Angiographic Restenosis Rates of Patients After Multilession Coronary Interventions

To the Editor:

Moussa and colleagues report restenosis in 43 (22%) of 201 lesions and 31 (37%) of 84 patients undergoing multivessel coronary stenting at angiographic follow-up at a mean of 5.2 months.1

Confirmation of the lesion-to-lesion independence of restenosis after balloon angioplasty or stenting has validated lesion-based restenosis analysis in patients with multivessel disease.2 Restenosis rates for patients with multiple treated lesions can therefore be calculated and equal the sum of the independent probabilities of restenosis.

Given a lesion restenosis rate of 22% after stenting, the proportion of patients with restenosis at ≥1 site for 2, 3, 4, or 5 treated lesions would be 39%, 53%, 63%, and 71%, respectively. Moussa et al treated 2 lesions in 66 patients, 3 lesions in 24 patients, 4 lesions in 5 patients, and 5 lesions in 3 patients, which gives a predicted restenosis rate by patient of 45%, slightly higher than the observed 37%. This difference may be due to chance or to clustering of restenosis in particular patients. Clustering is supported by the observation that 20 (47%) of 43 restenotic lesions occurred in 8 (10%) of 84 patients (P<0.05 by comparison of proportions). Further information on these 8 patients, including diabetic status, preprocedure lumen diameter, number of lesions treated, and number of stents used per lesion, should be provided. The existence of distinct lesion populations with differing propensities for restenosis may be of particular relevance to case selection.

Patients with multivessel disease may have lesions requiring dilation that are amenable to balloon angioplasty but not to stenting. Furthermore, restenosis rates are higher after vein graft interventions. The disproportionate impact of lesion restenosis rate and the number of lesions treated on the patient’s overall risk of restenosis should be underscored. On the basis of lesion restenosis rates from the STRESS,3 BENESTENT,4 and SAVED trials, a hypothetical patient who had 1 coronary stenosis stented, a second ballooned, and stent placement for a third vein graft lesion would have a predicted overall restenosis rate of 71%. In the study by Moussa et al,1 two thirds of the patients had only 2 lesions stented, which partly explains their good results.

What do the authors believe are the implications of these observations for case selection, including the issue of left ventricular dysfunction for which completeness of revascularization may be prognostically important? Should there be a limit to the number of lesions treated? Is a more complete follow-up, including coronary angiography, advisable in these patients?

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Response

The line of statistical reasoning used by Dr Mazeka and colleagues to calculate the theoretical probability of restenosis in patients with several lesions may be misleading for 2 reasons: (1) even though lesion characteristics play a major role in determining the probability of restenosis, genetic predisposition may still be a factor,1 so the assumption that there is “total” lesion-to-lesion independence is not true; (2) the probability of an event is the event’s long-run relative frequency in reported trials under similar conditions. In other words, for the probability calculations to be valid, the incidence of the event (restenosis) should be equally likely among all lesions treated. Clearly, the likelihood of restenosis depends on many factors that are not equally distributed among all lesions. The univariate and multivariate analyses of predictors of restenosis in our study2 illustrate that patients with long lesions, small vessels, or smaller final minimum lumen diameter are at higher risk for restenosis; genetic predisposition cannot be proved or disproved from our data.

Population-based studies, whether prospective or retrospective, can only serve as general guidelines. The profile of an individual patient in clinical practice may not always fit the profile of patients in a particular study. A patient with normal ventricular function and 3 focal lesions in vessels ≥3.0 mm in diameter may have a good clinical outcome with multivessel stenting, whereas a patient with poor ventricular function and 3 lesions in diffusely diseased vessels is at higher risk for cardiac events. The fact that the same number of lesions were dilated in both patients is not sufficient to assume that the probability of restenosis would be similar. Paradoxically, a higher probability of restenosis would be expected in a patient with a single long lesion in a small vessel than in a patient with 3 focal lesions in vessels ≥3.0 mm in diameter.

In our practice, we advise all patients, particularly those at high risk, to return for follow-up angiography. Clinical decision making based on angiographic evaluation coupled with clinical and functional assessment may be superior to decisions made only according to the symptoms of the patient.3

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Natural History of Infarct-Related Lesions

To the Editor:

We read with great interest the elegant study of Van Belle et al1 describing the natural history of the infarct-related lesion using coronary angioscopy. They found that most patients had yellow plaques (79%) and thrombus (77%) without appreciable changes in these features according to the elapsed time from the infarction. They concluded that infarct-related lesions require more than a month to heal, or in other words, that during this time most patients still have unstable plaques. They further suggested that these findings could explain the unique, untoward behavior of recently infarcted lesions either spontaneously or after percutaneous treatment. We wish to draw attention to some methodological aspects of their report. First, the true “natural history” of the pathological substrate of the infarct-related lesion would require serial angioscopic examinations (with each patient being his/her own control), with the obvious ethical implications. Alternatively, a much larger cohort of patients would have been required to derive definitive insights about the potential influence of the elapsed time from the infarction on the angioscopic data. Second, only 7% of the patients had postinfarction angina, and no information was provided concerning other clues for ischemia. Therefore, most patients underwent the procedure on anatomic grounds alone. In this context, the reasons to perform cardiac catheterization early or late (24 hours to 4 weeks) after infarction could imply a selection bias that may have influenced the results. Finally, any explanation for the “unique adverse behavior” of the infarct-related lesions will necessarily require that the angioscopic features of these patients are different from those of other patients with unstable angina and a more benign course. Furthermore, a control group seems especially necessary when the reported incidence of yellow plaque and thrombus was rather similar to that found in other patients with unstable angina.2,3

In a previous study,4 we analyzed the angioscopic characteristics of patients with recurrent ischemia (24 hours to 4 weeks) after infarction. Compared with other patients with unstable angina (but without previous infarction), patients with postinfarction ischemia had similar plaque characteristics (yellow plaque 80% versus 84%) but a higher incidence of associated thrombi (95% versus 68%), mainly at the expense of protruding occlusive thrombi. Although the simplified angioscopic classification used in the 2 studies was slightly different, it is of interest that the results of Van Belle et al1 fall in the middle of our 2 groups of patients.4 This further corroborates the suggestion4 that the presence of a red thrombus (mainly if occlusive) plays a significant pathogenic role in the recurrence of ischemia after myocardial infarction.

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Response

We welcome the opportunity to respond to the letter of Dr Alfonso regarding our recent article, in which we showed that the majority of infarct-related lesions had angioscopic evidence of instability even when studied 1 month after myocardial infarction.1

We agree with Dr Alfonso that the ideal approach to determine the “natural history” of the infarct-related lesion would be to perform serial angioscopic studies in a cohort of patients. However, as he points out, this would be difficult to justify on ethical grounds. Second, as we stated in our article, our institutional policy during the period of the study was to perform diagnostic catheterization after myocardial infarction and to perform ad hoc angioplasty in those patients with suitable anatomy. The findings of our study in such unselected patients cannot therefore be extrapolated to a population in whom the indications for angiography are more restrictive. However, we do not believe that the timing of angiography had a significant influence on our findings, because the major message of the article was that even when angioscopy was performed 1 month after infarction, there was a high incidence of angioscopic “instability.”

Finally, we agree that the presence of protruding red thrombi seems to be an important indicator of plaque instability, as suggested by the study performed by Dr Alfonso et al.2 In fact, in a previous study,3 we showed that the presence of protruding thrombi was a powerful predictor of late vessel occlusion after balloon angioplasty.

The results of our study, which demonstrates a high prevalence of thrombus even in asymptomatic patients after myocardial infarction, extends the work of Dr Alfonso by demonstrating that clinical stability in the postinfarction patient does not necessarily imply plaque stability.

The results of Dr Alfonso’s study in conjunction with our article emphasize the need for further research into the factors that influence plaque instability, both in patients with unstable angina and in those who have suffered a myocardial infarction.

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Erythrocyte Promotion of Platelet Reactivity Decreases the Effectiveness of Aspirin as an Antithrombotic Therapeutic Modality

To the Editor:

Vallés et al report persistent serotonin release from platelets prepared from patients with vascular disease who were taking aspirin (200 to 300 mg/d). These authors point to the potential clinical significance of their observation because serotonin stimulates vascular smooth muscle cell (VSMC) proliferation.

Serotonin is also a vasoconstrictor and can induce or enhance platelet shape change (PSC) and aggregation. PSC is an early phase of platelet activation that is aspirin resistant and precedes aggregation.

A link between serotonin and platelet activity was demonstrated in dyslipidemic patients in whom simvastatin (an effective lipid-lowering drug) reduced platelet hyperactivity and corrected the intraplatelet levels of serotonin. Furthermore, after PTCA, the addition of ticlopidine (a potent inhibitor of platelet activation) to aspirin and heparin normalized serotonin release from platelets.

Because some 95% of the serotonin in the blood is stored in erythrocytes, serotonin release other than mention of the well-recognized capacity of released platelet dense granule constituents to promote cell proliferation.

We are in complete agreement with Drs Jagroop and Mikhailidis that a very important function for released serotonin is the ability of this autacoid to induce vasoconstriction at a site of vascular injury. Increased levels of serotonin in plasma may indeed be correlated with vascular diseases, but at the present time it remains difficult to establish definitive cause-and-effect relationships in specific instances.

In our report, we demonstrated that in a significant number of patients with vascular disease, doses of aspirin frequently used for antithrombotic therapy were not sufficient to completely block the platelet reactivity that is promoted by erythrocytes.

This was evidenced by the insufficient blockade of both serotonin release and platelet recruitment by those doses of aspirin. This indicated that platelet reactivity persisted in the setting of inhibition of synthesis of thromboxane A2 (>94%) in all the patients. Thus, more than thromboxane A2 inhibition would be required to reduce ischemic complications in this patient population.

In addition, other conclusions can be derived from the data obtained in our study. First, an optimal dose of aspirin needs to be established for patients with occlusive arterial diseases to provide adequate aspirin-mediated inhibition of both platelet reactivity and the prothrombotic effects of erythrocytes. This can be achieved in normal volunteers with a daily low dose of aspirin interrupted biweekly with a single larger dose. We also suggest consideration of a similar approach for patients with vascular diseases. This concept is currently under study in our laboratory.

The other observation with important therapeutic implications and now being investigated in our laboratory is that patients under treatment can be classified into groups on the basis of the effect of aspirin on their platelet reactivity in the presence of erythrocytes. These findings indicate that there are individual differences in the response to aspirin in different patients. Thus, laboratory control of platelet reactivity in whole blood as a guide for antithrombotic therapy with aspirin is the modality for the future for optimization of aspirin therapy in patients.


Response

We thank Drs Jagroop and Mikhailidis for their interesting comments on our recent publication dealing with our observation that erythrocyte promotion of platelet reactivity serves to decrease the effectiveness of aspirin as an antithrombotic modality. In the research described, we used release of serotonin as a parameter of platelet activation. Although of great importance, we did not directly address the functional implications of serotonin release other than mention of the well-recognized ability of released platelet dense granule constituents to promote cell proliferation.


**Triglycerides and Postprandial Angina**

*To the Editor:*

We read with interest the article by Lundman et al., who, using Doppler ultrasound measurements of brachial artery diameter, showed that increasing plasma triglycerides and nonesterified fatty acids (NEFAs) decreases brachial artery reactivity in young, healthy men.

This study adds to recent work assessing the effects of NEFAs on vascular tone. Steinberg et al. recently demonstrated that NEFAs attenuated endothelium-mediated vasodilation in the femoral artery. Work from Stepniakowski and others has shown that NEFAs increase sympathetic drive and α-adrenergic receptor reactivity and tone. In the setting of a meal, we have shown that a high-fat meal leads to an ∼2-fold increase in calf vascular resistance in healthy elderly subjects. After an isocaloric, high-carbohydrate meal, this vasoconstriction was absent. In addition, we showed that administration (after a high-fat meal) of an insulin infusion that reproduces the profile seen after a high-carbohydrate meal prevents calf vasodilation. Thus, the data of Lundman et al., themselves, and others provide substantial support for a role for triglycerides and NEFAs in vascular regulation.

However, the conclusion made by Lundman et al. that the vasopressor action of triglycerides contributes to postprandial angina after a high-fat meal is incorrect. We have shown that a 2.5-MJ high-fat meal has no effect on exercise time or time to onset of >1-mm ST-segment depression in patients with angiographically documented coronary artery disease. In contrast to this finding, an isocaloric, high-carbohydrate meal, which produces plasma insulin levels double those necessary to completely suppress lipolysis led to significant reduction in exercise tolerance and time to onset of >1-mm ST-segment depression.

Although we agree that the link between metabolism and vascular regulation is important and warrants further exploration, one must exercise caution in extrapolating results in 1 vascular bed to those of other vascular territories. In addition, assessment of the interplay between vasopressor metabolites and vasodepressor substances (in particular, insulin) should be integral to any physiological conclusions drawn from studies in isolated vessels or vascular territories.

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**Response**

We thank Drs Kearney et al for their interest in our article showing decreased vascular reactivity in triglyceridemia provoked by infusion of Intralipid. We have read their article about postprandial angina during the first hour after a meal with great interest. To our surprise, they show that angina worsens after a carbohydrate but not after a fatty meal, the reason for this being unclear. We must admit that triglyceridemia or increased concentrations of free fatty acids are unlikely to be involved in the early phase of postprandial angina. The object of our study was to investigate the effects of triglycerides and free fatty acids on the endothelium without the influence of vasoactive hormones such as insulin, whereas Vogel and coworkers have studied the effects of a fatty meal on vascular reactivity and found that a high-fat meal but not an isocaloric, low-fat meal decreases vascular reactivity. The conclusion that triglycerides or free fatty acids might contribute to postprandial angina is speculative because we have not investigated the effects of triglycerides or free fatty acids on myocardial ischemia. However, we do not consider the results of our study contradictory to the findings of Kearney et al because the peak of triglyceridemia and free fatty acid levels occurs 2 to 3 hours after a fatty meal and might thus be involved in the later phase of postprandial angina.

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Natural History of Infarct-Related Lesions
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