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Angiotensin-converting Enzyme Inhibitors and Endothelial Function

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"Endothelial cells…(are)…more than a sheath of nucleated cellophane…" *Lord Florey, 1966*

We have now become quite accustomed to the fact that we can intervene with pharmacological therapy to modify the function of many organs or tissues. In fact, some interventions, such as the administration of a beta-blocker to a patient with angina or a myocardial infarction, have become so routine that we no longer pause to think that we are modifying cardiac chronotropic, lusitropic, and inotropic function every time we prescribe one of these agents. The same can be said of drugs that modify thyroid function, gastric secretory function, or suppress the immune system – to cite but a few of the interventions that are now routine in our therapeutic armamentarium.

In contrast, the same cannot be said of the endothelium, which, as shown by the not-so-old quotation from Lord Florey, is not generally considered an organ whose dysfunction can cause disease that can be reversed or ameliorated by specific interventions aimed at restoring or normalizing its function. However, the realization seems to be growing that the preservation of normal endothelial function is critical in maintaining vascular and circulatory homeostasis and that the loss of that function, as a primary or secondary process, may be a critical step in the pathogenesis of many common diseases, such as atherosclerosis or hypertension, as well as uncommon ones, such as hemolytic uremic syndrome or thrombotic thrombocytopenic purpura. In fact, in 1992, Mendelsohn and Loscalzo coined the word *endotheliopathy* to refer to "a clinical entity in which endothelial pathology provides an explanation for observed clinical abnormalities and for which evidence of endothelial dysfunction has accumulated in biochemical and clinical studies".

The possibility that endothelial dysfunction can cause disease should really come as no surprise, given the many important functions of the endothelium. Endothelial cells are both sensory and effector cells that interface with the bloodstream and can sense and respond to changes in flow, pressure, and levels of inflammatory cytokines or circulating hormones. The endothelium can secrete or activate mediators that regulate cell growth, cell migration and adhesiveness, apoptosis (programmed cell death), and composition of the extracellular matrix. Normally functioning endothelium would promote vasodilation, inhibit smooth muscle cell growth, impede the adhesion of leukocytes and platelets, and prevent intravascular thrombosis, while maintaining the ability to respond rapidly to damage to vascular integrity and hemorrhage with the appropriate defense mechanisms of vasoconstriction and thrombus formation. In contrast, dysfunctional endothelium would be persistently vasoconstrictive, prothrombotic, and proproliferative. The intricate integration of these mechanisms is such that vasoconstrictors, such as endothelin and angiotensin II, generally promote smooth muscle cell growth and migration, whereas vasodilators like nitric oxide (endothelial-derived relaxing factor) exhibit strong growth-inhibiting and antithrombotic effects (Table 1).

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Table 1: Vascular effects of endothelial-derived vasoactive factors	
Nitric oxide	**Endothelin/angiotensin II**
Vasodilator	Vasoconstrictors
Antithrombotic	Prothrombotic
Anti-inflammatory	Pro-inflammatory
Antiproliferative	Proproliferative
Antioxidant	Pro-oxidant
Anti-atherogenic	Pro-atherogenic

The tissue angiotensin system

The renin-angiotensin system plays a critical role in cardiovascular homeostasis by its participation in electrolyte balance, fluid balance, and control of blood pressure. Renin is an enzyme whose production in the kidney is regulated by changes in renal perfusion or blood flow. Renin exerts its action on angiotensinogen, a substrate produced in the liver, converting it to angiotensin I, an inactive peptide. Angiotensin-converting enzyme (ACE) catalyzes the conversion of angiotensin I to the potent vasoconstrictor peptide angiotensin II, which stimulates the production of aldosterone, a hormone that promotes salt retention.

Besides this well-known endocrine system, the production of angiotensin plays an important role at the local tissue level, where it can exert powerful paracrine and autocrine effects. This local system has been called the tissue angiotensin system as it is found in many tissues including, perhaps most importantly, the heart and vasculature. Through this system, ACE plays a critical role in the regulation of vasoactive substances in vascular tissues, including the endothelium.

From pharmacological and clinical studies, it is clear that ACE inhibitors exhibit additional local actions that are not related to hemodynamic changes and cannot be explained entirely by interference with the renin-angiotensin system and the inhibition of angiotensin II formation. ACE is identical to kininase II, which inactivates the nonapeptide bradykinin and other kinins. Therefore, some beneficial effects of ACE inhibitors may be due to the protection of locally produced bradykinin, particularly at the endothelial level. The accumulation of bradykinins elicits the production of vasodilators, such as nitric oxide, prostacyclin, and the diffusible endothelium-derived hyperpolarizing factor (EDHF).

The release of these endothelial vasodilators is impaired (or counterbalanced by the release of chemical or functional antagonists) in conditions characterized by endothelial dysfunction, such as atherosclerosis, hypertension, diabetes, hyperlipidemia, and reperfusion injury. Therefore, ACE inhibitors may have the potential to normalize endothelial function by decreasing the production of angiotensin II and potentiating the action of kinins.

Improving endothelial function with ACE inhibitors

The results of several clinical trials, including the Studies of Left Ventricular Dysfunction (SOLVD), the Survival and Ventricular Enlargement (SAVE) study, the Trandolapril Cardiac Evaluation (TRACE) trial, the Acute Infarction Ramipril Efficacy (AIRE) study, and the Survival of Myocardial Infarction Long-term Evaluation (SMILE) study, have provided abundant evidence that interference with the renin-angiotensin system by administration of an ACE inhibitor decreases the risk of myocardial infarction and sudden cardiac death in patients with coronary artery disease and left ventricular dysfunction. Of note, risk reduction was generally proportional to the duration of ACE-inhibitor therapy and initial risk of the specific population under study. Although the favorable impact of ACE inhibition on the risk of coronary events could be partially due to the hemodynamic effects of vasodilation, it has been postulated that another factor that may contribute to this significant and consistent risk reduction is the protective effect that ACE inhibitors appear to have on the endothelium.

Trials evaluating surrogate outcomes

Due to the realization, derived from studies in animal models, that it was possible to attempt to correct endothelial dysfunction and affect clinical outcomes, a number of clinical trials were initiated to evaluate the effects of ACE inhibitors on surrogate endpoints in carotid or coronary atherosclerosis. The outcomes evaluated in these trials have included endothelial function as assessed by vascular response to intracoronary acetylcholine; atherosclerotic progression in the carotid artery as evaluated by ultrasonography; and progression of coronary artery disease as measured by quantitative coronary angiography. A favorable impact in those surrogate outcomes has been demonstrated with cholesterol-lowering therapy and is generally accepted as a demonstration of efficacy of the intervention. Three double-blind, randomized trials with ACE inhibitors that follow such surrogate outcomes are currently in progress: the Study to Evaluate Carotid Ultrasound Changes with Ramipril and Vitamin E (SECURE), the Prevention of Atherosclerosis with Ramipril Therapy-2 (PART-2) study – also designed to assess carotid atherosclerosis – and the Simvastatin and Enalapril Coronary Atherosclerosis Trial (SCAT).

A fourth study, the Trial on Reversing Endothelial Dysfunction (TREND), is already complete; its results were published in 1996. TREND was a randomized, double-blind, placebo-controlled, multicenter, international trial that evaluated the effect of an ACE inhibitor, quinapril, on endothelial dysfunction in the epicardial coronary arteries of normotensive patients without left ventricular dysfunction. The primary endpoint of the study was the assessment of endothelium-dependent vasodilation by intracoronary acetylcholine infusion and quantitative coronary angiography. In a Doppler ultrasound substudy, the effect of quinapril on blood flow in coronary resistance vessels was evaluated by measurement of coronary flow velocity after intracoronary acetylcholine and adenosine infusion. Patients who had undergone a successful coronary intervention were randomized to receive either quinapril or placebo, which were begun 72 hours later. Quinapril was initiated at a dose of 10 mg/day and gradually increased to a target of 40 mg/day.

Six months later, treatment was discontinued for at least three days and coronary angiography and acetylcholine infusion were repeated to evaluate the endothelial-dependent vasomotor function in the target segment of the coronary artery. At baseline, acetylcholine caused similar decreases in coronary-artery diameter in both placebo and quinapril groups. This finding was consistent with endothelial dysfunction, as the normal endothelium should respond to acetylcholine with the release of vasodilators, the most important of which is nitric oxide. In contrast, in the dysfunctional endothelium, acetylcholine fails to elicit that response, acting instead on the muscarinic receptors of the vascular smooth muscle cells, which mediate vasoconstriction. After 6 months of therapy, decreases in arterial diameter similar to those at baseline were detected in the 54 placebo recipients. In contrast, the constrictive response to acetylcholine significantly diminished ($p<0.014$) at follow-up in the 51 patients who received quinapril.

The Doppler ultrasound substudy of coronary microcirculation enrolled 14 patients. Endothelial function was expressed as a ratio: blood flow response to the endothelium-dependent vasodilator acetylcholine/blood flow response to the direct-acting vasodilator adenosine. At baseline, these ratios were similar in placebo and quinapril groups. After 6 months, coronary flow response to acetylcholine alone improved with quinapril but diminished in the placebo group.

Trials evaluating clinical outcomes

Several trials have been performed or are in progress to evaluate the impact of ACE inhibition on clinical coronary outcomes in patients without left ventricular dysfunction. The Quinapril Ischemic Event Trial (QUIET) was a prospective, double-blind, placebo-controlled study that assessed the ability of quinapril to reduce the rate of cardiac ischemic events and to slow or prevent the development of coronary artery atherosclerosis, as assessed by serial angiography in normolipedemic patients with preserved left ventricular function. QUIET was the first large-scale investigation of the potential anti-atherogenic and anti-ischemic effects of ACE inhibitors. The study began in 1991 and recruitment of 1740 patients from 38 centers in the United States, Canada, and Europe was completed in 1992.

Within 72 hours of successful coronary angioplasty or atherectomy, patients were randomized to 20 mg of quinapril or placebo daily and followed for 3 years. At the end of the study period, coronary angiography was repeated. The efficacy of drug therapy was evaluated primarily on the basis of time-to-first-cardiac-ischemia endpoint, defined as sudden cardiac death, death within 28 days of proven myocardial infarction, nonfatal myocardial infarction, angina requiring hospitalization, coronary artery bypass grafting, or interventions such as angioplasty, atherectomy, or stenting.

The results of QUIET were presented last year at the European Society of Cardiology meeting in Birmingham, United Kingdom. Disappointingly, 20 mg/day of quinapril had no effect on the progression of coronary atherosclerosis or the incidence of coronary events during the study period, in contrast to consistent observations in previous trials of ACE inhibitors in patients with left ventricular dysfunction. The odds ratio for the primary composite endpoint of ischemic events was 1.04 (95% confidence intervals 0.89-1.22). For the hard endpoints of death, myocardial infarction, and resuscitated ventricular fibrillation/ventricular tachycardia, there was a trend in favor of quinapril, with a hazard ratio of 0.87 (quinapril, 48, versus placebo, 54) but, because the event rate was so low, the confidence limits were very wide (0.59-1.29). As well, no significant difference between the two groups was seen in the angiographic substudy, in which 477 patients were assigned to quantitative coronary angiography to evaluate progression of atherosclerosis. Some 47% of quinapril-treated patiernts were defined as progressors, compared to 49% of placebo-treated patients. Quantitative analysis of minimum lumen diameter demonstrated less progression in the quinapril group, particularly in patients with severe stenosis, but it failed to reach statistical significance.

The results of QUIET did not corroborate those of TREND, in which quinapril significantly ameliorated the sur-

rogate endpoints of endothelial dysfunction in patients with coronary artery disease and preserved left ventricular function. Does the failure of QUIET to demonstrate these benefits refute the endothelial-dysfunction hypothesis? Hardly. QUIET may be underpowered because of the high number of nonevaluable patients – 540 of 1740 patients were lost due to protocol violation – together with the low rate of hard endpoints. As well, the dose of quinapril used in QUIET may have been too low (20 mg daily vs 40 mg daily in TREND). The 20-mg dose was chosen for QUIET due to concerns that a higher dose may induce hypotension in this normotensive population. These concerns may be unfounded, given that, in TREND, which started at a later date, no significant difference in diastolic or systolic blood pressure was found in normotensive coronary patients taking placebo or 40 mg of quinapril.

Additionally, ACE inhibition may not be the only therapy required to restore endothelial function and achieve an improvement in clinical endpoints. In fact, it can be argued that the well-established benefits of lipid-lowering therapy in primary and secondary prevention of coronary disease is, in no small measure, due to the ability of that intervention to restore many parameters of normal endothelial function, which are known to be profoundly disturbed by hyperlipidemia. Although lipid-lowering therapy with several agents have demonstrated some benefits in surrogate endpoints, the powerful HMG-CoA reductase inhibitors or "statins" have settled, once and for all, the validity of the cholesterol hypothesis. Perhaps these considerations will also apply to the tissue angiotensin system. Of note, the marked discordance between the quantitatively slight benefits of lipid lowering in surrogate endpoints, such as the progression of atherosclerosis in regression trials, and the dramatic improvement in clinical endpoints has been attributed chiefly to an improvement in endothelial and vascular function that results in lesion stabilization and a lower incidence of plaque rupture and acute coronary thrombosis.

Ongoing trials

Several other trials have been initiated to evaluate the effect of ACE inhibition and other interventions on clinical coronary outcomes in patients without left ventricular dysfunction. The Heart Outcomes Prevention Evaluation (HOPE) trial is a randomized, double-blind, placebo-controlled, international study of over 9,500 patients with coronary disease. The active treatment group is receiving ramipril, with or without vitamin E, for up to 4 years. Primary outcomes include the rates of cardiovascular death, stroke, and myocardial infarction.

The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is a study in high-risk patients who are assigned to several antihypertensive therapies, including lisinopril, with or without concomitant pravastatin. Endpoints include fatal coronary disease, nonfatal MI, and all-cause mortality. ALLHAT has been ongoing for 2 years. The anticipated mean duration of follow-up is 6 years.

The Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) study will evaluate whether trandolapril affects the rates of myocardial infarction and cardiovascular death in 14,000 patients with chronic coronary artery disease and preserved left ventricular function.

Summary

Clinical trials with ACE inhibitors in patients with left ventricular dysfunction have demonstrated reductions in the incidence of coronary outcomes that appear to exceed the results expected from the hemodynamic effects alone, such as blood-pressure lowering. Therefore, it would appear likely that additional mechanisms of action are involved. One attractive possibility is that an improvement in endothelial function by ACE inhibition may be responsible for the favorable, and somewhat unexpected, effect on clinical coronary outcomes. Improved endothelial and vascular function could lead to atherosclerotic lesion stabilization and protection against plaque rupture and coronary thrombosis.

Confirmation of the endothelial-dysfunction hypothesis would have immense implications for cardiovascular disease – analogous perhaps to those of the confirmation of the cholesterol hypothesis. To date, available data are insufficient to determine whether ACE inhibitors will join lipid-lowering therapy in causing the regression or stabilization of atherosclerosis and in reducing coronary morbidity and mortality. Several ongoing trials may provide badly needed answers over the next few years. For hypertensive, normolipidemic patients with preserved left ventricular function who are at high risk for coronary events, ACE-inhibitor therapy that can improve endothelial function and plaque stability may provide a new and important measure of cardiovascular protection. Additionally, ACE inhibitors may constitute an important complement to the endothelial and vascular effects of lipid-lowering agents in hyperlipidemic patients.

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Upcoming Scientific Meetings

29 Jun-3 Jul 97
37th Annual Conference of Cardiovascular Disease Epidemiology and Prevention
Montreal, Quebec, Canada
(American Heart Association)
Tel.: 214-706-1100

29 Jun-3 Jul 97
4th International Conference on Preventive Cardiology
Montreal, Quebec, Canada
(Jerry Lou and Associates)
Tel.: 514-878-2530

30 Jun-3 Jul 97
2nd International Meeting on Interventional Cardiology
Eilat, Israel
(Kenes)
Tel.: +972 3 5140014

2-5 Jul 97
18th European Section Meeting of the International Society for Heart Research
Versailles, France
(Agence Ormes)
Tel.: +33 1 46 48 4648

20-24 Jul 97
12th International Interdisciplinary Conference on Hypertension in Blacks
London, England
(International Society on Hypertension in Blacks, Inc.)
Tel.: 404-875-6263

23-27 Jul 97

19th Annual Meeting of the International Society for Heart Research American Section: Cardiovascular
Injury, Repair, and Adaptation
Vancouver, British Columbia, Canada
(Venue West Conference Services Ltd.)
Tel.: 604-681-5226

Abstracts of interest

Relationship between angiotensin-converting enzyme levels and blood pressure: differences between african-americans and whites:

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Previous studies have demonstrated that African-Americans (AA) have lower plasman renin activity (PRA) than whites but the corresponding differences in serum angiotensin-converting enzyme (ACE) level have not been well studied. We examined the cross-sectional relationship between PRA, ACE and blood pressure (BP) in 110 AAs and 183 whites who were not on BP lowering medications. Three BP readings were during a clinic visit. PRA was assayed by radioimmunoassay and serum ACE levels were measured by spectrophotometry. Mean systolic and diastolic BPs were 123.9 and 77.7 mm Hg for AAs and 122.6 and 77.1 mm Hg for whites, respectively. PRA was significantly lower in AAs compared to whites (0.92 vs. 1.26 ng/ml/hr, respectively, $p<0.05$), but the corresponding values for ACE levels were similar (28.8 vs 29.6 unit/L, respectively). Renin activity was significantly and inversely associated with systolic (ß=3.1 mm Hg/ng/mL/hr in AAs and ß=2.1 mm Hg/ng/nL/hr in whites) and diastolic BP (ß=1.9 mm Hg/ng/mL/hr in AA's, and ß=0.7 mm Hg/ng/mL/hr in whites). ACE, however, was inversely associated with BP in AAs but positively associated with BP in whites. The interaction between ACE and race was significant for diastolic ($p=0.02$) BP and remained after adjustment for age, gender, body mass, heart rate, alcohol consumption, urinary excretion of sodium and potassium, and plasma renin activity. It was of borderline significance for systolic ($p=0.06$). These findings suggest that the association between ACE and BP is different in AAs and whites and may reflect underlying ethnic differences in regulation of BP.

Excerpted from *Canadian Journal of Cardiology*, 1997;13 (supplement B).

Influence of long-term therapy with ace inhibitors on clinical course and life quality in patients with congestive heart failure

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42 patients with congestive heart failure (CHF) of II-III NYHA class (ejection fraction, EF<45%) were treated with enalapril during 3 years. In all the patients the improvement of general condition was observed as well as the reduction of dyspnoe, decrease of nitrates and glycosides requirements, amelioration in respect to depression, mental and emotional life, fear feeling, dream quality. The tolerability of household physical activities was also improved. The EF increased by 47% (from 38.5% to 52.9%). In bicycle test the physical load tolerability increased by 50% (the load time increased from 206 sec to 310 sec). The number of patients who stopped the exercise test due to dyspnoe reduced twice while the number of patients, who reached the submaximum pulse rate increased significantly. In isometric physical load the improvement of cardiac output reaction was observed. During the observation period 8 patients (19%) died, that is much lower as compared to the average mortality rate for these NYHA classes (30% per year according to the literature data). Only one of them died due to the aggravation of CHF, one due to the ischemic stroke, the rest suddenly. The side effects occurred in 6 patients (1- allergy, 1 - cough, 4 - hypotension and dizziness in the beginning of the therapy). Thus, the long-term enalapril therapy prevents the CHF progression and improves the life quality of the patients with CHF.

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Prevention of remodeling after myocardial infarction by reperfusion and angiotensin converting enzyme inhibition

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Left ventricular remodeling can be attenuated by reperfusion of the infarct related artery or treatment with an ACE inhibitor. The purpose of this study was to detect the value of the ACE inhibitor enalapril on ventricular remodeling in patient's aggressively treated with thrombolysis and PTCA.

Methods: Seventy-one patients with an anterior infarction received in a double blind fashion 20 mg enalapril (E) or placebo (C), starting 48 hours after entrance in hospital. Trial medication was continued for 48 weeks. The influence of E on left ventricular end-diastolic volume (LVEDV) was assessed with echocardiography (ECHO).

Results: LVEDV increased during follow-up from 48.2 ± 9.9 ml/m2 to 59.4 ± 17.0 ml/m2 in C pts and from 61.9 ± 22.7 ml/m2 for E treated pts. The increase of volume was significant ($p<0.001$), but no difference between E and C could be observed. However, in patients with more than 70% stenosis in the coronary vessel an attenuation of remodeling by E compared to C could be observed. In this group (n=42) LVEDV increased during 1 year follow up from 48 ± 9.6 to 60.3 ± ml/m2 in C pts and from 47.0 ± 13.3 to 53.7± 17.9 ml/m2 for E treated pts ($p<0.03$) for E vs C). The difference remained after correction for infarct size. E had no influence on remodeling in pts without a > 70% stenosis (n=16) or in pts in which coronary anatomy was unknown (n=15).

Conclusions: In a patient population aggressively treated to reopen the infarct related vessel, addition of an ACE inhibitor only influenced the process of infarct expansion and remodeling in those patients who had after intervention a severe stenosis in the coronary artery.

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