

Symposium 12

Selected topics in cardiovascular pathology

Chairperson C Berry UK

Directional coronary atherectomy specimens. What have we learned from them?

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Atherosclerosis is the most common condition underlying morbidity and mortality in the industrialized parts of the world. Sudden death, acute myocardial infarction, chronic heart failure and cerebral complications are the most important sequelae of the disease. The characteristic pathology is that of an elevated intimal lesion composed of a central core of lipids encased by fibrous tissue containing smooth muscle cells and inflammatory cells among which macrophages dominate. Progressive growth of such lesions may eventually lead to significant luminal obstruction, causing impairment of organ perfusion such as that seen in patients with, for instance, stable exercise related angina pectoris. On the other hand, atherosclerotic lesions may cause abrupt and often severe symptoms, which are related to an acute complication of the atherosclerotic plaque. This consists of either plaque rupture (plaque fissure) or plaque erosion. Plaque rupture consists of fissuring of the fibrous cap, which separates the lumen from the central atheroma, inducing thrombosis with or without acute luminal obstruction. Plaque erosion is the situation in which the surface lining is eroded and mural thrombus induced. It has been shown that both these complications are related to presence of a lipid-related immune mediated inflammatory process.

Over the years it has been shown that atherosclerotic plaques with a large lipid core and a small often attenuated fibrous cap are prone to developing ruptures or erosions. For this reason these types of atherosclerotic plaques have been considered "at risk" or "unstable". Plaques dominated by fibromuscular tissue, with little or no discernable lipids, are considered "safe" or "stable". However, these observations were based on autopsy studies and, therefore, almost per definition lack the detailed precision of *in vivo* clinicopathological correlates. The introduction of directional coronary atherectomy (DCA) has opened gateways to this end.

DCA is an interventional cardiology procedure in which a catheter is introduced into the coronary artery carrying a cutting device on its tip. Once a culprit lesion has been identified and localized, the cutting device can be introduced and the lesion removed. The tissue can be retrieved and becomes available for microscopic evaluation. This then introduces the possibility to provide detailed correlations between the clinical state and the pathology of the lesion considered responsible for the clinical condition at the time. DCA, therefore, has contributed markedly to the understanding of the pathological mechanisms underlying acute coronary syndromes.

Patients with stable angina pectoris presented culprit lesions composed mainly of smooth muscle cells, with few inflammatory cells. On the other hand, patients with unstable angina pectoris (Braunwald class II, II) showed a significant increase in extent of inflammatory cells, closely related to the severity of the acute coronary syndrome. In fact, patients with acute myocardial infarction showed most inflammation in the culprit lesions. These studies have shown unequivocally that plaque inflammation plays a role in the onset of unstable angina and, on that basis, has initiated further investigations into the role of inflammatory mediators. One aspect distinctly revealed by DCA is that "stable" plaques may nevertheless contain foci of inflammation; an observation which has raised the question whether with time, morphologically stable plaques may turn into clinically unstable conditions. DCA procedures also have made it possible to demonstrate that interleukin-2 receptor activity on lymphocytes is significantly increased in culprit lesions of unstable angina and even more so in those obtained from patients with acute myocardial infarction, thus indicating recent onset activation. This is the most interesting since patients with acute onset of coronary syndromes have increased plasma levels of inflammatory markers, suggesting that infectious agents could play a role.

All in all, DCA tissue sampling has provided the unique opportunity to study the pathology of atherosclerotic plaques *in vivo*. The novel observations obtained provide the impetus for additional studies into the potential relationship between acute coronary syndromes and infection.

The endothelium as a multifunctional organ: From sepsis to tumor metastasis

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The ubiquity of the endothelium makes it a prime candidate for local regulation of interfacial interactions in organ function. On the basis of this role the endothelium itself can be regarded as a multifunctional organ. Endothelial cell functions constitute a delicate balance of opposing actions, which in the physiological situation are strictly controlled. The pathobiological role of the endothelium in various disease processes is best understood by viewing the imbalance in these opposing functions.

Blood contacting endothelium is nature's most efficient anti-thrombogenic surface. However, the endothelial regulation of hemo-

stasis involves the ability to produce not only numerous anticoagulatory substances, including prostacyclin, nitric oxide (NO), thrombomodulin, urokinase-plasminogen activator, and various heparan sulfate proteoglycans, but also a series of prothrombotic molecules, such as tissue factor, the coagulation factors V and VIII, the receptors for coagulation factors IX and X, as well as plasminogen activator inhibitor-1, which under various pathological conditions become predominant. Thus, under proinflammatory cytokines and bacterial toxins procoagulant activity in endothelial cells plays a central role in the manifestations of disseminated intravascular coagulation and septic shock. Sepsis can be regarded as the extreme form of inflammation. Morphological studies have indicated that the initial pathological lesions are to be found in endothelial cells. Nevertheless, even prior to these manifestations dysfunctional endothelium is hypothesized to be instrumental in the pathogenesis of the microcirculatory dysregulation which forms the basis of multiple organ failure. In this scenario endothelial cells in tandem with plasma and blood cell mediator systems change their function from an inflammatory regulator to uncontrollable amplification of the inflammatory response. As well as procoagulant activity, endothelial cell production of cytokines [interleukin(IL)-1 β , IL-6, IL-8, platelet-activating factor (PAF) etc.] and growth factors [platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), transforming growth factor (TGF)- β 1, granulocyte-macrophage colony-stimulating factor (GM-CSF), etc.] as well as up-regulation of cell adhesion molecules (CAMs) are all central to the clinical sequelae of sepsis and multiple organ failure, including disseminated intravascular coagulation, the interstitial fibrosis of adult respiratory distress syndrome (ARDS) and leukocyte sequestration. Evidence from our laboratory indicates that signal transduction pathways in the endothelium under these extreme proinflammatory stimuli may be distinct from the highly controlled physiological upregulation of inflammation. Thus, NF- κ B-independent pathways are clearly associated with the elevated endothelial expression of CAMs relevant for monocyte and granulocyte adhesion. This could provide the molecular basis for new therapeutic concepts in multiple organ failure.

Endothelial regulation of vascular tone via production of vasodilators (prostacyclin, NO) and vasoconstrictors (PAF, endothelin-1) is of vital importance especially in the arterial side of the circulation. The onset of endothelial dysfunction, for example in atherosclerosis, appears to correlate with an early loss of endothelium-dependent relaxation, which accompanies down-regulation of the constitutive expression of the endothelial NO synthase gene. In atherosclerosis, as well as in other vascular disorders, numerous other features of endothelial dysfunction become operative. Among these are, for example, the effects of altered shear stress, oxidant stress from activated blood cells, oxidation metabolites of lipoproteins, advanced glycation end products (in diabetes) and antiendothelial antibodies (in vasculitis forms).

Tumor intra- and extravasation are central elements in the metastatic process and involve tumor cell interactions with the endothelium. Various tumor-dependent mechanisms, including the production of reactive oxygen species, are operative in endothelial cell damage during the process of tumor extravasation. Tumor cell adhesion to the endothelium appears to involve CAMs which are also active in the physiological inflammatory reaction. Proinflammatory cytokines, such as tumor necrosis factor- α and IL-1 β , appear to promote tumor cell-endothelial cell adhesion via upregulation of these CAMs although the exact pathogenetic significance of this

CAM upregulation in tumor microvessels is still controversial. One hypothesis views the increased CAM expression as favorable to tumor metastasis by facilitating tumor cell adhesion prior to extravasation. Alternatively, these CAMs could support leukocytic infiltration into the tumor and thus represent part of the immune response of the host to the tumor.

The topic of angiogenesis has entered an exponential phase in current biomedical research and is relevant not only for tumor growth but also for chronic inflammation and wound healing, including the reaction to implanted biomaterials. Various angiogenic (e.g., vascular endothelial growth factor, bFGF, IL-8, E-selectin, hyaluron oligosaccharides) and angiostatic molecules (e.g., thrombospondin, platelet factor-4, interferon- γ , angiostatin, endostatin) have been described and offer the possibility of regulating the angiogenic response. The application of angiostatic factors such as angiostatin and endostatin as an antitumor strategy has been highly successful in experimental models, but still requires as yet unforeseen modifications in the human situation. Similar strategies employing drug-delivery systems could revolutionize the field of biomaterial implantation to control the wound healing reaction. However, considerable fundamental research is still essential before this can become a reality. This applies particularly to the development of suitable models employing human primary cultivated cells to simulate the situation *in vivo*. In addition, of special relevance to the pathology community is the need to systematically examine explanted biomaterials with respect to the angiogenic response, which appears to differ markedly from other species, including other primates.

Finally, one of the major challenges in endothelial research remains the understanding of the molecular basis and pathobiological significance of endothelial cell heterogeneity. While the structural variability of the endothelium has been known from anatomical observations for a long time, it is only relatively recently that the extent of functional heterogeneity of the endothelium has become a focus of attention. The latter must be regarded as one of the central elements in comprehending the organ manifestations of disease, for example, the sequence and pattern of hematogenous spread of malignancy, or organ failure in sepsis. To achieve this there must be a concerted effort of modern methodology applied to human tissue specimens, combined with relevant experimental models *in vivo* and *in vitro*.

The presentation will attempt to give a concise overview of these aspects of the pathobiology of the endothelium and will also draw on experimental data from the presenter's own laboratory.

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