Journal of
Cardiology & Cardiovascular Therapy

Review Article
Volume 1 Issue 1 - August 2015

J Cardiol Cardiovasc Ther


# Inflammation in Acute Coronary Syndromes: Systemic, Coronary Plaque, or Myocardial Source?

**Osmar Antonio Centurion***

*Departmento de Investigacion en Ciencias de la Salud, Sanatorio Metropolitano, Fernando de la Mora, Paraguay*

*Cardiology Division, First Department of Internal Medicine, Clinical Hospital, Asuncion National University, Paraguay*

**Submission: September 15, 2015; Published: September 21, 2015**

***Corresponding author:** Osmar Antonio Centurion, Professor of Medicine, Asuncion, National University, Cardiology Division, First Department of Internal Medicine, Clinical Hospital Trejo y Sanabria 1657, Sajonia Asuncion, Paraguay, Email: osmarcenturion@hotmail.com

**Abstract**

Atherosclerosis is the focal expression within the artery of a systemic disease, in which traditional cardiovascular risk factors and immune factors play a key role. It is well accepted that circulating biomarkers, reliably predict major cardiovascular events, including acute coronary syndromes (ACS) or death. The therapeutic management of patients with ACS in the last decade has shown a dramatic evolution in the understanding of reperfusion. The constant changes in the methodology of reperfusion invite to integrate the recent findings for a better management in the contemporary clinical practice [1-5].

Serum biomarkers reflecting the activity of biological processes involved in plaque growth or destabilization may provide great help in establishing the appropriate clinical management, and therapeutic interventions. The medicine based evidence strongly suggests the importance of an inflammatory ethiology in the ACS. The traditional coronary risk factors are known to terminate in a common final pathway that develops an inflammatory process in the artery wall [6,7]. Recent evidence indicates that the first steps in atherosclerosis are inflammatory in nature. The discovery of macrophages, T limphocytes, dendritic cells, and mast cells in atherosclerotic lesions; the detection of HLA class II antigen expression; and the finding of secretion of several cytokines point to the involvement of immune inflammatory mechanisms in the pathogenesis of atherosclerosis. Furthermore, atherosclerotic lesions contain immunoglobulin deposits and complement, strongly suggesting the involvement of complement activation in atherogenesis. Bacterial and viral infections have been implicated as potential initiating factors. Infections are known to increase blood viscosity, cause hypercoagulability, and influence the serum lipid profile. Endotoxin may also contribute to endothelial cell production of free radicals which may oxidize LDL-cholesterol [6-9]. In this inflammatory status several substances are liberated, namely, cytokines, C-reactive protein, tissue factors, that facilitates the development of arterial thrombus. Therefore, several Inflammatory markers are elevated in ACS. The sytemic levels of inflammatory marker in patients with stable angina are somewhat lower than those found in the ACS. The continuous refinements in the different therapeutic strategies, the combination of scientific understanding in the adequate utilization of novel inflammatory markers, the new pharmacologic agents, and the new techniques in PCI with newer drug-eluting stents will dissipate our doubts and improve our therapeutic management in ACS based on medical evidence. Interesting work has been accomplished in characterizing the source of inflammation in ACS. However, further studies are needed to clearly define the systemic, coronary plaque or myocardial source of inflammation to improve the therapeutic maneuvers to manage this very complex entity.

## Introduction

Inflammation of the artery wall is a critical component of atherosclerosis and brings about several pathological changes within the vessel wall such as edema, vasa vasorum dilation and proliferation, and immune cells infiltration. This atherosclerotic plaque formation is a chronic process starting early in life. Luminal narrowing is determined by gradual plaque growth and arterial remodeling. Plaque accumulation can be compensated for by expansive remodeling of the vessel wall, however, failure to enlarge and even constrictive remodeling also frequently occur [10,11]. The risk of plaque rupture depends on plaque composition rather than on plaque size. Lesions with a large lipid core and increase macrophage infiltration may have a higher risk for disruption than sclerotic plaques. It is now known that a soft lipid-rich core, a thin cap and inflammation in cap and shoulders of the plaque make it vulnerable for rupture [12,13].

A systemic inflammatory response often accompanies ACS, and its presence has been widely recognized as a marker of further coronary events [14]. Accumulating evidence suggests that inflammation within the atherosclerotic plaque contributes to its destabilization and subsequent disruption

[15-17]. Although debatable, the widely held view is that systemic inflammation in unstable angina originates from inflammatory proccess within the arterial wall after plaque disruption. Inflammation of the cap is considered as an important mechanism underlying cap destruction. Evidence for a role of inflammation in plaque rupture has been demonstrated by localization of inflammation and plaque rupture sites [12,16-19]. Evidence for local inmunological activation has been provided by the demonstration of activated T lymphocytes and macrophages and extensive expression of human leucocyte antigen class II molecules in the atherosclerotic plaque [20].

However, the focus of inflammation may not precisely reside within the coronary vessel itself but rather in the injured myocardium distal to the disrupted plaque. Therefore, the precise location and stimulus for the inflammatory response in ACS remains to be determined. Microscopic multifocal myocardial infarction associated with embolized platelet microthrombi has been well described in ACS and is believed to be the mechanism for the elevation in troponin T found in these patients [21,22]. On the other hand, several elevated systemic markers of inflammation were found to predict adverse events in patients with ACS. C-reactive protein, a non-specific marker of inflammation that also has a direct inflammatory activity in atherosclerosis has been associated with adverse cardiovascular outcomes in patients with coronary artery disease.

Suzuki et al. [23] provided insight into the link between systemic and coronary levels of inflammation which is associated with vulnerable coronary morphology in the setting of ACS. They examined systemic and culprit coronary levels of three inflammatory mediators such as high sensitive C-reactive protein (hs-CRP), interleukin-6 (IL-6), and matrix metalloproteinase-9 (MMP-9) in patients with the early phase of acute myocardial infarction (AMI). The measurements of culprit coronary levels of inflammatory markers were performed in the thrombus retrieved by the rescue percutaneous thrombectomy device. The morphology of the plaque was assessed with intravascular ultrasound. Suzuki et al. [23] found a nearly equivalent amount between systemic and culprit coronary levels of hs-CRP, but significantly higher concentrations of coronary levels of both IL-6 and MMP-9. These findings suggest a systemic production of acute phase CRP at the onset of ACS, and local production of both IL-6 and MMP-9 in culprit coronary lesions. They also found a positive relation of systemic levels of hs-CRP with coronary levels of IL-6 and suppose that systemic elevation of acute phase protein in response to culprit coronary production of inflammatory cytokines such as IL-6 may be the underlying mechanism of the link between systemic and coronary inflammation in the setting of ACS. Although, these inflammatory markers were measured at the early phase of AMI with minimal elevation of serum creatine kinase levels in order to minimize the influence of AMI in both systemic and coronary levels of inflammation, It is not known to what extent and the exact influence that myocardial cell damage might have exerted on the inflammatory markers.

CRP is an extremely sensitive, nonspecific, acute-phase reactant produce in response to most forms of tissue injury, infection, and inflammation, and regulated by cytokines, including IL-6, IL-1 and TNF-alpha [24-26]. There is substantial evidence that CRP may contribute directly to the pathogenesis of atherothrombosis. CRP is ligand binding protein that binds to the plasma membranes of damaged cells. Aggregated but not soluble native CRP selectively binds LDL and VLDL-cholesterol from whole plasma and could thereby participate in their atherogenic accumulation [27-29]. Complexed CRP also activates complement and can be proinflammatory. However, there are conflicting reports about the presence of CRP in atheromatous lesions, and claims that CRP affects platelet functions are also controversial [30-32]. The capacity of CRP to enhance tissue factor production suggests a possible causative link between increased CRP values and coronary events. The stimuli responsible for the generally modest elevations in plasma CRP predictively associated with coronary events are not known. They may arise in the atheromatous lesions themselves and reflect the extent of atherosclerosis and the local inflammation that predisposes to plaque instability, rupture, and occlusive thrombosis. On the other hand, increased CRP production may result from inflammation elsewhere in the body that is somehow proatherogenic and procoagulant. This latter alternative is in accord with the results of Suzuki et al. [23], since they found no significant differences in systemic or culprit coronary lesion of hs-CRP levels, suggesting rather a systemic production of acute phase CRP at the initiation of the ACS.

The complex interplay between factors intrinsic to the plaque and extrinsic events leading to coronary thrombosis is not yet completely understood. Coronary instability is thought to reflect local disruption of the vulnerable plaque. Postmortem studies in patients dying of AMI have consistently found inflammatory cell infiltration at the site of rupture of the culprit atherosclerotic plaque, thus suggesting that it might play a key role in determining Plaque disruption [16,33]. The demonstration of a higher prevalence of inflammatory cells in patients with ACS confirms the evidence accumulated over the past few years that atherosclerosis is an inflammatory disease [34]. It was reported that there is a significant and transient increase in activated T lymphocytes in the peripheral blood of patients with unstable angina [35], and Caligiuri et al. [36] found a specific proliferative response to proteins contained at the atherectomy specimens of unstable angina patients but not stable patients, thus suggesting that the antigenic triggers might be located at the site of the culprit lesion. These findings are in accord with those of Suzuki et al, since they found a significantly greater level of IL-6 and MMP-9 in culprit coronary lesion than in systemic levels [23]. Spagnoli et al. [37] suggested that acute MI is associated with activation of T lymphocytes, which in turn, with the release of interferon-gamma and other cytokines results in diffuse activation of various cellular types, including smooth muscle cells and monocytes and macrophages. Several observations support the concept that plaque instability is not merely a local


**How to cite this article:** Centurion OA. Inflammation in Acute Coronary Syndromes: Systemic, Coronary Plaque, or Myocardial Source? J Cardiol Cardiovasc Ther. 2015;1(1): 555551.

vascular accident but probably reflects more generalized pathophysiologic processes with the potential to destabilized atherosclerotic plaques throughout the coronary tree. Cell activation in atherosclerotic plaques can cause severe detrimental effects through a variety of different mechanisms, including thrombogenecity due to tissue factor expression, matrix degradation cause by enhanced release of matrix metalloproteinases, and vasoconstriction caused by enhanced release of endothelin [37,38]. The triggers responsible for diffuse cell activation throughout the whole coronary circulation of patients with ACS are likely to be multiple and may have a coronary or even non-coronary location.

In a very interesting and well performed investigation, Cusack et al. [39] demonstrated that there is an intracardiac inflammatory response in unstable angina that appears to be the result of low-grade myocardial necrosis. The ruptured plaque does not appear to contribute to the acute phase response. They performed measurents of inflammatory markers in blood sampled at the aortic root, at the coronary sinus, and distal to the culprit coronary lesion.

There was no difference in the levels of tumor necrotic factor-alpha (TNF-alpha) or IL-6 between the proximal and distal coronary artery despite the presence of a transcardiac cytokine gradient between the aortic root and coronary sinus. The rise in the level of both IL-6 and TNF-alpha between the aortic root and coronary sinus in patients with unstable angina suggests an intra-cardiac synthesis of these substances. They found no gradient in cytokine concentrations between the aortic root and the coronary vessel distal to the culprit lesion suggesting that the inflammatory response appear to lie within the downstreem myocardium. The relationship they found between intracardiac cytokine synthesis and troponin T elevation further suggests that the inflammatory response is related to necrosis within the myocardium [39]. Interestingly, patients with ACS and elevated levels of IL-6 experiment a further significant level increase post-angioplasty. Percutaneous coronary intervention in ACS patients is known to be associated with distal embolization within the coronary artery of platelet microthrombi and a significant risk of periprocedural AMI [40-42]. Therefore, this further significant increase of IL-6 after angioplasty might be related to myocardial microinfarction from platelet microaggregate embolization. The elevation of inflammatory markers in this setting would suggest that the inflammatory response is related to necrosis within the myocardium.

Although atherosclerosis is clearly multifactorial, it is now universally recognized that inflammation within the lesions contributes importantly to their initiation and progression [2]. Histo-pathological and immune-cytochemical observations suggest that active inflammatory processes may destabilize the fibrous cape tissue triggering plaque rupture and enhancing the risk of coronary thrombosis. Prospective epidemiological studies have shown a strong and consistent association between clinical manifestations of atherothrombotic disease and systemic marker of inflammation. However, larger studies are needed to determine the effectiveness of these markers in risk stratification and also to test their role in patients undergoing percutaneous coronary intervention. Indeed, further studies are warranted, as an improved understanding of this inflammatory process may lead to novel therapeutic approaches and better application of currently available therapies. There is no doubt that the constant refinements in the different therapeutic strategies, the combination of scientific understanding in the adequate utilization of novel inflammatory markers, the new pharmacologic agents, and the new techniques in PCI with newer drug-eluting stents [43-49] will dissipate our doubts and ameloriate our therapeutic management in ACS based on medical evidence. A lot has been accomplished in characterizing the source of inflammation in ACS. However, the investigation must go on to clearly define the systemic, coronary plaque or myocardial source of inflammation to improve the therapeutic manneuvers to manage this very complex entity.

## References


1. Boden WE, McKay RG (2001) Optimal treatment of acute coronary syndromes: An evolving strategy. N Engl J Med 344(25): 1939-1942.
2. Ridker PM, Luscher TF (2014) Anti-inflammatory therapies for cardiovascular disease. Eur Heart J 35(27): 1782-1791.
3. Yarlagadda RK, Boden WE (2002) Cardioprotective effects of an early routine invasive strategy for non-ST-segment elevation acute coronary syndromes: Are we all becoming interventional cardiologists? J Am Coll Cardiol 40(11): 1915-1918.
4. Anderson HV, Cannon CP, Stone PH, Williams DO, McCabe CH, et al. (1995) One year results of the thrombolysis in myocardial infarction (TIMI) IIIB clinical trial: A randomized comparison of tissue-type plasminogen activator versus placebo and early invasive versus early conservative strategies in unstable angina and non-Q-wave myocardial infarction. J Am Coll Cardiol 26(7): 1643-1650.
5. Eguchi K, Manabe I (2014) Toll-like receptor, lipotoxicity, and chronic inflammation: The pathological link between obesity and cardiometabolic disease. J Atheroscler Thromb 21(7): 629-639.
6. Hartmann P, Schober A, Weber C (2015) Chemokines and microRNAs in atherosclerosis. Cell Mol Life Sci 72(17): 3253-3266.
7. Usman A, Ribatti D, Sadat U, Gillard JH (2015) From lipid retention to immune-mediate inflammation and associated angiogenesis in the pathogenesis of atherosclerosis. J Atheroscler Thromb 22(8): 739-749.
8. Libby P, Hansson GK (1991) Involvement of the immune system in human atherogenesis: Current knowledge and unanswered questions. Lab Invest 64(1): 5-15.
9. Valtonen VV (1991) Infection as a risk factor for infarction and atherosclerosis. Ann Med 23(5): 539-543.
10. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ (1987) Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 316(22): 1371-1375.
11. Kataoka Y, Puri R, Nicholls SJ (2015) Inflammation, plaque progression and vulnerability: Evidence from intravascular ultrasound imaging. Cardiovasc Diagn Ther 5(4): 280-289.
12. Falk E, Shah PK, Fuster V (1995) Coronary plaque disruption. Circulation 92(3): 657-671.
13. Davies MJ, Richardson PD, Woolf N, Katz DR, Mann J (1993) Risk of thrombosis in human atherosclerotic plaques: Role of extracellular lipid, macrophage, and smooth muscle cell content. Br Heart J 69(5): 377-381.



**How to cite this article:** Centurion OA. Inflammation in Acute Coronary Syndromes: Systemic, Coronary Plaque, or Myocardial Source? J Cardiol Cardiovasc Ther. 2015;1(1): 555551.

14. Toss H, Lindahl B, Siegbahn A, Wallentin L (1997) Prognostic influence of increased fibrinogen and C-reactive protein levels in unstable coronary artery disease: The FRISC study. Circulation 96(12): 4204-4210.

15. van der Wal AC, Piek JJ, de Boer OJ, Koch KT, Teeling P, et al. (1998) Recent activation of the plaque immune response in coronary lesions underlying acute coronary syndromes. Heart 80(1): 14-18.

16. van der Wal AC, Becker AE, van der Loos CM, Das PK (1994) Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. Circulation 89(1): 36-44.

17. Kaartinen M, Pentilla A, Kovanen PT (1994) Accumulation of activated mast cells in the shoulder region of human coronary atheroma, the predilection site of atheromatous rupture. Circulation 90(4): 1669-1678.

18. Pasterkamp G, Schoneveld AH, van der Wal AC, Hijnen DJ, van Wolveren WJ, et al. (1999) Inflammation of the atherosclerotic cap and shoulder is common and locally observed feature in unruptured plaques of femoral and coronary arteries. Arterioscler Thromb Vasc Biol 19(1): 54-58.

19. Pasterkamp G, Borst C, Post MJ, Mali WP, Wensing PJ, et al. (1996) Atherosclerotic arterial remodeling in the superficial femoral artery: Individual variations in local compensatory enlargement response. Circulation 93(10): 1818-1825.

20. Jonasson L, Holm J, Skalli O, Gabbiani G, Hansson GK (1985) Expression of class II transplantation antigen on vascular smooth muscle cells in human atherosclerosis. J Clin Invest 76(: 125-131.

21. Davies MJ, Thomas AC (1985) Plaque fissuring-the cause of acute myocardial infarction, sudden ischemic death and crescendo angina. Br Heart J 53(4): 363-373.

22. Heeschen C, van Den Brand MJ, Hamm CW, Simoons ML (1999) Angiographic findings in patients with refractory unstable angina according to troponin T status. Circulation 100(4): 1509-1514.

23. Suzuki M, Saito M, Nagai T, Saeki H, Kazatani Y (2006) Systemic versus coronary levels of inflammation in acute coronary syndromes. Angiology 57(4): 459-463.

24. Baumann H, Gauldic J (1994) The acute phase response. Immunol Today 15(2): 74-80.

25. Thiele JR, Zeller J, Bannasch H, Stark GB, Peter K, et al. (2015) Targeting C-Reactive Protein in inflammatory disease by preventing conformational changes. Mediators of Inflammation. Article ID: 372432.

26. Murphy TM, Baum LL, Beaman KD (1991) Extrahepatic transcription of human C-reactive protein. J Exp Med 173(2): 495-498.

27. Volanakis JE, Narkates AJ (1981) Interaction of C-reactive protein with artificial phosphatidyl-choline bilayers and complement. J Immunol 126(5):1820-1825.

28. Li YP, Mold C, Du Clos TW (1994) Sublytic complement attack exposes C-reactive protein binding sites on cell membranes. J Immunol 152(6): 2995-3005.

29. Pepys MB, Rowe IF, Baltz ML (1985) C-reactive protein: binding to lipids and lipoproteins. Int Rev Exp Pathol 27: 83-111.

30. Volanakis JE (1982) Complement activation of C-reactive protein complexes. Ann N Y Acad Sci 389: 235-250.

31. Fang L, Moore XL, Dart AM, Wang LM (2015) Systemic inflammatory response following acute myocardial infarction. J Geriatr Cardiol 12(3): 305-312.

32. Fiedel BA, Simpson RM, Gewutz H (1982) Effects of C-reactive protein on platelet function. Ann N Y Acad Sci 389: 263-273.

33. Anderson KR, Popple A, Parker DJ, Sayer R, Trickey RJ, et al. (1979) An experimental assessment of macroscopic enzyme techniques for the autopsy demonstration of myocardial infarction. J Pathol 127(2): 93-98.

34. Ross R (1999) Atherosclerosis-an inflammatory disease. N Engl J Med 340(2): 115-126.

35. Neri Serneri GG, Prisco D, Martini F, Gori AM, Brunelli T, et al. (1997) Acute T-cell activation is detectable in unstable angina. Circulation 95(7): 1806-1812.

36. Caligiuri G, Paulsson G, Nicoletti A, Maseri A, Hansson GK (2000) Evidence for antigen-driven T-cell response in unstable angina. Circulation 102(10): 1114-1119.

37. Spagnoli LG, Bonanno E, Mauriello A, Palmieri G, Partenzi A, et al. (2002) Multicentric inflammation in epicardial coronary arteries of patients dying of acute myocardial infarction. J Am Coll Cardiol 40(9): 1579-1588.

38. Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, et al. (2000) Multiple complex coronary plaques in patients with acute myocardial infarction. N Engl J Med 343(13): 915-922.

39. Cusack MR, Marber MS, Lambiase PD, Bucknall CA, Redwood SR (2002) Systemic inflammation in unstable angina is the result of myocardial necrosis. J Am Coll Cardiol 39(12): 1917-1923.

40. The CAPTURE investigators (1997) Randomized placebo-controlled trial of abciximab before and during intervention in refractory unstable angina. Lancet 349(9063): 1429-1435.

41. Lincoff AM, Califf RM, Anderson KM, Weisman HF, Aguirre FV, et al. (1997) Evidence for prevention of death and myocardial infarction with platelet membrane glycoprotein IIb/IIIa receptor blockade by abciximab among patients with unstable angina undergoing percutaneous coronary revascularization. J Am Coll Cardiol 30(1): 149-156.

42. Libby P, Tabas I, Fredman G, Fisher E (2014) Inflammation and its resolution as determinants of acute coronary syndromes. Circ Res 114(12): 1867-1879.

43. Libby P (2013) Mechanisms of the acute coronary syndromes and their implications for therapy. N Engl J Med 368(21): 2004-2013.

44. Centurión OA (2010) Actual role of platelet glycoprotein IIb/IIIa receptor inhibitors as adjuntive pharmacological therapy to primary angioplasty in acute myocardial infarction: In the light of recent randomized trials and observational studies with bivalirudin. Open Cardiovasc Med J 4: 135-145.

45. Centurión OA (2011) Bivalirudin in contemporary PCI for non-ST-segment acute coronary syndromes: ¿What is the current role of platelet glycoprotein IIb/IIIa receptor inhibitor agents? Crit Pathways in Cardiol 10(2): 87-92.

46. Centurión OA (2015) Heparin versus Bivalirudin in contemporary percutaneous coronary intervention: A welcome back to an old friend unfractionated heparin. Crit Pathw Cardiol 14(2): 62-66.

47. Sojitra P, Doshi M, Galloni M, Vignolini C, Vyas A, et al. (2015) Preclinical evaluation of a novel abluminal surface coated sirolimus eluting stent with biodegradable polymer matrix. Cardiovasc Diagn Ther 5(4): 254-263.

48. Siontis GC, Stefanini GG, Mavridis D, Siontis KC, Alfonso F, et al. (2015) Percutaneous coronary interventional strategies for treatment of in-stent restenosis: a network meta-analysis. Lancet 386(9994): 655-664.

49. Liou K, Nagaraja V, Jepson N, Ooi SY (2015) Optimal duration of dual antiplatelet therapy following drug-eluting stents implantation: A meta-analysis of 7 randomised controlled trials. Int J Cardiol 201: 578-580.




**How to cite this article:** Centurion OA. Inflammation in Acute Coronary Syndromes: Systemic, Coronary Plaque, or Myocardial Source? J Cardiol Cardiovasc Ther. 2015;1(1): 555551.