Endothelial dysfunction in coronary heart disease is more than a systemic process

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This editorial refers to ‘Coronary endothelial dysfunction in patients with early coronary artery disease is associated with the increase in intravascular lipid core plaque,’ by B.-J. Choi et al., on page 2047

Since its initial description by our laboratory, now 27 years ago, much has been learned about the causes and consequences of human endothelial dysfunction. Impairment of endothelial function assessed by nitric oxide bioavailability (referred to as endothelial dysfunction) has been observed in atherosclerosis, is associated with traditional risk factors, and has been described in the setting of various systemic inflammatory disorders linked to high rates of coronary heart disease. Endothelial dysfunction exerts a key role in precipitating myocardial ischaemia during daily activities. Endothelial dysfunction confers adverse cardiovascular prognosis independently of known risk factors and also by becoming a pathophysiological target for both known and unknown cardiovascular risk factors. Fortunately, endothelial function can be restored with treatments that also improve long-term outcomes. Notably, failure of treatments to re-establish normal endothelial function among individuals with coronary heart disease or in individuals with hypertension identifies a subset of individuals who remain at high risk for adverse clinical events. Thus, endothelial function testing may ultimately be used to identify the non-responders and to individualize treatment with the purpose of preventing future clinical events. The pharmaceutical industry has recognized the importance of endothelial function testing as a tool for development of antiatherosclerotic drugs as endothelial function can change rapidly in response to interventions. Lastly, ‘endothelial biopsies’ which allow for the isolation of human endothelial cells are enabling investigators to characterize the biology of the endothelium on a molecular level. During this procedure, endothelial cells are removed from blood vessels using guide-wires and analysed, for example, for protein expression, protein modifications (e.g. serine phosphorylation or tyrosine nitration), and for the function of subcellular organelles, such as mitochondria. Endothelial biopsies have deciphered the molecular signatures of endothelial dysfunction in several human cardiovascular diseases, providing novel biomarkers of disease along with therapeutic targets that can be used for rational development of new treatments.

Despite these notable advances, many unanswered questions regarding human endothelial dysfunction remain. For example, although endothelial dysfunction is generally viewed as a ‘systemic’ process, it has long been recognized that endothelial dysfunction does not affect all arteries to the same extent and that, even within a single coronary artery, there are regional differences in endothelial function. Early in the course of human atherosclerosis, endothelial dysfunction is confined to sites of abnormal haemodynamic stresses, particularly the coronary branch points, which are areas of predilection for the development of atherosclerosis. Thus, in concert with systemic risk factors, local anatomy plays a role in the formation of human atherosclerotic lesions, presumably by altering shear stresses and thereby disturbing local coronary endothelial function. At the other end of the spectrum in human atherosclerosis, endothelial dysfunction is more pronounced at sites of culprit coronary lesions of patients presenting with unstable angina compared with non-culprit coronary segments in the same arteries or compared with stenotic segments of patients presenting with stable angina. Similarly, following myocardial infarction, endothelial dysfunction is more impaired in stenotic segments of infarct-related coronary arteries compared with non-infarct-related stenotic segments. While these studies have convincingly demonstrated regional heterogeneity in coronary endothelial function after an acute coronary syndrome (ACS), whether or not the marked endothelial dysfunction at sites of culprit plaques pre-dated the clinical event or was simply a consequence of the event remained unknown. After all, ACS is typically caused by disruption of an atherosclerotic plaque, resulting in the physical denudation and consequently functional loss of the underlying endothelium. Thus, to implicate endothelial dysfunction as a potential cause as opposed to a consequence of ACS, it is important to assess coronary endothelial function in the types of plaques that are...
prone to cause future ACS events, so-called vulnerable plaques, while these plaques are still intact as shown in Figure 1.

Vulnerable plaques are characterized by a large necrotic core, abundance of lipid, high density of inflammatory cells, positive remodelling, and a thin fibrous cap that separates the necrotic core from circulating blood. Several of these features can be identified by specialized imaging modalities, including spectral analysis of intravascular ultrasound (IVUS) radiofrequency data and near-infrared (NIR) spectroscopy. Recently, Lavi and colleagues correlated coronary plaque characteristics identified by spectral analysis of IVUS with coronary endothelial function assessed by vasomotor responses to acetylcholine in 30 patients with mild coronary atherosclerosis. Coronary segments with endothelial dysfunction had larger necrotic core plaques, and necrotic core size was the principal determinant of coronary endothelial dysfunction after adjustment for other predictors. Accordingly, this study suggested that marked local coronary endothelial dysfunction is associated with a large necrotic core, a key characteristic of vulnerable plaques (Figure 1).

Near-infrared spectroscopy is a widely used method to determine the chemical composition of substances, based on the spectral pattern of absorption or reflection of NIR light. NIR spectroscopy has been incorporated into catheters for intravascular imaging to quantify the amount of lipids in the wall of atherosclerotic arteries. Catheter-based NIR spectroscopy measurements have been validated in post-mortem and surgical endarterectomy specimens. Choi and colleagues at the Mayo Clinic have now used NIR spectroscopy to determine whether coronary endothelial dysfunction is associated with the lipid content of atherosclerotic plaques in 32 patients with chest pain and mild coronary artery disease by angiography. The NIR spectroscopy signal was interrogated in the proximal 6 cm of the left anterior descending artery and correlated topographically with coronary endothelial function assessed by acetylcholine. The key findings of the study were: (i) epicardial coronary artery endothelial dysfunction was related to the abundance of lipid in the vessel wall assessed by NIR spectroscopy; (ii) epicardial coronary endothelial dysfunction was not related to the burden of coronary atherosclerotic plaques as determined by IVUS; and (iii) lipid in the vascular wall impaired local epicardial endothelial function, without affecting microvascular endothelial function.

Choi and colleagues are to be congratulated on carrying out this study from which a number of conclusions can be drawn. First, lipid-rich vascular sites identified by NIR spectroscopy are a hallmark of vulnerable plaques, prone to causing ACS. The association of such lipid-rich areas with dysfunction of the overlying endothelium provides essential support for a link between endothelial dysfunction, plaque vulnerability indicated by the abundance of lipid, and ACS. Secondly, this study provides a biological basis for the heterogeneity of coronary endothelial dysfunction which has now been related topographically to disturbed shear stresses, necrotic cores, and, in this study, to lipid-rich areas (Figure 1). Thirdly, the study...
shows that in relation to endothelial dysfunction, plaque composition is more important than plaque burden. Fourthly, the concept of endothelial dysfunction as a ‘systemic’ process among patients with coronary heart disease may need refinement. We coined the phrase ‘systemic nature of endothelial dysfunction in atherosclerosis’ nearly 18 years ago after finding a correlation between coronary and brachial artery endothelial function. While the brachial artery, the most commonly used site for non-invasive endothelial function testing, is a sensitive barometer of the damaging effects of cardiovascular risk factors on the vascular endothelium and predicts long-term clinical outcomes, it does not fully recapitulate the complexities of endothelial function in coronary arteries. For example, the brachial artery lacks necrotic cores or lipid cores that adversely impact coronary endothelial function. Much useful information about endothelial function has been derived from non-invasive testing of peripheral arteries, however, as the studies from the Mayo Clinic demonstrate.

There are some limitations to the study. The present study has not characterized the biological mechanisms that link endothelial dysfunction to lipid-rich areas. As most NIR spectroscopy tissue signals are obtained from a depth of <1 mm from the luminal surface, lipid detected in this study was probably in close physical proximity to the overlying endothelium. The observed endothelial dysfunction might be a result of chemical substances released from lipid-rich areas that are harmful to the nearby endothelium. One possible example is lysophosphatidylcholine which is cleaved from oxidized lipids by the enzyme lipoprotein-associated phospholipase A2 (LpPLA2) and can cause endothelial dysfunction. Ongoing studies are testing this hypothesis by investigating whether inhibition of phosphatidylcholine generation by an LpPLA2 inhibitor darapladib can improve coronary endothelial function in patients with coronary atherosclerosis (ClinicalTrials.gov identifier: NCT01557088) and whether the improvement in endothelial function tracks accordingly with clinical outcomes in patients with stable or unstable coronary artery disease (ClinicalTrials.gov identifiers: NCT00799903 and NCT00799903). In addition, vascular lipids in their oxidized forms can improve coronary endothelial function in patients with coronary artery disease (ClinicalTrials.gov identifiers: NCT01557088) and can cause endothelial dysfunction.

Although some questions remain unanswered, the study by Choi et al. has made a key contribution to our understanding of coronary endothelial biology and its potential role in ACS by linking local coronary endothelial dysfunction to the abundance of lipid in the artery wall using NIR spectroscopy.

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References