VIEWPOINT

C reactive protein for risk stratification in acute coronary syndromes? Verdict: unproven

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Although C reactive protein is intimately involved with the pathogenic mechanisms that drive acute coronary syndromes, there is no evidence that it is helpful for identifying patient groups who might benefit from particular treatment strategies

Thrombogenesis at the site of plaque disruption is the final common pathway of acute coronary syndromes. Troponin release, which occurs either as a result of thrombotic coronary occlusion or thrombus microembolism (''minimal myocardial damage''), is a powerful predictor of cardiovascular morbidity and mortality, and the routine use of troponin assays has led to considerable improvements in our ability to risk stratify patients presenting with acute coronary syndromes. Determination of C reactive protein (CRP) concentration has been viewed as a possible method of further refining risk stratification in these patients.[1]

CRP, an acute phase protein produced mainly by the liver in response to interleukin 6, is a marker of inflammatory processes that contribute importantly to atherogenesis, plaque disruption, and thrombosis. Indeed products of thrombosis, including thrombin and platelet derived growth factor, themselves cause vascular smooth muscle cells within the ruptured plaque to augment production of interleukin 6 (IL-6), amplifying hepatic CRP release, and completing a vicious cycle of thrombosis and inflammation in acute coronary syndromes. CRP may have additional pathogenic effects—specifically by activating the complement system and promoting tissue factor release from monocytes.[1 2] Thus CRP is intimately involved with the pathogenic mechanisms that drive acute coronary syndromes, and is predictive not only of cardiovascular events in apparently healthy middle aged men and women[3] but also of outcomes following presentation with unstable angina and myocardial infarction.

RAISED CRP AND ADVERSE OUTCOMES

Recent data confirm that the association of raised CRP concentrations with adverse outcomes in acute coronary syndromes is independent of commonly used markers of risk, including ECG characteristics and troponin release.[4–11] These studies—many of which were primarily designed to assess various therapeutic strategies—represent the evidence base supporting the routine measurement of CRP concentrations for risk stratification in acute coronary syndromes. However, mechanisms associating CRP concentrations with cardiovascular morbidity and mortality in these patients remain controversial. Cusack and colleagues demonstrated a gradient in IL-6 concentrations between the aortic root and the coronary sinus gradient only in patients with unstable angina in whom troponin release occurred; in those requiring percutaneous intervention, sampling blood distal to culprit lesions revealed no cytokine gradient across the lesion.[12] In another study of patients presenting with non-ST elevation acute coronary syndromes, maximum but not baseline CRP concentrations showed univariate association with death and myocardial infarction, but there was no independent association once adjustment for other variables including troponin concentration had been made. In addition, CRP concentrations were directly related to maximum troponin concentrations, and both were lower in patients taking aspirin before presentation.[13] These studies suggest that in acute coronary syndromes CRP release is predominantly a response to, not a cause of, myocardial necrosis.

This not only explains why several studies have failed to demonstrate an independent association between CRP concentrations and outcome following acute coronary syndromes,[13–15] but also highlights the importance of methodological issues in those studies in which positive association has been reported. Troponin cut offs have varied between studies and, because a substantial proportion of CRP production in acute coronary syndromes is in direct response to myocardial necrosis for which troponin acts as a more sensitive and specific marker, high cut offs will tend to favour ''independent'' associations between CRP and outcomes.

What is questionable here is not the association but its independence of troponin release. For example, in the TIMI (thrombolysis in myocardial infarction) 11A substudy, CRP $\geqslant$ 15.5 mg/l in troponin negative patients apparently predicted a 14 day mortality of 5.8% compared to 0.4% in those with CRP $<$ 15.5 mg/l.[5] However, troponin concentrations were determined only from blood taken on presentation using an assay with a 0.2 μg/l cut off. Many of the ostensibly troponin negative patients would have been

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Abbreviations: CAPTURE, chimeric 7E3 antiplatelet therapy in unstable angina refractory to standard treatment; CRP, C reactive protein; FRISC, Fragmin during instability in coronary artery disease; IL, interleukin; TIMI, thrombolysis in myocardial infarction

termed troponin positive if the more usual cut off of 0.1 μg/l had been used and if concentrations had been determined in blood taken 12 hours after the onset of symptoms.

POWER OF CRP TO PREDICT CARDIOVASCULAR RISK

Conversely, in studies where standard cut offs and sampling times have been used the independent power of CRP to predict cardiovascular risk has not been as powerful as earlier studies have reported, with risk ratios generally less than 2.5. In the FRISC (Fragmin during instability in coronary artery disease) study, for example, the risk ratio for cardiovascular death after two years of follow up, associated with a CRP > 10 mg/l, was 2.3. This was similar to the risk ratios for age (1.6), diabetes (2.3), and a history of cardiac failure (1.8), but was substantially lower than those for troponin T 0.06–0.59 μg/l and troponin T > 0.6 μg/l, which were 6.4 and 10.8, respectively.[9] The ability of CRP to predict early—that is, less than 30 day—events is particularly open to question. The problems interpreting the results of the TIMI 11A substudy have already been described. Of the other studies only Heeschen and colleagues looked at early events and found that CRP did not predict death or myocardial infarction after 72 hours.[8] Similarly, in several other studies where no attempt was made to adjust for troponin, no association between CRP concentrations and in-hospital outcome could be demonstrated.[15–17]

Presumably the independent predictive power of CRP would have been diminished further by appropriate adjustment for ECG characteristics. ST shift and T wave inversion are, respectively, specific and sensitive markers of myocardial ischaemia and are not only consistent and independent predictors of cardiovascular risk but also identify patients who will benefit from various forms of treatment. Despite this, in many of the studies where an association between CRP concentrations and outcome that is independent of troponin has been demonstrated, ECG characteristics were either not entered into multivariate analysis at all,[5 7 10] were only loosely defined,[6] or—in the case of the FRISC and CAPTURE (chimeric 7E3 antiplatelet therapy in unstable angina refractory to standard treatment) studies—were inclusion criteria and were not therefore analysed.[8 9]

If CRP concentrations cannot be viewed as being clinically useful in patients who are defined as being high risk by either troponin release or electrocardiographic evidence of myocardial ischaemia, it is conceivable that they may be of some use in patients without these markers of risk.[1] Unfortunately the predictive power of CRP in patients who are both troponin negative and present without ECG evidence of ischaemia has not been specifically addressed. In the FRISC and CAPTURE studies, however, the incidence of death after two years' follow up and of death or myocardial infarction after six months' follow up was 2% and 3.2%, respectively, in troponin negative patients with CRP ⩾ 10 mg/l compared to an incidence of 0% in patients who were both CRP and troponin ''negative''.[8 9] Although interesting, these two studies are insufficient to determine the true value of CRP in troponin negative individuals and more data are needed.

CRP AND MANAGEMENT OF ACUTE CORONARY SYNDROMES

Troponin release reflects the end result of a thrombotic process and as such a variety of antithrombotic agents have been found to be effective only in acute coronary syndromes associated with a troponin rise.[18] Similarly subgroup analysis of the FRISC II study demonstrated that an aggressive invasive management of acute coronary syndromes leads to a significant reduction in mortality and morbidity in troponin positive patients and those with ST depression on the presenting ECG.[19] In contrast, there is little evidence that CRP values identify groups of patients who will benefit from a particular treatment. Ridker and colleagues demonstrated that in healthy volunteers those with the highest quartile CRP concentrations benefited the most from primary prevention with aspirin.[20] Similarly there is evidence that statins are particularly useful in a secondary preventative setting in those with raised CRP concentrations.[21] In the context of acute coronary syndromes, however, the CAPTURE study could not demonstrate that CRP concentrations identified those who benefit from abciximab and post-hoc analysis of the TIMI IIIB study revealed no evidence that CRP concentrations identify those who will benefit from an early invasive management strategy.[8 22]

In summary, the principal determinant of CRP release in patients with acute coronary syndromes is myocardial necrosis, and it is not surprising, therefore, that CRP measurement provides little incremental prognostic information, once troponin concentrations and ECG changes have been considered. There is certainly no evidence that CRP is helpful for identifying groups who might benefit from particular treatment strategies in acute coronary syndromes. This is not to diminish the importance of inflammatory mechanisms in the pathogenesis of atherosclerosis and plaque rupture, which underpins the emerging role of CRP for defining coronary risk in apparently healthy individuals. In the coronary care unit, however, ECG changes and troponin measurements remain the principle tools for risk stratification, and there is no compelling evidence that CRP measurements provide additional independent information.

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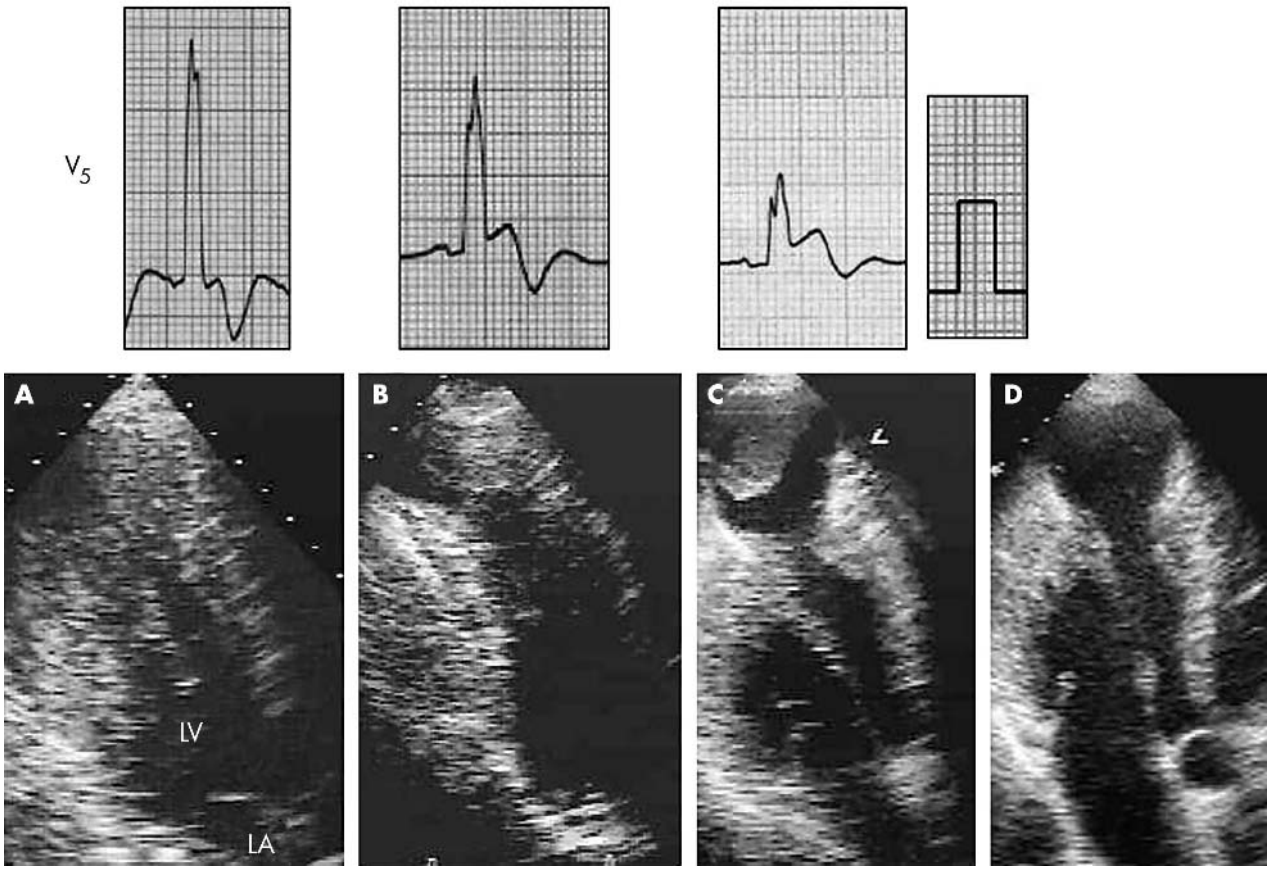
IMAGES IN CARDIOLOGY

Unusual morphologic changes in apical hypertrophic cardiomyopathy

A 60 year old man was referred to our clinic for further cardiac examination of negative T waves on the left side precordial ECG leads. Echocardiography demonstrated thickening of the left ventricular wall, particularly in the mid to apical region, which was compatible with apical hypertrophic cardiomyopathy (panel A). Five years later when R waves on the ECG declined slightly, the pattern of hypertrophy had changed to a type of mid ventricular obstruction (panel B). At that time, the intraventricular pressure gradient measured by catheterisation was 57 mm Hg. The patient was treated with a β blocker and disopyramide. However, the intraventricular pressure gradient did not completely disappear. The R waves gradually decreased with slight ST segment elevation during the ensuing 12 years. Under these conditions, the apical portion of the left ventricle became aneurysmal and there was a very large thrombus within this aneurysm (panel C). Fortunately, additional treatment with coumadin resulted in complete resolution of the thrombus without any systemic embolisation (panel D).

In this patient with hypertrophic cardiomyopathy, a sustained intraventricular pressure gradient, despite medical treatment, was related to the appearance of an apical aneurysm associated with thrombus formation.

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