Neuroendocrine Responses to Acute Myocardial Infarction

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A myocardial infarction (MI) causes ripples across an entire physiologic stress response. A loss of myocardial blood flow leads to regional myocardial necrosis. This in turn leads to local ventricular abnormalities in contraction and relaxation that compromise global cardiac function. The resultant hemodynamic derangements, such as a redistribution in cardiac output and elevated filling pressures, lead to regional circulatory abnormalities and ultimately a neuroendocrine response. These neuroendocrine responses to a MI are adaptive attempts to address the various aspects of the destabilizing events. Often these changes are transient, normalizing with recovery. Although potentially beneficial, the "overshoot" can participate in the pathologic response, becoming part of the problem rather than part of the solution. Injured endothelium releases endothelin, a potent coronary and systemic vasoconstrictor. Myocardial injury triggers increased activity of both the sympathetic nervous system and the renin-angiotensin system, and recent studies indicate that patient outcome may be predicted by the severity of these neurohormonal responses. However, modification of these responses may alter the clinical course of the underlying disease process.

Theoretically, many factors participate in the increased neuroendocrine response to acute MI. Pain and anxiety increase adrenomedullary release of epinephrine and norepinephrine. Decreased cardiac output and hypotension stimulate peripheral sympathetic activity and reduce renal blood flow, activating the renin-angiotensin system. Regionally, myocardial necrosis releases norepinephrine stores from the infarcted area. Furthermore, coronary insufficiency resulting in ischemia but not necrosis also releases myocardial norepinephrine. The recent discovery of an intact renin-angiotensin system completely within the heart raises the possibility of local activation of this endocrine system (1). The integrated action of these two systems on the myocardium and peripherally may result in mutual stimulation. Likewise, coronary thrombosis and local hypoxia result in release of the potent inotrope-vasoconstrictor endothelin. Furthermore, a persistent increase in circulating endothelin levels has been seen with systemic hypoperfusion. Lastly, the increased atrial pressures accompanying an acute MI raise atrial natriuretic peptide production and release (Table 1). These alterations in the myocardial substrate lead to transient impairment of the homeostatic baroreceptor regulation of cardiac function (2).

There is considerable evidence for increased neuroendocrine activity in both experimental infarction models and the clinical setting of acute MI. A number of studies have shown that myocardial necrosis leads to release of norepinephrine stores in the necrotic tissue (3-5). Infarction, however, is not a prerequisite for this phenomenon. Muntz et al (6) evaluated alterations in myocardial catecholamines during early ischemia in dogs. The left anterior descending artery was ligated and regional release of myocardial norepinephrine versus regional coronary blood flow was assayed. At one hour after ligation, catecholamines were identical in all regions of the myocardium. By three hours, however, a significant decrease in catecholamines was noted in the endocardium of the ischemic region. This was not seen in the less ischemic pericardial region. The authors noted that there is a redistribution of catecholamines from nerve terminals to other interstitial tissue compartments.

Thus, ischemia prior to infarction results in release of myocellular noradrenaline to surrounding interstitial spaces. Potential toxic effects of excessive extracellular norepinephrine are illustrated by observations of Gavras et al (7). Intravenous infusions of norepinephrine in rabbits resulted in extensive, often confluent, multifocal myocardial necrosis.

Increased activity of the renin-angiotensin system is also seen after a MI. Reduction in cardiac output resulting in decreased renal blood flow and renal perfusion pressure will increase the activity of this homeostatic system (8,9). Furthermore, increased renal sympathetic nerve traffic will also increase renin release (10). Finally, there is evidence that an intact renin-angiotensin system exists within the heart. Ertl (11) has demonstrated that a 30-second occlusion of a coronary artery in dogs results in increased renin activity and angiotensin II levels. The increased activity in the myocardial substrate leads to decreased renal blood flow and renal perfusion pressure will increase the activity of this homeostatic system (8,9). Furthermore, increased renal sympathetic nerve traffic will also increase renin release (10). Finally, there is evidence that an intact renin-angiotensin system exists within the heart. Ertl (11) has demonstrated that a 30-second occlusion of a coronary artery in dogs results in increased renin activity and angiotensin II levels. The increased activity in the myocardial substrate leads to decreased renal blood flow and renal perfusion pressure will increase the activity of this homeostatic system (8,9). Furthermore, increased renal sympathetic nerve traffic will also increase renin release (10). Finally, there is evidence that an intact renin-angiotensin system exists within the heart. Ertl (11) has demonstrated that a 30-second occlusion of a coronary artery in dogs results in increased renin activity and angiotensin II levels. The increased
vasoconstriction mediated by enhanced angiotensin II activity results in increased afterload and thus myocardial oxygen demand, potentiating the left ventricular dysfunction seen in an acute MI. Furthermore, the intriguing observation of Gavras et al (7) that intravenous angiotensin II in rabbits caused extensive acute MI. Furthermore, the intriguing observation of Gavras et al (7) that intravenous angiotensin II in rabbits caused extensive myocardial necrosis identical to that seen with norepinephrine raises the specter of further myocardial damage either directly or mediated indirectly by norepinephrine.

Recently the vasoconstrictive inotropic peptide, endothelin, has been isolated from the vascular endothelium of many species including man (12-14). Although the exact mechanisms controlling its release are unclear, animal studies have shown that thrombin formation and hypoxia, both seen in acute MI, stimulate endothelin release (15,16). Infusions of this potent coronary vasoconstrictor can result in further ischemia and infarct extension (17). One other potential action of endothelin is stimulating the release of atrial natriuretic factor (ANF) (18). ANF is also released by the increased sympathetic tone and elevated atrial pressures seen with an acute MI. In principle, this vasodilator saluretic should counteract vasoconstrictor effects of the other activated neuroendocrine mechanisms. ANF has a physiologic role in normals but seems to be overwhelmed by the increased activity of the sympathetic nervous system and renin-angiotensin-aldosterone system.

There is considerable clinical evidence that increased neuroendocrine activity is detrimental to patients after a MI (Table 2). These vasoconstrictor mechanisms increase myocardial oxygen demand and reduce supply by vasoconstricting the coronary bed and reducing blood flow. Therefore, they might be expected to promote infarct expansion, recurrent ischemia, reinfarction, heart failure, and arrhythmias. Early work was performed by Prakash et al (19) measuring urinary catecholamines in patients after acute MI. They demonstrated a correlation between neurohormonal activity and subsequent development of left ventricular failure, life-threatening arrhythmias, shock, and death. In fact, those patients with complicated postinfarction courses had significantly higher urinary catecholamines than patients with uncomplicated MI. These early observations led to the concept that increased catecholamines were predictors of the severity of infarction and the clinical outcome. That this increased sympathetic activity participated in the pathophysiology of acute MI was brought into focus by Karlsberg et al (20). They found increased levels of plasma norepinephrine and epinephrine within 4 hours of the onset of MI, prior to any creatine phosphokinase (CPK) release. There was a direct correlation between mean levels of epinephrine and norepinephrine, peak levels of epinephrine, and the levels of CPK generated by the MI. During follow-up, those patients with high levels of circulating catecholamines were also those with the poorest prognosis. The authors suggested that the magnitude of neurohormonal activation early in the course of an acute MI played a role in the extent of myocardial damage and the eventual mortality. Vaney et al (21) also demonstrated increased plasma norepinephrine and epinephrine after MI. They, too, noted the correlation between the size of the infarct and the levels of circulating catecholamines. Furthermore, they extended their observations to the renin-angiotensin system, finding that plasma renin activity increased after MI. In their series, patients with the greatest increase in neuroendocrine activity after a MI were those most likely to develop cardiogenic shock or ventricular fibrillation. Recently, Stewart et al (14) showed that persistently elevated plasma endothelin levels also identified patients who had a more complicated course and a worse prognosis.

Clearly, the larger the MI, the greater the neuroendocrine response and the worse the prognosis. However, the increased neuroendocrine activity after an infarction can independently contribute to infarct expansion and extension and worsening prognosis.

### Approach to a Myocardial Infarction

As “Telescoped Heart Failure”

One is struck by apparent pathophysiologic similarities of acute MI and heart failure. In both situations pump dysfunction is present. Both heart failure and MI result in depleted myocardial catecholamine stores. Again in both, inappropriate peripheral vasoconstriction is mediated by increased activity of the renin-angiotensin system and increased sympathetic tone. Finally, arrhythmias and sudden death are frequent occurrences in both situations.

Thus, acute MI and stable heart failure may be viewed as a physiologic continuum, and MI is essentially “telescoped heart failure.” This unifying physiologic outlook leads to potential unification in therapy. In the clinical situation, therapy that benefits one disease seems to hold promise for the other.

Beta-blockade is an accepted therapy following MI. A number of placebo-controlled trials have shown that beta-blockade improves survival and reduces reinfarction after a MI (22-24). This observation was also underscored in the recent Thrombolysis in Myocardial Infarction (TIMI) phase II trial (25). In this study, a subset of patients after thrombolytic therapy were randomized to metoprolol either immediately after infarction or six days later. The results of this study showed that those receiving metoprolol immediately postinfarction had a lower incidence of reinfarction and recurrence of ischemia. Interestingly and analogously, there is increasing interest in the use of beta-blockade to treat congestive heart failure (26). One randomized, placebo-controlled trial showed these drugs to improve patients with primary cardiomyopathy both functionally and symptomatically (27). Why these drugs might benefit patients with heart failure is unknown. Perhaps beta-blockade protects myocardium from further catecholamine mediated damage, or myocardial β-receptors may be “reset” leading to improved cardiac function.

Angiotensin-converting enzyme inhibitors are accepted therapy for the treatment of heart failure (28-30). These drugs have
been shown to improve patients symptomatically and functionally and, more recently, to improve survival. The Cooperative North Scandinavian Enalapril Survival Study utilized end-stage congestive heart failure patients (31), most of whom had ischemia as the underlying etiology of their left ventricular dysfunction. The study showed patients randomized to enalapril had significantly greater six-month and one-year survival than those patients receiving placebo. It has been shown experimentally that a converting enzyme inhibitor preserves myocardial contractile function in an ischemic segment stressed by either tachycardia or reperfusion (11). The ability of captopril to protect ischemic myocardium may represent a reduction in myocardial cellular toxicity mediated by angiotensin II. In a recent study, Pfeffer et al (32) showed that patients randomized after MI to receive a converting enzyme inhibitor had increased exercise capacity 3 to 12 months postinfarction when compared to a placebo-controlled cohort, this despite the presence of left ventricular dysfunction.

Thus, the lessons learned in the therapy of end-stage congestive heart failure appear to apply to acute MIs (telescoped congestive heart failure), and these preliminary studies offer an exciting promise to patients with ischemic heart disease. The ability to blunt the neurohormonal activity seen in an acute infarction promises to reduce complications and improve survival. Aggressive pharmacological therapies are an essential and appropriate complement to the aggressive intervention strategies pursued to treat MI.

References


