REVIEW ARTICLE

INTERNAL MAMMARY ARTERY SKELETONIZATION - REVIEW OF CURRENT EVIDENCE

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Abstract

Introduction: *nternal mammary artery (IMA) harvesting is a central part in coronary artery bypass grafting (CABG). The technique of harvesting the IMA - pedicled, skeletonized, or semi-skeletonized, may influence intra-operatory and post-operatory outcomes. We aim to review current evidence regarding the advantages and disadvantages of these techniques, and their performance in certain subsets of patients.*

INTRODUCTION

The IMA was first harvested and grafted in a live patient in 1960, an operation undertaken by Goetz[1]. During CABG expansion, the left IMA (LIMA) or the right IMA (RIMA) were harvested using a peddled technique, in which the IMA is detached and isolated form the interior chest wall with it's accompanying veins and varying amounts of fascia, muscle and adipose tissue.

The first description of skeletonization of the IMA, in which the IMA is harvested without the accompanying veins and soft tissues, was published by Keeley in 1987[2]. This author described a technique in which the IMA was harvested pedicled, and afterwards, to obtain greater length and facilitate the construction of sequential anastomoses, the pedicle was carefully dissected from the artery itself and discarded. This original paper focused on the greater length obtained for the conduit and affirmed the permeability of the grafts was not compromised in their at the time small experience of 20 patients.

After this first description of skeletonization, the technique underwent refinement, and the skeletonization is now carefully performed with the IMA still adherent to the best wall, leaving the pedicle in situ.

Skeletonization is now a fairly well-used technique, and is recommended as a preferred technique in both the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Guidelines[3] and the 2018 Myocardial Revascularization Guidelines of the European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS)[4].

Both Guidelines highlight the perceived advantages of skeletonization (lower risk of sternotomy infection, longer graft length, higher flow, versatility for sequential grafting) while also acknowledging potential for graft endothelial lesion and lower quality long-term grafting.

An intermediate technique, semi-skeletonization, has been described in 1997 by Hori and Suma[5] ,and consists of harvesting the IMA with both accompanying veins, but leaving muscle, fascia and adipose tissue in situ. This alternative technique seems to offer longer grafts, less post-operatory pain and respiratory complications, and less risk of IMA lesion, but has not been extensively adopted.[5]

We will now look at current evidence published for the advantages and disadvantages of each of these three techniques.

Length and number of distal anastomosis

The IMA is a medium diameter artery and convolutions are fairly common, due to the artery performing a route along the chest wall with varying orientations and angles. This characteristic of partial coiling of the artery allows it to, when freed from the accompanying tissues that aid and maintain the convolutions, be straighter and longer. The increased length allows it to reach more distal coronary targets. Most papers mention a significant increase in the length of the skeletonized grafts when compared with pedicled grafts, ranging from 1,0 to 5,9 cms[2,5-12]. One of the first large observational studies by Calafiore et al found that after papaverine injection skeletonized IMA´s were on average 3.5 cms longer than pedicled IMA´s.[13]

Semi-squeletonization also offers similar increases in length14. A meta-analysis by Hu et al found evidence for longer conduits with skeletonization15. Despite varying numbers referred to the elongation afforded by squeletonization, it is clear it offers more lengthy IMAs and the possibility to revascularize more distal vessels (a concept underlined by all papers which compared squeletonized vs. pedicled IMA´s mentioned in this review).

Flow after harvest

Researches were immediate flow after harvesting was compared in both groups frequently (but not always) show higher immediate flow in skeletonized IMAs [6-12]. This increase in flow has been attributed to a larger diameter for skeletonized IMA´s (being free of constricting surrounding tissue and undergoing a natural dilatation when clamped at the end of harvesting for a few minutes). The documented increases are normally in the range of 30-35 ml/min in extra flow in skeletonized[2,11] and semiskeletonized grafts[14]. This finding has been confirmed in a meta-analysis by Sá et al [16], which analysed 8 previous studies. Interestingly, in Sá et al´s research non-randomized studies had a higher increase in the flow of skeletonized IMA´s (additional 32.3 ml/min in non-randomized studies vs. additional 13.2 ml/min in randomized studies). This meta-analysis also suggested a greater increase in flow in women, older patients and diabetics with skeletonization. The clinical significance of higher flow in skeletonized grafts is presently unknown since the LAD natural distal flow is typically much lower than the usual IMA pedicled flow and the additional flow afforded by skeletonization may simply be unneccessary.[17]

Other authors have found no difference in immediate flow between skeletonized and pedicled IMA´s.[6,12]

Dreifaldt et al, in a recent randomized control trial published in 2021, found a flow less 50 ml/min in 40% of patients with pedicled IMA and 54% in their skeletonized IMA group, with no effect on late term (8 years) patency, which seemed more dependent on native anterior descending stenosis [18].

Sternal perfusion

Post-operatory sterna perfusion after IMA harvesting has been frequently studied through bone scintigraphy. Boodwhani et al [6] was one randomized trial showing a improvement in post-operatory sternal perfusion in skeletonized patients (assessed by post-surgical scintigraphy) - the increase in perfusion was most pronounced in the upper third of the sternum, and non-existent in the lower third of the sternum. These findings have been replicated in other RCT´s and metanalysis[19,20]. Loberboym et al [20] found that a pedicled IMA harvesting causes acute sternal ischemia, but that skeletonization or semiskeletonization do not. One study in patients undergoing BIMA harvesting has found less decreased sternal perfusion only in diabetics, and not in non-diabetic patients, in whom sternal perfusion was the same if skeletonization was performed or not [21]. Other authors with smaller non-randomized studies have found no such differences in post-operatory sternal perfusion studied through scintigraphy [22]. Kamiya et al [23] studied sternal perfusion through superficial and deep tissue oxygen with laser Doppler spectroscopy and found that skeletonization improves sternal hypoperfusion when compared to pedicled harvesting.

The finding that skeletonization seems to protect against post-operatory sternal perfusion has been replicated frequently in animal studies, unilateral or bilateral IMA harvesting in humans, and in different post-operatory times, but it is not universal in all studies and modes of harvesting [22]. Nevertheless, overall, skeletonization seems to offer a good result in the setting of BIMA harvesting regarding sternal perfusion.

Evidence on the influence of the method of harvesting on post-operatory sternal perfusion has been collated in a 2015 review article which concluded that IMA harvesting was associated with decreased post-operatory perfusion and that skeletonization might mitigate some of this hypoperfusion, including in diabetics and bilateral IMA (BIMA) harvesting settings.[24]

Deep sternal wound infection (DSWI)

It has long been known that IMA harvesting raises the risk of sternotomy infection[1], and that this risk is higher when BIMA harvesting occurs, in diabetic patients, women, obese patients with pulmonary disease and several other risk factors.

Smaller observational studies normally show no difference in DSWI in skeletonized vs. pedicled IMA harvesting [11-12,14]. Larger studies (observational and sub-analysis of RCT data) found that skeletonizing BIMA protects against the increased risk of DSWI compared with pedicled BIMA, even when patients are sicker [13,25-28], but this effect may be limited to men and exclude women.[29]

A meta-analysis of several studies regarding sternal perfusion, by Iddawela et al [30], published in 2021, and encompassing one RCT and 8 observational studies comprising 2050 patients with skeletonized BIMA harvesting and 1599 patients with pedicled BIMA harvesting found a very significantly lower risk of DSWI in skeletonized patients (OR 0.27, 95% CI 0.20-0.51, $p < 0.00001$).

IMA wall integrity

Because skeletonization involves directly mobilizing the IMA much more closely instead of manipulating the adjacente soft tissues, there is concern about vessel wall integrity after the harvesting. In addition, the stripping of adjacent soft tissues may theoretically compromise vasa vasorum of the IMA and deprive it of venous and lymphatic drainage and innervation , raising the possibility of further injury to the arterial wall.

Gaudino et al have not found differences in electron microscopy architecture and vessel wall integrity between skeletonized and pedicled IMA´s in a small study [31]. Cheng et al [24] also mention that luminal diffusion of O2 may reach 350 to 600 micron while the thickest part of medial IMA wall is normally under 150 micron and vasa vasorum do not play an important role in nourishing this same wall.

Nevertheless, it is important to note that skeletonization is a technically more demanding procedure with higher risks for IMA lesion if done incorrectly.

Long-term anastomosis patency

A few articles studied long-term patency of skeletonized IMA´s. Dreifaldt et al [18] studied graft patency at 3 years through conventional angiography and at 8 years by computed tomography and found patency over 90% in pedicled and skeletonized IMA´s, without difference in both groups. They also identified an LAD stenosis inferior to 70% as the most important variant associated with long-term graft failure. Other small and observational studies (some with blinded post-operatory angiography) found no difference in graft patency between both techniques in the medium or long-term [12] or showed good patency for skeletonized BIMA at 6 months by angiography[32]. Calafiore et all, in a large observational study, obtained angiography in some patients at 6 months and showed good skeletonized IMA patency.[13]

A meta analysis of studies on long term skeletonized IMA patency studied by conventional angiography and involving involving 1764 evaluated conduits (1145 skeletonized; 619 pedicled) has been performed by Sá et al and found that skeletonized IMA´s appear to be non-inferior to pedicled IMA´s regarding long term-patency. [33]

More recently, a subanalysis from the COMPASS trial has again raised concerns about skeletonized IMA patency. In COMPASS patients undergoing CABG, 720 received pedicled IMA´s and 282 skeletonized IMA´s. Of these, 1108 grafts were investigated at 12 months by computed tomography angiography (CTA) and the images observed by physicians blinded to the clinical and surgical course of the patients. At 12 months, patients receiving skeletonized IMA´s had a higher risk of complete IMA graft occlusion and more patients with an occluded graft in skeletonized IMA´s, despite the skeletonized conduits appearing intra-operatively to be of higher quality. [34]

Repeat revascularization /Major Adverse Cardiovacular Events/Mortality

A few small observational and randomized studies show comparable results for both techniques at short and medium term follow-up.[12,18]

Benedetto et al´s subanalysis of the effect of skeletonization in sternal wound healing in the ART trial´s cohort does not mention repeat revascularization or MACE but mentions that at 1-year mortality was similar whether IMA´s were unilateral or bilateral, and skeletonization did not influence mortality results[26].

In their landmark study using bilateral IMA harvesting, Calafiore et al showed that at 46 months patients who received skeletonized IMA´s had a higher survival (96,4 % +/- 0,8 vs. 95 % +/- 1,2 - $p<0,001$ and event-free survival (95,4 % +/- 0,7 vs. 91,4 % +/- 0,8 – p 0.001) (13). This finding may be related to the significantly higher number of distal anastomosis performed in skeletonized IMA patients (2,4 +/- 0,3 vs. 2,1 +/-0.4 - $p<0,001$). Iddawella et al´s meta-analysis also found no difference in short-term mortality between both techniques in BIMA. [13]

The recent COMPASS trial post-hoc analysis, on the other hand, documented a significantly higher risk of stroke (1,8% vs. 0,3 %, $p=0.02$), Major Adverse Cardiovascular Events (7,1% vs. 2,1%, $p=0,002$), and repeat revascularization (5,0 vs. 1,4%, $p=0,03$) in patients receiving skeletonized IMA´s after 12 months. [34]

Another recent study raising concerns about long-term results of skeletonization, by Gaudino et al, looked at the ART trial cohort along term and found that at 10 years mortality was similar between patients with skeletonised vs. pedicled IMAs. However, the MACE, repeat revascularization and eternal wound complications at

10 years were higher in the skeletonization group. This finding was not seen for surgeons with higher rates of skeletonization, suggestion surgeon experience influences long-term cardiovascular outcomes. [35]

Chest pain/parestesia

Non-anginal chest pain and long-term post-operatory paresthesia have been shown to be improved with IMA skeletonization in most studies that researched this particular aspect studies [6,11,12,36] but this finding is not universal [37]. 12 month quality of life was studied by Khan et al, and skeletonized IMA patients had significantly better scores on 36-Item Short Form Health Survey (eventhough both harvest techniques improved overall quality of life.38

On the other hand, a small randomised double blind study by Markham et al found that, despite skeletonization offering better freedom from chest pain and disestesia on the short term, after 21 weeks pedicled and skeletonized patients had a similar rate of these complaints. [39]

In semiskeletonization, a protection effect against chest pain/parestesia was also found by Wimmer-Greinekr et al at 3 and 6 months after surgery. [40]

Animal models

A few studies in animals models showed comparable short-term results in skeletonized and pedicled IMA´s regarding vessel wall integrity; they found that even though skeletonization induced adventitial neovascularization, it did not induce proliferation of smooth muscle cells in the media, which it is normally associated with vascular remodelling [41].

Results of skeletonization in radial (RA) and gastro-epiploic arteries (GEA) used for CABG

Bonini et al found worse angiographic performance of pedicled RA arteries when compared to skeletonized RA arteries.[42]

In a meta-analysis of several studies regarding skeletonization of RA and GEA arteries in CABG, Massey et al[43] identified some evidence showing improved sort-term graft patency, longer conduit length and increased number of sequential grafting as benefits of skeletonization, with no other apparent clinical benefits.

Surgery duration

Skeletonization apparently prolongs the duration of surgery in small observational studies, with additional minutes ranging from 2,7 to 23 minutes of difference between both techniques[6,12]. On the other hand, the recent meta-analysis by Iddawella et al comparing skeletonized vs. pedicled BIMA found no differences in operative time (despite skeletonized BIMA patients receiving more anastomosis (which may reflect heterogeneity of the studies used in the meta-analysis.[28]

In papers studying semi-skeletoniztion, however, the operative time seems to be equivalent to pedicled IMA harvesting.[14]

Post-operatory bleeding

Calafiore et at documented, in their large observational study, that at 12 hours, skeletonized patients had bled on average 542 +/- 306 ml vs. 674 +/- 531 in pedicled patients ($p<0.001$).[13]

In a recent RCT by Mazur et al, skeletonization reduced post-operatory bleeding at 12 hours and was associated with lower fresh frozen plasma transfusions.[44]

Other studies found a better performance of semi-skeletonization with lower chest drain output when compared with pedicled IMA harvesting.[40.45]

The meta-analysis by Idawella et al regarding BIMA harvesting also suggests that skeletonized BIMA harvesting is associated with significantly lower post-operatory bleeding .[30]

Post-operatory ventilation function

Two studies have explored alterations in pulmonary function in relation to skeletonization and found that skeletonization offers better outcomes in in forced vital capacity or forced expiration in the first second after CABG when compared with pedicled harvesting.[40,46]

Early post-operatory non-cardiac related outcomes

Several observational studies document improved extubation times, Intensive Care Unit (ICU) stays and total hospital stays in patients receiving skeletonized IMA´s, including in bilateral harvesting. These findings have been corroborated in Hu et al´s metanalysis [15]. Calafiore et al attribute these improved post-operatory results (despite being sicker patients) to improved patient selection and ICU care[13]. Others have not found differences in post-operatory ICU and hospital outcomes[12].

Diabetes mellitus

In dos Santos Filho et al´s [21] small observational study, in diabetics, post-operatory sternal blood flow appears to be better when the IMA is skeletonized, while if pedicled sternal perfusion is compromised. This effect was not seen in non-diabetics.

In Matsa et al´s fairly large observational study with bilateral skeletonized IMAs, DSWI frequency of diabetics was similar comparable with nondiabetics (2.6% vs 1.7% $p=0.4$). DSWI was significantly more frequent in obese diabetic women than in diabetics without both these risk factors (15% vs. 1.4%, $p<0.0001$).[9]

Peterson et al have found, in a large observational study, that skeletonization in the context of BIMA lowers superficial and DSWI in all patients, and that furthermore, in diabetic patients (including insulin-dependent diabetics), skeletonization offers an equivalent frequency of DSWI than in conventional BIMA patients (1,2% vs. 1,6 %, non-significant).[47]

In Benedetto et al´s sub analysis of the ART trial cohort, pedicled single IMA in insulin dependent patients and specially pedicled BIMA in all patients has been associated with a higher risk of any sternal complication. When using single IMA in all the cohort, skeletonization does not seem to add any protective effect on sternal infection, but when harvesting bilateral IMAs, skeletonization mitigates the risk of DSWI even in high risk groups including insulin dependent patients, females and obese patients.[26]

Bilateral IMA harvesting

In this reviewer have coveredseveral papers that studied the use of skeletonization in bilateral IMA harvesting. Most papers support the idea that bilateral skeletonization offers protection against superficial and DSWI [10,13, 16, 25, 26, 28-30] and more distal anastomosis per patient [10,13,30]. The effect of more complete arterial revascularization on long-term mortality is not clear.

Mitigating the drawbacks of skeletonization

A careful technique of harvesting and experience are probably paramount in the quality of long-term outcomes with skeletonization [35], allowing it´s expanding use in high risk cases without compromising quality of care. Two additional technical modifications may allow to lower risk of skeletinozation even further.

Kieser et al have shown. That use often harmonic scalpel, which is mulch less traumatic for soft tissues, results in mid-term equivalent results when compared with diathermy, while allowing a quicker harvesting time.[48] The harmonic scalpel´s lower tip temperature, when compared with electrocautery, may be an advantage against the risk of damaging the IMA wall and in improving post-operatory chest wall healing, but this hasn´t been documented yet.

Hidrosdissection, in which 10-20 ml of saline is injected between the endothoracic fascia and the IMA, may help develop a plane of harvesting, and lower electrical and temperature conductance to the IMA, making skeletonization safer.[49] The same technique has been described with injection of papaverine [50], but side-branch bleeding with this vasodilator may be a problem[51].

Semi-skeletonization may offer mitigation of full skeletonization technique - it has shown to be equivalent to pedicled harvesting in operative time, while diminishing post-operative bleeding, longer grafts and better post-harvesting flows [14, 20, 40, 45, 52].

CONCLUSION

Skeletonization of the IMA is a generally safe option when practiced by experienced surgeons, allowing longer grafts, better post-harvesting flows, more coronary vessels grafted and lower post-operatory bleeding, while not damaging the IMA wall and endothelium. The benefit of skeletonization on isolated IMA harvesting in low-risk patients is unknown, but it appears to lower risk of sternal wound infection in medium risk patients such as bilateral IMA harvesting, and may be ineffective for sternal wound protection in very high risk diabetic obese women. It´s long term mortality rate is apparently similar to pedicled harvesting but skeletonization may be associated with higher long-term MACE rates when compared to the pedicled technique, probably when performed by less trained surgeons.

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