Intracoronary Administration of AdvFGF-5 (Fibroblast Growth Factor-5) Ameliorates Left Ventricular Dysfunction and Prevents Myocyte Loss in Swine With Developing Collaterals and Ischemic Cardiomyopathy

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Background—Fibroblast growth factor (AdvFGF-5) improves regional function by stimulating myocyte hypertrophy without increasing myocardial perfusion in swine with hibernating myocardium. We performed the present study to determine whether AdvFGF-5 could prevent the progression of LV dysfunction in swine with ischemic cardiomyopathy.

Methods and Results—Swine were chronically instrumented with LAD and LCX stenoses to produce viable dysfunctional myocardium and studied 1 month after instrumentation in the closed-chest sedated state. Flow and regional function before and 30 days after intracoronary AdvFGF-5 (2×10^12 vp, n=9) were compared with animals receiving intracoronary AdvEGFP (2×10^12 vp, n=6). Histological analysis was performed to quantify myocyte size, myocyte nuclear density, apoptosis (TUNEL), and the frequency of myocytes in the proliferative phase of the cell cycle (Ki-67 staining). LAD wall-thickening (27±3 to 46±6%, P<0.05) and EF (39±4 to 56±3%, P<0.05) increased after AdvFGF-5. AdvFGF-5 increased maximal perfusion during adenosine vasodilation despite no differences in baseline flow or stenosis severity. After AdvFGF-5, TUNEL-positive myocytes decreased 6-fold and Ki-67 positive myocyte nuclei increased 2-fold. As a result, AdvFGF-5 produced a marked increase in myocyte nuclear density (957±54 to 1447±40 nuclei/mm², P<0.05).

Conclusion—These data indicate that AdvFGF-5 increases regional function and maximal perfusion distal to stenotic arteries when administered before the development of collaterals. This was associated with a reduction in myocyte apoptosis, an increase in Ki-67-positive myocytes, and an increase in myocyte number. Thus, AdvFGF-5 offers a potential therapeutic approach to prevent the progression of ischemic cardiomyopathy and heart failure. (Circulation. 2007;116[suppl I]:I-71–I-76.)

Key Words: ischemia • cardiomyopathy • growth substances • gene therapy

Fibroblast growth factors (FGFs) have multiple biological activities in vivo and in vitro including angiogenesis, ameliorating myocardial stunning, and increasing myocardial contraction. At a cellular level, FGFs can inhibit apoptosis, stimulate cell proliferation, and produce myocardial hypertrophy. All of these actions could be of significant benefit to the advanced failing myocardium.

Fibroblast growth factors can be administered therapeutically through a variety of approaches including in vivo adenoviral gene transfer. We previously demonstrated that regional function improves 2 weeks after intracoronary AdvFGF-5. This was accompanied by an increase in the number of myocytes in the growth phase of the cell cycle and increased myocyte nuclear density in collateral-dependent hibernating myocardium. Despite this there was no evidence of angiogenesis as regional myocardial perfusion during pharmacological vasodilation remained critically impaired. Thus, the effects on function were dissociated from myocardial perfusion suggesting that this type of intervention could be most beneficial when LV function was depressed.

We hypothesized that administering AdvFGF-5 in chronically stenotic arteries could be useful in preventing the progression of left ventricular (LV) dysfunction in heart failure. To study this, we evaluated a preclinical model of ischemic cardiomyopathy using chronically instrumented swine with 2 vessel coronary artery stenoses. In this model, regional as well as global LV dysfunction develops in the absence of infarction. We determined whether preemptive therapy with AdvFGF-5 could prevent myocyte loss from apoptosis or stimulate myocyte hypertrophy or regeneration.
as reflected by myocyte nuclear density. The results demonstrate the ability of AdvFGF-5 to retard the progression of heart failure and limit myocyte loss in ischemic cardiomyopathy.

Materials and Methods

Procedures and protocols conformed to institutional guidelines for the care and use of animals in research. The ischemic cardiomyopathy model was previously described. Briefly, pigs were sedated (Telazol; tiletamine 50 mg/mL and zolazepam 50 mg/mL/xylazine (100 mg/mL, 0.022 mg/kg im), intubated, and ventilated with a 0.5% to 2% isoflurane-oxygen mixture. Through a limited pericardiectomy, the proximal left anterior descending (LAD) and left circumflex (LCX) coronary arteries were instrumented with a Delrin occluder (1.5 mm). Antibiotics (cefazolin, 25 mg/kg and gentamicin, 3 mg/kg im) were given 1 hour before surgery and repeated after closing the chest. Analgesia included an intracostal nerve block (0.5% Marcaine) and intramuscular doses of butorphanol (2.2 mg/kg q6 hour) and flunixin (1 to 2 mg/kg qd).

Serial Physiological Studies

Initial physiological studies (n=15) were performed 1 month after instrumentation under sedation initiated with Telazol/xylazine and maintained with propofol (5 to 10 mg/kg/hr iv). Under sterile conditions, we inserted a 6-Fr introducer into the left brachial artery. A 5-Fr Sones catheter was positioned in the LV apex for microsphere injection. The introducer side port was used to monitor aortic pressure and perform blood withdrawal for microspheres. Animals were heparinized (100 U/kg) and hemodynamics allowed to equilibrate for at least 30-minutes. Regional wall-thickening was assessed with transbrachial echocardiography from a right parasternal approach. All pigs receiving gene transfer showed extensive anterolateral dysfunction but dyskinesis was not present under any condition. Systolic wall-thickening [% wall-thickening = (end-systolic wall thickness – end-diastolic wall thickness)/end-diastolic wall thickness] was measured in LAD and remote regions. Ventricular dimensions and LV mass were calculated using American Society of Echocardiography criteria. This was followed by LV microsphere injection to assess resting perfusion. Subsequently, pharmacological vasodilation was produced using adenosine (0.9 mg/kg/min iv) with phenylephrine infused and titrated to maintain mean blood pressure near resting values (74.2 ± 7.2 μg/kg/min), and microsphere flow measurements repeated. Previous studies have demonstrated that porcine model coronary resistance arteries do not constrict to phenylephrine. After flow measurements, selective left and right coronary angiography was performed using a 5-Fr Sones catheter. Using magnified projections images were analyzed in a blinded fashion. Minimum lesion diameter was referenced to the normal segment to calculate percent diameter stenosis of the LAD and LCX.

After completing baseline physiological measurements, we administered a replication deficient adenovirus containing AdvFGF-5 (n=9) or AdvEGFP (n=6) in a blinded fashion. Divided doses (total 2×10¹⁰ viral particles) were injected into the LAD, LCX, and right coronary arteries over 60 seconds, taking care to avoid reflux into the systemic circulation. Myocardial uptake was enhanced by an intracoronary infusion of histamine (25 μg/min for 3 minutes) to increase endothelial permeability. At the end of the study, catheters were removed and the animal recovered.

Physiological studies were repeated 4 weeks after AdvFGF-5 after which animals were euthanized under anesthesia. The LV was weighed and sectioned into 1-cm rings parallel to the atrioventricular groove from apex to base. Thin rings above each major ring were incubated in triphenyltetrazolium chloride (TTC) to assess infarction.

Microsphere Perfusion

Regional perfusion was assessed using 15-μm microspheres labeled with fluorescing dyes as previously described. We injected ~3×10⁶ microspheres into the LV while a reference sample was withdrawn at 6 mL/min for 90 seconds. At the end of the study, samples were taken from a midventricular ring, divided into 12 circumferential wedges with each cut into 3 transmural layers. Dyes were extracted using standard techniques and fluorescence quantified at selected excitation wavelengths.

Histopathology

Tissue adjacent to LAD and posterior descending arteries (normal) were fixed (10% formalin) and paraffin-embedded to make 5-μm thin sections. Point-counting of trichrome-stained sections was used to quantify connective tissue. Periodic-acid-Schiff stained sections were used to quantify myocyte diameter (100 transverse myocytes per region) in subendocardial and subepicardial thirds of the LV.

Tissue sections were incubated with either anti-Ki67 (a specific marker for cells that have reentered the cell cycle; mouse monoclonal antibody, clone MIB-1, Dako) and anti-cardiac Troponin I (cTnI, rabbit polyclonal antibody, Santa Cruz). Samples were posttreated with fluorescein isothiocyanate (FITC)-conjugated anti-mouse and TRITC-conjugated anti-rabbit antibody (Dako). Nuclei were stained with 4′,6-diamidino-2-phenylindole (DAPI). Images were acquired with a Leica Confocal Microscope (Bio-Rad MRC 1024), and Ki67-positive myocytes were counted (positive nuclei per section).

We quantified apoptosis using the fluorescent terminal deoxynucleotidyl transferase-mediated dUTP nick-labeling (TUNEL, Chemicon Inc) staining conjugated with FITC or TRITC as previously described. Myocyte nuclei were identified with cardiac Troponin I and TOPRO3 as described above. Approximately 300 to 400 fields were examined per sample. The extent of apoptosis was expressed by normalizing the results to the number of myocyte nuclei per mm² in each sample.

Statistical Analysis

Data are expressed as mean±SE. A 2-way ANOVA was used for the functional data, to account for both the treatment effect (FGF-5 versus EGFP) and the 2 studies (Initial versus Final). Perfusion and histological analyses were compared with a 2-way ANOVA to account for treatment and region (LAD, LCX, and Remote). When significant differences were detected, the Holm-Sidak test was used for all pairwise comparisons (SigmaStat 3.0). For data that was not normally distributed, square root and logarithmic transformations were performed (SigmaStat 3.0). Apoptosis data were analyzed with the Kruskal-Wallis ANOVA on ranks (SigmaStat 3.0). Differences in hemodynamic parameters between the AdvFGF-5-treated animals and AdvEGFP-treated animals were compared with an unpaired t test. Differences of P<0.05 were considered significant.

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

Results

Effects of AdvFGF-5 on Myocardial Perfusion

Stenosis severity at the end of the study was similar in each treatment group (LAD 97±1% AdvFGF-5 versus 96±1% in AdvEGFP; LCX 87±5% AdvFGF-5 versus 96±2% in AdvEGFP, P=ns). Hemodynamics and full-thickness flows are summarized in the Table and microsphere perfusion in Figure 1. After gene transfer, similar relative reductions in resting LV perfusion were observed in AdvFGF-5 (LAD 0.80±0.10 versus 0.95±0.10 mL/min/g in remote, P<0.05) and in AdvEGFP (LAD 0.97±0.24 versus 1.29±0.26 mL/min/g in remote, P=0.06) indicative of hibernating myocardium. Heart rate and aortic pressure were similar in each group, but LV end-diastolic pressure was lower and LVdP/dt was higher in animals receiving AdvFGF-5 (P<0.05). Four weeks after treatment with AdvEGFP, absolute vasodilated perfusion in control animals was severely impaired in LAD.
and LCX regions in comparison to remote normally perfused regions (Figure 1A). Treatment with AdvFGF-5 increased LAD and LCX vasodilated flow (LAD: 3.81 ± 0.42 vs AdvEGFP; LCX: 4.05 ± 0.56 in AdvFGF-5 versus 2.21 ± 0.78 in AdvEGFP, both P < 0.05). Likewise, there was a similar improvement in relative LAD and LCX flows to normal regions after AdvFGF-5 (Figure 1B). Thus, AdvFGF-5 improved coronary flow indicating functionally significant angiogenesis/arteriogenesis in the stenotic dysfunctional regions.

**Effects of AdvFGF-5 on Myocardial Function in Ischemic Cardiomyopathy**

Figure 2 summarizes the effect of AdvFGF-5 on serial measurements of global and regional myocardial function. One month after intracoronary AdvFGF-5, ejection fraction increased to 56% ± 3% whereas it declined to 39% ± 4% in animals receiving AdvEGFP (P < 0.05 versus AdvFGF-5). Resting wall-thickening was depressed in comparison to normally-perfused remote myocardium at the initial study (31% ± 6% in LAD versus 84% ± 7% in remote regions, P < 0.05). After AdvFGF-5, LAD wall thickening increased to 46% ± 6% (P < 0.05 versus initial) whereas it was unchanged in animals receiving AdvEGFP (28% ± 6% at initial to 27% ± 3%, p ns). TTC staining did not demonstrate significant necrosis and was similar in each group (0.3 ± 0.2% in AdvFGF-5 and 0.2 ± 0.1% of LV mass in AdvEGFP, P = ns). Likewise, point counting demonstrated no difference in connective tissue after AdvFGF-5 (LAD 5.7 ± 0.3% after AdvFGF-5 versus 5.5 ± 0.7% after AdvEGFP and LCX region 5.5 ± 0.4% after AdvFGF-5 versus 5.9 ± 0.8% after AdvEGFP, P = ns).

**Effects of AdvFGF-5 on Myocyte Apoptosis, Reentry of Myocytes into the Cell Cycle, and Myocyte Nuclear Density**

Figure 3 summarizes the effects of AdvFGF-5 on myocyte apoptosis. In animals treated with AdvEGFP, apoptosis was increased but similar in LAD and normal remote regions (103 ± 22/10⁶ myocyte nuclei in LAD versus 72 ± 15/10⁶ myocyte nuclei in remote, P = ns). Intracoronary AdvFGF-5 decreased apoptosis in both regions (13 ± 5/10⁶ myocyte nuclei in LAD and 7 ± 3/10⁶ myocyte nuclei in remote, both P < 0.05 versus AdvEGFP).

The frequency of Ki-67 staining, a marker of myocytes in the growth phase of the cell-cycle, was expressed in relation to the number of myocyte nuclei (Figure 4). We found Ki67-positive myocytes in the LAD and remote regions of animals treated with AdvEGFP (LAD 355 ± 725 and remote 5264 ± 612 per 10⁶ myocyte nuclei, P = ns). These values were similar to 2-vessel stenosis animals that did not receive AdvEGFP (data not shown). Intracoronary AdvFGF-5 increased Ki67-positive myocytes more than 2-fold (LAD 7105 ± 1208 and remote 5264 ± 612 per 10⁶ myocyte nuclei, each P < 0.01 versus AdvEGFP).

The LAD myocyte nuclear density in animals receiving AdvEGFP was significantly lower than the normal remote region (957 ± 54 versus 1224 ± 23, P < 0.01), reflecting progressive myocyte loss related to chronic myocyte apoptosis (Figure 5). After FGF-5, myocyte nuclear density was significantly higher (LAD 1447 ± 41 and 1612 ± 32 nuclei per mm² in remote, P < 0.01 versus AdvEGF) and similar to normal swine (1534 ± 65 myocyte nuclei/mm²). Nevertheless, a small relative difference between LAD and remote regions persisted.

**Effects of AdvFGF-5 on Myocyte Cellular Hypertrophy**

Although LV end-diastolic dimension (32 ± 1 to 35 ± 1 mm, P = 0.05) increased by only ~9% 4 weeks after AdvFGF-5, estimates of LV mass by echo measurement increased by 55% (61 ± 7 to 95 ± 7 g, P < 0.05, postmortem LV weight was 88 ± 6, P = ns versus echo measurement). At the same time, LAD myocyte diameter after AdvFGF-5 was smaller than seen in animals treated with AdvEGFP (11.2 ± 0.2 versus...
12.7±0.4 μm, P<0.05). The increase in LV mass coupled with the reduction in myocyte diameter is consistent with a preservation of myocytes as summarized in Figure 5.

Discussion

There are several important new findings from our study. First, in swine with simulated multivessel disease and viable dysfunctional myocardium, there is a prominent effect of AdvFGF-5 on regional as well as global LV function. The functional improvement was the result of AdvFGF-5 preventing myocyte loss as progressive LV dysfunction developed. This was secondary to decreased myocyte apoptosis as well as AdvFGF-5 stimulating myocytes to reenter the growth phase of the cardiac cell cycle. As a result, myocyte numbers were preserved. In contrast to swine with chronic coronary collaterals, AdvFGF-5 was able to increase flow during vasodilation when administered in the setting of a severe stenosis. Collectively, these results support the notion that exogenously administered FGFs can potentially retard the progression of heart failure in ischemic cardiomyopathy.

Effects of AdvFGF-5 on Flow and Function in Ischemic Cardiomyopathy

Treatment with AdvFGF-5 prevented the progressive decline in function that is typical of this model, which occurs in the absence of myocardial necrosis. Animals receiving an inactive construct (AdvEGFP) were similar to previously published studies in untreated animals5 indicating that the ob-
served increase in flow during adenosine vasodilation was directly related to FGF-5. The increase in maximal perfusion is the sine qua non of functional angiogenesis/arteriogenesis and contrasts with the lack of effect of AdvFGF-5 in swine with well developed collaterals and hibernating myocardium where flow was unchanged despite a chronic critical impairment in subendocardial flow reserve.4 Although speculative, the most likely reason for this difference is that other endogenous growth factors become upregulated in the myocardium as stenosis severity progresses and coronary flow reserve declines. This results in a permissive environment where FGF-5 can reduce minimal coronary resistance which probably occurs via arteriogenesis. Improvements in stress-induced dysfunction were also reported by Giordano et al when AdvFGF-5 was administered to swine with developing collaterals after circumflex ameroid occlusion.2 In stable collateral dependent myocardium, episodic metabolic myocardial ischemia may already be minimized to the point that it is no longer a sufficient stimulus to upregulate other endogenous signals needed for collateral growth. In support of this, we have previously demonstrated that swine with hibernating myocardium have a downregulation in regional oxygen consumption that allows the heart to minimize metabolic evidence of ischemia.11 As a result, AdvFGF-5 as a sole agent was insufficient to elicit an increase in collateral vasodilator reserve.4 Based on these findings, angiogenic strategies intended to improve perfusion are probably best administered at a time before coronary occlusion and collateral dependent myocardium develops. Thus, the variability in the endogenous substrate and timing of growth factor administration may be an important factor to consider in the future design of clinical trials which have thus far failed to result in objective increases in perfusion in humans with coronary artery disease.12

Effects of AdvFGF-5 on Myocyte Apoptosis, Reentry of Myocytes into the Cell Cycle, and Cellular Hypertrophy

Interestingly, AdvFGF-5 also elicited prominent effects on myocyte cell death, cell growth, and hypertrophy. Myocyte apoptosis was markedly decreased in animals receiving AdvFGF-5. At the same time, there was a 2-fold increase in the number of myocytes in the growth phase of the cell cycle.4 Although speculative, the most likely reason for this difference is that other endogenous growth factors become upregulated in the myocardium as stenosis severity progresses and coronary flow reserve declines. This results in a permissive environment where FGF-5 can reduce minimal coronary resistance which probably occurs via arteriogenesis. Improvements in stress-induced dysfunction were also reported by Giordano et al when AdvFGF-5 was administered to swine with developing collaterals after circumflex ameroid occlusion.2 In stable collateral dependent myocardium, episodic metabolic myocardial ischemia may already be minimized to the point that it is no longer a sufficient stimulus to upregulate other endogenous signals needed for collateral growth. In support of this, we have previously demonstrated that swine with hibernating myocardium have a downregulation in regional oxygen consumption that allows the heart to minimize metabolic evidence of ischemia.11 As a result, AdvFGF-5 as a sole agent was insufficient to elicit an increase in collateral vasodilator reserve.4 Based on these findings, angiogenic strategies intended to improve perfusion are probably best administered at a time before coronary occlusion and collateral dependent myocardium develops. Thus, the variability in the endogenous substrate and timing of growth factor administration may be an important factor to consider in the future design of clinical trials which have thus far failed to result in objective increases in perfusion in humans with coronary artery disease.12

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higher. Second, myocyte apoptosis was reduced by 5-fold after AdvFGF-5. Third, myocyte nuclear density was higher in animals treated with AdvFGF-5. Collectively, our results support the hypothesis that AdvFGF-5 contributes to functional remodeling through myocyte cell growth, prevention of cell death, and possibly by stem cell mobilization. This may therefore represent a potentially new approach to reverse the effects of myocyte loss in ischemic cardiomyopathy.

Methodological Limitations

Although we did not quantify the transfection efficiency of intracoronary gene transfer, the approach and dosing we used was identical to our previous study where we demonstrated that nearly 40% of the myocardial cells were EGFP-positive after using intracoronary histamine to facilitate first-pass adenoviral uptake. Because of the nature of this in vivo model and the multiple physiological and cellular actions of AdvFGF-5, it is difficult to unambiguously separate the potential effects of improved flow reserve in preventing apoptosis from direct actions of AdvFGF-5 on myocyte survival and function. Nevertheless, the frequency of apoptosis after AdvFGF-5 fell to values similar to those previously published in normal pigs. In addition, although function and coronary flow reserve were improved after AdvFGF-5, they were depressed below normal values suggesting that repetitive demand or supply-induced ischemia was still present. We did not characterize the time-course of FGF-5 expression in this study, but our previous results would suggest that it is transient when using an adenoviral vector. Finally, we cannot determine whether the effects we observed would translate into long-term improvements in flow, function, and myocyte survival or whether they would be comparable in the setting of more extensive vascular disease. Ruel demonstrated that the angiogenic response to surgically applied FGF-2 was impaired in hypercholesterolemic swine with collateral-dependent myocardium. Additional studies with longer follow-up and in models with vascular disease will be required to address these issues.

Clinical Implications

Our study provides support for the use of preemptive therapy with AdvFGF-5 to prevent the progression of LV dysfunction in patients with ischemic cardiomyopathy. The favorable effects on function and preservation of myocytes in a setting where there is active apoptosis suggests that administration of AdvFGF-5 may be more efficacious when given before the development of chronic collaterals or when used as an adjunctive therapy in patients with advanced ischemic cardiomyopathy and heart failure as compared with chronic angina, which has been the focus of most growth factor protein and gene transfer studies to date. Further studies evaluating AdvFGF-5 in other animal models of heart failure as well as clinical trials will be required to test this possibility.

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Disclosures

None.

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