Heart failure is a leading cause of mortality and morbidity in the United States and its prevalence continues to increase especially as the population ages.1 A significant cause of heart failure is ischemic heart disease.1 Myocardial infarction and chronic ischemic disease can lead to the loss of a substantial number of cardiac myocytes thus justifying attempts to design an efficacious regenerative therapeutic strategy.2,3 Initial studies have documented the safety and feasibility of administering stem or progenitor cells to restore the lost myocardium. Recently, intracoronary infusion of autologous c-kit+ cardiac stem cells in a phase 1 trial resulted in significant clinical improvements in patients with ischemic cardiomyopathy.4,5 These results provide hope for the development of therapeutic strategies to augment the limited regenerative potential of the heart.6 Even though the heart has regenerative capacity, it is clear that it is inadequate to replace the massive loss of cardiomyocytes in the setting of myocardial infarction(s).2,3 There is mounting evidence that after ischemic insults, several factors are activated that lead to the recruitment of progenitor cells to the site of injury.6-8 These results provide hope for the development of therapeutic strategies to augment the limited regenerative process for the failing heart. In this article, Penn et al9 report preliminary results on the safety and feasibility of injecting stromal cell-derived factor-1 (SDF-1) in the myocardium of patients with ischemic heart disease. SDF-1, also known as CXCL12, is a constitutively expressed and inducible chemokine that is transiently upregulated in response to tissue injury. Preclinical studies indicate that SDF-1 increases stem cell homing by stimulating the CXCR4 receptor in these cells. The CXCL12-CXCR4 axis has been shown to have antiapoptotic effects and induces angiogenesis and inhibits fibrosis. During myocardial infarction, the increased expression of SDF-1 has been thought to act as a cellular signal to attract potentially beneficial stem cells to repair, and possibly regenerate, damaged myocardium. SDF-1 expression is increased in the myocardium but only for the 7 days after an infarction. In this study, the investigators capitalize on the relationship between SDF-1 and stem cell homing and propose to prolong SDF-1 expression with the goal of promoting endogenous cardiac repair.

In this phase 1 open-label dose-escalation study, patients with ischemic cardiomyopathy received 1 of 3 doses of SDF-1: 5, 15, or 30 mg via endomyocardial injection. The patients were followed for 12 months with assessment of several outcomes, including major adverse cardiac events, noninvasive measurement of left ventricular function and volumes, changes in N-terminal probrain natriuretic peptide, quality of life, and myocardial perfusion, as measured by single-photon emission computed tomography imaging. Seventeen patients were enrolled, and 15 completed the 12-month follow-up. Overall, endomyocardial administration of SDF-1 was found to be feasible and safe. Although this phase 1 trial was designed primarily to assess the safety of the approach in humans, the authors report several efficacy end points. The limited number of patients precludes drawing firm conclusions on the beneficial effect of SDF-1 administration in this patient population, but a couple of parameters merit attention. The left ventricular function and volumes were stable over the 12-month follow-up without clear differences between the 3 treatment groups. Despite this, patients receiving the highest doses (15 and 30 mg) were found to have an improvement in their clinical status, including quality of life, 6-minute walk test, and New York Heart Association class.

The investigators used plasmid DNA to deliver SDF-1 to the myocardium. This delivery method induces short-term expression of SDF-1, which is a reasonable choice based on the biology of this agent.10 The efficiency of plasmid-based DNA delivery is quite low but is relatively safe and has low immunogenicity.10 In addition, plasmid DNA does not have packaging limitations that restricts the transgene size.11 In contrast, recombinant adenoviral vectors induce higher expression with a short-time course; however, the inflammatory response they cause would not be acceptable in this patient population.11 Recombinant adeno-associated vectors or lentiviruses, other viral vectors that are commonly used in cardiovascular applications, would induce long-term expression of SDF-1, which may cause untoward effects especially as the transgene would be expressed in other tissues.11

The investigators used a direct intramyocardial delivery route to express SDF-1 in peri-infarct areas. Fifteen 1-mL injections in the peri-infarct areas identified by cardiac echocardiography were performed in the patients. The primary advantage of this method is that plasmid delivery bypasses the
endothelial barrier. This results in a high local concentration at the injection site. In addition, by avoiding exposure to the blood, deactivation of the vectors by circulating DNAs can be prevented. There is also minimal exposure of the plasmid to off target organs, although local administration cannot completely avoid some systemic vector distribution. Despite using specialized infusion catheters with helical needles, the retention of plasmid or vector delivered by this method is quite low and decreases the efficiency of local expression.

Different experimental models have shown that SDF-1 regulates adult vasculogenesis and neovascularization. Interestingly, the authors report a significant improvement in myocardial perfusion (assessed by single-photon emission computed tomography imaging) in the 2 groups receiving the highest dose (15 and 30 mg) as compared with the low-dose (5 mg) group. The regional changes in myocardial perfusion, as well as myocardial viability, were not reported but would help in understanding the angiogenesis-dependent and -independent effects of SDF-1 in the failing heart.

There are specific issues with the design of the clinical trial that tempers enthusiasm for the positive data reported. As an open-label study without a placebo-controlled arm, it is difficult to place the clinical improvements in any context. At the 4-month follow-up, 3 of the 7 parameters measured trended toward a worsening state. N-terminal probrain natriuretic peptide along with end-systolic volume trended upward at the 12-month follow-up for the low- and mid-dose groups. The data do not suggest any concordance that would reduce false-positive rates. Combining the mid- and high-dose groups to gain statistical significance is also questionable; in fact, this statistical maneuver was not predefined in the clinical design. Finally, as is typical for a small phase 1 study, there were baseline imbalances among groups that could have resulted in meaningful differences.

Despite these shortcomings, this clinical trial shows the feasibility of this strategy to enhance recruitment of progenitor cells in patients with ischemic cardiomyopathy. Further clinical studies are eagerly anticipated.

**Acknowledgments**

The authors thank Dr Jane A. Leopold for helpful discussions regarding the article.

**Sources of Funding**

This work is supported by National Institute of Health R01 HL093183, a National Heart, Lung, and Blood Institute Program of Excellence in Nanotechnology (PEN) Award, Contract No. HHSN268201000045C, and P50 HL112324.

**Disclosures**

None

**References**


Myocardial Delivery of Stromal Cell-Derived Factor 1 in Patients With Ischemic Heart Disease: Safe and Promising
Roger J. Hajjar and Jean-Sebastien Hulot

Circ Res. 2013;112:746-747; originally published online February 21, 2013;
doi: 10.1161/CIRCRESAHA.113.300902
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/112/5/746

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at: http://circres.ahajournals.org/subscriptions/