

Evidence-based selection of the second and third arterial conduit



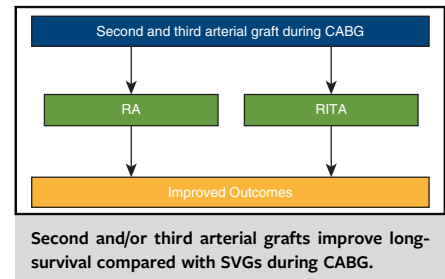
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Feature Editor Note—Few topics in cardiac surgery have been investigated more extensively than the use of multiple arterial grafts for coronary bypass surgery. After more than 4 decades of research, we have solid evidence that the patency rate of the radial artery is better than the patency rate of the saphenous vein at mid- and long-term follow-up. The evidence for the other arterial conduits is less robust. The clinical consequences of the improved patency are still unclear, due to the high level of treatment allocation bias in observational studies and the inconclusive results of the limited randomized evidence.

Few groups have contributed to the debate on multiple arterial grafting more than the Sunnybrook team under the lead of Dr Fremes. This superb review of the current state of the art on the topic is another important contribution that the JTCV Open readers, like myself, will greatly enjoy.

Mario Gaudino, MD, MSCE

The success of the left internal thoracic artery for grafting the left anterior descending (LAD) has encouraged the use of additional arterial grafts for some or all non-LAD targets instead of saphenous venous grafts (SVGs) in patients undergoing multivessel coronary artery bypass surgery (CABG). The use of additional arterial conduits is also often necessary for patients with poor venous conduit options. The most commonly used second and third arterial conduits are the right internal thoracic artery (RITA) and the radial artery (RA). Taggart and colleagues¹ originally reported in the *Lancet* that the use of bilateral internal thoracic arteries (BITAs) was associated with a late survival advantage compared with single internal thoracic artery (SITA) (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.70-0.94) in a meta-analysis of 7 observational studies of 15,962 patients.¹ In an updated meta-analysis of 38



CENTRAL MESSAGE

When appropriate, particularly in patients with long life-expectancy, we recommend the use of the RITA and/or RA as additional arterial grafts to improve long-term survival.

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observational studies (174,205 patients), BITA was similarly associated with reduced mortality late after surgery (incident rate ratio [IRR], 0.74; 95% CI, 0.69-0.80).² While most observational studies have suggested the benefit of either RITA or RA as additional arterial grafts during CABG, the retrospective nature of the data cannot account for the surgeon's ultimate decision to use one conduit versus another, which can be influenced by a variety of patient demographic, physical, angiographic, and prognostic factors.² Despite the reported benefit of BITA in observational studies, the Arterial Revascularization Trial (ART) found no difference between BITA versus SITA in their intention-to-treat analysis at 10-years. However, the high cross-over rate (~14%) and frequent use of RA grafts (~20%) in both groups might have biased the results.³ The 2018 European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery Guidelines on myocardial revascularization and the 2016 Society of Thoracic Surgeons (STS) Clinical Practice Guidelines on Arterial Conduits for Coronary Artery Bypass Grafting issued a strong recommendation for multiple arterial grafting in appropriate patients with long life expectancy, typically younger than 70 years (Class IIa).^{4,5} The choice of arterial grafts (RITA or RA) as a second and/or third arterial conduit is a matter of debate, although both guidelines cited the

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aforementioned BITA as a Class IIa indication in patients who do not have a high risk of sternal wound infection, whereas the RA receives a Class I indication over the SVG in patients with high-grade coronary artery stenosis in the 2018 ESC guidelines.

RITA

The RITA, being biologically similar to the LITA, has the potential to improve patient outcomes when multiple grafts are required. Benedetto and colleagues⁶ observed an increased incidence of SVG occlusion compared with arterial grafts (HR, 4.00; 95% CI, 1.67-16.00), when pooling data from 9 RCTs with a total of 2780 patients who underwent CABG and had long-term angiographic outcomes.

Four RCTs have compared the outcomes of BITA versus SITA.^{3,7-9} Myers and colleagues⁷ randomized 162 patients between strategies and found no clinical difference at 5 years in an underpowered trial. Nasso and colleagues⁹ compared BITA with SITA using the 2 different configurations: in situ LITA-LAD with composite RITA to the secondary lateral wall target or in situ RITA-LAD + in situ LITA to the secondary lateral wall target.⁹ The authors observed significantly better event-free survival ($P < .01$) using BITA but no difference in overall survival ($P = .59$) at 2 years (also probably underpowered to assess this outcome). Gaudino and colleagues⁸ demonstrated that SVG was an independent predictor of graft failure at a mean follow-up of 52 ± 11 months ($P = .03$) in a patency trial of 120 patients with previous stenting. Finally, the ART trial found no differences between the 2 groups, but several limitations were observed in this study (mentioned previously). The as-treated analysis did show an important benefit with multiple arterial grafting in terms of mortality and event-free survival (HR, 0.81; 95% CI, 0.68-0.95, and HR, 0.80; 95% CI, 0.69-0.93, respectively).

Despite the long-term survival benefit with the use of BITA, this technique has been associated with greater risk of sternal wound infection, particularly in patients with diabetes. By using skeletonized internal thoracic artery harvesting in either the general population and in patients with diabetes, the risk of deep sternal wound infection is similar, whereas the risk of superficial sternal wound infection is slightly increased, not affecting perioperative mortality.¹⁰

The benefits of BITA have also been associated with the surgeon's expertise in performing multiple arterial grafting. Gaudino and colleagues¹¹ described an inverse correlation of the BITA:SITA ratio with the rate of sternal wound infection and long-term mortality in a systematic review and meta-analysis. Likewise, Schwann and colleagues¹² observed an increased operative mortality with the use of BITA (risk-adjusted odds ratio, 1.38; 95% CI, 1.18-1.61) among US hospitals that used $<5\%$ of BITA in their CABGs, using the STS national database.¹²

RA

Carpentier initially described the use of RA in 1971; however, due to a high rate of early vessel occlusions, the graft was abandoned for several years. In the 1990s, the RA regained interest as a potential conduit.¹³ In a patient-level meta-analysis of 6 graft patency RCTs comparing RA versus SVG, vessel occlusion was 61 of 307 (19.9%) versus 28 of 345 (8.1%) for the SVG and RA groups, respectively (HR, 0.44; 95% CI, 0.28-0.70).¹⁴ In addition, the incidence of cardiac events (HR, 0.67; 95% CI, 0.49-0.90), myocardial infarction (HR, 0.72; 95% CI, 0.53-0.99), and repeat revascularization (HR, 0.50; 95% CI, 0.40-0.63) were significantly lower at 5 years in those receiving RA. The decrease in the composite outcome was largely driven by a reduction in repeat revascularization, which may have been influenced by protocol-mandated graft angiography. Following extended clinical follow-up to more than 10 years, and without further protocol mandated graft angiography, there was a significant reduction in the incidence of the composite outcome of death, myocardial infarction, or repeat revascularization (HR, 0.73; 95% CI, 0.61-0.88) and of the composite of death or myocardial infarction (HR, 0.77; 95% CI, 0.63-0.94).¹⁵ Nonetheless, the RA should be evaluated preoperatively by assessing the presence of collateral circulation via ulnar artery with the modified Allen test and noninvasive vascular imaging, such as duplex ultrasonography, which may assess the RA's size and determine the presence of plaques, stenoses, or calcifications.¹⁶ In addition, the RA should be avoided in patients who have undergone radial access angiography before CABG, as this may lead to intimal hyperplasia and medial dissections.¹⁶ RA's patency rate is also strongly influenced by the degree of stenosis in the target vessel.¹⁷ As a result, the 2018 ESC guidelines recommend the RA over SVG only in patients with high-grade coronary artery stenosis. Finally, due to its large medial cross-sectional area, the RA is susceptible to vessel spasm in the early postoperative period. Calcium channel blockers have been used during the perioperative period and up to 6 months postoperatively to minimize RA vasospasm, although results from randomized data are limited. Gaudino and colleagues¹⁸ reported no clinical benefit for patients using oral diltiazem 120 mg/daily started in the early postoperative period up to 1 year. The effect of calcium channel blockers has been associated with improved graft patency (HR, 0.20; 95% CI, 0.08-0.49) and clinical outcomes (major adverse cardiovascular events; HR, 0.52; 95% CI, 0.31-0.89) up to 108 months after the index procedure in the individual-level meta-analysis of 6 RCTs, although this is an observational result within a RCT meta-analysis.¹⁹ The 2016 STS Clinical Practice Guidelines on Arterial Conduits for Coronary Artery Bypass Grafting

recommend the use of intraoperative pharmacologic agents, such as calcium channel blockers with or without nitrates, to reduce acute intraoperative and perioperative spasm (Class IIa) without any recommendation regarding postoperative treatment.⁵

RA VERSUS RITA

The choice of a second arterial graft is based on patient characteristics (obesity, smoking, diabetes), which may increase the risk of sternal wound infection (for BITA) and sufficient ulnar collateral circulation (for RA). Nonetheless, the strength of the current evidence supports the RA over the RITA when both grafts are appropriate, particularly after the publication of individual-level meta-analysis of RCTs comparing RA versus SVG.¹⁴ However, few studies have directly compared the RA with the RITA as a second conduit, and the question of which arterial graft is superior remains. The Radial Artery and Clinical Outcomes (RAPCO) trial was an RCT that included 619 patients who were randomly assigned to a RA, free RITA, or SVG graft to the second most important target (after the LITA to LAD artery).²⁰ In a recent network meta-analysis of observational studies, Gaudino and colleagues²¹ investigated the effects of different second arterial grafts on late survival in 149,902 patients (RA, 16,201; SVG, 112,018; and RITA, 21,683), observing decreased late mortality with the use of the arterial graft (RA or RITA) compared with the SVG. When both arterial grafts were directly compared, they exhibited similar late mortality at 7 years (IRR, 0.96; 95% CI, 0.83-1.11). However, the RITA was associated with significantly greater risk of deep sternal wound infection (OR, 2.22; 95% CI, 1.09-4.54) and operative mortality (OR, 1.76, 95% CI, 1.21-2.55). Currently, the evidence derived from RCTs in support of arterial grafting is stronger for the RA than the RITA. As mentioned previously, the patient-level meta-analysis of 6 graft patency RCTs comparing RA versus SVG demonstrated RA's superiority.¹⁵ In addition, the 10-year results of the RAPCO trial have been reported, showing better patency rates (HR, 0.45; 95% CI, 0.23-0.88) and survival (HR, 0.53; 95% CI, 0.30-0.95) for the RA compared with the RITA.^{22,23}

The role of additional arterial grafts is controversial in patients older than 70 years of age. In the recently published RAPCO trial, graft failure was reduced in the RA compared with the study SVG in patients older than 70 years of age (HR, 0.40; 95% CI, 0.15-1.00), whereas clinical events were reduced but not significantly in the patients receiving an RA.²² In practice, we use the RA liberally in patients older than 70 years of age but are much more selective regarding the use of the RITA.

RIGHT GASTROEPIPLOIC ARTERY (RGEA)

The RGEA is an alternative arterial graft mostly used for posterior and inferior arteries of the heart. While some

studies suggest a greater risk of graft occlusion and early graft failure with the RGEA,²⁴ other studies show acceptable long-term survival rates of 80.9% and 81.4%, respectively, at 10 years, and superior overall survival when compared with SVG grafts (HR, 0.41, $P < .01$).²⁵ Most of the improved results using the RGEA are obtained if the artery is harvested using the skeletonized technique.²⁶ Due to spasm susceptibility and technical issues related the anatomy of the vessel, the STS Guidelines recommend the RGEA when there are poor conduit options, or to provide complete arterial revascularization.⁵

Regarding the SVG, most of the comparisons have been made with conventionally harvested saphenous veins. However, the "no-touch saphenous vein" has been associated with improved patency compared with conventionally harvested veins and also compared with the RA in small clinical trials.^{27,28}

THREE VERSUS TWO ARTERIAL GRAFTS

The use of more than 2 arterial grafts has not been as extensively investigated compared with the use of 2 arterial grafts, with no randomized data available.²⁹ Two RCTs have compared total arterial revascularization (TAR) versus CABG with at least one SVG (non-TAR).^{30,31} Nonetheless, the TAR population in these studies included patients with 2 or 3 arterial grafts, which does not allow a proper evaluation of the potential benefit of 3 arterial grafts over 2 during CABG. Yanagawa and colleagues³² reported a survival benefit of TAR over single or double arterial grafts (IRR, 0.85; 95% CI, 0.73-0.99) in a meta-analysis of mostly unadjusted studies. A meta-analysis of 8 propensity-matched retrospective studies reported a survival benefit of 3 arterial grafts compared with 2 (HR, 0.80; 95% CI, 0.75-0.87).³³ Most CABGs performed with 3 arteries included BITA + RA, with only a few using BITA + RGEA. However, the observational nature of the data precludes any definitive conclusions. Finally, Royse and colleagues³⁴ reported worse adjusted mortality for patients receiving more than one SVG (HR, 1.22; 95% CI, 1.15-1.30) or just one SVG (HR, 1.22; 95% CI, 1.14-1.30). Therefore, we believe that 3 arterial grafts during CABG should be considered in younger patients with prolonged life-expectancy.

CONCLUSIONS

When appropriate, particularly in patients with long life-expectancy (at least 10 years after CABG), we recommend the use of additional arterial grafts, favoring the RA over the RITA, to improve long-term survival and minimize the risk of adverse events. Three rather than two arterial grafts should be considered in younger patients with few comorbidities.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: CABG, coronary artery bypass grafting, RA, radial artery, RITA, right internal thoracic artery