Heart Failure

Local Controlled Intramyocardial Delivery of Platelet-Derived Growth Factor Improves Postinfarction Ventricular Function Without Pulmonary Toxicity

Patrick C.H. Hsieh, MD, PhD; Catherine MacGillivray, AD; Joseph Gannon; Francisco U. Cruz, MS; Richard T. Lee, MD

Background—Local delivery methods can target therapies to specific tissues and potentially avoid toxicity to other organs. Platelet-derived growth factor can protect the myocardium, but it also plays an important role in promoting pulmonary hypertension. It is not known whether local myocardial delivery of platelet-derived growth factor during myocardial infarction (MI) can lead to sustained cardiac benefit without causing pulmonary hypertension.

Methods and Results—We performed a randomized and blinded experiment of 127 rats that survived experimental MI or sham surgery. We delivered platelet-derived growth factor (PDGF)-BB with self-assembling peptide nanofibers (NFs) to provide controlled release within the myocardium. There were 6 groups with n=20 in each group: sham, sham+NF, sham+NF/PDGF, MI, MI+NF, and MI+NF/PDGF. Serial echocardiography from 1 day to 3 months showed significant improvement of ventricular fractional shortening, end-systolic dimension, and end-diastolic dimension with local PDGF delivery (P<0.05 for MI+NF/PDGF versus MI or MI+NF). Catheterization at 4 months revealed improved ventricular function in the controlled delivery group (left ventricular end-diastolic pressure, cardiac index, +dP/dt, −dP/dt, and time constant of exponential decay all P<0.05 for MI+NF/P versus MI or MI+NF). Infarcted myocardial volume was reduced by NF/PDGF therapy (34.0±13.3% in MI, 28.9±12.9% in MI+NF, and 12.0±5.8% in MI+NF/PDGF; P<0.001). There was no evidence of pulmonary toxicity from the therapy, with no differences in right ventricular end-systolic pressure, right ventricular dP/dt, bromodeoxyuridine staining, or pulmonary artery medial wall thickness.

Conclusions—Intramyocardial delivery of PDGF by self-assembling peptide NFs leads to long-term improvement in cardiac performance after experimental infarction without apparent pulmonary toxicity. Local myocardial protection may allow prevention of heart failure without systemic toxicity. (Circulation. 2006;114:637-644.)

Key Words: myocardial infarction • nanotechnology • tissue engineering • fibrosis • hypertension, pulmonary

Congestive heart failure is a leading cause of death in the United States and many other countries.1 The predominant cause of congestive heart failure is loss of myocardium due to coronary artery disease. Although myocardial injury can promote cardiac repair in some vertebrates,2,3 the human myocardium is incapable of adequate regeneration after infarction. Although cardiac regeneration is an exciting approach under intensive investigation, the reduction of acute cardiomyocyte loss remains an important strategy for heart failure prevention.4–8

Platelet-derived growth factor (PDGF) can activate cardioprotective signaling pathways in cardiomyocytes.8,9 However, delivered systemically, PDGF could have important adverse effects in other organs. For example, PDGF signaling may play an important role in the pathogenesis of pulmonary hypertension.10 The expression of the PDGF receptor is increased in the lungs of pulmonary hypertension patients11

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and in 2 different animal models of pulmonary hypertension.12,13 Interestingly, blocking the PDGF receptor reverses advanced pulmonary vascular disease.14 Thus, systemic delivery of PDGF could have adverse consequences, particularly for patients with cardiovascular disease.

Controlled delivery of therapeutic factors directly to injured tissues is one approach to limit systemic toxicity and improve efficacy of therapies. We have previously demonstrated that self-assembling peptide nanofibers (NFs) can be used to deliver and retain PDGF in the myocardium.8 This strategy protects the myocardium early after experimental coronary occlusion and after ischemia-reperfusion injury.8 However, the long-term benefits of this potential cardioprotective strategy have not been demonstrated. Furthermore, local controlled release into the myocardium could lead to
intrapulmonary delivery, because most myocardial capillaries drain into the pulmonary circulation. Therefore, we investigated the long-term effects of local myocardial PDGF delivery in a randomized and blinded study of 127 rats that survived experimental myocardial infarction (MI) or sham surgery. We analyzed hemodynamic performance, cardiac fibrosis, and pulmonary hypertension to provide insight into the potential therapeutic benefits and safety of this approach. These data demonstrate that controlled myocardial delivery of PDGF can improve long-term cardiac performance without apparent adverse pulmonary complications.

Methods

MI and Blinding

All animal protocols were approved by the Harvard Medical School Standing Committee on Animals. MI was produced by a permanent ligation of the left coronary artery in ~250-g male Sprague-Dawley rats (Charles River, Wilmington, Mass) as described previously.8 Preparation and injection of peptide NFs (peptide sequence AcN-RARADARADADA-CNhy; from Synpep, Dublin, Calif) without or with 100 ng/mL human PDGF-BB (PeproTech, Rocky Hill, NJ) was performed as described previously.8 The study was prospectively designed to continue until at least 20 rats survived at least 3 months in each of the 6 coded groups. All of the procedures were blinded and randomized. At the time of experimental MI, 1 syringe was prepared for each animal with saline volume challenge. The pressure-volume catheter was then inserted into the right carotid artery and advanced to the left ventricle. After stabilization, baseline left ventricular pressure-volume loops were recorded. To change preload, the inferior vena cava was transiently compressed through an incision in the upper abdomen. At the end of each catheterization, 30 µL of 25% saline was injected into the right atrium through the polyethylene catheter to determine the conductance. The volume calibration and the hemodynamic data were analyzed with commercial software (PVAN3.2; Millar Instruments).

Infarct Size Measurement

Left ventricles were fixed in 4% paraformaldehyde at 4°C overnight and then cut into 6 slices from the apex to the base. A histological section from each slice was stained with Masson’s trichrome as described previously.8 In each section, the infarcted and noninfarcted areas were measured by automated computer image analysis. By adding the 6 infarcted areas and dividing by the sum of the noninfarcted areas, the percentage of left ventricular volume that was infarcted was calculated. There were at least 11 animals from each group in this analysis.

<table>
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<th>Sham+NF/PDGF (n=20)</th>
<th>MI (n=22)</th>
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Values are mean±SEM. FS% indicates percent of fractional shortening; ESD, end-systolic dimension (mm); and EDD, end-diastolic dimension (mm).

*P<0.01 vs MI.
†P<0.05 vs MI.
‡P<0.05 vs MI+NF.
§P<0.05 vs sham.
Immunohistochemistry, Western Analysis, and Fluorescence Microscopy

Formalin-fixed, paraffin-embedded sections were prepared for immunohistochemistry as described previously.6 The antibodies used were anti–connective tissue growth factor (anti-CTGF; Abcam, Cambridge, Mass), anti–transforming growth factor (TGF)-β (Santa Cruz Biotechnology, Santa Cruz, Calif), and anti–α-smooth muscle actin (Sigma, St. Louis, Mo). For Western analysis, myocardial proteins were extracted with lysis buffer containing 1% (wt/vol) sodium dodecyl sulfate, 50 mmol/L Tris hydroxymethylaminoethane (pH 7.4), 5 mmol/L ethylenediaminetetraacetic acid supplemented with 4X sample buffer (Invitrogen, Carlsbad, Calif), and proteinase inhibitor cocktail (Sigma) at 1:200 dilution. The antibodies used were anti-CTGF (Abcam) and anti-TGF-β (Santa Cruz Biotechnology). Fluorescence microscopy was performed as reported previously6 with antibodies against isoclinic (Molecular Probes, Eugene, Ore) and α-smooth muscle actin (Sigma).

Regional Blood Flow and Pulmonary Medial Wall Thickness

Regional blood flow in the peri-infarcted area was measured with fluorescent microspheres as described previously.6 We measured the medial wall thickness of pulmonary arteries from the right lung with 20 muscular arteries per lung measured, grouped by external diameter of >75, 25 to 75, and <25 μm. The percentage of medial wall thickness to external diameter was determined as described by Nagaya et al.13

Statistical Analysis

Results are presented as mean±SEM. Statistical comparison was performed with t test or 2-way ANOVA. A probability value of $P<0.05$ was considered statistically significant.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Local Delivery of PDGF Improves Long-Term Cardiac Performance

We investigated 6 groups of rats surviving after surgery: sham (n=21), sham+NF (n=20), sham+NG/PDGF (n=20), MI (n=22), MI+NF (n=22), and MI+NF/PDGF (n=22). All rats underwent echocardiography at 1 day, 1 month, 2 months, and 3 months after surgery and catheterization for hemodynamic measurements at 4 months after surgery. Subsequently, hearts from each of the 6 treatment groups were randomly assigned to 1 of 3 subgroups: those studied for subsequent histological analysis (n=11 in each group), those studied for regional blood flow measurement (n=5 in each group), and those used for Western analysis (n=4 in each group).

Consistent with previous results,8 24 hours after MI, injection of NF/PDGF significantly improved left ventricular
fractional shortening (59.5±5.5% in the sham group, 37.7±9.2% in the MI group, and 54.2±14.1% in the MI+NF/PDG group, \(P<0.01\) for MI+NF/PDG versus MI and \(P<0.05\) for MI+NF/PDG versus MI+NF; Table 1) and end-systolic dimension (2.2±0.4 mm in the sham group, 3.5±0.8 mm in the MI group, and 2.4±0.8 mm in the MI+NF/PDG group, \(P<0.01\) for MI+NF/PDG versus MI; Table 1). Improvement of fractional shortening was sustained over 3 months in MI+NF/PDG animals compared with controls (Table 1). NF/PDG therapy also prevented cardiac dilation as measured by ventricular end-diastolic dimensions (Table 1).

Surprisingly, injection of NF with or without PDGF in the sham animals decreased fractional shortening and increased end-systolic dimension at 1 month but not at 2 months or 3 months, which suggests that injection of NF in noninjured myocardium may temporarily impair systolic function.

Four months after MI, there were no significant differences in hemodynamic data between the sham, sham+NF, and sham+NF/PDG animals (Table 2). In the animals with MI, injection of NF with PDGF demonstrated improvements in most of the hemodynamic parameters, including mean arterial pressure, left ventricular end-systolic and end-diastolic volumes, left ventricular end-diastolic pressure, ejection fraction, cardiac index, stroke work index, maximal slope of systolic and diastolic pressure increment (\(+\text{dP/dt}\) and \(-\text{dP/dt}\)), time constant of exponential decay (\(\tau\)), maximum elastance, slope of the relation between stroke work and end-diastolic volume, and slope of the relation between \(+\text{dP/dt}\) and end-diastolic volume.

To characterize the mechanisms by which NF/PDG injection led to improvement of cardiac performance 4 months after MI, we examined infarct volume from the left ventricle (\(n=11\) in each group). The percentage of infarcted to noninfarcted volume of myocardium was compared between groups. There was trivial volume of infarction in the sham, sham+NF, and sham+NF/PDG left ventricles relative to the infarcted ventricle (Figure 1A). Injection of NF with PDGF, but not NF alone, significantly reduced the infarcted volume (Figure 1A). Injection of NF with PDGF, but not NF alone, significantly reduced infarct volume percentage 4 months after infarction (34.0±13.3% in MI, 28.9±12.9% in MI+NF, and 12.0±5.8% in MI+NF/PDG, \(P<0.001\) for MI+NF/PDG versus MI and MI+NF; Figure 1B).

To examine whether cell proliferation or caspase activation was affected late after acute NF/PDG therapy, we studied bromodeoxyuridine (BrdU) and cleaved caspase-3 staining. There were fewer than 0.1% BrdU- or cleaved caspase-3-positive cells in the peri-infarcted myocardium at 4 months, and there were no differences in the number of BrdU- or cleaved caspase-3-positive cells among all of the study groups (data not shown).
Local Delivery of PDGF Does Not Induce Cardiac Fibrosis Factors
We then examined the levels of CTGF and TGF-β, 2 factors that may participate in fibrosis, in the left ventricles from the sham groups and in the infarcted, border, and remote areas of left ventricles from the MI groups using immunostaining.16 We found that CTGF was only slightly expressed in the nonischemic cardiomyocytes but was clearly induced in the ischemic cardiomyocytes even 4 months after infarction. By contrast, TGF-β was rarely detected in all of the hearts from the sham and MI groups, and if detected, TGF-β was mainly found in endothelial or inflammatory cells (data not shown). Using Western analysis, we examined the expression of CTGF and TGF-β in the mycardium and again did not find any difference among all 6 study groups (data not shown).

Local PDGF Therapy Increases Regional Blood Flow After Infarction
We then tested whether injection of NF/PDGF caused long-term vascularization in the myocardium, because we have previously found that injection of NF in normal myocardium led to early neovascularization.17 Interestingly, the overall capillary density in the peri-injected region from the sham, sham+NF, and sham+NF/PDGF hearts was not different (315±25 in sham, 298±49 in sham+NF, and 312±65 per mm² in sham+NF/PDGF, n=11 each group; Figure 2A). However, in the border zones from the MI hearts, injection of NF with PDGF, but not NF alone, significantly increased vascular density 4 months after infarction (64±43 in MI, 89±37 in MI+NF, and 197±51 per mm² in MI+NF/PDGF, P<0.01 for MI+NF/PDGF versus MI and MI+NF/PDGF versus MI+NF, n=11 in each group; Figure 2A).

Consistent with the vascular density measurements, regional blood flow in the peri-injected region from the sham, sham+NF, and sham+NF/PDGF hearts was not different (2.76±0.32 in sham, 3.12±0.26 in sham+NF, and 2.98±0.52 mL per minute per gram of myocardium in sham+NF/PDGF; Figure 2B). However, in the peri-infarcted region from the MI hearts, injection of NF with PDGF, but not NF alone, significantly increased regional blood flow 4 months after infarction (0.97±0.31 in MI, 1.20±0.48 in MI+NF, and 2.14±0.55 mL per minute per gram of myocardium in MI+NF/PDGF, P<0.01 for MI+NF/PDGF versus MI and MI+NF/PDGF versus MI+NF; Figure 2B).

Local PDGF Therapy Does Not Cause Pulmonary Hypertension
Because PDGF signaling may play a role for pulmonary hypertension in humans11 and in animals,1,2,13 we explored whether intramyocardial injection of NF/PDGF causes pulmonary complications. As shown in Table 2, at 4 months, there were no differences in right ventricular end-systolic pressure, end-diastolic pressure, or dP/dt among the sham, sham+NF, and sham+NF/PDGF groups. In the MI groups, right ventricular end-diastolic pressure was increased, and injection of NF with PDGF, but not NF alone, significantly decreased right ventricular end-diastolic pressure (1.9±0.2 in sham, 10.1±2.5 in MI, 9.0±1.6 in MI+NF, and 2.5±0.6 mm Hg in MI+NF/PDGF, P<0.01 for MI+NF/
the difficulty of delivering therapeutic molecules in a highly controlled manner. Because controlled local release of therapeutic proteins may avoid prolonged overexpression with viral transduction or rapid washout of proteins after simple injection, it provides an important option for delivering cardioprotection. In the present study, we demonstrate that direct intramyocardial injection of self-assembling peptide NFs with PDGF-BB improves cardiac function as long as 4 months after infarction. In addition, we show that this therapy does not cause pulmonary hypertension, a biologically plausible adverse effect. Given our previous measurements, we estimate that intramyocardial injection of a total of 8 ng of PDGF will not significantly increase the amount of systemic PDGF after injection, and 28 days after injection, only 1% of PDGF delivered by NFs will remain in the myocardium. These data demonstrate that early cardiac benefits of local therapy are sustained by both echocardiographic and invasive hemodynamic assessment, and we suggest that the traces of PDGF remaining after 1 month are unlikely to be actively influencing the myocardium.

In animals with MI, left ventricular ejection fraction and cardiac index were significantly improved by local delivery of PDGF; end-diastolic volumes were significantly reduced, which suggests attenuated remodeling in the treated animals. There was also significantly increased +dP/dt (maximal slope of systolic pressure increment), maximum elastance, and stroke work index with therapy. In addition, −dP/dt was increased and τ (the time constant of exponential decay) was decreased, which suggests improved diastolic function. Finally, the slopes of the relation between stroke work and end-diastolic volume and between +dP/dt and end-diastolic volume were increased, which strongly indicates improved contractility. Together, these results suggest that controlled release of PDGF improves both systolic and diastolic ventricular functions.

The volume of infarcted myocardium at 4 months was reduced by injection of NF/PDGF. We speculate that promoting cardiomyocyte survival in the early period after acute infarction is the dominant mechanism for NF/PDGF to improve long-term cardiac performance. However, we cannot exclude other potential beneficial mechanisms of PDGF, such as an antiinflammatory effect of PDGF and potential activation of stem/precursor cells, which may differentiate into cardiomyocytes and coronary vessels. Furthermore, the benefit of therapy could also represent attenuation of cardiomyocyte necrosis. In the present study, both vascular density and regional blood flow were improved by therapy, which suggests an angiogenic benefit of therapy. The increase in

**Figure 3.** Intramyocardial NF/PDGF injection does not increase medial wall thickness in pulmonary arteries. A, Immunohistochemical staining of α-smooth muscle actin (brown areas, upper photo) in paraformaldehyde-fixed, paraffin-embedded lung sections. Arteries were classified into 3 groups: large (L, external diameter >75 μm), medium (M, external diameter 25 to 75 μm), and small (S, external diameter <25 μm). The lower photo is a negative control without the primary antibody. B, Measurement of pulmonary arterial medial wall thickness, expressed by percentage of medial wall thickness from large, medial, and small arteries. Bar~20 μm.
regional blood flow is unlikely to be due to capillary density and suggests an increase in coronary resistance vessels. It is possible that NF/PDGF therapy increases regional blood flow by promoting vascular stability\(^22,23\) or production of vascular endothelial growth factor\(^24–26\) or by preserving overall myocardial architecture.

Because cardiac-specific overexpression of PDGF-D, another member of the PDGF family that activates the PDGF receptor-\(\beta\), has been reported to induce fibroblast overgrowth, collagen accumulation, and cardiac fibrosis,\(^27\) we examined whether injection of NF/PDGF had late proinflammatory effects in the heart. Our data suggest that controlled intramyocardial delivery of PDGF using peptide NFs may not promote cardiac fibrosis and instead reduces fibrosis. Moreover, because PDGF in the myocardium may circulate from myocardial capillaries into the pulmonary vasculature, we measured medial wall thickness and vascular smooth muscle cell proliferation in the pulmonary arteries. We found no evidence that intramyocardial PDGF delivery with NFs causes pulmonary arterial remodeling or hypertension.

One surprising finding in the present study is that injection of NFs in the sham control, with or without PDGF, significantly attenuated left ventricle fractional shortening and end-systolic dimension at 1 month but not at later times. It is possible that in normal myocardium, self-assembling NFs may interfere with physiological electromechanical function. At later time points, however, the electromechanical coupling may recover, possibly owing to degradation of the peptide NFs. Furthermore, we did not determine the therapeutic time window of NF/PDGF injection as a beneficial therapy. Because the time window after a patient presents is a critical factor in myocardial preservation, future investigation will be required to determine whether this therapy is effective hours after the initiation of the event. Finally, it is critical to explore this approach in larger animals, in which more injections will be required to deliver PDGF over the larger injured area, and benefits observed in different species will improve confidence that this therapy will be successful in humans.

In conclusion, the present study shows that local myocardial delivery of PDGF at the time of MI leads to sustained improvement in cardiac function. In addition, controlled intramyocardial PDGF delivery does not induce cardiac fibrosis or pulmonary hypertension. This potential therapy could be manufactured easily and inexpensively and could also be delivered in the catheterization laboratory. Because the therapy requires no cells, quality control may be straightforward. Furthermore, percutaneous application of this therapy may be feasible as an adjunct to acute coronary interventions that are already routinely performed for many patients with acute MI.

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**Disclosures**

None.


CLINICAL PERSPECTIVE

Because the predominant cause of congestive heart failure is death of cardiomyocytes due to myocardial infarction, strategies that prevent acute cardiomyocyte loss may also prevent the development of heart failure. One promising approach to protect cardiomyocytes is to deliver cardioprotective proteins directly to infarcted myocardium. We have previously used peptide nanofibers (NFs) to deliver and retain platelet-derived growth factor (PDGF)-BB, an endothelium-derived cardiomyocyte survival factor, in the myocardium during acute infarction. In the present study, using a randomized and blinded experimental design, we investigated the long-term effects of local PDGF delivery by serial echocardiography and catheterization at 4 months after myocardial infarction in 127 rats. We found that controlled local delivery of PDGF improved both cardiac systolic and diastolic function in the long term. Importantly, we also examined the potential adverse effects of PDGF, including pulmonary vascular hypertrophy, and found that controlled local delivery of PDGF by NFs may allow prevention of heart failure without extracardiac complications. These results suggest that local myocardial PDGF delivery with NFs may be therapeutically beneficial, particularly if this cardioprotection strategy can be implemented in the catheterization laboratory.
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