The Cardiology 1 (3-4) : 194-199, 2005

CRP and Ishemic Heart Disease

Huseyin Gunduz, Huseyin Arinc, Nuri Erguzel and Cihangir Uyan
Department of Cardiology, ¤zzet Baysal Faculty of Medicine,
Abant ¤zzet Baysal University, 14280 Bolu Turkey

Abstract: There are increasing evidences that chronic inflammation plays a role in all stages of the atherosclerotic process. A variety of inflamation markers have been shown to predict future cardiovascular risk, of these CRP the most extensively studied. The use of CRP may significantly add to our ability to correctly identify patients presenting with ischemic heart disease who are at high risk for future cardiovascular events. In addition to providing improved global risk prediction, CRP screening in specific populations may also provide a method of targeting preventive interventions, such as statin therapy. The role and use of CRP in ischemic heart diseases are main focuses of this article

Key words: CRP and ischemic heart disease

INTORDUCTION

Cardio Vascular Disease (CVD) is the major cause of death in the world. Atherosclerosis, the underlying cause of most CVD, is an inflammatory process that starts early in life and progresses slowly and silent for decades. Current evidence supports a central role for inflammation in all phases of the atherosclerotic process, from lesion initiation through to progression and, ultimately, the thrombotic complications of atherosclerosis[1-3].

Elevated levels of several inflammatory biomarkers have been demonstrated to have predictive value for future cardiovascular events. Of these potential markers, C-reactive protein (CRP) has been the most extensively studied. It may help predict short- and long-term cardiovascular outcomes, and the additional CRP screening to traditional lipid testing has the potential to identify individuals at high risk for future cardiovascular events who may benefit from target preventive interventions[4-6]

The role and use of CRP and inflammatory processes in the pathogenesis of ischemic heart diseases have been briefly discussed in this review.

C-reactive protein as biochemical indicator: C-reactive Protein (CRP) is a primitive acute phase inflammatory protein that is released in response to acute injury, infection, or other inflammatory stimuli, such as hypersensitivity reactions, inflammatory diseases, allograft rejection, malignancy, necrosis, and trauma, and is also increased during pregnancy[7,8]

CRP is known to be produced primarily in the liver, synthesized by hepatocytes in response to intermediary inflammatory cytokines particularly IL-6. There are other possible sites of CRP expression including atherosclerotic plaque, normal human artery, heart, kidney and adipocytes[9,10].

C-reactive protein has a normal range of less than 2 mg L^{1} in healthy individuals; with illness, this level increases in the first 6-8 h and can reach peak levels approaching 300 mg L^{1} after approximately 48 h[11]. Upon resolution of inflammation or tissue destruction, CRP level rapidly decline with anelimination half-life estimated at 4-9 h[12].

CRP level in healthy subjects over 24 h measured hourly was no significant individual diurnal variation, which makes it possible to measure CRP at any time of the day[13].Fasting samples are not required and samples have been shown to be stable at room temperature[14]. It is found that mean CRP level in serum was increasing slightly with age[15]. There is no difference in mean concentrations between men and women although higher levels are found late in pregnancy[12]. C-reactive protein levels are higher among smokers, and obese subjects. CRP levels are also associated with increased blood pressure, and are predictive of the development of hypertension[16,17].

CRP is easily and inexpensively measured, and standardized high-sensitivity (hs-CRP) assays are commercially available that provide similar results in stored, fresh or frozen plasma[18,19]. Several approaches have been used by investigators to measure hs-CRP, including the labeling of anti-CRP antibodies with either enzyme (ELISA), or fluorescent compound, and attaching the antibody either monoclonal or polyclonal to

Corresponding Author: Huseyin Gunduz,Department of Cardiology, ¤zzet Baysal Faculty of Medicine, Abant ¤zzet Baysal University, 14280 Bolu Turkey

polystyrene beads[20-25]. However, taking into account the moderate repeatability of CRP measurement over time, its predictive value could be even further improved by making several serial measurements[26].

CRP and atheroscleosis: CRP is an important cardiovascular risk factor and deposits in the arterial wall during atherogenesis, colocalizing with the terminal complement complex and foam cells. CRP upregulates the expression of adhesion molecules, and mediate proinflammatory factor induction in several kinds of cells in artery wall as well as circulating monocytes[27]. It increases opsonization of LDL and mediates the uptake of LDL into the macrophages, which then become foam cells.

Accumulating studies have been showed that CRP may be a direct cause of CVD. Those data suggest that CRP may indeed a direct proinflammatory factor involving in the initiation, evolution and progression of atherosclerosis. Furthermore, it has been found that baseline levels of CRP are a strong independent predictor of risk of future myocardial infarction (MI), stroke, peripheral vascular disease, and vascular death among healthy individuals including man and women without known vascular disease by several investigators[28,29] .

Clinical Evidence of CRP as a Predictor of ischemic heart disease: CRP level correlate with clinical severity of CAD and coronary events in both acute and subacute phases of myocardial ischemia. Myocardial ischemia without necrosis does not induce a rise of circulating CRP levels, as was demonstrated in patients with variant angina pectoris with documented episodes of myocardial ischemia[30,31]. Likewise, it has been shown that CRP levels are significantly lower in patients with stable angina than in those with unstable angina (UA) or MI.[32].

The potential association between CRP and cardiovascular prognosis was first illustrated in patients presenting with acute coronary syndrome (ACS)[33,34] and was confirmed the prognostic utility of CRP among patients presenting with ACS both in the short and long term[35-37] .

MI results in necrosis of cardiac muscle, which is a stimulus for CRP production[38]. hs-CRP levels rise in parallel to the amount of muscle necrosis, peaking at around day 2 post MI and then falling. Persistent elevations of hs-CRP 14 days after MI, suggesting ongoing inflammation, predict recurrent events[39].

In patients with UA, elevated hs-CRP is strong predictor of plaque instability. Liuzzo *et al*.[34] showed that patients with UA who had elevated blood CRP concentrations of = 3.0 mg LG^1 had more ischaemic episodes compared with patients with CRP levels = 3.0 mg LG^1. hs-CRP levels may guide management by stratifying patients into higher and lower risk groups.hs-CRP levels add prognostic information independent of troponin level and the two measurements together may give greater insight into the patient's global cardiovascular risk, thereby guiding management [40,41].

Recent data aonfirm that CRP is a strong independent predictor of short and long term mortality among patients with ACS treated revascularization[42]. Elevated CRP levels also may represent a biomarker for patients who are most susceptible to reocclusion. A recent analysis by Chew *et al*.[43] shows that CRP predicts the risk of death or MI at 30 days among patients undergoing percutaneous coronary intervention. Data from the FRISC-II study suggest that the benefits of an early invasive approach may be greatest among those with evidence of a heightened inflammatory response[44]. In the absence of an elevated inflammatory response, a less invasive approach may prove equally effective. In addition, among patients who undergo coronary artery bypass grafting, those with elevated CRP levels experience significant recurrent events in the 6 years following surgery compared with patients with normal or low CRP levels[45]. In patients receiving a cardiac transplant, elevated CRP levels may be a significant biomarker for cardiac allograft vasculopathy or rejection, or both[46].

The effect of medical tehrapy on CRP: Although no specific therapies have been developed to decrease CRP and there is no direct evidence that risk of future cardiovascular events is diminished by reducing CRP, studies have been showed that aspirin and statin are effective in decreasing the incidence of future coronary events in those with increased CRP concentration. Evidence suggests that all statins lower hsCRP levels. This effect was not dose dependent and not consistently associated with the statins' effect in reducing vascular risk[47]. Further data suggest that the benefits of statin therapy may be greatest among those with elevated CRP levels, either among post-MI patients[48]. or in the primary prevention setting[49].

The effect of aspirin on CRP levels is controversial[50,51], but the benefit of aspirin therapy in preventing future MI appears to be greatest among those with elevated CRP levels[28].

Recently, several other drugs administration have

also shown the decreased effects on serum CRP level including angiotensin II converting enzyme inhibitor, angiotensin II receptor blocker[52], beta blocker[53] as well as antiplelet drugs, for example ezetimibe[54] and clopidogrel[55] in small sample size clinical trials. The other interventions,

such as lifestyle changes, weight loss, stop smoking have also been demonstrated a benefit effects on those inflammatory markers, including CRP[56,57].

CONCLUSIONS

Measurement of CRP in addition to lipid levels may improve identification of individuals at risk for cardiovascular events[29], and that CRP may be an even stronger predictor than LDL-C level, particular when LDL-C is low[58], and may provide additional prognostic information to that conveyed by the Framingham risk score[59]

The CDC/AHA statement contains recommendations for the use of CRP in the diagnosis and management of cardiovascular disease. The use of the high-sensitivity CRP assay to perform at least two measurements, preferably 2 weeks apart, is advocated. To categorise risk, cut points for CRP according to approximate tertiles in the adult population have been suggested: low risk (= 1.0 mg LG^{1}), average risk (1.0-3.0 mg LG^{1}), and high risk (= 3.0 mg LG^{1})[62]. A CRP level >10 mg LG^{1} generally indicates the presence of a significant acute-phase response, and further assessment is required to determine the cause[60,61].

As a result the use of CRP and other novel inflammatory markers may significantly add to our ability to correctly identify patients presenting with ACS who are at high risk for future cardiovascular events. Individuals with evidence of heightened inflammation may benefit most from an aggressive modification of lifestyle and an intensification of proven preventive therapies such as aspirin and statins. Moreover, the benefits of an early invasive strategy may also be greatest among those with elevated levels of inflammatory biomarkers.

REFERENCES

1. Ross, R., 1999. Atherosclerosis an inflammatory disease. N. Engl. J. Med., 340: 115- 126.
2. Blake, G.J. and P.M. Ridker, 2002. Inflammatory bio-markers and cardiovascular risk prediction. J. Intern. Med., 252: 283- 294.
3. Li, J.J., C.H. Fang and R.T. Hui, 2005. Is hypertension an inflammatory disease? Med. Hypotheses, 64: 236-240.
4. Ferranti, S.D. and N. Rifai, 2002. C-reactive protein and cardiovascular disease: a review of risk prediction and interventions. Clin. Chim. Acta., 317: 1-15.
5. Rifai, N. and P.M. Ridker, 2001. High-sensitivity C-reactive protein: A novel amd promising marker of coronary heart disease. Clin. Chem., 47: 403-411.
6. Koenig, W., 2005. Predicting risk and treatment benefit in atherosclerosis: the role of C-reactive protein. Intl. J. Cardiol., 98: 199-206.
7. Du Clos, T.W., 2000. Function of C-reactive protein. Ann. Med., 32: 274-278.
8. Wilson, A.M., M.C. Ryan and A.J. Boyle, 2006. The novel role of C-reactive protein in cardiovascular disease: Risk marker or pathogen. Intl. J. Cardiol., 106: 291-297.
9. Yasojima, K., C. Schwab, E.G. McGeer and P.L. McGeer, 2001. Generation of Creactive protein and complement components in atherosclerotic plaques. Am. J. Pathol., 158: 1039- 1051.
10. Ouchi, N., S. Kihara, T. Funahashi, *et al*., 2003. Reciprocal association of Creactive protein with adiponectin in blood stream and adipose tissue. Circulation, 107: 671- 674.
11. Ballou, S.P. and I. Kushner, 1992. C-reactive protein and the acute phase response. Adv. Intl. Med., 37: 313-336.
12. Young, B., M. Gleeson and A.W. Cripps, 1991. C-reactive protein: A critical review. Pathology, 23: 118-124.
13. Meier-Ewert, H.K., P.M. Ridker, N. Rifai, N. Price, D.F. Dinges and J.M. Mullington, 2001. Absence of diurnal variation of C-reactive protein levels in healthy human subjects. Clin. Chem., 47: 426-430.
14. Ockene, I.S., C.E. Matthews, N. Rifai, P.M. Ridker, G. Reed and E. Stanek,2001. Variability and classification accuracy of serial high-sensitivity Creactive protein measurements in healthy adults. Clin. Chem., 47: 444-450.
15. MacLeod, C.M. and O.T. Avery, 1941. The occurrence during acute infections of a protein not normally present in blood. Isolation and properties of the C-reactive protein. J. Exp. Med., 73: 183.
16. Blake, G.J., N. Rifai, J.E. Buring and P.M. Ridker, 2003. Blood pressure, C-reactive protein, and risk of future cardiovascular events. Circulation, 108: 2993-2999.

17. Sesso, H.D., J.E. Buring and N. Rifai, *et al*., 2003. C-reactive protein and the risk of developing hypertension. JAMA, 290: 2945-2951.
18. Rifa,i N., R.P. Tracy and P.M. Ridker, 1999. Clinical efficacy of an automated highsensitivity C-reactive protein assay. Clin. Chem., 45: 2136- 2141.
19. Khuseyinova, N., A. Imhof and G. Trischler, *et al*., 2003.Determination of Creactive protein: Comparison of three high-sensitivity immunoassays. Clin. Chem., 49: 1691-1695.
20. Wilkins, J., J.R. Gallimore, E.G. Moore and M.B. Pepys, 1998. Rapid automated high sensitivity enzyme immunoassay of Creactive protein. Clin. Chem., 44: 1358-1361.
21. Ledue, T.B., D.L. Weiner, J.D. Sipe, S.E. Poulin, M.F. Collins and N. Rifai, 1998. Analytical evaluation of particle-enhanced immunonephelometric assays for C-reactive protein, serum amyloid A and mannose-binding protein in human serum. Ann. Clin. Biochem., 35: 745-753.
22. Macy, E.M., T.E. Hayes and R.P. Tracy, 1997. Variability in the measurement of C-reactive protein in healthy subjects: implications for reference intervals and epidemiological applications. Clin. Chem., 43: 52-58.
23. Kapyaho, K., M.G. Welin, P. Tanner, T. Karkkainen and T. Weber, 1989. Rapid determination of C-reactive protein by enzyme immunoassay using two monoclonal antibodies. Scand J. Clin. Lab. Invest., 49: 389-393.
24. Eda, S., J. Kaufmann, M. Molwitz and E. Vorberg, 1999. A new method of measuring C-reactive protein, with a low limit of detection, suitable for risk assessment of coronary heart disease. Scand J. Clin. Lab. Invest. Suppl., 230: 32-35.
25. Borque, L., L. Bellod, A. Rus, M.L. Seco and F. Galisteo-Gonzalez, 2000. Development and validation of an automated and ultrasensitive immunoturbidimetric assay for C-reactive protein. Clin. Chem., 46: 1839-1842.
26. Koenig, W., M. Sund, M. Frfhlich, H. Lfwel, W.L. Hutchinson and M.B. Pepys, 2003. Refinement of the association of serum C-reactive protein concentration and coronary heart disease risk by correction for withinsubject variation over time. Results from the MONICA-Augsburg studies 1984 and 1987. Am. J. Epidemiol., 158: 357-364.
27. Ballou, S.P. and R.P. Cleveland, 1991. Binding of human C-reactive protein to monocytes: Analysis by flow cytometry. Clin. Exp. Immunol., 84: 329-335.
28. Ridker, P.M., M. Cushman, M.J. Stampfer, R.P. Tracy and C.H. Hennekens, 1997. Inflammation, aspirin and the risk of cardiovascular disease in apparently healthy men. N. Engl. J. Med., 336: 973-9.
29. Ridker, P.M., C.H. Hennekens, J.E. Buring and N. Rafai, 2000. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N. Engl. J. Med., 342: 836-843.
30. Liuzzo, G., L.M. Biasucci, A.G. Rebuzzi, R. Gallimore, G. Caligiuri, G.A. Lanza, G. Quaranta, C. Monaco, M.B. Pepys and A. Maseri, 1996. Plasma protein acute-phase response in unstable angina is not induced by ischemic injury. Circulation, 94: 2373-2380.
31. Lagrand, W.K., C.A. Visser, W.T. Hermens, H.W. Niessen, F.W. Verheugt, G.J. Wolbink and C.E. Hack, 1999. C-reactive protein as a cardiovascular risk factor: more than an epiphenomenon? Circulation, 100: 96-102.
32. Mitra, B. and M. Panja, 2005. High sensitive C-reactive protein: a novel biochemical markers and its role in coronary artery disease. J. Assoc. Physicians India, 53: 25-32.
33. Berk, B.C., W.S. Weintraub and R.W. Alexander, 1990. Elevation of C-reactive protein in bactiveQ coronary artery disease. Am. J. Cardiol., 65: 168-172.
34. Liuzzo, G., L.M. Biasucci and J.R. Gallimore, *et al*., 1994. The prognostic value of C-reactive protein in severe unstable angina. N. Engl. J. Med., 331: 417- 424.
35. Morrow, D.A., N. Rifai and E.M. Antman, *et al*., 1998. C-reactive protein predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. Thrombolysis in myocardial infartion. J. Am. Coll. Cardiol., 31: 1460-1465.
36. Heeschen, C., C.W. Hamm, J. Bruemmer and M.L. Simoons, 2000. Predictive value of C-reactive protein and troponin T in patients with unstable angina: A comparative analysis. CAPTURE Investigators. Chimeric c7E3 AntiPlatelet Therapy in Unstable angina REfractory to standard treatment trial. J. Am. Coll. Cardiol., 35: 1535-1542.

37. Lindahl, B., H. Toss, A. Siegbahn, P. Venge and L. Wallentin, 2000 for the FRISC study group. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. N. Engl. J. Med., 343: 1139- 1147.
38. Casl, M.T., B. Surina and I. Glojnaric-Spasic, *et al*., 1995. Serum amyloid A protein in patients with acute myocardial infarction. Ann. Clin. Biochem., 32: 196-200.
39. Morrow, D.A., N. Rifai and E.M. Antman, *et al*., 1998. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: A TIMI 11a Substudy. Thrombolysis in myocardial infarction. J. Am. Coll. Cardiol., 31: 1460-1465.
40. James, S.K., P. Armstrong and E. Barnathan, *et al*., 2003. Troponin and C-reactive protein have different relations to subsequent mortality and myocardial infarction after acute coronary syndrome: a Gusto-IV substudy. J. Am. Coll. Cardiol., 41: 916-924.
41. Blake, G.J. and P.M. Ridker, 2003. C-reactive protein and other inflammatory risk markers in acute coronary syndromes. J. Am. Coll. Cardiol., 41: 37-42.
42. Mueller, C., H.J. Buettner and J.M. Hodgson, *et al*., 2002. Inflammation and long-term mortality after non–ST-elevation acute coronary syndrome treated with a very early invasive strategy in 1042 consecutive patients. Circulation, 105: 1412-1415.
43. Chew, D.P., D.L. Bhatt and M.A. Robbins, *et al*., 2001. Incremental prognostic value of elevated baseline C-reactive protein among established markers of risk in percutaneous coronary intervention. Circulation, 104: 992-997.
44. Lindmark, E., E. Diderholm, L. Wallentin and A. Siegbahn, 2001. Relationship between interleukin 6 and mortality in patients with unstable coronary artery disease: effects of an early invasive or noninvasive strategy. JAMA, 286: 2107-2113.
45. Milazzo, D., L.M. Biasucci and N. Luciani, *et al*., 1999. Elevated levels of C-reactive protein before coronary artery bypass grafting predict recurrence of ischemic events. Am. J. Cardiol., 84: 459-461.
46. Eisenberg, M.S., H.J. Chen and M.K. Warshofsky, *et al*., 2000. Elevated levels of plasma C-reactive protein are associated with decreased graft survival in cardiac transplant recipients. Circulation, 102: 2100-2104.
47. Balk, E.M., J. Lau and L.C. Goudas, *et al*., 2003. Effects of statins on nonlipid serum markers associated with cardiovascular disease: A Systematic Review. Ann. Intl. Med., 139: 670- 682.
48. Ridker, P.M., N. Rifai and M.A. Pfeffer, *et al*., 1998. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol And Recurrent Events (CARE) Investigators. Circulation, 98: 839-844.
49. Ridker, P.M., N. Rifai and M. Clearfield, *et al*., 2001. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. N. Engl. J. Med., 344: 1959-1965.
50. Feldman, M., I. Jialal, S. Devaraj and B. Cryer, 2001. Effects of low-dose aspirin on serum C-reactive protein and thromboxane B2 concentrations: a placebo-controlled study using a highly sensitive C-reactive protein assay. J. Am. Coll. Cardiol., 37: 2036-2041.
51. Ikonomidis, I., F. Andreotti and E. Economou, *et al*., 1999. Increased proinflammatory cytokines in patients with chronic stable angina and their reduction by aspirin.Circulation, 100: 793-798.
52. Lauten, W.B., Q.A. Khan, S. Rajagopalan, S.T. Lerakins, Rahman and S. Parthasarathy, *et al*., 2003. Usefulness of quinapril and irbesartan to improve the anti-inflammatory response of atorvastatin and aspirin in patients with coronary heart disease.Am. J. Cardiol., 91: 1116-1119.
53. Anzai, T., T. Yoshikawa, T. Takahashi, Y. Maekawa, T. Okabe and Y. Asakura, *et al*., 2003. Early use of beta-blockers is associated with attenuation of serum-Creactive protein elevation and favorable short-term prognosis after acute myocardial infarction. Cardiology. C-reactive protein a direct cause of cardiovascular diseases 505, 99: 47-53.
54. Ballantyne, C.M., J. Houri, A. Notarbartolo, L. Melani, L.J. Lipka and R. Suresh, *et al*., 2003. Effect of Ezetimibe coadministration with atorvastatin in 628 patients with primary hypercholesterolemia: A prospective, randomized, double-blind trial. Circulation, 107: 2409-2415.
55. Cha, J.K., M.H. Jeong, K.M. Lee, H.R. Bae, Y.J. Lim and K.W. Park, *et al*., 2002. Changes in platelet p-selectin and in acute atherosclerotic ischemic stroke treated with a loading dose of clopidogrel. J. Thromb Thrombolysis, 14: 145-150.
56. Esposito, K., A. Pontillo, C. Di Palo, G. Giugliano, M. Masella and R. Marfella, *et al*., 2003. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: A randomized trial. JAMA, 289: 1799-1804.

57. De Maat, M.P. and C. Kluft, 2002. The association between inflammation markers, coronary artery disease and smoking. Vasc Pharmacol., 39: 137-139.
58. Blake, G.J. and P.M. Ridker, 2001. Novel clinical markers of vascular wall inflammation. Circ. Res., 89: 763-771.
59. Ridker, P.M., N. Rifai, L. Rose, J.E. Buring and N.R. Cook, 2002. Comparison of Creactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N. Engl. J. Med., 347: 1557-1565.
60. Pearson, T.A., G.A. Mensah and R.W. Alexander, *et al*., 2003. Centers for Disease Control and Prevention; American Heart Association. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation, 107: 499- 511.
61. Pepys, M.B. and G.M. Hirschfield, 2003. C-reactive protein: A critical update. J. Clin. Invest., 111: 1805-1812.