Editorial

Prevention and Recovery of Hibernating Myocardium by Microvascular Repair

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“From small things, big things one day come.”
——Bruce Springsteen

Coronary artery disease, ischemic cardiomyopathy, and congestive heart failure continue to confer significant morbidity and mortality despite advances in medical therapy, percutaneous coronary interventions, and surgical revascularization. This unmet clinical need is the rationale for novel therapeutic strategies like therapeutic angiogenesis. Unlike traditional revascularization, which focuses on macrovascular solutions, angiogenesis seeks to improve the microcirculation by stimulating new capillary and collateral arterial vessel formation. Recently, there has been significant discussion on traditional revascularization, in particular the benefit of revascularization with coronary artery bypass surgery (CABG) in patients with left ventricular (LV) dysfunction in the Surgical Treatment for Ischemic Heart Failure (STICH) Trial. As opposed to mechanical revascularization, whether by CABG or percutaneous coronary intervention, therapeutic angiogenesis has the advantage of improving coronary microcirculation by harnessing existing physiological processes to address a biological problem.

A variety of strategies to promote therapeutic angiogenesis have been investigated, including delivery of proangiogenic genes, growth factors, and autologous stem cells aspirated or mobilized from the bone marrow or peripheral blood. These various approaches have demonstrated promising results in the treatment of organ-specific manifestations of systemic atherosclerosis, including peripheral artery disease, refractory angina, and ischemic cardiomyopathy, particularly in animal models and early human clinical trials of cell-based therapies. However, some of the larger therapeutic angiogenesis clinical trials using individual growth factors have not corroborated the exciting early results, indicating that additional work is necessary to determine the ideal agent(s) and delivery mechanism(s) to maximize efficacy and durability of the intervention while limiting off-target effects of angiogenesis. Additionally, thoughtful trial design and selection of end points that reflect the physiology of therapeutic angiogenesis and improve in the coronary microcirculation such as measurement of coronary flow reserve will be critical to moving the field forward.

In the current issue of Circulation, Banquet et al present a novel strategy of therapeutic angiogenesis for the prevention of ischemic cardiomyopathy and congestive heart failure after myocardial infarction (MI). Their aim was to identify novel synergistic combinations of angiogenic growth factors and to optimize delivery of these agents via a spatiotemporally controlled slow-release delivery system. They first demonstrated that the combination of fibroblast growth-factor-2 (FGF-2) and hepatocyte growth factor (HGF) synergistically stimulated endothelial cell and smooth muscle cell migration and proliferation in vitro in a murine heart microvascular endothelial cell model. This was corroborated in an in vivo corneal angiogenesis assay model, with more durable and extensive vascular networks at 1 year in corneas implanted with the combination of FGF-2 and HGF compared with either agent alone. They next designed an injectable growth factor delivery system using alginate capsules stabilized by albumin. This was optimized to release the 2 growth factors in a staged fashion, with FGF-2 release occurring immediately followed by HGF release 1 week later. Delivery in the slow-release system was found to be 3 to 6 times more potent compared with naked introduction of the identical growth factors in a mouse Matrigel plug in vivo model. Again, the combination of FGF-2 and HGF via this microcapsule delivery system synergistically outperformed either agent alone in terms of vascular density, vascular maturity, and vascular area in both in vitro and in vivo models.

Finally, intramyocardial delivery and optimized slow release of FGF-2 and HGF were evaluated in a rat model of myocardial infarction. Microcapsules containing FGF-2 plus HGF, FGF-2 alone, HGF alone, or placebo were injected along the infarct border zone in rats immediately after coronary artery ligation (n=102) or sham surgery (n=11). Rats were euthanized at 1 or 3 months and immunohistochemistry was performed. Monotherapy with FGF-2 resulted in increased vessel density compared with controls at 1 month, but the benefit was attenuated at 3 months. Conversely, HGF monotherapy effects were found to be most pronounced later at 3 months. Combination therapy was the most potent, with an early and sustained increase in vascular density and decreased cardiac collagen content. Magnetic resonance imaging at 3 months demonstrated increased cardiac perfusion localized to areas treated with FGF-2/HGF microcapsules but not in the FGF- or HGF-treated animals. These findings raise questions about the dosing of the single agents; prior reports in preclinical models have documented the efficacy of both FGF-2 and HGF. Echocardiography
revealed improved LV size and systolic function in the combination and FGF-2 groups. In light of the lack of finding of improved perfusion in the FGF-2 alone group, the improvement in LV function is more challenging to put into context. In vitro and in vivo studies provide evidence for activation of phospho-Akt and phospho–mitogen-activated protein kinase signaling pathways and increased expression of growth factor receptor levels; however, these findings do not fully explain the disparity between perfusion and LV function. The authors hypothesize that the sequential release pattern of FGF-2 initially triggering angiogenesis, followed by HGF and potent arteriogenesis, may be helpful for inducing mature blood vessel formation. They further speculate that the benefits of FGF-2 and HGF combination therapy exceed merely improving perfusion and may have direct cardioprotective effects, including reduction of cardiac fibrosis and improved cell-cell metabolic coupling.

These observations focus our attention on the larger discussion of revascularization in ischemic myocardium and the concept of prevention or recovery of hibernating myocardium. Traditionally, this has involved macrovascular solutions with recanalization or bypass of epicardial coronary arteries via percutaneous coronary intervention or CABG, respectively. Hypothesis 1 of the STICH trial investigated whether CABG plus intensive guideline-based medical therapy would reduce mortality and cardiovascular end points in patients with coronary artery disease and LV dysfunction compared with medical therapy alone.3 An accompanying study of a prespecified subgroup of the STICH patient population asked whether viability testing with dobutamine stress echocardiography or single-photon emission computed tomography identifies those most likely to benefit from CABG.8 Although there was no significant difference between the randomized groups with respect to the primary end point of death resulting from any cause, patients who actually received CABG plus optimal medical therapy fared significantly better than those who received medical therapy alone. Additionally, in a per-protocol comparison of the 537 patients randomized to medical therapy who did not cross over to CABG compared with the 555 patients randomized to CABG who had surgery, there was a significant mortality benefit from CABG (hazard ratio, 0.76; 95% confidence interval, 0.62 to 0.92; \( P = 0.005 \)). As-treated analyses clearly involve the introduction of bias and must be interpreted with caution. However, we believe that the STICH trial provides further credibility to the notion that improving perfusion in ischemic cardiomyopathy patients provides significant benefit (whereas being scheduled for surgery apparently does not). The failure of dobutamine stress echocardiography or single-photon emission computed tomography to identify those most likely to benefit from CABG is, in our view, more a statement that these imaging modalities are not capable of reliably assessing for hibernating myocardium as opposed to magnetic resonance imaging or invasive functional assessments or ultimately revascularization itself.

These issues highlight the importance of ongoing investigation of the pathophysiology of myocardial ischemia, the mechanisms of therapeutic angiogenesis, and optimal strategies to improve the coronary microcirculation via these interventions, either as standalone therapy or in conjunction with epicardial revascularization. Early preclinical models contributed to the proof of concept that delivery of agents such as stromal cell–derived factor 1 to injured myocardium can induce therapeutic stem cell homing and tissue regeneration.9 Human trials have investigated the use of cell and gene therapy either in the setting of an acute myocardial infarction or in patients with remote infarctions and ischemic cardiomyopathy manifesting with refractory angina or heart failure.10–14 These trials have shown promise in many cases, particularly those using cell-based strategies, and have furthered our understanding of the mechanisms of therapeutic angiogenesis. In particular, the demonstration that improvement in LV function induced by cell therapy was associated with significant improvements in coronary flow reserve has provided human evidence linking improvement in the microcirculation alone, induced by cell therapy, with recovery of hibernating myocardium15; additional recent human data provide further evidence of the independent role of the coronary microcirculation even in the early stages of atherosclerosis.16 The work by Banquet et al adds to the preclinical evidence that preservation of the microcirculation, in the setting of chronically occluded epicardial vessels, can preserve LV function. It also provides a potentially important pragmatic solution for sustained delivery of therapeutic proteins. On the other hand, the innate ability of stem or progenitor cells to secrete a repertoire of cytokines and growth factors for a sustained period will, in our view, likely drive continued clinical investigations in this area, particularly given the regulatory challenges in testing multiple agents in a single study. Going forward, investigation of strategies such as that used by Banquet et al with combinations of multiple growth factors or integration of gene and cell therapy, delivery of genetically modified progenitor cells, and novel sustained-release delivery vectors will continue to illuminate the mechanisms that may be exploited to effect ischemic tissue repair and, in our view, will ultimately lead to the routine use of biological therapies for the reversal of ischemic cardiomyopathy.

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References


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