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# Radial Artery as a Conduit for Coronary Artery Bypass Grafting: A State of the Art Primer

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Use of the radial artery (RA) as a conduit for coronary artery bypass grafting (CABG) was initially proposed by Carpentier's group, and has subsequently been the subject of numerous observational studies and of several randomized controlled trials (1-6). The RA is relatively easy to harvest, can reach all coronary territories without significant size mismatch with the coronary vessel, and leads to few if any site-related complications. However, the RA's medial layer is largely muscular, in contrast to the elastic internal lamina of the internal thoracic artery (ITA), which makes the RA more prone to spasm and atherosclerosis, as well as more sensitive to competitive flow.

Despite encouraging results, use of the RA has been limited worldwide. This may reflect a resistance to change from the widely accepted gold standard of CABG with LITA-LAD and therefore, a single arterial graft, which presents a short and familiar learning curve, and is easily reproducible by the vast majority of surgeons. Furthermore, current reluctance about use of the RA may also relate to the necessity for advanced planning (and patient consenting) to its harvest; the need to adapt the arterial line placement and the patient's positioning; perceived concerns about upper extremity arterial insufficiency and neurological complications (which fortunately are very rare) (7); and to the requirement for additional surgical assistant skills.

Finally, until recently, there has been a lack of compelling evidence supporting a change in practice towards widespread use of the RA. In this regard, the recent publication of a patient-level meta-analysis of randomized trials comparing the RA to the saphenous vein (SV), by Gaudino and colleagues, justifies reviewing the current evidence supporting the use of the RA for CABG as a superior alternative to SV, its indications and contraindications, as well as specific technical aspects that might impact results (8). These considerations, therefore, represent the focus of the present article.

## 1-Current evidence indicating better clinical outcomes with use of the radial artery

Large propensity-matched observational studies have shown that, in patients where the RA was used as the second graft, average survival is longer when compared to patients in whom the SV was used in the same setting (9,10). However, any observational study is inherently fraught with the potential for "confounding by indication" -a form of selection bias-, whether the data are pooled, propensity-matched, subjected to multivariable analysis, or none of the above (11). Randomized trials, in this context, are therefore indispensable to achieve valid conclusions.

It is logical to hypothesize that the enhanced long-term survival associated with the RA versus the SV in CABG performed with the LITA-LAD, in observational studies, may be due to a higher patency of the RA. However, among the 7 randomized trials comparing RA vs SV, only 3 directly compared the patency of RA and SV and involved more than 100 grafts (2,3,6). Only the two trials that extended follow-up beyond the first postoperative year found significantly higher patency for the RA (2,3). In contrast, comparable patency rates between the RA and SV were observed in the Veterans Administration, although the follow up was only 1 year (6)

Importantly, none of these RCT was powered to show a difference in clinical outcomes. A 2014 study-level meta-analysis of randomized trials found a significantly lower rate of

repeat revascularization but no reduced incidence of cardiac death and myocardial infarction in the RA group (12). Based on those observational outcome and RCT patency data, the ESC-EACTS 2014 MR Guidelines (Class I, LOE B) stated that the use of the RA at CABG is recommended over the SV, for target vessels with a high degree of stenosis (13). Similarly, the STS Arterial Revascularization Guidelines gave a class IIa (Level of Evidence: B) recommendation to the use of the RA (14).

To overcome the sample size limitations of individual trials in detecting differences in clinical outcomes, as well as some of the bias inherent to study-level meta-analyses, Gaudino et al. recently published a *patient-level* meta-analysis of randomized trials, where RA grafts were compared with SV grafts for CABG (15). The meta-analysis included only trials in which mid-term ( $\geq 2$  years) outcomes were available. The primary endpoint consisted of all-cause mortality, myocardial infarction (MI), and repeat revascularization (RR) during follow-up. Graft patency represented a secondary endpoint. A total of 6 randomized trials were selected, with a total of 1305 patients in whom individual data were analysed. Because of the design of the trials, the primary endpoint analysis was conducted on 5 trials and the secondary endpoint analysis was conducted on 4. After a mean follow-up of 60 months, the incidence of adverse cardiac events was significantly lower with the use of RA grafts (hazard ratio, 0.67; 95% confidence interval [CI], 0.49 to 0.90;  $P = 0.01$ ). Use of the RA was also associated with a lower incidence of MI (hazard ratio, 0.72; 95% CI, 0.53 to 0.99;  $P = 0.04$ ), and a lower incidence of RR (hazard ratio, 0.50; 95% CI, 0.40 to 0.63;  $P < 0.001$ ). However, the effect on MI was modest, and could have been the result of multiple testing; overall, the strongest effect was seen for repeat revascularization. Notably, there was no significant difference in all-cause mortality (hazard ratio, 0.90, RA versus SV, respectively; 95% CI, 0.59 to 1.41;  $P = 0.68$ ).

The secondary endpoint of the patient-level meta-analysis was graft patency, using the Fitzgibbon classification (15). At follow-up angiography (mean follow-up, 50 months) the use of RA grafts was associated with a significantly lower risk of occlusion (hazard ratio, 0.44; 95% CI, 0.28 to 0.70;  $P < 0.001$ ), which provides a plausible explanation for the observed differences in clinical outcomes.

Although meta-analysis of individual patient data is the gold-standard for synthesizing evidence across clinical studies, limitations also must be acknowledged. Each trial included very selected patients, used different inclusion and exclusion criteria, and involved various surgical techniques. The total number of patients ( $n=1036$ ) and the total number of events (166 experiencing the primary endpoint; 82 deaths) was low. Repeat revascularization, the statistically strongest effect, driving the primary endpoint, may have been inflated as 5 of the 6 included trials had primary angiographic endpoints and systematic angiographic follow-up. Finally, it is unknown to what extent the patients and care personnel were blinded to group assignment.

Taken together, these data reveal that although CABG is the most studied procedure in cardiac surgery, we still do not have a robust answer to whether a second arterial conduit (right internal thoracic or radial artery) improves clinical outcomes. Observational data universally point in the direction of better outcomes with the use of more than one arterial conduit, including the RA. However, this can be due to unmeasured and unmatched

confounders, leading to selection and treatment allocation biases even in propensity-matched series (17). Furthermore, demonstrating that better patency from a second arterial graft translates into improved survival is difficult to achieve, as survival after CABG is in large part determined by the status of the LAD, while grafts to non-LAD vessels may be more likely to affect other cardiac endpoints. The ART trial, which compared revascularisation using two internal thoracic arteries vs LITA-LAD plus vein grafts in 1554 patients, did not show a mortality benefit with the multiple arterial revascularization strategy, even though methodological issues, such as a high treatment crossover rate, might limit the generalizability of these findings (18). As such, another trial, appropriately powered for clinical endpoints, inclusive of the RA as an important -and potentially preferred- second arterial conduit, and with particular attention to surgical expertise and the curtailing of crossovers, is warranted. The latter considerations form the basis of the internationally-funded and currently ongoing ROMA study (19).

## 2-Indications and -Contra-indications

The Achilles' heel of the RA as a conduit for CABG is competitive flow through a moderately stenotic native target vessel, resulting in diminished RA flow and leading to a diffusely narrowed RA (20). When it occurs, this entity can be observed on coronary angiography and has been called the RA "string sign" (21). Not surprisingly, this condition has negative impacts on graft durability and clinical outcomes. Based on this physiologic concern, current guidelines advise that RA grafts be placed on target vessels with a high- grade upstream stenosis. In planning the appropriate deployment of RA grafts, it is worth remembering that although RA graft patency may decline with decreasing levels of proximal target vessel stenosis, it appears at least comparable to SV for the same level of target vessel stenosis (20). An alternate strategy to guide the use of the RA may be to consider the RA's cross-sectional area compared to the minimal cross-sectional area at the maximal target vessel stenosis (22), although external clinical validation remains pending.

Contraindications for use of the RA are poor collateral ulnar flow jeopardizing hand perfusion, diminutive size, and excessive atherosclerosis or calcification. Depending on the method used to assess the collateral circulation and on the cutoff used, 5-15% of RAs are deemed not to be usable for CABG. Diffuse calcification of the RA is not rare in patients with end-stage renal dysfunction or peripheral vascular disease, and is a contra-indication for RA use. Patients with vasospastic disorders or those requiring vascular access for dialysis also should not have their RA utilized at CABG. Finally, in patients who have undergone trans radial catheterization (TRC), use of the instrumented RA is discouraged. Reports have shown that TRC results in endothelial injury and vasomotor dysfunction, which may take months to recover and may result in premature graft failure (23).

What are then the modern indications for RA use at CABG, and what does the recent patient-level meta-analysis add to our knowledge? We believe that the use of the RA should *de facto* be considered during the planning of every CABG operation, given its easy harvesting, versatility in reaching all and any target vessels, its peri-operative safety comparable to traditional single arterial techniques, and its now clearly demonstrated superior late graft patency compared with the traditionally harvested SV (24). Of note, a no-touch technique for SV harvesting was shown to provide a significantly higher late graft

patency compared with a traditional SV harvesting method (25); however, randomized comparisons of using no-touch SV versus the RA at CABG are lacking.

Compared to the right ITA, the RA is now associated with stronger evidence of a clinical benefit and allows greater flexibility in terms of grafting strategy. Furthermore, its use does not increase the risk of sternal wound complications. Use of the RA is therefore particularly recommended in patients who have good life expectancy, who are at higher risk of sternal wound infection, such as obese patients, patients with diabetes or COPD (26), and for whom a complex grafting strategy (sequentials, baby Y-, and Y-grafts) is entertained. The RA is also easier to handle and often longer than the right ITA, has a more favorable volume/outcome relationship (24), and its use is probably more technically reproducible at the beginning of the learning curve in multi-arterial grafting.

Overall, the choice of conduits and grafting strategy for CABG, as many of our surgical decisions, is based in part on evidence, and in part on opinion, skills, and experience. To optimize outcomes in cardiac surgical practice, “the devil is in the details” with how to choose the right procedure for the right patient and how to execute it perfectly. It is presumed, as is the case with data derived from surgical RCTs, that those same patient selection and “details” were mastered by the experts who have performed the studies included in Gaudino et al.’s patient-level meta-analysis, and that the external generalizability of these findings may be centre- and surgeon-specific.

### 3-Technical aspects

#### **Evaluation of the collateral circulation of the hand**

To date, no large-scale study has compared the different methods used to assess the adequacy of the ulnar collateral circulation to the hand and, as such, no consensus exists on which preoperative exam/evaluation should be performed prior to harvesting the RA for CABG (27). Although some groups have reported reliable results by using the clinical, modified Allen’s test as a screening tool (and reserving more complex tests only to cases with a borderline Allen’s test) (28), many surgeons prefer to have an objective evaluation in all patients. Pulse-oximetry-based Allen’s test, Doppler, Echo-Doppler, and plethysmography have all been used with good results (29). In addition, Echo-Doppler offers the advantage of evaluating the RA’s diameter, the presence of atherosclerotic plaques, and can identify anatomical variations (high origin, high termination, or agenesis)

#### **Harvesting**

One of the purported reasons for the poor patency reported in the first RA series from the 1970’s may have been the high degree of trauma from harvesting. Although several possible technical variations exist for RA harvesting, the integrity of the conduit (and in particular of the endothelial layer) is of paramount importance and must be a priority for the surgeon. The thick muscular component of the RA makes the conduit prone to spasm, and a well-preserved and functional endothelial layer is key to modulating the vascular reactivity of the artery (30).

Traditionally, the RA has been harvested by using an open method, but minimally invasive and endoscopic harvesting are now employed by many. Several comparative studies and

meta-analyses have reported no difference between the different techniques, in terms of early and long-term clinical results (31); however, these studies were underpowered to detect differences in clinical outcomes. RA harvesting is associated with a low incidence of transient forearm dysesthesia and paresthesia and their incidence was similar between the open and endoscopic methods (32). Not surprisingly, endoscopic techniques provide better cosmetic results.

Although in most of the published series the RA has been harvested as a pedicle, skeletonization has been proposed by some groups (29). There is very limited evidence on the comparison of the two techniques in terms of patency rate. However, due to the aforementioned concerns about possible endothelial damage during harvesting and the lack of data suggesting a clinical advantage (as opposed to the case of the RITA), skeletonization is currently not recommended or viewed as a likely beneficial approach for the RA. Use of the harmonic scalpel facilitates both open and endoscopic harvesting, and may be a useful tool to reduce operative time.

A key part of the use of the RA is the preparation of the conduit. The RA fascia must be meticulously opened to assure full dilatation of the artery. Intraluminal injection of vasodilators (usually papaverine or milrinone) may increase the size of the conduit and prevent postoperative spasm. There is no agreement on the optimal composition of the intraoperative RA bathing solution, which aims both to minimize endothelial injury and optimally vasodilate the RA graft. It is important to note that the RA has a very thick muscular media, so it is unlikely that intraluminal administration of anti-spasmodic agents alone is enough to reach all vascular wall layers. For this reason, some authors have recommended to supplement intraluminal vasodilatation with sub-adventitial injection of vasorelaxing agents (33).

### **Grafting strategy**

The RA has an almost ideal length and diameter to be used as a simple, or sequential Y- or T-graft. Compared to the RITA, use of the RA greatly reduces the technical complexity of the operation and reduces the risk of sternal wound complications. However, composite grafts are more sensitive to competitive flow than aortic-based grafts and this is particularly relevant for a graft with high spastic potential like the RA.

### **Secondary prevention**

The majority of the groups prescribe calcium channel blockers or nitrate for 3-6 months after the operation in patients with RA grafts, although the evidence supporting their use is weak. In general, the use of a dihydropyridine agent for at least 3 months after surgery is recommended, although some groups do not use any long term anti-spasmodics.

### **4-In Summary**

Although the impact of RA on mortality is still unproved, the Radial Artery Database International Alliance *patient-level* meta-analysis has brought additional support for the use of the RA in coronary surgery providing solid evidence of a better patency of the RA compared with the SV and suggesting the possibility of better outcomes associate with its use. Much has been learned in the past 50 years of CABG practice about the use and behavior of arterial and venous grafts, but we are still learning and further research is needed. Unfortunately, we do not have a strong evidence basis for selecting bypass grafts

beyond great confidence in the left ITA to the LAD and superior arterial conduit patency. A large confirmatory trial on the use of multiple versus single arterial grafts for coronary bypass is currently under way (Randomized comparison of the clinical Outcome of single versus Multiple Arterial grafts: the ROMA Trial (34). Until the results of ROMA will be available, selection of the second (and third) coronary graft will be guided by patient characteristics, coronary disease patterns, and centre/operator experience.

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