Role of Endothelin-1 in Clinical Hypertension
20 Years On

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Hypertension is the most common risk factor worldwide for cardiovascular morbidity and mortality. Currently it is estimated that a quarter of the world’s adult population is hypertensive, and this number is projected to increase to 30% by 2025. Although, there exist a number of drug therapies for hypertension, proposed by Yanagisawa et al in their potential role that ET-1 may play in the development of biologically active ET-1 and a C-terminal fragment. converting enzyme (ECE) catalyzes the generation of the ET-1. This is cleaved to big ET-1, after which an ET-

A review in Hypertension 10 years ago outlined the potential role that ET-1 may play in the development of hypertension, as proposed by Yanagisawa et al in their original Nature article in 1988. This largely focused on preclinical data because, at that time, there was only 1 published study of ET receptor antagonism in patients with essential hypertension. There were also few data that focused on the relative benefits of selective or mixed ET blockade. Finally, the lack of longer-term data on safety and tolerability for these drugs made their place in the antihypertensive armamentarium unclear. In this review we aim to answer many of these questions and outline some of the key findings in this field from the last decade.

Biology of the ET System
The ET family consists of three 21-amino acid peptides (ET-1, ET-2, and ET-3) with powerful vasoconstrictor and pressor properties. Of the 3 peptides, ET-1 is the major vascular isoform and of most importance in the cardiovascular system. The gene product is the 212-amino acid prepro-ET-1. This is cleaved to big ET-1, after which an ET-converting enzyme (ECE) catalyzes the generation of the biologically active ET-1 and a C-terminal fragment.

ET-1 acts by binding to 2 distinct receptors, the ETA and the ETB receptors (ETAR and ETBR). ET receptors are expressed by a wide variety of cells and tissues. Within the vasculature, ETAR and ETBR, located on vascular smooth muscle cells, mediate the vasoconstrictor effects of ET-1. ETBRs are also found on vascular endothelial cells, where their activation results in vasodilation mediated mainly by NO.

In addition, ETBRs have a major role in the clearance of circulating ET-1. The plasma half-life of ET-1 in health is ~1 minute, with removal through receptor- and nonreceptor-mediated mechanisms. ET-1 binds to ETBR, with subsequent ligand-receptor complex internalization and intracellular degradation accounting for the majority of clearance, particularly in the pulmonary circulation, although the splanchnic and renal circulations also contribute. Therefore, a reduction in ETBR number, or ETBR blockade, may reduce ET-1 clearance, increasing plasma concentrations without altering production. For this reason and, importantly, because most ET-1 is released albuminally, plasma concentrations of ET-1 do not accurately reflect ET-1 production.

Early in vitro and in vivo experiments supported a role for ETBRs in the renal handling of salt and water and, thus, in the regulation of BP. The last decade has seen a number of elegant animal studies focusing on ET-mediated natriuresis and diuresis. These experiments suggest that collecting duct-derived ET-1 may mediate natriuresis and diuresis through actions on epithelial rather than endothelial ETBRs. Interestingly, these data provide insight into the role of renal ETBRs in salt and water regulation, while not excluding a contribution from extrarenal ETBRs.

There are, as yet, no studies of the role of the ETAR in salt and water balance in humans. However, salt-sensitive hypertension is common in black subjects, and this population has been shown to have higher plasma ET-1 concentrations than white hypertensive subjects and to have enhanced ETA-dependent vasoconstrictor tone. Additional clinical studies in this area would not only provide important information for conditions such as salt-sensitive hypertension but may also provide an explanation for the fluid retention that is often seen as an adverse effect of treatment with ET receptor antagonists.

ET Receptor Antagonists
The last 10 years have seen the clinical development of a number of selective ETAR and mixed ETAR antagonists (see...
Table in Reference 28). The difference between selective and mixed antagonists, however, is not pharmacologically well defined, making antagonist studies difficult to interpret. Selectivity is usually calculated from in vitro competitive receptor assays, but results may vary dependent on conditions. “Mixed” antagonists in clinical trials are still selective for the ET\(_A\)R, but the ratio of ET\(_A\)/ET\(_B\) affinity is generally <100-fold selective for ET\(_A\) over ET\(_B\) compared with \(\geq100\)-fold for ET\(_A\) selective agents.\(^{27}\) Thus, the degree of receptor selectivity achieved by any particular drug may depend on the dose used, with higher doses of modestly selective antagonists potentially no longer providing selective pharmacological blockade. Unfortunately, there have been no studies in humans to determine the functional selectivity of any of the so-called selective antagonists.

Lack of ET\(_A\)/R selectivity may account for the disappointing results observed in the clinical trials with ET antagonists in chronic heart failure. Although the case for activation of the ET system in chronic heart failure is clear, and the animal models and early clinical studies were extremely promising, the longer-term data did not live up to expectations. To date, 4 large multicenter, double-blind trials have been completed. The mixed antagonist bosentan was evaluated in both the Research on Endothelin Antagonism in Chronic Heart Failure (REACH-1) and Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure (ENABLE) studies. The former was terminated early because of adverse effects (elevated liver enzymes) attributed to the high dose of drug used (\(\geq500\) mg bd of bosentan). Consequently, ENABLE used a lower dose (125 mg bd) with a longer follow-up period. No benefits of bosentan treatment were observed, with an excess of adverse events in the treatment arm. These disappointing results were mirrored in the Enrasentan and Cooperative Randomised Evaluation (ENCOR) study with the mixed antagonist enrasentan (\(\sim100\)-fold ET\(_A\) selective)\(^{28}\) and the Endothelin A Receptor Antagonist Trial in Heart Failure (EARTH) Study, which used the relatively ET\(_A\) selective antagonist darusentan (\(\sim150\)-fold ET\(_A\) selective).\(^{29}\) All of these studies showed a rise in circulating ET-1,\(^{20,29}\) whereas plasma ET-1 might be expected to have fallen with hemodynamic improvement. All have used either mixed antagonists or may have used sufficiently high doses of selective ET\(_A\) antagonist to block the ET\(_A\)/R (as suggested by the rise in plasma ET-1). Indeed, it may be that a truly ET\(_A\) selective approach has not yet been studied in patients with chronic heart failure. Interestingly, a highly selective ET\(_A\) agent, sitaxsentan, caused a decrease in plasma ET-1 concentrations in chronic heart failure patients,\(^{31}\) and there are now studies with this compound focusing on diastolic heart failure,\(^{32}\) and their results are eagerly awaited.

Pulmonary arterial hypertension remains the only licensed indication for ET receptor antagonists. Currently, the 3 antagonists clinically available (in the United States, Europe, or both) are the selective ET\(_A\) antagonists sitaxsentan and ambrisentan and the mixed antagonist bosentan. Although the experimental data are conflicting,\(^{33,35}\) the clinical studies suggest that both selective ET\(_A\) and mixed ET\(_A/B\) approaches are beneficial,\(^{36,37}\) although studies have not been designed to show a survival benefit. Furthermore, it is difficult to ascertain whether these agents provide equivalent ET\(_A\)/R antagonism, so drawing conclusions about whether ET\(_A\)/R blockade provides additional benefit is difficult. There are also, at present, no robust head-to-head clinical trials comparing selective ET\(_A\) and mixed ET\(_A/B\) receptor antagonism.

ECE inhibitors provide another potentially exciting method of blocking ET-1 activity, especially if combined with angiotensin-converting enzyme (ACE) and neutral endopeptidase inhibition. These agents would act as mixed ET\(_A/B\) receptor antagonists without affecting ET\(_A\)-mediated ET-1 clearance. However, there may be problems with combining ECE, ACE, and neutral endopeptidase inhibition. First, there exist a number of non-ECE ET-1–generating enzymes,\(^{38}\) and, second, there is a potential risk of angioedema with these drugs. There has been difficulty synthesizing compounds with a sufficiently high degree of inhibition at each of these enzymes, and, apart from data for SLV-306,\(^{39}\) these agents have been slow to emerge.

**Essential Hypertension**

Initial evidence of a pressor action of ET-1 led to the speculation that it might be implicated in hypertension.\(^{3}\) Production of vascular ET-1 is increased in some but not all of the animal models of hypertension.\(^{4}\) Those models where ET-1 production is increased (mostly, but not exclusively, salt-dependent types) are associated with increased vascular growth and a response to both selective and mixed ET receptor antagonism composed of not only a modest reduction in BP but also a marked regression of vascular growth.\(^{4}\) This was initially demonstrated in deoxycorticosterone acetate-salt hypertensive rats\(^{40,41}\) and has since been unambiguously confirmed in a mouse model with endothelium-restricted overexpression of human prepro-ET-1, which exhibits inward hypertrophic remodeling of the resistance arteries, and vascular inflammation, in the absence of an elevation in BP.\(^{42,43}\)

An early study in humans compared plasma ET-1 concentrations among subjects with phaeochromocytoma (in the presence or absence of hypertension), those with essential hypertension, and healthy control subjects. Significantly higher levels of ET-1 were seen in those with phaeochromocytoma compared with the 2 other groups, and, among these, the presence of hypertension was associated with the highest plasma ET-1 concentrations. These findings supported a role for ET-1 in the development of clinical hypertension,\(^{44}\) although many solid cancers generate ET-1. In agreement with preclinical data, which suggested that the ET system was primarily activated in the more severe rodent models of BP elevation (such as deoxycorticosterone acetate-salt, Dahl salt-sensitive, and stroke-prone spontaneously hypertensive rats), the increased prepro-ET-1 message is found in the endothelium of small arteries of patients with moderate-to-severe hypertension.\(^{45}\) ET-1 message and protein are also increased in the vascular smooth muscle cells from larger elastic and muscular arteries of hypertensive patients.\(^{46}\) In local studies, Cardillo et al\(^{47}\) have suggested increased vascular ET system activity in patients with hypertension compared with normotensive control subjects and a greater forearm vascular response to mixed receptor antagonism compared with selective ET\(_A\) antagonism, consistent with an
increased importance of vascular smooth muscle vasoconstrictor ET \textsubscript{B}R in hypertension. Others have differed in their results.\textsuperscript{68} In both mice and rats, pharmacological or genetic inhibition of ET \textsubscript{B}R activity results in a severe form of hypertension that depends on the extent of salt intake.\textsuperscript{49,50} Although it is easy to speculate that some forms of clinical hypertension may be attributable to a lack of ET \textsubscript{B}R function, this idea has yet to be explored in clinical studies.

Few studies have investigated the longer-term antihypertensive effects of ET receptor antagonism in humans. Bosentan treatment for 4 weeks reduced BP in essential hypertensive patients as much as 20 mg of enalapril (\approx 6 mm Hg).\textsuperscript{6} Importantly, this reduction was achieved without activation of the sympathetic nervous system or the renin-angiotensin-aldosterone system. In another study, 6 weeks of darusentan, a selective ET \textsubscript{A}R antagonist, was also effective in lowering both systolic and diastolic BPs compared with placebo.\textsuperscript{51} There are currently no clinical studies that directly compare selective and mixed ET receptor antagonism at systemic doses in the treatment of hypertension, although both approaches clearly reduce BP.

**Hypertension Associated With Chronic Kidney Disease**

Renal function may influence the relationship between ET-1 and hypertension. First, as renal function declines, plasma ET-1 levels increase.\textsuperscript{52,53} It remains unclear whether the rise in plasma ET-1 in chronic kidney disease (CKD) is because of biologically active or simply immunologically competent peptide, but infusion of exogenous ET-1 to bilaterally nephrectomized rats results in a increased plasma half-life of ET-1 and a prolonged rise in BP compared with sham-operated rats\textsuperscript{54} consistent with the idea that elevated plasma ET-1 concentrations in CKD may contribute to hypertension. Second, there is an upregulation of renal ET-1 production in CKD,\textsuperscript{55} as reflected by increased urinary ET-1 excretion.\textsuperscript{53,56} The effects of exogenous ET-1 on the renal vasculature are vasoconstrictr, activating the renin-angiotensin-aldosterone system, and causing salt and water retention, both of which have the potential to raise BP. Animal data suggest that, in CKD, the renal vasculature may be more sensitive to the vasoconstrictor effects of ET-1 than in normal kidneys.\textsuperscript{57} Thus, an amplification of the renal vasoconstrictor effects of ET-1, promoting hypertension, could be envisaged in CKD.

Preclinical data suggest that, in CKD, selective ET \textsubscript{A}R antagonism may be preferential to mixed blockade.\textsuperscript{58,59} This is supported by clinical studies. In hypertensive patients with CKD, the systemic vasodilatation seen with acute ET \textsubscript{B}R blockade (associated with a reduction in BP of \approx 10 mm Hg) is attenuated by concomitant ET \textsubscript{A}R antagonism, suggesting that, at least in this disease state, vasoconstrictor ET \textsubscript{B}R activity is less important than ET \textsubscript{A}R vasodilatory function.\textsuperscript{60} It is noteworthy, however, that these were acute studies, and the effects of chronic dosing in patients with CKD remain unknown. Interestingly, most of the patients studied were already taking ACE inhibitors, and data from healthy subjects suggest a synergy between ET \textsubscript{A}R antagonism and ACE inhibition that is not only dependent on an unblocked ET \textsubscript{B}R but is also associated with a significant natriuresis.\textsuperscript{61} This is important clinically because patients with CKD are generally prescribed ACE inhibitors, not only for BP control but also for their renoprotective effects. Emerging data in diabetic nephropathy suggest a role for ET antagonism, on top of standard therapy, in reducing proteinuria\textsuperscript{62} and thereby potentially offering longer-term renal protection. There are currently no studies reported in nondiabetic, proteinuric CKD, although acute dosing studies have shown a reduction in effective filtration fraction,\textsuperscript{63} which would be expected to translate to a reduction in intraglomerular pressure and, consequently, proteinuria.

**Hypertension and the Metabolic Syndrome**

Insulin resistance and compensatory hyperinsulinemia contribute to the hypertension characteristic of the metabolic syndrome,\textsuperscript{64} in which data from in vitro, animal, and human studies suggest that ET-1 plays a role.\textsuperscript{65} In health, insulin promotes production of both ET-1 and NO from the vascular wall. In subjects with insulin resistance, NO release is impaired,\textsuperscript{65,66} whereas ET-1 production is preserved.\textsuperscript{67,68} Indeed, circulating ET-1 concentrations are elevated in patients with insulin resistance,\textsuperscript{69} and this is not thought to reflect reduced ET-1 clearance.\textsuperscript{70} Thus, in states of insulin resistance, an imbalance between the ET-1/NO systems favors vasoconstriction, which may be further amplified by a reduction in the inhibitory effects of NO on ET-1 production.\textsuperscript{71}

Animal studies support a role for ET-1 in the vasocnstrictive response to insulin and thereby development of hypertension in insulin-resistant states.\textsuperscript{70,72,73} Juan et al\textsuperscript{74} studied 2 groups of rats, 1 receiving a continuous insulin infusion, the other saline. The former was characterized by hyperinsulinemia and a gradual development of insulin resistance and hypertension. They also had higher plasma ET-1 concentrations than control animals. Both groups were then treated with daily intraperitoneal saline or a selective ET \textsubscript{A}R antagonist. The 2 groups receiving the intraperitoneal ET \textsubscript{A} antagonist had similarly reduced BP levels, whereas, of those receiving intraperitoneal saline, hyperinsulinemic rats had a significantly higher BP than controls.

Human studies also suggest that ET-1 contributes to hypertension in insulin-resistant states. Cardillo et al\textsuperscript{75} showed an increase in forearm blood flow with both selective ET \textsubscript{A}R and mixed ET \textsubscript{A,B}R antagonism in patients with type 2 diabetes compared with healthy individuals. Similarly, mixed ET \textsubscript{A,B}R antagonism produced both a significant increase in forearm blood flow, as well as a potentiation of endothelium-dependent vasodilation in hypertensive patients compared with control subjects.\textsuperscript{76} Taken together, these data suggest an increase in ET-1 activity in type 2 diabetes and hypertension compared with health. Although no measurements of insulin resistance were taken in these studies, one could hypothesize this as a potential mechanism for the upregulation in ET-1 activity. This is supported by a recent study that included subjects with varying degrees of insulin resistance and showed mixed ET \textsubscript{A,B}R antagonism to significantly increase forearm endothelium-dependent vasodilation in insulin-resistant but not insulin-sensitive subjects.\textsuperscript{77} At present, there are no systemic studies using either selective ET \textsubscript{A}R or mixed ET \textsubscript{A,B}R antagonists...
that examine hemodynamics in hypertensive patients with insulin resistance.

**Hypertension and Broader Cardiovascular Risk**

**Endothelial Dysfunction**

The endothelium is a crucial regulator of vascular tone, and its function is impaired in patients with hypertension and those at risk of hypertension, with a shift toward reduced vasodilation, associated with a proinflammatory and prothrombotic state. Endothelial dysfunction is recognized to be a key early determinant in the progression to atherosclerosis and is now well established to be independently associated with increased cardiovascular risk. Mice with endothelium-restricted overexpression of human progenitor ET-1 exhibit increased oxidative stress and endothelial dysfunction as demonstrated by an impaired vasodilator response to acetylcholine. Animal models of endothelial dysfunction have shown that antagonism of the ET system, predominantly via selective ET₄R antagonists, improves NO-mediated endothelial function, suggesting that ET-1, acting via the ET₄R, is involved in the pathogenesis of endothelial dysfunction.

**Atherosclerosis**

Atherosclerosis contributes to the development of atherosclerosis. In addition to its effects on BP, ET-1 is proinflammatory and is implicated in the development of atherosclerosis. Both ET₄ and ET₄R are highly expressed in smooth muscle cells and foamy macrophages in atherosclerotic models. Increased expression of ET-1 and ECE is seen in human arteries at different stages of atherosclerosis, and high levels of ET-1 have been found in human atherosclerotic lesions. Furthermore, plasma ET-1 concentrations correlate positively with the degree of atherosclerosis present. Importantly, not only is restoration of the impaired activity of the NO system seen after ET receptor antagonism in a range of animal models of atherosclerosis, but so too is a reversal of atherosclerotic lesion development. Thus, ET antagonists reduce the activity of the ET system, increase NO bioavailability, and slow the progression of atherosclerosis.

Several animal models have shown benefit of both selective ET₄ and mixed ET₄R antagonism in the development of atherosclerotic lesions. In humans, there are data that support a role for the ET₄R in coronary vascular tone and endothelial dysfunction in coronary artery disease; however, these were acute dosing studies, and there are as yet no randomized or chronic dosing clinical trials in patients with atherosclerosis.

**Arterial Stiffness and Isolated Systolic Hypertension**

Arterial stiffness is linked to endothelial dysfunction, and the 2 commonly coexist in patients at increased cardiovascular risk. A number of interventions that reduce arterial stiffness also improve endothelial function. To date, there have been few studies addressing the relationship between these 2 markers of cardiovascular disease after treatment. However, both animal and human studies suggest that the endothelium is an important regulator of arterial stiffness.

Basal endogenous NO generation decreases arterial stiffness in animals and humans. By contrast, ET-1 increases arterial stiffness, as shown in the ET-1–overexpressing mouse, in which vascular stiffness is increased in association with increased collagen deposition, and these effects are independent of BP. Furthermore, exogenous ET-1 has been shown recently to increase arterial stiffness in humans, and studies using ET₄R antagonists have show that endogenous ET-1 is responsible for maintaining arterial stiffness to a greater extent than NO. Thus, in endothelial dysfunction, where NO is downregulated and ET-1 upregulated, the balance will likely shift in favor of increased arterial stiffness.

Isolated systolic hypertension is common in the elderly and is associated with increased arterial stiffness. Treatments that not only lower BP but also reduce vascular stiffness would be particularly attractive in isolated systolic hypertension, considering that, in patients with CKD and hypertension, a greater survival is seen when both BP and arterial stiffness are reduced, as opposed to just BP alone. Currently there are no studies of the longer-term effects of ET receptor antagonism on arterial stiffness in any patient group.

**Proteinuria**

Proteinuria is a feature of hypertensive renal damage. Although traditionally a risk factor for renal disease progression, proteinuria is now an established independent risk factor for global cardiovascular risk. Albuminuria is incrementally associated with increased cardiovascular risk in both individuals with pre-existing risk (such as hypertensive patients) and in individuals with no known risk factors. This is true even in the presence of normal renal function. Importantly, in patients with hypertension, reduction of albuminuria confers cardiovascular protection.

Through its hemodynamic effects, ET-1 contributes to the development of proteinuria. Both acute and chronic selective ET₄ blockade have been shown to reduce proteinuria in patients with diabetic and nondiabetic proteinuric CKD, and these effects are abolished by concomitant ET₄R antagonism. As yet, it remains unclear to what extent these effects are explained by BP reduction alone. However, should ET receptor antagonists be found to have a potential for renal protection in addition to their BP-lowering effects, this, furthermore, on top of standard therapies, would clearly be an attractive therapeutic option for patients with CKD.

**Tolerability and Safety of ET Receptor Antagonists**

Adverse effects of ET receptor antagonists in clinical trials are common. The most frequently reported clinical adverse events are headache, peripheral edema, dizziness, nausea, nasal congestion, and dyspnea. These appear to be a class effect, likely relate to vasodilation, and do not often lead to treatment withdrawal. The mechanism of peripheral edema with ET receptor antagonism remains unclear. ET-1 acts in the renal tubule via the ET₄R to promote natriuresis and diuresis. Thus, peripheral edema associated with vasodilation could be aggravated by mixed ET₄R antagonists because of the reported ET₄R-mediated downregulation of the renal tubular epithelial sodium channel. However, this issue remains
unresolved, because in clinical trials fluid retention appears to occur with both selective ETAR and mixed ETAR antagonists. This may be because tubular ETARs are also involved in the development of fluid retention, but this issue remains unresolved. Another possible explanation for this edema may relate to the characteristics of the patients treated. ET-1 has an inotropic effect. Those with cardiac dysfunction may depend on ET-1–mediated inotropy, and so blockade of this could lead to cardiac decompensation and fluid accumulation. Until the issue of fluid retention is resolved, the ideal target population for ET receptor antagonists will remain an issue.

Liver toxicity is also a dose-dependent and, possibly, class effect. This has led not only to intense liver enzyme surveillance but also to an active search for the lowest efficacious drug dose in clinical trials. It remains to be firmly established, however, whether liver toxicity varies among ET receptor antagonists at equipotent doses. Finally, all of the ET antagonists are contraindicated in pregnancy, because they are teratogenic. Because these drugs have only been available for a relatively short time, for the orphan indication of pulmonary artery hypertension their balance of risks and benefits remains incompletely understood, and longer-term observational studies are needed.

Perspectives
Current data support a role for ET receptor antagonism in the management of essential hypertension and the hypertension associated with systemic disorders (see Figure). In addition to those described here, data are emerging in a number of other areas where BP control is often a problem, eg, after transplantation. ET-1 has been implicated in the hypertension-complicating heart, lung, and kidney transplants, and although animal data suggest a role for ET receptor antagonists in treating this hypertension, there are currently few human data. Although unlikely to be considered as first-line treatment, ET receptor antagonists are a promising new and innovative drug class to add to the antihypertensive arma-
mentarium. Currently, the selective ET_R antagonist darusentan is being evaluated for the treatment of resistant hypertension, in agreement with data that the system is activated in severe forms of hypertension. Importantly, ET_R-selective antagonists may have a particular role in the treatment of high-risk patients, such as those with salt-sensitive hypertension, those with progressive CKD, those who develop hypertension after transplantation, or those with hypertension as part of the metabolic syndrome or diabetes mellitus.

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