Endothelin: a new marker of risk of rapid coronary stenosis progression in patients with stable angina?

See page 1578 for the article to which this Editorial refers

Atherosclerotic coronary stenosis progression is a complex, largely episodic and unpredictable process involving, on the one hand, inflammatory mechanisms, enhanced vasoactivity and intra-plaque haemorrhage leading to plaque erosion and disruption and, on the other, healing processes including thrombus formation, accelerated proliferation of smooth muscle cells and neoangiogenesis. The majority of the episodes of plaque destabilization leading to coronary stenosis progression are clinically silent, thus the identification of pre-clinical markers capable of predicting rapid coronary stenosis progression represents an attractive challenge.

In 1985, Hickey et al. found that cultured endothelial cells produce a potent coronary vasoconstrictor. Three years later, Yanagisawa et al. purified from conditioned media of porcine aortic endothelial cells a 21-amino acid peptide with a molecular weight of 2492. This was named ‘endothelin’. Further studies from the same and other groups demonstrated that the new molecule was an extremely potent and long-lasting vasoconstrictor of vascular smooth muscle. Endothelin is released by endothelial cells in response to different substances such as angiotensin II, vasopressin, thrombin, bradykinin, transforming growth factor β, interleukin-1, insulin, insulin-like growth factor-1 and glucose. Changes in shear stress, mechanical pressure, coronary stretch, pH and cold also induce endothelin release. In turn, endothelin markedly potentiates the constrictor effects of other vasoconstrictors such as catecholamine, serotonin and angiotensin II. Interestingly, endothelin is not only a potent vasoconstrictor but also induces leucocyte adhesion, monocyte chemotaxis, platelet aggregation, stimulates the production of cytokines, promotes differentiation processes in vascular cells and has marked mitogenic properties that facilitate proliferation of endothelial and vascular muscle cells. Importantly, at the site of atherosclerotic plaques, oxidatively modified low-density lipoproteins activate macrophages, smooth muscle cells and polymorphonuclear leukocytes to secrete endothelin. All these actions mediated by a single molecule have suggested that endothelin may play a pivotal role in a number of cardiovascular conditions and particularly, at the coronary level, in the initiation and/or progression of the atherosclerotic process.

The development of sensitive assays has allowed the measurement of the plasma levels of endothelin in a number of cardiovascular conditions, and raised levels of endothelin have been shown in hypertension, cardiogenic shock, pulmonary hypertension, unstable angina, acute myocardial infarction, chronic heart failure, vasospastic angina and cardiac syndrome X. Furthermore, plasma endothelin levels have been shown to be associated with both the extent and the severity of peripheral and coronary atherosclerosis and increased activity of endogenous endothelin has been recently reported in patients with hypercholesterolaemia.

The paper by Zouridakis et al. in this issue adds a new dowel in the complex puzzle of coronary stenosis progression. The authors investigated the changes in diameter of coronary stenoses of 92 patients with stable angina on the waiting list for elective coronary angioplasty. After a mean interval of 5.5 months they found that plasma levels of endothelin, obtained at study entry, were significantly higher in patients with rapid coronary disease progression (‘progressors’) than in those without (‘non-progressors’). Multiple logistic regression analysis revealed that among the variables tested (endothelin, coronary artery disease risk factors, total and LDL cholesterol, levels of glucose, treatment with lipid lowering drugs) only endothelin was an independent predictor for disease progression.

The findings of this study are of pathogenetic and clinical interest. From a pathogenetic point of view, the results of this study expand previous data showing that endothelin is not only involved in the destabilization of atherosclerotic coronary plaque in patients with acute coronary syndromes but may also be responsible for rapid atherosclerotic plaque progression in patients with chronic stable syndromes. Indeed, in a previous in vitro study, Zeiher et al. evaluated the endothelin-1-like immunoreactivity at the site of coronary atherosclerotic lesions obtained by directional coronary atherectomy from patients with stable angina and patients with crescendo and post-infarction angina. These authors found that endothelin staining grade was significantly greater in patients with acute coronary syndromes compared to that observed in atherosclerotic plaque tissue obtained from patients with stable angina. In accordance with this finding, preliminary data indicate that...
the enhanced vasoreactivity of the culprit lesion in unstable angina is associated with an increased local release of endothelin\textsuperscript{[15]}. Now we learn that endothelin may also be involved in the mechanisms responsible for rapid coronary disease progression in patients with chronic stable angina. Of note, no difference in traditional risk factors were detected between progressors and non-progressors, suggesting that these factors, although important in the atherogenesis process, may not play a crucial role in the process of rapid disease progression.

In the clinical setting, the findings of Zouridakis et al.\textsuperscript{[13]} may have relevant implications as endothelin plasma levels may represent a new biochemical risk factor of rapid coronary artery disease progression in patients with stable angina pectoris. High baseline plasma levels of endothelin may identify a subgroup of patients with stable angina at increased coronary risk requiring closer medical attention. To this end, sensitive commercial assays for routine measurement of the plasma levels of endothelin are becoming increasingly available in most centres.

Although the study by Zouridakis et al.\textsuperscript{[13]} provides new information on a potential mediator for the progression of coronary artery disease, some important aspects deserve further evaluation. First of all, the association between high plasma levels of endothelin and rapid coronary stenosis progression does not imply a causal role for endothelin. Controlled clinical studies with the recently introduced endothelin receptor antagonists would be of great interest to elucidate this relevant pathogenetic aspect. Secondly, the lack of a clear association between high baseline plasma endothelin levels, rapid coronary disease progression and clinical events at follow-up weakens the clinical relevance of this finding. Of note, because of the small sample size, the relatively low cardiac risk of the study population and the short follow-up period, this study was probably not powered to detect differences in the clinical outcome between progressors and non-progressors. Indeed, apart from six patients (three progressors and three non-progressors) who had acute coronary events during follow-up, none of the remaining patients had a significant change in their symptoms or functional status during follow-up. Hopefully a more accurate and objective assessment of myocardial ischaemia resulting from coronary disease progression would be helpful to clarify the clinical relevance of high baseline endothelin levels in patients with stable angina. Finally, the potential relationship between endothelin and other recently recognized inflammatory risk factors for coronary plaque destabilization such as C-reactive protein, interleukins and adhesion molecules in the progression of coronary stenoses remains to be elucidated.

The knowledge of the basic mechanisms of coronary atherosclerosis progression and of the processes responsible for the transformation of a silent atherosclerotic coronary plaque into an active explosive lesion is a major challenge for modern coronary research. Endothelin has all the attributes necessary to play a crucial role in both processes and the pilot findings of Zouridakis et al.\textsuperscript{[13]} represent a useful observation to direct our future research.

A. GASPARDONE
Cattedra di Cardiochirurgia, Università di Roma Tor Vergata, Rome, Italy

References

\begin{enumerate}
\item \textcite{Mann J, Davies MJ. Mechanisms of progression in native coronary artery disease: role of healed plaque disruption. Heart 1999; 82: 265–4.}
\item \textcite{Ferri C, Properzi G, Santucci A. Endothelin-1: a pathogenetic factor in human diseases or a physiologist’s curiosity? High Blood Press 1995; 4: 1–19.}
\item \textcite{Luscher TF, Barton M. Endothelins and endothelin receptor antagonists. Therapeutic considerations for a novel class of cardiovascular drugs. Circulation 2000; 102: 2434–40.}
\item \textcite{Hasdai D, Holmes DR, Garrat KN, Edwards WD, Lermann A. Mechanical pressure and stretch release endothelin-1 from human atherosclerotic coronary arteries in vivo. Circulation 1997; 95: 357–62.}
\item \textcite{Kaski JC, Elliott PM, Salomone O et al. Concentration of circulating plasma endothelin in patients with angina and normal coronary angiograms. Br Heart J 1995; 74: 620–24.}
\item \textcite{Desideri GB, Gaspardone A, M. Gentile M, Santucci A, Giofré PA, Ferri C. Endothelial activation in patients with cardiac syndrome X. Circulation 2000; 102: 2359–64.}
\item \textcite{Zouridakis EG, Schwartzman R, Garcia-Moll X et al. Increased plasma endothelin levels in angina patients with rapid coronary artery disease progression. Eur Heart J 2001; 22: 1578–84.}
\item \textcite{Zeiher AM, Goebel H, Schachinger V, Hiling C. Tissue endothelin-1 immunoactivity in the active coronary atherosclerotic plaque. A clue to the mechanism of increased vasoactivity of the culprit lesion in unstable angina. Circulation 1995; 91: 941–7.}
\end{enumerate}