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Scientific Update™

The renin-angiotensin system, endothelial dysfunction, and vascular reactivity: The role of angiotensin-converting enzyme inhibition

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The renin-angiotensin system plays a fundamental role in cardiovascular homeostasis. Genetically determined differences within this system may place some individuals at higher risk for the development of cardiovascular disease. Angiotensin-converting enzyme (ACE) and endothelial dysfunction (a frequently observed and early event in the atherosclerotic process) are closely related. In the clinical setting of coronary artery disease, endothelial dysfunction – and its related nitric oxide and bradykinin deficiency and angiotensin II excess – can be lessened with the use of ACE inhibitors. In particular, administration of agents that have a high affinity for tissue ACE (e.g., quinapril) can effect important changes in the functional integrity of the endothelium.

The renin-angiotensin system and CAD

In abstract presentations at the 47th Annual Scientific Session of the American College of Cardiology, the importance of the renin-angiotensin system and its impact upon the vascular endothelium in coronary artery disease (CAD) was discussed. In addition, a poster presentation of the Canadian-based Brachial Artery Normalization of Forearm Function (BANFF) study elucidated the potential role of an angiotensin-converting enzyme (ACE) inhibitor with high tissue affinity in the treatment of CAD patients with endothelial dysfunction.

The renin-myocardial infarction link

Several epidemiologic studies have examined the relationship between plasma renin levels in patients with hypertension and the risk for ischemic events. For example, Alderman et al[1] described a fivefold increase in the risk of myocardial infarction (MI) among 1,717 hypertensive subjects with high versus low renin profiles, and this effect was independent of other established cardiovascular risk factors such as age, smoking status, cholesterol and glucose levels, and blood pressure levels. Blumenfeld et al[2] extended these findings in 349 consecutive patients hospitalized with suspected MI. Although those with confirmed MI (n=73) had baseline characteristics (such as age, systolic and diastolic blood pressure) similar to those without confirmed MI (n=276), the mean plasma renin level at entry was threefold higher in the former group (3.2 vs. 1.2 ng/mL/h, $p<0.0001$). In a multivariate analysis, plasma renin level was the predominant independent risk factor for acute MI ($p<0.00001$), giving more support to the concept that excessive activity of the renin system is associated with MI.

Genetic studies

A growing body of evidence indicates that locally generated vasoactive substances such as angiotensin II and nitric

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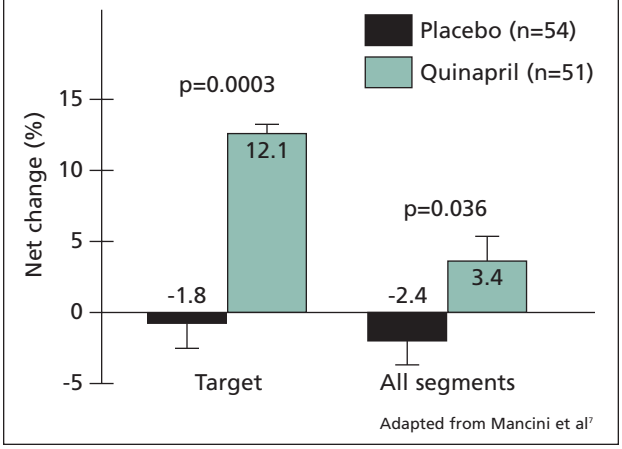
oxide (NO) are important determinants of the natural history of vascular disease. In particular, angiotensin II might promote vascular lesion formation by increasing vascular cell population through increased cell growth and decreased programmed cell death (apoptosis), and by altering the extracellular matrix composition.[3] A genetic polymorphism of the angiotensin II type-1 receptor is thought to be involved in the development of various cardiovascular diseases; however, the underlying mechanism remains unclear.

Van Geel et al[4] explored the effects of the angiotensin II type-1 receptor polymorphism on the response of vascular contraction to angiotensins I and II. They used excess segments of the internal mammary artery (IMA) obtained from 121 patients undergoing elective coronary artery bypass surgery. Contractions of arterial rings were measured in organ-bath experiments and genotypes were assessed using a standard polymerase chain reaction. The maximum contraction responses were seen in the IMAs of those patients with the CC (as compared to the AA or AC) genotype, indicating altered angiotensin II responsiveness in this subgroup of coronary artery disease patients.

To further explore the genetic role of the renin-angiotensin system, the same group of investigators[5] studied the influence of the ACE genotype on functional vascular responses to angiotensin II, using excess segments of the IMA in 137 patients undergoing elective coronary artery bypass surgery. Previously, Cambien et al[6] had demonstrated that the ACE-DD genotype, which identifies individuals with higher levels of circulating ACE, was more prevalent in middle-aged men with previous MI (n=610) than in a case-matched control group (n=733, p=0.007). This raises the possibility of ACE as a genetic predictor of CAD and its sequelae. In the study by Van Geel,[5] patients with the DD genotype (n=38) had increased plasma ACE-activity levels compared to patients with the II or ID genotype (n=99) (26.9±1.2 vs. 21.3±1.0 U/L, p=0.002). Functional vascular responses to angiotensin II in organ baths were decreased in the DD genotype group (36.2±5.1% vs. 55.7±4.6%, expressed as the percentage of response to phenylephrine; p=0.01). Thus, the ACE-DD genotype in patients with CAD appears to be associated with a chronic increase in plasma ACE activity and a decreased vascular response to angiotensin II; this would suggest that greater tissue ACE inhibition would be required to inhibit the activated renin-angiotensin system.

Figure 1: Net change (%±SE) in target and all segment response at an acetylcholine dose of 10^{-4} mol/L after 6 months in the TREND study



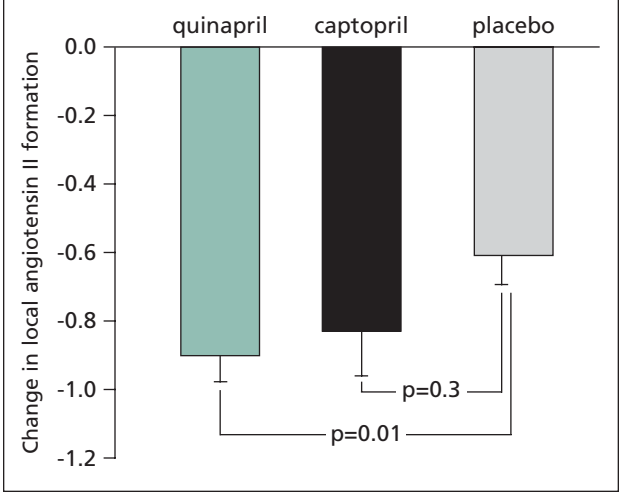
Adapted from Mancini et al[7]

ACE inhibition improves endothelial function

The renin-angiotensin system affects the vasculature through the actions of ACE, largely due to the consequences of angiotensin II production and bradykinin degradation. Angiotensin II in the vascular wall causes a decrease in production and/or release of NO, which can contribute to endothelial dysfunction. Since ACE inhibition prevents the degradation of bradykinin and inhibits angiotensin II (leading to less vasoconstriction and an increase in the levels of NO), ACE inhibitors should improve endothelial function.

This thesis is supported by the results of the Trial on Reversing Endothelial Dysfunction (TREND), a six-month, randomized, double-blind study assessing the impact of quinapril on endothelial function.[7] In patients undergoing percutaneous transluminal coronary angioplasty (PTCA) for significant stenosis in one or two arteries, the researchers identified an adjacent artery with endothelial dysfunction as their target artery. Endothelial dysfunction was defined as vasoconstriction in response to acetylcholine during a baseline angiogram. Between 12 and 72 hours after PTCA, patients were randomized to receive either placebo or quinapril (40 mg/day). Patients with potentially confounding conditions, such as hyperlipidemia treated with lipid-lowering therapy, or

Figure 2: Local angiotensin II formation. Difference between pEC_{50}'s (-log mol/L).



poorly controlled hypertension, were excluded. After six months, the response to acetylcholine infusion was assessed angiographically. While the placebo group showed no change in vasoconstrictor response to acetylcholine, the quinapril group demonstrated a marked improvement (figure 1). TREND suggests that the benefits of ACE inhibition are due to attenuation of the contractile and the superoxide-generating effects of angiotensin II, and to the enhancement of endothelial cell release of NO secondary to diminished breakdown of bradykinin. This marked improvement in endothelial function induced by an ACE inhibitor with a high affinity for tissue ACE (quinapril) is consistent with results from trials of lipid-lowering therapy that also show improvement in endothelial function as compared to placebo.[8,9]

Functional effects of ACE inhibitors on the human vasculature

Two recent studies have yielded important information on the impact of ACE inhibition in humans.

QUO VADIS

The inhibitory effects on tissue ACE of quinapril as compared to other ACE inhibitors was recently examined in the Quinapril on Vascular ACE and Determinants of Ischemia (QUO VADIS) study. This randomized, double-blind, placebo-controlled trial was designed to evaluate the effects of chronic ACE inhibition on angiotensin II formation in human vasculature and to establish functional differences between quinapril and captopril.

At 27±1 (range 7-112) days prior to elective coronary artery bypass surgery at one of two medical centers in The Netherlands, patients (n=187) without significant left ventricular dysfunction (ejection fraction >40%) were randomized to receive placebo, quinapril (40 mg o.d.), or captopril (50 mg t.i.d.). Segments of the IMA were obtained and contracted with increasing doses of angiotensin I and II (0.1 nM to 1 µM) in organ baths. Local angiotensin II formation was determined by two methods: the difference between pEC_{50}'s of the dose-response curves to angiotensin I and II; and the area between the dose-response curves.

While a comparable and significant reduction in mean blood pressure was observed among the quinapril- and captopril-treated as compared to placebo-treated patients (p=0.04), local angiotensin II formation was significantly reduced only in the quinapril group (p=0.01; see figure 2). This randomized study suggests functional differences between quinapril's and captopril's effects on local angiotensin II formation in humans.

Further evaluation of QUO VADIS patients will be undertaken one year following bypass surgery, when each group will undergo treadmill testing to compare the effects of treatment on cardiac ischemia (as compared to a pre-operative stress test). The final results are anticipated at the American Heart Association Annual Scientific Meeting in Dallas in November, 1998.

BANFF

Recent noninvasive assessment of endothelial dysfunction has been demonstrated with high-resolution ultrasound measurement of brachial artery flow and vasodilation. There is evidence that brachial artery dilation is impaired by the same factors that attenuate coronary vasodilation, and a correlation between brachial and coronary vasodilator responses has been described.

In the Canadian-based Brachial Artery Normalization of Forearm Function (BANFF) study,[10] patients with angiographically documented coronary artery disease underwent high-resolution ultrasound that assessed their brachial artery dilation in response to reactive hyperemia (5-minute blood-

pressure cuff occlusion followed by a release). Patients enrolled in the partial-block, crossover design trial were randomly assigned to one of four different, open-label drug sequences. Each drug was administered for 8 weeks with a 2-week washout period between treatments.

BANFF evaluated the effects of the ACE inhibitors quinapril (20 mg daily) and enalapril (10 mg daily), the direct angiotensin blocker losartan (50 mg daily), and the calcium-channel blocker amlodipine (5 mg daily) on flow-mediated vasodilation of the brachial artery. The most dramatic change from baseline in brachial-artery flow-mediated vasodilation was seen in those patients who had received 8 weeks of quinapril treatment (1.8±1.0% change from baseline, $p<0.02$). In contrast, there was no significant change in vasodilation with enalapril (-0.2±0.8%, $p=0.84$), losartan (0.8%±1.1%, $p=0.57$), or amlodipine (0.3±0.9%, $p=0.97$). Thus, only quinapril significantly improved flow-mediated (endothelial-dependent) vasodilation, suggesting that ACE inhibitors and other antihypertensive agents differ in their impact upon endothelial dysfunction.

Summary

The renin-angiotensin system plays a key role in the risk and development of cardiovascular disease. Angiotensin II and ACE gene polymorphism is associated with differences in endothelial function, and the impact of these genetically determined factors can vary between individuals. Endothelial dysfunction is an early and frequent manifestation of atherosclerotic heart disease. Administration of ACE inhibitors, particularly those with higher affinity for tissue ACE (e.g., quinapril), appears to be an effective means of altering endothelial dysfunction. Whether treatment specifically targeted at endothelial dysfunction in patients with coronary artery disease, hypertension, and congestive heart failure will translate into better long-term clinical outcome awaits large-scale trial results.

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