How to use C-reactive protein in acute coronary care

Luigi M. Biasucci, Wolfgang Koenig, Johannes Mair, Christian Mueller, Mario Plebani, Bertil Lindahl, Nader Rifai, Per Venge, Christian Hamm, Evangelos Giannitsis, Kurt Huber, Marcello Galvani, Marco Tubaro, Paul Collinson, Joseph S. Alpert, Yonathan Hasin, Hugo Katus, Allan S. Jaffe, and Kristian Thygesen*, the Study Group on Biomarkers in Cardiology of the Acute Cardiovascular Care Association of the European Society of Cardiology

Department of Cardiology B, Aarhus University Hospital, Tage Hansens Gade 2, Aarhus DK-8000, Denmark

Received 26 May 2013; revised 17 September 2013; accepted 23 September 2013; online publish-ahead-of-print 7 November 2013

Introduction

C-reactive protein is an acute phase protein and an established marker for detection, risk stratification, and monitoring of infections and inflammatory and necrotic processes. Because C-reactive protein is sensitive but not specific, its values must be interpreted in the clinical context. In patients with acute myocardial infarction (AMI), C-reactive protein increases within 4–6 h of symptoms, peaks 2–4 days later, and returns to baseline after 7–10 days.1

C-reactive protein has gained interest recently as a marker for risk stratification in acute coronary syndrome (ACS) when measured by high-sensitivity C-reactive protein assays. These assays have greater analytical sensitivity and reliably measure C-reactive protein concentrations within the reference range with low imprecision (5–10%).2

Because of evidence that atherosclerosis is an inflammatory disease, high-sensitivity C-reactive protein can be used as a biomarker of risk in primary prevention and in patients with known cardiovascular disease.3 The aim of this review is to evaluate the use of C-reactive protein in patients with acute coronary disease.

Biochemical and analytical issues

C-reactive protein is a non-specific first-line host defence mechanism.4 With stimulation by cytokines (e.g. interleukins and tumour necrosis factor-alpha), C-reactive protein synthesis in hepatocytes occurs within 4–6 h. Concentrations can rise 1000-fold or more over 24–48 h. C-reactive protein has been detected in atherosclerotic plaques; its possible role in atherosclerogenesis is summarized in Figure 1, but is still a matter of debate.5 Genetic variants account for 35–40% of the variability in high-sensitivity C-reactive protein.6

The in vitro stability of high-sensitivity C-reactive protein is excellent.2,7 Specific blood sampling conditions are not necessary. However, retesting may be necessary with some assays if there is marked lipaemia. Baseline and subsequent measures are in good agreement for risk stratification despite biological variability of 30–60%.2,7

The upper reference limit is method-dependent but usually <8 mg/L for standard assays.2,7 The distribution of high-sensitivity C-reactive protein concentrations is skewed in both genders with a 50th percentile of ~1.5 mg/L (excluding women on hormone replacement therapy). Race differences have been reported.8 Most studies have reported no relationship with age but circadian and seasonal variation.9 C-reactive protein concentrations are increased by smoking, obesity, and hormone replacement therapy and reduced by exercise, moderate alcohol drinking, and statin use.2,3,7 Correction for these factors is essential in reference range studies.

C-reactive protein assays are not standardized.2 We recommend the use of third-generation high-sensitivity C-reactive protein assays that combine features of standard and high-sensitivity C-reactive protein assays. Required assay precision should be <10% in the range of 3 and 10 mg/L.

Critical clinical concepts

(1) C-reactive protein concentrations are reported in mg/L.
(2) C-reactive protein test results are method-dependent, but classification of patients into risk categories is usually comparable.
(3) Third-generation high-sensitivity C-reactive protein assays are recommended.
(4) No specific patient preparation before blood sampling is necessary.
(5) The in vitro stability of C-reactive protein is high.
Clinical use of C-reactive protein in acute coronary syndrome

Higher C-reactive protein concentrations are associated with complex, vulnerable atherosclerotic plaques, suggesting that high-sensitivity C-reactive protein elevations represent a marker of systemic atherosclerotic plaque instability. Minor increases might reflect inflammation in coronary plaques or injured coronary walls after stenting. However, there is no association between C-reactive protein and the extent of coronary artery disease, and C-reactive protein has not been causally related to coronary events. Nonetheless, C-reactive protein elevations are associated with mortality but only weakly with recurrent MI.

C-reactive protein measurements have no value for the diagnosis of ST-segment elevation AMI (STEMI), since 41% of STEMI patients have low (<2 mg/L) concentrations on admission. Furthermore, in many, values are not significantly different in samples obtained 2–4, and 4–6 h after onset of symptoms. However, high C-reactive protein concentrations before percutaneous coronary intervention (PCI) in STEMI are related to recurrent MI and death rates at 1-year follow-up. Moreover, C-reactive protein values correlate with infarct size by magnetic resonance imaging, although markers of myocardial necrosis, such as cardiac troponin (cTn), correlate more closely while providing similar predictive value for mortality.

C-reactive protein measurements are not useful for the diagnosis of non-STEMI either. Its use has been advocated during the acute phase for risk stratification but conclusive evidence for its incremental value is absent. C-reactive protein is a predictor of short- and long-term cardiovascular complications in ACS, and C-reactive protein levels contribute incremental information over and above clinical risk scores or other biomarkers in some but not all studies. In addition, there are few studies to date of C-reactive protein together with more sensitive cTn assays and none with high-sensitivity cTn assays.

Figure 1 - Possible pathophysiological effects of C-reactive protein in atherosclerosis. Aggregated C-reactive protein selectively binds LDL and VLDL in serum, thereby potentially participating in the mechanisms involved in plaque formation and destabilization, and shows some of the key properties of antibodies and may contribute to immune responses by activation of antigen presenting cells. Procoagulant effects have been reported in vitro as well. C-reactive protein induces increased expression of adhesion molecules and modulation of NO synthesis. Dashed arrow represents weak evidence, whereas continuous arrow denotes evidence confirmed by several studies. APC, antigen presenting cell; CRP, C-reactive protein; LDL, low-density lipoprotein; NO, nitric oxide; VLDL, very low-density lipoprotein; TF, tissue factor.
C-reactive protein is not helpful in selecting an invasive or conservative strategy in ACS. However, an increased C-reactive protein level is an independent prognostic indicator for death or non-fatal MI following PCI. It is difficult to advocate C-reactive protein as a primary target for therapy since drugs that specifically influence only C-reactive protein alone do not exist. Nonetheless, in prevention studies post ACS, lower levels of C-reactive protein following statin therapy predict greater subsequent risk reductions.

Based on early studies, a decision limit for risk stratification of 10 mg/L was suggested although other limits have been proposed as well. C-reactive protein has usually been tested in samples drawn on admission, but the optimal time to assess risk has not been systematically investigated.

Critical clinical concepts

1. C-reactive protein is an established marker for diagnosing and monitoring infection, inflammation, and tissue injury.
2. C-reactive protein measurement in primary prevention predicts future cardiovascular events with significance similar to that of total and HDL cholesterol.
3. C-reactive protein measurement in secondary prevention predicts risk of recurrent MI, stroke, and cardiovascular death.
4. C-reactive protein measurements have no value for diagnosing AMI.
5. C-reactive protein release is related to infarct size and risk in STEMl patients.
6. C-reactive protein is not helpful for the choice of an invasive or conservative strategy in ACS.
7. C-reactive protein measurement after ACS and after PCI can be used to identify patients in whom an intensive risk factor modification is useful.
8. For cardiovascular prevention, a C-reactive protein value of >3 mg/L is considered high risk but a limit ≥10 mg/L seems more appropriate in ACS patients.

Conclusions and outlook

Given the central role of inflammation in the pathogenesis of atherothrombosis, this is an area of active research. There are many new inflammatory markers proposed for use, but at present none of them has emerged as clinically more useful than C-reactive protein. New ways of conceptualizing acute atherothrombotic diseases may facilitate new approaches in this critical field.

Conflict of interest: LB has been consultant for Siemens Diagnostics, Roche Diagnostics and Abbott Diagnostics; WK has received research grants from Roche Diagnostics and Radiometer A/S, lecture fees from Roche Diagnostics and Siemens Healthcare Diagnostics and has been member of the scientific advisory boards of Philips Healthcare, Siemens Healthcare, Beckman Coulter, FIOimi and bio-Merieux; HK holds a patent on the cardiac troponin T assay jointly with Roche Diagnostics; ASJ has received consulting honoraria from most of the major diagnostic companies including Beckman-Coulter and Siemens; MT has been member of the advisory boards of Roche Diagnostics and Abbott Diagnostics and he has received lecture honoraria from Biosite/Inverness, Abbott Diagnostics and Dade Behring; JA received lecture honoraria from Roche Diagnostics and Siemens Diagnostics; PC is member of the Diagnostics Advisory Committee of the National Institute of Clinical Excellence in the UK; CH has been consultant for Abbott Diagnostics and Roche Diagnostics; MG has been consultant for Roche Diagnostics and he has received research grants from Roche Diagnostics, Siemens Diagnostics and Beckman Coulter; MP received consulting honoraria from Siemens, Roche and Abbott Diagnostics; PV has received lecture honoraria and research grants from Abbott, Beckman Coulter, Roche Diagnostics, Siemens and is currently consultant for Abbott, bio-Merieux, Philips and Radiometer.

References

A 78-year-old male patient with advanced lung cancer and liver metastasis was admitted to our hospital because of persistent and critical airflow obstruction after acute myocardial infarction. He had a history of myocardial infarction and arteriosclerosis obliterans. Echocardiography showed akinesis of the cardiac apex, and aortographic studies revealed severe hypokinesis of the inferior wall, reflecting old infarction. His cardiac function was significantly impaired.

His blood pressure was 130/80 mmHg, and his heart rate was 100 beats per minute. Physical examination revealed that the patient was in a state of shock, with mild tachypnea and diaphoresis. The jugular venous pressure was elevated, and the apex beat was displaced laterally. The patient had a history of hyperkalaemia, and although no electrocardiographic abnormalities associated with hyperkalaemia were detected during hospitalization, he suffered sudden death due to ventricular fibrillation. The clinicians suspected hyperkalaemia was accompanied by elevated levels of aminotransferases and lactate dehydrogenase. Because his disease was an incurable malignancy, palliative care was chosen for his treatment.

Although no electrocardiographic abnormalities associated with hyperkalaemia were detected during hospitalization, he suffered sudden death due to ventricular fibrillation. The clinicians suspected that the uncontrolled hyperkalaemia had induced this fatal arrhythmia.

An autopsy was performed in which the lung cancer (pleomorphic carcinoma) with extensive blood-borne metastases was confirmed. Fresh myocardial necrosis was found to be superimposed on an area of fibrosis corresponding to old infarction in the left anterior wall (Panel A, arrowheads). This finding suggested that the precise cause of death was not hyperkalaemia but rather acute myocardial infarction.

We then investigated the coronary arteries thoroughly to identify a culprit vascular lesion. Surprisingly, a mixture of blood clot and tumour cell aggregation were identified endarterectomy of the left anterior descending artery (Panel B, asterisk). We surmised that coronary tumour embolism was a primary reason for his sudden death.

Tumour embolism is an extremely rare cause of acute myocardial infarction. However, clinicians should recognize it as a potential aetiology of acute coronary syndrome.

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2013. For permissions please email: journals.permissions@oup.com