Editorial

Oxidative stress, F₂-isoprostanes and endothelial dysfunction in hypercholesterolemia

Carlo Palombo a,b, *, Valter Lubrano a,c, Tiziana Sampietro a

1. Introduction

Hypercholesterolemia is reported to be associated both with enhanced oxidative stress, related to increased lipid peroxidation [1], and with augmented susceptibility to coronary vasoconstriction [2]. The abnormal coronary vasoreactivity is mainly attributed to endothelial dysfunction, which in hypercholesterolemic man has been demonstrated by several approaches, including coronary and forearm blood flow response to acetylcholine (ACh) [3,4], and flow-mediated dilation [5]. An increased generation of oxidized LDL is a major factor responsible for the vascular damage related to high cholesterol levels, and oxidative stress leads to increased breakdown and/or reduced bioavailability of NO in a number of experimental and clinical models [6]. F₂-isoprostanes, namely 8-epi-prostaglandin F₂ α (8-epi-PGF₂ α), have been recently proposed as reliable markers of oxidative stress in vivo [7,8].

Wilson et al. [9] in their study demonstrate that 8-epi-PGF₂ α causes a dose-dependent vasoconstriction in vitro, in pig coronary strips obtained from normal and hypercholesterolemic animals. Coronary vasoconstriction induced by 8-epi-PGF₂ α is shown to be modulated by endothelial NO, being increased after both endothelial denudation and L-NMMA administration in control animals. Hypercholesterolemic vessels (HV), in turn, show an increased coronary vasoconstriction to 8-epi-PGF₂ α, which is comparable to that observed in normal animals following endothelium denudation, specific for 8-epi-PGF₂ α, not being found with other vasoconstrictor prostanoids, and is attenuated by pretreatment with L-arginine or the NO donor NOR-3. These observations suggest a tonic vasoconstrictor activity dynamically opposed by NO, with the net vasomotor effect resulting from the balance of the two systems.

Furthermore, 8-epi-PGF₂ α in hypercholesterolemic animals shows increased circulating levels and increased deposit on the intimal surface of the vessel. The association between increased circulating level and increased intimal deposition of 8-epi-PGF₂ α supports the pathogenetic role of F₂-isoprostanes in determining vascular damage, and puts forward the hypothesis of the intimal disease as a dynamic process involving the arterial wall in the early stages of atherosclerosis, where the morphologic abnormality may be related to possibly reversible biochemical and histochemical changes more than to permanent structural abnormalities. Such an observation might help to explain significant changes detectable in large artery geometry in hypercholesterolemic man with endothelial activation after relatively short-term cholesterol lowering therapy [10].

2. Hypercholesterolemia and oxidative stress

Hypercholesterolemia is associated with an impaired endothelium-dependent relaxation, i.e. a diminished bioactivity of NO. Altered vasomotion in hypercholesterolemia is dependent on increased levels of oxidized LDL, which in ex vivo studies are shown to be able to impair signal transduction between endothelial cell surface receptors and NO production [11], to inhibit NO synthase activity [12], and to inactivate NO released from endothelial cells [13]. This last mechanism would lead to an accelerated breakdown of readily formed NO by augmented superoxide activity, being responsible for a decreased NO bioavailability [2,14]. The observation that low density lipopro-
3. Endothelial dysfunction and coronary tone

Endothelium-derived NO contributes to resting epicardial and microvascular coronary tone, and coronary risk factors including hypercholesterolemia are associated with reduced resting and stimulated bioavailability of NO from the human coronary circulation [18]. A defective endothelium-mediated vasodilation is a mechanism underlying an inappropriate vasoconstrictor response to stimuli inducing coronary vasodilation in presence of normal endothelium. In patients with hypercholesterolemia and coronary artery disease, coronary dilator response to ACh is inversely related to LDL susceptibility to oxidation and improves more when the antioxidant agent probucol is added to cholesterol-lowering treatment as compared to conventional therapy alone, thus suggesting a major role for oxidized LDL in the impairment of the endothelium-dependent coronary vasodilation [9–21].

4. The double facet of F₂-isoprostanes: markers of oxidative stress and modulators of coronary tone

The F₂-isoprostanes, a family of novel prostaglandin isomers generated by free radical-mediated peroxidation of arachidonic acid and LDL independently from cyclooxygenase [7], are generated in situ and subsequently recovered in blood and urine [22]. Proposed as potential markers of in vivo oxidative stress in atherothrombotic disease [8], their circulating levels have been reported to be increased in hypercholesterolemic patients [23], and increased accumulation has been recently documented in coronary arteries from patients with coronary artery disease as compared to dilated cardiomyopathies and controls [24]. Furthermore, urinary excretion of 8-epi-PGF₂α has been reported to be increased in patients with familial heterozygous hypercholesterolemia and to be lowered by dietary and/or drug cholesterol lowering treatment [25]. Their vasoconstrictor activity on several vascular beds, such as aortic and coronary, in vitro was recently reported [26], but their possible role in control of arterial tone, namely the coronary one, in physiologic and disease states was not yet demonstrated before the contribution of Wilson et al. [9].

5. Conclusions

A major contribution of the work of Wilson et al. [9], capable of representing a reference position in understanding the relations between hypercholesterolemia, endothelium-mediated coronary tone and oxidative stress, stands on the clear demonstration that a decreased NO bioavailability secondary to enhanced oxidative stress resulting from lipid peroxidation is responsible for the increased coronary vasoconstriction in hypercholesterolemia. Actually, the paper provides further support to the hypothesis that, despite in very advanced atherosclerosis expression of NO synthase in endothelium clearly declines, in several disease conditions including hypercholesterolemia and earlier stages of atherosclerosis, NO production is not altered but its bioavailability is reduced because of oxidative inactivation by excessive production of the superoxide anion O₂⁻ [27]. The observation of an increased dose-dependent vasoconstriction to 8-epi-PGF₂α in coronary arteries with intact endothelium from hypercholesterolemic pigs nicely mirrors the finding of increased time-dependent O₂⁻ generation observed by Ohara et al. [14] in rabbit aorta with endothelium from hypercholesterolemic rabbits.

Several cellular sources of reactive oxygen species are known, including also endothelial NO synthase, cyclooxygenase, lipooxygenase. Also this observation has relevant implication for the clinicians, focusing on the reduction of oxidative stress through plasma cholesterol lowering as primary therapeutic goal, as well as on the
administration of NO donors or precursors as additional measure for restoring a physiologic balance between coronary vasoconstric tors and vasodilator activity: oxidative stress from one side increases breakdown and decreases bioavailability of NO, whose tonic release is responsible for keeping the vasculature in an adequately dilated state, and from the other increases generation of vasoconstrictor products, namely prostanoids. Finally, 8-epi-PGF$_{2\alpha}$ reveals its double facet of marker of oxidative stress associated to lipid peroxidation and trigger of vasoconstriction in presence of wounded endothelium.

Acknowledgements

Authors are indebted to Dr Corrado Blandizzi MD, and to Professor Mario Del Tacca MD, from the Department of Oncology, Division of Pharmacology, of the Pisa University, for their cooperation. Elena Barberini is also acknowledged for editorial assistance.

References