuss the basic principles of endothelin biosynthesis and action, assess the evidence implicating endothelin in the pathophysiology of CHF and discuss the therapeutic potential of anti-endothelin drugs.

4. Endothelin biosynthesis and action

Though others had previously demonstrated the release of a polypeptide vasoconstrictor substance from endothelial cells in vitro [18,19], Yanagisawa et al. were the first to purify, sequence and clone the 21 amino acid structure of endothelin and its mRNA from the culture supernatant of porcine aortic endothelial cells in 1988 [20]. Though remarkable advances have been made since that original report in our understanding of the molecular basis of endothelin biosynthesis and action, the precise physiological role and importance of endothelin in healthy man remains ill-defined. Endothelin has been implicated as playing an important physiological role in cardiovascular regulation and a putative pathophysiological role in a range of disease states [21,22], but it is only now that the necessary pharmacological tools (in particular endothelin receptor antagonists) are becoming available which will allow the functional relevance of the peptide in health and disease to be more clearly defined.

A family of three structurally and functionally similar endothelin isopeptides exists (endothelin-1, -2 and -3), each encoded by distinct genes on chromosomes 6, 1 and 20 respectively [20–23]. Endothelin-1 is the predominant isoform synthesised in the human vasculature and has been characterised as the most potent vasoconstrictor substance known, demonstrating approximately ten times greater vasoconstrictor potency in vitro than angiotensin II [20]. Endothelin-2, though having similar vasoconstrictor potency to endothelin-1, is not detectable in human plasma and appears to be synthesised predominantly in the kidney and intestine [24,25]. Endothelin-3 is the least potent vasoconstrictor in the endothelin family. Though it is detectable in human plasma, its major source and physiological role are unclear. Precursor mRNA for endothelin-3 is detectable particularly in the central nervous system [26] but also in lung, kidney, pancreas and spleen [21,24,25].

Like several other biologically active peptides, each member of the endothelin family is initially synthesised as a larger prepropeptide of approximately 200 amino acid residues [20]. 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”. An unusual and unique processing step catalysed by endothelin converting enzyme (ECE) subsequently generates mature endothelin peptides from their respective big endothelin precursors [27]. In the case of endothelin-1, the 21 amino acid mature form of the peptide and its C-terminal fragment are generated via selective cleavage of the carboxy terminal of big endothelin-1 between positions 21 (tryptophan) and 22 (valine) (Fig. 1) [20,27].

The recent molecular cloning and sequencing of ECE represents a major advance in our understanding of endothelin biosynthesis [27]. Several ECE fractions with varying preferences for each of the big endothelins proba-
bly exist. The major physiologically relevant form of the enzyme in the human vasculature is believed to be a phosphoramidon-sensitive integral membrane metalloprotease, recently designated ECE-1 [27]. ECE-1 is expressed both intracellularly and on the surface of vascular endothelial cells, optimally active at neutral pH and converts big endothelin-1 more efficiently than big endothelin-2 or big endothelin-3. ECE-1 is distinct from neutral endopeptidase (endopeptidase-24.11), the physiological importance of which in endothelin processing is unclear. Neutral endopeptidase is another integral membrane glycoprotein with striking structural similarity to ECE-1 but a much broader substrate specificity [28]. It is probably best known for its ability to degrade the natriuretic peptides and angiotensin II, but it can also generate endothelin-1 from big endothelin-1, and degrade mature endothelin-1 [29,30].

Cultured vascular endothelial cells take around 30 minutes to release endothelin-1 after stimulation suggesting that production of the peptide requires de novo gene expression and protein synthesis [30]. More rapid increases in plasma endothelin-1 have been demonstrated in response to upright tilt [31] and to the cold pressor test [32], implying the existence of a non-endothelial "storage pool" of endothelin-1 that can be rapidly mobilised in response to specific physiological stimuli. Endothelin-1 immunoreactivity has been demonstrated in pulmonary neuroendocrine cells [33] and in granular form within the posterior pituitary [34], but the physiological relevance of these sources is not known.

Endothelial cells release endothelin-1 predominantly abluminally suggesting that the peptide acts mainly in a paracrine fashion to alter vascular smooth muscle tone [35]. Plasma endothelin-1 levels might therefore simply reflect overspill of endothelial cell synthesis and be poorly representative of local production and activity at the interface between endothelium and vascular smooth muscle. There is some evidence, however, that circulating endothelin-1 also has important biological activity, supporting a dual paracrine and hormonal role in cardiovascular homeostasis [36,37].

Two high affinity endothelin receptor subtypes, ET\textsubscript{A} and ET\textsubscript{B}, belonging to the G protein-coupled family have been identified in human tissues [38,39]. The molecular basis of receptor regulation and function have been discussed in more comprehensive fashion elsewhere [21,22,40]. ET\textsubscript{A} receptors have selective affinity for endothelin 1 and are expressed primarily on vascular smooth muscle cells and cardiac myocytes but not on endothelial cells. ET\textsubscript{B} receptors, which have equal affinity for each endothelin isoform, are expressed principally on endothelial cells but have also recently been shown to be expressed on vascular smooth muscle cells obtained from various human vessels [41]. Stimulation of ET\textsubscript{A} and ET\textsubscript{B} receptors on vascular smooth muscle cells results in sustained vasoconstriction, the final common pathway being an increase in intracellular calcium. Stimulation of ET\textsubscript{B} receptors on vascular endothelial cells conversely results in vasodilatation, probably via release of EDRF and prostacyclin. This distribution of ET\textsubscript{A} and ET\textsubscript{B} receptors (see Fig. 2) helps to explain why the pressor effects of bolus injection of endothelin-1 are preceded by transient hypotension [42]. Recent functional studies have indicated that there is probably a far greater diversity of endothelin receptor subtypes than was initially thought, but at present there are insufficient data to extend the receptor classification [43]. A third postulated ET\textsubscript{C} receptor with selective
affinity for endothelin-3 has been identified in *Xenopus laevis* dermal melanophores but has yet to be cloned in human or other mammalian tissues [44].

There is considerable variation in endothelin receptor expression between species as well as variation between vascular beds within the same species [45]. Studies with isolated healthy human vessels have suggested that the ET₄ receptor is the principal subtype mediating endothelin-1 induced vasoconstriction in humans with little or no ET₃ mediated constriction [45,46]. The ET₄ receptor also appears to be functionally more important in the human skin microcirculation [47]. However, as described above, ET₄ receptor mRNA has been demonstrated in the media of various human vessels [41,45] and several groups have demonstrated ET₄ receptor mediated constriction of human vessels in vitro [48–51] and in vivo [52]. The studies which suggested little or no ET₃ receptor mediated constriction examined responses in larger conductance vessels rather than those responsible for determining resistance. It has been suggested that ET₄ receptor mediated constriction might be relatively more important in smaller resistance vessels [50,52].

5. How might endothelin contribute to the pathophysiology of chronic heart failure?

Endothelin-1 has characteristically slow onset and uniquely sustained vasopressor activity and probably acts as both a locally active paracrine factor and circulating hormone in the regulation of arterial and venous tone [53–55]. Local ECE inhibition and selective ET₄ receptor blockade in the forearm vasculature of healthy volunteers [56] and patients with CHF [57] substantially increase forearm blood flow, suggesting that endogenous generation of endothelin-1 contributes to maintenance of basal vascular tone in healthy humans and also to peripheral vascular resistance in patients with CHF. Plasma levels of endothelin-1 have been shown to correlate inversely with various objective measures of exercise capacity in CHF, suggesting a possible pathophysiological role for the peptide in the characteristic impairment of skeletal muscle perfusion and resultant exercise intolerance [58].

In addition to its direct arterial and venoconstrictor actions, endothelin-1 may augment the action of other vasoconstrictor and neuroendocrine mechanisms in CHF. Endothelin-I enhances conversion of angiotensin I to angiotensin II in cultured endothelial cells [59] and increases adrenal synthesis of both adrenaline [60] and aldosterone [61]. Furthermore, angiotensin II and arginine vasopressin increase endothelin-1 secretion from cultured endothelial cells [62] and a significant correlation has been demonstrated between plasma levels of angiotensin II and endothelin-1 in patients with CHF [63]. Thus, endothelial synthesis of endothelin-1 and renin–angiotensin–aldosterone system activation may potentiate each other and synergistically augment vasoconstriction and sodium retention in CHF. Sub-pressor concentrations of endothelin-1 potentiate contractile responses to catecholamines and serotonin [64], and also angiotensin II [65], suggesting that even basal physiological production of endothelin-1 might amplify vasoconstrictor reflexes in CHF. Conversely, the endogenous vasodilators EDRF [66], prostacyclin [67] and atrial natriuretic peptide [68] may act as physiological antagonists of endothelin-1. Each can inhibit endothelial
production of endothelin-1, and also antagonise its vasoconstrictor and mitogenic actions.

The renal vasculature is up to ten times more sensitive to the vasoconstrictor effects of endothelin-1 than other vascular beds [69]. Endothelin-1 constricts both afferent and efferent renal arterioles in vitro, contrasting with the selective effect of angiotensin II on the efferent arteriole [70]. In animals, systemic administration of sub-pressor doses of endothelin-1 modestly reduces both renal plasma flow and glomerular filtration rate, and minimally increases urinary sodium loss [69]. Higher doses of endothelin-1 cause more profound reductions in renal plasma flow and glomerular filtration rate associated with marked sodium retention [55,69]. There is a relative paucity of data regarding the renal actions of endothelin-1 in humans. In contrast to the animal studies, intravenous infusion of even low dose exogenous endothelin-1 in healthy subjects has anti-natriuretic effects in the absence of significant changes in renal plasma flow or glomerular filtration rate [71]. Infusion of higher concentrations of endothelin-1 sufficient to increase plasma levels threefold (such as are seen in experimental and human CHF) causes more profound sodium retention and reductions in both renal plasma flow and glomerular filtration rate. Whether endothelin-1 contributes to the pathophysiological renal vasoconstriction and sodium retention of human CHF is not yet known. Indeed, relatively little is known about the physiological role of endogenous endothelin-1 in the healthy human kidney let alone in the pathogenesis of disease.

Endothelin-1 also has mitogenic properties, promoting cell division, hypertrophy and DNA synthesis in vascular smooth muscle cells and cardiac myocytes through induction of proto-oncogenes c-fos and c-myc [72]. As with angiotensin II, endothelin-1 may therefore play a role in myocardial and peripheral vascular remodelling in CHF. Endothelin-1 might also have important direct cardiac effects in CHF. Infusion of low doses of endothelin-1 into animals causes blood pressure and heart rate to rise, while higher doses cause cardiac output to fall probably secondary to a combination of direct coronary vasoconstriction and increased systemic vascular resistance [37,55]. The physiological or pathophysiological importance of endogenous endothelin-1 in the modulation of myocardial contractility in humans has still to be established.

6. Plasma endothelin in chronic heart failure

The preferential abluminal secretion of endothelin-1 by the vascular endothelium is usually cited as the reason for the observation that circulating levels of the peptide in healthy man and in various pathophysiological states are well below the threshold required to elicit vasoconstriction in vitro. It remains unclear why systemic administration of endothelin-1 at doses sufficient to reproduce the plasma levels seen in pathophysiological states such as CHF has biological (including pressor) activity. [36,51,11].

There have been several reports of elevated plasma endothelin-1 concentrations in various animal models of heart failure and in patients with CHF (Table 1) [73–82]. On average, total circulating endothelin-1 immunoreactivity is increased two- to three-fold in CHF of all aetiologies in proportion to the symptomatic and haemodynamic severity of the syndrome. Some of the variability seen in endothelin-1 levels in these various studies is likely to have arisen from the use of different immunoassay antibodies with varying degrees of cross reactivity with the other endothelin and big endothelin peptides. It has been suggested that there may be a predominant increase in plasma big endothelin-1 in CHF, indicating either enhanced synthesis or secretion of big endothelin 1 or diminished generation of mature endothelin-1 by ECE [79,81]. Circulating big endothelin-1 itself has negligible biological activity but represents a potential source of mature endothelin-1. Whether or not there is any alteration in vascular ECE activity in CHF is unknown.

It is possible that some of the elevation in plasma endothelin-1 seen in patients with heart failure may be a consequence of reduced plasma clearance. Indeed reduced clearance of exogenously administered endothelin-1 has been reported in dogs with heart failure induced by rapid ventricular pacing [83]. The lung [84], liver [84] and kidney [85] have been shown to play a role in clearance of exogenously administered endothelin-1 in healthy man, but there are only very limited data regarding clearance of endogenously generated endothelin-1 in either healthy man or in patients with heart failure. McMurray et al. reported net uptake of endothelin-1 in the renal circulation in patients with heart failure [74] while Good et al. reported no difference in endothelin-1 concentrations across the

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Table 1

Plasma endothelin in chronic heart failure

<table>
<thead>
<tr>
<th>Authors</th>
<th>Aetiology of heart failure</th>
<th>Elevation in plasma ET-1</th>
</tr>
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<tbody>
<tr>
<td>Hiroe et al., 1991</td>
<td>IDCM</td>
<td>×4.4</td>
</tr>
<tr>
<td>McMurray et al., 1991</td>
<td>IDCM, IHD, HT, V</td>
<td>×2.3</td>
</tr>
<tr>
<td>Cody et al., 1992</td>
<td>NS</td>
<td>×2.5</td>
</tr>
<tr>
<td>Rolchheffer et al., 1992</td>
<td>IDCM, IHD, HT, V</td>
<td>×1.8</td>
</tr>
<tr>
<td>Lerman et al., 1992</td>
<td>IDCM, IHD</td>
<td>×1.7</td>
</tr>
<tr>
<td>Stewart et al., 1992</td>
<td>IDCM</td>
<td>×5</td>
</tr>
<tr>
<td>Pacher et al., 1992</td>
<td>IDCM, IHD, HT</td>
<td>×2.9 b</td>
</tr>
<tr>
<td>Cacoub et al., 1993</td>
<td>IDCm, IHD, HT, V</td>
<td>×1.75</td>
</tr>
<tr>
<td>Wei et al., 1994</td>
<td>IDCM, IHD</td>
<td>×1.8 b</td>
</tr>
<tr>
<td>Tsutamoto et al., 1994</td>
<td>IDCM, IHD, HT, V, HOCM</td>
<td>×2.5</td>
</tr>
</tbody>
</table>

ET = endothelin, IDCM = idiopathic dilated cardiomyopathy; IHD = ischaemic heart disease; HT = hypertension; VT = valvular disease; HOCM = hypertrophic obstructive cardiomyopathy; NS = not specified.

\(^{b}\) Assay in this study measured plasma big endothelin-1 rather than endothelin-1.

\(^{a}\) Assay in this study measured combined plasma endothelin-1 and big endothelin-1 immunoreactivity.
renal, pulmonary or hepatic circulations in heart failure patients [63]. Conversely, Stewart et al. reported that arterial endothelin-1 levels were lower than venous levels in patients with pulmonary hypertension suggesting reduced pulmonary clearance [86]. Recent evidence suggests that endothelial \( \text{ET}_B \) receptors may be important in the clearance of endothelin-1 from the circulation [87]. Administration of non-selective [88,89] and selective \( \text{ET}_B \) receptor antagonists in vivo appears to increase plasma endothelin-1 levels (presumably as a result of a reduction in \( \text{ET}_B \) receptor mediated clearance) while administration of selective \( \text{ET}_A \) receptor antagonists has no such effect [88]. Further comparative studies of the effects of selective and non-selective endothelin receptor antagonists are required to determine what effect heart failure has on endothelial \( \text{ET}_B \) receptor function and plasma clearance of endothelin-1.

Several neurohormonal and physical factors probably contribute to the elevation in plasma endothelin-1 in CHF. 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 endothelin-1 in vitro, all of which could be relevant in CHF [20–22]. The vascular endothelium is probably the principal source of circulating endothelin-1 in CHF, the pulmonary vascular bed perhaps being of particular importance [82]. It is interesting to note that although captopril inhibits endothelin-1 secretion by endothelial cells in vitro [90], treatment of CHF patients with an ACE inhibitor has been reported to have no effect on plasma levels of endothelin-1 [91].

7. Plasma endothelin and the severity of chronic heart failure

As with other neuroendocrine systems, the severity of haemodynamic disturbance in CHF appears to be a major determinant of plasma endothelin-1. Plasma levels are highest in those CHF patients with the poorest ventricular function and the greatest derangement of systemic and pulmonary haemodynamics [73,75,76,79–82]. Plasma endothelin-1 correlates positively with New York Heart Association clinical class (Fig. 3) [73,75,76,80,82] and inversely with left ventricular ejection fraction [76,78,80]. A unique observation not seen with other plasma markers of neuroendocrine activation is that plasma endothelin-1 correlates positively with the severity of pulmonary hypertension in CHF (Table 2) [75,79,80,82]. A similar correlation has been found in patients with primary pulmonary hypertension and secondary pulmonary hypertension not due to CHF [86], but whether the elevation in endothelin-1 is simply a marker of the occurrence of pulmonary hypertension or is of true pathophysiological importance remains speculative.

Measurement of plasma big endothelin-1 in patients with CHF has prognostic value, a higher concentration predicting a greater chance of clinical deterioration, need for cardiac transplantation or risk of death (Table 3) [79]. Plasma endothelin-1 measured in the subacute phase after myocardial infarction has also been shown to correlate strongly with one year mortality [92]. An interesting parallel is that renin–angiotensin–aldosterone system activation is most marked in CHF patients with the greatest haemodynamic derangement and the worst prognosis. It is in these patients that ACE inhibition has been shown to be of most benefit, and it is tempting to speculate that those CHF patients with the highest plasma endothelin-1 might benefit most from any novel anti-endothelin therapeutics.

Table 2
Correlation of plasma endothelin-1 with pulmonary haemodynamics in chronic heart failure

<table>
<thead>
<tr>
<th>Plasma endothelin-1 vs.</th>
<th>( r )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic PAP</td>
<td>0.74</td>
<td>&lt; 0.002</td>
</tr>
<tr>
<td>Diastolic PAP</td>
<td>0.76</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean PAP</td>
<td>0.78</td>
<td>&lt; 0.0003</td>
</tr>
<tr>
<td>RAP</td>
<td>0.56</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>PVR</td>
<td>0.67</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

PAP = pulmonary arterial pressure; RAP = right atrial pressure; PVR = pulmonary vascular resistance.

(From Cody et al.: Circulation 1992;85:504–9)

<table>
<thead>
<tr>
<th>Clinical course</th>
<th>Big endothelin-1 concentration (fmol/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable (n = 33)</td>
<td>2.7 ± 0.9 *</td>
</tr>
<tr>
<td>Transplanted (n = 11)</td>
<td>5.8 ± 3.0 (( P &lt; 0.001 ) vs. *</td>
</tr>
<tr>
<td>Died (n = 9)</td>
<td>5.4 ± 1.7 (( P &lt; 0.001 ) vs. *</td>
</tr>
</tbody>
</table>

(From Pacher et al.: Am J Cardiol 1993;71:1293–9)
8. Endothelin receptors in chronic heart failure

It is not surprising that many of the physical and hormonal factors which have been shown to affect endothelial synthesis of endothelin-1 have also been shown to affect endothelin receptor expression in vitro e.g. angiotensin II stimulates both endothelin-1 synthesis [62] and receptor down-regulation [93]. Accordingly, various alterations in endothelin receptor density and affinity have been described in different animal models of CHF [94-96]. In rats with CHF induced by aorticocaval shunting, renal glomerular endothelin receptor density was reduced [94]. Similarly, in rabbits with CHF secondary to surgically induced aortic regurgitation and banding, endothelin receptor density in the myocardium and kidney were reduced while renal but not myocardial receptor affinity was increased [95]. In a rat coronary ligation model of CHF, there was a reduction in density but an increase in affinity of mesenteric arterial receptors while ventricular receptor density and affinity were unchanged [96]. In this model, the initial vasodilator response to intravenous infusion of endothelin-1 was preserved while the subsequent pressor response was attenuated. The systemic and renal vasconstrictor effects of systemically administered endothelin-1 have also been reported to be attenuated in dogs with CHF induced by rapid ventricular pacing [83].

Collectively, these animal studies suggest a tendency to endothelin receptor down-regulation in CHF. They are, however, of limited value in terms of predicting the regulation of endothelin receptors and clarifying the pathophysiological role of endogenous endothelin-1 in patients with CHF. Furthermore, none of the animal studies have addressed the differential regulation of ET_A and ET_B receptors, an important issue with regard to the potential therapeutic use of endothelin receptor antagonists in patients with CHF. Forearm vasoconstriction to brachial artery infusion of endothelin-1 has been shown to be blunted in patients with CHF compared to healthy control subjects, a finding consistent with the animal studies discussed above. Interestingly, forearm vasoconstriction to brachial artery infusion of the selective ET_B receptor agonist sarafotoxin S6c was found to be enhanced in CHF patients compared to controls, suggesting that constrictor ET_B receptors might be of increased functional importance in the peripheral circulation of CHF patients [97].

9. Preliminary evidence that endothelin is important in the pathophysiology of chronic heart failure

Studying the effects of agents which block either the generation or action of endothelin-1 in vivo is the only way to clarify its putative pathophysiological role in CHF. Such studies have yielded persuasive preliminary evidence that anti-endothelin drugs have therapeutic potential in CHF. In the first clinical study of an endothelin receptor antagonist, acute bolus administration of the non-selective endothelin receptor antagonist bosentan on mean arterial pressure (MAP), systemic vascular resistance (SVR), cardiac index (CI) and pulmonary capillary wedge pressure (PCWP) in patients with severe chronic heart failure. (Adapted from Kiowski et al.: Lancet 1995;346:732-36)

Collectively, these preliminary studies indicate that endothelin-1 contributes importantly to vascular resistance in CHF and suggest that anti-endothelin drugs may be therapeutically useful as vasodilator agents, even in patients already receiving treatment with an ACE inhibitor. If anti-endothelin strategies can additionally be shown to antagonise the anti-natriuretic and mitogenic actions of endothelin-1 in vivo then this would further emphasise their therapeutic potential in CHF.

10. What would be the optimum anti-endothelin strategy be in chronic heart failure?

The two most obvious anti-endothelin therapeutic strategies worth consideration in CHF are ECE inhibition
(analogous to ACE inhibition) and endothelin receptor blockade (analogous to angiotensin II receptor blockade). Though an important advance in the field of endothelin research has been the molecular characterisation of ECE [27], no specific and selective inhibitors of the enzyme have been developed. Various selective and non-selective endothelin receptor antagonists potentially suitable for human therapeutic use are at various stages of clinical development [99], but further clarification of the role of ETA and ETB receptors in mediating various actions of endothelin-1 in vivo is required before the optimum means of receptor blockade for CHF can be determined. The evidence that both ETA and ETB receptors mediate vasoconstriction [48–52,97] suggests that a non-selective receptor antagonist or a specific ECE inhibitor would be required to achieve optimal inhibition of the constrictor effects of endogenous endothelin-1. The ideal receptor antagonist would probably be able to block ETA and ETB receptors on vascular smooth muscle cells, but would preserve endothelial ETB receptor-mediated vasodilatation. Such receptor antagonists with differential selectivity for constrictor and dilator ETB receptor subtypes have not yet been developed.

11. Summary

Though much has still to be learned about the various actions of endothelin-1 in human physiology, current evidence suggests an important role for the peptide in the pathophysiology of CHF. The development of novel and more effective therapeutic strategies for CHF is an important priority in cardiovascular medicine, and anti-endothelin drugs appear to offer promise in this regard. The impact of ACE inhibitors has been such that for a new treatment modality to be of real value in CHF, it will need to offer haemodynamic benefit over and above that already obtained with an ACE inhibitor; anti-endothelin drugs seem to have this potential [57,98]. Ongoing studies with agents which inhibit either the generation or actions of endothelin-1 will clarify its role in the pathophysiology of CHF and determine whether anti-endothelin drugs represent a further therapeutic advance in the treatment of this disease.

References


