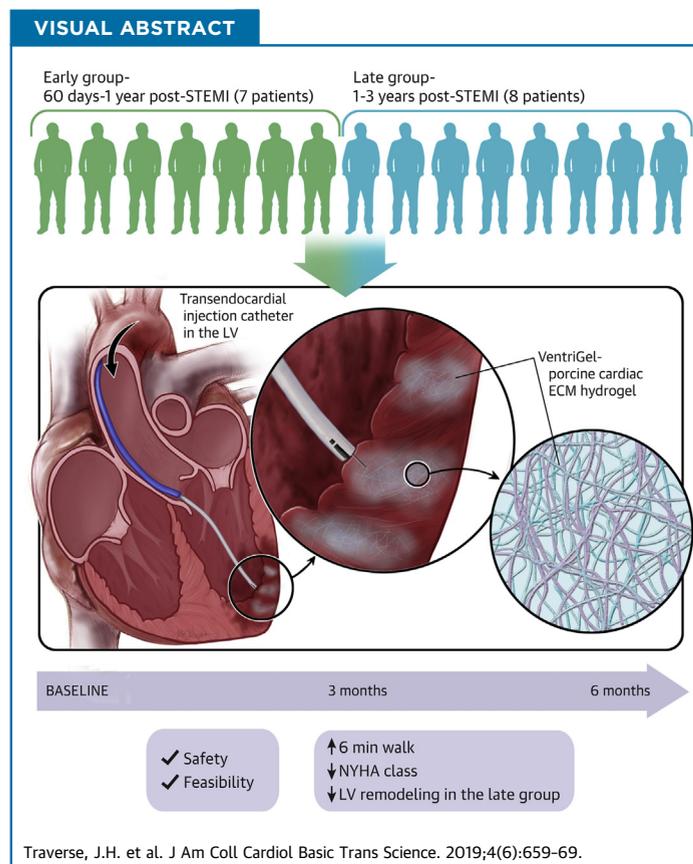


CLINICAL RESEARCH

First-in-Man Study of a Cardiac Extracellular Matrix Hydrogel in Early and Late Myocardial Infarction Patients



Jay H. Traverse, MD,^a Timothy D. Henry, MD,^b Nabil Dib, MD,^c Amit N. Patel, MD,^d Carl Pepine, MD,^e Gary L. Schaer, MD,^f Jessica A. DeQuach, PhD,^g Adam M. Kinsey, PhD,^g Paul Chamberlin, MD,^g Karen L. Christman, PhD^h



HIGHLIGHTS

- A first-in-man clinical trial was completed with VentiGel, an extracellular matrix hydrogel derived from decellularized porcine myocardium, in post-MI patients.
- Results from the trial support the safety and feasibility of transendocardial injection of VentiGel in post-MI patients with left ventricular dysfunction.
- Although the study was not designed to evaluate efficacy, there were suggestions of improvements including increases in 6-min walk test distance and decreases in New York Heart Association functional class across the entire cohort of patients.
- Improvements in left ventricular remodeling were mainly observed in patients who were treated >1-year post-MI as opposed to <1 year.
- Results from the trial warrant further evaluation in larger randomized, controlled clinical trials.

ABBREVIATIONS
AND ACRONYMS**BNP** = B-type natriuretic peptide**CMR** = cardiac magnetic resonance**ECM** = extracellular matrix**EF** = ejection fraction**LV** = left ventricular**LVEDV** = left ventricular end-diastolic volume**LVESV** = left ventricular end-systolic volume**MI** = myocardial infarction**MLWHFQ** = Minnesota Living with Heart Failure Questionnaire**NYHA** = New York Heart Association

SUMMARY

This study evaluated the safety and feasibility of transendocardial injections of VentiGel, a cardiac extracellular matrix hydrogel, in early and late post-myocardial infarction (MI) patients with left ventricular (LV) dysfunction. VentiGel was delivered in 15 patients with moderate LV dysfunction ($25\% \leq \text{LV ejection fraction} \leq 45\%$) who were between 60 days to 3 years post-MI and were revascularized by percutaneous coronary intervention. The primary endpoints were incidence of adverse events and abnormal clinical laboratory results. This first-in-man study established the safety and feasibility of delivering VentiGel in post-MI patients, thus warranting further evaluation in larger, randomized clinical trials. (J Am Coll Cardiol Basic Trans Science 2019;4:659-69) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Over the past 2 decades, there has been extensive interest in using regenerative medicine to treat patients with myocardial infarction (MI) and ischemic heart failure. Although several growth factor and gene therapeutics have been explored, the vast majority of trials have tested different types of stem cells (1). However, tissues are not just comprised of cells but also include a scaffolding framework, the extracellular matrix (ECM). The ECM contains numerous proteins and proteoglycans with a unique tissue-specific composition that provides cues, which influence all aspects of cell behavior necessary for proper tissue function as well as repair (2). After an MI, there is not only cell death but also an inflammatory response and up-regulation of matrix metalloproteinases that degrade the native cardiac ECM (3). After the initial inflammation, the area is replaced by a collagen-rich scar. With the goal of replacing this abnormal microenvironment with healthy myocardial ECM cues to facilitate cardiac repair, we developed an injectable, catheter-deliverable hydrogel derived from porcine decellularized myocardial ECM (4). This material can be stored in a lyophilized form and rehydrated with sterile water to form a liquid that gels into a porous and fibrous scaffold upon intramyocardial injection, enabling

endogenous cell infiltration and cardiac repair (4,5). In vitro analyses showed the potential of the material to promote recruitment and/or proliferation of vascular cells and stem cells as well as cardiac differentiation of stem cells (4,6-10). In rat MI models, the hydrogel promoted a pro-remodeling instead of a proinflammatory environment, increased neovascularization, and reduced fibrosis. The hydrogel also decreased border zone cardiomyocyte apoptosis, led to a shift in cardiomyocyte metabolism, and increased cardiac muscle leading to improvements in global cardiac function (5,11). In a more translatable porcine MI model, the material increased cardiac muscle, reduced fibrosis, and led to significant improvements in both global and regional function after percutaneous, transendocardial delivery (12). Importantly, preclinical safety studies showed biocompatibility, hemocompatibility, and lack of arrhythmias (5,12). This work motivated testing the material, commercially termed VentiGel (Ventrix, Inc., San Diego, California), in post-MI patients.

Accordingly, we developed a first-in-man, single-arm, multicenter trial to evaluate the safety, feasibility, and preliminary efficacy of percutaneous transendocardial delivery of VentiGel in early and late MI patients with left ventricular (LV) dysfunction. This injectable biomaterial approach represents

From the ^aMinneapolis Heart Institute, Minneapolis, Minnesota; ^bThe Carl and Edyth Lindner Center for Research and Education at The Christ Hospital, Cincinnati, Ohio; ^cDignity Health Mercy Gilbert Medical Center, Gilbert, Arizona; ^dDewitt Daughtry Family Department of Surgery, Division of Cardiothoracic Surgery, University of Miami, Leonard M. Miller School of Medicine, Miami, Florida; ^eUniversity of Florida College of Medicine, Gainesville, Florida; ^fDivision of Cardiology, Rush University Medical Center, Chicago, Illinois; ^gVentrix, Inc., San Diego, California; and the ^hDepartment of Bioengineering, Sanford Consortium for Regenerative Medicine, La Jolla, California. This study was supported by Ventrix, Inc., San Diego, California. Drs. Kinsey and Christman and KLC are cofounders of Ventrix, Inc.; Drs. DeQuach, Chamberlin, and Christman are consultants and receive income from Ventrix, Inc.; Drs. Kinsey and Christman are board members of Ventrix, Inc.; Dr. Kinsey is an employee of Ventrix, Inc.; Drs. Dib, DeQuach, Kinsey, and Chamberlin hold equity interest in Ventrix, Inc. Dr. Dib is owner of Tri LLC and UltraNav Medical LLC; and a consultant for BDS and CSI. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Basic to Translational Science* [author instructions page](#).

Manuscript received June 20, 2019; revised manuscript received July 26, 2019, accepted July 27, 2019.

an alternative paradigm to cell-based regenerative medicine strategies (13).

METHODS

TRIAL DESIGN AND PATIENT POPULATION. This phase 1 trial was approved by the Food and Drug Administration and the institutional review boards of each participating clinical center. Eligibility for the trial included patients with their first ST-segment elevation MI treated by percutaneous coronary intervention within the past 60 days to 3 years who had moderate LV dysfunction ($25\% \leq$ LV ejection fraction [EF] $\leq 45\%$). The enrollment criteria were intentionally broad so that we could begin to evaluate the safety and potential efficacy of VentriGel in both early and late MI patients. The primary objective was to investigate the safety and feasibility of a single dose of VentriGel delivered via multiple sequential endomyocardial injections using the MyoStar catheter guided by the NOGA cardiac mapping system (Biologics Delivery Systems, Cordis Corporation, Hialeah, Florida). The primary endpoints were incidence of adverse events and abnormal clinical laboratory results.

The secondary objective was to investigate the preliminary efficacy of VentriGel by measuring the changes in various parameters from baseline to 3 and 6 months after the procedure. The secondary endpoints included evaluation of LV volumes, EF, and scar size by cardiac magnetic resonance (CMR), serum B-type natriuretic peptide (BNP) level, the 6-min walk test distance, quality of life using the Minnesota Living with Heart Failure Questionnaire (MLWHFQ), and New York Heart Association (NYHA) functional classification assessment.

Patients who experienced their first ST-segment elevation MI treated by percutaneous coronary intervention within the past 60 days to 3 years and had an LVEF between 25% and 45% by baseline screening echocardiogram were recruited and enrolled at 6 sites. LVEF was determined by 2-dimensional transthoracic echocardiography performed in accordance with the American Society of Echocardiography guidelines. Key exclusion criteria included sustained ventricular tachycardia, LV thrombus, significant coronary artery stenosis requiring percutaneous or surgical revascularization within 6 months of enrollment, heart failure due to any cause other than index MI, and NYHA functional class IV heart failure in the prior 6 months. Additional details including full inclusion/exclusion criteria are provided in the [Supplemental Appendix](#). An independent safety advisory board was chartered to

review safety data after the first 9 patients and ad hoc.

PROCEDURES. VentriGel, an ECM hydrogel derived from decellularized porcine myocardium, was manufactured at a single Good Manufacturing Practice facility and provided to trial sites as lyophilized material in sterile vials and stored frozen. Immediately before the procedure, VentriGel was resuspended in sterile water and loaded into 1-ml syringes for injection. All patients underwent electromechanical mapping with the NOGA XP system (Biosense Webster, Irvine, California). The area of infarct was determined by <6.9 mV univoltage potential. All patients received sequential injections of VentriGel (0.3-ml individual injections up to a total of 18 injections or 5.4 ml) using a MyoStar catheter into the infarct and border zone areas with a wall thickness >8 mm as defined by the screening echocardiogram. Each injection was delivered over 45 s through a 27-gauge needle. A limited echocardiogram was obtained immediately post-injection to rule out pericardial effusion. Patients were routinely discharged at 24 h post-procedure with a cardiac event monitor for 30 days. Patients received a follow-up phone call on day 5 post-discharge; returned for safety visits on days 7 (± 2 days), 14 (± 2 days), 30 (± 2 days), 90 (± 4 days), and 180 (± 7 days); and received a telephone follow-up at 12 months (± 14 days). The 24-h Holter monitoring was performed at screening and at 90 and 180 days. Cardiac MRI was performed according to imaging guidelines provided by the Yale Cardiovascular Research Group at baseline and at 90 and 180 days. The 6-min walk test was performed according to American Thoracic Society guidelines at baseline and at 90 and 180 days. NYHA functional classification and MLWHFQ were obtained at baseline and at 30, 90, and 180 days.

DATA AND STATISTICAL ANALYSIS. Data were recorded in case report forms and monitored against source documentation for accuracy by clinical study monitors. Independent centralized core laboratories (Yale Cardiovascular Research Group, New Haven, Connecticut, and KCRI, Krakow, Poland) provided all MRI image analysis. Statistical analysis was performed with GraphPad Prism version 8.01 (GraphPad Software, La Jolla, California). Categorical variables are summarized by counts and proportions. Descriptive data of continuous variables are summarized using mean and standard error of the mean. Data were compared using a repeated-measures mixed-effects model in Prism. This mixed model uses a compound symmetry covariance matrix and is fit using restricted maximum likelihood. A Geisser-Greenhouse correction was used where sphericity could not be assumed.

TABLE 1 Patient Demographics and Baseline Characteristics			
	VentriGel Treatment (N = 15)	Patients <12 Months Post-MI at Treatment (n = 7)	Patients >12 Months Post-MI at Treatment (n = 8)
Age, yrs	59.6 ± 8.8	57.7 ± 10.3	61.3 ± 7.5
Female	3 (20.0)	2 (28.6)	1 (12.5)
White, non-Hispanic	12 (80.0)	6 (85.7)	6 (75.0)
White, Hispanic	1 (6.7)	1 (12.5)	0 (0)
African American	2 (13.3)	0 (0)	2 (28.6)
Body mass index, kg/m ²	30.0 (4.4)	29.1 (4.1)	30.7 (4.7)
Tobacco use			
Former	10 (66.7)	5 (71.4)	5 (62.5)
Current	1 (6.7)	1 (14.3)	0 (0)
Diabetes mellitus	3 (20.0)	2 (28.6)	1 (12.5)
Hypertension	7 (46.7)	4 (57.1)	3 (37.5)
Dyslipidemia	12 (80.0)	4 (57.1)	8 (100)
Previous PCI	15 (100)	7 (100)	8 (100)
Previous CABG	3 (20.0)	0 (0)	3 (37.5)
NYHA functional class			
I	3 (20.0)	1 (14.3)	2 (25.0)
II	11 (73.3)	5 (71.4)	6 (75.0)
III	1 (6.7)	1 (14.3)	0 (0)
Time from MI to injection (months)	15.2 ± 10.6	6.5 ± 2.9	22.8 ± 8.7

Values are mean ± SD or n(%).
CABG = coronary artery bypass grafting; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

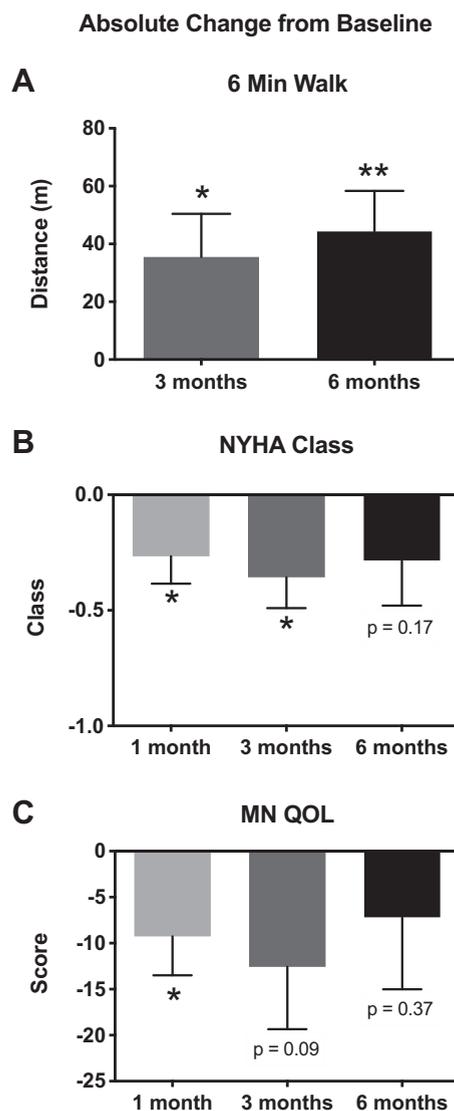
Each follow-up time point was compared with baseline with a paired Student's *t*-test. Significance was accepted at $p < 0.05$. Given the small, exploratory nature of this study, there were no adjustments for multiple comparisons.

RESULTS

PATIENTS. All patients gave written informed consent; 22 patients were consented and screened, and 15 patients were subsequently enrolled between September 2015 and July 2017 (Supplemental Table 1). The majority of patients were men ($n = 12$) and had Class II heart failure ($n = 11$). Age ranged from 45 to 69 years, and other pertinent baseline characteristics are summarized in Table 1. Concomitant medications are listed in Supplemental Table 2. VentriGel was delivered between 3 and 35.5 months post-MI. Enrolled patients were divided with approximately one-half of the patients treated <12 months post-MI and one-half of the patients treated >12 months post-MI (Table 1). Thirteen of the 15 patients received all 18 injections. The 2 remaining patients received 15 and 16 injections due to injection requirement restrictions such as wall thickness minimum.

SAFETY. Overall, VentriGel was well tolerated, and there were no deaths or patients who discontinued from the study. No adverse event was reported as

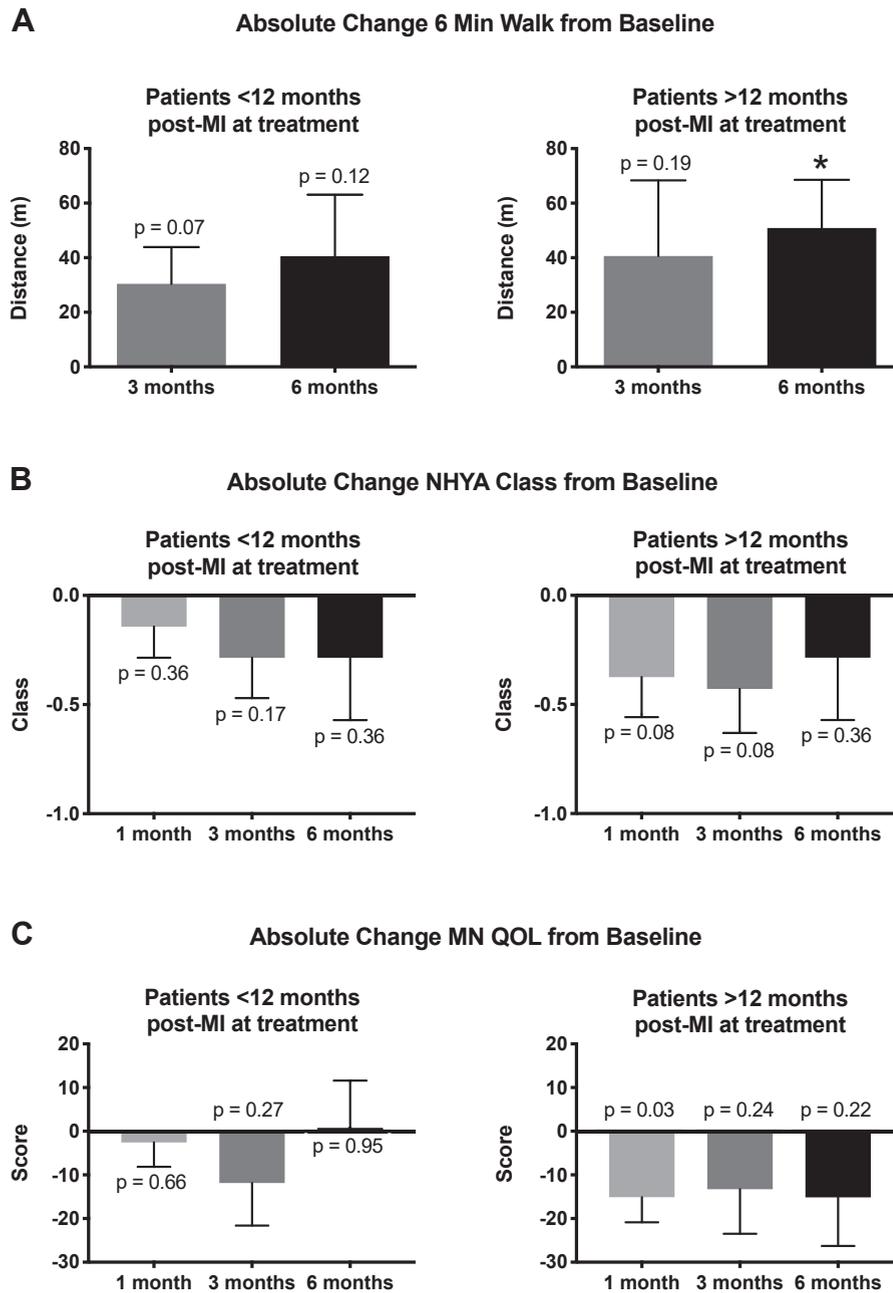
FIGURE 1 Changes in Exercise Capacity, Heart Failure Class, and Quality of Life



Absolute changes in (A) the 6-min walk test distance, (B) NYHA functional class, and (C) Minnesota Living With Heart Failure Questionnaire (MNLWHFQ) score from baseline to follow-up visits are shown for the total cohort. The *p* value is for the paired Student's *t*-test between follow-up and baseline.
* $p < 0.05$. ** $p < 0.01$. MN = Minnesota; NYHA = New York Heart Association; QOL = quality of life.

definitely related to VentriGel (Supplemental Table 3) or the mapping/injection procedure. One major adverse cardiac event, cardiogenic shock, and 1 moderate event, complete heart block, both in the first patient treated were reported as possibly related for study treatment. This patient's history included trifascicular block, which was added as an exclusion

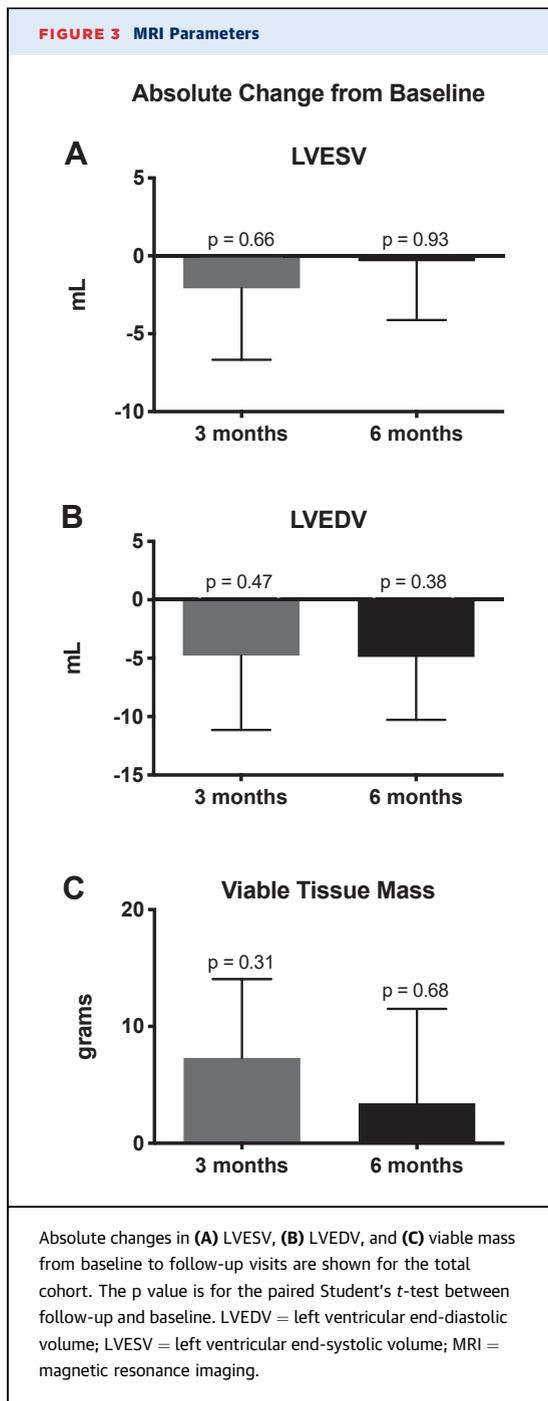
FIGURE 2 Changes in Exercise Capacity, Heart Failure Class, and Quality of Life in Early and Late MI Patients



Absolute changes in (A) the 6-min walk test distance, (B) NYHA functional class, and (C) MNLWHFQ score from baseline to follow-up visits are shown for patients <12 months post-MI and >12 months post-MI at treatment. The p value is for the paired Student's t-test between follow-up and baseline. *p < 0.05. MI = myocardial infarction; other abbreviation as in Figure 1.

criterion based on recommendations by the safety advisory board for the final 13 patients. One intracardiac thrombus was reported as possible for the mapping/injection procedure. No significant ventricular arrhythmias were found by Holter monitoring.

One episode of nonsustained ventricular tachycardia was reported as not related to VentiGel. There were no clinically meaningful changes in the clinical laboratory results. As expected by the injection procedure, a small, nonsignificant increase in C-reactive



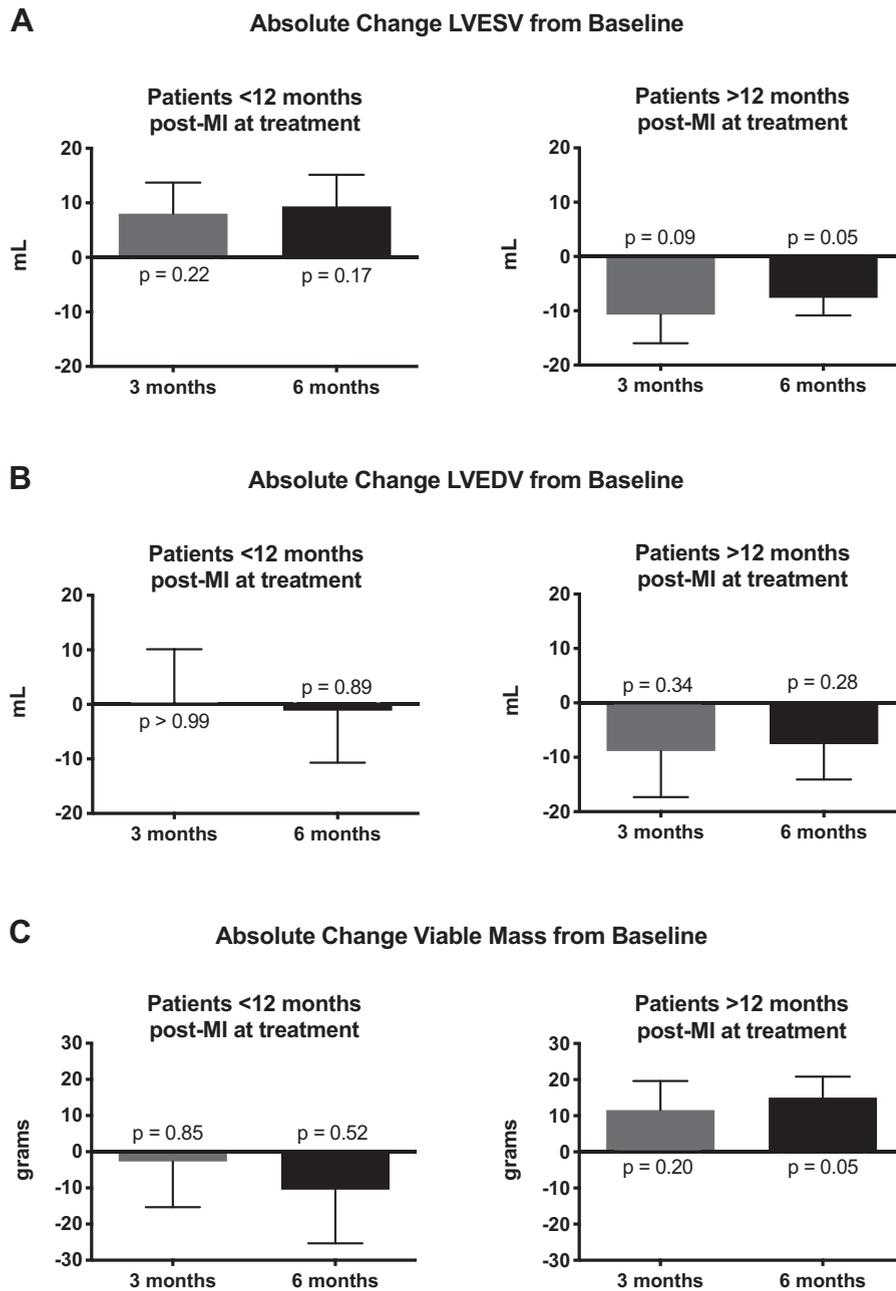
protein was observed 1 day after the injection procedure but not at other time points (Supplemental Table 4).

EFFICACY SIGNS. A 6-min walk test was evaluated at baseline and 3- and 6-month follow-up visits as a measure of functional exercise capacity. In the total cohort, treatment with VentriGel significantly increased the maximum walk distance with time post-injection ($p = 0.004$) at 3 and 6 months. The

walk distance was significantly greater than at baseline with average changes of +35.6 m ($p = 0.033$) and +44.4 m ($p = 0.007$), respectively (Figure 1A, Supplemental Figure 1A, Supplemental Table 5). This corresponded to improvements in NYHA functional class and the MLWHFQ quality of life score. NYHA functional class significantly decreased at 1-month post-treatment ($p = 0.041$), and this overall decrease was similar at 3 and 6 months (Figure 1B, Supplemental Figure 1B, Supplemental Table 6). The MLWHFQ score likewise significantly decreased at 1 month ($p = 0.045$), and a similar decrease was observed at 3 and 6 months but was nonsignificant (Figure 1C, Supplemental Figure 1C, Supplemental Table 6). Improvements in the walk distance (Figure 2A, Supplemental Figure 2A), NYHA functional class (Figure 2B, Supplemental Figure 2B), and the MLWHFQ score (Figure 2C, Supplemental Figure 2C) tended to be better in the late MI subset (>12 months post-MI) versus the early MI subset (<12 months post-MI).

Cardiac function was evaluated using MRI at baseline and at the 3- and 6-month follow-up visits. Thirteen of 15 patients were evaluated at 3 months, and 14 of 15 patients were evaluated at 6 months. In the 14 patients who were evaluated with MRI at 6 months, 11 patients had maintained or decreased LV end-diastolic volume (LVEDV) or LV end-systolic volume (LVESV) compared with baseline at the final follow-up. Although numerical averages for the total cohort decreased (Figure 3, Supplemental Figure 3), post hoc analysis revealed that decreases in LV volumes occurred predominantly in the late MI subset (>12 months post-MI) versus the early MI subset (<12 months post-MI) (Figures 4A and 4B, Supplemental Figures 4A and 4B, Supplemental Table 7). At 6 months, both LVESV and LVEDV decreased by approximately 8 ml ($p = 0.051$ and $p = 0.280$, respectively) in those patients treated >12 months post-MI. Similarly, changes in viable mass were more notable in the late MI population (Figure 4C, Supplemental Figure 4C, Supplemental Table 7). No major changes were observed in EF or scar size (Supplemental Table 7). The first treated patient received a pacemaker, which prevented follow-up MRI analysis; however, echocardiography was performed at 3 and 6 months and analyzed by the core laboratories. This patient's EF increased from 40.6% at baseline to 44.6% and 46.9% at 3 and 6 months, respectively. LV diameters likewise improved compared with baseline. The LV end-systolic diameter decreased from 4.16 cm at baseline to 4.15 cm and 4.13 cm at 3 and 6 months, respectively, whereas the LV end-diastolic diameter

FIGURE 4 MRI Parameters in Early and Late MI Patients

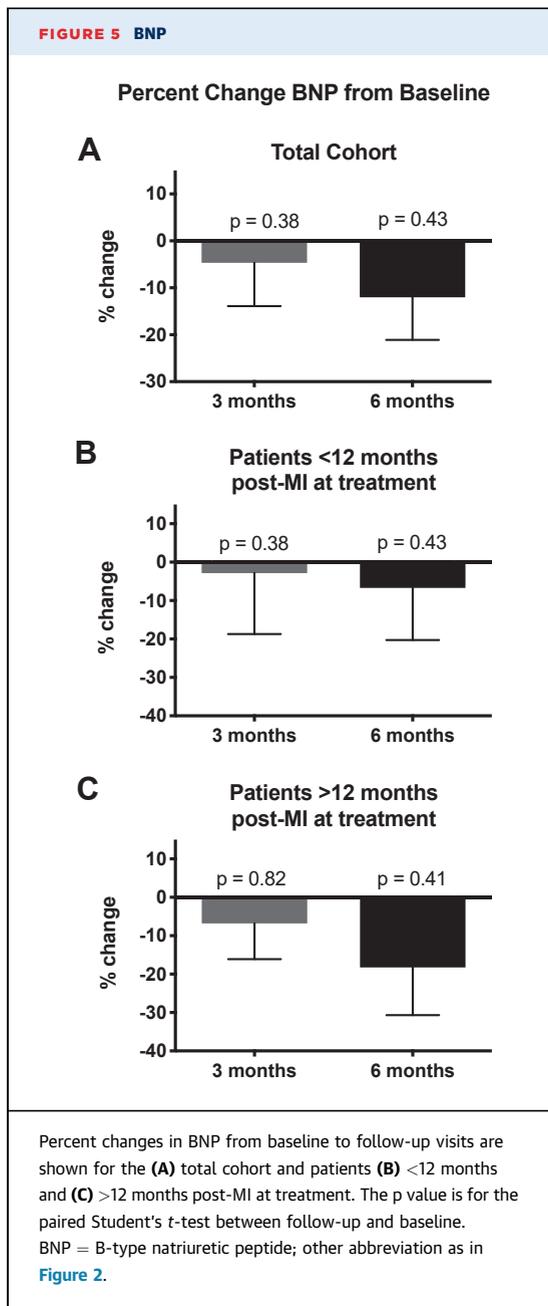


Absolute changes in (A) LVESV, (B) LVEDV, and (C) viable mass from baseline to follow-up visits are shown for patients <12 months post-MI and >12 months post-MI at treatment. The p value is for the paired Student's t-test between follow-up and baseline. Abbreviations as in Figures 2 and 3.

decreased from 5.23 cm at baseline to 4.80 cm and 5.01 cm at 3 and 6 months, respectively.

BNP decreased by approximately 5% and 12% at 3 and 6 months in the 13 patients with follow-up, although this was not significant (Figure 5A,

Supplemental Figure 5A, Supplemental Table 8). Similar to LV volumes, those in the late MI subset (>12 months post-MI) had the greatest decreases in BNP (Figures 5B and 5C, Supplemental Figures 5B and 5C).



DISCUSSION

To the best of our knowledge, this study is the first clinical trial to evaluate an injectable biomaterial delivered via percutaneous transendocardial injections for cardiac repair. We observed findings that support the initial safety and feasibility of injecting VentiGel, an ECM hydrogel derived from porcine myocardium, in post-MI patients with LV dysfunction. The trial was also the first demonstration of using a decellularized ECM hydrogel in any tissue in patients.

The concept of injectable biomaterials for treating MI was first introduced in the early 2000s (14-17). At that time, it was postulated that an injectable biomaterial may improve cardiac function by acting as an internal wall support to increase infarct wall thickness. Other materials were developed based on this hypothesis, including 2 alginate-based materials (polysaccharide hydrogels derived from seaweed) that were evaluated in clinical trials. Algisyl-LVR (LoneStar Heart, Inc., Laguna Hills, California) was delivered via surgical-based epicardial injections in patients with heart failure with both ischemic and nonischemic etiologies, whereas BL-1040/IK-5001 (Bellerophon Therapeutics, Warren, New Jersey) was delivered via intracoronary infusion in patients with acute MI (18,19). In phase 2 studies, Algisyl-LVR significantly improved exercise capacity but not measures of LV remodeling (20,21), and IK-5001 likewise failed to reduce progressive LV remodeling (22). Later preclinical studies have shown that passively supporting the infarct wall does not improve long-term cardiac function and suggest that the cell and tissue response to injected biomaterials play a dominant role in cardiac remodeling (23,24). VentiGel is a relatively weak hydrogel, about 2 orders of magnitude lower than the stiffness of healthy myocardium (25), and therefore would not be expected to act as a mechanical support; rather, it was designed to be delivered via a catheter and upon injection assemble into an open porous and fibrous scaffold to allow for endogenous cells to repopulate and remodel the matrix. By acting as a new physical scaffold with appropriate pore size and fiber diameter as well as containing the ECM cues of normal, healthy myocardium, the goal was to recreate a new micro-environment in the heart. Therefore, this trial was the first to evaluate a proreparative hydrogel in the heart.

Although numerous injectable biomaterials have now been evaluated in preclinical studies in MI and heart failure models, few have actually been delivered via a catheter because this poses unique material design constraints (26,27). The quick gelling nature, high viscosity, and/or lack of hemocompatibility prevent the majority of injectable biomaterials from this type of minimally invasive delivery modality. VentiGel was specifically designed to have the appropriate viscosity and gelation kinetics to facilitate transendocardial delivery, and extensive preclinical safety studies have shown hemocompatibility and a lack of arrhythmias (5,12). This study demonstrated the safety and feasibility of transendocardial delivery of VentiGel in post-MI patients with 15 to 18 injections being performed in all patients and without

serious adverse events observed to be definitely related to material or mapping/injection procedure. The first patient, whose pre-treatment history included a trifascicular block, had 2 adverse events (cardiogenic shock and heart block) that were deemed as possibly related to the study treatment; however, this patient improved in measures of LV remodeling (as determined by echocardiography), the 6-min walk test distance, and BNP levels at 3 and 6 months. Based on the safety advisory board's review, modest changes to the inclusion criteria (around arrhythmias) and additional early visits to the clinical site 1-week post-treatment were added to the study for the remaining 13 patients who were enrolled. No such serious adverse events were subsequently observed.

Although this phase 1 study was not designed to evaluate efficacy, there were suggestions of improvements including increases in the 6-min walk test distance and decreases in NYHA functional class across the entire cohort of patients. Enrollment criteria were set between 60 days and 3 years because it was unknown whether VentriGel would be more effective in earlier- versus later-stage MI patients. Therefore, 1 goal of this study was to inform the appropriate patient population to enroll in future studies. Post hoc analysis revealed that improvements in LV remodeling data, viable mass, and BNP levels were mainly observed in patients who had their MI >12 months before treatment. The lack of observed improvements in early MI patients (<12 months post-MI) may be a result of a more variable baseline in these patients as the infarct and peri-infarct regions recover from ischemic injury. In patients, infarct remodeling is typically thought to occur over the first several months, although studies have suggested that the dynamic time period of infarct healing is, in fact, a longer process (28,29). Overall, there were few increases in cardiac medications, and those that did occur were in the early subset of patients. No discernable changes were noted in EF, although this is not surprising given that parallel changes in LVEDV and LVESV can result in calculation of the same EF; this phenomenon has been observed in other heart failure trials (30,31). The suggested improvements in patients treated >12 months post-MI largely mirror results across the small and large animal preclinical studies with VentriGel in which the most notable changes were in LVESV and increases in cardiac muscle. In these later patients, there were trending decreases in LVESV and increases in viable mass at 6 months after treatment. In a rat MI model, analysis of gene expression in the infarct wall using whole transcript

microarrays showed changes in several tissue processes that suggests the hydrogel creates a new template for healing in the infarct (11). After injection, the fibrous and porous nature facilitates endogenous cell infiltration; over approximately 3 weeks, host cells remodel the temporary matrix similar to a healing wound (12). Altered pathways included blood vessel and cardiac development. Other shifts included a decrease in cell death, an altered inflammatory response, reduced cardiomyocyte hypertrophy, reduced fibrosis, and an altered myocardial metabolism (11). Although these studies were performed in a subacute MI model, we anticipate that in the later chronic MI patients, VentriGel is likely acting through similar pathways. In patients with ischemic cardiomyopathy, cardiomyocyte apoptosis continues to occur through the stages of acute MI, subacute MI, and all the way to end-stage heart failure (32). Moreover, cardiac metabolism is dysregulated in patients with heart failure (33), and it is now known that the collagen scar is, in fact, a dynamic tissue with collagen turnover and myofibroblasts, which are present for years in patients and continue to generate fibrogenic signals (34).

Although initial attempts at regenerative medicine for the heart focused on cell transplantation, there has been increasing focus in preclinical studies on biomaterials or matrix-based approaches to recreate a more appropriate microenvironment for tissue repair (35). In both cardiovascular and noncardiovascular applications, translation of biomaterial-alone therapies to facilitate endogenous repair is recently on this rise (13). Overall, these technologies, such as VentriGel, have significant advantages over the traditional regenerative medicine paradigm. For example, they can be off-the-shelf and cost-effective and do not have the burdens associated with supplying a living product. In the case of VentriGel, the cost of manufacturing is at least 2 orders of magnitude less than cell therapies, and, therefore, it could be a scalable and potentially cost-effective treatment for heart failure.

STUDY LIMITATIONS. The major limitation of this phase 1 study is that it was an uncontrolled, single-arm trial with a small number of patients not powered to evaluate efficacy. A single-arm trial was performed in this first-in-man study because of the difficulty of applying a transendocardial injection procedure in a control group, especially in earlier MI patients where there is less evidence of safety. Moreover, VentriGel is regulated as a device in Europe and Japan given that it acts as a new physical

scaffold to enable cell infiltration, and early device trials do not typically include a control group. Another limitation is that the patients' MIs spanned a relatively large post-infarction time period when the biologic response to VentiGel may vary. Thus, the optimum time to deliver VentiGel remains to be determined and will require a larger trial. However, the beneficial response of patients whose infarcts were >12 months appears to be an encouraging starting point going forward. Importantly, the study used state-of-the-art MRI imaging rather than echocardiography, which helped reduce variability. Because injections were limited to wall thickness of >8 mm, we were frequently precluded from injecting into the infarct zone as was performed in the pre-clinical porcine studies (12).

CONCLUSIONS

These results support the safety and feasibility of transendocardial injection of VentiGel in post-MI patients with LV dysfunction and introduces a new potential treatment for patients with heart failure. This trial was novel in many regards including the first injectable biomaterial to be delivered in patients using transendocardial injections, translation of the first preoperative hydrogel for the heart, and translation of the first decellularized ECM hydrogel in any tissue. As such, the significance of this trial reaches beyond the cardiac field because there have been numerous preclinical studies evaluating decellularized ECM hydrogels in various applications in other tissues (36). Although there is a long precedence of using porcine-derived materials, including decellularized ECM patches (37), this trial was the first to test an injectable hydrogel form of decellularized ECM in patients and therefore provides important safety and feasibility data and opens up the possibility of using ECM hydrogels in many other applications.

Importantly, this study also provides support for the safety and feasibility of treating post-MI patients with VentiGel and warrants further evaluation in larger randomized clinical trials.

ACKNOWLEDGMENTS The authors thank the patients that participated in this study. They thank Kelly Wilson, Tracey Early, Marilyn Mendez, Carlyn Sander, Matthew Brobeck, Jennifer Vermillion, Nusrat Jahan, Kelli Jones, Nicole Bostick, and Sarah Long for assistance with recruitment and follow-up of patients. They also thank Warren Sherman and Anthony DeMaria for thoughtful advice regarding the clinical trial design.

ADDRESS FOR CORRESPONDENCE: Dr. Karen L. Christman, Department of Bioengineering, Sanford Consortium for Regenerative Medicine, 2880 Torrey Pines Scenic Drive, La Jolla, California 92037. E-mail: christman@eng.ucsd.edu. OR Dr. Jay H. Traverse, Minneapolis Heart Institute, 920 East 28th Street, Suite 300, Minneapolis, Minnesota 55407. E-mail: trave004@umn.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Initial safety and feasibility of percutaneous transendocardial injections of VentiGel, a porcine-derived decellularized ECM hydrogel, was established in post-MI patients with potential effects on LV remodeling in patients >12 months post-MI.

TRANSLATIONAL OUTLOOK: Larger randomized controlled trials should be performed to further evaluate the safety and efficacy of transendocardial injections of VentiGel in post-MI patients.

REFERENCES

- Perin EC, Miller L, Taylor DA, Willerson JT, editors. *Stem Cell and Gene Therapy for Cardiovascular Disease*. Cambridge, MA: Academic Press, 2016.
- Swinehart IT, Badyak SF. Extracellular matrix bioscaffolds in tissue remodeling and morphogenesis. *Dev Dyn* 2016;245:351-60.
- Mann DL. Mechanisms and models in heart failure: a combinatorial approach. *Circulation* 1999;100:999-1008.
- Singelyn JM, DeQuach JA, Seif-Naraghi SB, Littlefield RB, Schup-Magoffin PJ, Christman KL. Naturally derived myocardial matrix as an injectable scaffold for cardiac tissue engineering. *Biomaterials* 2009;30:5409-16.
- Singelyn JM, Sundaramurthy P, Johnson TD, et al. Catheter-deliverable hydrogel derived from decellularized ventricular extracellular matrix increases endogenous cardiomyocytes and preserves cardiac function post-myocardial infarction. *J Am Coll Cardiol* 2012;59:751-63.
- DeQuach JA, Mezzano V, Miglani A, et al. Simple and high yielding method for preparing tissue specific extracellular matrix coatings for cell culture. *PLoS One* 2010;5:e13039.
- French KM, Boopathy AV, DeQuach JA, et al. A naturally derived cardiac extracellular matrix enhances cardiac progenitor cell behavior in vitro. *Acta Biomater* 2012;8:4357-64.
- French KM, Maxwell JT, Bhutani S, et al. Fibronectin and cyclic strain improve cardiac progenitor cell regenerative potential in vitro. *Stem Cells Int* 2016;2016:8364382.
- Gaetani R, Yin C, Srikumar N, et al. Cardiac derived extracellular matrix enhances cardiogenic properties of human cardiac progenitor cells. *Cell Transplant* 2016;25:1653-63.
- Bejleri D, Streeter BW, Nachlas AL, et al. A bioprinted cardiac patch composed of cardiac-specific extracellular matrix and progenitor cells for heart repair. *Adv Healthc Mater* 2018;7:e1800672.
- Wassenaar JW, Gaetani R, Garcia JJ, et al. Evidence for mechanisms underlying the functional

benefits of a myocardial matrix hydrogel for post-MI treatment. *J Am Coll Cardiol* 2016;67:1074-86.

12. Seif-Naraghi SB, Singelyn JM, Salvatore MA, et al. Safety and efficacy of an injectable extracellular matrix hydrogel for treating myocardial infarction. *Sci Transl Med* 2013;5:173ra25.

13. Christman KL. Biomaterials for tissue repair. *Science* 2019;363:340-1.

14. Christman KL, Fok HH, Sievers RE, Fang Q, Lee RJ. Fibrin glue alone and skeletal myoblasts in a fibrin scaffold preserve cardiac function after myocardial infarction. *Tissue Eng* 2004;10:403-9.

15. Christman KL, Vardanian AJ, Fang Q, Sievers RE, Fok HH, Lee RJ. Injectable fibrin scaffold improves cell transplant survival, reduces infarct expansion, and induces neovasculature formation in ischemic myocardium. *J Am Coll Cardiol* 2004;44:654-60.

16. Christman KL, Lee RJ. Biomaterials for the treatment of myocardial infarction. *J Am Coll Cardiol* 2006;48:907-13.

17. Rane AA, Christman KL. Biomaterials for the treatment of myocardial infarction a 5-year update. *J Am Coll Cardiol* 2011;58:2615-29.

18. Frey N, Linke A, Suselbeck T, et al. Intracoronary delivery of injectable bioabsorbable scaffold (IK-5001) to treat left ventricular remodeling after ST-elevation myocardial infarction: a first-in-man study. *Circ Cardiovasc Interv* 2014;7:806-12.

19. Lee RJ, Hinson A, Bauernschmitt R, et al. The feasibility and safety of Algisyl-LVR as a method of left ventricular augmentation in patients with dilated cardiomyopathy: initial first in man clinical results. *Int J Cardiol* 2015;199:18-24.

20. Anker SD, Coats AJ, Cristian G, et al. A prospective comparison of alginate-hydrogel with standard medical therapy to determine impact on functional capacity and clinical outcomes in patients with advanced heart failure

(AUGMENT-HF trial). *Eur Heart J* 2015;36:2297-309.

21. Mann DL, Lee RJ, Coats AJ, et al. One-year follow-up results from AUGMENT-HF: a multicentre randomized controlled clinical trial of the efficacy of left ventricular augmentation with Algisyl in the treatment of heart failure. *Eur J Heart Fail* 2016;18:314-25.

22. Rao SV, Zeymer U, Douglas PS, et al. Bio-absorbable intracoronary matrix for prevention of ventricular remodeling after myocardial infarction. *J Am Coll Cardiol* 2016;68:715-23.

23. Rane AA, Chuang JS, Shah A, et al. Increased infarct wall thickness by a bio-inert material is insufficient to prevent negative left ventricular remodeling after myocardial infarction. *PLoS One* 2011;6:e21571.

24. McGarvey JR, Pettaway S, Shuman JA, et al. Targeted injection of a biocomposite material alters macrophage and fibroblast phenotype and function following myocardial infarction: relation to left ventricular remodeling. *J Pharmacol Exp Ther* 2014;350:701-9.

25. Johnson TD, Lin SY, Christman KL. Tailoring material properties of a nanofibrous extracellular matrix derived hydrogel. *Nanotechnology* 2011;22:494015.

26. Johnson TD, Christman KL. Injectable hydrogel therapies and their delivery strategies for treating myocardial infarction. *Expert Opin Drug Deliv* 2013;10:59-72.

27. Hernandez MJ, Christman KL. Designing acellular injectable biomaterial therapeutics for treating myocardial infarction and peripheral artery disease. *JACC Basic Transl Sci* 2017;2:212-26.

28. Schroeder AP, Houlind K, Pedersen EM, Nielsen TT, Egeblad H. Serial cardiac magnetic resonance of global and regional left ventricular remodeling during 1 year after acute myocardial infarction. *Cardiology* 2001;96:106-14.

29. Pokorney SD, Rodriguez JF, Ortiz JT, Lee DC, Bonow RO, Wu E. Infarct healing is a dynamic process following acute myocardial infarction. *J Cardiovasc Magn Reson* 2012;14:62.

30. Jessup M, Greenberg B, Mancini D, et al. Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID): a phase 2 trial of intracoronary gene therapy of sarcoplasmic reticulum Ca²⁺-ATPase in patients with advanced heart failure. *Circulation* 2011;124:304-13.

31. Perin EC, Borow KM, Silva GV, et al. A phase II dose-escalation study of allogeneic mesenchymal precursor cells in patients with ischemic or nonischemic heart failure. *Circ Res* 2015;117:576-84.

32. Abbate A, Biondi-Zoccai GG, Baldi A. Pathophysiologic role of myocardial apoptosis in post-infarction left ventricular remodeling. *J Cell Physiol* 2002;193:145-53.

33. Rowe GC, Jiang A, Arany Z. PGC-1 coactivators in cardiac development and disease. *Circ Res* 2010;107:825-38.

34. Sun Y, Weber KT. Infarct scar: a dynamic tissue. *Cardiovasc Res* 2000;46:250-6.

35. Taylor DA, Chandler AM, Gobin AS, Sampaio LC. Maximizing cardiac repair: should we focus on the cells or on the matrix? *Circ Res* 2017;120:30-2.

36. Spang MT, Christman KL. Extracellular matrix hydrogel therapies: in vivo applications and development. *Acta Biomater* 2018;68:1-14.

37. Badyalak SF. The extracellular matrix as a biologic scaffold material. *Biomaterials* 2007;28:3587-93.

KEY WORDS biomaterial, catheter, heart failure, injectable, myocardial infarction

APPENDIX For supplemental material, please see the online version of this paper.