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EDITORIAL COMMENT

Pericardial Delivery of Biological Agents

The Next Frontier?*

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Heart failure (HF) is estimated to affect 6.5 million Americans and it is expected to increase by 46% by the year 2030 (1). Despite development of evidenced-based medical and surgical therapies, 1-year mortality remains as high as 30% and 5-year mortality at 50% (1). Current data support the use of beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and implantable cardioverter-defibrillator/cardiac resynchronization therapies to decrease mortality. However, despite improvement in survival, patients are living with a worse quality of life and frequent hospitalizations.

Understanding the mechanical and pathophysiologic mechanisms responsible for the remodeling and worsening of HF has promoted the development of innovative treatments including microRNA, stem cell therapy, biologic agents, and hydrogels. These experimental approaches often require direct access to the myocardium or extensive pharmacoengineering to target medications to diseased cells (2–4). Even direct injection of stem cells into the myocardium has resulted in significant cell leakage and washout resulting in >90% of cells removed in just the first hour (5,6). As an approach to solve this problem, researchers have used tissue engineering to explore a variety of biopolymers to increase the efficiency of delivery of stem cells and other biologic agents (4,6–10). Hydrogels have also been used to improve cardiac functional capacity in patients with severe HF as demonstrated in the Augment-HF trial (11). With these advances in HF therapy there is a need to deliver these targeted therapies directly at their site of action.

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In this issue of *JACC: Basic to Translational Science*, Garcia et al. (12) examined the effectiveness of a new biomaterial pericardial delivery catheter in a porcine model. The device consists of 2 internal lumens to maintain biomaterial components separate during delivery. Polyethylene glycol hydrogels with dithiothreitol as the cross-linking component were injected into the pericardial space; these were delivered into a fenced area (created by the device) for in situ mixing and crosslinking. Access into the pericardial space was obtained via a "dry" pericardiocentesis (13,14). The polymer was successfully delivered in 9 pigs without observed adverse events including no access complications, device placement or deployment malfunctions, or sustained arrhythmias. Assessment immediate post-deployment and at 4 to 6 weeks revealed no changes in hemodynamic profile and no evidence of pericarditis. Only 1 infection occurred; however, the authors concluded it was not a procedure-related infection.

This article highlights the feasibility of an epicardial approach to deliver new HF therapies via the pericardial space. Epicardial approaches have been used routinely by electrophysiologists since 1997 when epicardial ventricular tachycardia mapping was first described (14). More recent data have come from the LARIAT suture delivery system, which uses a similar epicardial approach to ligate the left atrial

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appendage to prevent left atrial appendage thrombus formation and as adjunctive therapy to treat atrial fibrillation patients (15). Data suggest that pericardial access for ventricular tachycardia ablations has a major complication rate of 4% to 5% with the most common being early bleeding/early tamponade in 1.8% to 4.4% of all cases (16,17). Chest pain is common and can be severe. In 1 series almost all patient had chest pain and were treated with nonsteroidal anti-inflammatory drugs (17). Chest pain is anticipated to be worse in these procedures given the inflammation caused by the epicardial ablation. Minor complications included dry right ventricle (RV) puncture ranging from 5% to 17% and access into the pleural space. Pericardial access for the LARIAT device used a similar pericardial approach with 3% to 5% of patients experiencing access-related complications. The most common complication reported was pericarditis ranging from 2.3% to 15%. RV perforation occurred between 1.1% and 5% of cases. However, the use of a micropuncture needle for pericardial access has resulted in a significant decrease in pericardial access-related complications including RV perforation and tamponade (15,18). These reports demonstrate the safety of an epicardial approach to deliver advance cardiac therapies with limited complications when using a micropuncture needle rather than a standard pericardiocentesis needle.

Intracoronary and intravenous delivery of novel treatments have been most practical for delivery but they have been limited by myocardial uptake and systemic recirculation. Epicardial administration was hypothesized to improve drug uptake by acting as a reservoir and eliminating undesired systemic effects of medications (19). Additionally, epicardial administration of biopolymers limits any potential embolic event that could occur during polymerization of the biopolymer if administered intravenously. A variety of therapeutic agents have been tested in animal trials for intrapericardial injection including nitric oxide, growth factors, acellular biomaterials, stem cells, and gene therapies (11,19–23). The methods to access the pericardial space varied and included intrajugular access with RV perforation, subxiphoid access using standard pericardiocentesis kits, and thoracotomy. Of these approaches, only thoracotomy allowed direct delivery of the therapeutic substance onto the effected myocardium. The first in human case report of such intervention was reported in 2015 where a 68-year-old man with severe HF was injected with human embryonic stem cell-derived cardiac progenitor cells on a fibrin scaffold in a previously infarcted area during a coronary artery bypass graft procedure (7). Further human trials are needed to characterize the safety and efficacy of these therapeutics and a minimally invasive approach for delivery of these therapies may allow a broader demographic of patients to receive advanced interventions. The approach highlighted in this article allows safe access to the pericardial space and the deployment of the devices allows localization and trapping of the substance in the desired location for maximal epicardial delivery and concentration.

There are some limitations to the described approach by Garcia et al. (12) worth highlighting. Patients who have had prior cardiac surgeries are likely to have pericardial adhesions, thus limiting pericardial access. Many therapeutics available for this device are targeted for patients with HF and they may have previously had a coronary artery bypass graft resulting in fibrosis and adhesions. Other inflammation or radiation to the chest may also preclude patients from getting this intervention (24). Second, like the LARIAT device, general anesthesia is required and the backup of a cardiothoracic surgeon may be necessary in case of perforation. This may limit the wide adaptation of this approach by smaller centers. Additionally, although epicardial localization may be sufficient for a very limited number of advanced therapies, most studies have been conducted using an intracoronary or direct myocardial injection approach. It remains unclear which strategy provides the best outcome. Intracoronary approaches are limited by perfusion of the periscar area and endothelial cell migration, whereas intramyocardial injections previously required an open procedure and the overall retention rates remain $<$10% (25,26). The CHART-1 trial used a percutaneous nitinol-based curved needle delivery catheter system to deliver stem cells into the pericardium and resulted in improved retention of myocardial stem cells (37.7 $\pm$ 7.1% vs. 10.0 $\pm$ 2.8%) (27). A percutaneous injection catheter with a suction tip (LoneStar Heart, Laguna, California) to prevent leakage of polymers into the bloodstream is being evaluated for endocardial injections of an alginate polymer for patients with HF (28). Future development of a hybrid device consisting of a double lumen catheter for epicardial intramyocardial delivery could be used to deliver hydrogels into the myocardium without the need for cardiac surgery while mitigating the risk of embolic events.

The development of this device described by Garcia et al. (12) proves to be a promising step toward acceleration in the growth of HF therapies that require direct injection or contact with the myocardium; however, recent hydrogel and stem cell

therapies require intramyocardial access that cannot yet be performed with this device (12). More trials with a larger number of patients are required to demonstrate the safety of a "dry" pericardial access and efficacy of delivery of biologically active agents with this device.

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