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Editorial

Effect of ACE Inhibitors on Endothelial Dysfunction: Unanswered Questions and Implications for Further Investigation and Therapy

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Summary. **Experimental studies have suggested that angiotensin-converting enzyme (ACE) inhibitors may have an important role in blocking the progression of and/or reversing endothelial dysfunction. The extrapolation of these experimental studies to the clinical situation has, however, been disappointing. Studies of forearm-mediated endothelial vasodilatation in patients with hypertension with captopril, enalapril, and cilazapril have been negative. The finding of the Trial in Reversing Endothelial Dysfunction (TREND) that the administration of quinapril to normotensive patients with coronary artery disease in part restores endothelial-mediated coronary vasodilation, as assessed by intracoronary administration of acetylcholine, has important implications for future therapy and raises several important questions. The differences in the TREND and previous studies of ACE inhibitors on endothelial dysfunction may be due to mechanistic differences in endothelial dysfunction in patients with coronary artery disease and hypertension. Although in general there has been a good correlation between endothelial dysfunction as assessed by forearm flow and coronary endothelial dysfunction as assessed by acetylcholine, these vascular beds may be affected differently by therapeutic interventions, especially with an ACE inhibitor, which may affect shear stress and angiotensin II formation in different vascular beds differently. Third, one needs to question whether the effect of quinapril on coronary endothelial dysfunction is a class effect or unique to quinapril. It will be necessary to test the effectiveness of other ACE inhibitors on coronary endothelial dysfunction in humans before concluding that the beneficial effects of quinapril are due to a class effect.**
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Experimental studies in a variety of animal species, disease models, and with a variety of angiotensin-converting enzyme (ACE) inhibitors have suggested that ACE inhibitors may have an important role in blocking the progression of and/or reversing endothelial dysfunction [1–6]. These studies have far reaching implications for the therapy of a number of important disease entities, including atherosclerosis and its consequences, hypertension, heart failure, and possibly diabetes mellitus. Endothelial dysfunction is thought to be an early common pathway for these and other diseases involving the vascular wall [7]. The production and release of nitric oxide (NO) by the normal endothelium is essential for the vasodilator effect of a number of physiologic and pharmacologic mediators, prevents the adherence and infiltration of monocytes onto and into the vascular wall, as well as preventing the adherence and activation of platelets with subsequent thrombosis [7–10]. Thus, the finding in experimental studies that ACE inhibitors can prevent or reverse endothelial dysfunction has given hope to the prospect that these agents might have an effect on the natural history of several diseases that affect the vascular wall, beyond blood pressure reduction, prevention of left ventricular hypertrophy, and ventricular remodeling.

The mechanism by which ACE inhibitors prevent and/or reverse endothelial dysfunction is speculative. Angiotensin II has been shown to be an important oxidant [11,12]. At physiologic concentrations angiotensin II has been shown to increase the production of superoxide ions and lipid peroxidase, as well as to increase macrophage-mediated oxidation of LDL cholesterol [11]. Free radical formation can interfere with the formation and/or release of nitric oxide from the endothelium [13]. Angiotensin II causes the oxidation of LDL cholesterol and facilitates the migration of LDL cholesterol into the vascular wall independent of its oxidation [11,14]. Angiotensin II has also been shown to stimulate various cytokines that attract monocytes and their infiltration into the vascular wall with subsequent foam cell formation [15]. Angiotensin II has also been shown to cause the release of endothelin [16], which in itself is an important mitogen and vasoconstrictor. Angiotensin II alone or in combination with endothelin also causes vasoconstriction, an

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increase in blood pressure, and shear stress, which could affect endothelial function [17]. ACE inhibitors, by blocking the formation of angiotensin II and/or by preventing bradykinin degradation, would tend to prevent these deleterious effects. Furthermore, ACE inhibitors have been shown to increase antioxidant defense mechanisms, such as superoxide dismutase [18], which would tend to prevent NO destruction.

The extrapolation of these experimental studies and theoretic considerations to the clinical situation has, however, been disappointing. For example, Creager and Roddy, in a study of patients with hypertension and endothelial dysfunction, could not demonstrate a beneficial effect of either captopril or enalapril administered for a 2 month period on endothelial-dependent forearm vasodilatation [19]. Similarly, Kiowski et al, could not demonstrate a beneficial effect of the ACE inhibitor cilazapril on endothelial-dependent forearm vasodilatation in patients with hypertension treated for 20 weeks [20]. Although the acute administration of captopril has been reported to reverse endothelial dysfunction in hypertensive patients [21] this study was done during the administration of the drug, while the studies by Creager and Roddy [19] and Kiowski et al. [20] were done after drug withdrawal to examine whether chronic drug administration had altered vascular structure and/or function.

In view of these negative studies of chronic ACE inhibition in humans, it is of interest to find that the ACE inhibitor quinapril administered for 6 months to nonhypertensive patients with coronary artery disease and endothelial dysfunction resulted in a significant reversal of coronary artery endothelial dysfunction. The Trial in Reversing Endothelial Dysfunction (TREND) studied the effect of quinapril 40 mg daily or placebo in 105 patients with coronary artery disease who at baseline coronary arteriography had demonstrable endothelial dysfunction, as evidenced by a loss of vasodilatation to the intracoronary administration of acetylcholine [22]. The patients in this study all had single or double-vessel coronary artery disease (>50% diameter stenosis), requiring nonsurgical revascularization and one adjacent major coronary artery with <40% diameter stenosis that had not been revascularized. Endothelial dysfunction had to be present in the adjacent coronary artery (a ≥5% reduction in mean lumen diameter or no response to acetylcholine) to be included. Patients with a history of hypertension could be included if they were controlled with a systolic blood <160 mmHg and a diastolic pressure of <90 mmHg. At the end of the 6 month follow-up period, the study drug was withdrawn for 3 days and endothelial dysfunction was reevaluated by intracoronary acetylcholine. Patients randomized to quinapril were found to have had a significant improvement in endothelial dysfunction of 12% compared with 0.8% at a dose of 10^{-4} ml/l of acetylcholine in those randomized to placebo ($p = 0.002$), without any significant effect of quinapril on systemic blood pressure.

Virdis et al. [23] have also shown that captopril 50 mg bid administered for 1 year to 16 patients with essential hypertension and angiographically normal coronary arteries, and then withdrawn for 2 weeks, improved forearm blood flow in response to acetylcholine infusion in a subset of eight patients who had a positive dipyridamole echocardiographic stress test, suggestive of microvascular coronary artery disease. They also found a baseline abnormality in forearm blood flow to the endothelial-independent vasodilator nitroprusside, as well as an improvement in forearm flow in response to nitroprusside after the year of therapy with captopril. This data suggests an improvement in vascular structure as a result of effective antihypertensive therapy rather than a change in endothelial function perse. A reversal of vascular structural abnormalities in patients with hypertension has been previously seen in patients treated with an ACE inhibitor [24] as well as a calcium channel blocking agent [25]. Although there may have been a structural change in the coronary vessels of patients in the TREND [22] study, they had a vasodilator response to nitroglycerin at baseline and did not show a change in their response to nitroglycerin after therapy with quinapril, suggesting that the primary effect of quinapril in this situation, in contrast to the study by Virdis et al. [23], was a change in endothelial function.

The positive findings in the TREND study in regard to an improvement in endothelial function in patients with coronary artery disease treated with quinapril compared with the negative findings in patients with hypertension treated with captopril, enalapril, and cilazapril [19,20,23], raise several important questions that will need to be answered before the data from the TREND study [22] can be placed in proper prospective.

First, the patients in the TREND study [22] all had angiographically proven coronary artery disease, whereas those in the studies by Creager et al. and Kiowski et al. [19,20] had hypertension without known coronary artery disease, and the patients studied by Virdis et al. had angiographically normal coronary arteries. While endothelial dysfunction has been found in most patients with hypertension, it is not found in all patients [26], whereas the situation in patients with angiographic evidence of atherosclerotic coronary artery disease appears to be more homogenous [27–29]. It is possible that endothelial dysfunction in patients with hypertension is in some way mechanistically different from that in early atherosclerosis. Shear stress may affect endothelial dysfunction and vessel structure quantitatively or qualitatively differently than lipid and/or other coronary risk factor–induced endothelial dysfunction. For example,

it could be postulated that oxidized LDL cholesterol and subsequent free radical formation might be more important in atherosclerosis-induced endothelial dysfunction, while shear stress may be the critical factor in patients with hypertension without the accumulation of LDL cholesterol in the vascular wall and that a reduction in blood pressure, rather than a reduction in LDL cholesterol, might be more important in this situation. Hypertension and atherosclerosis could also have quantitative and or qualitatively different effects on the formation, release, or effect of NO on smooth muscle cells.

Second, the studies by Creager and Roddy [19], Kiowski et al. [20], and Virdis et al. [23] focused on forearm-mediated endothelial dysfunction, while the TREND study [22] examined coronary endothelial dysfunction. In general, there has been a good correlation between endothelial dysfunction assessed by forearm flow and coronary endothelial dysfunction [27]. However, the endothelium in different vascular beds and in different sized arteries has been shown to differentially modulate the local conversion of angiotensin (AT) I to AT II [28]. Thus, it is possible that different vascular beds and segments within a vascular bed respond differently to different therapeutic interventions depending upon local ACE concentration and differential effects of the intervention on local shear stress. While it is convenient to study brachial artery endothelial dysfunction, one should be cautious in any extrapolation to other vascular beds without a careful prospective study of each intervention, especially with an ACE inhibitor which may affect shear stress and AT II formation in different vascular beds differently.

Third, one needs to question whether the effect demonstrated on the coronary endothelium by quinapril is a class effect of ACE inhibitors or is unique to quinapril or a particular group of ACE inhibitors. Quinapril is lipophilic and has been shown to be tightly bound to vascular ACE [32]. While on the basis of animal experiments one might predict that both lipophilic ACE inhibitors such as ramapril [3] and relatively hydrophilic ACE inhibitors such as enalapril [4], as well as sulfhydro-containing [2] and non–sulfhydro-containing ACE inhibitors [3] would be effective in humans, there may be important differences in the time and magnitude of their effectiveness. Thus, it will be necessary to test and demonstrate the effectiveness of other ACE inhibitors, such as the hydrophilic ACE inhibitors, on coronary endothelial dysfunction in humans before concluding that the beneficial effects of quinapril noted in the TREND study are a class effect.

While these and other more fundamental questions will need to be answered by careful prospective clinical research over the next several years, it is reasonable to predict that the results of the TREND study [22], if confirmed, will have important implications, at least for patients with coronary artery disease. One would anticipate that quinapril and possibly other similar ACE inhibitors will prove effective in preventing the development of new atherosclerotic lesions, progression of early atherosclerotic lesions, plaque rupture, and possibly thrombosis after plaque rupture, with a resultant decrease in ischemic events. A reversal of coronary endothelial dysfunction should also have an important effect on coronary vasomotor tone, with a consequent improvement in exercise and/or "silent" myocardial ischemia. Previous studies of ACE inhibitors have not, however, shown a uniform beneficial effect on angina pectoris. Cleland et al. [33], for example, found in fact that captopril increased the frequency of anginal episodes and use of nitroglycerin, possibly by inducing a coronary "steal." This and other studies testing the antiischemic effect of ACE inhibitors were, however, for the most part of relatively short duration, around 3 months. It may require longer term administration, possibly 6 months, before endothelial dysfunction is reversed as seen in the TREND study [22]. Conversely, as mentioned earlier, the ACE binding characteristics of quinapril [32] and possibly other lipophilic ACE inhibitors may make them unique. One might also postulate that the beneficial effects of quinapril on coronary endothelial dysfunction seen in TREND [22] would complement strategies such as LDL-cholesterol lowering. LDL-cholesterol lowering by decreasing the potential for oxidation of LDL cholesterol has been shown to prevent and/or reverse endothelial dysfunction both in animals and humans [34–36]. The reversal of endothelial dysfunction by LDL-cholesterol reduction is associated with a significant decrease in new coronary artery lesion formation, progression of minimal coronary artery disease, and ischemic events [37–39]. These mechanisms, as mentioned earlier, are common to ACE inhibitors, and hence ACE inhibitors could be postulated to have a synergistic or additive effect to LDL-cholesterol lowering strategies as well as an independent effect in patients in whom LDL cholesterol is not elevated or pathophysiologically of importance.

Whether or not these predictions will prove accurate will in part be answered in the near future by ongoing large-scale prospective studies, such as QUIET [40], HOPE [41], and PEACE [42], in which the effect of ACE inhibitors on ischemic events and mortality are being investigated. Regardless of the outcome of these studies, it is likely that the provocative findings in the TREND study [22], in conjunction with previous experimental studies, will stimulate further basic and clinical investigation, and the likelihood that we will have a better understanding and possibly new opportunities for the secondary and possibly primary prevention of ischemic heart disease and other diseases affecting the vascular wall in which endothelial dysfunction appears to be an early common pathway.

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