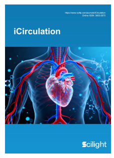
Scilight

iCirculation

https://www.sciltp.com/journals/iCirculation



Review

Which Is Better? Pedicled versus Skeletonized Internal Mammary Artery Grafts in Coronary Artery Bypass Grafting: Emphasis on the Antispastic Role of Perivascular Adipose

Guo-Wei He [1,2,3]

[1] Department of Cardiovascular Surgery & The Institute of Cardiovascular Diseases, TEDA International Cardiovascular Hospital, Tianjin University & Chinese Academy of Medical Sciences, Tianjin 300457, China; gwhezj@163.com or gwhe@tju.edu.cn; Tel.: +86-22-6520-9089; Fax: +86-22-6520-8732

[2] Tianjin Key Laboratory of Molecular Regulation of Cardiovascular Diseases and Translational Medicine, Tianjin 300457, China

[3] Division of Cardiothoracic Surgery, Department of Surgery, Oregon Health & Science University, Portland, OR 97239, USA

How To Cite: He, G.-W. Which Is Better? Pedicled versus Skeletonized Internal Mammary Artery Grafts in Coronary Artery Bypass Grafting: Emphasis on the Antispastic Role of Perivascular Adipose. *iCirculation* **2026**, *1*(1), 4. https://doi.org/10.53941/icirculation.2026.100004

Received: 2 December 2025
Revised: 13 February 2026
Accepted: 25 February 2026
Published: 7 April 2026

Abstract: Background: The internal mammary artery (IMA) is the conduit of choice for coronary artery bypass grafting (CABG). While it can be harvested as a pedicled (with surrounding tissue) or skeletonized (stripped bare) graft, the optimal technique remains debated. The perivascular adipose tissue (PVAT) surrounding the IMA is no longer considered inert but is a bioactive organ secreting vasoactive adipokines. This review synthesizes the evidence on the role of PVAT in IMA vasoreactivity and its implications for the choice of harvesting technique. **Methods:** A systematic literature search was conducted in PubMed/MEDLINE, Embase, and CENTRAL up to 1 December 2025 for original studies investigating PVAT function in human IMA or comparing pedicled vs. skeletonized harvesting with relevant vasomotor or clinical outcomes. Data were extracted and synthesized narratively. **Results:** The included studies consistently demonstrate that IMA-PVAT exerts a potent anticontractile and vasorelaxant effect. This is mediated through multiple pathways, including the release of adiponectin, which enhances endothelial nitric oxide synthase function, and the production of non-nitric oxide, non-prostanoid relaxing factors that act directly on vascular smooth muscle. *Ex vivo* studies show conflicting results that skeletonization, by removing PVAT, may or may not augment vasoconstrictive responses and increase susceptibility to spasm but preservation of PVAT definitively preserves vasorelaxation properties of IMA. Though less definitive and conflicting, clinical studies, particularly a recent large post-hoc RCT analysis, suggest that harvesting of the IMA during CABG surgery using a skeletonized technique was associated with a higher rate of graft occlusion and worse clinical outcomes than the traditional pedicled technique. **Conclusions:** PVAT is an integral, protective component of the human IMA, providing a multimodal defense against vasospasm. The pedicled harvesting technique, by conserving PVAT, leverages these inherent vasorelaxant properties and is physiologically superior for minimizing graft spasm. Surgical strategy should consider the antispastic benefit of the pedicled IMA, balanced against the potential sternal wound healing and length advantages of skeletonization in high-risk patients.

Keywords: CABG; IMA; internal mammary artery; perivascular adipose

1. Introduction

1.1. Clinical Context: Coronary Artery Disease and the Central Role of CABG

Coronary artery disease (CAD) remains a leading cause of global mortality. Coronary artery bypass grafting (CABG) is the standard of care for patients with complex multivessel disease, offering superior long-term survival and freedom from major adverse cardiac events compared to percutaneous intervention in selected populations [1,2]. The success of CABG is intrinsically linked to the long-term patency of the conduits used. Since its introduction by Kolessov [3] and subsequent popularization, the internal mammary artery (IMA), particularly the left IMA to the left anterior descending artery, has become the gold-standard conduit due to its exceptional long-term patency, which exceeds 90% at 10 years [4,5]. This superior performance is attributed to its inherent biological properties, including a favorable endothelial function with pronounced nitric oxide (NO) and endothelium-derived hyperpolarizing factor (EDHF)-mediated responses, and relative resistance to atherosclerosis [6–8].

1.2. The Surgical Dilemma: Pedicled versus Skeletonized Harvesting

A persistent technical debate in contemporary cardiac surgery revolves around the optimal method for IMA harvest. The conventional pedicled (or conventional) technique involves isolating the IMA with a cushion of surrounding tissue, including parietal pleura, venous tributaries, lymphatics, and, crucially, the perivascular adipose tissue (PVAT). This method preserves the surrounding tissues and reduces the possible mechanical damage on the IMA. In contrast, the skeletonized technique entails meticulous dissection to isolate the IMA alone, completely stripping it of all adjacent tissue [9,10]. Apart from the possible damage on the IMA wall during this procedure and more technical demand, proponents of skeletonization argue for reduced sternal devascularization, particularly critical in diabetic patients undergoing bilateral IMA grafting, potentially lowering the risk of deep sternal wound infection [11,12]. It may also facilitate the achievement of greater graft length [13]. However, this technique may inflict greater mechanical and thermal trauma to the vessel wall, potentially impairing its endothelial and vasomotor function [14,15].

1.3. The Paradigm Shift in PVAT Biology: From Inert Packing to Bioactive Organ

Historically regarded as a passive structural support, PVAT has been recognized as a dynamic, multifunctional paracrine organ in the last two decades [16,17]. It secretes a plethora of biologically active substances, termed "adipokines", which exert profound effects on the adjacent vasculature. These include vasorelaxant factors such as adiponectin [18], leptin [19], hydrogen sulfide (H_2S) [20], and prostacyclin [21], as well as vasoconstrictors like angiotensin II and reactive oxygen species. The net effect of PVAT on vascular tone is context-dependent, but in healthy states, it typically exhibits an anticontractile or vasorelaxant phenotype in human internal thoracic artery (IMA) [22,23].

1.4. The Knowledge Gap: Translating PVAT Biology to IMA Graft Function

While the biological role of PVAT in physiology and disease is increasingly appreciated, its specific impact on human IMA graft function and the implications for the pedicled versus skeletonized debate have not been systematically synthesized. The removal of PVAT during skeletonization may inadvertently deprive the IMA of a critical source of vasoprotective factors, potentially predisposing the graft to vasospasm—a significant clinical concern during and after CABG [24,25].

1.5. Rationale and Objective of This Systematic Review

Our recent work demonstrated that the PVAT surrounding the human IMA exerts a potent vasodilatory effect, which is partially preserved even in the absence of endothelium and NO synthase activity, and is mediated, at least in part, by calcium-dependent adiponectin release [26]. This finding provides a compelling physiological rationale for preserving PVAT. Therefore, this systematic review aims to critically appraise and synthesize the existing evidence regarding the functional role of PVAT in human IMA vasoreactivity and to evaluate the hypothesis that pedicled harvesting, by conserving PVAT, confers a superior antispastic profile compared to skeletonization.

2. Materials and Methods

2.1. Search Strategy

A comprehensive and systematic literature search was conducted to identify all relevant original research articles. The search was performed from the inception of each database until 1 December 2025, across three major electronic databases: PubMed/MEDLINE, Embase (via Ovid), and the Cochrane Central Register of Controlled Trials (CENTRAL). The core search strategy for PubMed, combining Medical Subject Headings (MeSH) and free-text terms, is detailed in Figure 1.

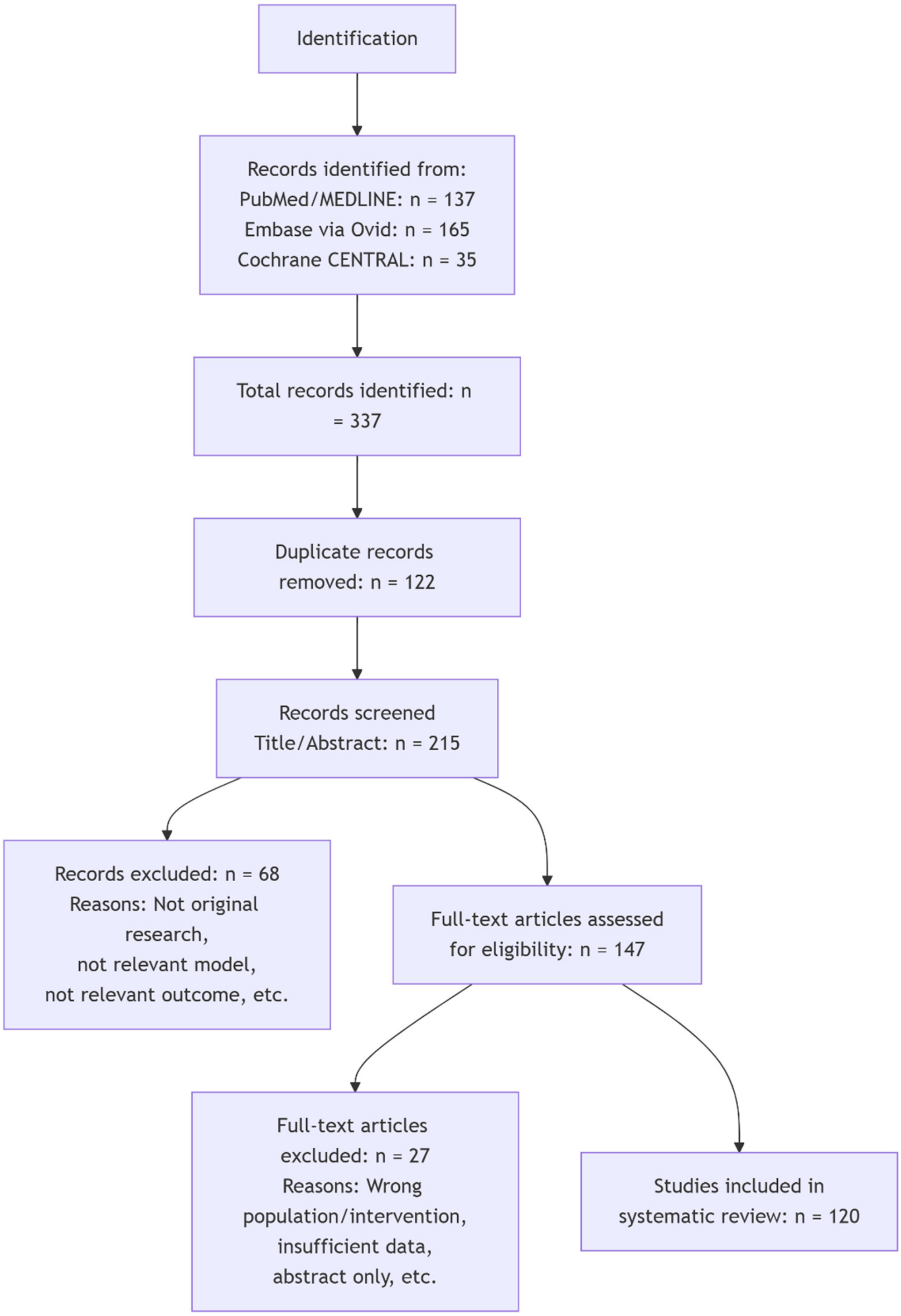


Figure 1. The flow chat of the search strategy.

The searching terms were: ("Internal Mammary Artery"[Mesh] OR "Internal Mammary Artery" OR "Internal Mammary Arteries" OR "Internal Thoracic Artery" OR "ITA" OR "IMA") AND ("Adipose Tissue"[Mesh] OR "Adipose Tissue, Perivascular"[Mesh] OR "Perivascular Adipose Tissue" OR "PVAT" OR "Adipokines"[Mesh] OR "Adiponectin" OR "Leptin") AND ("Vasodilation"[Mesh] OR "Vasoconstriction"[Mesh] OR "Vasospasm" OR "Vasomotor" OR "Graft Occlusion, Vascular"[Mesh] OR "Myograph" OR "Organ Bath" OR "Vascular Smooth

Muscle"[Mesh] OR relaxation OR vasodilator) AND **NOT** (review[pt] OR meta-analysis[pt] OR editorial[pt] OR comment[pt] OR letter[pt]).

Reference lists of included articles were manually screened for additional eligibility.

2.2. Eligibility Criteria (PICOS Framework)

Inclusion criteria were pre-defined using the PICOS framework:

- **Population (P):** Studies utilizing human IMA tissues from CABG patients or organ donors, or clinical studies of CABG patients receiving IMA grafts.
- **Intervention (I):** Investigation of IMA PVAT presence/activity, its derived factors (e.g., adiponectin), or the pedicled harvesting technique.
- **Comparator (C):** Comparison of IMA with PVAT (PVAT+) vs. without PVAT (PVAT−), pedicled vs. skeletonized grafts, or effects of PVAT-derived factors vs. control.
- **Outcomes (O):**
    - *Primary:* Vasomotor function (relaxation, contraction, basal tone).
    - *Secondary:* Adipokine secretion, graft patency, graft-related clinical outcomes (e.g., spasm).
- **Study Types (S):** Original research articles (*Ex vivo*, *in vitro*, clinical studies). Reviews, meta-analyses, editorials, and case reports (n < 10) were excluded.

2.3. Study Selection Process

The study selection process followed the PRISMA guidelines [BMJ. 2021;372:n71]. After duplicate removal, titles/abstracts were screened, and full texts of potentially eligible studies were assessed against the PICOS criteria by the author. The PRISMA flow diagram illustrates this process (Figure 1).

2.4. Data Extraction and Quality Assessment

Data were extracted using a standardized form. The quality of *ex vivo* studies was assessed using a customized checklist evaluating sample size, blinding, randomization, tissue viability, and statistical reporting. Clinical studies were assessed using the Newcastle-Ottawa Scale [BMJ. 2021;372:n71], and RCTs were assessed using the Cochrane RoB 2.0 tool [BMC Med Res Methodol. 2014 Mar 26;14:43].

3. Results

3.1. Results of the Search and Study Selection

The systematic search and selection process, culminating in the inclusion of relevant studies, are depicted in the PRISMA flow diagram (Figure 1).

3.2. Study Characteristics

The key characteristics of the included studies, including design, population, interventions, and main outcomes, are summarized in Tables 1 and 2.

Table 1. Summary of Key Studies on PVAT and IMA Harvesting Technique—Experimental & Mechanistic Studies.

First Author, Year	Study Design	Key Groups/Focus	Main Findings Related to PVAT and Vasomotor Function
Gao YJ, 2005 [23]	*Ex vivo* myography	IMA ± PVAT	PVAT attenuated contractions to serotonin. The anticontractile effect was reduced by L-NNA and abolished by endothelium removal, indicating an endothelium-dependent NO-mediated component.
Malinowski M, 2008 [24]	*Ex vivo* myography	IMA ± PVAT, ±L-NNA, ±Indomethacin	PVAT released a potent anticontractile factor that reduced serotonin-induced contractions. This effect was independent of NO and prostacyclin.
Margaritis M, 2013 [27]	*Ex vivo*/Molecular	Human vessels and PVAT	Identified a novel pathway where adiponectin from PVAT activates endothelial NO synthase (eNOS) in the adjacent vessel wall, linking PVAT to endothelial function.
Deja MA, 1999 [11]	Clinical and *Ex vivo* myography	IMA ± PVAT	Skeletonization does not damage the endothelial function of the LITA. Higher free blood flow and available LITA length should encourage the use of skeletonized LITA in clinical practice.
Ozen G, 2021 [21]	*Ex vivo* organ bath	IMA	PVAT of IMA exerts its anti-contractile effect independently from prostanoids. Retaining PVAT in human IMA preparations may have potential clinical implications to improve coronary bypass graft patency.
Wei JH, 2023 [28]	*Ex vivo* myography	IMA PVAT exposed to Homocysteine	Homocysteine impaired the anticontractile function of PVAT, demonstrating that PVAT can become dysfunctional under metabolic stress.
Wei JH, 2025 [29]	*Ex vivo* myography	IMA PVAT	In a hyperhomocysteinemia model, inhibition of soluble epoxide hydrolase ameliorated PVAT dysfunction, identifying epoxyeicosatrienoic acids as a PVAT-derived relaxing factor.
Zhang YF, 2025 [26]	*Ex vivo* myography	IMA ± PVAT, ±Endothelium, ±L-NNA	PVAT significantly enhanced AdipoRon and A23187-induced relaxation. This effect was partially independent of NO and endothelium. A23187 stimulated adiponectin release from PVAT.

Table 2. Summary of Key Studies on PVAT and IMA Harvesting Technique—Clinical & Surgical Outcome Studies.

First Author, Year	Study Design	Key Groups/Focus	Main Findings Related to PVAT and Vasomotor Function
Deja MA, 1999 [11]	Clinical Cohort (287 nonskeletonized vs. 70 skeletonized LIMA)	Pedicled vs. Skeletonized LIMA	Skeletonization does not damage the endothelial function of the LIMA. Higher free blood flow and available LIMA length should encourage the use of skeletonized LIMA in clinical practice.
Calafiore AM, 1999 [30]	Clinical Cohort (304 pedicled vs. 842 skeletonized conduits)	Pedicled vs. Skeletonized BIMA	Similar midterm clinical results and angiographic patency between pedicled and skeletonized bilateral IMA grafts with a lower rate of sternal wound complications in skeletonized bilateral IMA group.
Gaudino M, 2003 [16]	Clinical (15 patients)	Pedicled vs. Skeletonized IMA	Skeletonized IMAs had a higher propensity for intraoperative spasm and exhibited heightened contractility to serotonin *ex vivo*.
Mannacio V, 2011 [31]	Randomized Trial (100 Pedicled vs. 100 Skeletonized IMA patients)	Pedicled vs. Skeletonized IMA	Skeletonization of the left IMA provided significantly higher early flow capacity and better graft flow reserve.
Ohira S, 2019 [13]	Clinical Cohort (14,249 BIMA patients)	BIMA in 14,249 patients	Early outcomes of BIMA grafting were satisfactory regarding deep sternal wound infection and operative mortality.
Van den Eynde J, 2019 [12]	Clinical Cohort (1487 non-skeletonized vs. 413 skeletonized IMA)	Skeletonized vs. Pedicled BIMA in Diabetics	Skeletonization technique is associated with a clear reduction in the incidence and grade of sternal wound complications in diabetic patients receiving BIMA grafts.
Zientara A, 2018 [32]	Clinical Trial	Skeletonized IMA: Ultrasonic vs. Electro-scalpel	An ultrasonic scalpel provided better preservation of the endothelial layer and vessel wall integrity in skeletonized IMA harvesting compared to conventional electrosurgery.
Lamy A, 2021 (COMPASS) [33]	Post-hoc RCT Analysis (1002 patients)	Pedicled vs. Skeletonized IMA	Harvesting of the IMA during CABG surgery using a skeletonized technique was associated with a higher rate of graft occlusion and worse clinical outcomes than the traditional pedicled technique.
Abfalterer H, 2024 (HARVITA) [34]	RCT Protocol	Pedicled vs. Skeletonized IMA	A published protocol for an ongoing randomized trial designed to compare graft function and clinical outcomes; results are pending.

Abbreviations: IMA: Internal Mammary Artery; PVAT: Perivascular Adipose Tissue; NO: Nitric Oxide; BIMA: Bilateral Internal Mammary Arteries; RCT: Randomized Controlled Trial.

3.3. Results and Findings

3.3.1. Clinical Context and Guideline Recommendations

The strategic importance of CABG and the pivotal role of the IMA are framed by large-scale comparative outcomes research as mentioned above [1–5]. A pooled analysis of individual patient data by Head et al. [1] demonstrated the long-term mortality benefit of CABG over percutaneous coronary intervention for complex coronary artery disease. This evidence underpins the strong recommendations for CABG and IMA use in major international guidelines, including the 2018 ESC/EACTS guidelines [2] and their subsequent 2022 review [3]. The historical foundation for this practice was laid by a series of studies and the IMA as the conduit of choice was cemented by long-term patency studies, such as the landmark report by Tatoulis et al. [5] on over 2000 arterial grafts and the work on complete arterial revascularization by Buxton et al. [6]. The physiological superiority of arterial grafts over saphenous veins, characterized by superior endothelial function and nitric oxide release, provides the biological rationale for these clinical outcomes [7–9], as systematically classified by He and Yang [10].

3.3.2. The Surgical Dilemma of IMA Harvesting Technique

The method of IMA harvest—pedicled versus skeletonized—introduces a significant surgical dilemma, balancing graft physiology against post-operative complications. Support of use of skeletonized IMA is based on increasing the length of IMA [11] and reducing the risk of sternal wound complications [12,13], the latter was supported by retrospective analyses such as Van den Eynde et al. [12], and large database studies like Ohira et al. [13]. The reduction of sternal devascularization is a key mechanism for this benefit. However, this advantage may come at a physiological cost. The IMA is a heterogeneous structure, as detailed by Sahar et al. [14], although other studies showed that skeletonization does not affect IMA wall integrity [15] or early vasoreactive profile [16]. It should be realized that there is lack of large multi-center clinical trials on the comparison of harvesting technique as to pedicled versus skeletonized. The above early studies were conducted in small clinical samples and therefore no definitive conclusions could be made.

3.3.3. The Functional Role of PVAT

The critical discovery that reconciles these observational findings is the recognition of PVAT as a dynamic, vasoactive organ. Löhn et al. [17] and Gollasch [18] identified PVAT as a source of a potent "vascular relaxing factor". This factor comprises a cocktail of mediators, including the adipokine adiponectin, identified as a novel humoral vasodilator by Fésüs et al. [19], and leptin, which Momin et al. [20] showed acts as an endothelium-independent vasodilator in human coronary disease. Further research identified hydrogen sulfide (H_2S) as a key PVAT-derived vasodilator [21], along with various prostanoids [22]. The translation of these findings to the human IMA was pivotal. Gao et al. [23] demonstrated that IMA-PVAT exerts a potent anticontractile effect. This was confirmed by Malinowski et al. [24], who crucially identified that this effect is largely independent of nitric oxide and prostacyclin. The clinical relevance of this physiological finding has been powerfully supported argued by Numaguchi et al. [25], who suggested preserved PVAT around the IMA appears to be protected from metaflammation and consecutive adipose tissue remodeling, which may contribute to the decreased atherosclerotic plaque burden in the ITA. Our most recent study [26] has clearly demonstrated that PVAT significantly enhanced AdipoRon and A23187-induced relaxation. This effect was partially independent of NO and endothelium. A23187 stimulated adiponectin release from PVAT. The vasodilator effect of the PVAT on the IMA is particularly clinically relevant given the common clinical need for pharmacological vasodilators like papaverine and glyceryl trinitrate-verapamil to manage graft spasm [35].

3.3.4. Modern Surgical Techniques and Graft Assessment

Contemporary surgical practice has evolved with techniques aimed at minimizing invasiveness and improving outcomes. Niinami et al. [28] reported excellent long-term results with off-pump CABG using exclusively in-situ arterial grafts. Graft patency remains the ultimate metric, with prospective studies like that of Zhao et al. [29] comparing novel conduits to the pedicled IMA. The adoption of robotic surgery is advancing rapidly, with Fu et al. [36] reporting on large series of robotic-assisted multivessel CABG, Jung et al. [37] on clipless harvesting techniques, and Nisivaco et al. [38] comparing left versus right IMA use in totally endoscopic surgery. These advanced techniques are detailed in comprehensive surgical guides [39]. The method of skeletonization itself impacts the vessel; Zientara et al. [32] showed that low-thermal-damage devices better preserve endothelial integrity than conventional electrosurgery. The vascular redox environment, including factors like tetrahydrobiopterin, is crucial for maintaining endothelial function [40]. The clinical application of skeletonized IMAs for complex, sequential grafting has been extensively documented by Ji et al. [41–43].

3.3.5. Vasodilator Strategies and PVAT in Pathological States

Given the inherent risk of graft spasm, especially in skeletonized conduits, the use of vasodilator solutions is a critical intraoperative consideration. Studies have compared the efficacy of various agents, including nitroglycerin-verapamil solutions in the IMA [35,44] and skeletonized IMA graft preparation in which nifedipine, cilnidipine, and diltiazem were used [45]. Further, the function of PVAT is not static and is adversely altered in disease states. Cybularz et al. [46] found impaired endothelial function and gene expression in IMA-PVAT from obese patients with coronary artery disease. The pursuit of optimal revascularization strategies continues, with investigations into complete arterial revascularization using bilateral IMAs in various configurations, including T-grafts and in-situ arrangements [47–52], and the use of composite Y-grafts [53]. The composition of the IMA wall itself, influenced by factors like dietary fatty acids, can also affect its vasodilatory capacity [54].

3.3.6. Sternal Complications and Graft Configurations

Sternal healing with pedicle versus skeletonized IMA is one of the major concerns for IMA grafting. A significant driver for the skeletonized technique is the reduction of deep sternal wound infection (DSWI), particularly in bilateral IMA grafting. This is supported by multiple studies [12,55,56], which confirm the association between pedicled harvesting of bilateral IMA and increased sternal risk. Interestingly, in a classical study [55], we conclude that bilateral IMA grafting does not increase operative mortality in properly selected patients. However, this procedure should be carefully chosen in elderly (≥70 years) patients and for emergency operations. Further, obese patients have a high risk for sternal infection after bilateral IMA grafting [55].

Other technical adaptations have also been proposed to reduce this risk [56]. Preoperative patient factors, such as the SYNTAX score, can influence graft patency outcomes [57]. While concerns existed that skeletonization might damage the arterial neural network, Gaudino et al. [58] found that innervation is largely preserved. It was also demonstrated that metabolic demand can override the potential difference in sympathetic vasoconstriction in both pedicled and skeletonized ITA grafts [59]. The safety of skeletonization has also been demonstrated in other arterial conduits, such as the radial artery [60,61] and the gastroepiploic artery [62,63], with studies showing preserved endothelial function and good clinical results.

3.3.7. Graft Flow, Patency, and Endothelial Function

Early graft function is often assessed by flow measurement. A randomized study by Mannacio et al. [31] found that skeletonization of the left IMA, beyond traditional proven advantages, provided significantly higher flow capacity and better graft flow reserve. On the other hand, the pedicled IMA remains a versatile graft, useful in complex scenarios like reoperative surgery [64], and its function can be assessed postoperatively with echo-Doppler [65]. The long-term patency of arterial grafts is influenced by factors such as competitive flow [66] and the preservation of endothelial function over time [67]. The use of other pedicled arterial grafts, such as the right gastroepiploic artery, further expands the options for total arterial revascularization [68]. Technical reports on the use of bilateral IMAs in robotic-assisted surgery via lateral thoracotomy also highlight its versatility [69].

3.3.8. Basic Research on Molecular Mechanisms and Recent Breakthrough Evidence of PVAT

The molecular understanding of PVAT's function has deepened substantially. Margaritis et al. [27] demonstrated that PVAT-derived adiponectin activates endothelial NO synthase in human vessels via a caveolin-1-mediated mechanism, a pathway detailed by Cheng et al. [70]. The vasodilatory role of leptin, involving distinct endothelial mechanisms, was further elaborated [71]. Beyond adipokines, it has been reported that PVAT modulates vascular function through endothelium-dependent mechanisms involving hydrogen peroxide [72] and hydrogen sulphide (H_2S) [73]. The anticontractile effect of PVAT, identified in rat models [74] is a conserved physiological phenomenon. However, this benefit is vulnerable to dysfunction, as seen in diabetes, where PVAT promotes NADPH oxidase activity [75], and in hyperhomocysteinemia, which impairs PVAT function [76]. The most recent and direct evidence comes from our study [26] that demonstrated in an *ex vivo* human IMA study that pedicled IMA grafts, with preserved PVAT, have a significantly superior antispastic profile compared to skeletonized grafts. We further found that epoxyeicosatrienoic acids (EETs) act as PVAT-derived relaxing factors, and their pathway is a target for therapeutic restoration in dysfunction [77]. Others also found that PVAT correlates to coronary atherosclerosis [78]. Figure 2 illustrates the characteristics of pedicled vs. skeletonization of IMA grafts with emphasis on the role of PVAT.

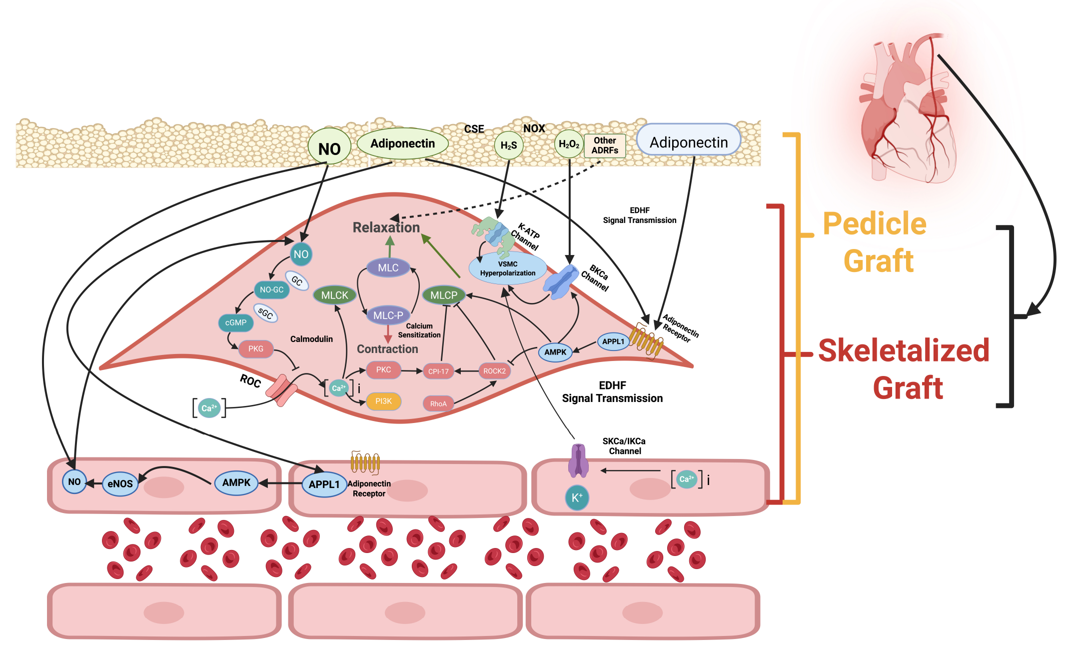


Figure 2. Illustration of the characteristics of pedicled vs. skeletonization of IMA grafts with emphasis on the role of PVAT. PVAT releases a number of vasorelaxant substances including nitric oxide (NO), adiponectin, and others. The pedicled IMA has intact surrounding PVAT that may release those vasorelaxant substances and therefore is in favor of protection of the relaxation with antispastic role of the IMA grafts (Adapted with permission from Ref. [26], Copyright 2025, Elsevier). Abbreviations: CABG, coronary artery bypass grafting; AC, adipose cell; VSMC, vascular smooth muscle cell; EC, endothelium cell; PVAT, perivascular adipose tissue; ADRFs, adipose-derived relaxing factors; IMA, internal mammary artery; NO, nitric oxide; K^+, potassium; eNOS, endothelial nitric oxide synthase; AMPK, AMP-activated protein kinase; APPL1, adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1; sGC, soluble guanylate cyclase; cGMP, cyclic guanosine monophosphate; PKG, protein kinase G; MLC, myosin light chain; MLCP, myosin light chain phosphatase; EDHF, endothelium-derived hyperpolarizing factor; SKCa/IKCa, small/intermediate conductance calcium-activated potassium channels; BKCa, large-conductance calcium-activated potassium channel; K_V, voltage-dependent K^+ channel; VSMC, vascular smooth muscle cell; L-NNA, NG-Nitro-L-arginine; ROCK2, Rho-associated coiled-coil-containing protein kinase 2; PKC, protein kinase C.

3.3.9. Clinical Outcomes and the Current Equipoise

The translation of these physiological advantages into clinical outcomes is the subject of ongoing research. An early study by Calafiore et al. [30] suggested that the use of skeletonized BIMA conduits allowed surgeons to increase the number of bilateral IMA anastomoses per patient with a lower rate of sternal wound complications and angiographic results similar to those obtained with pedicled BIMA conduits, and the conclusion is supported by Takami et al. [79]. They concluded that compared with pedicle harvesting, complete skeletonization of IMA may make it possible to anastomose an ITA with a larger diameter in coronary artery bypass grafting, which leads to increased graft flow by decreasing vascular resistance. Dalén M et al. in a recent study [80] found no significant differences in all-cause mortality or major adverse cardiovascular events rates between the 2 ITA harvesting methods. The most important study in a large-scale post-hoc analysis of the COMPASS randomized clinical trial in 1002 patients by Lamy et al. [33] found that harvesting of the IMA during CABG surgery using a skeletonized technique was associated with a higher rate of graft occlusion and worse clinical outcomes than the traditional pedicled technique. They also suggested that future randomized clinical trials are needed to establish the safety and patency of the skeletonized technique. Fortunately, the ongoing, prospective HARVITA trial, as per its published protocol [34], aims to provide a definitive randomized comparison between a skeletonized versus pedicled technique.

The IMA's specific physiological properties, including increased contractility at the distal end and bifurcations, inform optimal grafting strategy [81–83]. A recent study [84] reveals significant differences in PTM crotonylation between human IMA and SV, shedding light on the biological mechanisms underlying the functional disparities between these grafts and form a scientific basis for developing specific methods including new anti-oxidative drugs and gene therapy to improve the long-term graft patency.

The late endothelial function of free versus pedicled IMA grafts has been studied, showing good preservation in both [67] and the use of free graft of the right IMA was suggested [85]. Further, the use of both post-bifurcation branches has been shown technically feasible and may be selectively considered for skeletonized conduits and limited to non-LAD targets [86]. Skeletonization of the radial artery has been associated with improved angiographic results [61], and the use of only pedicled arterial conduits has been reported even in specific populations like Kawasaki disease patients [87].

Bilateral skeletonized IMA grafting in off-pump surgery has shown good early results [53], and coronary bypass using only in-situ bilateral ITAs and the gastroepiploic artery has been demonstrated to be feasible [88]. Skeletonization of the gastroepiploic artery in off-pump surgery also shows good early results [63], and the use of the right IMA and saphenous vein when the left IMA is unavailable has been studied with flow measurement [89].

The use of multiple arterial grafts did not seem to increase the incidence of early in-hospital major complications [90]. A recent report revealed a decreasing trend in the use of off pump in the UK since 2008. This is likely to be multifactorial and raises the question of whether it should be a specialized revascularization technique [91].

It should be mentioned that due to heterogeneity in patient populations, advances in surgical techniques over time, and differences in outcome definitions and measurement techniques, the results from various studies may not be consistent. Large clinical trials may solve such problems in the future.

3.3.10. IMA Graft Spasm and Strategy to Overcome Spasm in Pedicled and Skeletonized IMA

A report indicated that among 5762 patients who underwent isolated CABG, 7 patients (0.12%) experienced refractory spasm of coronary arteries and grafted conduits, including the left IMA, and an additional 18 patients (0.31%) experienced perioperative vasospasm of a single coronary artery or of a grafted conduit [92]. This suggests that the confirmed perioperative vasospasm in coronary arteries or grafts is approximately 0.43% (25 of 5762 patients) in all CABG surgery. It is possible that clinically the real incidence of IMA spasm is higher than this because some transient or less severe spasm may not be recorded in the ICU. This fact evoked a clinical need for anti-spasm treatment in the IMA graft.

Early studies [93,94] on pharmacological antispastic agents derived a large variety of methods. The search for the best pharmacological methods to overcome IMA spasm has been continued [95–115] with many new pharmacological vasorelaxant agents such as new calcium channel blockers developed. The pharmacological mechanism to relax the IMA varies, with some of these agents that are endothelium-dependent. The effect of new generations of calcium channel blockers on the IMA relaxation such as amlodipine [105], cilnidipine [108], azelnidipine [103], benidipine [101], efonidipine [95] has been investigated. New protocols by using combination of vasodilators such as nicardipine and nitroglycerin cocktail [109], fasudil and nitroglycerin cocktail [97]. Fasudil and isosorbide dinitrate cocktail [110] has been reported and some of those have been used clinically [111]. Finally, AVE3085, an enhancer of endothelial NO synthase has been studied on its endothelial protection in the IMA [112,113,115]. Because those pharmacological agents may have dual mechanisms with direct relaxation of IMA and indirect relaxation through stimulating NO release, whether the preservation of PVAT in the pedicled IMA grafts may facilitate the NO release requires further clarification. Nevertheless, with PVAT preservation, its antispastic role in the IMA has been well demonstrated.

3.3.11. Future Research Directions

Although the preservation of PVAT may reduce the incidence of spasm of the IMA graft, to eliminate the possible spasm it is necessary to use vasodilators for antispastic purposes. This is a continuing work in the future to find the best vasodilators for use during the harvesting as well as during the perioperative period. Further, when bilateral IMAs are used, to avoid or reduce possible sternal infection particularly in the obese patients, skeletonization techniques may be applied. Under such circumstances, it may be necessary to develop more effective antispastic methods for the skeletonized IMA grafts.

4. Summary and Conclusions

In summary, the cumulative weight of the evidence demonstrates that the perivascular adipose tissue of the IMA is a potent source of vasoactive mediators that confer a robust, multi-mechanistic defense against vasospasm. The pedicled harvesting technique, by preserving this bioactive PVAT layer, maintains the graft's innate antispastic capacity, powerfully supported by recent direct clinical comparison. While the skeletonized technique in BIMA grafting is indispensable for reducing sternal wound complications in high-risk patients, the physiological evidence firmly establishes the pedicled IMA as the benchmark for optimal graft function from an antispastic perspective. Therefore, the choice of harvesting technique should be a deliberate, patient-specific decision that weighs the demonstrated physiological benefits of an intact PVAT-IMA unit against the individual's risk profile for sternal complications and length requirement. Future research should focus on strategies to protect PVAT function in comorbid states and on long-term patency outcomes from randomized clinical trials.

Funding

This work was supported by the National Natural Science Foundation of China (82370350 and 82170353), Tianjin Key Medical Discipline Construction Project (TJYXZDXK-3-036C) and Special Fund for High Quality Development Project.

Acknowledgments

The author thanks the National Science foundation of China for support. The author also thanks Emma Jun Wang for help of making the Figure 1 and You-Feng Zhang for help of making the Figure 2 & graphical abstract.

Conflicts of Interest

The author declares no conflict of interest. Given the role as Editor-in-Chief, G.-W.H. had no involvement in the peer review of this paper and had no access to information regarding its peer-review process. Full responsibility for the editorial process of this paper was delegated to another editor of the journal.

Use of AI and AI-Assisted Technologies

During the preparation of this work, the author used [Deep SeekR1] to help searching references and checking English. After using this tool, the author carefully reviewed and edited the content as needed and takes full responsibility for the content of the published article.

References

1. Head, S.J.; Milojevic, M.; Daemen, J.; et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: A pooled analysis of individual patient data. *Lancet* **2018**, *391*, 939–948.
2. Neumann, F.J.; Sousa-Uva, M.; Ahlsson, A.; et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur. Heart J.* **2019**, *40*, 87–165.
3. Byrne, R.A.; Fremes, S.; Capodanno, D.; et al. 2022 Joint ESC/EACTS review of the 2018 guideline recommendations on the revascularization of left main coronary artery disease in patients at low surgical risk and anatomy suitable for PCI or CABG. *Eur. J. Cardio-Thorac. Surg.* **2023**, *64*, ezad286.
4. Kolessov, V.I. Mammary artery-coronary artery anastomosis as method of treatment for angina pectoris. *J. Thorac. Cardiovasc. Surg.* **1967**, *54*, 535–544.
5. Tatoulis, J.; Buxton, B.F.; Fuller, J.A. Patencies of 2127 arterial to coronary conduits over 15 years. *Ann. Thorac. Surg.* **2004**, *77*, 93–101.
6. Buxton, B.F.; Fuller, J.A.; Tatoulis, J. Evolution of complete arterial grafting. For coronary artery disease. *Tex. Heart Inst. J.* **1998**, *25*, 17–23.
7. Lüscher, T.F.; Diederich, D.; Siebenmann, R.; et al. Difference between endothelium-dependent relaxation in arterial and in venous coronary bypass grafts. *N. Engl. J. Med.* **1988**, *319*, 462–467.
8. He, G.W.; Liu, Z.G. Comparison of nitric oxide release and endothelium-derived hyperpolarizing factor-mediated hyperpolarization between human radial and internal mammary arteries. *Circulation* **2001**, *104*, I344–I349.
9. Liu, Z.G.; Ge, Z.D.; He, G.W. Difference in endothelium-derived hyperpolarizing factor-mediated hyperpolarization and nitric oxide release between human internal mammary artery and saphenous vein. *Circulation* **2000**, *102*, 296–301. https://doi.org/10.1161/01.cir.102.suppl_3.iii-296.

10. He, G.W.; Yang, C.Q. Comparison among arterial grafts and coronary artery. An attempt at functional classification. *J. Thorac. Cardiovasc. Surg.* **1995**, *109*, 707–715.
11. Deja, M.A.; Woś, S.; Gołba, K.S.; et al. Intraoperative and laboratory evaluation of skeletonized versus pedicled internal thoracic artery. *Ann. Thorac. Surg.* **1999**, *68*, 2164–2168.
12. Van den Eynde, J.; Heeren, A.; Szecel, D.; et al. Skeletonisation contributing to a reduction of sternal wound complications: A retrospective study in OPCAB patients. *J. Cardiothorac. Surg.* **2019**, *14*, 162. https://doi.org/10.1186/s13019-019-0985-9.
13. Ohira, S.; Miyata, H.; Yamazaki, S.; et al. Deep sternal wound infection after bilateral internal thoracic artery grafting: Insights from a Japanese national database. *J. Thorac. Cardiovasc. Surg.* **2019**, *157*, 166–173.e1. https://doi.org/10.1016/j.jtcvs.2018.06.101.
14. Sahar, G.; Shavit, R.; Yosibash, Z.; et al. The physiologic and histologic properties of the distal internal thoracic artery and its subdivisions. *J. Thorac. Cardiovasc. Surg.* **2015**, *149*, 1042–1050.
15. Gaudino, M.; Toesca, A.; Nori, S.L.; et al. Effect of skeletonization of the internal thoracic artery on vessel wall integrity. *Ann. Thorac. Surg.* **1999**, *68*, 1623–1627.
16. Gaudino, M.; Trani, C.; Glieca, F.; et al. Early vasoreactive profile of skeletonized versus pedicled internal thoracic artery grafts. *J. Thorac. Cardiovasc. Surg.* **2003**, *125*, 638–641.
17. Löhn, M.; Dubrovska, G.; Lauterbach, B.; et al. Periadventitial fat releases a vascular relaxing factor. *FASEB J.* **2002**, *16*, 1057–1063.
18. Gollasch, M. Vasodilator signals from perivascular adipose tissue. *Br. J. Pharmacol.* **2012**, *165*, 633–642.
19. Fésüs, G.; Dubrovska, G.; Gorzelniak, K.; et al. Adiponectin is a novel humoral vasodilator. *Cardiovasc. Res.* **2007**, *75*, 719–727.
20. Momin, A.U.; Melikian, N.; Shah, A.M.; et al. Leptin is an endothelial-independent vasodilator in humans with coronary artery disease: Evidence for tissue specificity of leptin resistance. *Eur. Heart J.* **2006**, *27*, 2294–2299.
21. Fang, L.; Zhao, J.; Chen, Y.; et al. Hydrogen sulfide derived from periadventitial adipose tissue is a vasodilator. *J. Hypertens.* **2009**, *27*, 2174–2185.
22. Ozen, G.; Topal, G.; Gomez, I.; et al. Control of human vascular tone by prostanoids derived from perivascular adipose tissue. *Prostaglandins Other Lipid Mediat.* **2013**, *107*, 13–17.
23. Gao, Y.J.; Zeng, Z.H.; Teoh, K.; et al. Perivascular adipose tissue modulates vascular function in the human internal thoracic artery. *J. Thorac. Cardiovasc. Surg.* **2005**, *130*, 1130–1136.
24. Malinowski, M.; Deja, M.A.; Gołba, K.S.; et al. Perivascular tissue of internal thoracic artery releases potent nitric oxide and prostacyclin-independent anticontractile factor. *Eur. J. Cardiothorac. Surg.* **2008**, *33*, 225–231.
25. Numaguchi, R.; Furuhashi, M.; Matsumoto, M.; et al. Differential Phenotypes in Perivascular Adipose Tissue Surrounding the Internal Thoracic Artery and Diseased Coronary Artery. *J. Am. Heart Assoc.* **2019**, *8*, e011147. https://doi.org/10.1161/JAHA.118.011147.
26. Zhang, Y.F.; Hou, H.T.; Yang, Q.; et al. Perivascular adipose on relaxation of internal mammary artery with surgical implications: Better antispastic effect of pedicle than skeletal grafts. *J. Thorac. Cardiovasc. Surg.* **2025**, *in press*. https://doi.org/10.1016/j.jtcvs.2025.10.033.
27. Margaritis, M.; Antonopoulos, A.S.; Digby, J.; et al. Interactions between vascular wall and perivascular adipose tissue reveal novel roles for adiponectin in the regulation of endothelial nitric oxide synthase function in human vessels. *Circulation* **2013**, *127*, 2209–2221.
28. Niinami, H.; Endo, Y.; Morita, K.; et al. Long-Term Outcomes Following Off-pump Coronary Artery Bypass Grafting Using Only 3 In situ Arterial Grafts. *Eur. J. Cardiothorac. Surg.* **2025**, *67*, ezaf289.
29. Zhao, T.Y.; Wang, B.J.; Liu, C.; et al. Comparing 3-month and 1-year patency rates of no-touch great saphenous vein and pedicled left internal mammary artery in off-pump coronary artery bypass grafting: A prospective non-inferiority study. *Front. Cardiovasc. Med.* **2025**, *12*, 1547482.
30. Calafiore, A.M.; Vitolla, G.; Iaco, A.L.; et al. Bilateral internal mammary artery grafting: Midterm results of pedicled versus skeletonized conduits. *Ann. Thorac. Surg.* **1999**, *67*, 1637–1642.
31. Mannacio, V.; Di Tommaso, L.; De Amicis, V.; et al. Randomized flow capacity comparison of skeletonized and pedicled left internal mammary artery. *Ann. Thorac. Surg.* **2011**, *91*, 24–30.
32. Zientara, A.; Komminoth, P.; Seifert, B.; et al. Skeletonized internal thoracic artery harvesting: A low thermal damage electrosurgical device provides improved endothelial layer and tendency to better integrity of the vessel wall compared to conventional electrosurgery. *J. Cardiothorac. Surg.* **2018**, *13*, 105.
33. Lamy, A.; Browne, A.; Sheth, T.; et al. Skeletonized vs. Pedicled Internal Mammary Artery Graft Harvesting in Coronary Artery Bypass Surgery: A Post Hoc Analysis from the COMPASS Trial. *JAMA Cardiol.* **2021**, *6*, 1042–1049.
34. Abfalterer, H.; Ruttmann-Ulmer, E.; Grimm, M.; et al. Randomized comparison of HARVesting the Left Internal Thoracic Artery in a skeletonized versus pedicled technique: The HARVITA trial-study protocol. *Interdiscip. Cardiovasc. Thorac. Surg.* **2024**, *38*, ivae045.

35. Formica, F.; Ferro, O.; Brustia, M.; et al. Effects of papaverine and glycerylnitrate-verapamil solution as topical and intraluminal vasodilators for internal thoracic artery. *Ann. Thorac. Surg.* **2006**, *81*, 120–124.
36. Fu, Y.; Hong, Y.; Ding, T.; et al. Early outcomes and follow-up of robotic-assisted multivessel coronary artery bypass with in situ bilateral internal thoracic artery: Report of 221 patients in a single center. *J. Thorac. Cardiovasc. Surg.* **2025**, *170*, 1639–1647.
37. Jung, Y.C.; Chong, Y.; Kang, M.W.; et al. Clipless internal mammary artery harvesting for minimally invasive coronary artery bypass grafting using the shear-tip harmonic scalpel. *J. Thorac. Dis.* **2024**, *16*, 3711–3721.
38. Nisivaco, S.; Kitahara, H.; Abutaleb, A.; et al. Robotic Totally Endoscopic Coronary Bypass to the Left Anterior Descending Artery: Left Versus Right Internal Thoracic Artery Grafts. *J. Surg. Res.* **2023**, *291*, 139–150.
39. Marín-Cuartas, M.; Kang, J.; Davierwala, P.M.; et al. Step-by-step harvesting of various grafts for coronary artery bypass surgery. *Multimed. Man. Cardiothorac. Surg.* **2021**, *2021*. https://doi.org/10.1510/mmcts.2021.076.
40. Cerrato, R.; Crabtree, M.; Antoniades, C.; et al. Effects of Endothelin-1 on Intracellular Tetrahydrobiopterin Levels in Vascular Tissue. *Scand. Cardiovasc. J.* **2018**, *52*, 163–169.
41. Ji, Q.; Xia, L.; Shi, Y.; et al. Sequential Grafting of in Situ Skeletonized Left Internal Mammary Artery to the Left Coronary System. *Int. Heart J.* **2018**, *59*, 727–735.
42. Ji, Q.; Xia, L.; Shi, Y.; et al. In Situ Skeletonized Right Internal Mammary Artery Bypass Grafting to Left Anterior Descending Artery. *Int. Heart J.* **2018**, *59*, 35–42.
43. Ji, Q.; Shi, Y.; Xia, L.; et al. Revascularization of Left Coronary System Using a Skeletonized Left Internal Mammary Artery—Sequential vs. Separate Grafting. *Circ. J.* **2017**, *82*, 102–109.
44. Ray Mohapatra, C.K.; Mishra, P.; Saxena, P.; et al. Use of nitroglycerin and verapamil solution by organ bath technique in preparation of left internal thoracic artery for coronary artery bypass surgery. *Indian. Heart J.* **2017**, *69*, 772–776.
45. Fukuda, S.; Nakamura, Y.; Egi, K.; et al. Comparison of direct effects of clinically available vasodilators; nitroglycerin, nifedipine, cilnidipine and diltiazem, on human skeletonized internal mammary harvested with ultrasonic scalpel. *Heart Vessel.* **2016**, *31*, 1681–1684.
46. Cybularz, M.; Langbein, H.; Zatschler, B.; et al. Endothelial function and gene expression in perivascular adipose tissue from internal mammary arteries of obese patients with coronary artery disease. *Atheroscler. Suppl.* **2017**, *30*, 149–158.
47. Rieß, F.C.; Behrendt, C.A.; Amin, W.; et al. Complete arterial revascularization using bilateral internal mammary artery in T-graft technique for multivessel coronary artery disease in on- or off-pump approach: Does gender lose its historical impact on clinical outcome? *Eur. J. Cardio-Thorac. Surg.* **2017**, *52*, 917–923.
48. Gu, C.X.; Yang, J.F.; Zhang, H.C.; et al. Off-pump coronary artery bypass grafting using a bilateral internal mammary artery Y graft. *J. Geriatr. Cardiol.* **2012**, *9*, 247–251.
49. Cho, W.C.; Kim, J.B.; Jung, S.H.; et al. Revascularization of the left anterior descending artery area using a single left internal thoracic artery: Auto-Y composite grafting or sequential bypassing. *J. Thorac. Cardiovasc. Surg.* **2011**, *142*, 1464–1468.
50. Glineur, D.; Djaoudi, S.; D'horre, W.; et al. Endothelium-dependent and endothelium-independent vasodilator response of left and right internal mammary and internal thoracic arteries used as a composite Y-graft. *Eur. J. Cardiothorac. Surg.* **2011**, *40*, 389–393.
51. Asai, T.; Suzuki, T.; Nota, H.; et al. Off-pump coronary artery bypass grafting using skeletonized in situ arterial grafts. *Ann. Cardiothorac. Surg.* **2013**, *2*, 552–556.
52. Obed, D.; Fleissner, F.; Martens, A.; et al. Total Arterial Revascularization with Radial Artery and Internal Thoracic Artery T-Grafts Is Associated with Superior Long-Term Survival in Patients Undergoing Coronary Artery Bypass Grafting. *Ann. Thorac. Cardiovasc. Surg.* **2020**, *26*, 30–39. https://doi.org/10.5761/atcs.oa.19-00226.
53. Kim, K.B.; Cho, K.R.; Chang, W.I.; et al. Bilateral skeletonized internal thoracic artery graftings in off-pump coronary artery bypass: Early result of Y versus in situ grafts. *Ann. Thorac. Surg.* **2002**, *74*, S1371–S1376.
54. Andreasen, J.J.; Aardestrup, I.V.; Eschen, R.B.; et al. Fatty acid composition of the internal mammary artery in relation to dietary intake of marine n-3 polyunsaturated fatty acids and association with flow-mediated vasodilation. *Cell Mol. Biol.* **2010**, *56*, 10–17.
55. He, G.W.; Ryan, W.H.; Acuff, T.E.; et al. Risk factors for operative mortality and sternal wound infection in bilateral internal mammary artery grafting. *J. Thorac. Cardiovasc. Surg.* **1994**, *107*, 196–202.
56. Sakic, A.; Chevtchik, O.; Kilo, J.; et al. Simple adaptations of surgical technique to critically reduce the risk of postoperative sternal complications in patients receiving bilateral internal thoracic arteries. *Interact. Cardiovasc. Thorac. Surg.* **2013**, *17*, 378–382.
57. Kinoshita, T.; Asai, T.; Suzuki, T. Preoperative SYNTAX score and graft patency after off-pump coronary bypass surgery. *Eur. J. Cardiothorac. Surg.* **2013**, *44*, e25–e31.
58. Gaudino, M.; Toesca, A.; Glieca, F.; et al. Skeletonization does not influence internal thoracic artery innervation. *Ann. Thorac. Surg.* **2004**, *77*, 1257–1261.

59. Une, D.; Shimizu, S.; Kamiya, A.; et al. Both skeletonized and pedicled internal thoracic arteries supply adequate graft flow after coronary artery bypass grafting even during intense sympathoexcitation. *J. Physiol. Sci.* **2010**, *60*, 407–413. https://doi.org/10.1007/s12576-010-0109-8.
60. Maruyama, T.; Kohno, H.; Ishida, K.; et al. Change of luminal diameter of skeletonized and non-skeletonized radial artery graft at early and late postoperative period. *Heart Vessel.* **2016**, *31*, 474–481.
61. Amano, A.; Takahashi, A.; Hirose, H. Skeletonized radial artery grafting: Improved angiographic results. *Ann. Thorac. Surg.* **2002**, *73*, 1880–1887.
62. Shi, J.; Iesaki, T.; Kubota, N.; et al. Skeletonization with an ultrasonic scalpel is as safe as a non-skeletonized dissection in preserving the endothelial function of the human gastroepiploic artery. *Interact. Cardiovasc. Thorac. Surg.* **2009**, *8*, 216–220.
63. Kamiya, H.; Watanabe, G.; Takemura, H.; et al. Skeletonization of gastroepiploic artery graft in off-pump coronary artery bypass grafting: Early clinical and angiographic assessment. *Ann. Thorac. Surg.* **2004**, *77*, 2046–2050.
64. Eren, E.; Balkanay, M.; Toker, M.E.; et al. Pedicled right internal mammary artery for reoperative off-pump revascularization of left anterior descending coronary artery. *Tex. Heart Inst. J.* **2006**, *33*, 143–147.
65. Agrifoglio, M.; Di Matteo, S.; Antona, C.; et al. Pedicled arterial grafts in coronary surgery: Postoperative echo color-Doppler study. *J. Cardiovasc. Surg.* **1996**, *37*, 53–57.
66. Lust, R.M.; Zeri, R.S.; Spence, P.A.; et al. Effect of chronic native flow competition on internal thoracic artery grafts. *Ann. Thorac. Surg.* **1994**, *57*, 45–50.
67. Kushwaha, S.S.; Bustami, M.; Tadjkarimi, S.; et al. Late endothelial function of free and pedicled internal mammary artery grafts. *J. Thorac. Cardiovasc. Surg.* **1995**, *110*, 453–462.
68. Isomura, T.; Hisatomi, K.; Hirano, A.; et al. Use of the right gastroepiploic artery as a pedicled arterial graft for coronary revascularization. *Eur. J. Cardiothorac. Surg.* **1993**, *7*, 38–41.
69. Srivastava, S.; Gadasalli, S.; Agusala, M.; et al. Use of bilateral internal thoracic arteries in CABG through lateral thoracotomy with robotic assistance in 150 patients. *Ann. Thorac. Surg.* **2006**, *81*, 800–806.
70. Cheng, K.K.; Lam, K.S.; Wang, Y.; et al. Adiponectin-induced endothelial nitric oxide synthase activation and nitric oxide production are mediated by APPL1 in endothelial cells. *Diabetes* **2007**, *56*, 1387–1394; Erratum in *Diabetes* **2016**, *65*, 3218. https://doi.org/10.2337/db16-er10a.
71. Lembo, G.; Vecchione, C.; Fratta, L.; et al. Leptin induces direct vasodilation through distinct endothelial mechanisms. *Diabetes* **2000**, *49*, 293–297.
72. Gao, Y.J.; Lu, C.; Su, L.Y.; et al. Modulation of vascular function by perivascular adipose tissue: The role of endothelium and hydrogen peroxide. *Br. J. Pharmacol.* **2007**, *151*, 323–331.
73. Emilova, R.; Dimitrova, D.; Mladenov, M.; et al. Cystathionine gamma-lyase of perivascular adipose tissue with reversed regulatory effect in diabetic rat artery. *Biotechnol. Biotechnol. Equip.* **2015**, *29*, 147–151. https://doi.org/10.1080/13102818.2014.991565.
74. Soltis, E.E.; Cassis, L.A. Influence of perivascular adipose tissue on rat aortic smooth muscle responsiveness. *Clin. Exp. Hypertens. A* **1991**, *13*, 277–296.
75. Antonopoulos, A.S.; Margaritis, M.; Coutinho, P.; et al. Adiponectin as a link between type 2 diabetes and vascular NADPH oxidase activity in the human arterial wall: The regulatory role of perivascular adipose tissue. *Diabetes* **2015**, *64*, 2207–2219.
76. Wei, J.H.; Qi, H.; Zhou, Y.; et al. Homocysteine impairs the anticontractile/vasorelaxing activity of perivascular adipose tissue surrounding human internal mammary artery. *Eur. J. Cardiothorac. Surg.* **2023**, *64*, ezad406.
77. Wei, J.H.; Qi, H.; Wang, X.C.; et al. Inhibition of soluble epoxide hydrolase ameliorates hyperhomocysteinemia-induced perivascular adipose tissue dysfunction: Revealing epoxyeicosatrienoic acid as a perivascular adipose tissue-derived relaxing factor. *Eur. J. Pharmacol.* **2025**, *1006*, 178181.
78. Zierold, S.; Buschmann, K.; Gachkar, S.; et al. Brain-Derived Neurotrophic Factor Expression and Signaling in Different Perivascular Adipose Tissue Depots of Patients with Coronary Artery Disease. *J. Am. Heart Assoc.* **2021**, *10*, e018322. https://doi.org/10.1161/JAHA.120.018322.
79. Takami, Y.; Ina, H. Effects of skeletonization on intraoperative flow and anastomosis diameter of internal thoracic arteries in coronary artery bypass grafting. *Ann. Thorac. Surg.* **2002**, *73*, 1441–1445.
80. Dalén, M.; Dismorr, M.; Glaser, N.; et al. Skeletonized Versus Pedicled Harvesting of the Internal Thoracic Artery and Long-Term Clinical Outcomes in Coronary Artery Bypass Surgery. *J. Am. Heart Assoc.* **2024**, *13*, e034354. https://doi.org/10.1161/JAHA.124.034354.
81. He, G.W. Contractility of the human internal mammary artery at the distal section increases toward the end. Emphasis on not using the end of the internal mammary artery for grafting. *J. Thorac. Cardiovasc. Surg.* **1993**, *106*, 406–411.
82. He, G.W.; Ryan, W.H.; Acuff, T.E.; et al. Greater contractility of internal mammary artery bifurcation: Possible cause of low patency rates. *Ann. Thorac. Surg.* **1994**, *58*, 529–532.

83. He, G.W.; Acuff, T.E.; Yang, C.Q.; et al. Middle and proximal sections of the human internal mammary artery are not "passive conduits". *J. Thorac. Cardiovasc. Surg.* **1994**, *108*, 741–746.
84. Sun, W.T.; Chen, H.X.; Hou, H.T.; et al. Protein post-translational modification crotonylation of TXN and GLO1 in artery and vein grafts for coronary artery surgery. *Redox Biol.* **2025**, *82*, 103608. https://doi.org/10.1016/j.redox.2025.103608.
85. Shin, H.; Yozu, R.; Hashizume, K.; et al. Free right internal thoracic artery as a second arterial conduit: Modification of proximal anastomosis for improvement of graft patency. *Ann. Thorac. Cardiovasc. Surg.* **2001**, *7*, 155–158.
86. Sahar, G.; Wolak, A.; Matsa, M.; et al. Concomitant grafting of both postbifurcation internal thoracic artery branches. *Innovations* **2015**, *10*, 14–20.
87. Li, J.Y.; Chen, M.R. Complete myocardial revascularization using only pedicled arterial conduits in Kawasaki disease. *J. Formos. Med. Assoc.* **2000**, *99*, 507–509.
88. Nishida, H.; Tomizawa, Y.; Endo, M.; et al. Coronary artery bypass with only in situ bilateral internal thoracic arteries and right gastroepiploic artery. *Circulation* **2001**, *104*, I76–I80.
89. Zhang, G.; Zhao, Z.; Chen, Y.; et al. Use of the right internal mammary artery and the great saphenous vein for left anterior descending artery revascularization in patients whose left internal mammal artery cannot be used: A study based on transit-time flow measurement. *J. Cardiothorac. Surg.* **2020**, *15*, 126.
90. Chan, J.; Comanici, M.; Dong, T.; et al. National Variation in the Use of Multiple Arterial Grafting in Isolated Coronary Artery Bypass Grafting in the United Kingdom. *Eur. J. Cardiothorac. Surg.* **2025**, *67*, ezaf402. https://doi.org/10.1093/ejcts/ezaf402.
91. Chan, J.; Dimagli, A.; Dong, T.; et al. Trend and early clinical outcomes of off-pump coronary artery bypass grafting in the UK. *Eur. J. Cardiothorac. Surg.* **2023**, *64*, ezad272. https://doi.org/10.1093/ejcts/ezad272.
92. Lorusso, R.; Crudeli, E.; Luca, F.; et al. Refractory spasm of coronary arteries and grafted conduits after isolated coronary artery bypass surgery. *Ann. Thorac. Surg.* **2012**, *93*, 545–551.
93. He, G.W.; Rosenfeldt, F.L.; Buxton, B.F.; et al. Reactivity of human isolated internal mammary artery to constrictor and dilator agents: Implications for treatment of internal mammary artery spasm. *Circulation* **1989**, *80*, I141–I150.
94. He, G.W.; Buxton, B.F.; Rosenfeldt, F.L.; et al. Pharmacologic dilatation of the internal mammary artery during coronary bypass grafting. *J. Thorac. Cardiovasc. Surg.* **1994**, *107*, 1440–1444.
95. Yin, X.Y.; Hou, H.T.; Li, M.R.; et al. A New Method for Antispastic Effect in Coronary Artery Bypass Grafts by Using a L- and T-Type Calcium Channel Blocker Efonidipine. *Basic. Clin. Pharmacol. Toxicol.* **2025**, *137*, e70077. https://doi.org/10.1111/bcpt.70077.
96. Duman, I.; Tanyeli, Ö.; Dereli, Y.; et al. The effects of botulinum toxin A and papaverine on human saphenous vein and internal mammary artery grafts: An *in vitro* study. *Arch. Med. Sci.* **2021**, *18*, 1607–1616. https://doi.org/10.5114/aoms/110157.
97. Hou, H.T.; Wang, Z.Q.; Wang, J.; et al. Antispastic Effect of Fasudil and Cocktail of Fasudil and Nitroglycerin in Internal Thoracic Artery. *Ann. Thorac. Surg.* **2023**, *115*, 1152–1161. https://doi.org/10.1016/j.athoracsur.2021.11.079.
98. Sun, W.T.; Hou, H.T.; Chen, H.X.; et al. Calcium-activated potassium channel family in coronary artery bypass grafts. *J. Thorac. Cardiovasc. Surg.* **2021**, *161*, e399–e409. https://doi.org/10.1016/j.jtcvs.2019.11.016.
99. Kinoshita, T.; Tawa, M.; Suzuki, T.; et al. Suppression of Graft Spasm by the Particulate Guanylyl Cyclase Activator in Coronary Bypass Surgery. *Ann. Thorac. Surg.* **2017**, *104*, 122–129. https://doi.org/10.1016/j.athoracsur.2016.10.003.
100. Ertuna, E.; Turkseven, S.; Amanvermez, D.; et al. Effects of levosimendan on isolated human internal mammary artery and saphenous vein: Concurrent use with conventional vasodilators. *Fundam. Clin. Pharmacol.* **2016**, *30*, 226–234. https://doi.org/10.1111/fcp.12185.
101. Hou, H.T.; Wang, J.; Wang, Z.Q.; et al. Effect of Benidipine in Human Internal Mammary Artery and Clinical Implications. *Ann. Thorac. Surg.* **2016**, *101*, 1789–1795. https://doi.org/10.1016/j.athoracsur.2015.10.029.
102. Sarikaya, S.; Onk, A.; Boztosun, B.; et al. The effect of nebivolol on internal mammary artery blood flow during coronary artery bypass graft surgery. *Perfusion* **2014**, *29*, 315–320. https://doi.org/10.1177/0267659113517921.
103. Gao, G.; Liu, X.C.; Jing, W.B.; et al. Vasorelaxation induced by new third-generation dihydropyridine calcium antagonist azelnidipine in human internal mammary artery. *Ann. Thorac. Surg.* **2013**, *96*, 1316–1321. https://doi.org/10.1016/j.athoracsur.2013.05.020.
104. Bai, X.Y.; Liu, X.C.; Yang, Q.; et al. The interaction between human urotensin II and vasodilator agents in human internal mammary artery with possible clinical implications. *Ann. Thorac. Surg.* **2011**, *92*, 610–614. https://doi.org/10.1016/j.athoracsur.2011.03.094.
105. Bai, X.Y.; Liu, X.C.; Jing, W.B.; et al. Effect of amlodipine in human internal mammary artery and clinical implications. *Ann. Thorac. Surg.* **2010**, *90*, 1952–1957. https://doi.org/10.1016/j.athoracsur.2010.08.007.
106. Ding, R.; Feng, W.; Li, H.; et al. A comparative study on in vitro and in vivo effects of topical vasodilators in human internal mammary, radial artery and great saphenous vein. *Eur. J. Cardiothorac. Surg.* **2008**, *34*, 536–541. https://doi.org/10.1016/j.ejcts.2008.05.050.

107. Onomoto, M.; Tsuneyoshi, I.; Yonetani, A.; et al. Differential pharmacologic sensitivities of phosphodiesterase-3 inhibitors among human isolated gastroepiploic, internal mammary, and radial arteries. *Anesth. Analg.* **2005**, *101*, 950–956. https://doi.org/10.1213/01.ane.0000172114.30383.23.
108. Fan, L.; Yang, Q.; Xiao, X.Q.; et al. Dual actions of cilnidipine in human internal thoracic artery: Inhibition of calcium channels and enhancement of endothelial nitric oxide synthase. *J. Thorac. Cardiovasc. Surg.* **2011**, *141*, 1063–1069. https://doi.org/10.1016/j.jtcvs.2010.01.048.
109. He, G.W.; Fan, L.; Furnary, A.; et al. A new antispastic solution for arterial grafting: Nicardipine and nitroglycerin cocktail in preparation of internal thoracic and radial arteries for coronary surgery. *J. Thorac. Cardiovasc. Surg.* **2008**, *136*, 673–680.e2. https://doi.org/10.1016/j.jtcvs.2007.12.019.
110. Zhang, Y.F.; Hou, H.T.; Yang, Q.; et al. Significant Antispastic Effect of Combined Fasudil and Isosorbide Dinitrate on Internal Mammary Artery in Coronary Artery Bypass Grafting. *Basic Clin. Pharmacol. Toxicol.* **2025**, *138*, e70148.
111. Zheng, S.Y.; Wu, M.; Huang, J.S.; et al. Use of antispastic nicardipine and nitroglycerin (NG) cocktail solution increases graft flow during off-pump coronary artery bypass grafting. *J. Cardiovasc. Surg.* **2012**, *53*, 783–788.
112. Yang, Q.; Xue, H.M.; Wong, W.T.; et al. AVE3085, an enhancer of endothelial nitric oxide synthase, restores endothelial function and reduces blood pressure in spontaneously hypertensive rats. *Br. J. Pharmacol.* **2011**, *163*, 1078–1085. https://doi.org/10.1111/j.1476-5381.2011.01308.x.
113. Xuan, C.; Chang, F.J.; Liu, X.C.; et al. Endothelial nitric oxide synthase enhancer for protection of endothelial function from asymmetric dimethylarginine-induced injury in human internal thoracic artery. *J. Thorac. Cardiovasc. Surg.* **2012**, *144*, 697–703. https://doi.org/10.1016/j.jtcvs.2012.01.020.
114. Wei, W.; Chen, Z.W.; Yang, Q.; et al. Vasorelaxation induced by vascular endothelial growth factor in the human internal mammary artery and radial artery. *Vascul Pharmacol.* **2007**, *46*, 253–259. https://doi.org/10.1016/j.vph.2006.10.009.
115. Hou, H.T.; Wang, J.; Zhang, X.; et al. Endothelial nitric oxide synthase enhancer AVE3085 reverses endothelial dysfunction induced by homocysteine in human internal mammary arteries. *Nitric Oxide* **2018**, *81*, 21–27. https://doi.org/10.1016/j.niox.2018.10.001.