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.

Marco Ranucci, MD, FESC^a

Federico Ambrogi, PhD^b

Valeria Pistuddi, GCSE^a

^aDepartment of Cardiothoracic and Vascular Anesthesia and ICU

IRCCS Policlinico San Donato

San Donato Milanese

Milan, Italy

^bDepartment of Clinical Sciences and Community Health

University of Milan

Milan, Italy

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

Reply to the Editor: