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Therapeutic Neovascularization for Refractory Angina—Are We Any Closer?

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Angina (Latin *ango*, to press tightly or strangle) is the hallmark symptom of ischemic heart disease and, as the etymology reflects, can be extremely debilitating. The cornerstones of angina management are maximization of medical therapy and attempts at complete revascularization, often at great lengths. For example, chronic total occlusion percutaneous coronary intervention is often pursued for anginal relief despite a limited effect on major adverse cardiac events (MACE) in randomized controlled trials (RCTs).[1] Unfortunately, despite major advancements in revascularization techniques and pharmacotherapy over the past several decades, a significant number of patients continue to experience refractory angina (RA). Additionally, as survival continues to improve, the prevalence of RA is on the rise and warrants further attention.[2]

Although RA is often attributed to epicardial coronary artery disease not amenable to surgical or percutaneous revascularization, an important shift in the understanding of RA relates to the additional role of microvascular dysfunction in perpetuating this disease process.[3] This is highlighted by the persistence of angina in some patients despite successful elimination of all hemodynamically significant epicardial coronary lesions and by the presence of angina in some patients with normal epicardial coronary arteries. This understanding has fueled the development of novel interventional and biologic approaches aimed at improving myocardial blood flow independent of epicardial vessels. These have included transmyocardial laser revascularization, cardiac shockwave therapy, stem cell therapy, and proangiogenic growth factor therapy.[2] Each of these approaches has shown promise in preclinical models to promote neovascularization and reduce ischemia, albeit with efficacy limitations in clinical trials which have hindered their adoption into practice thus far.[4] That being said, neovascularization addresses the fundamental pathophysiology of RA and, thus, justifies ongoing efforts to identify optimal therapeutic strategies.

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Proangiogenic growth factor therapy, in particular, is appealing for its potential to directly stimulate blood vessel growth. In this issue of *JSCAI*, Weeraman et al[5] performed the first meta-analysis of RCTs evaluating the effect of proangiogenic growth factor therapy in patients with RA ineligible for revascularization. A total of 16 RCTs were included, conducted between 2001 and 2017, using vascular endothelial growth factor (VEGF) or fibroblast growth factor delivered as recombinant proteins or through gene therapy. Pooled outcomes were all-cause mortality, MACE, myocardial perfusion, Canadian Cardiovascular Society (CCS) angina class, and exercise tolerance. Subgroup analyses were performed for delivery method, vector, and protein type. Special attention was given to risk of bias, with 2 RCTs deemed high risk because of lack of blinding. The results of the meta-analysis showed that proangiogenic growth factor therapy was safe and significantly reduced MACE and CCS class compared with the control but did not significantly reduce all-cause mortality. In addition, there was no effect of these treatments on exercise tolerance. Finally, myocardial perfusion was shown to be significantly improved only in studies that used positron emission tomography for this assessment but not in those that used single-photon emission computed tomography. Subgroup analysis was limited by large differences in sample size but pointed toward a significant reduction in MACE with the intracoronary delivery route. No differences in MACE were appreciated between vector types (plasmid vs adenoviral) or growth factors (VEGF vs fibroblast growth factor).

Despite limitations common to many meta-analyses, such as heterogeneity and variable follow-up durations, the results of this study are encouraging and demonstrate a beneficial signal for proangiogenic growth factor therapy that was not previously appreciated in individual RCTs. Notably, most of these RCTs were placebo-controlled and double-blinded, which minimizes the potent placebo effect that was largely at play in early trials of transmyocardial laser revascularization, for example.[6] Moreover, this meta-analysis raises several important questions, perhaps one of the most interesting being the reason for lack of improvement in exercise tolerance despite improvement in MACE and CCS class. Should an improvement in this key functional outcome not also accompany neovascularization? We believe that this question, at heart, relates to the specific biological processes being induced by these growth factors. The term angiogenesis is frequently used to denote new blood vessel growth, but angiogenesis is one of several types of neovascularization and refers specifically to the sprouting of new capillaries from existing postcapillary venules. These nascent capillaries, initially quite fragile, are not as adaptable to physiologic increases in blood flow demand, which may limit their functional effect.[7] Moreover, without connecting to larger conduit vessels, such capillary networks may not have the capacity to substantially improve myocardial oxygen delivery, especially during exercise. Accordingly, it may be particularly important that biological therapies stimulate other types of neovascularization such as arteriogenesis and vasculogenesis. Arteriogenesis refers primarily to the maturation of existing collateral arteries in response to changes in shear forces that accompany flow-limiting lesions, which typically results in more competent vasculature that is able to restore and sustain blood flow to a greater degree.[7] Notably, arteriogenesis typically results in collateral vessel growth that can be visualized angiographically, as opposed to an increase in capillary density alone. Vasculogenesis refers to de novo formation of vessels from progenitor cells, as in during embryonic development or in response to CD34-selected stem

cell therapy.[8] Current proangiogenic gene therapies target a combination of angiogenesis and arteriogenesis to varying degrees depending on the combination of growth factor isoform, dose, and mode of delivery.[9] Therapeutic strategies that place importance on arteriogenesis may have better success in improving functional outcomes and quality of life for patients.

The field of proangiogenic gene therapy has come a long way. Although key mechanistic, technical, and methodological questions remain, progress continues to be made. Indeed, the heightened appreciation for the role of different growth factor isoforms in activating distinct biological processes has paved the way for the EXACT trial—a phase I/II trial evaluating the safety and efficacy of a novel adenoviral vector expressing 3 synergistic isoforms of VEGF, which was shown in preclinical testing to have a more potent and physiologic angiogenic response when compared with single isoforms of VEGF.[10] Outstanding questions relate to the optimal choice of gene vector and route of delivery, clinical trial design and end point evaluation, and optimal patient selection. Perhaps, more important are questions related to the use of gene therapy to induce growth of a robust vasculature able to deliver substantial amounts of flow to myocardium that would otherwise become ischemic during exercise. Nevertheless, with an abundance of data and experiences from the past 2 decades to build on, the field is certainly closer to answering these questions and, better yet, to clinical success.

Declaration of Competing Interest

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References

1. Brilakis ES, Mashayekhi K, Tsuchikane E, et al. Guiding principles for chronic total occlusion percutaneous coronary intervention. Circulation. 2019;140(5):420–433. 10.1161/CIRCULATIONAHA.119.039797 [PubMed: 31356129]
2. Povsic TJ, Henry TD, Ohman EM. Therapeutic approaches for the no-option refractory angina patient. Circ Cardiovasc Interv. 2021;14(2), e009002. 10.1161/CIRCINTERVENTIONS.120.009002 [PubMed: 33541098]
3. Kaski J-C, Crea F, Gersh BJ, Camici PG. Reappraisal of ischemic heart disease. Circulation. 2018;138(14):1463–1480. 10.1161/CIRCULATIONAHA.118.031373 [PubMed: 30354347]
4. Lantz R, Quesada O, Mattingly G, Henry TD. Contemporary management of refractory angina. Interv Cardiol Clin. 2022;11(3):279–292. 10.1016/j.iccl.2022.03.002 [PubMed: 35710283]
5. Weeraman D, Jones DA, Hussain M, et al. Pro-angiogenic growth factor therapy for the treatment of refractory angina: a meta-analysis. J Soc Cardiovasc Angiogr Interv. 2023;2(1):100527
6. Leon MB, Kornowski R, Downey WE, et al. A blinded, randomized, placebo-controlled trial of percutaneous laser myocardial revascularization to improve angina symptoms in patients with severe coronary disease. J Am Coll Cardiol. 2005;46(10):1812–1819. 10.1016/j.jacc.2005.06.079 [PubMed: 16286164]
7. Simons M Angiogenesis. Circulation. 2005;111(12):1556–1566. 10.1161/01.CIR.0000159345.00591.8F [PubMed: 15795364]
8. Iwasaki H, Kawamoto A, Ishikawa M, et al. Dose-dependent contribution of CD34-positive cell transplantation to concurrent vasculogenesis and cardiomyogenesis for functional regenerative recovery after myocardial infarction. Circulation. 2006; 113(10):1311–1325. 10.1161/CIRCULATIONAHA.105.541268 [PubMed: 16534028]

9. Asahara T, Bauters C, Zheng LP, et al. Synergistic effect of vascular endothelial growth factor and basic fibroblast growth factor on angiogenesis in vivo. Circulation. 1995;92(9):365–371. 10.1161/01.CIR.92.9.365

10. Povsic TJ, Henry TD, Ohman EM, et al. Epicardial delivery of XC001 gene therapy for refractory angina coronary treatment (the EXACT trial): rationale, design, and clinical considerations. Am Heart J. 2021;241:38–49. 10.1016/j.ahj.2021.06.013 [PubMed: 34224684]