Is Skeletal Myoblast Transplantation Clinically Relevant in the Era of Angiotensin-Converting Enzyme Inhibitors?

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Background—There is compelling experimental evidence that autologous skeletal muscle (SM) cell transplantation improves postinfarction cardiac function. This study assessed whether this benefit is still manifested in the clinically relevant setting of a treatment by ACE inhibitors.

Methods and Results—A myocardial infarction was created in 99 rats by coronary artery ligation. They were divided into 4 groups. Two groups did not receive any drug and were intramyocardially injected 7 days after the infarct with either culture medium alone (control rats, n=16) or autologous SM cells (2.3×10⁶ myoblasts) previously expanded ex vivo for 7 days (myoblasts, n=24). Two other groups received the ACE inhibitor perindoprilat (1 mg·kg⁻¹·d⁻¹), started the day of the infarct and continued uninterruptedly thereafter, and underwent time-matched procedures, that is, they were intramyocardially injected at 7 days after infarction with either culture medium alone (ACE inhibitors, n=22) or autologous SM cells (2.5×10⁶ myoblasts) previously expanded ex vivo for 7 days (ACE inhibitors+myoblasts, n=37). Left ventricular function was assessed by 2D echocardiography. At the end of the 2-month study, left ventricular ejection fraction (%) mean±SEM) was increased in all groups (myoblasts, 37.4±1.2; ACE inhibitors, 31.6±1.7; ACE inhibitors+myoblasts, 43.9±1.4) compared with that in control rats (19.8±0.7) (P<0.0001). The improvement in ejection fraction was similar in the ACE inhibitor and the myoblast groups (31.6±1.7 versus 37.4±1.2, P=0.0636). However, in the ACE inhibitor+myoblast group, this improvement was greater than that seen in hearts receiving either treatment alone (43.9±1.4 versus 31.6±1.7 in the ACE inhibitor group and 43.9±1.4 versus 37.4±1.2 in the myoblast group, P<0.0001 and P=0.0084, respectively).

Conclusions—These data provide further support for the clinical relevance of autologous SM cell transplantation in that its cardioprotective effects are additive to those observed with ACE inhibitors. (Circulation. 2001;104[Suppl I]:I-223-I-228.)

Key Words: heart failure • muscles • transplantation • myocardial infarction • angiotensin

Over the past years, there has been accumulating evidence that the function of infarcted myocardium could be improved by transplantation of autologous skeletal myoblasts. Of note, this benefit has been documented in both small¹–⁴ and large⁵ animal models of myocardial infarction (created by cryoinjury or coronary artery ligation) and with the use of various methods of functional assessment including Langendorff perfusion,⁶ micromanometry and sonomicrometry,¹²,¹⁴ and echocardiography.⁹ The morphological correlate of these data has been the detection of myotubes generated in the recipient myocardium from grafted myoblasts and identified by skeletal muscle-specific antibodies. However, it remains uncertain whether some of these myotubes may alter their phenotype toward a cardiac-like pattern.⁶,⁷ Likewise, the type of coupling, if any, between engrafted myotubes and host cardiomyocytes is another yet unsettled issue.⁸

From a practical standpoint, however, a major limitation of these studies is that they have assessed the functional effects of skeletal myoblast transplantation in medically untreated animals. The situation is obviously different for patients who have had a myocardial infarction and in whom ACE inhibitors, in particular, have become standard therapy because of their positive impact on left ventricular (LV) function and ultimate survival.⁹,¹⁰

The primary goal of this study was thus to determine whether the functional benefits of myoblast transplantation would still be apparent in the presence of a clinically relevant protocol of ACE inhibitor administration in rats with severe myocardial injury.

Methods

All experiments were performed in accordance with the “Principles of Laboratory Animal Care” formulated by the National Society for...
Medical Research and the “Guide for the Care and Use of Laboratory Animals” prepared by the Institute of Laboratory Animal Resources, Commission on Life Science, National Research Council, and published by the National Academy Press, revised 1996.

Myocardial Infarction Model

The operative procedures were performed in male Wistar rats weighing 310 g. Under anesthesia with ketamine (50 mg/kg IP) and xylazine (10 mg/kg IP), the animals were intubated and tracheally ventilated with a volume-cycled small-animal ventilator (Harvard Rodent Ventilator, Harvard Apparatus Co, Inc). Through a left-sided thoracotomy, the myocardial infarction was created by ligation of the left coronary artery, between the left atrium and the right pulmonary outflow tract, with a 7/0 polypropylene suture (Ethicon, Inc). The aim of the procedure was to create a major impairment in LV function to ensure that the model would be clinically relevant.

Functional Assessment

One week after myocardial infarction and 1 and 2 months after transplantation, LV function was studied by 2D echocardiography in animals anesthetized with ketamine (50 mg/kg IP) and xylazine (10 mg/kg IP).

Transthoracic 2D echocardiography was performed with the use of a commercially available 13- to 15-MHz linear-array probe (15L8) specially designed for cardiac ultrasonics studies in rat models and connected to a numeric ultrasound device (Sequioa 512, Acuson Corp). The animals were placed in the supine or lateral position on a warming pad. Parasternal 2D echocardiographic views of the heart were then obtained with the following machine settings: space time T1, contour 3, and delta 5.

End-diastolic and end-systolic long-axis views of the LV were then standardized as follows: inclusion of the apex, the posterior papillary muscle, the mitral valve, and the aortic root. Two-dimensional echocardiographic measurements were then performed with the cine-loop feature to retrospectively obtain adequate visualization of these fast-beating hearts. This device allows a 160-Hz maximal frame rate with high axial and lateral resolutions. Numeric images were then reviewed at a slower frame rate to catch true end-diastolic and end-systolic phases.

End-diastolic and end-systolic areas (A) were obtained by hand-tracings of the LV endocardial contours on the frame showing the largest (and the smallest) LV cavity size by using the cine-loop acquisition, according to the American Society of Echocardiography leading edge method.11 On these frames, end-diastolic (or end-systolic) lengths (L) of the LV were obtained by tracing a line connecting the more distal part of the apex and the center of a line connecting the mitral annular hinge points. End-diastolic and end-systolic volumes (LVEDV and LVESV, respectively) were then calculated by means of the single-plane area-length method12 (volume = \(8\times\pi/3 \times L\)) as previously used with the same protocol in infarcted rats.13-19 LV ejection fraction (LVEF%) was calculated as \((LVEDV - LVESV)/LVEDV\) \times 100.

All measurements were averaged on 3 consecutive cardiac cycles and were analyzed by 2 independent observers who were blinded to the treatment status of the animals. Interobserver variability was assessed from 2 sets of baseline measurements in 10 randomly selected rats by means of Bland and Altman analysis.16 The correlation between measurements performed blindly by the two independent observers was very close for linear (r > 0.95, SEE < 0.1 mm), volume (r > 0.93, SEE = 0.2 mL), and EF (r > 0.95, SEE = 4%) measurements.

Skeletal Muscle Cell Expansion

The myoblast culture process was performed as previously reported.3 Briefly, excisional right and left tibialis anterior muscle biopsy followed by enzymatic dissociation with collagenase IA (2 mg/mL, Sigma Chemical Co) and trypsin-EDTA (0.25%, Gibco BRL) allowed primary skeletal muscle cell isolation and expansion in a culture medium composed of F12 (HAM) with 20% FBS (vol/vol), 1% (vol/vol) penicillin-streptomycin (10 000 UI/mL to 10 000 \(\mu g/mL\), Gibco BRL), and 5 ng/mL basic fibroblast growth factor (Sigma Chemical Co). Seven days after initial plating, the cells were harvested and resuspended in 0.15 mL volume for intramyocardial transplantation.

Experimental Groups

One hundred seventy-one animals underwent myocardial infarction through a lateral thoracotomy. Ninety received a treatment by the ACE inhibitor perindoprilat (1 mg · kg\(^{-1}\) · d\(^{-1}\) in the drinking water), started the day of the infarction and continued uninterrupted thereafter. Eighty-one received no ACE inhibitors.

One week after the infarction, a time at which the acute postinfarction inflammatory response has been shown to be terminated,17 124 rats had survived. They underwent a baseline echocardiographic assessment (after infarction but before transplantation).

Then, at the time of transplantation, they were randomly subjected to an intramyocardial injection (0.15 mL) of myoblasts or culture medium in the infarcted area by means of a 30-gauge needle under general anesthesia and tracheal ventilation, through an inferior midline minsternotomy.

In the ACE inhibitor–treated group, 74 rats survived (mortality rate of 17.8%, 16 of 90). Thirty-seven animals were intramyocardially transplanted with the 7-day cultured autologous myoblasts. All these rats survived and underwent an echocardiographic assessment 1 month after transplantation. Therefore they were included in the study as the ACE inhibitor+myoblast group (n = 37). At 2 months after transplantation, 36 rats were still alive and underwent the last echocardiographic assessment.

Thirty-seven rats only received an intramyocardial injection of culture medium. Twenty-two survived at 1 month after transplantation and underwent an echocardiographic assessment. They were included in the study as the ACE inhibitor group (n = 22). Only 20 animals survived at 2 months after transplantation and underwent the last echocardiographic assessment.

In the non–ACE inhibitor–treated group, 50 rats survived (mortality rate of 38.3%, 31 of 81). Twenty-five animals received an intramyocardial injection of cultured autologous myoblasts. Twenty-four of them survived at 1 month after transplantation and underwent an echocardiographic assessment. They were included in the study as the myoblast group (n = 24). All these animals survived at 2 months after transplantation and underwent the last echocardiographic assessment.

Twenty-five animals were intramyocardially injected with culture medium alone. Only 16 survived at 1 month after transplantation and underwent an echocardiographic assessment. They were included in the study as the control group (n = 16). Fourteen rats were still alive at 2 months after transplantation and underwent the last echocardiographic assessment.

To sum up, 99 animals were studied from a functional standpoint by 2D echocardiography. They were divided, as indicated above, into 4 groups: control rats (n = 16), receiving no drug and no myoblasts; myoblasts (n = 24), receiving no drug but myoblasts (2.3 \(\times\) 10^6); ACE inhibitors (n = 22), receiving perindoprilat but no myoblasts; and ACE inhibitors+myoblasts (n = 37), receiving perindoprilat and myoblasts (2.5 \(\times\) 10^6).

A flowchart of the protocol is depicted in Figure 1.

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**Figure 1.** Experimental protocol. MI indicates myocardial infarction; Tx, transplantation.
Immunohistological Assessment

Cellular Count at Time of Transplantation
A sample of the transplanted cells was plated onto 12-well dishes in 0.2 ml culture medium and incubated with desmin mouse antihuman antibody (1:200, DAKO, A/S-Denmark) followed by Cy3-conjugated anti-mouse antibody (1:200, Jackson Immuno Research Laboratories, Inc.). The cells were studied under phase contrast and fluorescent illumination with an inverted microscope (Olympus Optical Co, LTD). Photographs of several fields were then randomly taken. The proportion of myoblasts was calculated by dividing the number of desmin-positive cells counted on immunofluorescent pictures by the total number of cells counted on phase contrast pictures.

Autopsy
At 2 months after transplantation, after the last echocardiographic assessment, the rats were given an overdose of ketamine and xylazine. The ventricles were cross-sectioned at the midpoint of the long axis, frozen in isopentane cooled with nitrogen, and sectioned to yield 8-μm-thick slices with a cryostat. The slides were stained with hematoxylin and eosin staining for standard histological studies. Immunohistological studies were performed as described previously. Briefly, the slides were rinsed in PBS and fixed with cold 4% paraformaldehyde for 1 hour and, after several washes, with Cy3-conjugated anti-mouse antibody (1/200, Jackson Immuno Research Laboratories, Inc). The cells were studied under phase contrast and fluorescent microscopy.

Photographs of several fields were then randomly taken. The proportion of engrafted myoblasts between the 2 groups.

Statistical Analysis
The data are expressed as mean±SEM. All analyses were performed with appropriate software (StataView, SAS Institute Inc.). Comparisons of continuous variables among the control, myoblast, ACE inhibitor, and ACE inhibitor+myoblast groups were studied by a 1-way ANOVA. If the F ratio from the ANOVA was significant, a Scheffé test was used to specify pairwise differences. A Bonferroni correction was then used to refine the results. Longitudinal studies comparing echocardiographic data within each group, before and 1 and 2 months after transplantation, were achieved with the use of paired t tests. The critical α-level for these analyses was set at P<0.05.

Results

Characterization of Injection Suspension
Skeletal muscle cells were identified as desmin-positive cells. In the myoblast group, 10^7 cells were transplanted. The amount of myoblast was 2.3×10^6±4.3×10^5 (23%), ranging from 1.1×10^6 to 8×10^5. In the ACE inhibitor+myoblast group, 8.5×10^6 were intramyocardially delivered. The number of injected myoblasts was 2.5×10^6±3.1×10^6 (29.4%), ranging from 10^5 to 7.6×10^6.

Thus there was no significant difference in the numbers of engrafted myoblasts between the 2 groups.

Functional Assessment
The major functional results are summarized in Figure 2. There was no significant difference in baseline (after infarction but before transplantation) echocardiographic parameters among the 4 groups. Thus, LVEF was 27.5±0.9% in control rats, 27.2±1.1% in the myoblast group, 24.3±1.8% in the ACE inhibitor group, and 27.7±0.9% in the ACE inhibitor+myoblast group (P=0.16). At the 1- and 2-month time points, there was a significant improvement of ejection fraction in the myoblast group compared with the corresponding values seen in control rats (35.2±1.4% versus 19.9±0.7% and 37.4±1.2% versus 19.8±0.7%, P<0.0001, respectively). In the ACE inhibitor group, a functional improvement was also noticed at 1 and 2 months compared with control rats (31.5±2% versus 19.9±0.7% and 31.6±1.7% versus 19.8±0.7%, P<0.0001, respectively). Rats of the combined therapy group, receiving both perindoprilat treatment and autologous skeletal muscle cell transplantation, had cardiac function improved to a greater extent than those receiving each treatment alone at 2 months after engraftment (43.9±1.4% versus 37.4±1.2% in the myoblast group and 43.9±1.4% versus 31.6±1.7% in the ACE inhibitor group, P=0.0084 and P<0.0001, respectively). The difference was not as marked at 1 month, when the improvement was significant only when compared with the ACE inhibitor group (38.5±1.1% versus 31.5±2%, P=0.0048). There was no significant difference between the myoblast and the ACE inhibitor groups either at 1 or at 2 months after myoblast injection (35.2±1.4% versus 31.5±2% and 37.4±1.2% versus 31.6±1.7%, P=0.38 and P=0.06, respectively).

The data analysis of the functional outcome within each group over the 2-month study period showed a dramatic decrease in LVEF in the control group at 1 month compared with baseline (19.9±0.7% versus 27.5±0.9%, P=0.0001). In contrast, a significant improvement of LV function was noticed in the myoblast group at 1 month compared with baseline (35.2±1.4% versus 27.2±1.1%, P=0.0001). Moreover, this improvement continued at 2 months when compared with 1-month values (37.4±1.2% versus 35.2±1.4%, P<0.0001). The ACE inhibitor group showed almost the same pattern of changes at 1 month...
Two-Dimensional Echocardiographic Data of 94 Surviving Rats at 2 Months After Intramyocardial Injections: Left Ventricular End-Diastolic and End-Systolic Areas and Volumes

<table>
<thead>
<tr>
<th></th>
<th>End-Diastolic Surface, cm²</th>
<th>End-Diastolic Volume, mL</th>
<th>End-Systolic Surface, cm²</th>
<th>End-Systolic Volume, mL</th>
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<tr>
<td>Control rats (n=14)</td>
<td>1.63±0.05</td>
<td>1.26±0.06</td>
<td>1.36±0.04</td>
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<td>Myoblasts (n=24)</td>
<td>1.37±0.03*</td>
<td>0.99±0.04§</td>
<td>1.04±0.03#</td>
<td>0.62±0.03∥</td>
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<td>ACE inhibitors (n=20)</td>
<td>1.44±0.04†</td>
<td>1.06±0.05</td>
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<tr>
<td>ACE inhibitors+myoblasts (n=36)</td>
<td>1.42±0.03‡‡</td>
<td>1.07±0.04¶</td>
<td>1.04±0.03††</td>
<td>0.61±0.03¶¶</td>
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Values are presented as mean±1 SEM.

*P<0.0003, †P<0.024, ††P<0.0027 vs control rats, respectively; §P<0.0002, ||P<0.0087, ¶P<0.0054 vs control rats, respectively; #P<0.0001, **P<0.027, †††P<0.0001 vs control rats, respectively; ‡‡P<0.0001, §§P<0.0006, ||||P<0.0001 vs control rats, respectively.

(31.5±2% versus 24.2±1.8%), without further benefit at 2 months (31.6±1.7% versus 31.5±2%, P=0.42). In the ACE inhibitor+myoblast group, functional changes were similar to those yielded by the myoblast group at 1 and 2 months after transplantation, but the increase in LVEF was of greater magnitude (38.5±1.1% at 1 month versus 27.7±0.9% at baseline and 43.9±1.4% at 2 months versus 38.5±1.1% at 1 month, P<0.0001, respectively).

The results concerning LV end-diastolic and end-systolic areas and volumes are shown in the Table.

Immunohistology

Myofibers were identified in the myocardium transplanted with myoblasts. The skeletal origin of these muscular structures, revealed throughout the infarcted area, was assessed by positive immunostaining for fast skeletal myosin heavy chain, a specific marker of skeletal muscle (Figure 3). The expression of rat cardiac α-myosin heavy chain revealed cardiac muscle fibers surrounding the scar tissue (Figure 4). Until now, we have found no evidence for connections between grafted myoblasts and host cardiomyocytes.

Discussion

The major findings of the present study are that (1) ACE inhibitors and myoblast transplantation exert equally protective effects on postinfarction LV function, and (2) the combination of these two treatment modalities provides a greater functional improvement than either therapy alone.

LV functional assessment was performed in vivo by 2D echocardiography with the use of a numeric machine allowing recording of more than 20 heart scans at a rate of 400 beats/min.

LV volumes were extrapolated from areas and lengths of the left ventricles assuming an ellipsoid shape. This area-length 2D echocardiography single-plane method \( (8 \times A^2/3 \times \pi \times L) \) has been validated in infarcted human hearts\(^1\) and in murine models\(^2\) of heart disease.

However, it is true that this method is usually less accurate than biplane measurements in the setting in clinical infarct,\(^1\) but this limitation does not necessarily apply to the murine heart in which the biplane method has not yet been validated.

Moreover, preliminary studies from our group\(^1\) have suggested that after ligation of the anterior descending coronary artery in the murine heart (as performed in the current study), infarction involves constantly and predominantly the LV apex (frequently with an aneurysmal formation). In this case, the short-axis view of the LV is difficult to standardize and frequently overpasses the infarct area, leading to an underestimation of the extent of the infarction (with smaller volumes and greater ejection fractions). Thus the use of the area-length single-plane 2D echocardiography method might lead only to an underestimation of the differences observed here between groups. In the present study, we used the single-plane area-length method because 2D measurements are more appropriate than those performed in the M-mode. Because of its technical characteristics, the 13- to 15-MHz transducer used in this study allowed precise identification of end-systolic and end-diastolic frames on 2D echocardiograms.

Figure 3. Serial sections of transplanted area 2 months after cell transplantation. Top, Multinuclear elongated structures typical of myotubes (arrow). Original magnification ×40. Bottom, expression of fast skeletal myosin heavy chain by skeletal muscle tissue. Myotube indicated in top panel is positively stained in this microphotograph (arrow). Asterisk indicates cross-sectioned myofibers. Original magnification ×40.
The novel finding of this study is that the postinfarction LV function of perindopril-treated rats further improved after myoblast transplantation. In this combined therapy group, LV remodeling was not significantly different from that seen in the 2 single-therapy (myoblasts or ACE inhibitors) groups. Thus, the observation of a significantly higher ejection fraction suggests the additional involvement of an active systolic effect, which is consistent with data previously reported in a rabbit model of cryoinjury with sonomicromanometry to assess LV function. This observation is of clinical relevance in that it shows that myoblast transplantation is not an alternative to ACE inhibitors but should rather be viewed as an additional therapeutic option in patients whose heart failure becomes drug-resistant. It is also noteworthy that the kinetics of improvement yielded by perindopril and myoblasts displayed different time profiles. Thus, the ejection fraction of myoblast-transplanted hearts further improved between 1 and 2 months, and this improvement was even more manifest in the presence of ACE inhibitors, cardiac injections. Thus, our 1- and 2-month echocardiographic assessments were fully relevant.

A second finding of the present study is that among rats that did not receive ACE inhibitors, those transplanted with skeletal myoblasts had higher LVEFs at 1 and 2 months after the procedure than control rats receiving culture medium only. Moreover, the functional improvement was closely correlated with the number of injected myoblasts ($R^2=0.819$, $P<0.0001$). This observation provides additional evidence for the efficacy of autologous skeletal muscle cell transplantation to improve postinfarction function in a dose-dependent fashion. The mechanism whereby this improvement occurs remains, however, unsettled. In a rabbit model of cryonecrosis, Atkins and coworkers have reported that the primary effect of autologous skeletal myoblast transplantation was to preserve diastolic function, whereas the effect on systolic function was less consistent. The present study, as well as our previous data, suggests that the beneficial effects of grafted myoblasts on postinfarction function are, at least in part, related to an increase in contractility. This view is further supported by our recent findings made in a sheep model of endocoronary occlusion that regional wall motion increases in the grafted areas, as assessed by Doppler tissue imaging (unpublished data). A similar observation has actually been made in the first patient in whom we implanted autologous skeletal myoblasts. That the contractile properties of implanted cells is a key factor of successful outcome after their intramyocardial engraftment can also be marshaled from the observation that fetal cardiomyocytes are more effective than smooth muscle cells and fibroblasts in improving postinfarction LV function. A similar result has also been demonstrated by the Taylor group when comparing the functional benefits provided by skeletal myoblasts and fibroblasts. The lack of gap junctions between grafted myoblasts and host cardiomyocytes does not preclude them to positively affect systolic function if one assumes that the islets of implanted cells can be mechanically recruited by the contraction of the surrounding recipient myocardium.

The observation that among non–cell-transplanted animals, those receiving perindoprilat had a better postinfarction functional outcome than their untreated counterparts is consistent with the well-documented salutary effects of ACE inhibitors given after a myocardial infarction. Indeed, Pfeffer et al demonstrated, in their pioneering experimental works, that the chronic administration of captopril improved the hemodynamic parameters of infarcted rat hearts as the result of its preload- and afterload-reducing properties. Moreover, this ACE inhibitor had a pronounced effect on prolonging survival in this model of coronary artery ligation–induced infarction. Since the first clinical studies, this class of drugs has earned its place along with aspirin, β-blockers, and thrombolytic agents as medical therapies proven to reduce mortality rates and is now routinely used, even in the case of acute myocardial infarction. In the present study, we used the ACE inhibitor perindoprilat, which also demonstrated its efficacy in a myocardial infarction model similar to ours. Concerning the impact of ACE inhibitors on hemodynamics parameters, it is a fact that one mechanism of action of this therapy includes the well-known reduction of mean arterial blood pressure. Although preload and afterload were not controlled for in our study, it remains that LV sizes (areas and volumes) were not different between groups before intramyocardial injections. Thus, our 1- and 2-month echocardiographic assessments were fully relevant.

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References


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*Circulation*. 2001;104:I-223-I-228
doi: 10.1161/hc37t1.094593

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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