Cardiac Angiotensin Is Upregulated in the Hearts of Unstable Angina Patients

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Patients with acute coronary syndromes commonly harbor multiple complex coronary plaques. Plaque instability is probably a widespread inflammatory process throughout the coronary vessels. Such a notion makes selection of the “culprit lesion” difficult. A recent clinical example from our coronary care unit is shown in the Figure. The patient is a 62-year-old man who experienced his first episode of severe anterior chest pain. The initial electrocardiogram showed an acute ST segment elevation anterior myocardial infarction. The emergency physician selected thrombolytic therapy and the patient was referred to our coronary care unit. His ST segments reverted to baseline. Early that same afternoon, a second episode of chest pain occurred. This time, his electrocardiogram showed a shift in axis and ST segment elevation in the inferior leads. At cardiac catheterization, the left anterior descending coronary artery was open, albeit diseased. The right coronary artery was occluded but could be opened. The second episode of ST segment elevation resolved as well. What is responsible for the generalized plaque instability in patients with an acute coronary syndrome? How does inflammation contribute? What role does the renin-angiotensin-aldosterone system (RAAS) play, and can the system operate locally? The study by Neri Serneri et al in this issue may provide some mechanistic answers. They tested the notion that the RAAS acts locally to cause generalized inflammation in the smaller coronary vessels of patients with unstable angina pectoris.

The hypothesis seems a reasonable one on the basis of trial results. The Heart Outcomes Prevention Evaluation study showed that an angiotensin-converting enzyme (ACE) inhibitor reduced cardiovascular death and myocardial infarction. ACE inhibitors have also reduced the need for revascularization after stenting and reduced subsequent events in patients with angina pectoris. The notion that the RAAS operates locally in the heart has achieved acceptance, albeit not without considerable initial resistance. Although the arguments for renin production in the heart are not compelling, angiotensinogen, ACE, and aldosterone can be made by the heart. Whether renin is actually made in the heart is moot, because the enzyme can be taken-up from the blood. Moreover, other enzymes can cleave angiotensinogen in the heart, including chymase.

In an earlier study, Neri Serneri et al showed that in patients with unstable angina, the heart produces Ang II. In that study, cardiac biopsies were performed at the time of bypass surgery. Messenger RNAs for angiotensinogen, ACE, and the AT1 receptor were elevated in patients with unstable angina compared with other controls. The study provided compelling evidence that the heart can contribute Ang II to the circulation, at least in patients with unstable angina. However, the causes and consequences were uncertain. Now, Neri Serneri et al have taken the issue of a cardiac RAAS a significant step further. They recruited patients with unstable angina, stable angina, and patients undergoing cardiac catheterization for other reasons. The 43 unstable angina patients were randomized to treatment with an ACE inhibitor (ramipril), an AT1 receptor blocker (valsartan), or placebo before surgery. The authors wanted to know whether a treatment directed at reducing the cardiac RAAS would alter any Ang II-related effects.

The investigators confirmed their earlier findings that the hearts from unstable angina patients produced Ang II. Furthermore, inflammatory cells were present in the hearts of the unstable angina patients. Tumor necrosis factor (TNF)-α, IL-6, interferon (IFN)-γ, and inducible nitric oxide synthase (iNOS) were expressed to greater degrees as well. Interestingly the nonischemic and potentially ischemic areas showed no difference in cytokine or iNOS expression. The endothelial cells were the major site of RAAS gene, cytokine, and iNOS expression. The ACE inhibitor and AT1 receptor blocker treatments reduced TNF-α, IL-6, IFN-γ, and iNOS expression; however, the treatments did not decrease the numbers of inflammatory cells. The data show that unstable angina involves the coronary microvasculature, where the cardiac RAAS induces a localized, innate, immunity-mediated, inflammatory process.

The authors did not directly address the issue of how Ang II may have elicited the inflammatory responses they observed. However, they refer to earlier studies showing that Ang II induces free radical generation, particularly through NAD(P)H oxidase stimulation, with subsequent signaling via Akt and JAK-STAT pathways. The subsequent signaling involves the transcription factors nuclear factor-κB and activator protein-1, among others. The immune-mediated inflammatory component largely involved HLA-DR-bearing T cells, macrophages, and endothelial cells. The drug treatment markedly reduced TNF-α, IL-6, and iNOS gene expression...
but did not reverse the cellular infiltrates. Of course, a 5-day treatment does not constitute a clinical trial. Nevertheless, possibly Ang II is not the only mediator of endothelial cell activation in the hearts of unstable angina patients. Ang II can affect T-cell behavior directly and induce cellular IFN-γ secretion and IL-2 production. 12 Ang II also influences dendritic cell migration. 13 Earlier studies have already shown that in unstable angina patients, widespread inflammation occurs along the entire coronary bed, involving far more than the culprit lesion.1,14

The authors did not study the second “A” in the RAAS, namely aldosterone. In addition to Ang II, the heart can also produce aldosterone, at least when it is failing.15 Experimental evidence has been presented that aldosterone production is increased in ischemic myocardium by tissue-specific activation of myocardial aldosterone synthesis.16 The presence of aldosterone can augment Ang II signaling via the AT 1 receptor. 17 Aldosterone can also activate mononuclear cells. 18 The authors’ intentions were not focused on aldosterone. However, the RAAS does not stop with Ang II.

The mechanism leading to cardiac RAAS activation is unclear. The phenomenon was not observed in the patients with stable angina. The investigators included careful controls to eliminate the effects of extracorporeal circulation on ischemia-reperfusion injury. The patients did not have elevated troponin levels. Local oxygen tension was not measured and the expression of oxygen sensing components was not determined. However, ischemia as a triggering mechanism appears unlikely. Unfortunately, little is known about local RAAS regulation. Neri Serneri et al found that chymase gene activity was no different across the patient groups.2 Renin mRNA was not detected in any group. The AT 3 receptor gene expression was not affected. Only angiotensinogen, ACE, and the AT 1 receptor were upregulated in the unstable angina patients. Neither renin nor chymase appears to have been rate-limiting in this study. Whereas for the circulating RAAS, an increase in salt intake reduces renin, Ang II, and aldosterone levels, and data exist that cardiac Ang II production may actually increase with a high salt intake. 19 Salt intake was not reported; however, I regard a role for salt-induced cardiac RAAS upregulation in the unstable angina patients as unlikely. Nor is it probable that differences in circulating plasma renin activity were responsible; the patients did not have heart failure. Effects of brain natriuretic peptide and aldosterone cannot be excluded but also appear unlikely. Thus, the signal for cardiac RAAS upregulation and its origin remain obscure.

Also still to be explored are the paracrine, autocrine, or even the intracrine actions of Ang II within the inflamed myocardium. The authors’ study suggests that the endocrine mechanisms we usually attribute to the actions of Ang II were not operative here. Instead, the results describe a paracrine mode of action. The endothelial cells were the primary site of Ang II production rather than the cardiomyocytes. This finding appears a bit surprising. An earlier study showed an autocrine release of Ang II in cardiac myocytes exposed to
stretch. That study demonstrated how cardiac cells could convert mechanical stimuli into growth signals. Renin was not necessary for the process. Another remarkable possibility is that Ang II signaling, complete with its AT1-receptor, might have taken part intracellularly. Such intracellular Ang II signaling has been shown in vascular smooth muscle cells. This possibility implies an intracrine signaling mechanism.

The anticardiac RAAS treatment regimen given for a relatively short period downregulated a variety of mediators in the hearts of unstable angina patients, compared with placebo treatment. An additional clinical implication from the study by Neri Serneri et al and other studies is that unstable angina patients are not adequately treated by the mere stenting of their culprit lesion. An anti-inflammatory medical regimen is necessary directed at lipid-lowering, blocking the RAAS, and limiting neuroadrenergic transmission. Finally, patient-oriented clinical investigators can only be encouraged by this study. Basic questions can still be addressed in patients. The best model for humans remains human.

References


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