Expression of Angiotensin II and Interleukin 6 in Human Coronary Atherosclerotic Plaques: Potential Implications for Inflammation and Plaque Instability

Schieffer B, Schieffer E, Hilfiker-Kleiner D, et al.
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This study attempts to localize angiotensin II, angiotensin II type 1 (AT1) receptor, ACE, and IL-6 within human coronary atherosclerotic plaques and to investigate the interaction of IL-6 with angiotensin II in vitro. IL-6, which has both anti-inflammatory and proinflammatory activities, is a central regulator of acute phase protein secretion in smooth muscle cells and in the migration and differentiation of activated macrophages.

In smooth muscle cell culture, angiotensin II induces IL-6 transcription and protein release up to 6- to 7-fold for 60 minutes. This response is abolished by the AT1 receptor blocker, losartan. In human atherosclerotic plaque obtained from patients with ischemic cardiomyopathy, macrophages, ACE, angiotensin II, AT1 receptor, and IL-6 colocalize to the shoulder region. In directional atherectomy samples from patients with unstable angina and in postmortem samples from patients who died from myocardial infarction (MI), colocalization of macrophages, renin-angiotensin system (RAS) components, and IL-6 appeared strong. Chymase-containing mast cells were not positive for angiotensin II or IL-6. These findings suggest that the RAS plays an important role in the inflammatory process.

This study, coupled with the recently published Heart Outcomes Prevention Evaluation (HOPE) clinical study, extends our understanding of the importance of the RAS in patients with atherosclerosis.[4] The HOPE study of 9297 patients with coronary artery disease, peripheral vascular disease, stroke/transient ischemic attack, or diabetes showed that the risk of cardiovascular death, MI, or stroke was reduced by 26% with treatment with ramipril, an ACE inhibitor, over a mean follow-up period of 5 years. This protective effect was independent of blood pressure reduction.

The HOPE clinical study, coupled with morphologic observations in the study by Schieffer and colleagues, clearly represents a major step in our understanding and treatment of plaque rupture.

Unfortunately, the event rates remain high in the treatment group in the HOPE study (14% combined outcome, 10.4% total mortality). Certainly, the RAS is an important component in inducing plaque instability, but it is probably not the only pathway. The combination of aggressive lipid-lowering therapy plus ACE inhibition seems to be the state-of-the-art medical therapy for preventing plaque rupture. Whether there is a synergistic effect between the 2 therapies remains to be determined.

References

1. Libby P. Molecular bases of the acute coronary syndrome. *Circulation.* 1995;91:2844-2850.
2. Kishimoto T, Akira S, Narazaki M, Taga T. Interleukin-6 family of cytokines and gp130. *Blood.* 1995;86:1243-1254.
3. Alderman MH, Madhavan S, Ooi WL, et al. Association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension. *N Engl J Med.* 1991;324:1098-1104.
4. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high risk patients. The Heart Outcomes Prevention Evaluation Study. *N Engl J Med.* 2000;342:145-153.

Vascular Biology

Two Views of Nitric Oxide

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Two areas of nitric oxide activity are evaluated: the consequences of reduced bioavailability in hemodialysis patients and the results of overactivity in patients following myocardial infarction.

Cardiovascular disease is the leading cause of death in patients with chronic renal failure undergoing hemodialysis. The increased cardiovascular events in these patients are attributed largely to accelerated atherothrombosis and hypertension. Nitric oxide produced by endothelium is a critical mediator of endothelium-dependent vasodilation and also regulates the interaction of the endothelium with platelets and leukocytes. Thus, nitric oxide is believed to play a key role in the maintenance of healthy vascular structure and function. Recent studies have shown an impairment of nitric oxide–dependent, flow-mediated vasodilation in patients with chronic renal failure who are undergoing dialysis. These observations suggest that reduced bioavailability of nitric oxide may occur in dialysis patients, contributing to enhanced atherothrombosis.

Hemodialysis Impairs Endothelial Function via Oxidative Stress: Effects of Vitamin E-Coated Dialyzer

Miyazaki H, Matsuoka H, Itabe H, et al.
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Miyazaki and colleagues evaluated endothelial function before and immediately after hemodialysis in 12 patients with chronic renal failure who were receiving maintenance hemodialysis. The authors determined changes in brachial artery diameter by ultrasonography and changes in flow velocity by Doppler techniques, in response to reactive hyperemia induced by releasing a cuff that had occluded the brachial artery for 4.5 minutes. The authors also measured circulating levels of oxidized low-density lipoprotein (oxLDL) before and after hemodialysis. Immediately after hemodialysis with a dialyzer that was not coated with vitamin E, there was a 35% increase in the circulating level of oxLDL and a significant impairment of flow-mediated (reactive hyperemia-induced) vasodilation (Figure 2). Interestingly, when a dialyzer coated with vitamin E was used, there was no significant change in circulating oxLDL concentration or flow-dependent vasodilation. Use of the dialyzer coated with vitamin E did not change circulating vitamin E levels. Response to nitroglycerin, a nonendothelium-dependent vasodilator, was not affected by dialysis.

This interesting paper highlights the fact that hemodialysis itself increases oxidative stress and impairs endothelium-dependent vasomotor function. Over time, these adverse effects of hemodialysis may contribute to accelerated atherothrombosis in patients with chronic renal failure. Use of a dialyzer coated with vitamin E prevented increases in oxidative stress without a change in circulating vitamin E levels, suggesting that such dialyzers may work by altering oxidative changes occurring on the surface of the dialysis membrane rather than through any systemic effects. The effect of dialyzers coated with vitamin E on cardiovascular morbidity and mortality in patients with chronic renal failure will need to be established with further studies.

Shock syndrome following acute myocardial infarction is generally associated with extensive loss of functioning myocardium and carries an extremely high mortality, usually in excess of 75% to 80%. Although, in recent years, aggressive use of early reperfusion and revascularization strategies has reduced mortality in patients with cardiogenic shock, the gains have been quite modest, and mortality rates of 40% to 60% continue to be reported. Severe hypotension is common in such patients and invariably requires the use of inotropic-vasopressor agents and intraaortic balloon counterpulsation. Despite such therapy, however, many patients remain hypotensive, with evidence of renal and other vital organ hypoperfusion. Furthermore, the use of conventional inotropic and vasoconstrictor agents is frequently complicated by chronotropic and arrhythmogenic effects, limiting the usefulness of these agents.

L-NMMA (a Nitric Oxide Synthase Inhibitor) Is Effective in the Treatment of Cardiogenic Shock

Cotter G, Kaluski E, Blatt A, et al.
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Cotter and colleagues reported the use of nitromonomethylarginine (L-NMMA), a nitric oxide synthase inhibitor with potent vasoconstrictor effects, in 11 post–

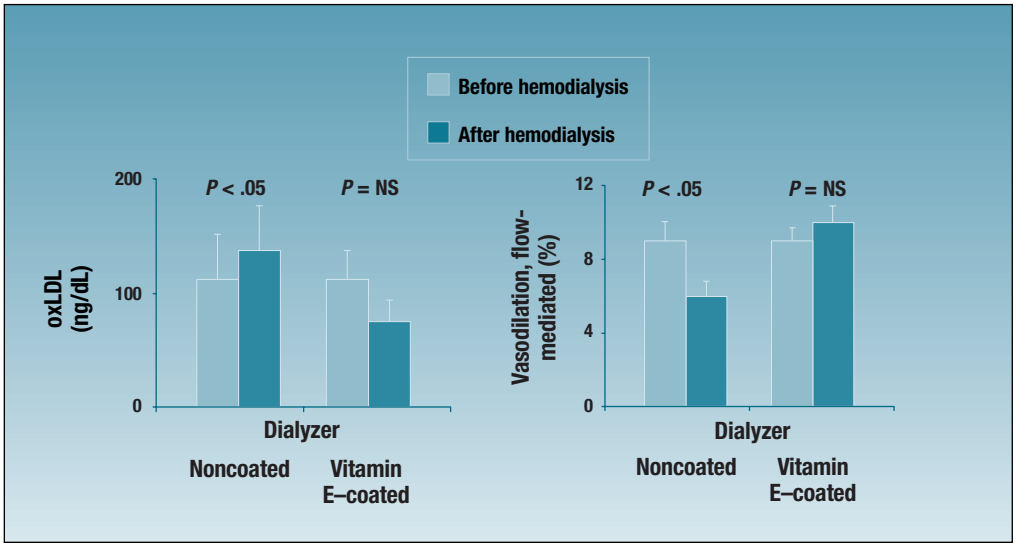

Figure 2. Effect of hemodialysis on plasma oxLDL (A) and on endothelial function (B). (oxLDL, oxidized low-density lipoprotein.)

myocardial infarction patients in cardiogenic shock refractory to standard therapy, including aggressive acute revascularization. The patients were elderly (mean age, 71 ± 10 years) with a mean left ventricular ejection fraction (LVEF) of 23 ± 5%. Intravenous L-NMMA (1 mg/kg bolus plus 1 mg/kg/h infusion for 5 hours) resulted in a rapid and substantial increase in mean arterial pressure, accompanied by a marked increase in urinary output. Interestingly, there was a small but short-lived increase in pulmonary capillary wedge pressure and a small but short-lived decrease in cardiac output. The overall clinical results were quite striking, with 7 of 11 patients surviving the inhospital phase and reported to be alive 1 to 3 months after discharge, with a mean LVEF of 31 ± 4%. The 4 nonsurvivors died of multiorgan failure, sepsis, sepsis and hemorrhage, or cholesterol embolism syndrome within the first week following administration of L-NMMA. The authors suggest that excessive activation of neurohormonal mediators, including nitric oxide, may contribute to and perpetuate the hemodynamic vicious cycle in cardiogenic shock and that manipulation of the nitric oxide pathway may emerge as a novel treatment for severe hemodynamic depression accompanying cardiogenic shock.

Although the overall results appear to be very impressive in a very high-risk cohort, the study is limited somewhat by the small number of subjects. This provocative study demonstrates a favorable survival effect of a novel agent with selective vasoconstrictor effects devoid of any chronotropic or cardiac stimulant actions. Further evaluation of L-NMMA and possibly of other modulators of the nitric oxide pathway, in conjunction with acute reperfusion and other supportive interventions in cardiogenic shock, appear warranted.

Infection

Linking *Chlamydia* and Heart Disease

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Information is increasingly available on the relationship between inflammation and atherosclerosis, particularly the development of vulnerable plaque, which is a key factor in acute ischemic syndromes, including acute infarction and unstable angina. Pathology studies have yielded substantial data on how this plaque develops. A central component is a lipid-rich core that may occupy 50% of the plaque volume. Vulnerable plaque, however, is not always easy to detect. It may not be assessed as severe even by coronary angiography. Intense efforts are under way to improve the detection process, using temperature sensors, electron beam CT, and MRI, among others.

Inflammation plays a central role. In pathology studies, plaque-causing acute ischemic syndromes are characterized by local inflammation that includes mast cells, T lymphocytes, and monocyte macrophages. These cells are, in part, responsible for production of cytokines and proteases, particularly specific-matrix metalloendopeptidases. These agents result in weakening of the fibrous cap over the lipid-rich core, with destruction of the matrix and disorganization of collagen. Such weakening is the hallmark of vulnerable plaque; when subjected to a triggering stress, such plaque can rupture, with thrombus formation, leading to unstable angina, acute infarction, or sudden death.

Given the central role of inflammation in the genesis of vulnerable plaque, there has been substantial interest in an infectious etiology. Early studies showed that atherosclerosis developed in an animal model of lymphomatosis. Since then, other models and human tissue studies have suggested a possible infectious etiology. Several agents have been evaluated; prominent among them are *Chlamydia pneumoniae, Chlamydia psittaci,* and *Chlamydia trachomatis*. The exact mechanism by which *Chlamydia* may cause cardiovascular disease remains unclear but may involve production of an endotoxin and heat shock protein as well as an autoimmune process.