Intracoronary administration of autologous adipose tissue-derived stem cells improves left ventricular function, perfusion, and remodelling after acute myocardial infarction

Christian Valina1, Kai Pinkernell1, Yao-Hua Song2, Xiaowen Bai2, Sanga Sadat2, Richard J. Campeau1,3, Thierry H. Le Jemtel1, and Eckhard Alt1,2*

1Department of Medicine, Section of Cardiology, Tulane University Health Sciences Center, New Orleans, LA 70112, USA; 2Department of Molecular Pathology, MD Anderson Cancer Center, University of Texas, SCRB2, Box 951, 7435 Fannin Street, Houston, TX 77054, USA; and 3Department of Radiology, Section of Nuclear Medicine, Tulane University Health Sciences Center, New Orleans, LA 70112, USA

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Aims This study was designed to assess whether intracoronary application of adipose tissue-derived stem cells (ADSCs) compared with bone marrow-derived stem cells (BMSCs) and control could improve cardiac function after 30 days in a porcine acute myocardial infarction/reperfusion model.

Methods and results An acute transmural porcine myocardial infarction was induced by inflating an angioplasty balloon for 180 min in the mid-left anterior descending artery. Two million cultured autologous stem cells were intracoronary injected through the central lumen of the inflated balloon catheter. Analysis of scintigraphic data obtained after $28 \pm 3$ days showed that both absolute and relative perfusion defect decreased significantly after intracoronary administration of ADSCs or BMSCs (relative $30 \text{ or } 31\%$, respectively), compared with carrier administration alone ($12\%$, $P = 0.048$). Left ventricular ejection fraction after 4 weeks increased significantly more after ADSC and BMSC administration than after carrier administration: $11.39 \pm 4.62$ and $9.59 \pm 7.95\%$, respectively vs. $1.95 \pm 4.7\%$, $P = 0.02$). The relative thickness of the ventricular wall in the infarction area after cell administration was significantly greater than that after carrier administration. The vascular density of the border zone also improved. The grafted cells co-localized with von Willebrand factor and alpha-smooth muscle actin and incorporated into newly formed vessels.

Conclusion This is the first study to show that not only bone marrow-derived cells but also ADSCs engrafted in the infarct region 4 weeks after intracoronary cell transplantation and improved cardiac function and perfusion via angiogenesis.

KEYWORDS Myocardial infarction; Heart failure; Angiogenesis

Introduction Over the recent years, cellular cardiomyoplasty has been an area of intense research. A variety of cell types have been shown to work beneficially, especially in the ischaemic myocardium of rodents and small animals.1–3 Among the cell types used so far, mesenchymal stem cells seem to be highly advantageous for cellular therapy. MSCs are multipotent, might be immune-privileged,4,5 and can be expanded easily ex vivo. MSCs isolated from adult bone marrow have shown a great potential for cell therapy because these cells possess multipotent capabilities,5 proliferate rapidly, induce angiogenesis, and differentiate into myogenic cells.6,7 Recently, a multipotent stem cell population with high proliferate potential was isolated from human adipose tissue.8 Aside from the possible pain and morbidity associated with a bone marrow biopsy, the use of adipose tissue has the advantage of being able to obtain a high number of mesenchymal stem cells (2–10%), whereas bone marrow aspirate typically yields only two to...
three mesenchymal cells per 100,000 cells. In most patients, adipose tissues are abundantly available and can be routinely harvested. Thus, adipose tissue appears to be a convenient and preferable source of stem cell recovery for cardiac therapy, compared with bone marrow. The transdifferentiation potential of ADSCs has been shown recently in several studies.8–11 ADSCs have been shown to differentiate into endothelial cells, incorporate into vessels, and promote postischaemic neovascularization in nude mice.12 Transplantation of monolayered ADSC reversed wall thinning in the scar area and improved cardiac function in rats with myocardial infarction.13 The engrafted sheet formed a thick stratum with newly formed vessels.

To explore the potential therapeutic application of ADSCs in a pre-clinical large animal model using the same instrumentation and standard of care as in humans, we compared the effects of intracoronary administration of ADSCs, BMSCs, or carrier on left ventricular (LV) function, vascular density, and wall thickness (WT) in a porcine model of transmural myocardial infarction.

Methods

Experimental animals

All procedures were performed in accordance with protocols approved by the Institutional Committee for Animal Care and Use of Tulane University and complied with the guide for the Care and Use of Lab Animals (NIH publication no. 86-23, revised 1985, study protocol 2749). A total of 31 female farm pigs (30.8 ± 5.4 kg) were used in the study.

Experimental design

Thirty-one animals were randomized in the study. Animals that survived the initial infarction induction (21 pigs, three pigs per group) were followed for 28 ± 3 days. Perfusion defect was assessed by standard SestaMIBI evaluation protocols adjusted by our clinical nuclear department to the chest geometry of the pigs. The team who performed the cath procedure was blinded to the randomization protocol. The randomization code was retrieved at the time who performed the cath procedure was blinded to the randomization protocol. The randomization code was retrieved at the time.
Perfusion and functional assessment with 99mTc-Sestamibi

SPECT imaging was performed in the anaesthetized animal in a supine position under a single head nuclear gamma camera (Philips Arc-3000, ADAC Laboratories/Philips Medical Systems, Milpitas, CA, USA). SPECT images were acquired with a circular 180° acquisition of 64 projections with an acquisition time of 20 s per image. From the raw data, dedicated software (AutoSPECT + InStill 5.0, Ultra Myocardial Display Version 3.41 and AutoQUANT 5.1, ADAC Laboratories) was used to analyse LV parameters including LV wall motion and wall thickening. The percentage of the LV that was compromised by the initial perfusion defect, the size of the final infarct as percentage of the LV at the time of follow-up, and the degree of myocardial 'salvage' as a percentage of the LV was calculated as the size of the initial perfusion defect minus the final size of the infarct (initial perfusion defect or infarct)/(initial perfusion defect) = % salvaged. The salvage index was calculated as the percentage of the LV that was salvaged divided by the percentage that was compromised by the initial perfusion defect (% LV salvaged)/(% of LV initial perfusion defect) = salvage index. The analysis was performed in the scintigraphic core lab by two independent operators blinded to randomization. Mean intra- and interobserver variability in the defect assessment was similar and equal to 2±3% of the LV.

Wall thickness and infarct area

Digital images were taken from heart slices to calculate the WT ratio and the area of infarcted myocardium. LVWT was determined at the centre of the infarct and compared with the thickness of non-infarcted myocardium (LVWT ratio: WT infarct/WT non-infarcted). A line was drawn from the endocardial to the epicardial border in all three areas. For the border zone, two lines were drawn on both sides of the infarct area for a total of four measurement points (infarct, border zones 1 and 2, and non-infarcted myocardium).

The infarct area and the non-infarcted myocardium were measured in every heart slice (Figure 1C). The basal side of the slices was used, whereas the right ventricle was excluded. After calibration, the areas of infarct and non-infarcted myocardium were delineated and calculated by MetaMorph. The infarct size was compared with the LV size and the ratio expressed in percent [infarct area/(infarct area + non-infarcted myocardial area)].

Immunohistochemistry

Fluorescent immunostaining for eGFP was carried out to identify the transplanted cells in the heart. The following antibodies were used for this study: rabbit anti-von Willebrand factor (vWF) (Dakocytomation), mouse anti-SMA (Zymed, Laboratories Inc., San Francisco, CA, USA), mouse anti-Desmin (Dakocytomation), mouse anti-Ki67 (Zymed), mouse anti-Troponin T (Santa Cruz), and rabbit anti-GFP (Santa Cruz). Samples of infarct tissue, border zones, non-infarcted myocardium from every slice were excised and fixed in formalin, embedded, and cut in 5 μm sections. After deparaffinizing and rehydrating, the slides were subsequently incubated with diluted primary antibody and then secondary antibodies, as described earlier.11

Capillary density

Neoangiogenesis was evaluated in paraffin-embedded sections stained for vWF using 3-3 diaminobenzidine tetrahydrochloride (DAB) as a chromogen. Sections were treated following the above protocol up to incubation with the secondary antibody which, in this protocol, was biotinylated goat anti-rabbit IgG (Zymed, Laboratories Inc.). After washing in PBS, streptavidin peroxidase (Zymed, Laboratories Inc.) was applied in an additional incubation step for 20 min (37°C). DAB (Zymed, Laboratories Inc.) was used as a chromogenic substrate and the colour reaction was carried out for
3–10 min and the slides were washed before they were covered with Crystal/Mount (Biomeda, Foster City, CA, USA). In each pig, a slice from three separate areas of the border zone was counted. Pictures were taken under light microscopy at $\times 40$ magnification in five random fields (0.1 mm$^2$ area each) per slide. Only vessels with a diameter equal or below 10 $\mu$m on a perpendicular cut were counted. The capillary density was expressed as counts per 0.1 mm$^2$.

**Statistical analysis**

All values are presented as mean ± standard deviations. The differences between the groups were assessed with the use of contingency tables for categorical data and the non-parametric Kruskal–Wallis test for continuous data. A two-tailed $P$-value of $\leq 0.05$ was considered statistically significant.

**Results**

Of the 31 animals randomized in the study, 10 died during the induction of myocardial infarction, as it was aimed to induce a large, transmural infarction. In a previously performed pilot study, no reflow was observed in a number of pigs after intracoronary cell injection. The reason was a distal vascular occlusion at the capillary level. The maximal number of cells that could be safely administered was found to be 10 millions (in this disease model in pigs, at this weight). Therefore, in the main study, a total of two million cells (0.06 million cells/kg) was used. We also added an intensified antithrombotic drug regimen (pre-/post-treatment with aspirin and clopidogrel) and administration of low-molecular-weight heparin and eptifibatide during the procedure. We gave enoxoparin 0.7 mg/kg BW IV after the sheath was placed and a second dosage of 0.3 mg/kg BW IV 4 h later and 1.0 mg/kg BW SC at the end of the procedure (day of cell transplantation). In addition, eptifibatide was given two times as a bolus (180 $\mu$g/kg BW, first bolus after the first angiography, and second bolus 10 min later) and as an infusion (2 $\mu$g/kg BW/min) until the end of the procedure. We did not have any bleeding complications, despite the intensified drug regimen. The remaining 21 pigs (n = 7 per group) were divided into three groups: (i) BMSC, (ii) ADSC, or (iii) control.

**Characteristics of mesenchymal stem cells before implantation**

The cultured pig ADSCs are positive for CD90 (97.3 ± 0.62%), CD44 (98.27 ± 0.38%), and CD29 (98.2 ± 0.87%) and negative for CD31 (0.03 ± 0.05%), CD45 (0.45 ± 0.41%), and CD11 (0.17 ± 0.17%). These cells were spindle-shaped (Figure 2A) and expressed eGFP after lentiviral transduction (Figure 2B). The proportion of eGFP-expressing cells by flow cytometry averaged 33 ± 13% (ADSC 31 ± 16% and BMSC 35 ± 10%).

**Stem cell engraftment and phenotype after implantation**

Immunostaining for GFP verified the presence of the intracoronary-administered ADSCs in the LV at day 30 (Figure 2C). The engrafted cells were distributed within and around the vasculature. Most of the GFP$^+$ stem cells were stained positively for vWF, alpha-smooth muscle actin, and desmin in the ADSC (Figure 3) and BMSC (Figure 4) groups, indicating the endothelial and smooth muscle phenotypes of GFP$^+$ cells. The co-staining of the GFP$^+$ cells with endothelial and smooth muscle markers in the vasculature (Figures 3 and 4A, B and D) indicates that the stem cell transplantation may result in the formation of new vessels. Cell proliferation as evidenced by positive Ki 67 overlay staining was rare in the carrier group (Figure 5C), but was easily detected in the ADSC (Figure 5C) and BMSC (Figure 5D) groups. Despite extensive search, no co-staining for troponin T and GFP was observed in the ADSC and BMSC groups (Figures 5E and 4E).

**Capillary density**

The capillary vessel density in the infarct border zone was determined by staining for vWF. Positively stained vessels with a diameter ≤10 $\mu$m were considered to be capillaries. The capillary count observed per group in 0.1 mm$^2$ fields was significantly greater in the ADSC-treated animals [123.0 ± 44.9; confidence interval (CI) 110.0–136.0] than in the carrier group (93.6 ± 32.1; CI 79.0–108.0). The difference in capillary density of BMSC-treated animals (107.0 ± 50.4; CI 93.0–121.0) vs. control was not statistically significant; analysis of variance for all groups: 0.019, post hoc comparison between individual groups: BM vs. ADSC: 0.16; BM vs. sham: 0.19; ADSC vs. sham: 0.002.

**Wall thickness**

Only a pairwise comparison of ADSC vs. sham therapy resulted in a significant increase in WT ($P = 0.003$ using $t$-test), whereas there was no significance level when BMC vs. sham ($t$-test) or when the group of sham, BMC, and ADSC was compared simultaneously (Figure 6A) ($P = 0.14$ for all groups, Kruskal–Wallis test).
Figure 3  Phenotypes of engrafted MSCs in border zone of adipose tissue-derived stem cell injected pig. Hoechst 33342 staining for nuclei (a), eGFP<sup>+</sup> cells (b), specific antibodies (c), and overlay image (d) in the following order: (A) vWF, (B) ASMA, (C) Ki67, (D) desmin, and (E) TnT.

Figure 4  Phenotypes of engrafted MSCs in the border zone of bone marrow-derived stem cell injected pig. Hoechst 33342 staining for nuclei (a), GFP<sup>+</sup> cells (b), specific antibodies (c), and overlay image (d) in the following order: (A) vWF, (B) ASMA, (C) Ki67, (D) desmin, and (E) TnT.
Figure 5  Immunostainings in the border zone of sham pigs. Hoechst 33342 staining for nuclei (a), anti-eGFP staining (b), specific antibodies (c), and overlay image (d) in the following order: (A) vWF, (B) ASMA, (C) Ki67, (D) desmin, and (E) TnT.

Figure 6  Wall thickness (A), left ventricular ejection fraction (B), myocardial salvage percentage (C), and myocardial salvage index (D) were compared between the adipose tissue-derived and bone marrow-derived stem cell groups in a 4-week follow-up.
Left ventricular ejection fraction

LVEF at baseline following the induction of the myocardial infarction was similarly reduced by 12.6 ± 7.2% in the control, 14.3 ± 6.1% in the ADSC, and 17.9 ± 4.7% in the BMSC groups (NS). At 4 weeks of follow-up, LVEF improved by 1.9 ± 4.7% in the control, 11.4 ± 4.6% in the ADSC, and 9.6 ± 8.0% in the BMSC groups (P = 0.02 for all three groups by Kruskal–Wallis test). Although there were no significant differences between the treatment groups, both were significantly improved when compared with control (pairwise analysis) (Figure 6B).

Nuclear cardiac imaging

Absolute myocardial salvage was significantly greater in the ADSC and BMSC groups than in the control group (10.3 ± 5.2, 12.0 ± 7.9, and 4.1 ± 2.2, respectively, P = 0.027 for all three groups by the Kruskal–Wallis test). Pairwise analysis also showed similar results (Figure 6C). The myocardial salvage index was also significantly greater in ADSC and BMSC groups when compared with carrier (ADSC 0.30 ± 0.17, BMSC 0.31 ± 0.16, and 0.12 ± 0.07, P = 0.048 for all three groups by the Kruskal–Wallis test). Pairwise analysis also showed similar results (Figure 6D).

Figure 7  Nuclear imaging. Bull’s eye visual and semi-quantitative polar plot analysis of perfusion defect (blue zone) in a representative pig injected with tissue-derived stem cell at baseline (A) and follow-up (B). The antero-apical perfusion defect has visually decreased along with a decrease in extent from 45 to 32% of the calculated left ventricular mass on follow-up. Gated short- and long-axis images in control (C) and adipose tissue-derived stem cells (D) at baseline end-diastolic (a) and end-systolic (b) and follow-up end-diastolic (c) and end-systolic frames (d). Little improvement in perfusion defect and thickening is seen in the control pig, whereas modest improvement is seen in both parameters in an ADSC pig (fine arrow: control, bold arrow: adipose tissue-derived stem cells, white arrow: apex at baseline, and yellow arrow: at 4 weeks of follow-up). AutoQUANT derived 3D surface-rendered LV end-diastolic and end-systolic contours (Figure 7E and F) showed a significant improvement in LV wall motion in the representative ADSC pigs when compared with a carrier pig at follow-up in both end-diastolic and end-systolic frames. Especially, at end systole, a resumption of inward contraction was clearly identifiable at the antero-apical infarct region (white arrow) compared with the absent or even paradoxical wall movement in the control group at end systole. The end-diastolic volume for the control at baseline (Figure 7Ea) and follow-up (Ec) and that for the ADSC
pig at baseline ($F_b$) and follow-up ($F_c$) are 93.7 and 106.0 and 90.4 and 89.6 mL, respectively. The end-systolic volume for the control at baseline ($E_b$) and follow-up ($E_d$) and that for the ADSC pig at baseline ($F_b$) and follow-up ($F_d$) are 57.7 and 63.3 and 54.7 and 45.9 mL, respectively.

Table 1 shows the absolute values of cardiac functions at baseline and follow-up.

In summary, we found that the transplanted ADSCs significantly improved LV function and expressed endothelial and smooth muscle cell markers and incorporated into newly formed vessels.

### Discussion

This is the first study to evaluate the feasibility and effectiveness of adipose-derived stem cells for cellular cardio-myoplasty in an experimental MI model that closely reproduces the current procedural management of MI, including medication and instrumentation used in humans. Four weeks after intracoronary administration of ADSCs into the infarcted myocardium, LV perfusion, function, and remodelling were substantially improved. This improvement was similar to that observed after intracoronary administration of BMSC.

Our FACS data are in agreement with that reported by Miranville et al. and Rehman et al., which freshly isolated ADSCs containing a small percentage of CD45+ cells which diminished after 72 h culture.

Immunohistochernical analysis revealed that the implanted cells differentiated into endothelial cells (ECs) and smooth muscle cells (SMCs), which incorporated into newly formed vessels. Our findings are consistent with previous studies that angiogenesis may contribute to the maintenance of cardiac function by preservation of the remaining, viable hibernating cardiomyocytes and by stem cell-induced neovascularization that may help to meet the greater demands of the residual myocardium in the border zone that would otherwise undergo apoptosis. It has been shown that the preservation of border zone WT can be achieved by the inhibition of apoptosis through induction of angiogenesis. As most cardiomyocytes within the area at risk are irreversibly damaged after 3 h of occlusion, the salvage effect assumed to be due to preservation of cells in the border zone through stem cell mediated anti-apoptotic and neoangiogenic effects.

Therapeutic enhancement of neovascularization through transplantation of bone marrow-derived and adipose-derived stem cells is associated with long-term salvage and survival of viable tissue. Similarly, ADSCs differentiated into endothelial cells as demonstrated by an abundance of human CD31-positive cells lining regenerated vessels in a nude mouse hindlimbs ischaemia model. The significant improvement in LV function at 30 days assessed by $^{99m}$Tc-Sestamibi was apparently not related to a direct transdifferentiation of ADSCs or BMSCs into cardiomyocytes. Our findings are in agreement with the report by

<p>| Table 1 Angiographic (A), $^{99m}$Tc-Sestamibi (B), and cardiac functional data at baseline and follow-up and histopathological data (C) |
|---------------------------------------------------------------|-------------|-------------|-------------|-------------|</p>
<table>
<thead>
<tr>
<th>A</th>
<th>LVEF at baseline</th>
<th>ADSC</th>
<th>BMSC</th>
<th>Control</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF at 4-week follow-up</td>
<td>33.14 ± 5.54%</td>
<td>37.62 ± 4.23%</td>
<td>38.36 ± 9.22%</td>
<td>n.s.</td>
<td></td>
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<tr>
<td>Change of LVEF from baseline to post-cell transplantation (absolute numbers)</td>
<td>−14.31 ± 6.12%</td>
<td>−17.90 ± 4.67%</td>
<td>−12.63 ± 7.19%</td>
<td>n.s.</td>
<td></td>
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<tr>
<td>Change of LVEF from post cell transplantation to follow up</td>
<td>11.39 ± 4.62%</td>
<td>9.59 ± 7.95%</td>
<td>1.95 ± 4.70%</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>QPS at baseline</td>
<td>ADSC</td>
<td>BMSC</td>
<td>Control</td>
<td>$P$-value</td>
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<tr>
<td>QPS at follow-up</td>
<td>35.71 ± 7.04%</td>
<td>39.14 ± 9.63%</td>
<td>33.71 ± 4.61%</td>
<td>n.s.</td>
<td></td>
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<tr>
<td>Myocardial salvage</td>
<td>25.43 ± 8.36%</td>
<td>27.14 ± 8.84%</td>
<td>29.57 ± 4.86%</td>
<td>n.s.</td>
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<tr>
<td>Salve index</td>
<td>10.29 ± 5.15%</td>
<td>12.00 ± 7.85%</td>
<td>4.14 ± 2.19%</td>
<td>n.s.</td>
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<tr>
<td>Infarct area (total)</td>
<td>24.30 ± 4.27%</td>
<td>28.49 ± 9.77%</td>
<td>29.55 ± 13.80%</td>
<td>n.s.</td>
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<td>Infarct area (only LV)</td>
<td>25.27 ± 5.82%</td>
<td>31.73 ± 11.10%</td>
<td>30.90 ± 12.39%</td>
<td>n.s.</td>
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<tr>
<td>C</td>
<td>Wall thickness ratio</td>
<td>ADSC</td>
<td>BMSC</td>
<td>Control</td>
<td>$P$-value</td>
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<tr>
<td>Heart rate at baseline</td>
<td>0.75 ± 0.05</td>
<td>0.69 ± 0.21</td>
<td>0.58 ± 0.14</td>
<td>n.s.</td>
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<tr>
<td>Heart rate after cell transplantation</td>
<td>0.82 ± 5</td>
<td>0.72 ± 7</td>
<td>0.73 ± 14</td>
<td>n.s.</td>
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<td>Heart rate at follow-up</td>
<td>0.88 ± 5.8</td>
<td>94.3 ± 18.9</td>
<td>89.3 ± 29</td>
<td>n.s.</td>
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</table>

QPS, quantitative perfusion scintigraphy.
Intracoronary administration of autologous ADSC

Table 2  Comparison of recent studies on intracoronary delivery of stem cells

<table>
<thead>
<tr>
<th>Author</th>
<th>Animal</th>
<th>Cell type</th>
<th>Cell number</th>
<th>Cell size</th>
<th>Anticoagulants</th>
</tr>
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<tbody>
<tr>
<td>Vulliet</td>
<td>Dog</td>
<td>BMSC</td>
<td>0.5 × 10⁶/kg</td>
<td>19.4 μm</td>
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</tr>
<tr>
<td>Moelker</td>
<td>Swine</td>
<td>Human USSC</td>
<td>100 × 10⁶</td>
<td>20 μm</td>
<td>Heparin</td>
</tr>
<tr>
<td>Valina</td>
<td>Swine</td>
<td>ADSC or BMSC</td>
<td>2 × 10⁶ (0.06 × 10⁶/kg)</td>
<td>20.8 μm (ADSC)</td>
<td>Aspirin, clopidogrel, heparin,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19.3 μm</td>
<td>eptifibatide, enoxaparin</td>
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</table>

BMSC, bone marrow-derived mesenchymal stem cells; USSC, umbilical cord blood stem cells; ADSC, adipose tissue-derived stem cells.

Silva et al.²¹ that bone marrow-derived MSCs co-localized with endothelial and smooth muscle cells, but not with cardiomyocytes in a canine chronic ischaemia model.

Transdifferentiation into cardiomyocytes has been reported previously with BMSCs,²⁰,²²,²³ although negative studies have also been reported.²⁴ We and others have shown that ADSCs can express biochemical markers characteristic of cardiomyocytes.¹¹,²⁵–²⁷ Cardiomyocyte differentiation requires a number of crucial growth factors that are released from precursor cells, acting in an autocrine fashion on specific plasma membrane receptors to prime a cardiogenic decision.²⁸ A better understanding of the interstitial milieu, i.e. the cytokines/growth factors produced by infarcted heart and injected stem cells, may define critical signalling molecules for cardiomyocyte differentiation. Although both ADSCs and BMSCs improved LV function, only ADSCs significantly improved LV remodelling as evidenced by an increase in the LV WT ratio and capillary density. Our data are in line with the report from Moelker et al.²⁹ that bone marrow-derived cells do not reverse remodelling. Although there is a statistical difference in effects on LV function, only ADSCs exerted similar beneficial effects on LV function but not on LV remodelling. The beneficial effects of ADSCs on myocardial interstitial oedema after reca-

Clinical studies such as the TOPCARE³⁰ and BOOST³¹ trials infused cells within 4–5 days after MI. However, it has also been shown that myocardial interstitial oedema after reca-

Conclusion

After intracoronary administration into acutely infarcted myocardium, ADSCs transdifferentiate into endothelial and vascular smooth muscle cells and improve LV function, remodelling, and over time, perfusion in a porcine MI model that closely reproduces the current clinical management of the human disease. In this experimental MI model, ADSCs and BMSCs exert similar beneficial effects on LV function but not on LV remodelling. The beneficial effects of ADSCs on LV function and remodelling documented in this experimental large animal model warrant further investigation of the therapeutic usefulness of intracoronary injection of ADSC at the time of revascularization in patients with acute MI.
Limitations
The optimal time point for MSC delivery is still controversial. Although clinical studies injected cells 4–5 days after MI, pre-clinical studies on large animals injected cells immediately after MI. Ideally, this issue will be investigated thoroughly in large animals prior to clinical trials. Future studies designed to compare the beneficial effect at various time points are certainly warranted. Furthermore, the numbers of injected cell reported in the literature varies greatly; the optimal cell number, the choice of pre-cultured vs. freshly isolated cells warrants further investigation.

The current study is a first feasibility, safety, and efficacy assessment and comparison of the use of non-bone marrow cells in a clinically relevant model of infarction. This proof of concept is an important step for further studies. We acknowledge, however, that harvesting and culturing of the ADSCs reflect only limited clinical merits as the patients with infarction typically will not report for stem cells harvest 2 weeks prior to infarction, unless someone is willing to freeze their cells. However, such an approach would be compromised by considerable logistical limitations.

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Conflict of interest: K.P. is currently an employee of Cytori Therapeutics. R.J.C. is on Bristol-Myers Squibb speakers’ bureau, for which he receives honoraria in conjunction with presentations that involve Tc-99m Sestamibi.

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Intracoronary administration of autologous ADSC


