

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Limiting Myocardial Damage during Acute Myocardial Infarction by Inhibiting C-Reactive Protein

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Approximately 1.1 million Americans have an acute myocardial infarction each year. The size of the infarction is a major determinant of both the risk of death and the likelihood of subsequent heart failure. For this reason, a goal of therapy is to reduce the size of the infarct. Current treatments focus on restoration of coronary blood flow (through reperfusion) and reduction of myocardial oxygen demand (e.g., through the use of beta-blockers). Research during the past two decades, however, has tried to elucidate the critical steps in the injury and subsequent killing of myocardial cells, with the hope that antagonizing these steps may provide new cardioprotective therapies. To this end, Pepys et al.¹ recently reported that they used a small molecule that binds and inhibits human C-reactive protein (CRP) to reduce the size of myocardial infarctions.

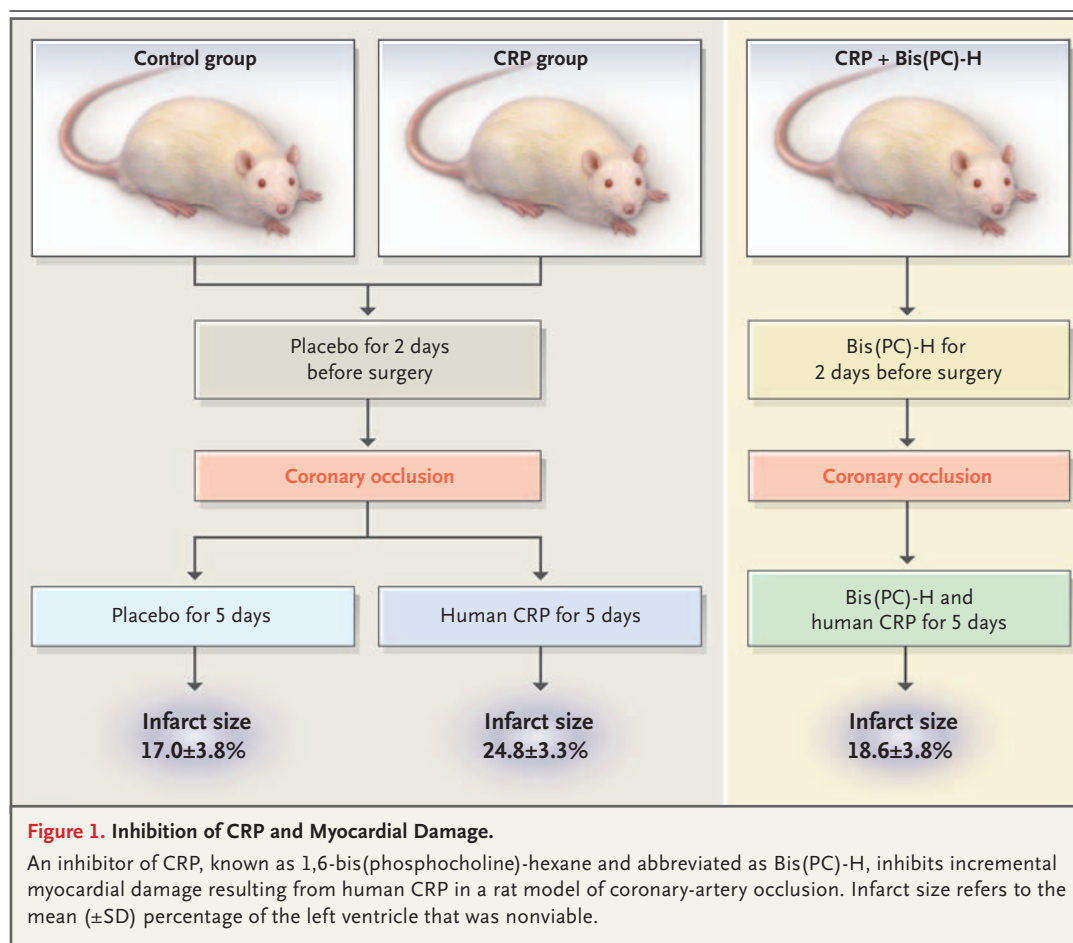
CRP is an acute-phase serum protein that is synthesized by hepatocytes. During infection, inflammation, and tissue injury, the serum level of CRP rises by a factor of up to several thousand. The physiologic roles of CRP are not known, but it may contribute to innate immunity and suppression of autoimmunity. Baseline CRP levels are moderately elevated in obese persons or those who smoke or have diabetes or hypertension. Even in otherwise apparently healthy subjects, elevations in CRP may predict coronary events. CRP levels increase dramatically in patients with myocardial infarction beginning 6 hours after the onset of ischemia and peaking at approximately 50 hours. CRP values after acute myocardial infarction predict outcome, including death and heart failure.² The binding of CRP to phosphocholine groups in damaged cell membranes leads to complement activation, which may cause further tissue damage. In fact, CRP and complement are found in infarcted human myocardial tissue.³ CRP may also bind other ligands, including the

Fcγ receptor, through which it may modulate several signaling pathways.

Using the x-ray crystallographic structure of human CRP bound to free phosphocholine and building on their experience in developing a drug that binds and depletes the closely related protein serum amyloid P component, Pepys et al. designed a small molecule, 1,6-bis(phosphocholine)-hexane (abbreviated Bis(PC)-H), that binds CRP and prevents interactions between CRP and its various ligands, as well as CRP-induced complement activation.

Next, Pepys et al. took advantage of the ability of Bis(PC)-H to inhibit CRP to determine the role of CRP-induced complement activation in the pathogenesis of myocardial infarction (Fig. 1). Infarction was induced by surgical occlusion of the left coronary artery. The investigators used a rat model to exploit the fact that human CRP, but not rat CRP, can activate rat complement. They had previously shown that human CRP increases the size of myocardial infarctions in rats in a complement-dependent way.⁴

Five days after coronary occlusion, the average size of the infarct among rats in the control group treated with placebo was 17.0 percent of the size of the left ventricle. A second group underwent the coronary-occlusion procedure but received human CRP for five days starting shortly after surgery. The average size of the infarct in this group was 24.8 percent of the size of the left ventricle, reflecting additional damage to the left ventricle resulting from the superimposition of human CRP onto coronary occlusion. A third group was treated like the second group (i.e., the rats underwent coronary occlusion followed by treatment with human CRP) except that the rats in this group received Bis(PC)-H starting two days before surgery and continuing for five days after surgery. The average size of the infarct in this



group was 18.6 percent of the size of the left ventricle and not significantly different from that in the control group. Missing from the study is the following internal control: the measurement of the area at risk — the amount of myocardium subjected to ischemia — in each group. If one assumes that the areas at risk in each group were similar, Bis(PC)-H almost completely abrogated the increase in infarct size that resulted from human CRP.

In a parallel experiment, Bis(PC)-H had no effect on infarct size in rats that underwent left coronary occlusion but did not receive human CRP. This finding indicates that inhibition of rat CRP had no effect, which is consistent with the inability of rat CRP to activate complement. It also shows that Bis(PC)-H did not substantially influence other signaling pathways that are critical to the pathogenesis of myocardial infarction.

Additional work is needed to delineate the precise mechanisms underlying these observa-

tions. The most straightforward explanation for the effects is that the binding of Bis(PC)-H to circulating human CRP prevents the latter from binding to damaged myocardial cells, thereby abrogating human CRP-dependent complement activation. However, other potential mechanisms (e.g., the disruption of the binding of CRP to Fc γ receptors) were not explored.

Do these studies in animals predict that Bis(PC)-H will be useful in limiting infarct size in myocardial infarction in humans? Although this study provides proof of concept, one wonders about the extent to which CRP drives myocardial damage during myocardial infarction in humans. The plausibility of this hypothesis is supported by the fact that the human CRP levels in the rats in the second group (the CRP group) analyzed by Pepys et al. were similar to the levels in myocardial infarction in humans. In addition, the prognostic significance of acute elevations in CRP levels in myocardial infarction in

humans is consistent with an important role for CRP-mediated myocardial damage, although this relationship is only an association and does not necessarily represent cause and effect.³ Ultimately, however, an experiment using humans is required to determine the relative contribution of CRP-dependent mechanisms to myocardial damage during infarction in humans.

Another issue regarding the clinical applicability of the present study is that a model of persistent coronary occlusion without reperfusion was used. In contrast, prompt restoration of coronary blood flow is standard therapy for myocardial infarction involving ST-segment elevation. The extent to which myocardial damage is CRP-dependent in this more clinically relevant example remains to be determined.

The timing of drug delivery may also be relevant to the ability of Bis(PC)-H to limit myocardial damage in humans. In the study in rats, Bis(PC)-H was administered two days before coronary occlusion, an approach that will not be available in the case of myocardial infarction in humans. It may be possible, however, to use a quicker, intravenous route of administration in humans. Nevertheless, initiating the drug soon after the onset of ischemia will presumably be important, so that the drug will be in the system before CRP levels begin to rise.

If progress continues and studies in humans are warranted, an in-depth safety evaluation will

be mandatory. In particular, any adverse consequences of inhibiting CRP must be identified, given the possibility that other inflammatory or infectious conditions may coexist in patients with acute myocardial infarction.

These caveats notwithstanding, Pepys et al. provide exciting data from studies in animals. In addition, the availability of a CRP inhibitor will facilitate experiments to determine the role of human CRP in normal biologic processes and disease states including atherogenesis, plaque instability, stroke, infection, inflammatory diseases, and autoimmunity.

No potential conflict of interest relevant to this article was reported.

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