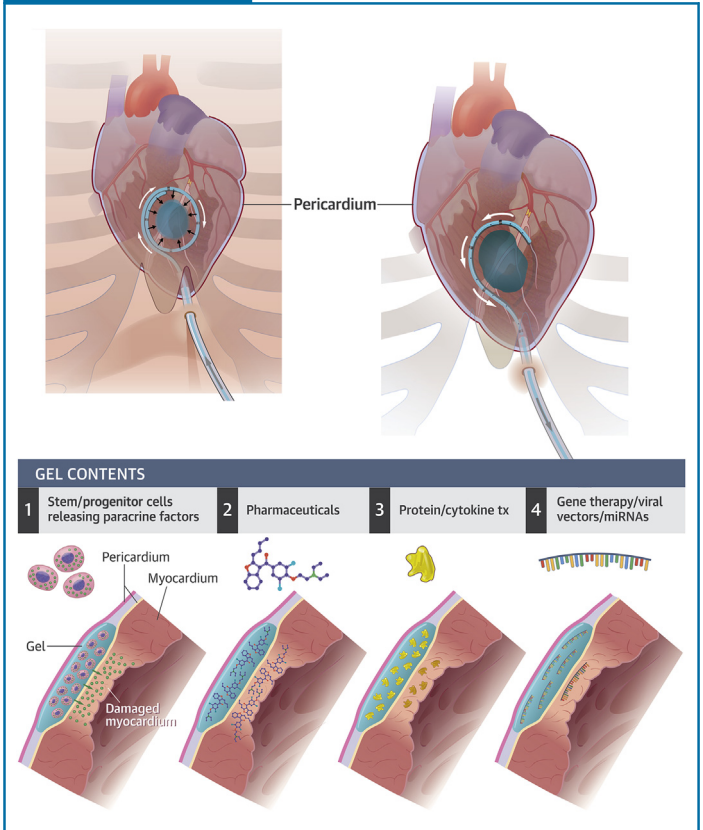
JACC: BASIC TO TRANSLATIONAL SCIENCE
VOL. 2, NO. 5, 2017
ISSN 2452-302X
http://dx.doi.org/10.1016/j.jacbts.2017.06.003

NOVEL TRANSLATIONAL METHODS

A Minimally Invasive, Translational Method to Deliver Hydrogels to the Heart Through the Pericardial Space

Jose R. Garcia, MS,[a] Peter F. Campbell, MD,[b] Gautam Kumar, MBBS,[c,d] Jonathan J. Langberg, MD,[c] Liliana Cesar, DVM,[e] Lanfang Wang, MS,[c] Andrés J. García, PhD,[a] Rebecca D. Levit, MD[c]

VISUAL ABSTRACT



Garcia, J.R. et al. J Am Coll Cardiol Basic Trans Science. 2017;2(5):601–9.

HIGHLIGHTS

- **The pericardial space is an unexploited anatomic location for hydrogel delivery.**
- **Hydrogels can be delivered to the pericardial space in a localized, minimally invasive manner, without detectable hemodynamic effects.**
- **Pericardial hydrogel delivery is a new strategy to direct therapeutics to the heart with reduced systemic delivery and off-target effects.**

From the [a]Woodruff School of Mechanical Engineering, Petit Institute for Bioengineering and Bioscience, Georgia Institute of Technology, Atlanta, Georgia; [b]Innovatië LifeSciences, Santa Clara, California; [c]Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia; [d]Division of Cardiology, Atlanta VA Medical Center, Atlanta, Georgia; and [e]T3 Labs-Translational, Testing and Training Laboratories, Inc., Atlanta, Georgia. Dr. Campbell and Dr. Levit are listed as inventors on a patent application filed by Emory University on technology related to the delivery device. Dr. Levit is a principal in a startup company, CorAmi LLC, which seeks to commercialize this technology but as of yet has no investment, revenue, or intellectual property. Funded by Coulter Translational Research Partnership, Georgia Research Alliance. All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received April 5, 2017; revised manuscript received May 21, 2017, accepted June 1, 2017.

ABBREVIATIONS AND ACRONYMS

CVD = cardiovascular disease

miRNA = micro-ribonucleic acid

PEG = polyethylene glycol

SUMMARY

Biomaterials are a new treatment strategy for cardiovascular diseases but are difficult to deliver to the heart in a safe, precise, and translatable way. We developed a method to deliver hydrogels to the epicardium through the pericardial space. Our device creates a temporary compartment for hydrogel delivery and gelation using anatomic structures. The method minimizes risk to patients from embolization, thrombotic occlusion, and arrhythmia. In pigs there were no clinically relevant acute or subacute adverse effects from pericardial hydrogel delivery, making this a translatable strategy to deliver biomaterials to the heart. (J Am Coll Cardiol Basic Trans Science 2017;2:601–9)

Despite pharmacological and technologic advances, cardiovascular diseases (CVD) remain the leading cause of morbidity and mortality in the United States, costing $215.6 billion per year (1). More patients are surviving, but with heart failure, arrhythmias, and poor quality of life. Micro-ribonucleic acid (miRNA), gene therapy, stem cells, cytokines, and other biologics are new treatments that have shown promise in preclinical and early phase clinical trials (2–4). Many of these therapies require focused delivery of the therapeutic to the heart, or even localization to particular anatomic areas, such as the peri-infarction region. Dilution of these therapeutics by systemic administration increases cost and risks off-target effects. For example, poor retention of stem cells in the heart is thought to limit efficacy in clinical trials (5–7). The proangiogenic cytokine vascular endothelial growth factor encourages neoangiogenesis and cardiac regeneration (8) but can also accelerate tumor metastasis (9). Efficient, targeted, and temporally appropriate delivery of therapeutics to the heart are keys to their successful translation into clinical use.

SEE PAGE 610

Early phase clinical trials are underway using hydrogels as therapeutic agents for cardiac repair (10–12). Both solid patches and injectable gel materials are under investigation and may have benefits for different applications. Cardiac patches and solid materials have been tested as structural support for the heart in a clinical trial (13) and therapeutic delivery platforms in numerous preclinical studies (14). Their widespread use is limited by the need for surgical placement. Injectable materials with liquid or gel phases, such as decellularized matrix, alginate, and engineered hydrogels, can provide scaffolds, tactile signals, and structural support for cardiac regeneration and repair (10,11,15,16). Biomaterial gels are particularly suited to deliver stem cells to the heart and retain viable cells at the site of delivery (12,17). Other materials are in preclinical trial for delivery and sustained release of miRNAs, cytokines, and other therapeutics (4,18,19). Whereas biocompatible materials may be beneficial for the treatment of CVD, there are no dedicated delivery methods that are safe and minimally invasive.

There are challenges inherent to delivering biomaterials to the heart. Open heart surgery, although feasible, is less desirable from a cost and patient perspective. Catheter delivery using commercially available single-lumen coronary catheters or Noga XP Cardiac Navigation System (Biosense Webster, Diegem, Belgium) cannot keep material components separate as they travel to the heart and thus cannot control the timing of material interaction and gelation. Premature gelation causes clogging within catheter lumen. Delayed gelation can lead to embolization, stroke, and failure to deliver material to targeted area. Another challenge with biomaterial delivery to the heart is the potential for inducing arrhythmias if the electrical conductivity of the material creates a substrate for a re-entrant circuits as it interdigitates between cardiomyocytes. Therefore the development of material-specific strategies is necessary for the safe, precise, and practical delivery of biomaterial to the heart.

The pericardium is a novel site for therapeutic delivery that has been shown in animal studies to act as a reservoir for drug delivery to the heart (20–22). The advent of epicardial ablations and external left atrial appendage ligation has demonstrated the feasibility of accessing a “dry” pericardial space for therapeutic purposes (23–25). Herein we describe a minimally invasive device to deliver biomaterials to the heart by using the pericardial space as a novel anatomic site for biomaterial delivery. Our device uses the existing anatomic structures to form a temporary compartment for gel delivery. Features of the device eliminate the risk of premature gelation and embolization and allow