founding; “adjusting” the results (whether by stratification, conventional multiple regression modeling, or regression modeling of propensity scores) can never wholly remove the effect of confounding, although adjustment would be expected to weaken the effect estimates (ie, move the estimates closer to no benefit). However, if patients who received the apparently more beneficial intervention had less favorable prognostic characteristics, then the finding is unlikely to be explained by confounding; “adjusting” the results will still not wholly remove the effect of confounding, but adjustment would be expected to strengthen the effect estimates (ie, move the estimates further away from no benefit).

RITA and RA grafts may be used to revascularize different sites (circumflex or right coronary) and in different ways (in situ or pedicle grafts). In our observational study, we recognized that grafts to the right coronary artery are more prone to failure and carefully controlled the analysis for site of graft. However, we did not control for the specific ways in which the conduits were grafted. Whether one should do so depends on the extent to which a surgeon’s preferred grafting strategy is attributable to the properties of the conduit being grafted. We regard differences in the way that the two conduits are grafted as aspects of the overall strategies of using the RA or RITA as arterial conduits.

The power of survival analyses is a function of the number of events observed (eg, deaths or cardiac-related events). The number of events is increased both by the number of subjects and the duration of follow-up. Despite a median duration of follow-up of only approximately 1.5 years in the NRS,² compared with 2.5 years in the interim analysis of the RCT,¹ the former analysis of survival free from cardiac-related events had considerably more power.

It is not clear to us why using a composite outcome should invalidate the findings of the NRS or why Buxton and colleagues criticize this practice, because they used it themselves (they reported cardiac event-free survival and mortality alone, as we did). In our study, the cardiac-related “event” of recurrent angina was assigned with reference to the findings of exercise tolerance tests in exactly the same way for both groups, thereby minimizing bias as far as possible. Combining events hierarchically is the recognized way to analyze mul-

tipl events that may be attributable to the underlying condition and that may be affected by the interventions being compared. This practice has been used in the analysis of many internationally renowned RCTs, for example, combining mortality and nonfatal myocardial infarction^{4,5} and mortality and heart failure.⁶ It is likely to be important when mortality is rare, or when mortality does not reflect outcomes that are important to patients⁷; there is presumably no argument that recurrent angina matters to patients. The issue of key importance is the avoidance of differential bias in the assessment of events. Results are typically shown for events in a hierarchy of severity, for example, actuarial survival and cardiac event-free survival. Participants in a study who die should not be censored or omitted from analyses of cardiac event-free survival, except in special circumstances.

There is a danger that research groups become entrenched in their views about the likely answer to a research question before appropriate evidence becomes available. We emphasize that this is not our position and that we were careful in our criticism⁸ of the interim report of the RCT¹ to restrict our comments to technical points. It is perhaps unfortunate that the two articles appeared at a similar time. Before performing our retrospective analysis, we had no prior expectation that the RA would be better; rather, we were concerned to ensure that patients receiving RA grafts were not being disadvantaged, as suggested by many other researchers. We believe that our observational analysis suggests that using the RA instead of the RITA may have benefits for patients, and that the benefits may be large; these are exactly the circumstances in which the surgical community should collaborate to perform a definitive RCT.

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Methylene blue as drug of choice for catecholamine-refractory vasoplegia after cardiopulmonary bypass

To the Editor:

The excellent article written by Leyh and colleagues motivated this letter.¹ We hope to share some of our extensive experience with methylene blue (MB). It is important to observe that Leyh and colleagues examined the results of MB therapy for norepinephrine refractory vasoplegia “after cardiopulmonary bypass (CPB),” although this kind of situation may happen before and even during CPB.

Our ongoing laboratory experiments have proved the usual safe doses of MB in regard to possible endothelium dysfunction. We have performed studies in porcine arteries (coronary, renal, superior mesenteric, and hepatic), rabbit aortas, and canine femoral arteries. By comparing sham animals with animals that received intravenous (IV) MB, we found differences only in intermediary concentrations in dose-response curves to the calcium ionophore

(A23187), which causes receptor-independent nitric oxide release.

A single dose of IV MB (2 mg/kg, 20-minute infusion time), as used by Leyh and coworkers, was our first option in 1995.² We are frequently asked about dose, infusion, and route (venous or arterial). Many colleagues tell us that they only observed a transient effect using a 1 or 2 mg/kg IV bolus. In our opinion, the IV MB bolus is a rescue treatment. It is important to maintain a continuous infusion. In some cases, we use a continuous infusion for more than 48 or 72 hours. Because the lethal doses of MB are well known (40 mg/kg), it is possible to use higher doses if necessary. In regard to the infusion route, in at least 1 anecdotal case, we observed a catastrophic reaction to protamine without response to norepinephrine or an IV MB bolus of 2 mg/kg. CPB was again established with high flow, but we were unable to increase the mean arterial pressure even with norepinephrine infusion. The situation was controlled only by using MB infusion in the CPB arterial line again. Grayling and Deakin³ presented this approach using MB during CPB to treat valve endocarditis in a case of ongoing septicemia.

In Argentina, Levin and colleagues⁴ performed a prospective, randomized study including 638 patients who underwent cardiac surgery, 56 (8.8%) of whom fulfilled the vasoplegic postoperative criteria. The overall mortality was 27 patients (4.2%), 6 (10.7%) of whom were in the vasoplegic syndrome group and 21 (3.6%) of whom were in the control group ($P = .02$). The 56 patients with vasoplegic syndrome were randomized to IV MB (1.5 mg/kg, 1-hour infusion time) (28 patients) or placebo (28 patients). The general and surgical characteristics of these 2 populations were quite similar. There were no deaths in the MB group and 6 deaths (21.4%) in the placebo group. The MB resolution vasoplegia time course was approximately 2 hours in all cases. In those treated only with vasopressors (8/28 patients, 28.6%), vasoplegia persisted for more than 48 hours.

Since Gomes and colleagues⁵ described vasoplegic syndrome, we speculate, as surgeons in undeveloped countries, whether the vasoplegia was caused by some failure in CPB material or drug quality control.

MB is increasingly used, for example in liver transplantation. As there are few papers about its use in cardiac surgery it is

possible that cardiac surgical teams do not consider vasoplegic syndrome to be a catastrophic and unexpected problem, and it may be underestimated.

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Reply to the Editor:

The results from the studies performed by Evora and colleagues^{1,2} encouraged us to use methylene blue (MB) as a rescue treatment in catecholamine refractory vasoplegia after cardiopulmonary bypass (CPB).³ We used an intravenous MB dose of 2 mg/kg as an infusion with a positive effect in 92% of our patients. We selected this dose because the majority of MB side effects obviously do not occur when a dose of MB of 2 mg/kg or less is administered.⁴⁻⁶ We have no experience with continuous MB infusion for more than 48

hours. Continuous MB infusion could be an option for patients not responding to a single dose of MB. However, more scientific evidence is mandatory to define the role of MB in the treatment of catecholamine refractory vasoplegia after CPB (eg, multicenter, prospective, and randomized studies). Even more important is a better understanding of the mechanism triggering vasoplegia after CPB to avoid this potentially lethal complication, because a preoperative selection process to identify patients prone to vasoplegia after CPB could result in prophylactic treatment with guanylate cyclase inhibitors.

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