EDITORIAL COMMENT

Endothelin, the Bad Actor in the Play: A Marker or Mediator of Cardiovascular Disease*

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Endothelins (ETs) are a family of three endothelium-derived 21 amino acid vasoactive peptides (1–3). Of these, ET-1 possesses the most potent vasoconstrictive properties described to date (1,2). Although identified just over 10 years ago, there has already been a phenomenal amount of research conducted regarding the role of ET-1 in cardiovascular disorders (3–19). Endothelin-1 has been incriminated as playing an important role in the whole spectrum of cardiovascular diseases, including systemic hypertension, atherosclerosis, acute ischemic syndromes, heart failure, stroke and pulmonary hypertension (5–19).

Although it is well-known that ET-1 causes dose-dependent vasoconstriction by increasing intracellular Ca++, it has several other important biological actions, including mitogenic properties, stimulation, secretion and increased activity of several key hormones and autacoids such as angiotensin II, aldosterone, nitric oxide, arginine–vasopressin, and prostacyclin (2,3). The production and release of ET-1 is also regulated by other vasoactive substances like angiotensin II, catecholamines, arginine vasopressin, thrombin and insulin (2–5). Because of these intricate relationships between ET-1 and other vasoactive substances, it is often difficult to distinguish whether ET is a mediator or a marker.

The biological effects of ET are mediated by two different receptors, ET_A and ET_B, which have different pharmacological properties and distribution in various tissues (2–4). The ET_A receptors, which are found predominantly on vascular smooth cells, are involved in mediating vasoconstriction and mitogenic effects of ET-1, whereas ET_B receptors, which exist in endothelial cells, predominantly mediate vasodilation by release of EDRFs (nitric oxide and prostacyclin) (2,3). In addition, ET_B receptors may be involved in the release of aldosterone from zona glomerulosa and to a lesser extent may also mediate vasoconstriction and mitogenic effects of ET, especially in disease states. Although ET-1 and ET-3 have equal affinity for ET_B receptors, ET-1 has significantly greater affinity for ET_A receptors. The ETs bind tightly to their receptors in a “pseudo-reversible” manner, and their slow dissociation from receptor sites probably accounts for the prolonged action of ETs (2). A clear understanding of receptor pharmacology is crucial because, in patients with cardiovascular disorders where ET-1 levels are chronically increased, there could be perturbation in the function of ET receptors.

The significance of alterations in ET receptor function is illustrated in the article by Cowburn et al. in this issue of the Journal of the American College of Cardiology (20). This study of patients with left ventricular systolic dysfunction (LSVD) demonstrated that the infusion of equimolar concentration of ET-3, which is a relatively selective ET_B receptor agonist, resulted in a similar degree of vasoconstriction as that produced by ET-1 (20). These findings suggest that, in contrast to their predominantly vasodilatory effects observed in normal subjects, the stimulation of ET_B receptors in patients with LSVD mediates systemic vasoconstriction (20). Although the precise reason for this altered response cannot be ascertained from the findings reported in the paper by Cowburn et al., it is reasonable to assume that endothelin receptor functions are perturbed in patients with LVSD and CHF. It is conceivable that, in patients with CHF, ET receptors are downregulated, resulting in attenuated response to ET-1 infusion. Conversely, it is also possible that ET_B receptor stimulation cannot produce vasodilation in patients with CHF because of the associated endothelial dysfunction, which prevents the increase in nitric oxide production usually observed secondary to ET_B receptor stimulation. The authors suggested that it is possible that ET-3 could mediate vasoconstriction by ET_C receptors, although such receptors have not yet been isolated in humans (20). A clear understanding of the altered receptor physiology and responsiveness of ET receptors is essential before any significant investment is made regarding the evaluation of ET receptor blockers in chronic heart failure (CHF). This is particularly relevant because there are a number of compounds that are now available in this class and some of them are nonselective (ET_A/ET_B) whereas others are ET_A selective blocking agents. If the results of the study reported by Cowburn et al. are reinforced by other studies, it would seem that nonselective ET_A/ET_B receptor blockers would be preferable to achieve maximum vasodilation and hemodynamic benefits in patients with CHF (20).

However, the issue is much more complex, because findings of an earlier article published in the Journal of the American College of Cardiology by Wada et al. (18) showed that, in dogs with CHF induced by rapid ventricular pacing, only selective ET_A receptor blockade was associated with favorable effects on hemodynamic parameters and diuresis.

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whereas ET$_B$ receptor blockade had reverse hemodynamic effects. Also, results of the REACH-1 study reported at the 71st Scientific Session of the American Heart Association indicated that bosentan, a nonselective ET$_A$/ET$_B$ receptor blocker, resulted in favorable hemodynamic effects in patients with CHF. However, in the REACH-1 study there was no significant improvement in the exercise capacity of patients treated with bosentan. These findings showing dissociation between hemodynamic improvement and functional capacity suggest that blockade of ET$_B$ receptors might have prevented the vasodilatory response necessary for increased blood flow to the skeletal muscles during exercise (19). Furthermore, treatment with bosentan was also associated with abnormalities in liver function tests, which might prevent its clinical development. Although there are a number of new ET$_A$ selective blockers that apparently do not have the same degree of hepatotoxic effects as bosentan, their clinical usefulness is still unproven because they have not yet been tested in large clinical trials in patients with CHF. Well-designed, prospective, placebo-controlled, randomized clinical trials using ET blockers should be conducted. It is known that, despite the well-proven benefits of therapy with ACE inhibitors, a significant proportion of patients with CHF continue to be symptomatic and remain at risk of death. A number of recent studies have also shown that ET-1 levels are increased in patients with CHF and predict adverse clinical outcome and risk of death (15–17). Therefore, it would seem reasonable to systematically examine the added benefit of therapy with ET blockers on top of treatment with ACE inhibitors and beta-blockers. This is especially important in light of the findings from recent studies showing significant reductions in levels of ET-1 after treatment with beta-blocker therapy and treatment with the ACE inhibitor fosinopril (21,22). Future studies should also attempt to answer the critical question regarding the role of ET-1 as a marker or mediator in CHF. It is conceivable that ET-1 levels are more of a marker of the severity of CHF because, as shown in the studies with the ACE inhibitor fosinopril and beta-adrenergic blocking agent, improvement in CHF status itself is associated with reductions in ET-1 levels (21–22). Clearly, more work is needed in this area before independent role of ET-1 and the therapeutic rationale for its blockade in CHF can be firmly established.

**ENDOTHELINS IN SYSTEMIC HYPERTENSION**

Because ET-1 is currently the most potent vasoconstrictor known and because ET-1 also exerts profound renal effects, it is not surprising that it has been incriminated in the pathogenesis of systemic hypertension (1–6). There is, however, a great deal of controversy regarding its role in hypertension (6–8). It is known that chronic infusion of ET-1 is associated with sustained increases in blood pressure and that there is increased sensitivity to endothelin in experimental models of hypertension (6,7). The role of ET-1 in hypertension has been documented in patients with hemangioendotheliomas and the cyclosporine-induced hypertension by showing that removal of the tumor and therapy with ET antagonist, respectively, restore blood pressure to normal levels (7). However, despite these interesting observations, the role of ETs in most of the population with systemic hypertension remains questionable (6–8). An interesting study by Mangieri et al. published earlier in the *Journal of the American College of Cardiology* (9) provided some new findings in this area. In this study, Mangieri et al. evaluated the response of plasma ET-1 during handgrip exercise in normotensive young male offspring of hypertensive parents (9). Their results demonstrated that, compared with offspring of normotensive parents, there was significantly greater rise in ET-1 levels during handgrip exercise in young offspring of hypertensive parents (9). These findings suggest that high levels of ET-1 in these individuals might be an independent marker of risk for developing hypertension later in life. It is conceivable that the offspring of hypertensive parents already have evidence of endothelial dysfunction, which precedes development of hypertension and a high level of ET-1 produced during handgrip exercise or mental stress is actually a marker of endothelial dysfunction. The role of ET-1 in the pathophysiology of hypertension, however, will remain uncertain until future studies can determine whether ET-1 is a marker, mediator, or both, in patients with hypertension.

**ENDOTHELINS AND ATHEROSCLEROSIS**

There is a growing body of evidence that suggests that ET plays a significant role in the process of atherosclerosis at the cellular level (10). The data available from both human and experimental models of atherosclerosis have shown that the production as well as the activity of ET are enhanced by established risk factors such as hypercholesterolemia, hyperinsulinemia, hypertension and smoking (10). Oxidized LDL and insulin are both strong stimuli for ET production and secretion. This is not surprising, given the fact that all of these risk factors cause endothelial dysfunction, and that endothelium is the major source of ET production. It is known that, in addition to its profound vasoconstrictive action on systemic and coronary arteries, ET also has significant chemotactic and mitogenic effects stimulating hypertrophy and hyperplasia of vascular smooth muscle cells (10). In addition, ET can promote microvascular platelet thrombi by potentiating platelet aggregation. Because all of these processes are important in the development of atherosclerosis, ET potentially plays an important role in the process of atherosclerosis. However, many other neurohormones have similar properties, raising the critical question about the independent role of ET in atherosclerosis. This question can only be answered by specific studies designed to examine the relative roles of important vasoactive hormones in the same experiment.
ENDOTHELIN IN ACUTE ISCHEMIC SYNDROMES AND MYOCARDIAL INFARCTION

Many studies have demonstrated that ET levels are consistently increased in patients with acute ischemic syndromes and MI (11–14). Mechanistically, the increase in ET levels in acute ischemic syndromes could be multifactorial and related to endothelial injury due to plaque fissuring or rupture, ischemia, vasospasm and reperfusion. It is also known that thrombin, which plays a pivotal role in acute MI, is a potent stimulus for ET release. High levels of ET can also potentiate the effects of other vasoactive peptides on the vessel wall. After MI, ET-1 can play a role in the process of LV remodeling by potentiating the effects of catecholamines and angiotensin II on myocardial cell hypertrophy. The important question is whether ET is a marker or mediator in acute ischemic syndromes, especially because it is known that ET is also an acute phase reactant. Whatever the precise role may be, the data from several recent studies show that ET levels rise rapidly after MI in most patients (12–14). The ET levels usually return to baseline within 72 h in patients with uncomplicated MI; however, in patients with cardiogenic shock, CHF, and LV dysfunction after MI, the levels stay elevated beyond the acute phase (13,14). Follow-up studies in these patients have shown that higher levels of ET predict adverse long-term prognosis and poor survival (13,14). Preliminary data from a recent study suggest that nonselective ET receptor antagonists can block the trophic effects of ET and reduce collagen synthesis, which in turn can modify the process of postinfarction remodeling (24). On the basis of these data, it would seem reasonable to investigate if ET receptor blocker therapy is of clinical benefit in high-risk, post-MI patients. It would, however, be critical to examine whether the treatment with ET receptor blockers adds to the proven cardioprotective effects of beta-blockers and ACE inhibitors after MI.

FUTURE IMPLICATIONS

The available evidence suggests that, in addition to its powerful vasoconstrictive action, ET-1 has several other properties that could play a significant role in the pathogenesis of many cardiovascular disorders. However, because of the significant interactions of ET-1 with other vasoactive substances, its independent role needs to be further examined. Many clinical studies have demonstrated increased production and increased sensitivity to ET-1 in patients with systemic hypertension, acute ischemic syndromes, MI, CHF and pulmonary hypertension. Despite the available data from published clinical studies in patients with cardiovascular conditions, the precise role of ET-1 in the pathophysiologic processes of these conditions has not been established. The important question remains: Is ET-1 a marker, a mediator, or both, in these disorders? Clearly, we need to obtain some clear answers to this fundamental question before getting too enthusiastic and consumed with the clinical usefulness of ET receptor blockers in cardiovascular disorders.

REFERENCES

20. Cowburn PJ, Cleland JGF, McArthur JD, et al. Endothelin_B receptors are functionally important in mediating vaso-


