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Radial artery as a conduit for coronary artery bypass grafting: a state-of-the-art primer

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INTRODUCTION

The use of the radial artery (RA) as a conduit for coronary artery bypass grafting (CABG) was initially proposed by the Carpentier group, and subsequently it has been the subject of numerous observational studies and of several randomized controlled trials (RCTs) [1–6]. The RA is relatively easy to harvest, can reach all the 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 (Fig. 1).

Despite encouraging results, the use of the RA has been limited worldwide. This may reflect a resistance to change from the widely accepted gold standard of CABG with Left internal thoracic artery-Left anterior descending artery (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 the use of the RA may also be related to the necessity of advanced planning (and obtaining patient consent) for 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 the requirement for additional surgical assistant skills. Finally, until recently, there has been a lack of compelling evidence supporting a change in practice towards the 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 *et al*. [8], justifies a review of 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. These considerations, therefore, represent the focus of this editorial.

CURRENT EVIDENCE

Large propensity-matched observational studies have shown that average survival in patients in whom the RA was used as the second graft 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]. In this context, randomized trials 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 versus SV, only 3 directly compared the patency of RA and SV and involved more than 100 grafts [2, 3, 6]. Only 2 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 duration was only 1 year [6].

Importantly, none of these RCTs were powered to show a difference in clinical outcomes. A 2014 study-level meta-analysis of

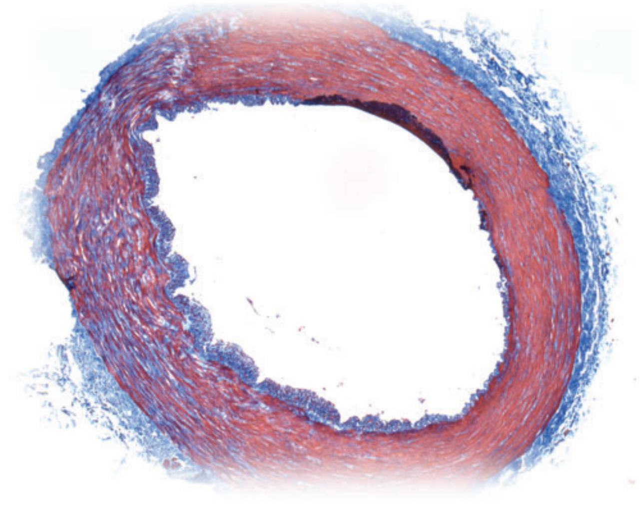

Figure 1: Masson's trichrome stain of a segment of radial artery at ×5 magnification showing the thick-walled muscular media in red.

randomized trials found a significantly lower rate of repeat revascularization (RR) but no reduced incidence of cardiac death and myocardial infarction (MI) in the RA group [12]. On the basis of those observational outcomes and RCT patency data, the 2014 European Society of Cardiology-European Association of Cardiothoracic Surgery (ESC-EACTS) guidelines on myocardial revascularization (class I, Level of Evidence B) stated that the use of the RA is recommended only for target vessels with a high degree of stenosis [13]. Similarly, the STS guidelines on arterial revascularization provided a class IIa, Level of Evidence B recommendation to the use of the RA [14]. The 2018 ESC/EACTS guidelines on myocardial revascularization recently issued stated that an additional arterial graft should be considered in appropriate patients (IIaB) and that the use of the RA is recommended over the SV in patients with high-grade coronary artery stenosis (IB) [15].

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.* [8] recently published a 'patient-level' meta-analysis of randomized trials, where RA grafts were compared with SV grafts for CABG. The meta-analysis included only trials in which mid-term (≥2 years) outcomes were available. The primary end point consisted of all-cause mortality, MI and RR during follow-up. Graft patency represented a secondary end point. 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, primary end point analysis was conducted on 5 trials, and secondary end point analysis 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) 0.49–0.90; $P = 0.01$]. The use of the RA was also associated with a lower incidence of MI (hazard ratio 0.72, 95% CI 0.53–0.99; $P = 0.04$) and a lower incidence of RR (hazard ratio 0.50, 95% CI 0.40–0.63; $P < 0.001$). However, the effect on MI was modest and could have been the result of multiple testing. Overall, the strongest effect was seen for RR. Notably, there was no significant difference in all-cause mortality (hazard ratio 0.90, RA versus SV, respectively; 95% CI 0.59–1.41; $P = 0.68$).

The secondary end point of the 'patient-level' meta-analysis was graft patency, using the Fitzgibbon classification [16]. 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 0.28–0.70; $P < 0.001$), which provides a plausible explanation for the observed differences in the clinical outcomes.

Although a meta-analysis of individual patient data is the gold standard for synthesizing evidence across clinical studies, limitations must also be acknowledged. Each trial included a selective group of 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 end point; 82 deaths) were low. RR, the statistically strongest effect, driving the primary end point, may have been inflated as 5 of the 6 included trials had primary angiographic end points and systematic angiographic follow-up. Finally, the extent to which the patients and care personnel were blinded to group assignment is unknown.

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 RA) improves clinical outcomes. Observational data universally point in the direction of better outcomes with the use of more than 1 arterial conduit, including the RA. However, this can be due to unmeasured and unmatchable 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 largely determined by the status of the LAD, while grafts to non-LAD vessels may be more likely to affect other cardiac end points. The ART trial, which compared revascularization using 2 internal thoracic arteries versus 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, which is appropriately powered for clinical end points, 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].

INDICATIONS AND CONTRAINDICATIONS

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' [5]. Not surprisingly, this condition has negative impacts on graft durability and clinical outcomes. On the basis of this physiological concern, the 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 [21], although external clinical validation remains pending.

Contraindications for the 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 cut-off 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 contraindication for the use of the RA. Patients with vasospastic disorders or those requiring vascular access for dialysis should not have their RA used as a conduit for CABG. Finally, in patients who have undergone transradial catheterization, the use of the instrumented RA is discouraged (Fig. 2). Reports have shown that transradial catheterization results in endothelial injury and vasomotor dysfunction, which may take months to heal and may result in premature graft failure [22].

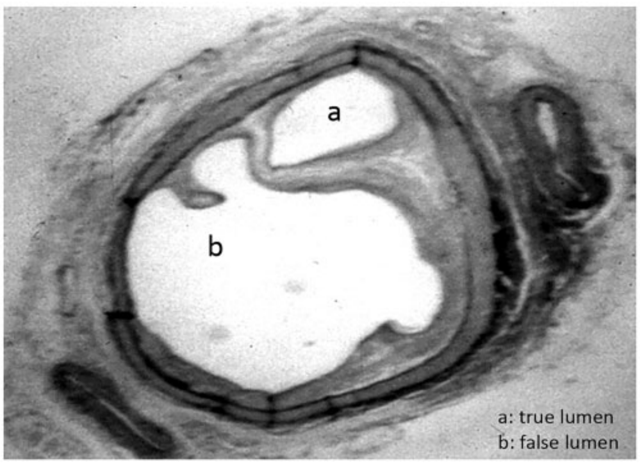

Figure 2: Segment of a radial artery showing dissection of the arterial wall secondary to radial artery catheterization.

What are then the modern indications for the use of the RA for 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, no size mismatch, versatility in reaching any target vessels, its perioperative safety, comparable to traditional single arterial techniques and its now clearly demonstrated, superior late graft patency compared with the traditionally harvested SV [23] (Fig. 3). Of note, a no-touch technique for SV harvesting was shown to provide a significantly higher late graft patency compared with the traditional SV harvesting method [24]; however, randomized comparisons of the no-touch SV technique versus the use of the RA for CABG are lacking.

Compared to the right ITA, the RA has recently been 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. The use of the RA is therefore particularly recommended in patients with a good life expectancy, who are at higher risk of sternal wound infection, such as obese patients, patients with diabetes or chronic obstructive pulmonary disease, and for whom a complex grafting strategy (sequentials, baby Y- and Y-grafts) is entertained [25]. The RA is also easier to handle and is often longer than the right ITA; it has a more favourable volume/outcome relationship, and its use is probably more technically reproducible at the beginning of the learning curve in multiarterial grafting [23]. Although some groups have used the RA in acute ischaemia scenarios, data on the interaction between inotropes and vasoconstrictors and the RA are limited, and therefore its use in emergency CABG is discouraged. Also, there is paucity of data available on the use of RA in patients with left ventricular (LV) dysfunction, as well as the absence of a significant interaction between LV dysfunction and the main effect of the RA in an individual patient meta-analysis [8]. If an ideal RA patient, for surgeons embarking on the use of the RA, could be identified,

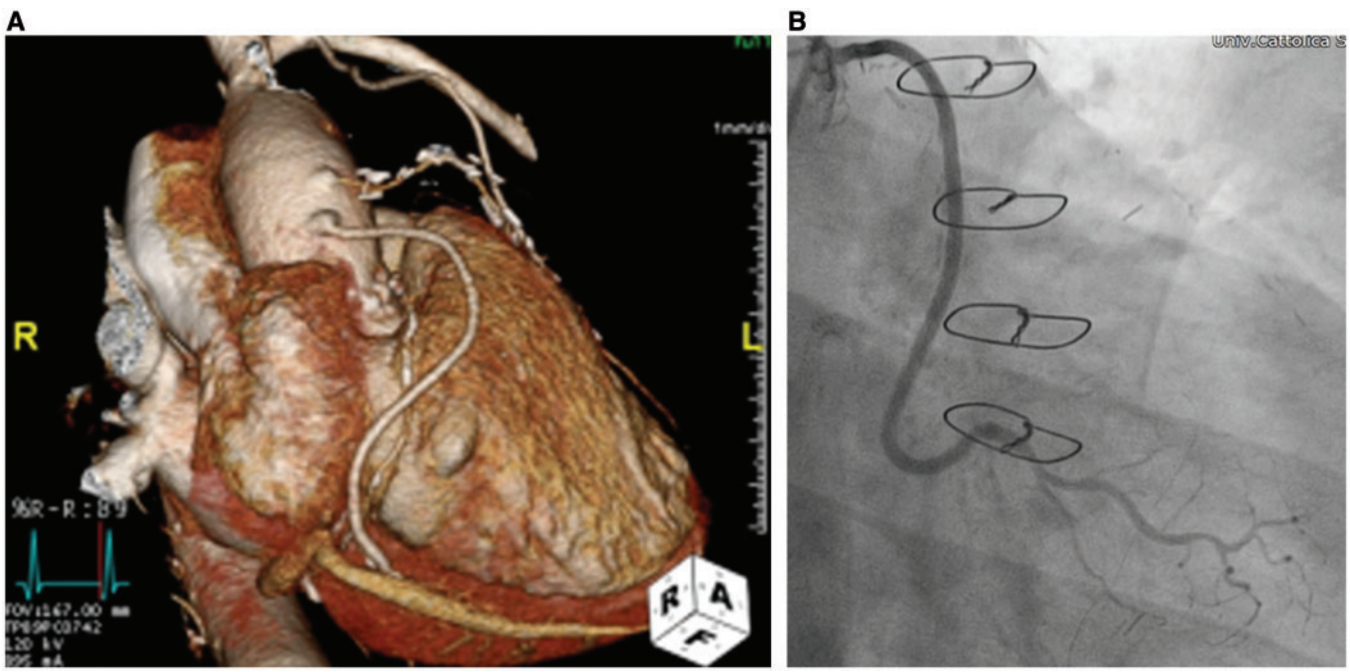

Figure 3: Postoperative angiographic controls of the radial artery. (**A**) Sixty-four slices computed tomography angiography showing the radial artery (with no clips) anastomosed to the posterior descending artery. (**B**) Conventional coronary angiography of the radial artery anastomosed to an obtuse marginal artery showing excellent graft-coronary size congruence.

this would include non-urgent patients with a high degree of target vessel stenosis and a low probability of needing perioperative vasoconstrictors.

Overall, the choice of conduits and the grafting strategy for CABG, as is with many of our surgical decisions, is based in part on evidence, opinion, skills and experience. To optimize outcomes in cardiac surgical practice, 'the devil is in the details', requiring adequate knowledge on 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 selections 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.

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 [26]. Although some groups have reported reliable results 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) [27], many surgeons prefer to have an objective evaluation in all the patients. Pulse-oximetry-based Allen's test, Doppler's test, echo-doppler and plethysmography have all been used with good results [28]. In addition, Echo-Doppler offers the advantage of evaluating the RA's diameter and the presence of atherosclerotic plaques, and identifying anatomical variations such as high origin, high termination (Fig. 4) or agenesia.

Figure 4: High termination of the radial artery into a small branch to the anterior aspect (white arrow) and a larger branch to the dorsal aspect of the hand (black arrow). The latter curves and follows an aberrant route passing round the external border of the radius.

Harvesting

One of the purported reasons for the poor patency reported in the first RA series from the 1970s may have been the high degree of trauma from harvesting. Although several possible technical variations exist for RA harvesting, the integrity of the conduit (particularly the endothelial layer) is of paramount importance and must be a priority (see video on open radial artery harvesting at https://mmcts.org/tutorial/947). 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 [29].

Traditionally, the RA has been harvested using an open method, but minimally invasive and endoscopic harvesting are now employed by many surgeons. Several comparative studies and meta-analyses have reported no differences between the different techniques, in terms of early and long-term clinical results [30]; however, these studies were underpowered to detect differences in clinical outcomes. RA harvesting is associated with a low incidence of transient forearm dysaesthesia and paraesthesia, and their incidence was similar between the open and endoscopic methods [31]. Not surprisingly, endoscopic techniques provide better cosmetic results.

Although the RA has been harvested as a pedicle in most of the published series, skeletonization has been proposed by some groups [28]. There is very limited data on the comparison of the 2 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. The use of the harmonic scalpel facilitates both open and endoscopic harvesting, and this 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. An 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 to both minimize endothelial injury and optimally vasodilate the RA graft. It is important to note that the RA has a very thick muscular media, and so it is unlikely that intraluminal administration of antispasmodic agents alone is enough to reach all the vascular wall layers. For this reason, some authors have recommended to supplement intraluminal vasodilatation with a subadventitial injection of vasorelaxant agents [32].

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, the use of the RA greatly reduces the technical complexity of the operation and 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 such as the RA [33].

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 antispasmodics.

SUMMARY

Although the impact of RA on mortality is still unproved, 'patient-level' meta-analysis of the Radial Artery Database International Alliance 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 associated with its use. Much has been learned in the past 50 years of CABG practice about the use and behaviour of arterial and venous grafts, but we are still learning and further research is needed. Unfortunately, we do not have a strong evidence base 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) [19]. Until the results of ROMA are available, a selection of the second (and third) coronary graft will be guided by patient characteristics, coronary disease patterns and centre/operator experience.

Conflict of interest: none declared.

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