Substrates of acute coronary syndromes: new insights into plaque rupture and erosion

Thomas F. Lüscher, MD, FESC
Editor-in-Chief, Zurich Heart House, Careum Campus, Moussonstrasse 4, 8091 Zurich, Switzerland

Atherosclerotic plaques of various types are the substrate of acute coronary syndromes (ACS), which represents the most serious complication of the disease process. Atherosclerosis develops over decades; in fact it already tends to start in childhood. In a thought-provoking review article, ‘Lifetime risk: childhood obesity and cardiovascular risk’, David Celermajer from the Royal Prince Alfred Hospital in Camperdown, Australia and John Deanfield from University College London remind us of the potential threat of the current worldwide childhood obesity epidemic. As a result of the almost 50% increase in childhood obesity in the last 25 years, substantial concerns have been raised about the future burden of cardiovascular disease that could ensue. The authors review the evidence beyond current guideline knowledge linking early life obesity with adverse changes in cardiovascular structure and function already in childhood, discuss the focus on lifetime risk resulting from it, and highlight the potential effects of early lifestyle interventions.

The issue continues with a Current Opinion by the ESC Working Group on Myocardial and Pericardial Diseases and members of the European Society of Human Genetics entitled ‘The current role of next-generation DNA sequencing in routine care of patients with hereditary cardiovascular conditions’, with Jens Mogensen from the Odense University Hospital in Denmark as the lead author. The most widely recognized indication for genetic testing in patients with cardiomyopathies, arrhythmic syndromes, aortopathies, and other cardiovascular diseases with Mendelian inheritance is to identify a causative mutation and subsequently provide pre-symptomatic or predictive testing of relatives who might be at risk of developing the disease in the future. Cascade screening of family members ensures adequate surveillance of carriers and allows non-carriers to be discharged from follow-up. A number of studies have reported a greater cost-effectiveness combining molecular and clinical screening compared with clinical investigations only. Previously, genetic testing was based on conventional techniques, but technological advances, so-called next-generation sequencing, allow investigation of large numbers of genes, making mutation analysis much faster and cheaper. Analysis of large numbers of genes may, however, result in identification of a number of sequence variants of unknown clinical significance. As a result, cardiologists and clinical geneticists who counsel and manage families are facing the challenge of determining the clinical relevance of such results. This opinion paper gives an overview of the principles of next-generation sequencing and gives guidance for the interpretation of sequencing results. In addition, issues related to genetic counselling and ethical considerations are discussed.

Acute coronary syndromes remain the most important and potentially lethal clinical event in patients with coronary artery disease. Plaque rupture is considered to be the most important underlying cause. Superficial erosion of atheromata is an often overlooked, but no less important mechanism of many ACS, yet it arises from unknown mechanisms. The first FAST TRACK clinical research paper entitled ‘Toll-like receptor 2 and neutrophils potentiate endothelial stress, apoptosis, and detachment: implications for superficial erosion’ by Peter Libby from Brigham and Women’s Hospital in Boston aims to uncover the molecular mechanism of superficial plaque erosion and focuses on the activation of Toll-like receptor 2 (TLR2). Indeed, TLR2 and neutrophils localize at sites of superficially eroded human plaques. In vitro, TLR2 ligands such as hyaluronic, a matrix macromolecule abundant in eroded lesions, lead to the production of reactive oxygen species, endoplasmic reticulum stress, and apoptosis. Co-incubation of neutrophils with endothelial cells potentiated these effects and induced endothelial apoptosis and detachment. The authors then categorized human atherosclerotic plaques based on morphological features associated with superficial erosion into ‘stable’ fibrotic or ‘vulnerable’ lesions. Morphometric analyses of the human atheroma localized neutrophils and neutrophil extracellular traps near clusters of apoptotic endothelial cells in smooth muscle-rich plaques. The number of luminal apoptotic endothelial cells correlated with neutrophil accumulation, the amount of neutrophil extracellular traps, and TLR2 staining in smooth muscle cell-rich plaques, but not in ‘vulnerable’ atheromata. The authors conclude that these in vitro observations together with analyses of human plaques indicate that TLR2 stimulation followed by neutrophil participation may render smooth muscle cell-rich plaques susceptible to superficial erosion and thrombotic complications by inducing endothelial stress and apoptosis, and favouring detachment.

The second clinical research paper, ‘Plaque rupture and intact fibrous cap assessed by optical coherence tomography portend a different outcome in patients with acute coronary...’ published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2015. For permissions please email: journals.permissions@oup.com.
syndrome’, by Giampaolo Niccoli et al. from the Catholic University of the Sacred Heart, in Rome, Italy extends these findings. The authors enrolled 139 consecutive patients, 92 with non-ST elevation myocardial infarction (NSTEMI) and 47 with STEMI, undergoing coronary angiography and optical coherence tomography (OCT) imaging. Culprit lesions were classified as plaque rupture or intact fibrous cap. Plaque rupture was detected in 59% of patients, with no differences in clinical, angiographic, or procedural characteristics compared with those with intact fibrous cap. However, the composite of cardiac death, non-fatal myocardial infarction, unstable angina, and target lesion revascularization at 32 months occurred significantly more often in patients with plaque rupture than in those with intact fibrous cap (39% vs. 14%). Indeed, plaque rupture was an independent predictor of outcome at multivariable analysis, with an odds ratio of 3.7. The authors conclude that patients with ACS presenting with plaque rupture as the culprit lesion by OCT have a worse prognosis compared with patients with intact fibrous caps (most probably reflecting superficial endothelial erosion as described in this issue by Libby et al). A comprehensive Editorial by Fernando Alfonso from the Hospital Universitario de La Princesa in Madrid puts these findings neatly into the clinical context.

In the third paper, entitled ‘Expression of functional tissue factor by neutrophil extracellular traps in culprit artery of acute myocardial infarction’, by Konstantinos Ritis and colleagues from the Democritus University of Thrace in Alexandroupolis, Greece, the findings of Libby and Niccoli are expanded to the occluding thrombus in STEMI patients. Thrombotic material and surrounding blood from the infarct-related coronary artery, specifically to neutrophil extracellular traps, are chromatin filaments released by activated polymorphonuclear neutrophils that are decorated with granule proteins with various properties and have been implicated in thrombosis. The authors selectively sampled thrombotic material and surrounding blood from infarct-related and non-infarct-related coronary artery during primary percutaneous coronary intervention as described previously in 18 patients with STEMI. Isolated thrombi contained polymorphonuclear neutrophils and neutrophil extracellular traps decorated with tissue factor, the initiating protein of the coagulation cascade known to be found in coronary thrombi. Although tissue factor was expressed intracellularly in circulating polymorphonuclear neutrophils of STEMI patients, active tissue factor was specifically exposed by neutrophil extracellular traps obtained from the site of plaque rupture. Treatment of neutrophil extracellular trap structures with DNase I abolished tissue factor activity. In vitro treatment of control polymorphonuclear neutrophils with plasma obtained from either infarct-related or non-infarct-related arteries induced intracellular tissue factor expression, but not neutrophil extracellular traps. Indeed, an interaction between polymorphonuclear neutrophils and thrombin-activated platelets was required for the formation of neutrophil extracellular traps and tissue factor exposure. The authors conclude that in patients with STEMI, the interaction of thrombin-activated platelets with polymorphonuclear neutrophils at the site of plaque rupture results in local neutrophil extracellular trap formation and delivery of active tissue factor, and in turn thrombus formation. The manuscript is accompanied by an Editorial by Lina Badimon from the Barcelona Cardiovascular Research Center in Spain, a recognized expert in the field.

The fourth manuscript, ‘Ranking of psychosocial and traditional risk factors by importance for coronary heart disease’, by Peter Schnohr and colleagues from the Frederiksberg Hospital in Denmark returns to prevention. In their large prospective Copenhagen City Heart Study involving 8882 participants free of cardiovascular disease, the authors ranked psychosocial and traditional risk factors by their importance for coronary heart disease. During follow-up, 1731 non-fatal and fatal coronary events occurred. In men, the highest ranking risk factors for coronary heart disease were vital exhaustion, with a hazard ratio (HR) of 2.36, and systolic blood pressure (>160 mmHg or blood pressure medication vs. <120 mmHg), with a risk of 2.07. In women, smoking had a HR of 1.74 and vital exhaustion a HR of 2.07. Vital exhaustion ranked first in women and fourth in men by population-attributable fraction of 27.7% and 21.1%, respectively. Finally, vital exhaustion significantly improved overall risk prediction. The authors conclude that vital exhaustion is one of the most important risk factors for coronary heart disease, emphasizing the importance of psychosocial factors in risk prediction scores. This paper is accompanied by a balanced Editorial by Russell Vincent Luepker from the University of Minnesota.

The editors hope that this issue of the European Heart Journal will capture the interest of its readers.

References
A rare case of left internal mammary artery disease before bypass surgery

Sushil P. Tripathi, Prafulla G. Kerkar, Charan P. Lanjewar, and Milind S. Phadke

A 55-year-old man presented with history of diabetes, hypertension and past history of right coronary artery disease 10 years back. He did not give any history suggestive of peripheral vascular disease, no supraclavicular bruit, and no difference in upper and lower extremity blood pressures. He presented with history of typical new onset angina since 1 month. He was subjected to echocardiography which showed good left ventricular systolic function, grade II diastolic dysfunction, and structurally normal heart. He underwent diagnostic coronary angiogram, which showed proximal left anterior descending artery (LAD) diffuse disease from the ostium with maximum 90% stenosis, followed by mid LAD tubular 80% lesion and another 70% discrete lesion; he had insignificant non-flow limiting plaques in left circumflex and right coronary artery. Because of the diffuse disease of the LAD from the ostium, revascularization in the form of left internal mammary artery (LIMA) graft to LAD was planned. Left internal mammary artery was cannulated with 6 Fr internal mammary artery catheter.

Selective LIMA angiography showed significant (>90%) stenosis in the proximal part as shown in the images (Panels A–C) making this excellent graft unavailable for the coronary artery bypass graft (CABG). Left subclavian and vertebral arteries were disease free. Moreover, patient was successfully operated with saphenous vein graft to LAD. The use of the LIMA to bypass the LAD is the ‘gold standard’ of coronary artery revascularization. In this case report, we demonstrated that LIMA disease though very infrequent, its routine evaluation during coronary angiography prior to CABG should be a common practice especially when ischaemia in the LAD territory is present.

Panel (A) Anteroposterior projection showing significant (>90%) LIMA stenosis. (B) Left anterior oblique projection showing significant LIMA stenosis. (C) Right anterior oblique projection showing significant disease in the LIMA.