M.R. developed and patented an algorithm for monitoring oxygen diffusing capacity and carbon dioxide production during cardiopulmonary bypass, which is presently manufactured by LivaNova. All other authors have nothing to disclose with regard to commercial support.

CARDIAC SURGERY ASSOCIATED ACUTE KIDNEY INJURY AND THE ROLE OF CARDIOPULMONARY BYPASS TECHNIQUE

Reply to the Editor:

We appreciated the comments of Santarpino and associates¹ on our recently published randomized controlled trial² comparing the effects of conventional perfusion versus goal-directed perfusion (GDP) on cardiac surgery-associated (CSA) acute kidney injury (AKI). Santarpino and associates¹ raised a number of points that in their opinion could have “diluted” the beneficial effects of GDP, which they recognize as effective in reducing CSA-AKI. Some of the points raised were already discussed in our article, but we are happy to go more into these details.

We agree that many patients had a cardiopulmonary bypass (CPB) time shorter than expected, and this certainly decreased the risk of CSA-AKI, therefore decreasing the power of the study. For this reason, we included a subanalysis for patients with between 1 and 3 hours of CPB, and this actually resulted in a larger effect of GDP in decreasing the AKI stage 1 rate (the odds ratio decreased from 0.45 to 0.39). It is possible that, as Santarpino and associates¹ suggest, a further subanalysis stressing the differences in CPB duration might result in more significant effects of the GDP; however, the sample size is probably not large enough to allow this approach.

With respect to the observation period for adjudicating the CSA-AKI (48 hours), we disagree with Santarpino and associates.¹ CSA-AKI is defined on the basis of the serum creatinine changes within 48 hours from surgery by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria,³ and we stuck to this well-established definition. There is a rationale behind this choice. We wanted to investigate the effects of a CPB technique on AKI rate; however, AKI after heart surgery is multifactorial, and one of the main determinants is postoperative low cardiac output. Extending the window of observation beyond 48 hours would mean including more AKI events not directly related to the CPB technique. Santarpino and

associates¹ are correct that other measures of kidney function (such as neutrophil gelatinase-associated lipocalin) may be useful; however, changes in markers are not clinical outcome measures. They are useful for interpretation, but a randomized clinical trial should have a well-established clinical outcome as primary end point. The same applies to hemolysis data, which are certainly a good marker for perfusion techniques but were outside the purposes of our trial.

The mortality issue is probably overestimated by the Santarpino and associates.¹ The difference between groups is negligible (6 cases in the GDP arm and 4 in the control arm). And, of course, the trial was underpowered for mortality. A randomized, controlled trial is usually powered for the primary end point, and we are sure that Santarpino and associates¹ would admit that in modern cardiac surgery, with mortality rates around 2% to 3%, powering a study on CPB techniques for mortality actually requires thousands of patients. We therefore do not think that we could address the mortality issue, even reaching the total number of 700 subjects. In this respect, we agree with Santarpino and associates¹ that additional studies focused on high-risk patient populations are certainly needed to completely highlight the role of GDP as an outcome determinant in adult cardiac surgery.

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THE VAGARIES OF GOAL-DIRECTED PERFUSION AND THE TROUBLE WITH RANDOMIZED TRIALS

Reply to the Editor:

Author has nothing to disclose with regard to commercial support.

A randomized, controlled trial (RCT) by Ranucci and coauthors,¹ recently published in the *Journal*, has triggered understandable questions and comments. These comments addressed multiple areas surrounding the study design and results of an RCT that compared goal-directed perfusion (mainly based on oxygen delivery) with conventional cardiopulmonary perfusion techniques. One of these comments, by Santarpino and colleagues,² appears in this issue of the *Journal* and points out some uncertainties in the study design and interpretation of this RCT.

Surgeons tend to think of RCTs as the criterion standard of evidence that directs surgical therapy. It is worth pointing out some cautions in this interpretation. RCTs were introduced into clinical medicine when streptomycin was evaluated for the treatment of tuberculosis in 1948, and they have since become the standards for assessing the effectiveness of therapeutic agents or interventions.³ An RCT by definition compares 2 similar populations that differ only by planned comparable interventions. The key operative descriptors of this definition are “similar populations” and “planned comparable interventions.” To make inferences about a given intervention, investigators start with a hypothesis, enter applicable patients, randomly treat patients with an equivalent intervention, blind investigators and patients to the treatment, and enter enough patients to limit type 2 errors (ie, have a large enough sample to make sure that negative outcomes are really negative).^{4,5} Key and essential features of an RCT are shown in Table 1 and are worth considering in any publication that reports RCT results. Further, there are cautions that readers should adopt when reading any journal article, especially ones that describe comparative trials.⁵

Randomized trials addressing aspects of cardiovascular perfusion are rare,⁶ and because of the complexity of performing RCTs, as described in Table 1, many studies dealing with cardiopulmonary perfusion are not true RCTs. In fact, many key components of cardiopulmonary bypass (CPB) are not grounded in the results of RCTs. Importantly, comparisons of nonrandomized observational studies with RCTs suggest that useful information can be obtained from these nonrandomized studies and that these nonrandomized studies provide important clinical information in certain areas where RCTs are unable to be performed for practical or monetary reasons.⁷

So, how should we respond to randomized trials like the one by Ranucci and coauthors,¹ and to the critiques such as those of Santarpino and colleagues²? The simple answer to these questions is to approach with caution. Perhaps the

TABLE 1. Critical features of a randomized controlled trial (modified from Nichol and colleagues⁴)

- Clearly defined hypothesis
- Well-defined end point
- Clearly defined subject selection
- Equivalent, feasible treatment options
- Adequate randomization and blinding
- Patient stratification, especially in small trials
- Adequate sample size to ensure appropriate statistical power of a negative result
- Anticipation of problems encountered during trial—eg, dropouts, crossovers, loss to follow-up

message that should be in the back of readers' minds when they see a report that describes an RCT is that all randomized trials are not the same.

With these cautions in mind, how should we treat the implications of the trial by Ranucci and coworkers¹ and the critical comments by Santarpino and colleagues²? The article of Ranucci and coworkers¹ has some shortcomings, some of which are pointed out in the commentary by Santarpino and coauthors.² Important limitations of the trial of Ranucci and coworkers² include a poorly defined hypothesis, an end point that is complex or poorly defined, inability to blind perfusionists and surgeons to treatments, limited patient stratification according to relevant covariates, and failure to account for frequency of end points, patient dropouts, and patient losses in determining needed sample size. These limitations are probably predictable given the subtleties of CPB. As the commentary by Santarpino and colleagues² points out, there was no stratification of study patients according to cardiopulmonary bypass times, and there are questions about the adequacy of end point measurements (ie, time until development of acute kidney injury). One critique that is recognized both by the authors of the RCT¹ and by the commentary of Santarpino and colleagues² is that sample size limitations likely add notes of caution to the conclusions drawn from the RCT.

It is easy to be critical of this study, but there are some positive features that are apparent from both the critical commentary and the RCT itself. First, and perhaps most importantly, there is a scarcity of RCTs that deal with CPB. The fact that CPB gained a preeminent place in cardiac surgery cannot be attributed to randomized trials. There is very little in the practice of cardiac perfusion that stems from RCTs. Almost all the evidence supporting safe and effective CPB stems from observational studies. The attempt by Ranucci and coworkers¹ to interject RCTs into the practice of CPB is thus both commendable and novel. Is the study of Ranucci and coworkers¹ rigorous? No. Is there room for critical comments? Yes. Are there important take-home messages that stem from the study of Ranucci and coworkers¹? Yes. What does the article by Ranucci and

coworkers¹ offer? The article validates the possibility of performing multicenter randomized trials in patients having cardiac operations. Further, there is a signal that the use of goal-directed perfusion that is based on oxygen delivery is safe and probably equivalent to traditional CPB. Possibly the single most important benefit of the article of Ranucci and coworkers¹ is that it serves as challenge to stimulate further randomized studies about cardiac operations and the conduct of cardiopulmonary perfusion.

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