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LETTERS TO THE EDITOR

Vasomotor Effects and Pathophysiologic Relevance of F_2-Isoprostane Formation in Vascular Diseases

We read with the utmost interest the study by Iuliano et al. (1). The investigators showed for the first time that concentrations of 2-F_2-isoprostane regioisomers, i$PF_{2\alpha}$-III (15-F_{2t}-IsoP) and i$PF_{2\alpha}$-VI (5-F_{2t}-IsoP), were markedly increased in the coronary sinus following percutaneous transluminal coronary angioplasty (PTCA). In their study, the levels of i$PF_{2\alpha}$-III in the coronary sinus after angioplasty, measured by GC/NICI-MS, were 125 pg/ml, which is equivalent to 0.35 nmol/l. Such levels are in the same range as plasma samples in nonsmokers (0.103 nmol/l [2], in ruptured aortic aneurysm 0.436 nmol/l [3]) and umbilical cord arterial samples in newborns (0.898 nmol/l [4]), although caution should be taken when comparing these results as the methodology used to measure i$PF_{2\alpha}$-III was different. Such data do not support the conclusion that these concentrations are similar to the EC_{50} values observed with i$PF_{2\alpha}$-III on porcine and bovine coronary arteries that are in the micromolar range (5). Indeed, the potency of i$PF_{2\alpha}$-III was in the micromolar range in most studies performed on conductance vessels, including coronary arteries (6), although data on human coronary arteries are lacking.

Consequently, the concentrations observed in this study (1) are unlikely to induce a vasoactive effect in conductance vessels. In contrast, the potency of i$PF_{2\alpha}$-III in the microcirculation is higher, and in some studies close to the nanomolar range (6). As a consequence, whereas the concentrations reported in the Iuliano et al. study (1) are unlikely to contribute to epicardial coronary artery vasoconstriction, local concentrations may be sufficiently high to induce intramyocardial artery vasoconstriction. Further in vivo and in vitro studies are required to determine whether isoprostanes might contribute to vasoconstriction in vascular diseases.

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REPLY

Cracowski et al. raise an important issue related to the putative biologic effect of F_2-isoprostanes (iPs) in human coronary arteries after percutaneous transluminal coronary angioplasty (PTCA). We observed an increase of isoprostanes i$PF_{2\alpha}$-III and i$PF_{2\alpha}$-VI in the coronary sinus immediately after PTCA and suggested that this elevation not only reflected reperfusion-mediated oxidative stress but could also play a role in the untoward effects of this procedure. In particular, iPs may facilitate platelet activation and coronary vasospasm, two phenomena that occur early after PTCA and are responsible for coronary thrombosis and arrhythmia.

Used as markers of oxidant stress, F_2-iPs are increased not only in clinical settings associated with ischemia-reperfusion but also in settings characterized by chronic inflammation such as atherosclerosis, chronic bronchitis and systemic lupus erythematosus (1–3). The F_2-iPs may also have biologic relevance because they enhance platelet response to the common agonists and elicit a vasomotor response. However, it is still unclear whether these effects can occur in clinical settings associated with enhanced oxidative stress. An in vitro study demonstrated that i$PF_{2\alpha}$-III was not able to elicit platelet aggregation, but in a range of concentration between 10 nmol/l and 10 μmol/l increased the magnitude of platelet response to subthreshold concentrations of arachidonic acid, collagen and adenosine diphosphate (ADP) (4). Patients with diabetes and hypercholesterolemia show a significant correlation between i$PF_{2\alpha}$-III and 1-dehydrothromboxane B_2 values, suggesting a potential link between platelet aggregation and lipid peroxidation (5,6). This was corroborated by the concomitant decrease of i$PF_{2\alpha}$-III and 11-dehydrothromboxane B_2 in patients given 100 to 600 mg/d vitamin E. These data suggest that the circulating levels of i$PF_{2\alpha}$-III may be relevant to clinical settings in which platelet activation and enhanced oxidative stress coexist. Because these two phenomena coincide after PTCA, it is conceivable that a link exists between them, taking into account that in some patients the circulating levels of i$PF_{2\alpha}$-III after PTCA were close to 1 nmol/l. We agree with Cracowski and colleagues that the circulating levels of i$PF_{2\alpha}$-III were likely too low to elicit a direct vasomotor response in the coronary circulation. However, values of the two isoprostane regioisomers measured specifically by us in the coronary sinus cannot be extrapolated to Morrow et al.'s (7) total isoprostane assay with $PGF_{2\alpha}$ as internal standard. Even if it did give a quantitative impression of total iPs, this method is quantitatively imprecise, measuring a host of unresolved peaks. Similar amounts of one isoprostane, such as i$PF_{2\alpha}$-III, which is not a very abundant one, suggests that an accurate estimate of total iPs in the coronary circulation would be much higher than in peripheral plasma. Also, it is very difficult to extrapolate from one iP to the effects and local concentration of myriad ones released at the site of free radical burst on the vascular wall.

Finally, it has never been studied, as in the case of platelet aggregation, whether $iPF_{2\alpha}$-III is able to amplify the vasomotor response to other agonists. This effect should be studied in the future before concluding that the concentration of this isoprostane in the coronary circulation has no role in the vasospasm occurring after PTCA.

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Percutaneous Revascularization Versus Beating Heart CABG or CABG With Cardiopulmonary Bypass in Patients With Refractory Myocardial Ischemia

Morrison et al. (1) recently reported the results of a very important multicenter randomized trial comparing percutaneous coronary intervention (PCI) versus coronary artery bypass graft surgery (CABG) for patients with refractory myocardial ischemia and risk factors for adverse outcomes with CABG. It clearly appears that PCI is an alternative to CABG for patients with medically refractory myocardial ischemia at high risk for adverse outcomes with CABG. Incidentally, the study was initiated in February 1995 when multivessel beating heart CABG via sternotomy was popularized by Buffolo et al. (2). The study by Morrison et al. (1) does not address the techniques used to accomplish CABG in this study. If CABG was performed using cardiopulmonary bypass, then the study fails to mention the cardioprotective strategies used, as this may be an important factor in the rates of perioperative myocardial infarction (MI) and clinical outcomes (3). Unless strict cardioprotective criteria were used, it is indeed possible that various surgeons from various centers used different cardioprotective strategies: ventricular fibrillation versus ischemia, crystalloid versus blood cardioplegia, antegrade versus retrograde delivery of cardioplegia and warm versus cold cardioplegia (3). In addition, the methods fail to mention whether off-pump CABG was utilized, and if so, for which type of patients. Although initial results of off-pump CABG in low-risk patients is encouraging, patients with high preoperative risk factors (octogenarians, recent MI, reoperative CABG, left ventricular ejection fraction <40%, previous stroke) seem to derive marked advantages from the off-pump technique (4). Prospective randomized trials with longitudinal clinical and angiographic follow-up are needed to better define the real advantages and limits of this new clinical strategy in all patients, especially in high-risk groups. Preliminary data at mid-term follow-up is very encouraging for coronary revascularization on the beating heart (5–8).

Finally, if these studies are further corroborated, then the surgical strategy itself (beating heart versus traditional CABG using cardiopulmonary bypass) may prove to be an additional factor in comparisons of revascularization methods in high-risk patients. We commend Morrison et al. (1) for conducting a very important and timely study.

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