Heart disease is the cause of significant morbidity and mortality in the United States, with estimates of ≈800,000 new acute coronary events each year, a disease accounting for a substantial proportion of the national healthcare expenditure.1,2 On a cellular level, the events after a myocardial infarction (MI) include a change in the composition of the extracellular matrix, with a shift toward collagen deposition, hypocontractile scar formation, myocyte apoptosis, and progressive ventricular dilatation.3 The deleterious remodeling that occurs over time leads to augmentation in the stress–strain relationship of ventricular myocytes, inefficient contractility, and, ultimately, heart failure. When current treatments for coronary artery disease fail, they usually do so because microvascular perfusion is not adequately restored—a critical, independent predictor of ventricular remodeling, reinfarction, heart failure, and death.4

In an effort to restore microvascular perfusion, various cytokines have been used to stimulate angiogenesis, with moderate success. One such cytokine, stromal cell–derived factor 1-α (SDF-1), is a key regulator of hematopoietic stem cell trafficking between the bone marrow and peripheral circulation and effectively localizes endothelial progenitor cells (EPCs) to areas of ischemia.5,6 SDF-1 has been shown by our group and others to increase vasculogenesis, decrease cardiac myocyte

**Background**—Exogenously delivered chemokines have enabled neovascularogenic myocardial repair in models of ischemic cardiomyopathy; however, these molecules have short half-lives in vivo. In this study, we hypothesized that the sustained delivery of a synthetic analog of stromal cell–derived factor 1-α (engineered stromal cell–derived factor analog [ESA]) induces continuous homing of endothelial progenitor cells and improves left ventricular function in a rat model of myocardial infarction.

**Methods and Results**—Our previously designed ESA peptide was synthesized by the addition of a fluorophore tag for tracking. Hyaluronic acid was chemically modified with hydroxyethyl methacrylate to form hydrolytically degradable hydrogels through free-radical–initiated crosslinking. ESA was encapsulated in hyaluronic acid hydrogels during gel formation, and then ESA release, along with gel degradation, was monitored for more than 4 weeks in vitro. Chemotactic properties of the eluted ESA were assessed at multiple time points using rat endothelial progenitor cells in a transwell migration assay. Finally, adult male Wistar rats (n=33) underwent permanent ligation of the left anterior descending (LAD) coronary artery, and 100 μL of saline, hydrogel alone, or hydrogel+25 μg ESA was injected into the borderzone. ESA fluorescence was monitored in animals for more than 4 weeks, after which vasculogenic, geometric, and functional parameters were assessed to determine the therapeutic benefit of each treatment group. ESA release was sustained for 4 weeks in vitro, remained active, and enhanced endothelial progenitor cell chemotaxis. In addition, ESA was detected in the rat heart >3 weeks when delivered within the hydrogels and significantly improved vascularity, ventricular geometry, ejection fraction, cardiac output, and contractility compared with controls.

**Conclusions**—We have developed a hydrogel delivery system that sustains the release of a bioactive endothelial progenitor cell chemokine during a 4-week period that preserves ventricular function in a rat model of myocardial infarction. (Circulation. 2013;128[suppl 1]:S79-S86.)

**Key Words:** angiogenesis ■ endothelial progenitor cell ■ injectable hydrogels ■ myocardial infarction

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apoptosis, increase cardiac myocyte survival, and preserve ventricular geometry.1–10 The functional and regenerative benefits of SDF-1 treatment are directly related to its ability to bind its receptor, CXCR4. However, there is a temporal mismatch between the peak expression of SDF-1 and upregulation of CXCR4 on bone marrow and cardiac stem cells. Within an hour of ischemia, cardiac SDF-1 expression is rapidly upregulated in the heart, whereas CXCR4 peaks at 96 hours, by which time SDF-1 is nearly absent.5,11,12 Contributing to this mismatch is that SDF-1 is rapidly cleared from the circulation and cleaved by matrix metalloproteinase-2 and CD-26.13–16

To address the temporal mismatch in the SDF-1:CXCR4 axis, SDF-1 concentration within cardiac tissue must be maintained during the course of several weeks to prolong its trophic effects on CXCR4+ cells, thereby optimizing angiogenesis, cardiac myocyte preservation, and ventricular performance. In the current study, we hypothesized that a hyaluronic acid (HA)-based hydrogel could sustain the release of our previously reported engineered SDF-1 analog (ESA) over several weeks, resulting in the temporal realignment of the SDF:CXCR4 axis and consequently improved angiogenesis, limited ventricular remodeling, and preserved cardiac function in a rat model of MI.

Methods

Custom Peptide Synthesis

We have previously reported on the design and synthesis of an ESA.7,17 Briefly, the CXCR4 receptor–binding N terminus and the molecular-stabilizing C terminus were preserved, whereas the central β-pleated sheet was deleted and replaced with 2 proline linker residues. Using mathematical modeling, this modified sequence was predicted to retain a 3-dimensional protein configuration as similar to the native SDF-1α as possible. The designed protein was synthesized using solid-phase peptide synthesis, where the N-α-amino acids are incorporated into the peptide in a stepwise fashion while one end is attached to a solid support matrix. In addition, we added HiLyte Fluor TR (AnaSpec, San Jose, CA) during the synthesis process as a fluorophore tag for use in the in vitro studies, and HiLytefluor 750 (AnaSpec, San Jose, CA) was added for the in vivo study.

Macromer Synthesis

Sodium hyaluronate (74 kDa, Lifecore) was chemically modified with hydroxyethyl methacrylate (HEMA) to incorporate a terminal methacrylate group for free-radical–initiated crosslinking and ester bonds to introduce hydrolytic degradation.19 Briefly, HEMA was reacted with succinic anhydride via a ring-opening polymerization in the presence of N-methylimidazole to obtain HEMA-COOH, which was then coupled to a tetrabutylammonium salt of HA in the presence of 4-dimethylaminopyridine. The resulting HA macromer with the presence of N-methylimidazole to obtain HEMA-COOH, which is attached to a solid support matrix. In addition, we added HiLyte fluorophore tag for use in the in vitro studies, and HiLytefluor 750 (AnaSpec, San Jose, CA) was added for the in vivo study.

Hydrogel Gelation

To form hydrogels rapidly on injection into the myocardium, a 2-component redox initiator system consisting of ammonium persulfate and N,N,N′,N′-tetramethylethylenediamine was used. Ammonium persulfate and N,N,N′,N′-tetramethylethylenediamine were added to a final concentration of 10 mM/L in 4% (wt/vol) HEMA-HA solution and kept on ice. The kinetics of gel formation were characterized with rheometry at 37°C by monitoring the storage (G′) and loss (G″) modulus with time, while applying oscillatory strain (20 mm° 1° cone geometry, 1% strain, 1 Hz, Texas Instruments AR 2000ex). For in vitro release kinetics, 25 μg ESA was added per 50 μL gel precursor solution, and 50 μL gels were formed in cylindrical molds for 30 minutes at 37°C. Gels were incubated in 1 mL PBS supplemented with 1% BSA at 37°C, and buffers were refreshed every 2 days. Fluorescence of eluted ESA from each 2-day sample, extending during a 4-week period, was quantified on a microplate reader (TECAN, Austria), whereas HA content was quantified with a uronic acid assay.20 After 28 days, hydrogels were enzymatically degraded with hyaluronidase (800 U/mL, Sigma) and evaluated for remaining ESA and HA.

EPC Chemotaxis

Bone marrow mononuclear cells were isolated from the long bones of syngeneic adult male Wistar rats (Charles River) by density centrifugation with Histopaque 1083 (Sigma-Aldrich), plated on vitronectin-coated dishes and cultured in endothelial basal medium-2 supplemented with EGM-2 SingleQuot (Lonza) containing human epidermal growth factor, fetal bovine serum, vascular endothelial growth factor, basic human fibroblast growth factor, recombinant human long R3 insulin-like growth factor-1, ascorbic acid, heparin, gentamicin, and amphotericin-B. Media was changed on culture day 4, and nonadherent bone marrow mononuclear cells were discarded, enriching for the EPC phenotype.

A modified transwell migration assay (Neuro Probe, Gaithersburg, MD) was used to assess EPC migration. Briefly, 8-μm filters were loaded into control and experimental chambers. Seven-day EPCs cultured in endothelial-specific media on vitronectin-coated plates were trypsinized, counted, and brought to a concentration of 90 cells/μL in Dulbecco’s PBS. The bottom chamber was loaded with either Dulbecco’s PBS or the eluted ESA from the hydrogel at each respective 2-day time point. Dulbecco’s PBS from hydrogel without ESA served as a control. A 560-μL cell suspension was added to the top chamber of each well. All chambers were incubated at 37°C for 3.5 hours in 5% CO2. The cells remaining in the top chamber were wiped clean with a cotton swab, and the filter was removed, placed on a glass slide, and mounted with Vectashield+4',6-diamidino-2-phenylindole (Vector Laboratories). Slides were visualized on a DF5000B Leica fluorescence microscope and analyzed via LASAF version 2.0.2 (Leica, Wetzlar, Germany) software. Boyden chamber analyses were performed in triplicate.

Animal Care and Biosafety

Male Wistar rats weighing 250 to 300 g were obtained from Charles River Laboratories (Wilmington, MA). Food and water were provided ad libitum. All experiments pertaining to this investigation conformed to the Guide for the Care and Use of Laboratory Animals, published by the US National Institutes of Health (Eighth Edition, 2011). The protocol was approved by the Institutional Animal Use and Care Committee of the University of Pennsylvania (protocol number 803394).

Animal Model

MI was induced in 33 male Wistar rats using an established and highly reproducible model. Briefly, the rats were anesthetized in a 2-L induction chamber (VetEquip, Pleasantville, CA), and 3% isoflurane was continuously delivered. A 16-gauge angiocatheter was used for endotracheal intubation and connected to mechanical ventilation (Hallowell EMC, Pittsfield Mass) where 1% isoflurane was maintained throughout the operation. A thoracotomy was performed through the left fourth intercostal space, the heart was exposed, and a 7-0 polypropylene suture was placed around the left anterior descending artery 2 mm below the left atrium. The suture was briefly snared to verify the size and location of myocardial ischemia based on color change and was permanently tied down to produce a large anterolateral MI.3–5,17,18 The animals were then randomized into 3 groups and received 4 separate peri-infarct intramyocardial injections of saline (100 μL; n=8), hydrogel alone (100 μL; n=10), or hydrogel+25 μg ESA (100 μL; n=15). The thoracotomy was closed in multiple layers, and tissue adhesive (VetBond; 3M, Minneapolis, MN) was applied over the incision. All rats were implanted with subcutaneous microchips (BioMedic Data Systems, Boise, ID) and recovered from anesthesia. Buprenorphine (0.5 mg/kg) was administered for postoperative pain control.
Echocardiographic and Hemodynamic Assessment

Left ventricular (LV) geometry and function were evaluated preoperatively and at 4 weeks in all animals.21 A Phillips Sonos 5500 revD ultrasound system (Philips Medical Systems, Amsterdam ND) was used, with a 12-MHz transducer at an image depth of 2 cm. LV parasternal short-axis 2-dimensional and M-mode images at the level of the papillary muscle were used to obtain echocardiographic data. All analyses were performed by a single investigator who was blinded to the treatment groups.

Four weeks after LAD ligation, all 3 groups of animals underwent invasive hemodynamic measurements with a pressure–volume conductance catheter (SPR-869; Millar Instruments, Inc.). The catheter was calibrated via 5-point cuvette linear interpolation with parallel conductance subtraction by the hypertonic saline method. Rats were anesthetized as above, and the catheter was introduced into the LV using a closed-chest approach via the right carotid artery. Measurements were obtained before and during inferior vena cava occlusion to produce static and dynamic pressure–volume loops under varying load conditions. Data were recorded and analyzed with LabChart version 6 software (AD instruments) and ARIA Pressure Volume Analysis software (Millar Instruments, Inc.). Finally, cardiac output was assessed by placing a 2.5-mm periaortic Doppler flow probe (Transonic Systems, Ithaca, NY) around the ascending aorta.

In Vivo ESA Release

In a subset of 6 animals from the hydrogel+ESA group, in vivo fluorescence of ESA was quantified using a Pearl Impulse small animal imaging system (LI-COR, Lincoln, NE) on postinjection day 1 and every 4 days thereafter through the 4-week time point to visualize intramyocardial ESA. Animals were anesthetized with 1% isoflurane via nose cone, the left chest was shaved, and the animals were placed in the right lateral decubitus position on the imaging platform with the left chest closest to the camera. Dynamic images were obtained using the 800-nm channel of the instrument (785/820 nm excitation/emission), with standardized parameter settings scaled to the same maximum values. Estimates of the fluorescence of ESA were determined by fixed regions of interest over the heart, and signal intensity was calculated using the manufacturer’s software. Signal intensity for each time point was normalized to the peak signal observed for each animal, and the ratio for each time point was averaged for all 6 animals. Animals from the saline group (n=3) served as negative controls. Animals from the saline group (n=3) served as negative controls.

Histological Analysis and Immunohistochemistry

To assess ventricular geometry, infarct size, and microvascular angiogenesis, hearts were explanted in a subset of 11 animals after the invasive hemodynamic assessment was performed (saline, n=3; hydrogel, n=4; hydrogel+ESA, n=4) and flushed with PBS and then injected retrograde with Tissue Tek optimum cutting temperature (OCT) compound (Sekura, The Netherlands) through the aorta and pulmonary artery. Hearts were submerged in OCT, frozen, and stored in a −80°C freezer. Orientation of hearts during freezing was standardized so as to result in consistent positioning during the sectioning process. Eight 10-µm-thick sections were prepared from each heart at the level of the papillary muscles and stained with hematoxylin and eosin or Masson’s trichrome. Standardized digital photographs were taken with a Nikon D5100 SLR camera (Nikon, Tokyo, Japan). Photographs were uploaded to ImageJ (v1.46b) and the size of the infarct assessed with digital planimetry. Two 10-µm-thick sections from each animal were stained with antibodies directed against von Willebrand factor to quantify capillary density. Sections were fixed with HistoChoice (Amresco, Solon, OH), blocked in 10% fetal bovine serum, and incubated with sheep anti–von Willebrand factor (conjugated to fluorescein isothiocyanate, 1:100 dilution; Abcam) for 2 hours. Donkey anti-goat antibody–fluorescein isothiocyanate (Abcam 7121, 1:1000) was used as a secondary reagent, and sections were counterstained with 4’,6-diamidino-2-phenylindole to visualize nuclei. Immunofluorescent images were acquired and analyzed as above. Group blinded counts were averaged more than 4 fields per specimen.

Statistical Analysis

All analyzed variables approximated a normal distribution, and values for continuous variables are reported as mean±SD. Pairwise Student t tests were used to compare continuous variables between groups, and a Bonferroni correction was used to account for multiple comparisons. Statistical significance was set at P<0.025. Analyses were performed with STATA (StataCorp, College Station, TX) statistical software package, version 12.1.

Results

Hydrogel Formation

HEMA-HA gels were formed rapidly through the mixing of 2 solutions that each contain components of the ammonium persulfate/N,N,N’,N’-tetramethylmethylenediamine free-radical initiator system (Figure 1). Gelation occurred within 1 minute, and the crosslinking reaction reached a plateau within 30 minutes on addition of ammonium persulfate/N,N,N’,N’-tetramethylmethylenediamine (TEMED) initiators (B).

Figure 1. Hydrogel formation. Hydroxyethyl methacrylate (HEMA)–modified hyaluronic acid macromers synthesized with terminal vinyl double bonds for free-radical–initiated crosslinking into gels and eser groups to introduce hydrolytic degradation of the gels (A). Monitoring storage (G′, elastic component) and loss (G″, viscous component) moduli over time with rheometry show that solid gels form from an injectable liquid solution within minutes on addition of ammonium persulfate (APS)/N,N,N’,N’-tetramethylmethylenediamine (TEMED) initiators (B).
minutes. By using this crosslinking route, we are able to inject the liquid precursor solution through a syringe and form solid gels under physiological conditions (Figure 1).

**Hydrogel Degradation and ESA Release Kinetics**

ESA release was sustained for ≥28 days in vitro when encapsulated in degradable HEMA-HA hydrogels (Figure 2). An initial burst release of ESA was observed during the first few days due to ESA that was not encapsulated during gel formation or encapsulated in the periphery of the gels. Similarly, an initial burst release of HA was observed because of HEMA-HA polymers that were not incorporated into the gels during the crosslinking reaction. After this initial period, ESA release was steady for ≈20 days while the gels remained intact. After the gels began to hydrolyze and HA was released, the rate of ESA release increased because of less restricted diffusion within the gels. Ultimately, the hydrogels completely degraded into soluble components and released any remaining contents.

**Hydrogel Release of ESA Remains Functional**

Using a transwell migration assay, EPCs showed significant chemotaxis toward ESA released from the gels, indicating that the peptide remains active after gel encapsulation and release (Figure 2). Importantly, the ESA remained active throughout the entire 28-day in vitro study. Significant increases in EPC chemotaxis were also observed in samples from the hydrogel alone compared with PBS, which is attributed to the HA degradation products being released from the material.

**Tracking ESA Within the Heart After MI**

Using ESA that had been conjugated with a near-infrared wavelength fluorophore (ie, HiLyte Fluor 750, 753/778 nm excitation/emission), we were able to image ESA in the heart to quantify the dynamics of ESA release from hydrogels. Rats treated with the fluorescently tagged ESA encapsulated in hydrogels manifested a strong fluorescent signal for the first 10 days, followed by a steady decline in signal until a plateau at day 24, when there was no difference in signal compared with the saline control group (Figure 3). The quantitative data for ESA localized to the heart are shown in Figure 3 and demonstrate that encapsulated ESA is released from hydrogels during a 24-day time period in vivo.

**Hydrogel+ESA Improves Hemodynamics After MI**

Echocardiographic assessment of cardiac structure and function revealed significant benefits in the hydrogel+ESA group compared with controls (Table). At 4 weeks, LV diameter at end diastole was reduced in the hydrogel+ESA group compared with the saline group (hydrogel+ESA, 0.635±0.113 cm; saline, 0.767±0.126 cm; P=0.02); however, there was no statistical difference compared with the hydrogel alone group (0.692±0.200 cm; P=0.2). LV ejection fraction was preserved and significantly greater in the hydrogel+ESA group compared with the saline (hydrogel+ESA, 62.2±6.1%; saline, 39.7±14.2%; P<0.001) and hydrogel alone groups (49.7±13.9%; P=0.01). In addition, cardiac output and contractility were improved in the hydrogel+ESA group compared with the saline and hydrogel alone groups (Table).

**Hydrogel+ESA Result in Preservation of Ventricular Geometry, Smaller Infarcts, Greater Borderzone Capillary Density, and Upregulation of CXCR4+ Cells**

Histological analyses showed smaller ventricular areas in the hydrogel+ESA group compared with saline control (37.6±0.9 mm²; 49.7±4.9 mm²; P=0.01) but was statistically similar to the hydrogel alone group (39.9±9.9 mm²; P=0.4), whereas the infarct fraction of the LV was significantly smaller in the
hydrogel+ESA group compared with controls (hydrogel+ESA, 2.1±1%; saline, 13.0±5.6%; \( P < 0.001 \); hydrogel, 4.0±3.6%; \( P = 0.05 \)). Representative images are shown in Figure 4. Analysis of immunofluorescently labeled von Willebrand factor showed a significant increase in capillary density in the hydrogel+ESA group and hydrogel alone group compared with the saline group. Quantitative analysis of capillary density showed 43.1±12.3 capillaries/high powered field (HPF) in the hydrogel+ESA group compared with 11.8±2.9 capillaries/HPF in the saline group (\( P < 0.001 \)) and 36.4±11.7 capillaries/HPF in the hydrogel alone group (\( P = 0.1 \)). In addition, there were significantly more CXCR4+ cells in the hydrogel+ESA group (17.8±7.6 cells; hydrogel, 6.3±1.5 cells; \( P = 0.02 \); saline, 2.3±0.9 cells; \( P = 0.003 \); Figure 5).

Discussion

During the past 5 years, investigations into intramyocardial injection of bioengineered, chemically modified materials after MI have shown promising results, causing thicker, stiffer infarcts, limiting infarct expansion and preserving LV geometry. Although promising, it may be very useful to improve on these techniques through further biological targets, such as stimulating a robust angiogenic response and localizing progenitor cells to the site of infarction. HA-based hydrogels offer an intriguing benefit because they are able to provide both support to the infarcted myocardium during the acute phase and a platform for the delivery of potent chemokines, where release is controlled with diffusion and hydrolytic degradation.

In the present study, we used an HA-based hydrogel to encapsulate ESA to sustain release of this polypeptide during a 1-month time period. The hydrogel was chemically engineered to degrade more than 1 month, which was confirmed in vitro by a uronic acid detection assay. We were able to show that functional ESA can be released from the hydrogels during the entire month, recruiting EPCs in a transwell migration.

Table. Left Ventricular Function

<table>
<thead>
<tr>
<th></th>
<th>Saline</th>
<th>Hydrogel Alone</th>
<th>Hydrogel+ESA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output, mL/min</td>
<td>27.0±8.6; ( P = 0.008 )</td>
<td>34.9±8.5; ( P = 0.009 )</td>
<td>46.1±10.4</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>39.7±4.2; ( P &lt; 0.001 )</td>
<td>49.7±13.9; ( P = 0.01 )</td>
<td>62.2±6.1</td>
</tr>
<tr>
<td>LVIDd, cm</td>
<td>0.767±0.126; ( P = 0.02 )</td>
<td>0.692±0.200; ( P = 0.2 )</td>
<td>0.635±0.113</td>
</tr>
<tr>
<td>ESPVR</td>
<td>6.4±5.6; ( P &lt; 0.001 )</td>
<td>12.6±3.8; ( P = 0.004 )</td>
<td>20.1±6.5</td>
</tr>
</tbody>
</table>

\( P \) values refer to comparison between hydrogel+ESA group and the control group; saline or hydrogel alone. ESA indicates engineered stromal cell–derived factor analog; ESPVR, end systolic pressure volume relationship; and LVIDd, left ventricular diameter at end diastole.
assay across all time points. Interestingly, the hydrogel alone group also stimulated migration of EPCs, albeit to a lesser extent than hydrogel+ESA, a finding that is supported by previous studies and likely because of the interaction of HA with the membrane protein CD44 on EPCs.19,27,28

Our in vivo studies demonstrated that treatment with hydrogel+ESA resulted in smaller infarcts, stimulated angiogenesis at the borderzone, and preserved LV geometry and function. Again, we observed that treatment with hydrogel alone stimulated a moderate amount of angiogenesis at the borderzone and maintained LV geometry, findings that are consistent with previous literature showing that biochemically modified gels can limit infarct expansion by providing structural support to the myocardium, resulting in improved

![Figure 4](http://circ.ahajournals.org/)

Figure 4. Hematoxylin and eosin stain (H&E) and Masson’s trichrome staining. Left ventricular (LV) area and infarct fraction were calculated from histological sections. Shown are representative sections from H&E-stained sections (A, saline; B, hydrogel alone; C, hydrogel+engineered stromal cell-derived factor analog [ESA]) and Masson trichrome–stained sections (D, saline; E, hydrogel alone; F, hydrogel+ESA). Graphs (G) and (H) show differences in LV wall area and fibrosis, respectively. *P<0.05. †Error bars represent SD.

![Figure 5](http://circ.ahajournals.org/)

Figure 5. Immunohistochemistry with von Willebrand factor (vWF) and CXCR4. Analysis of immunofluorescent expression of vWF revealed a significant increase in the hydrogel+engineered stromal cell-derived factor analog (ESA) group. Representative photomicrographs from each group are shown (A). The hydrogel+ESA group had significantly more CXCR4+ cells at 4 weeks (CXCR4; green). Nuclei are stained blue with 4′,6-diamidino-2-phenylindole (B). Quantitative analysis of capillaries (C) and number of CXCR4+ cells (D). *P<0.05. †Error bars represent SD. FITC indicates fluorescein isothiocyanate.
hemodynamic functioning. Finally, we were able to successfully track ESA more than 24 days using fluorescent imaging, confirming that our hydrogels sustained release of ESA in vivo as we originally proposed.

It is noteworthy the degree to which the hydrogel alone group derived structural and functional benefit in this study. Although this is not a new finding, it is interesting that HA hydrogels can limit infarct expansion and preserve ventricular geometry, causing improved hemodynamics. It is likely that these benefits are multifactorial in nature, resulting from the structural properties of the gel itself, as well as the interaction of HA with CD44 on bone marrow progenitor cells. Ultimately, however, we have shown that hydrogel and ESA have a synergistic effect on the heart after MI, resulting in improved structure and function of cardiac myocytes and upregulation of CXCR4+ cells. Despite the similarities in angiogenesis between the hydrogel and hydrogel+ESA groups, improved hemodynamic function was observed in the hydrogel+ESA group. This is most likely because of the fact that the role of ESA is not merely to attract bone marrow progenitor cells but also to recruit endogenous cardiac progenitor cells to the infarct borderzone. Through its interaction with CXCR4+ cardiac myocytes, ESA may lead to preservation of cardiac cells through reduced apoptosis via CXCR4 pathways, leading to improved hemodynamics. In a very eloquent knockout model, Dong et al. support the above hypothesis by showing that the SDF-1:CXCR4 axis is vitally important for the preservation of cardiac function after MI, specifically identifying SDF-1 binding to CXCR4+ cardiac cells as paramount to retention of cardiac myocytes, reduction in infarct size, and localization of cardiac stem cells at the borderzone—and all without altering vascular density.

One limitation of this study is that it was performed in an acute animal model of MI, where the treatment was given immediately after coronary artery ligation. Although this satisfies our scientific search for how hydrogel-encapsulated ESA interacts with ischemic myocardium, the positive findings reported here may not be generally applied to clinical situations where treatment modalities must be effective in the setting of chronic heart failure. Chronic post-ischemic changes offer a complex problem to the investigator, where deleterious remodeling and a diminutive stem cell supply must be overcome. However, as a proof-of-principle study and a starting point, we have effectively shown that sustained release of ESA by injectable hydrogels is possible in the heart.

In summary, we have been able to develop a hydrogel delivery system that sustains release of the potent EPC chemokine ESA more than 1 month and have shown it to be effective both in vitro and in vivo. This dual treatment approach temporarily aligns the SDF:CXCR4 axis by prolonging peak ESA levels to match the time course of upregulation of CXCR4 on progenitor cells, resulting in improved angiogenesis and optimized LV function.

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Disclosures
None.

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Sustained Release of Engineered Stromal Cell–Derived Factor 1-α From Injectable Hydrogels Effectively Recruits Endothelial Progenitor Cells and Preserves Ventricular Function After Myocardial Infarction
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