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EDITORIAL

The LIMA: A Drug-Eluting Graft and Coronary Flow Shock Absorber

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The primary challenge of coronary artery bypass graft (CABG) surgery is the durability of graft patency. Patients with failed grafts experience an overall higher clinical event rate, with graft failure to the left anterior descending territory being the most detrimental.[1] Aside from anastomotic technical issues, multiple mechanisms contribute to graft failure. They include patient-related risk profile, graft—coronary artery flow mismatch, target vessel anatomic features, hemodynamic factors, hypercoagulability, and biologic mechanisms involved in plaque formation and atherosclerosis progression.[2] Among different bypass conduits, the superiority of the left internal mammary artery (LIMA) as a vascular graft to restore blood supply in the coronary circulation has long been established. The superior durability of LIMA in terms of long-term patency and coronary flow supply compared with other conduits routinely used in CABG, such as the radial artery or the saphenous vein (SV), has historically been attributed to its specific structural attributes and mechanical properties. Differences in endothelial cell function, extracellular matrix composition (eg, a relatively higher elastin content), or cellular arrangement in the tunica media appear to equip the LIMA to be better adapted in enduring the mechanical forces triggered by flow shear stress and wall strain of the coronary flow dynamics and pulsatility. In this issue of *Mayo Clinic Proceedings*, Shadrin and colleagues[3] assemble a comprehensive review on biologic and functional differences in graft conduits for CABG. They are to be congratulated for providing a visionary and balanced revision of the current knowledge, providing physiologic and biologic insights on graft function as well as novel insights on genomic and proteomic profiles of graft conduits; such "omic" profiling enables the development of novel therapeutic strategies. These authors postulate that in addition to superior passive mechanical characteristics, the LIMA displays active biologic function. They describe this as an "autocrine" function that is related to secretion of bioactive molecules such as nitric oxide and the production of endothelial cell—derived microparticles. In particular, they highlight the potential role of specialized exosomes carrying a crucial cargo of combined vasodilatory, antioxidant, and other biologically active molecules, including microRNAs with antiproliferative and antiatherosclerotic properties. These biologic functions are the foundation for high long-term LIMA patency rates and may further have an impact on downstream vessel properties, instigating the regression of coronary atherosclerosis. As an example, in case of composite SV-LIMA grafts, such autocrine activity may possibly prevent postgrafting degeneration of the vein conduit because of improved flow dynamics.[4] Although these intriguing hypotheses are mainly based on clinical observations in patients undergoing CABG surgery,[5] of considerable interest are the specific molecular signals that are released by LIMA conduits to the downstream vasculature.[6] As the authors themselves point out, the analysis of the exosomal output is essential for a better characterization of the LIMA endocrine function, potentially allowing its molecular editing, ensuring long-term performance and patency. As suggested recently,[7] this goal could ideally be achieved by employing a systematic approach realized with modern molecular methods (omics) combined with disease modeling approaches.

A first approach to assess the exosomal graft output and role of LIMA as a drug-eluting graft—the LIMA may be considered a drug-eluting graft—may be by

deciphering the molecular profile of the microparticles released under flow conditions that mimic the coronary circulation. Because the LIMA obtained from patients is often not amenable to be used routinely as research material, arteries from animals (eg, pigs) could be employed to measure the release of endothelial cell–derived nanoparticles and microRNAs using, for example, real-time polymerase chain reaction or sequencing methods. The employment of bioreactors simulating the coronary circulation[8] could then be useful to assess the role of variable flow/pressure patterns on the release of these signals, either under ideal working conditions or simulating variable levels of competitive flow experienced by the graft under real implanting conditions, as already assessed in large-animal models.[9] In addition to investigating the variation in the "endocrine" function of the LIMA in response to changes in the flow/pressure pattern or to competitive flow, this approach could also be used to investigate the molecular and structural changes of the LIMA itself. Indeed, mechanical signaling may play a major role in the pathologic differentiation of vascular grafts (ie, the SV), where the wall strain imposed by the sudden shift from venous to coronary circulation plays an important role in activation and recruitment of adventitial cells prone to differentiate into smooth muscle cells underlying neointima accumulation.[10] In such an experimental setting, new mechanically regulated molecular targets may be uncovered in addition to conventional tissue analysis by using next-generation omics techniques. Of interest is single-cell/single-nuclei RNA sequencing that delineates the transcriptome of individual cell types characterized on the basis of phenotype-specific markers.[11] These analyses could finally be complemented by adoption of targeted/untargeted proteomics to assess the variation of the extracellular matrix composition during flow/pressure-dependent remodeling.[12]

Other than its drug-eluting graft role as a potential endocrine regulator of downstream vasculature homeostasis, the LIMA may also function as a flow/pressure "shock absorber," especially when LIMA conduits are employed in composite grafts upstream of the SV graft, preventing neointima accumulation in the venous segment. In this regard, the review in this issue of *Mayo Clinic Proceedings* appropriately discusses the possibility that molecular signals such as nitric oxide or beneficial miRNAs transferring from the LIMA to the SV segment could improve the poor flow dynamics of the SV on the basis of their biochemical or molecular effects. Whereas this is in line with the conclusions of the original article cited in support of this hypothesis,[13] one may also speculate that the compliance of LIMA conduits placed upstream of the SV grafts could in part absorb the high level of wall strain generated by the coronary circulation. This hypothesis is in agreement with the reported characteristics of the wall strain stress in LIMA vs SV grafts based on computational flow dynamics[4] and could be explored, again, with systematic approaches achieved with bioreactors and high-throughput molecular profiling.

In summary, the article by Shadrin and colleagues highlights the existence of biologic roles of the LIMA as an effector of CABG remodeling. In addition to stimulating the investigation of the nature and timing of these signals, this article unveils new perspectives for ex vivo CABG conditioning, notably the SV graft, whose durability is far shorter than that of LIMA, to reduce short- and long-term SV graft degeneration.

POTENTIAL COMPETING INTERESTS

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