Heart Metab. (2013) 60:38-39

Can infective agents be respectable etiopathogenetic factors for acute coronary syndromes?

Dr Alda Huqi, Cardiovascular Medicine Division, Cardio Thoracic Department, University of Pisa, Pisa, Italy

Correspondence: Dr Alda Huqi, Cardiovascular Medicine Division, Cardio Thoracic Department, University of Pisa, Via Paradisa 2, 56100 Pisa, Italy
Tel: +39 32972 56426, e-mail: alda_h@hotmail.com

A policeman sees a drunk man searching for something under a streetlight and asks what the drunk has lost. He says he lost his keys and they both look under the streetlight together. After a few minutes the policeman asks if he is sure he lost them here, and the drunk replies, no, that he lost them in the park. The policeman asks why he is searching here, and the drunk replies "this is where the light is".

Atherosclerosis is a multifactorial disease and, among others, inflammation and activation of immune system play well established roles [1, 2]. In ACS, epicardial thrombosis with abrupt vessel occlusion is a crucial final event, initiated at the site of a "vulnerable plaque" [3]. Until recently, plaque rupture was considered predominantly mechanical, occurring at sites of vessel narrowing with turbulent blood flow [4]. However, removal of coronary stenosis has never proved to prevent ACS. On the other hand, exacerbation of inflammatory [5] and specific immune mechanisms has been implicated in platelet function modulation and thrombus formation in ACS [6, 7]. Therefore, pathophysiological pathways underlying the dynamic changes that ultimately cause coronary thrombotic occlusion represent an area of intense interest and research.

Inflammatory response in ACS includes systemic immune activation, local inflammation of the atherosclerotic plaque and immune reactions associated with the thrombotic event itself [8, 9]. Given the profound involvement of immune activation in ACS, infections and other systemic inflammatory reactions have also been proposed to increase the risk of ACS. Indeed, up to 30% of myocardial infarctions occur after upper respiratory tract infections [10], and chronic infectious agents such as *Chlamydia pneumoniae* or oral pathogens, initially linked to atherosclerosis, have been found to increase the risk of ACS [11–13]. In a very recent issue of *Circulation*, Pessi et al [14] assessed bacterial DNA in thrombus aspirates of 101 patients with STEMI and sought to determine the association between bacterial findings and oral pathology. They used real-time quantitative polymerase chain reaction with specific primers and probes to detect bacterial DNA from several oral species and *C. pneumoniae*. Bacterial DNA typical of endodontic infection was identified in 78.2% of thrombi, and periodontal pathogens were measured in 34.7%. In addition, bacteria-like structures (including whole bacteria) and monocyte/macrophage markers for bacteria recognition and inflammation were detected by transmission electron microscopy and immunohistochemistry analysis, respectively. In a subgroup of 30 STEMI patients examined with panoramic tomography, there was a significant association between periapical abscesses and oral viridans streptococci DNA-positive thrombi. The authors concluded that dental infection and oral bacteria, especially viridans streptococci, may be associated with the development of acute coronary thrombosis.

Such results are in line with another recent study, which also showed a lack of association between the severity of coronary atherosclerosis and periodontal

ABBREVIATIONS

ACS: acute coronary syndrome; **STEMI:** ST-segment elevation myocardial infarction

bacteria [15]. A number of mechanisms that explain an infective etiology of atherosclerosis and ACS, including direct effects on vascular cells, circulating cytokines and inflammatory mediators, as well as initiation of autoimmune reactions have been proposed [16]. Returning to the above-mentioned study, the presence of bacterial DNA together with co-stimulation of immune-specific cells in the thrombus aspirates may suggest that these pathogens disseminate into systemic circulation, migrate to coronary plaques, and cause and/or maintain inflammation of the coronary artery [17].

At present the role of infective agents in ACS is not completely understood. Nonetheless, antimicrobial therapies have already been tested in ACS prevention trials [18–20]. Although treatment results have been contrasting, the objective evidence of bacterial particles in the coronary thrombi should further enhance research in this direction. Indeed, while technological progress has permitted continuous improvement in coronary artery plaque and thrombus removal, this should not prevent us from exploring other, maybe less evident, but probably as relevant causes of ACS. ■

REFERENCES

1. Libby P, Folco E (2011) Tension in the plaque: hypoxia modulates metabolism in atheroma. Circ Res 109(10):1100-1102
2. Libby P, Ridker PM, Hansson GK (2011) Progress and challenges in translating the biology of atherosclerosis. Nature 473(7347):317-325
3. Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA,et al (2012) ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 33(20):2569-2619
4. Arbab-Zadeh A, Nakano M, Virmani R, and Fuster V (2012) Acute coronary events. Circulation 125(9):1147-1156
5. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al (2004) Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case–control study. Lancet 364(9438):937-952
6. Finn AV, Nakano M, Narula J, Kolodgie FD, Virmani R (2010) Concept of vulnerable/unstable plaque. Arterioscler Thromb Vasc Biol 30(7):1282-1292
7. Gori AM, Cesari F, Marcucci R, Giusti B, Paniccia R, Antonucci E, et al (2009) The balance between pro- and anti-inflammatory cytokines is associated with platelet aggregability in acute coronary syndrome patients. Atherosclerosis 202(1):255-262
8. Manthey HD, Zernecke A (2011) Dendritic cells in atherosclerosis: functions in immune regulation and beyond. Thromb Haemost 106(5):772-778
9. Healy AM, Pickard MD, Pradhan AD, Wang Y, Chen Z, Croce K, et al (2006) Platelet expression profiling and clinical validation of myeloid-related protein-14 as a novel determinant of cardiovascular events. Circulation 113(19):2278-2284
10. Madjid M, Naghavi M, Litovsky S, Casscells SW (2003) Influenza and cardiovascular disease: a new opportunity for prevention and the need for further studies. Circulation 108(22):2730-2763
11. Tiirola T, Sinisalo J, Nieminen MS, Silvennoinen-Kassinen S, Paldanius M, Saikku P, et al (2007) Chlamydial lipopolysaccharide is present in serum during acute coronary syndrome and correlates with CRP levels. Atherosclerosis 194(2):403-407
12. Rosenfeld ME, Campbell LA (2011) Pathogens and atherosclerosis: update on the potential contribution of multiple infectious organisms to the pathogenesis of atherosclerosis. Thromb Haemost 106(5):858-867
13. Ishihara K, Nabuchi A, Ito R, Miyachi K, Kuramitsu HK, Okuda K (2004) Correlation between detection rates of periodontopathic bacterial DNA in coronary stenotic artery plaque [corrected] and in dental plaque samples. J Clin Microbiol 42(3):1313-1315
14. Pessi T, Karhunen V, Karjalainen PP, Ylitalo A, Airaksinen JK, Niemi M, et al (2013) Bacterial signatures in thrombus aspirates of patients with myocardial infarction. Circulation 127(11):1219-1228
15. Ohki T, Tabashi Y, Kohno T, Yoshizawa A, Nishikubo S, Watanabe S, et al (2012) Detection of periodontal bacteria in thrombi of patients with acute myocardial infarction by polymerase chain reaction. Am Heart J 163(2):164-167.
16. Epstein SE, Zhu J, Najafi AH, Burnett MS (2009) Insights into the role of infection in atherogenesis and in plaque rupture. Circulation 119(24):3133-3141
17. Li X, Kolltveit KM, Tronstad L, Olsen I (2000) Systemic diseases caused by oral infection. Clin Microbiol Rev 13(4):547-558
18. Cannon CP, Braunwald E, McCabe CH, Grayston JT, Muhlestein B, Giugliano RP, et al (2005) Antibiotic treatment of Chlamydia pneumoniae after acute coronary syndrome. N Engl J Med 352(16):1646-1654
19. Davis MM, Taubert K, Benin AL, Brown DW, Mensah GA, Baddour LM, et al (2006) Influenza vaccination as secondary prevention for cardiovascular disease: a science advisory from the American Heart Association/American College of Cardiology. Circulation 114(14):1549-1553
20. Lamontagne F, Garant MP, Carvalho JC, Lanthier L, Smieja M, Pilon D (2008) Pneumococcal vaccination and risk of myocardial infarction. CMAJ 179(8):773-777