

Current status of arterial grafts for coronary artery bypass grafting

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For over a decade there has been accumulating evidence that the use of more than a single arterial graft during coronary artery bypass grafting can improve clinical outcomes. However the vast majority of patients in most developed countries still only receive a single arterial conduit even in the presence of multivessel coronary artery disease. This review summarizes the current evidence for the use of a second internal mammary artery and/or radial artery graft. While in comparison to vein grafts the superior patency of internal mammary artery grafts is well established, there now exists strong and consistent evidence of the superior patency of radial arteries over the longer term. Likewise, there is a rapidly growing body of evidence that the superior patency of both these arteries in comparison to vein grafts translates into improved clinical outcomes.

Keywords: Coronary artery bypass grafting (CABG); internal mammary artery (IMA); radial artery graft



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Arterial revascularisation for coronary artery bypass grafting

Almost three decades ago Loop and colleagues published their landmark study describing that the routine use of an internal mammary artery (IMA) graft, rather than exclusive use of saphenous vein graft (SVG), during coronary artery bypass grafting (CABG) led to improved survival and was accompanied by a reduction in the subsequent incidence of myocardial infarct, recurrent angina and the need for repeat intervention (1). Although several other surgical groups were also simultaneously promoting the use of an IMA for CABG, it was the strength of the survival and other clinical benefits of an IMA, identified in the Cleveland Clinic publication, which led to a widespread increase in its use throughout the world. Since then a considerable body of evidence has emerged confirming the benefits of the IMA graft, much of which now extends into the second and third decades of follow-up (2,3).

The improved benefits of an IMA graft over exclusive use of SVGs is almost certainly due to its markedly superior long-term patency. Structurally, the IMA has

a discontinuous internal elastic lamina and a relatively thin media with multiple elastic laminae and absence of a significant muscular component, which explains a reduced tendency for spasm and the development of atherosclerosis. In contrast, the SVG has a thinner, more permeable endothelium and a thinner, less elastic and more muscular media. Physiologically, the IMA has significantly increased rates of nitric oxide production in both basal and stimulated states. As a consequence of these structural and functional differences the SVG is far more susceptible to thrombosis and the development of intimal hyperplasia (a precursor to atherosclerosis) in response to endothelial damage and lipid metabolism. Consequently, while the IMA has patency rates in the region of 90-95% ten to fifteen years after CABG, SVG failure occurs in approximately 50% of grafts five to ten years after surgery with significant atheroma in most of the remaining grafts (4,5).

More than a decade ago several groups were already reporting the additional survival benefit of a second IMA over a single IMA. Our group published a systematic review of these studies in the *Lancet* in 2001 (6) and reported that in a comparison of over 11,000 patients with a single

IMA and 4,500 with bilateral IMA grafts, that the hazard ratio for mortality was 0.81 with bilateral IMA grafting. This translated into a need-to-treat value of 13-16 patients to have one extra survivor. However the obvious caution is that this was not a randomized trial, and that although the patients were well matched for important baseline characteristics including age, gender, LV function and diabetes, which by themselves can predict likely longevity independent of the presence of knowledge of coronary artery disease, there is still the potential for bias by other known and unknown confounding factors. Since then, numerous other studies have also supported the additional survival benefit with a second IMA graft (7-12).

Despite such evidence, the stark fact is that only 5-10% of patients in most developed countries actually receive bilateral IMA grafts. The most frequently cited reasons for not routinely using both IMA grafts are a potential increase in perioperative mortality, morbidity, increased duration of operation and an increased risk of sternal wound problems (13). The only published randomized trial to address these issues is the Arterial Revascularisation Trial (ART) (14). This is an ongoing trial of 3,102 patients randomized to single or bilateral IMA grafts and conducted in 28 centers in seven countries. While enrolment has been completed and a one-year interim analysis published (15), the primary outcome of ART is 10-year survival, with final results expected in 2018. The one-year outcomes showed that the application of a second IMA added around 23 minutes to the duration of surgery but made no difference to the incidence of death, stroke or myocardial infarction, at both 30 days and one year (all being around 2% at one year).

Importantly there was, however, a statistically significant increase in the incidence of sternal wound reconstruction from 0.6% in the single IMA group to 1.9% in the bilateral IMA group, which translated into a need-to-harm number of 78 patients (15). However, it must be considered that almost half of the patients requiring sternal wound reconstruction had diabetes, in comparison to around one-quarter of patients in the overall trial. The presence of diabetes, coronary obstructive pulmonary disease, obesity and advanced age are well-recognized risk factors for impaired sternal wound healing and consequently the use of both IMA should be used cautiously in such patients and particularly when more than one risk factor is present. Furthermore there is strong evidence that using a skeletonized technique to harvest IMA grafts, rather than a pedicled technique, results in better preservation of blood supply to the chest wall and a reduced incidence of sternal

wound problems (16).

The radial artery

The radial artery (RA) was first used by Carpentier and colleagues in 1974 (17) but subsequently abandoned due to high failure rates (18). Structurally the RA has a thin continuous intima of endothelial cells, a single internal elastic lamina and a relatively thick media of tightly-packed smooth muscle cells, which predisposes to spasm, occlusion and thrombosis (19). Furthermore, histopathological comparison of proximal and distal RA segments demonstrate significantly reduced luminal diameter and increased intimal hyperplasia distally (20). Although the incidence of atherosclerosis is greater in the RA compared to the IMA (5.3% *vs.* 0.7%), this is still very low and demonstrates overall resistance to atherosclerosis (19). Even so, the RA still has a relatively low rate of atherosclerosis at around 6% (21). In 1992 Acar and colleagues re-popularized the use of the RA when they reported a series of 56 radial artery grafts with 100% patency (22).

Patency of RA vs. SVG over the short and long-term

Four systematic reviews have addressed the issue of graft patency comparing the RA and SVG. A 2010 meta-analysis of five RCTs showed equivalent RA (14.1%) and SVG (14.6%) failure at a mean follow-up of 22 months (23). In contrast, Athanasiou and colleagues compared patency rates of 3678 RA and 7506 SVG from thirty-five studies, at short- (less than one year), medium- (one to five years) and long- (greater than five years) term follow-up (24). The analysis showed no significant difference in the short-term [odds ratio (OR) 1.04] but significantly better RA patency over the medium- (OR 2.06) and long- (OR 2.28) term. Similarly, Hu and colleagues reported in a meta-analysis comparing occlusion rates of RA and SVG to non-LAD target vessels, at mean follow-up of 56 (range, 12-74) months, of a significantly reduced risk of occlusion of RA grafts (relative risk 0.507) (25). Likewise, Cao and colleagues compared angiographic outcomes in 859 RA and 849 SVG from five RCTs at one- and four-years (26). At one-year there was no significant difference in occlusion between RA and SVG grafts (9.1% *vs.* 12.7%, OR 0.71) but a far higher incidence of string sign in the RA grafts (7.4% *vs.* 1.0%, OR 7.97). However at four years RA occlusion was significantly lower (2.7% *vs.* 14.7%, OR 0.17) with no significant difference in string sign (2.7% *vs.* 0%,

OR 3.55). Again, while there was no difference in perfect patency reported at one-year (79.2% *vs.* 82.5%, OR 0.79), RA grafts had significantly higher perfect patency at four years (89.9% *vs.* 63.1%, OR 5.19).

It is now very well established through numerous studies that the severity of stenosis in the native coronary artery is critical to both the short- and long-term patency of the RA, because of the potentially negative effects of competitive flow when the stenosis is below 70-80% (27,28). Furthermore it needs to be recognized that visual estimates of the severity of coronary stenoses are frequently very inaccurate when compared to more objective measurements such as fractional flow reserve. Finally, the competitive flow that will remain will be much greater in a 4 mm vessel with a 70% stenosis than a 2 mm vessel with an equivalent stenosis.

Clinical outcomes RA vs. SVG

Overall, only one RCT comparing RA and SVG has demonstrated superior clinical outcomes with RA grafts. RAPS reported more death from cardiac causes, non-fatal MI and repeat revascularization with SVG rather than RA grafts at late outcome (29). Goldman *et al.* showed no difference in death, MI, stroke and repeat revascularization between RA and LSV grafts at one-year (30) while the RSVP trial showed no difference in mortality at five years in an older population (mean age >70 years) (31). In contrast, several larger propensity matched registries have reported survival benefits with RA rather than SVG at three, six and fourteen years follow-up and particularly in diabetic patients (32-34).

In summary, current literature suggests that there is no difference in functional patency between RA and LSV grafts over the first year. However, there is strong and accumulating evidence for higher mid- and long-term patency rates for the RA in comparison to SVG, due to an ongoing attrition of vein grafts over the long-term. There is now also growing evidence that the superior long-term patency of the RA is translating into substantial improvements in clinical outcomes.

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