EDITORIAL COMMENT

Endothelium: A New Target for Cardiovascular Therapeutics*

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During the past two decades, it has been well established that vascular endothelium plays a pivotal role in maintaining vascular tone. It is of interest to note that the initial discovery of endothelial-dependent vasodilation by Furchgott and Zawadzki (1) in 1980 occurred as a result of an accidental finding due to an error of a research assistant. In their seminal paper, Furchgott and Zawadzki (1) reported that the thoracic aorta and a variety of other arteries obtained from experimental animals exhibited relaxation in response to acetylcholine (ACh) only if the endothelium was intact (1). Subsequent investigations in their laboratory revealed that ACh stimulated the release of a diffusible relaxing substance from endothelial cells, later referred to as endothelium-derived relaxing factor (EDRF) (2). It was not until 1986 that Furchgott and coworkers, as well as Ignarro et al., independently proposed that EDRF is nitric oxide (NO) (3,4).

The discovery of NO and other mediators released by the endothelium has subsequently led to tremendous interest of investigators in this field throughout the world. During the last 10 years, we have seen an exponential growth in our knowledge and understanding of the role of endothelial dysfunction in a variety of cardiovascular conditions (5–20). It has been demonstrated that endothelial dysfunction might indeed be the initiating event in the process of atherosclerosis and vascular remodeling, which subsequently leads to clinical coronary artery disease (CAD) (21,22).

Accordingly, there has been an ongoing, aggressive search for therapeutic choices suitable for reversing endothelial dysfunction with the hope that such therapeutic intervention, if instituted early in the course of the disease, might prevent and/or modify the subsequent risk of clinical disease and related cardiac events (6–25). The magnitude of interest in this area can be best illustrated by the large number of articles published on the endothelium and related issues from 1997 to 1999. A recent Medline search revealed that, on average, during this period in excess of 1,200 articles per year were published in the English language regarding investigations dealing with vascular endothelium in humans, and, of these, nearly 550 articles specifically describe the effects of various cardiovascular therapeutic agents on the endothelium. Indeed, the time has come to recognize the endothelium as an important and new target for cardiovascular therapeutics. The article by Anderson et al. (26) in this issue of the Journal comparing the effects of four cardiovascular drugs on endothelial function in patients with CAD is a further testament to the growing interest in this area.

The BANFF study. The Brachial Artery Normalization of Forearm Function (BANFF) study (26) was a well-designed, randomized, crossover trial examining the effects of quinapril, enalapril, losartan and amlodipine on flow-mediated vasodilation of brachial artery in 80 patients with proved CAD. The investigators selected two different angiotensin converting enzyme (ACE) inhibitors because of varying tissue affinities. Compared with enalapril, quinapril has a relatively higher affinity for tissue ACE, and therefore it could potentially be more effective in restoring endothelial function (12). Losartan was chosen because angiotensin type 1 (AT1) receptor blockers are gaining in popularity in clinical practice. Unlike ACE inhibitors, these drugs are extremely well tolerated and, regardless of the source, they block the effects of angiotensin II at the receptor level. Furthermore, theoretically the comparison of the effects of AT1 receptor blockers with those of ACE inhibitors provided the opportunity to indirectly evaluate the therapeutic role of bradykinin potentiation by ACE inhibitors in improving endothelial function. Although the study design is complex due to the randomized crossover of each patient to at least three of the four study medications, the investigators were successful in obtaining the ultrasound data for 194 (80%) of the 240 assigned treatment periods in the study population (26). It is also important to recognize that, although patients with left ventricular (LV) dysfunction, uncontrolled hypertension, type I diabetes mellitus, uncontrolled hypercholesterolemia (total cholesterol >6 mmol/l) and active smoking were excluded, the enrolled patients did have some of the usual characteristics seen in patients with CAD (e.g., 50% had history of hypercholesterolemia, and 26% had hypertension) (26). One of the important features of this study is that effects of several cardiovascular drugs could be evaluated by noninvasive ultrasound technique in a reproducible manner. This is perhaps the first large study of its kind and paves the way for future clinical trials with a number of different cardiovascular drugs in various cardiac disorders where endothelial functions are perturbed.

The results of the BANFF study reported by Anderson et al. (26) in this issue of the Journal reveal that, in this
comparative trial of four vasoactive drugs, only treatment with quinapril was associated with significant improvement in flow-mediated vasodilation of the brachial artery in patients with proved CAD. These findings are consistent with the results of the Trial on Reversing Endothelial Dysfunction (TREND) (9), which revealed significant improvement in coronary artery vasoreactivity after six months of treatment with quinapril. However, in the TREND study (9), treatment with quinapril was compared only to placebo, which still left unanswered the question of the importance of tissue affinity of various ACE inhibitors in improving endothelial function.

**Is tissue affinity of ACE inhibitors important?** The results of the BANFF study have provided some answers to this important question by comparing the effects of enalapril (an ACE inhibitor with low tissue affinity) with those of quinapril (an ACE inhibitor with high tissue affinity) (12,26). The fact that, by contrast to the beneficial effects of quinapril noted in the study, the treatment with enalapril did not show any significant change in the flow-mediated dilation (FMD) would tend to suggest that drugs with higher tissue affinity for ACE are likely to be more effective in restoring endothelial function (12,13,26). However, caution is needed before definitive conclusions are drawn from these results. It is conceivable that a higher dose of enalapril than the one selected in the BANFF study could be more effective (16–18). That, however, seems unlikely because in another recent study, Hornig et al. (13) demonstrated that, compared with quinapril, increasing doses of enalaprilat (up to 20-fold dose of quinapril) given intraarterially did not produce significant improvement in flow-dependent (endothelium-mediated) dilation (FDD) of radial artery in patients with chronic heart failure who had impaired FDD at baseline. By contrast to the lack of efficacy with enalaprilat, treatment with quinaprilat given intraarterially was associated with improvement in the FDD (13). These data provide support for the differential effects of the two ACE inhibitors observed in the BANFF study and suggest that drugs with higher affinity for tissue ACE might indeed be more effective in improving endothelial function (12,26).

It is, however, important to recognize that there are other potential reasons for the superior effects of ACE inhibitors on endothelial function improvement. It is well known that ACE inhibitors also block the effects of kininase II, the enzyme responsible for the breakdown of bradykinin (15,21,22,32). By preventing the degradation of bradykinin, ACE inhibitors make more bradykinin available, which in turn results in increased synthesis and release of NO from endothelial cells (15,29). Indeed, many investigators have claimed the bradykinin potentiating effects of ACE inhibitors to be a primary reason for their favorable effects on endothelial function (15,29). However, until recently no direct evidence was available to support this concept. The recent study by Hornig et al. (32) evaluated the role of bradykinin in mediating the vascular effects of ACE inhibition with quinaprilat in humans. In order to evaluate the specific role of bradykinin, FDD was evaluated when quinapril was given alone and in combination with a bradykinin (B2) receptor blocker, icatibant (32). The results of this study showed a significant improvement in FDD with quinapril, which was blocked by icatibant, suggesting that the beneficial effects of ACE inhibitors on endothelial function are indeed mediated, at least in part, by bradykinin (32). There is also other evidence that had shown increased plasma levels of bradykinin with ACE inhibitors in humans (33).
The role of ACE gene polymorphism. Another interesting aspect of the BANFF study is that Anderson et al. (26) evaluated the effects of study drugs based on ACE gene polymorphism. Although still somewhat controversial, it has been suggested that the DD genotype is associated with increased risk of MI, which might be related to higher levels of circulating and tissue ACE activity associated with the deletion allele (19,34,35). Because of the higher levels of tissue ACE activity in the DD genotype, it would have been reasonable to predict that, in the BANFF study, the noted beneficial effects of quinapril would be more pronounced than in the ID or II genotype (26,34–36). To the contrary, Anderson et al. (26) report that the improvement in FMD with quinapril was restricted to the ID and II genotypes, and minimal, if any, improvement was noted in the DD genotypes. The precise reason for these counterintuitive findings is difficult to ascertain; however, several possibilities exist. First, it is not clear from the results reported what percentage of patients were in each group in the BANFF study (26). Based on population genetics, it would be expected that only 25% (even lower in Chinese) of the cohort would be DD genotype, whereas the other 75% would be ID or II, thereby making the numbers with the DD genotype quite small, especially in light of the small magnitude of change in FMD (26,37). Furthermore, it is also conceivable that patients with the DD genotype had such high levels of tissue ACE activity that they attenuated the effects of quinapril (26). It is also conceivable that such excessive tissue ACE activity results in high oxidative stress (30,31). It has also been shown recently that individuals with the DD allele have a shorter half-life of bradykinin, which could explain the lack of improvement in FMD, as it depends upon the amount of NO released by the endothelial cells (38). Whatever the reason might be, these findings relating the improvement in endothelial function to ACE genotype do raise important questions that should be further investigated in future trials.

Clinical relevance of the findings. The important question for the clinician is what do these findings mean in clinical practice? The clinical relevance of these findings is indeed difficult to establish for several reasons. Although some studies have shown that response of the brachial artery to various vasoactive substances is closely related to response of the coronary arteries, this has not been convincingly established (7,8). Furthermore, it has also been shown that different vascular beds can demonstrate varying responses to vasoactive stimuli, which makes it difficult to translate the clinical relevance of many of the studies in peripheral circulation. Finally, perhaps the major limitation is that data are lacking regarding the clinical impact of endothelial dysfunction and its subsequent improvement. We have little, if any, data to suggest that the presence of endothelial dysfunction as assessed in the BANFF study is predictive of future vascular events (26). Because of the lack of such data, and no information regarding the clinical impact of improvement in endothelial function, it is difficult to assess the clinical significance of the findings reported. Despite these limitations, it would appear reasonable to conclude that, based on results of the BANFF study, ACE inhibitors such as quinapril, with higher affinity for tissue ACE, appear to be superior to those with lower tissue affinity (26). Although clinical studies had been lacking in this area, the recent results of the Heart Outcome Prevention Evaluation (HOPE) study demonstrating significant reduction with ramipril (also a high tissue affinity ACEI) in all cardiovascular end points in high-risk patients are a testament to the clinical efficacy of these agents (39). It is important to note that in the HOPE study, treatment with ramipril was compared only with placebo, thereby leaving unanswered the question of the comparative efficacy of various ACE inhibitors with varying tissue affinity in the clinical setting. It is doubtful that any such study will be performed soon, so clinicians will have to make their own judgments from the available data.

Future direction. Although it is exciting to read the results of the BANFF study, there is need for further research in this area. First, we need to have more studies that carefully examine the relationship between the vascular response to various stimuli in the peripheral circulation and the response observed in the coronary circulation in the same individuals. Before any significant clinical emphasis is given to the beneficial effects of various cardiovascular therapies on endothelial function, it is essential to demonstrate that the presence of endothelial dysfunction is predictive of subsequent risk of cardiovascular events. Finally, we need randomized clinical trials to critically examine the effects of various therapies (that improve endothelial function) on clinical outcome. Rapidly emerging interest regarding the effects of cardiovascular therapies on endothelial function makes it crucial for such trials to be conducted soon so that clinicians can prescribe the appropriate therapy based on evidence-based medicine.

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