Isoprostanes: Are They More Than Physiological Biomarkers of Lipid Peroxidation?

To the Editor:

Isoprostanes are currently used as biomarkers of lipid peroxidation in humans.1 Minuz et al2 recently showed that urinary levels of 15-F2t-IsoP were increased in hypertensive patients suffering from renovascular disease, confirming the experimental data showing that renovascular hypertension and activation of the renin-angiotensin system in general is associated with an increased lipid peroxidation. Conversely, data obtained from 25 patients with essential hypertension showed that urinary levels of 15-F2t-IsoP were not significantly different in comparison with controls. Similarly, we showed that the urinary levels of 15-F2t-IsoP were not increased in untreated patients with mild-to-moderate hypertension.3 In our study, the mean systolic and diastolic blood pressure was similar to Minuz’s essential hypertensive patients, but because our patients were never treated, their hypertension was probably less severe. Both studies are consistent with the hypothesis that oxidative stress is not increased in the early stages of human essential hypertension. However, they do not rule out the possibility that essential hypertension is associated with an increased oxidative stress at later stages, as a consequence of hypertension. A large number of studies show that isoprostane levels are increased in cigarette smokers, homocystinemia, diabetes mellitus, and hypercholesterolemia.4 We now have evidence that renovascular, but not essential, hypertension is associated with increased F2-isoprostane levels. It is likely that the increased levels observed are related to an increased production of these compounds rather than a variation of their clearance.

There is no doubt that isoprostanes are key biomarkers to investigate the role of free radical generation in the pathogenesis of human disorders. However, are they more than physiopathological biomarkers? Two fields of investigation remain unknown. Firstly, F2-isoprostanes are biologically active. They mediate vasoconstriction in conductance arteries as well as resistance microvessels, and vascular smooth muscle cells mitogenesis. Whether isoprostanes are involved in cardiovascular physiology and pathogenesis remains to be investigated. Secondly, F2-isoprostane levels correlate with disease severity indexes in diseases such as cardiac failure or pulmonary hypertension. Could F2-isoprostane quantification provide prognostic information in such diseases? In other words, does increased lipid peroxidation, similar to inflammation, represent a marker of increased risk of major cardiovascular events in such patients, and could F2-isoprostane represent a prognostic biomarker similar to high-sensitivity C-reactive protein? There is today no evidence that they do.

The study of Minuz provides important data concerning the formation of F2-isoprostanes in hypertension. Whether these compounds are more than physiopathological biomarkers of lipid peroxidation needs now to be further investigated.

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Response

We agree with the substance of Drs Cracowski’s and Baguet’s comments. In fact, our recently published study1 did provide evidence for a pathophysiological role of F2-isoprostanes in mediating persistent platelet activation in patients with renovascular disease. This may reflect the biological activity of 8-iso-PGF2α and other iso-eicosanoids in amplifying the platelet response to other agonists.2 A similar relationship between enhanced formation of bioactive F2-isoprostanes and persistent platelet activation has been reported in association with hypercholesterolemia,3 type 2 diabetes mellitus,4 and visceral obesity.5 Whether the rate of in vivo lipid peroxidation, as reflected by F2-isoprostane excretion, helps predict major vascular events is an interesting question that deserves further investigation. In the recent study of Davì et al,5 the C-reactive protein level was linearly correlated with the excretion rate of 8-iso-PGF2α in a group of otherwise healthy women with abdominal adiposity and free of other cardiovascular risk factors. Thus, the interplay between low-grade inflammation, lipid peroxidation, and platelet activation, as characterized in the paradigm of visceral obesity, may have broader implications for cardiovascular risk assessment and management.

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