though the surgical technique was not as defined in the protocol. We understand the correspondents' concern about possible selection bias due to the exclusion of patients who did not receive the correct graft or in whom the surgeon did not target the correct artery. However, such decision is logical because it is not reasonable to assess the patency of a radial graft when no such graft exists. The same applies to assessing flow to a vascular bed that was actually not grafted. We consider that, in a study such as this, angiographic analysis on "per-treatment" principles is the correct approach. We further note that this decision was made a priori.

Finally, the conclusions of the article are correct given the data available. Furthermore, all the necessary information is available in detail for readers to understand the limitations that surround such conclusions. There is no attempt to mislead and whether our report will influence surgical attitudes remains uncertain. Furthermore, it is an "open verdict" and we cannot see how it could jeopardize future randomized controlled trials, given our conclusion that "the continued evaluation of the RA is justified." For our part, we are very committed to carrying out good randomized trials in cardiac surgery and will continue to do so in a branch of medicine where, relatively speaking, they are uncommon.

Rinaldo Bellomo, MD

Department of Intensive Care and Research

David L. Hare, MD

Department of Cardiology

Brian F. Buxton, MD

Department of Cardiac Surgery

Austin Hospital

Melbourne, Victoria, Australia

References

1. Buxton B, Raman JS, Ruengsakulrach P, Gordon I, Bellomo R, Hare D, et al. Radial artery patency and clinical outcomes: five-year interim results of a randomized trial. *J Thorac Cardiovasc Surg.* 2003;125:1363-71.
2. Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. *Lancet.* 2002;359:1686-9.
3. Caputo M, Reeves B, Marchetto G, Mahesh B, Lim K, Angelini GD. Radial versus right internal thoracic artery as a second arterial conduit for coronary surgery: early and mid term outcomes. *J Thorac Cardiovasc Surg.* 2003;126:39-47.
4. Goodman SN. Toward evidence-based medical statistics. 2: The Bayes Factor. *Ann Intern Med.* 1999;130:1005-13.
5. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics.* 1979;35:549-56.
6. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized controlled trials requiring prolonged observation of each patient. 1. Introduction and design. *Br J Cancer.* 1976;34:585-612.

doi:10.1016/j.jtcvs.2003.08.050

Reply to the Editor:

The choice between the right internal thoracic artery (RITA) or radial artery (RA) for the second coronary artery bypass conduit remains hotly debated, as evidenced by 2 recent publications in the *Journal*, one a randomized controlled trial¹ and the other a retrospective observational study.²

The interim 5-year result of our randomized controlled study suggested that the clinical outcomes of the RITA and the RA groups were similar. This differed from the conclusion drawn from the cohort study reported by Caputo and colleagues,² which suggested a clinical benefit from using the RA compared with the RITA. It is important to consider possible reasons for such an apparent difference in conclusions.

Caputo and colleagues' study² differed from the randomized trial. There was no assessment of graft patency, and they included additional end points. Obviously, cohort studies can never control for unrecognized factors. Therefore, an observational study should always be regarded as providing less reliable evidence than a randomized trial.³ This has recently been highlighted by the complete reversal of opinion as to the benefits of hormone replacement therapy once the results of randomized trials became available. One important factor that may not be well controlled in an observational study of this sort is the surgeon. The choice of graft was "entirely at the discretion of the surgeon." If some surgeons strongly preferred one type of operation, or even used it exclusively, this means that the comparison based on the observational data may suffer from bias because of confounding with the expertise of the surgeon.

Our comparison of cardiac event-free survival in the randomized controlled trial showed no significant differences, but this does not necessarily mean that the 2 studies are in conflict.

For our RA versus RITA comparison, the estimates and 95% confidence intervals (CIs) were 91% (76%-99%) for the RA group and 82% (63%-99%) for the RITA group. Because of the small numbers, these CIs are very wide and therefore consistent with a number of different possible underlying realities ("hypotheses"), namely, that the RA and RITA have the same cardiac event-free survival, that the RITA is better than the RA, and that the RA is better than the RITA. The latter is suggested by Caputo and coworkers.² Our study is not yet in conflict with this because, for example, our findings are consistent with a "true" cardiac event-free survival of 90% for the RA group and 70% for the RITA group; both of these values are in the respective CIs, and if they were the true values, which they could be, that would be consistent with Caputo and colleagues' findings.

Biologically, the left internal thoracic artery and RITA are similar and when grafted to the left anterior descending and circumflex coronary arteries⁴ have almost identical results. However, when the RITA is grafted to the right coronary system, there is a significant reduction in patency. For example, in the first 5 years of our internal thoracic artery program from 1984 to 1989, patency of the in situ RITA graft to the distal right coronary artery or its branches was approximately 75%. Because of the high graft failure rate of in situ RITA grafts when used on the right side, most surgeons, including ourselves, have favored using the RITA graft to the left system,⁵ either as a free or in situ graft. This latter strategy results in better graft survival curves that separate by 6 years.⁶ Caputo and coworkers,² on the other hand, used an in situ or pedicled graft in 94% of patients. Furthermore, 53% of the RITA grafts were attached to the right coronary or posterior descending artery where results could be less than optimal.² Therefore, although some of their analyses adjusted for the target artery and the authors thus claim that the results were not compromised, it is not clear whether adjustment was made for the type of proximal anastomoses (in situ vs free).

The clinical end point used by Caputo and colleagues² was a composite of death, myocardial infarction, repeat coronary bypass or percutaneous coronary intervention, and recurrent angina. Unfortunately, any composite outcome measure is only as

good as its weakest end point because all outcomes are treated as having equal value. It is no surprise that the composite end point used by Caputo and colleagues is largely dependent on the presence of recurrent angina, which is responsible for 31 of 43 clinical events in the RITA group and 10 of 15 clinical events in the RA group. There were no objective criteria set for diagnosing "recurrent angina," which is always a difficult end point to assess in clinical trials. The clinical wisdom and validity of assigning the same statistical weight to angina and death defy common sense, because most patients would value the 2 quite differently.

The duration of follow-up in the study of Caputo and colleagues² is short, a median of 1.8 years for the patients receiving a RITA graft and only 1.5 years for those receiving an RA graft. It is clear that this is a short-term study result and thus more likely to reflect perioperative factors rather than the development of graft disease.⁷ The study is too short to make any long-term conclusions. In our randomized trial,¹ the number of patients who had reached 5 years follow-up was relatively small, and therefore longer-term conclusions are also limited. A more appropriate conclusion for the study of Caputo and colleagues would be that, in the short term, the RITA used as an in situ pedicle graft to the right coronary system seems to result in an inferior clinical outcome when compared with the RA.

Caputo and colleagues² attempted to control analytically for confounding factors. In the Cox proportional hazards model for mortality, this means they were attempting to adjust for other explanatory variables with very small effective sample sizes (1 death in the RA group and 5 deaths in the RITA group). Such an analysis is ambitious, to say the least. An alternative form of analysis, which would probe the comparability of the groups in terms of their profiles, would be to use the propensity score approach.⁸ This would model the surgeon's choice of operation in terms of explanatory variables at the time of the operation. It could show that there are non-comparable subsets of the patient groups and would more generally permit an analysis that more closely mimicked a randomized trial than analyses based on modeling the outcomes in terms of all the explanatory variables.

In light of these observations, we believe that a more balanced conclusion should have highlighted the limitations of using composite outcomes to increase statistical power and raised the possibility that an in situ RITA graft placed in the right coronary system, at least in the short term, might result in inferior results. It should have also emphasized that these observations cannot be extrapolated to include free RITA grafts (used in only 6% of patients) or in situ RITA grafts placed in the left system, where many remain patent for more than 20 years.

There are satisfactory existing data to guide current surgical practice, but obviously the long-term results from trials of prospectively randomized patients are required.

Brian F. Buxton, MD

Rinaldo Bellomo, MD

Ian Gordon, PhD, AStat

David L. Hare, MD

Austin Hospital

Melbourne, Australia

References

1. Buxton BF, Raman JS, Ruengsakulrach P, Gordon I, Rosalion A, Bellomo R, et al. Radial artery patency and clinical outcomes—5-year interim results of a randomized trial. *J Thorac Cardiovasc Surg.* 2003;125:1363-70.
2. Caputo M, Reeves BC, Marchetto G, Mahesh B, Lim K, Angelini GD. Radial versus right internal thoracic artery as a second artery conduit for coronary surgery: early and mid-term outcomes. *J Thorac Cardiovasc Surg.* 2003;126:39-47.
3. The Oxford Centre for Evidence-Based Medicine. Available at: http://www.cebm.net/levels_of_evidence.asp. Accessed.
4. Buche M, Schroeder E, Chenu P, Gurne O, Marchandise B, Pompilio G, et al. Revascularization of the circumflex artery with the pedicled right internal thoracic artery: clinical functional and angiographic midterm results. *J Thorac Cardiovasc Surg.* 1995;110:1338-43.
5. Dion R, Etienne PY, Verhelst R, Khoury G, Rubay J, Bettendorf P, et al. Bilateral mammary grafting. Clinical, functional and angiographic assessment in 400 consecutive patients. *Eur J Cardiothorac Surg.* 1993;7:287-93.
6. Schmidt SE, Jones JW, Thornby JJ, Miller CC, Beall AC. Improved survival with multiple left-sided bilateral internal thoracic artery grafts. *Ann Thorac Surg.* 1997;64:9-14.
7. Lytle BW. Radial versus right internal thoracic artery as a second arterial conduit for coronary surgery: early and midterm outcomes. *J Thorac Cardiovasc Surg.* 2003;126:5-6.
8. Rosenbaum PR, Rubin DE. Reducing bias in observational studies using subclassification on the propensity score. *J Am Stat Assoc.* 1984;79:516-24.
doi:10.1016/j.jtcvs.2003.10.045

Reply to the Editor:

In this issue, Buxton and colleagues comment on 2 recent articles in the *Journal* reporting evidence about the effects of choosing the right internal thoracic artery (RITA) or radial artery (RA) for the second arterial conduit for bypass grafting. The 2 articles reported interim results of a randomized controlled trial (RCT)¹ and a non-randomized study (NRS).²

Buxton and colleagues advance several alternative explanations to reconcile the apparently conflicting findings of the two studies: (1) There were differences in study design, that is, the greater susceptibility, in general, of observational data to bias. (2) Specifically, there was the possibility of inadequate control in the observational study for differences between groups in graft site and grafting strategy. (3) There was a short duration of follow-up in the observational study. (4) A composite outcome (survival free from cardiac-related events) was used in the observational study. (5) The findings are, in fact, consistent with one another given the imprecision of the findings of both studies.

In the absence of data from well-conducted RCTs with sufficient duration of follow-up, it is not possible to distinguish between these options; the last one is, arguably, the most parsimonious. As we stated,² such a trial is the only way to answer the question, and Buxton and colleagues agree with this point of view. However, the stated suggestions raise a number of methodologic points that may be of interest to readers.

The respective merits of RCTs and NRSs are debated almost as "hotly" as those of the RITA and RA.³ If an NRS of an intervention suggests useful benefits for patients, the intervention should be further investigated in an RCT whenever possible. RCTs and NRSs differ primarily with respect to their susceptibility to selection bias, leading to potential confounding.³ In an NRS, the likely direction of confounding can be inferred by inspecting the distribution of prognostic factors across groups. If patients who received the apparently more beneficial intervention had more favorable prognostic characteristics, then the finding may be explained by con-