Noncardiac Surgery in CAD Patients

To the Editor:

The article by Eagle et al. provides interesting data that may have important implications in the management of patients with coronary artery disease (CAD) who are scheduled for noncardiac surgery. This is an extremely interesting and complex subject, in part because of the difficulty in assessing cardiac risk in CAD patients and because of the paucity of data to guide management strategies aimed at reducing the risk of perioperative cardiac complications.

Indeed, there is an urgent need for management tactics in CAD patients to reduce or suppress perioperative coronary events (myocardial infarction [MI] or cardiac death). In this regard, the authors accomplished a superb task in summarizing data from the CASS trial.1,2

There are, however, some issues of concern in this report. The data presented in this study appear to be derived from retrospective observations in patients from the CASS registry and randomized groups who underwent noncardiac surgeries. In the design of CASS, a portion of patients from the registry were randomized to treatment according to specific clinical and angiographic criteria.1 Because treatment of CAD was dictated by physician and patient preference,1 it is likely that significant bias was introduced into the various analyses of treatment outcomes. It appears unlikely that use of various statistical tools while these data are evaluated will compensate for the observational nature of the analyses.

It is interesting to note that in the high-risk noncardiac surgery groups (vascular, thoracic, and head and neck), patients without evidence of CAD had higher rates of perioperative MI than did CAD patients with prior CABGs. In such patients, one would expect the opposite findings.

To help explain the reported findings on outcome, one should consider the available medical therapy options at the time of the start of and follow-up of CASS.3 Medical therapy was based on administration of sublingual nitroglycerin, isosorbide dinitrate, and nitroglycerin ointment.3 The use of propranolol was suggested but not closely monitored. The decision to prescribe a given treatment was left to the referring and treating physicians. Similarly, management of risk factors was suggested, and enforcement of these interventions was left to the discretion of the treating physician. Therefore, there was a rather limited effort, based on the prevailing clinical practice, to provide optimal antianginal–anti-ischemic medical therapy or to furnish supervised intensive risk factor modification aimed at “stabilizing” coronary plaques. More aggressive medical intervention could have contributed to a better outcome among patients without prior CABG.

The authors have highlighted several important points, such as identifying specific procedures associated with higher risk of MI or death. It was also suggested that the higher-risk subcategory of patients undergoing noncardiac procedures may derive the benefit, if any, from prior CABG.

The stimulating suggestions from this study1 should be evaluated in large, prospective, randomized studies using optimal myocardial revascularization and medical therapies. Only after such trial(s) are completed will definitive data be available to assist the clinician in making a recommendation for myocardial revascularization or intensive medical therapy in stable CAD patients scheduled for noncardiac surgery.

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questions would be the performance of a randomized trial. We described such a trial in an editorial several years ago. Currently, a pilot phase of a trial examining the influence of medical therapy versus revascularization in these patients is under way in the Veterans Affairs system. Although a similar trial has been proposed to the National Institutes of Health, this project has not received sufficient prioritization to be funded. Part of the funding concerns for this trial are due to the very large numbers and long-term follow-up that would be required to develop a satisfactory answer. Because the short-term risks of coronary revascularization for many patients can only be overcome by long-term benefit, any trial designed to study patients isolated to the perioperative period is not likely to show a benefit from revascularization.

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Adenosine-Induced Preconditioning of Human Myocardium?

To the Editor:

Although the article by Leesar and coworkers in the June 3, 1997, issue of Circulation concludes that “adenosine preconditioning of human myocardium,” in our opinion their investigation in 30 patients undergoing balloon angioplasty (PTCA) and pretreatment with normal saline or adenosine (2 mg/min for 10 minutes) merely allows them to reiterate their introductory statement that “to the best of our knowledge, evidence that adenosine can precondition human myocardium in vivo is still lacking.” First of all, the fact that there have been recent studies demonstrating reduced signs of myocardial ischemia during repeated balloon inflations does not necessarily suggest the existence of ischemic preconditioning in the conventional, ie, biochemical, sense. As long as the contribution of the gradual opening of collateral channels with successive balloon occlusions is not accounted for in the observed phenomenon of attenuated myocardial ischemia, ischemic “preconditioning” may be not a biochemical but a biophysical process of collateral recruitment due to the temporally increasing effect of a pressure gradient across the anastomoses between the nonstenotic donor vessel and the occluded recipient vessel. Hence, the finding that such a thing as ischemic preconditioning, in the normally used sense of the word, exists in humans is very controversial and is inversely associated with whether or not the authors accounted for collaterals.

Second, and considering the effects of adenosine on the resistance and conductance vessels of the coronary circulation, it is similarly disputable whether there is such a thing as adenosine-induced preconditioning or whether the phenomenon of mitigated myocardial ischemia during coronary occlusion on adenosine administration is actually pharmacologically induced collateral recruitment. After all, exogenously administered adenosine is known to cause not only profound microvascular coronary dilatation but also increased flow indexes through collateral channels. Therefore, as long as Leesar et al do not treat coronary collaterals as a covariable in the outcome of reduced myocardial ischemia in response to adenosine administration before PTCA, they cannot conclude that “adenosine preconditions human myocardium,” or else the scientific community has to redefine preconditioning by extending its meaning to hemodynamic events such as enhanced flow along an increased (collateral) pressure gradient.

Finally, it is hard to imagine that the ST-segment shifts of the intracoronary ECGs shown in Figure 1 of the article by Leesar et al amount to 20 mm and more (up to 60 mm). The y axis of this graph must have been mixed up with that of Figure 2 illustrating the summed ST-segment shifts of all 11 surface ECG leads.

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Response

Contrary to what Seiler et al assert, several studies support the notion that alleviation of ischemia after the first balloon inflation during PTCA is a manifestation of ischemic preconditioning (PC). Although Seiler et al cite a paper by Dupouy et al as evidence that ischemic PC does not exist in humans, the results of that study do not support the conclusions of the authors for reasons that have been detailed elsewhere. Seiler and colleagues assert “the finding that such a thing as ischemic preconditioning exists in humans is inversely associated with whether or not the authors accounted for collaterals.” This assertion is incorrect. Although Cribier et al found increased collateral perfusion during subsequent balloon inflations, they observed that in individual cases, myocardial ischemia decreased with repeated inflations despite the fact that there was no evidence of improved collateral circulation. Thus, the increased tolerance to ischemia did not correlate with indexes of collateral function. In patients undergoing PTCA of the left anterior descending coronary artery, Tomai et al demonstrated that the average peak flow velocity recorded in the right coronary artery during the first and second balloon inflation (an index of collateral recruitment) was not significantly different, yet there was increased tolerance to ischemia during the second inflation. In that study, only ~20% of the patients exhibited a modest increase in blood flow velocity at the end of the second inflation compared with the first inflation, and again, this increase did not correlate either with the changes in ST-segment shifts or with the severity of chest pain. Using a similar technique, Kyriakidis et al found that only ~30% of the patients exhibited progressive collateral recruitment after the first inflation. It should be noted that the blood flow velocity changes in the contralateral coronary artery have been shown to be a reliable index of collateral perfusion during PTCA and to be more accurate than other indexes, such as measurements...
of occlusion pressure through the balloon catheter or coronary angiography.

A recent study by Sakata et al\(^6\) demonstrates that enhanced tolerance to ischemia occurred in patients undergoing PTCA in whom there was no recruitable collateral circulation during balloon inflation, as assessed by myocardial contrast echocardiography. Unlike coronary angiography, which only detects collateral vessels with a diameter $>100$ m, contrast echocardiography reflects myocardial perfusion in the occluded bed and therefore is a more sensitive technique. These studies\(^6\) indicate that ischemic PC develops during repetitive balloon inflations in the course of PTCA independently of changes in collateral perfusion.

It should also be pointed out that evidence of collateral recruitment during PTCA has been found in only $\approx 20\%$ to $50\%$ of the patients.\(^3\)\(^-\)\(^6\) If the increased tolerance to ischemia observed during subsequent balloon inflations were due solely to collateral recruitment, then one would expect this phenomenon to occur only in a minority of the patients. Instead, our study,\(^7\) as well as many other studies (reviewed in Reference 2), have demonstrated increased tolerance to ischemia in most or even all of the patients. In addition, this increased tolerance to ischemia during subsequent inflations can be abolished by pharmacological manipulations, such as glibenclamide\(^9\) and adenosine receptor antagonists.\(^9\)\(^-\)\(^10\) If the mechanism responsible for this increased tolerance to ischemia were solely collateral recruitment, it seems unlikely that glibenclamide and adenosine antagonists would block it.

Seiler et al speculate that in our study,\(^7\) administration of adenosine caused enhanced tolerance to ischemia during the first inflation simply by inducing collateral recruitment. This speculation is unsupportable for several reasons. First, we allowed a 10-minute interval between the end of the adenosine infusion and the first balloon inflation. The plasma half-life of adenosine in humans is on the order of seconds. We have recently studied 3 patients in whom we infused intracoronary adenosine at the same dose used in our previous study\(^7\) (2 mg/min for 10 minutes) and measured coronary flow with a 0.014-inch Doppler guidewire and quantitative coronary angiography at baseline, at the end of adenosine infusion, and 5 and 10 minutes later. In all 3 patients, adenosine-induced hyperemia subsided completely within 10 minutes of the end of the adenosine infusion. Therefore, any vasodilation induced by adenosine in our study\(^7\) should have resolved before the first balloon inflation. Second, Seiler et al seem to confuse the effects of intravenous adenosine with those of intracoronary adenosine. In order for collateral flow to increase in the presence of a complete coronary occlusion, collateral vessels need to be dilated in their entire length, not just within the collateral-dependent vascular bed. Because in our study adenosine was administered by the intracoronary route and produced no changes in systemic hemodynamics, it seems unlikely that adenosine diluted the portion of collateral vessels that was outside of the collateral-dependent vascular bed. (In contrast, intravenous adenosine may dilate the entire length of collateral vessels.) Taken together, the above considerations strongly support the conclusion that the enhanced tolerance to ischemia after pretreatment with adenosine\(^7\) was unrelated to increased collateral perfusion.

With regard to the measurements of ST-segment shifts on the intracoronary ECG, it would appear that Seiler and coworkers are not familiar with the pertinent literature. Numerous previous studies have reported ST-segment shifts $>1$ mV (10 mm) during PTCA\(^4\)\(^-\)\(^10\) (reviewed in Reference 2). In these studies, ST-segment elevation has been found to be much lower in the surface ECG than in the intracoronary ECG. Obviously, the precise magnitude of the ST-segment shifts can vary depending on a number of factors, including, among others, the size of the ischemic region, the exact position of the intracoronary wire, and the duration of the inflation.
How, then, does this issue result in selection bias? It is probable that physicians would be less likely to give thrombolytic agents to patients without a confirmatory ventilation/perfusion scan or pulmonary angiogram. Because it is almost certain that some of these patients were inaccurately diagnosed with PE, they may not have been receiving appropriate care for their true problem. Therefore, it is possible that patients with cardiopulmonary disease other than PE, who may have been more likely to die secondary to inaccurate diagnosis, were more frequently treated with heparin as opposed to thrombolysis. Given the relatively low number of deaths, there need not have been many such patients to skew the results. Fortunately, there is an easy way to address this concern. Reanalysis of the data excluding patients without definitive diagnosis of PE should be performed. If the results remain compelling, then the evidence in support of thrombolytic therapy for major PE is much stronger. If the results, however, fail to reveal a benefit of thrombolysis, the readers of Circulation deserve to know this, given the increased cost and bleeding risk associated with thrombolytic therapy.

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Response
Dr Metersky’s letter gives us the opportunity to stress some important issues regarding the management of acute major pulmonary embolism (PE):

It is not correct to question the diagnosis of acute PE in 27% of our patients just because they did not undergo pulmonary angiography or ventilation/perfusion lung scan. In fact, all but 6 of these 191 patients (97%) had echocardiographic evidence of acute right ventricular pressure overload and/or pulmonary hypertension according to the criteria listed in the Methods section of our article.1 bedside echocardiography is a valuable noninvasive diagnostic tool in patients with clinically suspected acute PE, especially in the emergency room or intensive care unit. The diagnostic accuracy and reliability of echocardiographic findings has been demonstrated repeatedly by our work group2,3 as well as by others.4 Besides, echocardiography is particularly useful for risk stratification and prognostic assessment of patients in the setting of acute PE.5 Therefore, confirmation of major PE by echocardiography “alone” is by no means a “tremendous design flaw” or a factor causing selection bias, as Dr Metersky suggests. In fact, rather the opposite is true: a study including only patients who are able to undergo angiographic or scintigraphic procedures would unavoidably select a clinically stable patient group with favorable prognosis. This point of view is strongly supported by the recently published results of the Management and Prognosis of Pulmonary Embolism Registry.6

In our study,1 statistical analysis focusing only on the subgroup of patients with pulmonary angiograms or lung scans (n=528) would yield a 30-day mortality rate of 4.3% in patients given thrombolytic treatment as opposed to 9.7% in heparin-treated patients (P=0.05). Of particular importance, however, is the fact that the independent effect of early thrombolysis on death risk as assessed by multiple logistic regression analysis would remain virtually unchanged (odds ratio of 0.44 as opposed to 0.46 in the entire patient population). As might be expected, the 95% confidence interval would become slightly larger (0.18 to 1.11) and the P value slightly higher (0.08) due to the smaller number of patients considered in such a statistical model.

In conclusion, it would be, in our opinion, inappropriate and misleading to alter the inclusion criteria of the present registry retrospectively, because we would only consider patients with better in-hospital outcome without further improving the (already high) diagnostic accuracy of cardiac ultrasound. On the other hand, the association found between thrombolysis and the prognosis of acute major PE remains compelling irrespective of which diagnostic procedures were performed in each case. Thus, our results do suggest a clinical benefit of thrombolytic treatment for clinically stable patients with acute major PE. Of course, a definite statement on this issue must await the results of a prospective randomized trial, as already stressed in our article.1

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Platelet PI4 Polymorphism, Myocardial Infarction, and Extent of Coronary Artery Disease
To the Editor:
In a recent study published in your journal by Carter et al,1 strong evidence was found of an association between the PI4A allele of the glycoprotein IIb/IIa gene and myocardial infarction in men younger than 47 years old. In addition, a relationship of this polymorphism with cholesterol levels and the extent of coronary artery disease was also observed in multivariate analyses.

Association of the PI4A genotype and coronary disease is controversial. After the original study of Weiss et al2 reporting an association of PI4A and coronary disease, others failed to find the same association.3,4

A study based on a population of 178 men younger than 50 years old and diagnosed with coronary disease was recently performed by our group in Spain. The prevalence of PI4A was 24% in case subjects compared with 26% in age- and sex-matched control subjects. We also investigated whether the PI4A allele was associated with other risk factors.5 We found that 43 patients who were PI4A carriers showed significantly higher concentrations of LDL cholesterol. For the 43 patients (24%) with the PI4A allele, LDL cholesterol was 4.3±1.9 mmol/L; for...
the 135 (76%) who had the PlA_{A1A1} allele, LDL cholesterol was 3.7±0.9 mmol/L (P=0.02).

Finally, we agree with these authors that differences in PlA prevalence may represent either a type I statistical error or differences in the phenotype according to the studied populations. Furthermore, the association between high LDL cholesterol levels and the PlA_{A2} allele could explain the relationship found between this polymorphism and the extent of coronary artery disease.

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Response
As Batalla and colleagues point out, a number of studies have failed to confirm the associations of PlA_{A2} with atherothrombosis observed by Weiss et al and ourselves; however, a recent study by Walter et al described a significant association of PlA_{A2} with coronary stent thrombosis. The identification of genetic risk factors for atherothrombosis is hampered by complex interactions with a variety of environmental factors in the pathogenesis of this disorder. These factors will cluster differently in different populations, which may explain the inconsistent findings with regard to PlA reported so far. Age is an important factor to consider in genetic association studies because it is likely that the greatest contribution of genetic factors to the pathogenesis of atherothrombosis will be observed in young subjects. However, potential interactions with other classic risk factors should always be considered when the associations of genetic polymorphisms with atherothrombosis are analyzed.

We have found a significant interaction of PlA with cholesterol in young subjects with myocardial infarction, and similarly Batalla and colleagues report higher levels of LDL cholesterol in PlA_{A2}-positive individuals with coronary artery disease than in PlA_{A1} homozygotes. In addition, in 505 subjects with acute atherothrombotic stroke and 435 healthy control subjects, we have found a significant association of PlA_{A2} with stroke in nonsmokers but no significant association in smokers, as well as a 50% incidence of PlA_{A2} in those younger than 50 years of age. In these subjects, we have also found a significant association of the HPA-3 polymorphism of glycoprotein IIb with poststroke mortality (A.M. Carter, A.J. Catto, and P.J. Grant, unpublished observation, 1998). These findings serve to highlight the potential role of polymorphisms of glycoprotein IIb/IIIa in atherothrombosis, as well as the importance of considering gene-environment interactions. Additional knowledge of these interactions will help to target subjects most at risk in whom more aggressive antiplatelet treatments could be initiated.

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