

Authors: E. AGABITI-ROSEI - G. AMBROSIO - L. BADIMON - JP. BASSAND - A. BAYÉS DE LUNA - M.E. BERTRAND - E. CHAZOV - S. CHIERCHIA - J. CLELAND - D. CLEMENT - D. COKKINOS - N. DANCHIN - R. DIETZ - P. DOMINIAK - I. EDES - E. ERDMANN - R. FERREIRA - H.R. FIGULLA - W. FLAMENG - I. GRAHAM - G. JACKSON - W. JANUSZEWICZ - J.C. KASKI - P. KEARNEY - W. KLEIN - F. KOLBEL - M. KOMAJDA - W. KÜBLER - J.L. LOPEZ-SENDON HENTSCHEL - G. MANCIA - W.J. MCKENNA - T. MEINERTZ - J. MLCZUCH - D. MULCAHY - E. O'BRIEN - A. OTO - J. PAPP - W.J. PAULUS - J. POLONIA - I. PRÉDA - L.A. PROVIDENCIA - J. REID - W.J. REMME - W. RUZYLO - Z. SADOWSKI - P. SERRUYS - P. SLEIGHT - J. SOLER-SOLER - J. SOMERVILLE - P.G. STEG - H.A.J. STRUIJKER BOUDIER - B. SWYNGHEDAUW - L. TAVAZZI - M. TENDERA - P. TOUTOUZAS - A. VAHANIAN - J.L. VANOVERSCHELDE - J. WIDIMSKY - M. YACOB

Increased cholesterol levels in circulating red blood cells: a marker of coronary artery disease instability?

The disruption of the fibrous cap of vulnerable coronary atheromatous plaques leads to the acute coronary syndrome (ACS), ie, myocardial infarction and unstable angina.¹ Several factors contribute to atherosclerotic plaque vulnerability and disruption, including the presence of a thin fibrous cap, a reduced concentration of vascular smooth muscle cells, the accumulation of activated macrophages in the cap shoulder, and, very importantly, the size of the necrotic lipid core.^{1,2}

The size of the lipid core appears to play a vital role regarding the stability of the plaque.^{1,3} Davies et al⁴ showed that cap rupture is more likely to occur when the lipid core occupies >40% of the area of the atherosclerotic plaque.⁴ Aggregation of lipoproteins and their phagocytosis or endocytosis by macrophages contribute to the accumulation of cholesterol within plaques⁵ and thus to the growth of the lipid core. Cells belonging to the monocyte/macrophage lineage are important in plaque disruption. Apoptotic macrophages are an important source not only of proinflammatory cytokines and metalloproteases but also of cholesterol within plaques. It is unlikely, however, that all of the cholesterol contained in the atheromatous lipid core derives from macrophages alone, as the atherosclerotic lipid core has a remarkably high content of free cholesterol,⁶ while it is established that most of the cholesterol contained in foam cell is not free but esterified.⁵ Recently, observations by Arbustini et al,⁷ in patients with pulmonary hypertension, and Kolodgie et al,⁸ in coronary patients suffering sudden death, suggested a possible role of circulating erythrocytes in the progression of atherosclerotic plaques. In fact, they reported that erythrocyte membranes were abundantly present in the necrotic core of the coronary lesions of these subjects, suggesting that red blood cells may actively contribute to plaque growth. Of interest, erythrocyte membranes contain large amounts of free cholesterol.⁹ The presence of free cholesterol in the lipid core of atheromatous lesions is likely to be associated with the occurrence of neovascularization, which—as shown by several authors—allows erythrocytes to enter the core of the plaque. Kolodgie et al,⁸ Purushothaman et al,¹⁰ and Moreno et al¹¹ have shown that angiogenesis and intraplaque hemorrhage are important in the development of vulnerable atherosclerotic plaques.

Our recent findings

In view of the above, we recently sought to assess whether total cholesterol content of erythrocyte membranes (CEM) differs in

patients with stable angina pectoris and those with ACS.¹² We also investigated whether CEM may represent both a marker of plaque vulnerability and a pathogenic mechanism of ACS in coronary artery disease (CAD) patients. To this end we assessed consecutive patients with angina pectoris; 120 had chronic stable angina (CSA) (83 men, aged 64±11 years) and 92 ACS (67 men, aged 66±11 years). In addition, we recruited 65 individuals (41 men, aged 63±13 years) with atypical chest pain and completely normal coronary arteries on angiography, who were considered to represent a control group. Established risk factors for CAD were similar in the two groups, with the exception of family history of CAD and dyslipidemia, which were more common in stable CAD patients than in ACS patients. The medications taken by both groups at study entry were also similar, with the exception of β -blockers, statins, angiotensin-converting enzyme (ACE) inhibitors, and aspirin, which, as expected, were significantly more common in the stable CAD group. Angiographic CAD was similar in the two patient groups and so were total cholesterol, triglyceride, and LDL cholesterol levels. HDL cholesterol levels were higher in the stable CAD group and CRP levels were higher in the ACS patient group.¹²

CEM was measured using an enzymatic assay. CEM levels (median and interquartile range) were higher ($P < 0.001$) in ACS patients (184 g/mg; range 130 to 260 g/mg) compared with CSA patients (81 g/mg; range 54 to 109 g/mg). Of interest, total plasma cholesterol concentrations did not correlate with CEM levels ($r = 0.046$, $P = 0.628$).

Conclusion. Our study showed for the first time that CEM concentration is significantly higher in patients with ACS compared with CSA patients, and these findings suggest that CEM may be a marker of atheromatous plaque growth and vulnerability.

J.C. KASKI – London, UK

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