EDITORIAL

The putative role of isoprostanes in human cardiovascular physiology and disease: following the fingerprints

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Are isoprostanes more than physiopathological biomarkers of lipid peroxidation? Could they play a role in human cardiovascular physiology and disease?

Isoprostanes are arachidonic acid metabolites produced through a free radical dependent mechanism. They are formed in situ on phospholipids, at sites of free radical generation. Once released from cell membranes by phospholipases, isoprostanes circulate in the plasma in free form, and are potentially available for agonist receptor interaction.

Increased formation of isoprostanes was first described in cigarette smokers. Since this study, their increased formation has been observed in a large number of diseases including atherosclerosis and coronary heart disease. Some reports also showed that isoprostanes concentrations were increased in the pericardial fluid and urine of patients suffering from heart failure. Isoprostane concentrations increased with the functional severity of heart failure. The study by Nonaka-Sarukawa and colleagues in this issue of Heart further supports the hypothesis that oxidative stress, assessed by urinary 15-F$_2$t-isoprostane concentrations, is increased in patients with congestive heart failure and correlates with the severity of the disease. They showed that 15-F$_2$t-isoprostane values decreased in the 14 days following hospital admission. Interestingly, 15-F$_2$t-isoprostane values were correlated with plasma B type natriuretic peptide (BNP). These data raise an important issue: in addition to being a pathophysiological marker of oxidative injury, the quantification of F$_2$t-isoprostanes might represent a prognostic marker in heart failure—that is, a marker of morbidity, as suggested by the authors. However, no clinical studies aimed at testing isoprostanes as a prognostic marker, with strong end points such as mortality or morbidity, are available in heart failure as well as other cardiovascular diseases.

ROLE OF ISOPROSTANES IN CARDIOVASCULAR DISEASE

In vitro, F$_2$t-isoprostanes induce vasoconstriction and mitogenesis, and stimulate endothelial cells to bind monocytes, one of the key initial events in atherosclerosis. Another important and still unresolved enigma is to determine whether isoprostanes are more than simply a biomarker of lipid peroxidation—that is, do isoprostanes play a role in human cardiovascular physiology and disease? The major problem we face is that no specific inhibition of 15-F$_2$t-isoprostane (or other isoprostanes) can currently be achieved. Belhassen and colleagues recently showed that S1886, a TP-receptor antagonist, improved both acetylcholine and flow mediated vasodilation in patients suffering from coronary artery disease (CAD) treated with aspirin (100 mg/day). This study suggests that TP-receptor agonists other than platelet derived thromboxane A$_2$ are implicated in blood flow regulation, at least in patients with CAD. Similar data on healthy subjects would strengthen the hypothesis that such compounds play a role in vascular physiology. The main and appealing hypothesis raised by the authors is that isoprostanes could be a candidate. The same TP receptor agonist, but not aspirin, was effective in atherosclerosis inhibition in apo E-KO mice, showing that TP receptor blockade is affected by a mechanism independent of platelet derived thromboxane A$_2$, whereas isoprostane suppression with vitamin E retards atherogenesis in the same animal model. Similarly, another TP receptor antagonist (L670596), but not cyclooxygenase 2 (COX-2) inhibition, prevented pulmonary hypertension and endothelin-1 upregulation in 60% O$_2$ mediated pulmonary hypertension in newborn rats.

To date, do we have sufficient evidence to conclude in favour of isoprostanes? Certainly not. Firstly, aside from prostaglandin H$_2$-thromboxane A$_2$ and isoprostanes, the TP receptors share other endogenous ligands such as HETE. One may reasonably suppose that other arachidonic acid derivatives will be discovered as endogenous TP receptor agonists in the future. Secondly, although unlikely, the candidate compound could be thromboxane A$_2$ itself. Although aspirin given at 100 mg/day completely inhibits platelet derived thromboxane A$_2$, COX is expressed in all tissues, and one cannot rule out that endothelial cells may still be able to produce thromboxane A$_2$, especially in CAD patients in whom the ability of endothelial cells to release prostacyclin is decreased.

WHICH ISOPROSTANES ARE INVOLVED?

An important challenge remains to determine which isoprostanes could be involved. Unlike prostaglandins, the non-specific free radical mechanism of their formation leads to 64 different isoprostanes for each isoprostane family, which mean hundreds of different compounds. Most attention was initially focused on 15-F$_2$t-isoprostane, which was the first commercially available isoprostane. The available data strongly suggest that the effects of 15-F$_2$t-isoprostane are mediated by the activation of the TP receptors acting as a full or partial agonist. Other isoprostanes belonging to the F-family, such as 9-epi-15-F$_2$t-isoprostane and 15-epi-15-F$_2$t-isoprostane, are biologically active, although less potent, whereas...
5-F2t-isoprostane and its 5-epimer possess no vasomotor effects. Aside from the F-family, isoprostanes with an E-ring are even more potent. Furthermore, Morrow and colleagues have shown that A,-isothromboxanes are formed in vivo. Because of the inherent instability of the thromboxane A, ring, no research into the vascular effects of A,-isothromboxanes is available. However, considering the potency of thromboxane A, A,,-isothromboxanes are potentially interesting candidates.

In conclusion, the study by Nonaka-Sarukawa and colleagues further adds to our knowledge concerning the pathophysiological variations of isoprostanes in human cardiovascular physiology and disease. In the future we must try to determine whether these compounds are more than physio-pathological biomarkers of lipid peroxidation. Considering we have no direct evidence, to date, concerning their involvement in the pathogenesis of cardiovascular diseases, we will have to follow the fingerprints.

REFERENCES

IMAGES IN CARDIOLOGY

Myocardial bridge-like arterial graft compression by draining tube

A patient with exertional angina and left main and two vessel coronary artery disease (left anterior descending and circumflex artery), with normal left ventricular function, underwent elective coronary artery bypass grafting, on extracorporeal circulation. The obtuse marginal branch was considered ungraftable, and a composite arterial graft (left internal mammary anastomosed to the radial artery) was inserted to the distal left anterior descending artery (LAD). After an 8-hour coronary bypass operation, the bypass graft was noted to have a moderate stenosis at the anastomosis and mild impairment of the diastolic filling of the left main artery. Proximal to the crossing point, compression. Proximal to the crossing point, a moderate stenosis at the anastomosis between the mammary and the radial arteries is also shown.

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