The 3 R's: The radial artery, the right internal thoracic artery, and the race for the second best

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Central Message

We discuss the meta-analysis performed by Benedetto and colleagues of propensity-matched observational studies comparing the right ITA versus the radial artery as the second arterial conduit.

See Article page 1083.

Since the seminal article by Loop and coworkers¹ that demonstrated the long-term durability of the internal thoracic artery relative to saphenous vein grafts (SVGs), much attention has been given to additional arterial conduits. The primary contenders have been the right internal thoracic artery (RITA) and the radial artery (RA). During the last decade, we have seen substantial growing evidence to show that (1) bilateral internal thoracic artery grafting is a superior approach to single internal thoracic artery grafting,²⁻⁶ albeit with the much anticipated 10-year results of the randomized, controlled trial (RCT) of bilateral internal thoracic artery grafting versus single internal thoracic artery grafting still pending (Arterial Revascularisation Trial),⁷ and (2) RA or RITA is superior to SVG as the second conduit.⁸⁻¹¹ In the context of such evidence, the use of arterial grafting has also been supported by our society guidelines¹² (including Society of Thoracic Surgeons,¹³ American College of Cardiology Foundation and American Heart Association,¹⁴ and European Society of Cardiology and European Association for Cardio-Thoracic Surgery¹⁵). Given the relative success of both RITA and RA, a debated topic is which of these conduits is the next best after the left internal thoracic artery? Although we assume that the RITA (similar to the left internal thoracic artery) is biologically superior to the RA, it is not clear whether this translates into better patency and clinical outcomes. To this end, there have been 2 RCTs comparing RITA with RA^{16,17} and numerous conflicting observational studies.¹⁸⁻²¹

In this issue, Benedetto and colleagues²² performed a meta-analysis of 8 observational, propensity matched studies that specifically compared RITA to the RA as the second arterial conduit. Of the potential 15,374 patients (RITA, n = 6739; RA, n = 8635), matching resulted in 2992 pairs with a follow-up ranging from 45 to 168 months. RITA was associated with a 25% risk reduction for late death (hazard ratio, 0.75; *P* = .028; n = 8 studies) and a 63% risk reduction for repeat revascularization (hazard ratio, 0.37; *P* = .03; n = 3 studies). The risk of sternal wound

complications was 3-fold higher when RITA was harvested in a pedicled fashion and similar to that of RA when harvested in a skeletonized fashion. These findings are consistent with results from Melbourne in total arterial revascularization, which support a strategy of bilateral internal thoracic artery grafting.^{23,24}

There are some important points worth discussing about the article of Benedetto and colleagues.²² For the primary analysis of long-term mortality, although the RITA was found to have a strong protective effect relative to the RA, there was a moderate amount of statistical heterogeneity for this outcome (I^2 = 66.5%; 95% confidence interval, 29.1%-84.2%), indicating a great deal of variability among the 8 studies. Such heterogeneity could have been due to differential baseline characteristics, institutional differences in surgical decision making, postoperative management, or follow-up among the included studies. Similarly, the rate of repeat revascularization was also higher in the RA group than in the RITA group; again this was associated with even greater heterogeneity (I^2 = 74.7%; 95% confidence interval, 15.9%-92.4%). Such results should be taken with caution in the context of such high variability.

Furthermore, the details of surgical decision making about conduit selection and targets are not reported. It is known that RAs do well when grafted to target vessels with high-grade stenoses,^{8,25} presumably as a result of decreased competitive flow; as such, given that right coronary arteries tend to be larger in diameter than left

coronary arteries, the right coronary should have a critical lesion (>90%) for RA grafting.¹⁴ Lack of a high-grade right coronary artery target vessel stenosis could explain the better late mortality results with RITA grafting seen in the left or right coronary artery subgroup analysis and not in the left coronary artery subgroup.

This was a meta-analysis of studies that used matching by propensity score; this technique was applied in the original publications to adjust for important bias in the selection of the second arterial conduit; an example is a recent publication by Schwann and colleagues¹⁸ included in the meta-analysis in which the RITA group was clearly a lower risk cohort than was the RA group, and both were at lower risk than the patients receiving single internal thoracic artery grafts. Other indirect evidence of bias in the original studies is that of the 15,374 patients studied, only 2992 well matched pairs were identified. Furthermore, Benedetto and colleagues²² aggregated the hazard ratios and confidence intervals, whereas having individual patient level data would have been ideal for this research question. The statistical plan that was used requires that the original propensity matches were satisfactory and that the summary statistics adjusted for the matched nature of the data. Benedetto and colleagues²² have tried to summarize the extent to which the original studies were compliant with these requirements. If the original studies were not completed properly, the validity of the meta-analysis comes into question. Given all those caveats, the point estimates for the RITA-RA comparison still generally favor the RITA. In addition, the point estimates for operative mortality favor the RA (point estimates should be accurate, even if the confidence intervals are not).

Although observational studies along with propensity scores and other adjusting mechanisms are important, especially in areas in which performing RCTs are not feasible, RCTs inarguably remain the scientific method of choice for pursuing the most unbiased and accurate estimates of treatment effects. As mentioned previously, there has been 2 RCTs that have compared the RITA to the RA. In an earlier study reported by Gaudino and coworkers,¹⁷ patients with previous angioplasty ($n = 120$) were randomized to receive either a RITA, RA, or SVG to the obtuse marginal artery. They reported that at a mean follow-up of 52 ± 11 months, the patency of the RITA was 95% (38/40) and that of the RA was 97.5% (39/40), whereas SVG patency was reduced at 82.5% (33/40). A much larger RCT, the Radial Artery Patency and Clinical Outcomes (RAPCO),¹⁶ presented their 10-year results at the 2016 Annual Meeting of The American Association for Thoracic Surgery. Group 1 consisted of 394 patients younger than 70 years (or <60 years for those with diabetes) who were randomly allocated to receive either a free RITA or a RA to the second most important coronary target after the left anterior descending coronary artery. The RAPCO group

reported superior actuarial survival with RA than with RITA ($P = .032$) and a trend toward better event-free survival ($P = .085$); patency was also numerically greater in the RA than in the RITA ($P = .057$ by Kaplan-Meier, not published). This remarkable longitudinal study may raise more questions than it answers, but it is the most persuasive evidence to date relevant to this research question and reinforces the importance of randomized trials in surgery.

Although the 10-year RAPCO¹⁶ results contradict the main outcome of this meta-analysis, Benedetto and colleagues²² did do a sensitivity analysis including the earlier midterm RAPCO results and showed a new hazard ratio of 0.77. Again, the heterogeneity was high in the new pooled analysis. Furthermore, although not all baseline demographic characteristics are known in the meta-analysis, the group 1 RAPCO patients were well characterized and were younger by design (mean age <60 years)²⁶ and included few patients with diabetes ($\leq 11\%$ in the RA and RITA group), and the majority of both the RITA and RA grafts went to the left coronary system. One might speculate that such patient demographic characteristics would favor the RITA group rather than the RA group, if anything.

Benedetto and colleagues²² should be congratulated for undertaking this study, which pooled the results of late outcomes comparing the RITA versus RA from high-quality observational studies involving propensity scoring. The results come at an opportune time, when there is a growing surge of evidence showing that both the RITA and RA grafts do well compared with SVGs. In the era of advanced percutaneous coronary intervention, where single- or double-vessel coronary artery bypass grafting is a rarity and triple-vessel coronary artery bypass grafting is the standard, the question of superiority of RITA versus RA as the second conduit maybe a moot question. Perhaps the next generation of questions should address the incremental benefit of more complete or total arterial revascularization.

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