REVIEW

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Left Internal Mammary Artery as an Endocrine Organ: Insights Into Graft Biology and Long-term Impact Following Coronary Artery Bypass Grafting

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Abstract

The left internal mammary artery (LIMA) is considered the criterion standard vessel for use in coronary artery bypass grafting. In recent decades, countless studies have documented its superiority over other arterial and venous coronary artery bypass grafting conduits, although the full mechanisms for this superiority remain unknown. A growing body of literature has unveiled the importance of extracellular vesicles known as exosomes in cardiovascular signaling and various pathologic states. In this review, we briefly compare the clinical longevity of the LIMA relative to other conduits, explore the effects of varying grafting techniques on clinical and angiographic outcomes, and provide physiologic insights into graft function on a cellular and molecular level. Finally, we explore exosome signaling as it pertains to atherosclerosis in support of the LIMA as an "endocrine organ."

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Coronary artery bypass graft (CABG) surgery has revolutionized the treatment of patients with coronary artery disease since its initial description in the 1950s. Early experience utilized the left internal mammary artery (LIMA) implanted directly into the left ventricular myocardium (Vineberg procedure).[1] Although there was early enthusiasm for this approach, it was never effective in relieving ischemia and subsequently became obsolete.[2] During this early phase, saphenous vein grafts (SVGs) became the standard of care because they were more easily obtainable and had excellent flow initially. Eventually, the LIMA made a resurgence and became widely used as a direct coronary implant, bypassing coronary occlusions upstream. Even today, combination procedures with a LIMA to the left anterior descending artery (LAD) and SVGs to other ischemic territories remain the standard of care. Irrefutable information has been gained about the longevity of LIMA arterial grafts compared with venous bypass grafts. Numerous studies have documented improved short- and long-term graft patency (97% vs 82% at 18 months and 87% to 96% vs 55% to 73.6% at 10 years) as well as clinical outcomes (mortality, myocardial infarction, reoperation, need for percutaneous intervention) when using a LIMA compared with an SVG,[3-7] with generally accepted 10-year patency of 95% for the LIMA. Several landmark trials in the early 2000s, namely the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) study[8] and the SoS (Stent or Surgery) trial,[9] further documented that CABG was superior to percutaneous coronary intervention (PCI) in patients with multivessel coronary artery disease in terms of the need for repeated revascularization, myocardial infarction, and all-cause mortality. By 2004, guidelines from the joint American College of Cardiology and American Heart Association indicated CABG as the preferred treatment for disease of the left main coronary artery, severe

triple-vessel disease, and diffuse disease that is not amenable to treatment with PCI.[10] Currently, LIMA remains the graft of choice owing to its excellent clinical performance, although the high prevalence of multivessel disease necessitates the use of adjunct grafts such as SVGs or other arterial conduits.

Although the clinical superiority of the LIMA as a coronary graft is well established, the scientific reasons for this superiority remain unclear. This article focuses on the vascular biology of the LIMA, the effects of its implantation on downstream vessels, and the potential future applications for designing arterial grafts.

COMPARISON ACROSS ARTERIAL GRAFTS

The LIMA (or left internal thoracic artery) as a criterion standard is an in situ LIMA (is-LIMA) that requires only one anastomosis at the site of the coronary artery, although it may also be used as a sequential graft. Certain circumstances, however—proximal internal mammary artery injury/stenosis or higher length requirement—may necessitate free grafting of the LIMA (f-LIMA). However, recent trials directly comparing is-LIMA with f-LIMA documented significantly higher rates of graft failure (stenosis >75%) at 18 months in the f-LIMA group relative to the is-LIMA group (14.3% vs 0%[11]; 23.3% vs 8.5%[12]). It has been postulated that severing of the vasa vasorum, which supply blood to the LIMA, as well as denervation of the artery in the process of harvesting, may limit the ability of an f-LIMA to maintain appropriate blood supply and autoregulation, contributing to its long-term failure.[13] Similar preservation of the vasa vasorum has been associated with improved patency within SVGs as well,[14] highlighting its role in preserving graft function.

The right internal mammary artery (RIMA)/right internal thoracic artery has a similar structure and function compared with the LIMA, although its origination from the right subclavian artery increases technical complexity and possible risk of deep sternal wound infections, thereby limiting its use in CABG. Recent studies have indicated no significant difference in the conduit patency between in situ RIMA and is-LIMA grafted onto the LAD during a mean 3-year follow-up (95.0% to 97.2% vs 96.6% to 97.4%, respectively).[15,16] A longer-term study documented slightly diverging results following a 17-year follow-up (85% for RIMA vs 92% for LIMA),[17] suggesting possible inherent differences between RIMA and LIMA grafts. Not surprisingly, a recent meta-analysis of 29 studies encompassing nearly 90,000 patients revealed that the use of bilateral internal mammary arteries during CABG enhances 10-year survival relative to grafting with LIMA and saphenous veins (hazard ratio, 0.78),[18] presumably due to enhanced long-term patency of internal mammary arteries relative to saphenous veins. Although bilateral internal mammary artery grafting was associated with a mild increase in deep sternal wound infections, improvements in long-term overall and cardiovascular event-free survival outweighed this marginal risk.[18]

In the early 1970s, Carpentier et al[19] and Edwards et al[20] introduced the radial artery (RA) and the right gastroepiploic artery (GEA), respectively, as analogous conduits for use during CABG, with each requiring a separate minimally invasive operation for harvesting. Long-term (8- to 10-year) patency rates of GEA grafts have ranged from 70.2% to 90.2%,[21-23] still inferior to those seen with LIMA grafts. Similarly, RA grafts have a wide range of patency rates at 9 to 10 years (79.2% to 91.6%).[24-29] However, in patients presenting with acute myocardial ischemia, the RA patency rate at 5 years was reported to be considerably lower (51% to 73%).[30-32] Importantly, the vasa vasorum of both the GEA and RA grafts are fully severed during surgical harvesting, which may partially contribute to their lower long-term patency rates, akin to the differences across f-LIMA and is-LIMA. It should be noted that morphologic parameters, including target vessel territory and diameter and the degree of stenosis, can strongly influence the long-term graft patency, with

occlusion odds ratios as high as 3, depending on the prespecified cutoffs.[24]

A landmark study termed RAPCO (Radial Artery Patency and Clinical Outcomes) completed in 2015 reassessed the efficacy of RA grafting and documented clear superiority over RIMA and SVG, with 10-year patency rates of 85% to 89%.[33] In part due to these results and its relative ease of harvest from the arm, the RA received class IA recommendations for use as a second conduit for CABG according to the 2018 ESC/EACTS (European Society of Cardiology/European Association for Cardio-Thoracic Surgery) guidelines.[34] Still, in 2021 a report by the Society of Thoracic Surgeons showed that fewer than 5% of patients with CABG received an RA as a second arterial conduit.[35] Two main reasons have been suggested to explain such low use. First, there are several circumstances in which the RA cannot be harvested, such as anatomic variations with high birth or termination, diffuse calcinosis/vasculitis, recent (<3 months) angiography via radial access, arteriovenous fistula involving the RA, insufficient ulnar artery compensation, or posttraumatic RA injury.[35] Secondly, and perhaps more profoundly, until very recently, there remained limited objective data comparing long-term effects of multiple vs single arterial grafts. Similar to the Society of Thoracic Surgeons data, a recent large Canadian study (almost 50,000 enrolled patients) found that total arterial revascularization was performed rarely (4.9% of CABG cases) but was associated with improved long-term (9-year) cardiovascular outcomes, although graft patency rates were not assessed.[36] A recently launched clinical trial (Randomization of Single vs Multiple Arterial Grafts [ROMA]) is designed to address this question and is estimated to be completed by 2030.

COMPOSITE AND SEQUENTIAL GRAFTS

Several modifications to standard surgical grafting techniques have been proposed to improve long-term clinical and graft outcomes. First, a sequential grafting method can increase the number of epicardial coronary targets receiving the bypassed flow. Initial studies using sequential grafting of the LIMA (generally to the diagonal artery followed by the LAD) produced varying results, with similar overall graft patency rates relative to nonsequential LIMA grafts, albeit with some evidence of decreased flow at the distal sequential anastomosis.[37-40] When utilizing this method for the RA, it was noted that a sequential side-to-side anastomosis maintained 100% patency at 10 years (compared to 88.7% of end-to-side anastomoses), again highlighting the potential utility of the RA in total arterial grafting.[41]

A second approach involves composite grafting, either via a T- or Y-graft (end-to-side anastomosis) or serial graft (end-to-end anastomosis) of free bypass grafts (RA, GEA, saphenous vein, or RIMA) to an is-LIMA prior to reaching the distal coronary targets. Early studies with LIMA-RA and LIMA-RIMA Y-composite grafts revealed excellent early (2- to 36-month) patency rates (93% to 98.1%)[15,42,43] with improved long-term (10-year) survival rates relative to standard LIMA-saphenous vein (noncomposite) grafts in larger studies.[44,45] In the recent SAVE-RITA (Saphenous Vein Versus Right Internal Thoracic Artery) trial, SVGs were directly compared with the RIMA for use in LIMA Y-grafts and were found to have noninferior patency rates at 1 year (97.9%)[46] and 10 years (94.9%),[47] albeit with small sample size (100 to 200 patients). However, despite promising results with composite Y-grafts, there remains concern about the adequacy of a single bypass for multiple coronary territories and compromised blood flow to the LIMA-LAD, as well as the effects of competitive flow on graft longevity.[48] Alternatively, serial grafts can be utilized when a full-length LIMA is unavailable due to severe left ventricular enlargement, difficulty/injury in LIMA harvesting, or calcification of the middle/distal LIMA causing blood flow restriction. A recent study using a LIMA + SVG anastomosed to the LAD documented no increase in major adverse cardiac events or mortality at 5 years relative to the standard LIMA-LAD

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approach.[49] Furthermore, the LIMA + SVG exhibited 94% patency rates at 25 months, comparable to standard LIMA-LAD grafts and approximately 10% higher than matched aortocoronary SVGs, believed to be, in part, due to excess LIMA-derived nitric oxide (NO),[49] although the exact mechanisms remain unknown.

EFFECT OF REVASCULARIZATION ON NATIVE ATHEROSCLEROSIS

Although the differences in graft patency and clinical outcomes based on graft type are well documented, considerably less is known regarding the effect of revascularization on native vessel atherosclerosis. A recent study found that arterial grafts (LIMA, RAs) protect native coronary vessels from atherosclerotic disease progression by as much as 5-fold over 10 years relative to SVGs.[50] Post-hoc analysis of the MASS (Medicine, Angioplasty, or Surgery Study) II trial indicated a significant decrease in disease progression in the LAD when a LIMA graft is used compared with an SVG.[51] In comparison with PCI to the LAD, revascularization with a LIMA carries a significantly lower risk of not only conduit disease progression (hazard ratio, 0.18 to 0.27) but also downstream coronary disease progression (hazard ratio, 0.34 to 0.39), with no significant benefit noted in the latter between bare metal stents and drug-eluting stents.[52] These studies further suggest that the improved patient outcomes with LIMA grafting likely stem from a combination of improved graft patency as well as decreased atherosclerosis progression, preventing future adverse events. Corroborating this apparent "endocrine function," numerous case reports have revealed coronary plaque regression following a LIMA graft to the LAD, with occasional near-complete resolution of visible plaque.[53-55] In contrast, no similar reports have been documented for SVGs, and only modest decreases in atherosclerotic plaque volume and total atheroma volume (1% to 10%) have been observed with intense lipid-lowering therapy (achieved low-density lipoprotein cholesterol level of 60 to 70 mg/dL [to convert value to mmol/L, multiply by 0.0259]).[56-58] As such, LIMA grafting appears to achieve antiatherosclerotic effects beyond those achieved by optimized medical management. Deconvolution of the molecular cues the LIMA graft provides to the coronary artery would provide new insights into novel and potentially curative technologies to reverse coronary artery disease.

PHYSIOLOGIC INSIGHTS INTO GRAFT FUNCTION

It is well established that the LIMA and saphenous veins, although sharing several functional and structural properties, exhibit crucial anatomic and physiologic differences.[59,60] Both the internal mammary arteries and saphenous veins consist of a tunica intima, media, and adventitia, with smooth muscle cells (SMCs) within the tunica media and a layer of endothelial cells (ECs) lining the lumen of the vessel. The endothelium of the LIMA contains significantly less fenestrations compared with that of saphenous veins, which may prevent the extravasation of lipoproteins and subsequent atherogenesis. Unsurprisingly, SVGs become exposed to substantially higher levels of shear stress following a CABG. In this process of "arterialization," it is believed that endothelial injury leads to rapid neointimal growth from infiltration of SMCs, proteoglycan, and type I/III collagen, triggering the higher proclivity toward luminal stenosis.[60] Such atherosclerotic changes have been observed as early as 13 months after CABG, with the development of a necrotic core and foam cell accumulation between 1 and 3 years.[60] Ex vivo perfusion cultures from SVGs revealed higher intimal and medial cell proliferation relative to those obtained from the LIMA.[61] In addition to the higher levels of shear stress, SVGs are exposed to higher transluminal pressures relative to their native state. Interestingly, high-pressure distention during preparation of SVGs has been shown to induce a pressure-dependent up-regulation of several biomarkers, including platelet EC adhesion molecule and vascular cell adhesion molecule, both of which are central in

TABLE. Gene Expression and Proteomic Differences Across CABG Conduits

Reference, year	Pathway	Protein (*gene*)	CABG conduits compared	Results	Significance	Reference
Antoniades et al,[70] 2008	Vasoreactivity	GTP-cyclohydrolase I (*GCH1*)	LIMA and SV	LIMA expresses higher levels of *GCH1*	GCH1 regulates a cofactor for eNOS synthesis, leading to higher NO levels in LIMA	Antoniades et al[70]
Tadjkarimi et al,[71] 1992		cGMP	LIMA and SV	LIMA has increased levels of cGMP at baseline and if stimulated	Higher cGMP levels in LIMA lead to improved vasodilation	Tadjkarimi et al[71]
He et al,[72] 2011 Gaudino et al,[73] 2003		eNOS (*NOS3*)	LIMA, SV, and RA	LIMA expresses higher levels of eNOS	LIMA has higher levels of NO	He et al[72] Gaudino et al[73]
Wackenfors et al,[74] 2003		Endothelin receptor type A and B (*EDNRA*, *EDNRB*)	LIMA, SV, and coronary arteries	Endothelin receptors more highly expressed in SV	LIMA is relatively protected from endothelin-induced vasoconstriction	Wackenfors et al[74]
Subramanian et al,[75] 1986		Prostacyclin	LIMA and SV	LIMA produces higher levels of prostacyclin at baseline and if stimulated	Higher prostacyclin levels in LIMA reduce vasoconstriction and platelet aggregation	Subramanian et al[75]
Mangoush et al,[66] 2008 Schmalfuss et al,[76] 1999	Oxidative stress	SOD1 (*SOD1*)	LIMA and RA	LIMA demonstrates increased SOD activity	LIMA exhibits increased protection against oxidative stress	Mangoush et al[66] Schmalfuss et al[76]
Yang et al,[77] 1998 Turner et al,[78] 2007	Cell proliferation and migration	p42 MAPK1 *(MAPK1)*	LIMA and SV	SV shows increased sensitivity to PDGF with increased p42 MAPK1 protein levels	p42 MAPK1 activation via PDGF leads to increased cell proliferation in SVs relative to LIMA	Yang et al[77] Turner et al[78]
Del Rizzo et al,[79] 2002		c-Fos (*FOS*)	LIMA, SV, and RA	PDGF-induced expression of c-Fos is greatest in SV SMCs	Arterial conduits are more resistant to mitogenic effects of PDGF due to lower c-Fos expression	Del Rizzo et al[79]
Friedl et al,[80] 2004		TGF-β1 (*TGFB1*)	LIMA and SV	SV exhibits higher TGF-β1 expression	Increased TGF-β1 activity in SVs induces intimal hyperplasia	Friedl et al[80]
Zhu et al,[81] 2013		ECM-related genes (*COL4A4*, *COL11A1*, *FN1*, *TNC*, *THBS1*, *FBLN1*, *MMP3*,	LIMA and SV	SV SMCs have higher expression of ECM-related genes	SV SMCs have more migrating capacity	Zhu et al[81]

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TABLE. Continued

Reference, year	Pathway	Protein (*gene*)	CABG conduits compared	Results	Significance	Reference
		MMP9, *TIMP3*, *WNT5A*, *SGCD*)				
Mitra et al,[82] 2009 Sur et al,[83] 2014 Hata et al,[84] 2005		Phosphatase and tensin homologue deleted on chromosome 10 (*PTEN*)	LIMA and SV	*PTEN* activity is higher in LIMA SMCs	Absence of high *PTEN* levels in SV SMCs increases their proliferative capacity	Mitra et al[82] Sur et al[83] Hata et al[84]
Alattar et al,[85] 2014		Neuropilin 1 (*NRP1*)	LIMA and SV	SVs have higher NRP1 expression within adventitia	Higher levels of NRP1, a co-receptor for VEGF, within SV walls increases susceptibility to intimal hyperplasia development	Alattar et al[85]
Jia et al,[86] 2007		Cx43 (*GJA1*)	LIMA and SV	Angiotensin II and IGF-1 stimulates Cx43, which leads to higher SMC proliferation in SVs than LIMA	Growth factor–induced Cx43 expression leads to higher proliferation in SV SMCs	Jia et al[86]
Payeli et al,[87] 2008	Thrombosis	TF, tPA (*TF*, *PLAT*)	LIMA and SV	LIMA exhibits lower TF but higher tPA levels	Differential TF/tPA expression leads to longer clotting times and slower SMC migration in LIMA	Payeli et al[87]
Arishiro et al,[88] 2010	Inflammation	Cx43 (*GJA1*)	LIMA and RA	Cx43 correlates with NF-κβ in RA SMCs but not in LIMA SMCs	LIMA SMCs show decreased inflammatory response	Arishiro et al[88]
Li et al,[89] 2002	Atherosclerosis	oxLDL receptor-1 (*OLR1*)	LIMA, SV, and carotid arteries	oxLDL receptor-1 expression is increased in SV, carotid arteries, and atherosclerotic plaques	LIMA exhibits fewer oxLDL receptors, possibly protecting from atherosclerosis	Li et al[89]

CABG, coronary artery bypass graft; cGMP, cyclic guanosine monophosphate; Cx43, connexin 43; EMC, extracellular matrix; eNOS, endothelial nitric oxide synthase; IGF-1, insulin-like growth factor 1; LIMA, left internal mammary artery; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B; NO, nitric oxide; oxLDL, oxidized low-density lipoprotein; PDGF, platelet-derived growth factor; RA, radial artery; SMC, smooth muscle cells; SOD1, superoxide dismutase 1; SV, saphenous vein; TF, tissue factor; TGF-β1, transforming growth factor β1; tPS, tissue plasminogen activator; VEGF, vascular endothelial growth factor. For expansion of gene symbols, use search tool at www.genenames.org.

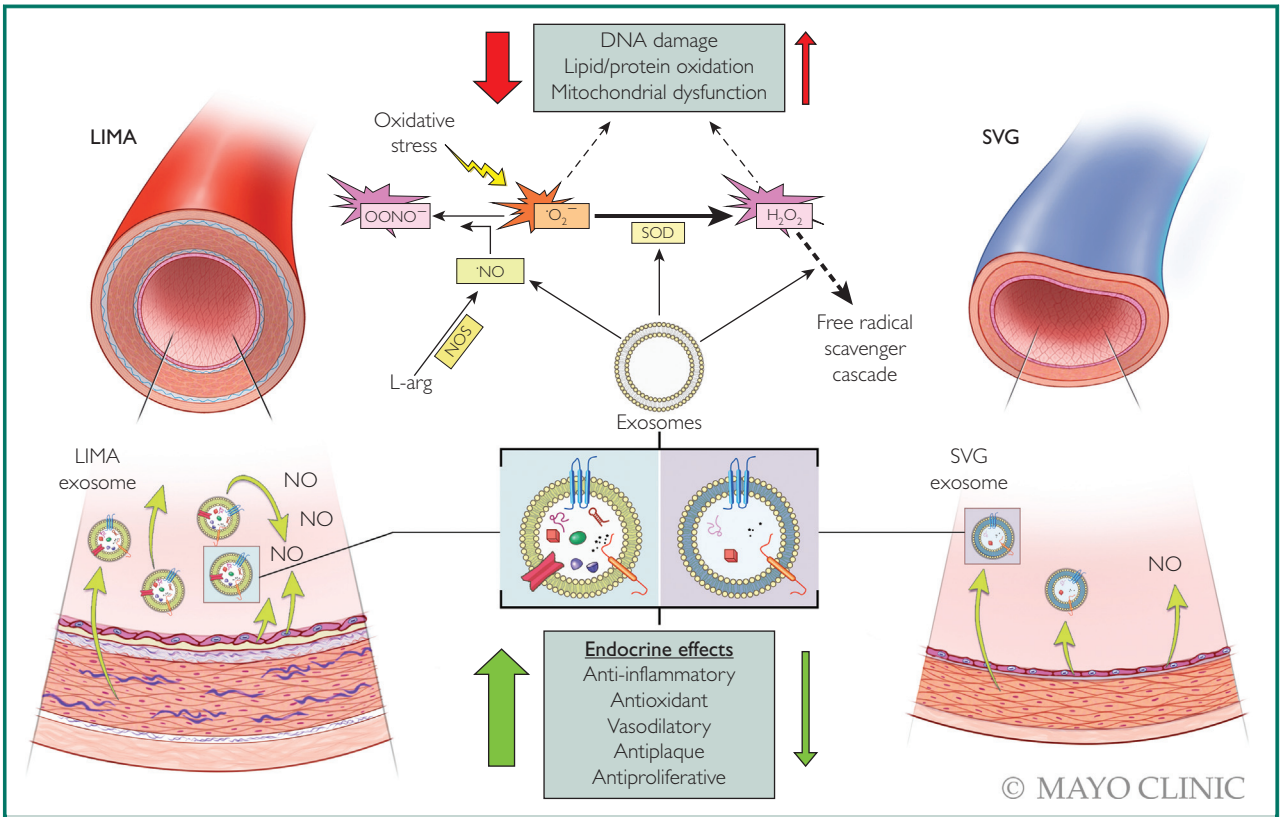

FIGURE. Proposed "endocrine" differences contributing to variable graft function among left internal mammary artery (LIMA) grafts and saphenous vein grafts (SVGs). The LIMA and SVGs are believed to secrete different types of exosomes containing microRNA, proteins, and other small molecules. Relative to those from SVGs, exosomes from the LIMA are thought to be rich in substances that induce nitric oxide (NO) production, scavenge free radicals via induction of super oxide dismutase (SOD), and reduce the proliferative effects of vascular smooth muscle cells. These combined actions lead to vasodilatory and anti-inflammatory effects that likely contribute to the enhanced longevity of LIMA grafts. L-arg, L-arginine.

recruitment of inflammatory cells and progression to atherosclerosis.[62] Because SVGs are subjected to high pressures both during the preparation and after grafting, such findings offer an additional explanation for increased atherogenesis in SVGs.

Across arterial grafts, the RA contains a higher proportion of SMCs and less elasticity relative to the LIMA, with increased endogenous expression of RhoA/Rho kinase pathway proteins that are responsible for its propensity toward vasospasm.[63] Additionally, comparative histopathology has documented that intimal hyperplasia, arteriosclerosis, and medial calcification are more likely to develop in the RA than in the LIMA.[64] Appropriately, the RA has a more robust increase in tension with application of vasoconstrictive agents (norepinephrine, potassium chloride, phenylephrine, and endothelin-1)[65,66] as well as the absence of histamine-induced relaxation[67] during in vitro testing, which although appropriate for its native anatomic location, could lead to reduced blood flow during states of systemic stress. Similarly, the GEA has been noted to have increased contractility relative to the LIMA in response to norepinephrine and angiotensin II, highlighting its propensity toward vasospasm like the RA,[68] although histamine-induced relaxation has been noted to be similar.[69] To our knowledge, no ex vivo studies have been performed analyzing the functional differences between innate LIMA and RIMA.

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DIFFERENCES IN GENOMIC AND PROTEOMIC PROFILES OF CABG CONDUITS

A number of studies have previously assessed the gene expression and proteomic differences across the SMCs and ECs comprising typical CABG conduits (Table[70-90]). Key differences in the expression of genes related to vasoreactivity, oxidative stress, cell migration and proliferation, inflammation, and atherosclerosis have been described across the various grafts.

Importantly, the LIMA and other vascular grafts differ in the activity of a key regulator of vessel wall homeostasis, NO. Nitric oxide is a gas that is continuously synthesized from the amino acid L-arginine by the constitutive calmodulin-dependent enzyme NO synthase within the ECs lining the vessel lumen. Stimulation of NO production is mediated predominantly via nonreceptor pathways (by shear stress from blood flow) with additional autocrine/paracrine signaling (from bradykinin stimulating endothelial B_2 kinin receptors). Subsequently, NO stimulates cyclic guanosine monophosphate production within nearby SMCs, causing vasorelaxation. Early studies indicated that relative to saphenous veins, the LIMA exhibits increased NO release,[91,92] NO-mediated protection from serotonin-induced constriction,[93] and uniquely NO-mediated vasodilation from exogenous L-arginine.[94] Collectively, other studies have indicated that the LIMA exhibits increased NO bioactivity and decreased propensity toward vasoconstriction due to differential protein expression (Table). NO is also instrumental in scavenging reactive oxygen species produced by oxidative stress, quenching superoxide ion O_2^- to form the less oxidizing $OONO^-$ (Figure) and thereby reducing O_2^--mediated DNA damage, lipid and protein oxidation, and mitochondrial dysfunction. To deal with oxidative stress, cells utilize the enzyme superoxide dismutase, which converts O_2^- into the less reactive H_2O_2, proceeding down the free radical scavenger cascade (Figure). Comparison studies have similarly documented increased activity of superoxide dismutase and related enzymes in LIMA explants relative to SVGs, conferring the LIMA with increased protection from oxidative stress and subsequent cellular damage (Table).

Among the other cardiovascular pathways, evidence has revealed extensive differences in the expression of mRNA and proteins involved in cellular migration and proliferation across CABG conduits. Typical mitogens such as platelet-derived growth factor B, angiotensin II, and insulin-like growth factor 1 result in higher activity and expression of key proliferative proteins such as p42 mitogen-activated protein kinase, c-Fos, neuropilin 1, transforming growth factor-β1, and certain matrix metalloproteinases in the SMCs of SVGs and RAs, increasing their propensity toward accelerated intimal hyperplasia (Table). Conversely, these pathways are markedly reduced within the SMCs of LIMA explants, leading to cellular quiescence and low levels of inflammation. Similarly, proteins involved in thrombosis (tissue factor) and the development of atherosclerotic plaques (oxidized low-density lipoprotein receptors) exhibit reduced expression in LIMA SMCs, decreasing the risk of eventual graft failure (Table) through plaque rupture or luminal stenosis.

ROLE OF EXOSOMES IN CARDIOVASCULAR SIGNALING

Outside the aforementioned differences on a genomic/proteomic level, relatively little is known about other secretory substances that differ across ECs and SMCs comprising the LIMA and saphenous veins. Recently, it has been discovered that nano-sized lipid vesicles known as exosomes are secreted by a variety of cell types and have been implicated in intercellular communication, angiogenesis, and numerous other cellular functions,[95] as well as protection in pathologic states such as ischemic reperfusion injury[96] and atherosclerosis.[97] Intriguingly, exosomes enriched in certain shear stress—induced microRNAs (miR-143/145) secreted by ECs have been reported to be protective against atherosclerosis.[98] Conversely, atherosclerotic conditions promote packaging of endothelial miRNA-92a-3p into exosomes, which are subsequently

transferred to neighboring ECs and promote intimal proliferation and cellular migration.[99] Studies have documented up-regulation (miR-21, miR-34a, miR-146a, miR-146b-5p, miR-210, miR-1273)[100,101] and down-regulation (miR-125a-5p, miR-155, miR-199a/b-3p, miR-221, miR-100)[101-103] of particular microRNAs within atheromatous plaques relative to the atheroma-free internal mammary arteries. A number of other microRNAs have been expressed differentially depending on the cell types associated with atheromatous plaques (leukocytes, vascular SMCs, ECs).[104] Of particular interest is miR-126, the most abundant microRNA in ECs, which is also highly expressed within exosomes. Studies have found that exosome-mediated transfer of miR-126 promotes EC repair in an electric denudation model of endothelium[105] and appropriately attenuates intimal hyperplasia in a rat model of vein graft disease.[106] A recent review compiled data on exosome-derived microRNAs from 92 studies, highlighting unique exosomal profiles based on cell lineages.[107] Interestingly, ischemic cardiomyocytes were noted to release exosomes containing miR-222/143, which subsequently promote angiogenesis.[108] Similarly, miR-217 from cardiac exosomes was found to promote pathologic cardiac hypertrophy and fibrosis by regulating phosphatase and tensin homologue deleted on chromosome 10,[109] a molecule previously noted to have higher activity in the LIMA relative to SVGs (Table). Other microRNAs such as miR-92a-3p from EC-derived exosomes, miR-342-5p from circulating exosomes, and miR-31 from adipose stem cell—derived exosomes have all been reported to protect the heart from ischemia, while EC exosome—derived MST1 and VCAM1 inhibit cell autophagy and regulate local inflammatory responses.[107,110] As such, it is likely that the increased longevity of LIMA grafts is secondary to specialized exosomes that deliver a crucial combination of vasodilatory and anti-inflammatory compounds such as NO, antioxidant, and antiatherogenic microRNAs and other antiproliferative proteins (Figure), which may also provide downstream atherosclerotic protection during composite grafting. However, the full exosomal or "endocrine" profile of vascular cells comprising the various CABG conduits (arterial vs venous) is currently unknown. Understanding of exosomal output from these different grafts will allow better characterization of their endocrine influence and potentially either allow, in the long-term, molecular editing of harvested grafts to ensure optimal performance following implant.

CONCLUSION AND FUTURE DIRECTIONS

Since the introduction of the LIMA in CABG, an overwhelming amount of evidence has documented its superiority over SVGs with respect to longevity and patency rates. Although other arterial grafts have been utilized with high success rates and have shown efficacy in halting progression of atherosclerosis, only the LIMA has thus far been associated with spontaneous regression of downstream atheromatous plaques. Numerous molecular pathways related to inflammation, cell proliferation and migration, thrombosis, and vasodilation have been implicated in the success of LIMA grafting. The collective proteome and microRNA content within this unique tissue likely provides inherent and downstream perfusion benefit through antiproliferative, anti-inflammatory, antioxidant, and vasodilatory cues. Understanding of the protective secretory profile germane to the vascular cells comprising the LIMA in relation to other surgical conduits serves to unlock new opportunities in the development of platforms to reverse coronary artery disease. With the emergence of 3D printing, genetic engineering, and other nanotechnologies, it may be possible to synthetically mimic the endocrine function of the LIMA, thereby creating an "off-the-shelf" conduit (and potentially modified drug-eluting stents) that provides maximal beneficial properties to the diseased coronary vessels.

POTENTIAL COMPETING INTERESTS

Dr Behfar has been a member of the board and received grants and royalties from Rion LLC, has patents from Cardio3 Biosciences and Rion LLC, and has stock in Rion LLC, Deverra Therapeutics, and Sorrento Therapeutics, Inc. The other authors report no competing interests.

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Abbreviations and Acronyms: **CABG,** coronary artery bypass graft; **EC,** endothelial cell; **f-LIMA,** free grafting of the left internal mammary artery; **GEA,** gastroepiploic artery; **is-LIMA,** in situ left internal mammary artery; **LAD,** left anterior descending artery; **LIMA,** left internal mammary artery; **NO,** nitric oxide; **PCI,** percutaneous coronary intervention; **RA,** radial artery; **RIMA,** right internal mammary artery; **SMC,** smooth muscle cell; **SVG,** saphenous vein graft

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