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Systolic Contraction Within Aneurysmal Rabbit Myocardium Following Transplantation of Autologous Skeletal Myoblasts

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Objective. **Transplantation of autologous skeletal myoblasts (SKMB) into infarcted heart (or cellular cardiomyoplasty, CCM) augments myocardial performance in animal models of myocardial infarction. However, the effect of CCM in the setting of ventricular aneurysm has not been evaluated. This study analyzes the effects of transplanted SKMB on regional wall motion in a rabbit model of postinfarct ventricular aneurysm. We hypothesize that CCM, performed early after myocardial infarction, prevents the progression of dyskinetic wall motion.**

Methods. **Twenty-six rabbits underwent apical left ventricular cryoinfarction and soleus muscle biopsy for *in vitro* isolation of skeletal myoblasts. At 2 weeks postinfarct, the presence of ventricular aneurysm was detected in 23/26 animals by sonomicrometry and micromanometry. Seventeen of 23 animals were randomized to receive either 108 autologous myoblasts (CCM) or vehicle. Regional stroke work, percent systolic shortening, and synchronicity of regional wall motion were determined prior to, and four weeks following, injection (CCM; $n = 9$; vehicle, $n = 8$). Wall motion was evaluated under baseline and stress (dobutamine, 10 (g/kg/min) conditions. Six animals did not undergo randomization, but their hearts were used to measure the size of infarction.**

Results. **Four weeks following treatment of animals with ventricular aneurysm, systolic contractile activity was present in most animals treated with myoblasts but in none treated with vehicle (5/7 *versus* 0/6, respectively, $P < 0.05$). Dobutamine tended to accentuate the differences seen at baseline between the groups.**

Conclusions. **This study demonstrates a high incidence of systolic contractile activity in a previously aneurysmal region of myocardium following CCM and may represent a novel therapy for the prevention and treatment of postinfarct aneurysm.**

Key Words: **cellular cardiomyoplasty; heart failure; ventricular aneurysm; myocardial infarction; skeletal myoblastas.**

INTRODUCTION

Ventricular aneurysm results from replacement of contractile myocardium with compliant scar tissue and is estimated to occur in up to 22% of patients following acute myocardial infarction—most commonly after anterior wall infarction [2]. Mortality following myocardial infarction is higher in patients with aneurysms when compared to those without aneurysms, even when ejection fraction is comparable [3]. Cell-based therapeutic modalities for the treatment of ischemic heart disease are under intense investigation due to the prospect of improved myocardial performance postinjury. Recent studies from several laboratories including our own have demonstrated improved function of hypokinetic myocardium following intramyocardial transplantation of autologous skeletal myoblasts (cellular cardiomyoplasty, or CCM) in a variety of animal models and clinically [1, 4, 5]. However, the effects of skeletal myoblasts (SKMB) in the setting of postinfarct ventricular aneurysm have not been investigated. We present a model of postinfarct ventricular aneurysm and evaluate the effects of CCM on regional wall motion within the aneurysm. We hypothesize that transplantation of autologous skeletal myoblasts into

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dyskinetic myocardium following myocardial infarction will have favorable effects on aneurysmal wall motion.

METHODS

Creation of Aneurysm

New Zealand White rabbits (n = 26) were subjected to myocardial infarction by a freeze—thaw method and evaluated 2 weeks later to determine the presence of ventricular aneurysm. All animals received humane care in accordance with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIH publication 86-23, revised 1985). Animals were sedated with ketamine (55 mg/kg) and intubated. Under general anesthesia (isoflurane 1–5%), a left thoracotomy was performed in the third intercostal space, and the pericardium was opened. Myocardial aneurysm was created by cryoinfarction of the anterior—inferior portion of the left ventricle (LV). A −70°C cryoprobe was placed on the anterior—apical LV for 3 min and then removed, allowing the myocardium to thaw. Compared to coronary artery ligation, infarction by this method more consistently leads to homogenous myocardial necrosis and subsequent aneurysm formation [4]. A concomitant soleus muscle biopsy was performed, and subsequent myoblast isolation and expansion were performed as previously described in our laboratory [1]. The incisions were closed, and the animals were allowed to recover in a supervised animal care facility.

Two weeks following myocardial infarction, animals were returned to the operating room, where a repeat thoracotomy was performed under general anesthesia (as described above). A left ventricular micromanometer was placed into the left ventricular cavity through a small incision in the left atrium and secured in place with a purse-string suture. Two ultrasonic transducers were placed on the short-axis epicardial surface of the left ventricle within the area of prior myocardial infarction. Simultaneous pressure-segment length loops were obtained under light anesthesia and ventilatory arrest. Aneurysmal wall motion was confirmed by observation of systolic expansion of the infarcted segment of myocardium and dyskinetic wall motion by sonomicrometry. Of the 26 animals that underwent cryoinfarction, 23 developed LV aneurysms as documented by sonomicrometry and micromanometry, and only these animals were used for further investigation. Six of 23 animals were euthanized at 2 weeks to allow measurement of infarct size by planimetry.

Cell Delivery

Animals displaying ventricular aneurysm were randomly assigned to receive either autologous skeletal myoblasts (CCM, n = 9) or vehicle (n = 8). The area of myocardial infarction between the sonometric transducers was infiltrated with either 10^8 autologous skeletal myoblasts suspended in DMEM (0.8 ml) or DMEM alone (0.8 ml). Injections were performed through a single puncture site in the myocardium, with a protective purse-string suture to prevent retrograde efflux of injectate from the puncture site. The chest was closed over chest tubes, and the animals were allowed to recover for 4 weeks. At this time, the animals that survived (CCM, n = 7; vehicle, n = 6) were subjected to a final hemodynamic study under general anesthesia with left ventricular micromanometry and sonomicrometry. Regional systolic wall motion and global hemodynamics were recorded. Animals were euthanized following hemodynamic evaluation, and hearts were harvested and placed in 30% sucrose—PBS solution at 4°C in preparation for histological sectioning.

Functional Assessment

Functional assessment was performed by an investigator blinded to treatment status. Ventricular aneurysm was documented by visual inspection, and by the presence of dyskinetic wall motion from the pressure-segment length relationship. Hemodynamic parameters obtained included systolic blood pressure (SBP), end-diastolic pressure (EDP), heart rate (HR), and dP/dt_{max}. Pressure-segment length loops were obtained by simultaneous digital recording of LV pressure and sonometric transducer waveform. Stroke work (SW) was calculated as the integral of the pressure-segment length loop ($SW < \int P(dl)$) over one heart beat, using custom-designed software. This was averaged over several beats, and the mean SW was recorded. Systolic shortening fraction (SS) was calculated as dBE [minus] dEE/dBE, where dBE and dEE are the distances between the sonometric transducers at beginning ejection and end ejection, respectively. Aneurysmal myocardium displays negative values of SW and SS since the transducers mover farther apart during systole. In contrast, contracting myocardium displays positive values of SW and SS due to shortening of the segment during systole. Hemodynamic studies were performed at baseline and during infusion of dobutamine (10 (g/kg/min)).

Histology

Heart specimens were stored for 24 h in 30% sucrose PBS at 4°C and embedded in Tissue-Tek media for subsequent sectioning. The region of myocardial infarction was divided into three blocks, and 10 short-axis cross-sectional segments (8-(m-thickness)) were obtained from each block. The sections were stained with Hematoxylin and Eosin or Masson's Trichrome and were analyzed by light microscopy. Wall thickness in the central portion of the scar was measured from histological sections. Each cross-sectional slide was examined in 10 random areas within the central portion of the scar, and the average score for each animal was recorded. A pathologist blinded to the treatment status of each animal assigned injury scores based upon the degree of cellularity and the cytoplasmic-to-nuclear ratio of cells seen within the infarct. A score of 1 was assigned for microscopic appearance of high cellular density and presence of cells with high cytoplasmic-to-nuclear ratio. A score of 3 was assigned for microscopic appearance of scar tissue with cells displaying low cytoplasmic-to-nuclear ratio. A score of 2 was assigned for intermediate findings. A separate group of six animals that underwent creation of ventricular aneurysm was analyzed to determine the size of the infarcted segment of myocardium as previously described. Briefly, the heart was removed, and the LV surface area was quantified by planimetry. The infarct segment was excised from the LV, and its area was quantified as well. The percent infarction was defined as the ratio of infarct to total LV surface area.

Statistical Analysis

All data are expressed as mean ± standard error of the mean. Differences in SBP, EDP, HR, wall thickness, and injury scores were compared by two-way analysis of variance and post-hoc Sheffe subtesting to determine statistical significance. The difference between the numbers of animals in each group displaying contraction within the aneurysm 4 weeks after treatment was compared by Fisher exact test. Differences in mean values of SW and SS were compared by nonparametric Kruskal–Wallis analysis and post-hoc subgroup comparison. P values less than 0.05 were considered to be statistically significant.

RESULTS

Systolic blood pressure, EDP, and dP/dtmax were similar between myoblast- and vehicle-treated animals prior to treatment and 4 weeks following treatment (Table 1). Likewise, mean heart weight, body weight (Table 2), and heart weight to body weight ratios were similar between groups (data not shown).

TABLE 1

Hemodynamic Characteristics of All Animals Prior to and Following Treatment

	Vehicle (n = 6)		Myoblast (n = 7)	
	Preinjection	Postinjection	Preinjection	Postinjection
Body weight (kg)	ND	3.2 ± .2	ND	3.3 ± .4
Heart weight (g)	ND	7.39 ± 1.2	ND	7.71 ± 1.7
SBP (mmHg)	52 ± 2.4	44 ± 4.1	49 ± 3.9	51 ± 4.7
EDP (mmHg)	67.0 ± 12.2	5.1 ± .6	6.0 ± 1.1	7.3 ± 2.7
HR (bpm)	206 ± 913	215 ± 9	199 ± 7	198 ± 10
LV dP/dt_{max} (mmHg/s)	1938 ± 207	1457 ± 235	1698 ± 139	1614 ± 133

ND = Not determined; SBP = systolic blood pressure; EDP = end-diastolic pressure; HR = heart rate; LV = left ventricular.

Ventricular Aneurysm Formation

Ventricular aneurysm was documented by the presence of dyskinetic wall motion (negative values of SW and SS) from sonometric and micromanometric measurements. In addition, bulging of the aneurysmal segment during systole was visible in these animals. Two weeks following cryoinfarction, 23 of 26 animals demonstrated ventricular aneurysm, as evidenced by negative SW and SS (Table 2, preinjection, baseline). Animals displaying contractile or hypokinetic myocardium were excluded from further analysis. Clinical assessment of animals was performed by veterinary staff and investigators blinded to the treatment status of the animals. No mortality was encountered within 2 weeks after cryoinfarction. The mortality within 4 weeks following intramyocardial injection was similar between animals receiving myoblasts (2/9) or vehicle (2/8). The mortality was attributable to empyema and sepsis in two animals, congestive heart failure in one, and one intraoperative death. Only animals surviving to the point of final hemodynamic study were included in the final analysis: myoblasts (n = 7) and vehicle (n = 6). Bilateral pleural effusions were seen in most animals at the time of euthanasia, but symptoms of severe congestive heart failure (anasarca, respiratory distress, anorexia) were only documented in one animal, which subsequently died prior to the end of the study. The mean surface area of the aneurysmal segment as measured by planimetry in the separate group of six animals at 2 weeks was 1.43 ± 0.27 cm2. The mean percent infarct calculated from the ratio of infarct to LV surface area was 22 ± 4%.

Effect of CCM on Wall Motion

Five of seven surviving animals that received injection of autologous skeletal myoblasts into the aneurysm showed positive SW and SS after 4 weeks, suggesting reversal of myocardial dyskinesis (Fig. 1, right panel). However, two of seven CCM animals continued to show aneurysmal dilation despite CCM, as documented by persistently negative values of SW and SS (Fig. 1, right panel). Even with inclusion of these two animals, mean values of SW and SS were significantly higher 4 weeks after CCM when compared to pretreatment (Table 2, myoblast, baseline, preinjection versus postinjection). Animals treated with intramyocardial injection of vehicle had persistent ventricular aneurysm after 4 weeks, as demonstrated by continued worsening of negative SW and SS (Fig. 1, left panel;

TABLE 2

Regional Myocardial Contractility in Ventricular Aneurysm Under Baseline and Stress Conditions

	Vehicle (n = 6)		Myoblast (n = 7)	
	Baseline	Dobutamine	Baseline	Dobutamine
Systolic contractile activity, n (%)	0/6 (0%)	0/6 (0%)	5/7 (71%)*	5/7 (71%)*
Stroke work				
Preinjection SW (erg)	−895 ± 296	−1642 ± 515	−481 ± 160	−975 ± 183
Postinjection SW (erg)	−1281 ± 829	−2080 ± 823	473 ± 320*†	1315 ± 672*†
Systolic shortening				
Preinjection SS (%)	−1.4 ± .4	−2.6 ± .3	−.98 ± .2	−2.1 ± .2
Postinjection SS (%)	−3.1 ± 2	−2.6 ± .7	1.0 ± .6*†	1.2 ± 1.3*†

* $P < 0.05$ Myoblast *versus* vehicle.
† $P < 0.05$ Postinjection *versus* preinjection.

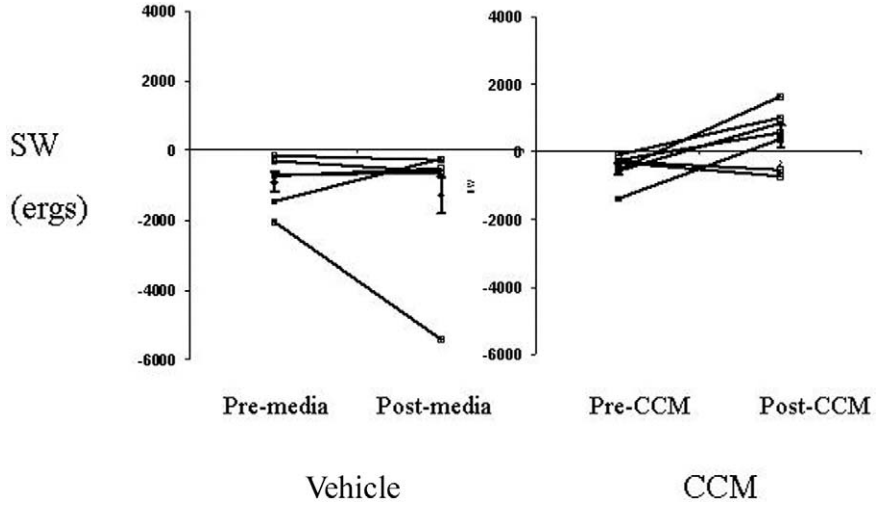

FIG. 1. Stroke work values before and 4 weeks after treatment in each animal receiving myoblasts (CCM) or vehicle. Persistently negative values of SW are seen after injection of vehicle. Treatment with myoblasts results in conversion from negative to positive SW in 5/7 animals 4 weeks after treatment.

Table 2, vehicle, baseline, preinjection versus postinjection). The number of animals displaying systolic contractile activity within the aneurysm 4 weeks after treatment was significantly higher in the myoblast-treated compared to vehicle-treated group (5/7 versus 0/6, $P < 0.05$ by Fischer exact test). Similarly, the mean values of SW and SS were significantly higher in the myoblast-treated compared to vehicle-treated animals ($P < 0.05$ by Kruskal–Wallis test, Table 2).

Effect of Adrenergic Stimulation on Wall Motion

The effect of dobutamine on wall motion within the ventricular aneurysm was assessed prior to and 4 weeks following treatment. Prior to treatment, in both groups, dobutamine stimulation resulted in persistently negative values of SW and SS, indicating persistence of the ventricular aneurysm under adrenergic stimulation (Fig. 2A and B, left panel). Four weeks following treatment with vehicle, negative values of SW and SS were seen at baseline and after dobutamine stimulation. In animals treated with myoblasts, mean SW and SS values were positive 4 weeks after treatment, both at baseline and after dobutamine. In the two animals in the CCM group with persistent ventricular aneurysm at baseline 4 weeks following CCM, adrenergic stimulation resulted in persistently negative SW and SS. Nevertheless, mean values tended to increase following dobutamine administration when compared to baseline, although the differences were not statistically significant (Fig. 2B, right panel; Table 2, myoblast, postinjection, baseline versus dobutamine).

Histological analysis was performed to compare the degree of myocardial injury in each group of animals. The average injury score following cryoinfarction was equivalent between myoblast-treated and vehicle-treated animals (2.8 ± 0.23 versus 2.5 ± 0.31, respectively). Wall thickness at the central portion of the aneurysm was measured from corresponding histological sections and was not significantly different between myoblast-treated compared to vehicle-treated animals (0.4 ± 0.02 versus 0.4 ± 0.04, respectively). Although we were unable to quantify differences in the histological appearance of stained sections between myoblast-treated and vehicle-treated animals, two myoblast-treated animals demonstrated islands of cells with high cytoplasmic-to-nuclear ratios consistent with progenitor cell morphology (Fig. 3) that was absent in the vehicle-treated animals. These two animals demonstrated positive SW and SS at the time of final hemodynamic assessment.

DISCUSSION

Left ventricular aneurysm can be documented in up to 20% of patients following acute myocardial infarction and is associated with increased mortality. Although ventricular aneurysms are commonly diagnosed months to years following acute myocardial infarction, early development of aneurysm or regional dyskinesis may be underappreciated [6]. A prospective echocardiographic study of 158 patients suffering myocardial infarction found that 43% of aneurysms form within 5 days, and no aneurysms form after 3 months postmyocardial infarction [2]. The mechanisms underlying the reduced ejection fraction in the presence of a ventricular aneurysm include mechanical dyskinesis during systole and contractile dysfunction of bordering viable myocardium [7, 8]. The ability to prevent aneurysm is very limited and its treatment can be associ-

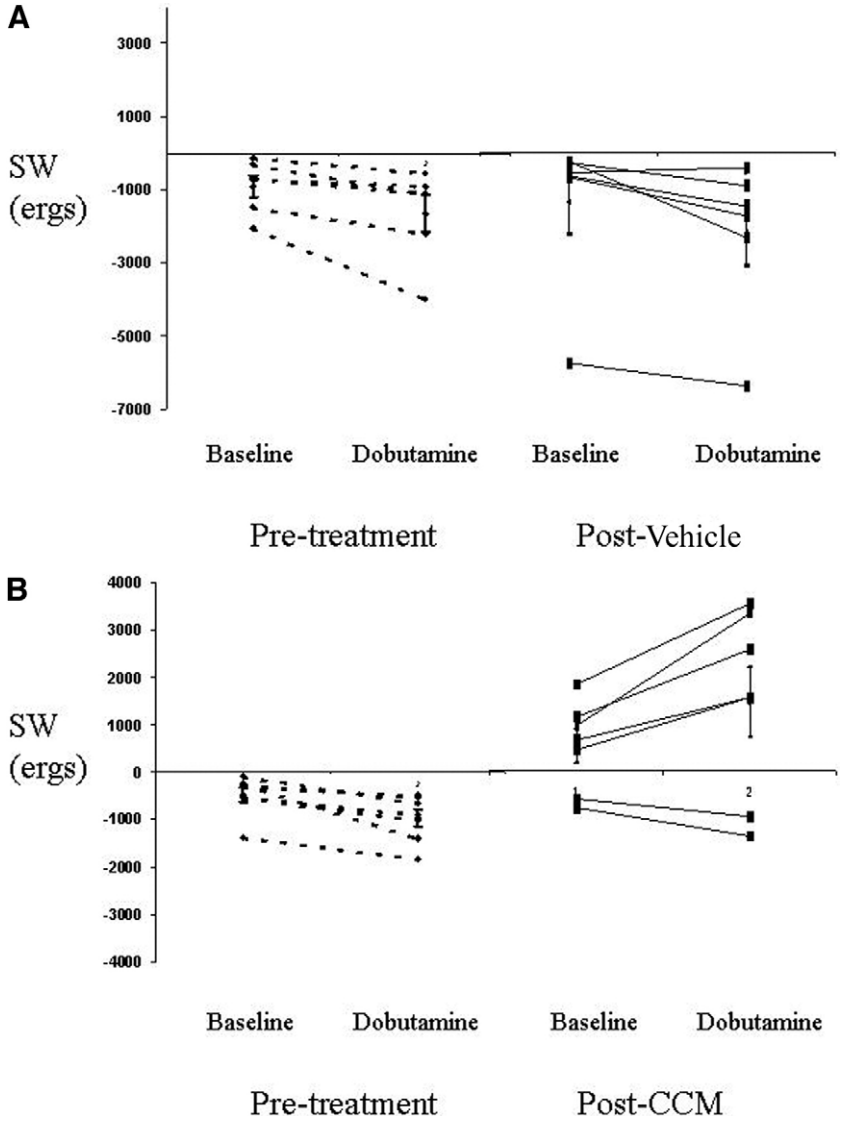

FIG. 2. Stroke work values at baseline and after administration of dobutamine in each animal receiving vehicle (A) or CCM (B). Values presented include stroke work prior to, and 4 weeks following, treatment.

ated with high mortality, depending upon the function of the remaining myocardium. Repair of aneurysm in the setting of coronary artery disease and prior myocardial infarction has been associated with mortality as high as 20%, with a 10-year survival rate of 55% [9, 10].

Although the effects of CCM have been evaluated in animal models of hypokinetic, but still contractile myocardium, the effects of myoblast transfer on ventricular aneurysm have not been studied. We present a model of postinjury ventricular aneurysm and demonstrate favorable effects of CCM in this model. Injection of autologous skeletal myoblasts into postinfarct aneurysmal myocardium improves wall motion 4 weeks after treatment. In contrast, sham treatment yields no improvement and persistent aneurysm at 4 weeks.

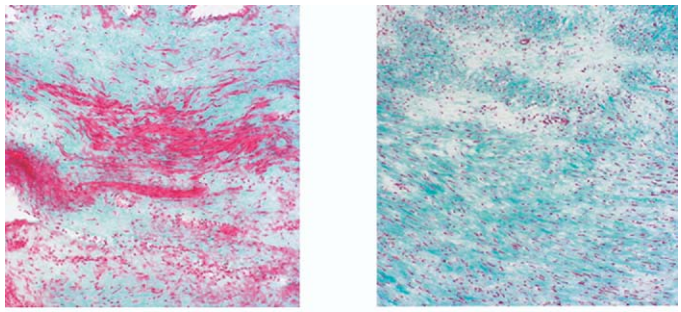

FIG. 3. Gross histological appearance of representative sections from animals treated with 108 myoblasts or vehicle (Masson Trichrome stain, magnification, ×40). Islands of cells with high cytoplasmic-to-nuclear ratio were seen on histological sections of several, but not all, myoblast-treated animals.

This increase of wall motion suggests that CCM may be useful to prevent aneurysm progression after myocardial infarction.

We used cryoinfarction instead of coronary artery ligation due to the reproducibility of transmural infarction, consistency of infarct size, and increased likelihood of aneurysm formation with the former [4]. The morphology of the injury created by this technique is a cone-shaped myocardial infarction with complete central myocardial necrosis and peripheral regions of ischemic, but viable, myocardium [11]. The incidence and timing of ventricular aneurysm formation in cryoinjured animals is similar to that seen clinically and in other animal models of postinfarction aneurysm [2, 6, 12, 13]. The disadvantage of this model is the potential physiological difference between the cryoinfarct model and clinical myocardial infarction. The animals in the study did not show signs of severe CHF, and no mortality was encountered in either group within 2 weeks after cryoinfarction. The benign clinical presentation is likely due to adequate compensation by the surrounding normal myocardium with an infarct size of ~22%. Despite the limitations of the model, we were able to demonstrate a favorable effect of CCM upon ventricular aneurysm.

The response of the infarcted myocardium to dobutamine stress was evaluated prior to and following intervention. The persistence of dyskinetic wall motion following administration of dobutamine concurs with the histological finding of transmural infarct, demonstrating functionally that the area to be treated was completely infarcted, with no obvious ability for further myocyte recruitment. After treatment, five of seven animals receiving skeletal myoblasts demonstrated positive SW and SS at baseline and after dobutamine administration, indicative of systolic contractile activity. However, two treated animals demonstrating aneurysmal wall motion at baseline continued to display aneurysmal wall motion after administration of dobutamine, suggesting either inadequate engraftment or electrical/mechanical dissociation from surrounding contractile myocardium.

The interval between myocardial infarction and treatment with either autologous skeletal myoblasts or vehicle was 2 weeks, an interval chosen because prior studies have demonstrated improved myocardial function when treatment is performed at this time [14–16]. However, the optimal time following myocardial infarction at which maximal functional benefit of CCM is obtained may be earlier or later. This remains to be established [17,18]. Similarly, although this study evaluated the effects of cell-based therapy on myocardial dyskinetic motion early after myocardial infarction, it did not address the effects of such a therapy on well-formed aneurysms that are detected months or years after myocardial infarction.

The mechanisms underlying the regional functional improvement are poorly understood. A conversion from negative to positive SW and SS within the aneurysms of most myoblast-treated animal was seen, despite the lack of clear histological evidence for cell engraftment in these animals. The lack of histological evidence for significant engraftment despite functional improvement has been previously reported [19]. There are several possible explanations for this disparity. Injected cells may affect surrounding myocardium by eluting growth factors in a paracrine fashion, and thus, significant engraftment may not be necessary to affect favorable functional outcome [20]. Technically, the disparity may be a function of sampling error. Our evaluation of the histological specimens involved random sampling of several areas within the infarct. Yet important areas of engraftment may have been missed. Sparse engraftment within the infarct may result in an underwhelming histological appearance, yet result in significant physiological improvement. A similar phenomenon has been demonstrated in clinical studies in which functional improvement was seen in patients despite sparse engraftment [21].

Future studies are needed to address several important issues raised by this study. One area that needs further investigation is the impact of CCM on global myocardial performance and survival. We did not show an improvement in SBP, dP/dtmax, EDP, or HR following CCM. The small size of the aneurysm in comparison to surrounding normal myocardium (22% infarct by surface area) may explain why an improvement in regional function did not translate into improved in global function. More sensitive load-independent measurements may be required to demonstrate improvements in global myocardial function after CCM, but this makes CCM less appealing if no impact on clinically relevant measures of global performance is seen.

The synchrony of contraction seen within the aneurysm after CCM is surprising given previous findings of electrical isolation of the transplanted cells within infarcted myocardium [17]. The contribution of stretch-induced myocyte contraction to this synchrony of contraction remains to be proven, but is a likely explanation given the SKMB contraction just after the beginning of ejection.

Our findings are consistent with other studies that have evaluated the use of cell-based therapy for ventricular aneurysm. Surgical repair combined with delivery of fetal cardiomyocytes or bioengineered smooth muscle grafts demonstrates favorable effect on LV dimensions after myocardial infarction in rats [22, 23]. Mesenchymal stem cells delivered to infarcted swine myocardium via epicardial patch have been shown to improve LV systolic thickening fraction within that region of myocardium [24]. Although this study dem-

onstrated favorable effects of skeletal myoblasts on ventricular aneurysm, the use of other cell types may yield similar results.

This study describes a rabbit model of ventricular aneurysm and demonstrates favorable effects of local injection of autologous skeletal myoblasts upon regional wall motion within aneurysm. Not only did CCM prevent the further dyskinesis seen in vehicle-treated animals, but it also resulted in contraction within the aneurysm in most animals. The mechanism underlying the improvement is not fully understood, and further investigation is underway to elucidate this. Although further experimentation is required to determine the optimal timing and long-term effects of myoblast therapy in this setting, CCM represents a novel therapeutic strategy for the prevention and treatment of ventricular aneurysm following transmural myocardial infarction.

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