Exercise-Induced Suppression of Postprandial Lipemia: A Possible Mechanism of Endothelial Protection?

To the Editor:

We wish to propose a novel hypothesis of how exercise may beneficially modulate endothelial function. The benefit of exercise in the prevention of cardiovascular disease is undisputed, but the underlying mechanisms responsible for this beneficial effect, which are independent of traditional cardiovascular risk factors, remain poorly understood. Recently, attention has been focused on the influence of exercise on the endothelium, its functions, and its interactions with blood components.1,2 Exercise training enhances NO and suppresses endothelin-1 production by the endothelium,3 thus potentially shifting the balance toward vasodilation and anti-atherosclerosis. Improved endothelium-dependent vasodilation (EDV) in both the coronary and peripheral vessels following exercise training has been demonstrated by a number of studies in human subjects of different age and risk groups.4,5 In hypercholesterolemic patients, this improvement is independent of fasting lipid profile modification.6

In cell culture experiments, shear stress induces an upregulation of endothelial NO synthase with resultant increase in NO production and release. With exercise training of small muscle groups, such as a handgrip exercise, the local increase in blood flow directly enhances EDV through shear stress mechanisms.7 However, dynamic exercises that use larger muscle groups, such as bicycle ergometer training, produce a systemic enhancement of EDV.8,9 In this setting, the systemic increase in shear stress is small, and it has been suggested that the systemic enhancement of EDV may be the result of metabolic or neurohumoral factors, which are modified by exercise.9 However, to date no likely candidates have been identified.

It has long been known that exercise training lowers postprandial lipemia:10 an environment which is considered to be proatherogenic.11 There is accumulating evidence that postprandial lipemia exerts its deleterious effect on the cardiovascular system by causing endothelial dysfunction.12 There are now several studies demonstrating that postprandial lipemia induced by eating a fatty meal causes significant impairment of EDV in healthy humans and that the degree of impairment correlates with the rise in postprandial plasma triglyceride levels.13-15 We believe it is plausible that postprandial plasma lipid levels (and/or their composition) represent the missing systemic factor that links exercise training with the general improvement in endothelial function observed in vivo. Thus, in daily life, regular exercise suppresses postprandial lipemia, and through this, endothelial function is enhanced. This intriguing hypothesis links for the first time the effects of exercise on postprandial lipemia and endothelial function, which until now have been investigated separately. To provide support for this hypothesis, novel study protocols that investigate the effects of exercise training and fat-meal challenge in combination on the outcome measure of EDV are required. Furthermore, because a reduction in postprandial lipemia has been observed after a single exercise session,16 if the hypothesis is true, an equally rapid enhancement of EDV may also be seen with much shorter training periods than in previous studies.

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Physiological Variations of Isoprostanes: A Step Forward?

To the Editor:

Ide et al1 recently reported that 15-F2t-IsoP urinary levels were higher in healthy young men compared with healthy premenopausal women, showing that lipid peroxidation is increased in the former group. Isoprostanes appear to be specific and sensitive biomarkers of lipid peroxidation2 and are widely used in clinical trials. Unlike the S-series and the 15-F2t-IsoP metabolites, our knowledge of the physiological variations of 15-F2t-IsoP is increasing, essential criteria before assessing this biomarker in pathological states. The study by Ide et al provides important but incomplete information concerning the physiological variations of 15-F2t-IsoP in humans. This study was meticulously performed, using a validated assay.3 The numerous exclusion criteria (smoking, hypertension, dyslipidemia, diabetes, alcoholism, medication including vitamins and oral contraceptives) give weight to the validity of the results, because few biases are likely to have been introduced. Furthermore, four potential limita-
tions of the study that the authors outline in the discussion can reasonably be ruled out: the confounding effects of exercise or of diet, the enzyme dependent production of 15-F_2t-IsoP, and the lack of measurement of 15-F_2t-IsoP metabolites in their study. Extreme endurance exercise increases 15-F_2t-IsoP levels in humans, but moderate exercise does not.\textsuperscript{4,5} Similarly, F_2-isoprostane levels are not modified by the lipid content of the diet.\textsuperscript{6,7} In addition, the cyclo-oxygenase–dependent formation of 15-F_2t-IsoP that was demonstrated in vitro is negligible in humans in clinical settings.\textsuperscript{10} Lastly, the measurement of 15-F_2t-IsoP metabolites together with the parent compound provides an integrated index of 15-F_2t-IsoP formation,\textsuperscript{2,9} but there is no evidence that the metabolite levels alone are a better marker of oxidative stress.

The major criticism that should be made is that whereas the distribution of isoprostanes in women seems to follow normality, this is not the case for men, in whom the median 15-F_2t-IsoP level is obviously lower than the mean. Because the differences observed between men and women are driven by 3 men, this may lead to the hypothesis that a subgroup of men, but not men in general, has a higher 15-F_2t-IsoP urinary level. Furthermore, it should be pointed out that the measurement of isoprostanes was obtained from a small subgroup of patients, in whom median should be used rather than mean for describing 15-F_2t-IsoP urinary levels. Interestingly, anti-oxidant vitamin supplementation led to a significant reduction of 15-F_2t-IsoP levels in men but not in women. Such data further support the hypothesis proposed by Patrignani et al\textsuperscript{12} that the basal rate of lipid peroxidation is the major determinant of the response to anti-oxidant vitamin supplementation.

In conclusion, this study suggests a sex difference in the basal rate of lipid peroxidation, but it does not enable a definitive conclusion concerning the physiological variations of 15-F_2t-IsoP in men and women. Confirmation of these preliminary results in another clinical trial including a large number of men and women with isoprostane measurements as the primary endpoint is required. However, from now on, it seems unavoidable to match patients in terms of sex in clinical studies with 15-F_2t-IsoP as a biomarker.

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We thank Hiroyuki Tsutsui for providing us details from his study.

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Physiological Variations of Isoprostanes: A Step Forward? Response to Letter to the Editor

We are grateful to Drs Cracowski, Stanke-Labesque, and Bessard for thoughtful comments and appreciate the great interest in our recent article on the difference in oxidative stress between healthy young men and women.\textsuperscript{3}

First, we have to admit that the number of healthy individuals for the measurement of 8-iso-PGF2alpha is small in this study. It is clearly needed to confirm our results in larger number of the study subjects. However, our conclusion is considered to be valid because thioarbituric acid–reacting substances (TBARS) data also supported this notion. Moreover, the rate of cellular respiration, which is probably the dominant source of reactive oxygen species in the physiological state, might be higher in men and lead to greater oxidative stress.\textsuperscript{2} Second, even though a putative 2,3-dinor-5,6-dihydro-8-iso-PGF_2alpha, a metabolite of 8-iso-PGF_2alpha (IPF_2alpha),\textsuperscript{2,3} is a better marker of in vivo oxidative stress,\textsuperscript{3} the addition of other biomarkers of oxidative stress such as 8-hydroxydeoxyguanosine (8-OHdG)\textsuperscript{9} or plasma oxidized LDL (Ox-LDL)\textsuperscript{4} would increase the strength and relevance of the results obtained by using 8-iso-PGF2alpha. Finally, the doctors’ comments regarding the overlap between the majority of two groups in terms of both TBARS and 8-iso-PGF2alpha levels are quite incisive. These data are consistent with those by Patrignani et al\textsuperscript{12}, indicating that the basal rate of lipid peroxidation is the major determinant of the response to antioxidant vitamin supplementation.

Despite the increasing knowledge of the role of reactive oxygen species in atherogenesis, it remains uncertain whether oxidative stress is of clinical significance in the pathophysiology of atherosclerotic cardiovascular diseases in humans. Moreover, the postulated beneficial effects of antioxidant supplementation on these patients remain also to be confirmed. Biomarkers of in vivo oxidative stress such as 8-iso-PGF2alpha offer a valuable tool for investigating these crucial issues. The present study suggests that sex may imply potential effects on these markers adding to other well-known risk factors including hypercholesterolemia, diabetes mellitus, and cigarette smoking.

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MMP Inhibition and Lumen Loss After Balloon Angioplasty or Stenting

To the Editor:

With interest we read the paper by Cherr et al.1 reporting the negligible effect of matrix metalloproteinase (MMP) inhibition on constrictive remodeling and intimal hyperplasia after balloon angioplasty and stenting, respectively. As the authors mentioned, the results are at odds with observations from several published studies that have reported a significant reduction of late lumen loss after intervention by MMP inhibition.2-4 Several possible explanations were proposed to account for these differences, including route of administration and lack of activity of the compound used by Cherr et al.2

First, we agree with the authors that the spectrum of MMP inhibitory activity, and thus clinical effects, may significantly differ among compounds. Marimastat and GM6001 are two nonspecific MMP inhibitors with potent inhibitory MMP-1 activity that have significant plasma MMP inhibitory activity and a marked inhibition of MMP-1. However, other explanations for these controversial results may be considered.

Second, we feel that differences in animal models may also explain the lack of significant effect on postangioplasty constrictive remodeling in the study by Cherr et al. In an earlier publication, Geary et al.5 described that, in the nonhuman primate, the vessel area did not constrict but enlarged after balloon dilation at 4 weeks. Surprisingly, the vessel area at 4 weeks did not differ compared with the area at 4 days, demonstrating the absence of constrictive remodeling in the primate arterial injury model. This is in contrast with the human and pig model in which constrictive remodeling is evident both in the acute and chronic phases of vessel injury.5 Based on the earlier reported absent constrictive remodeling response in the human model, we speculate that the MMP inhibitory effect in the primate model may have a significant effect on expansive remodeling 4 weeks after balloon angioplasty.

Third, serial intravascular ultrasound examination has been used as an endpoint in other studies; it is the most accurate method to study temporal changes in vessel area.

Studies on the effect of MMP inhibition on in-stent restenosis have also resulted in contradictory observations. Cherr et al.2 did not find inhibition of in-stent restenosis using their broad-spectrum MMP inhibitor (RO113-2908). However, MMP inhibitors have significantly inhibited in-stent hyperplasia in at least two different animals.6,7 Based on these inconsistent outcomes, we agree with the authors that additional research is needed to define the spectrum of MMP that plays a role in the response to local arterial injury.

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In Response:

We recently documented that a broad-spectrum MMP inhibitor had no effect on artery wall remodeling and intimal hyperplasia after angioplasty or stenting in nonhuman primates.1 Thirty one cynomolgus monkeys had consumed an atherogenic diet for more than two years to create large and complicated iliac atherosclerotic lesions. Angioplasty and stenting were then performed, and animals were randomly assigned to a 4-week continuous infusion of a potent MMP inhibitor (RO113-2908) or vehicle. Despite demonstrating significant plasma MMP inhibitory activity and a marked inhibition of angiogenesis, treatment did not prevent constrictive artery wall remodeling or neointimal accumulation at sites of angioplasty or stenting.

As outlined in their letter, our results are at odds with reports by Pasterkamp and colleagues.2-4 It is important to first acknowledge that a number of earlier studies not referenced in their letter failed to show that MMP inhibition causes durable improvement in the response to angioplasty (refer to Discussion1). Consistent with these studies and our results, Pasterkamp and colleagues did not achieve a significant reduction in neointimal hyperplasia after iliac angioplasty by treating micro pigs, or rabbits with the broad-spectrum MMP inhibitors batimastat,2 marimastat,3 and GM6001,4 respectively. However, in contrast to our results, they did achieve improved artery wall remodeling after angioplasty in pigs treated with batimastat2 or marimastat.3 The effect of GM6001 on constrictive remodeling in their rabbit double-injury model was not reported.4 In their letter, Pasterkamp and colleagues suggest the failure of RO113-2908 to improve artery wall remodeling after angioplasty in
atherosclerotic monkeys may reflect a lack of constrictive remodeling in this model. This is not the case. In a previous study from our group, Mondy et al. characterized the remodeling response in 37 atherosclerotic monkeys one month after iliac angioplasty (as in the present study) and documented frequent artery wall shrinkage. The correlation between late changes in artery wall size and lumen area was highly significant \( r=0.72, P<0.001 \) with 14 of 37 arteries shrinking to a size smaller than their baseline before angioplasty. Moreover, 12 of 29 injured arteries in the present study had constricted to a size smaller than their reference artery (EEL area ratio) 4 weeks after angioplasty and of these more than half were in the treatment group. Thus, constrictive remodeling did occur and it was not inhibited by treatment.

Our study was the first to report the effects of a MMP inhibitor on stent neointimal thickening. Pasterkamp and colleagues contrast our negative result with their recent study in rabbits in which GM6001 reduced stent neointimal area by 29% but failed to significantly alter the response to angioplasty. They also refer to an abstract summarizing a small study of batimastat-coated stents placed in pig coronary arteries. A “low-dose” coating reduced neointimal area by 33% compared with control stents, but the effect was not significant for a “high-dose” coating. Furthermore, lumen caliber was similar in all groups.

Given marked differences in experimental design, we do not find it surprising that treatment effects have varied. Responses to angioplasty and stenting in primates with preexisting advanced atherosclerosis are being compared with those following angioplasty in Yucatan micropigs with lesions first induced by balloon injury and high-fat diet or to those following angioplasty in nonatherosclerotic Landrace pigs and following double balloon injury and stenting in nonatherosclerotic New Zealand White rabbits. Each model also used a different MMP inhibitor, drug dose, and drug delivery protocol.

Pasterkamp and colleagues used broad-spectrum inhibitors with activity against MMPs and other proteases including the sheddases such as TNF-α-converting enzyme (TACE). Thus, high-dose marimastat, batimastat, and GM6001 may have indirectly altered inflammatory responses to angioplasty and stenting. RO113-2908 is a more selective agent with no activity against TACE and relatively less activity against MMP-1. This may help explain differences in treatment effects in the stent models and in which chronic inflammation is thought to play a more important role in promoting neointimal hyperplasia. Lastly, Pasterkamp and colleagues used very high drug doses and potentially achieved greater MMP inhibition. However, these doses have been associated with toxicity in animals and humans. We selected the dose of RO113-2908 based on safety studies in nonhuman primates and achieved steady-state plasma levels above the IC\(_{50}\) for relevant MMPs. Drug activity was validated at the tissue level where we documented significant inhibition of angiogenesis in subcutaneous polyvinyl alcohol sponge sterilization.

Clearly, a negative result in a primate model that so closely depicts the pathology in human restenosis warrants discussion in light of positive effects observed in lower species. Pasterkamp and colleagues have raised important questions, and we appreciate the opportunity to provide our perspective. Additional studies will be necessary to reconcile these differences and to provide guidance for preclinical development of MMP inhibitors to prevent restenosis.

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Physiological Variations of Isoprostanes: A Step Forward?
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