Stem Cells in cardiac Surgery

Alireza A. Ghavidel MD
Winter 2016
rhc.ac.ir

Original papers

Med Ultrason 2015, Vol. 17, no. 2, 160-166
DOI: 10.11152/mu.2013.2066.172.effbm

Effectiveness of bone marrow mononuclear cells delivered through a graft vessel for patients with previous myocardial infarction and chronic heart failure: an echocardiographic study of left ventricular remodeling.

Fujian Duan*[1], Zhi Qi*[1], Sheng Liu[2], Xiuzhang Lv[1], Hao Wang[1], Yiming Gao[1], Jianpeng Wang[1]

[1]Department of Echocardiography, [2]Department of Cardiovascular Surgery, Fuwai Hospital & Cardiovascular Institute, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Tsinghua University, Peking Union Medical College, Beijing, China.

Abstract

Aims: The graft of stem cells to treat ischemic cardiomyopathy is popular in many clinical trials. The aim of this study was to evaluate the effectiveness of isolated coronary artery bypass graft combined with bone marrow mononuclear cells (BMMNC) delivered through graft vessels to improve left ventricular remodeling of patients with previous myocardial infarction and chronic heart failure using echocardiography. **Material and methods:** Patients with previous myocardial infarction and chronic heart failure were randomly allocated to one of the two groups: CABG only (18 patients), or CABG with BMMNC transplantation (24 patients). Echocardiographic parameters were measured on B-mode imaging, 3D imaging and color flow imaging. **Results** Post-operative LVEDD (end-diastolic dimension of left ventricle), LVESD (end-systolic dimension of left ventricle), LVEDV (end-diastolic volume of left ventricle), LVESV (end-systolic volume of left ventricle), LVEDVI (LVEDV indexed to body surface area), LVESVI (LVESV indexed to body surface area), LV-mass (mass of left ventricle) and LV-massI (LV-mass indexed to body surface area) were significantly improved compared with those obtained prior to operation in CABG+BMMNC group (al $p<0.05$). The same parameters were not significantly different pre- and postoperative in the CABG group (al $p>0.05$). Postoperative mitral regurgitation score was not significantly different from those prior to operation in both groups (al $p>0.05$). In Chi-square tests, LVEDD, LVESD, LVEDV, LVESV, LVEDVI, LVESVI, LV-mass, LV-massI were determinants of the left ventricular remodeling. **Conclusion:** The improvement of left ventricular remodeling in

Table I. Baseline Characteristics

Clinical date	CABG+BMMNC group (n=24)	CABG group (n=18)	P value
Age,y	57.88±8.52	56.56±9.09	0.881
Man,%	95.8	94.4	0.679
BSA,m2	1.81±0.12	1.78±0.13	0.723
NYHA function class	3 (2,3)	2 (2,3)	0.239
No.of grafts	4 (4,5)	4 (4,5)	0.331
CPB time,min	90(61,103)	89(78,116)	0.198
Clamping time,min	60(50,67)	55(48,70)	0.868
Ventilation time,h	16(13,20)	17(14,20)	0.332
ICU stay,days	3(3,5)	3(3,4)	0.221
6-min walking test	452(408,495)	433(382,497)	0.206
BNP,ng/L	1302(714,1676)	890(680,1646)	0.431
Hypertension,%	16.7	11.1	0.481

Table III. Echocardiographic parameters in CABG group

	pre-surgen (mean±SD)	1 year later (mean±SD)	P value
LVEDD (mm)	56.66±6.76	54.61±6.64	0.364
LVESD (mm)	45.67±6.27	41.66±8.05	0.105
LVEDV (ml)	167.61±42.10	156.78±36.30	0.414
LVESV (ml)	106.94±27.68	95.56±28.92	0.236
LVEDVI (ml/m^2)	93.76±23.65	87.17±15.36	0.285
LVESVI (ml/m^2)	59.84±13.59	53.02±13.48	0.140
LV-mass (g)	242.11±60.56	233.50±60.51	0.672
LV-massI (g/m^2)	135.41±28.56	129.95±27.43	0.562
MR score	1.28±0.75	1.17±1.29	0.755

Table II. Echocardiographic parameters in CABG+BMMNC group

	pre-surgen (mean±SD)	1 year later (mean±SD)	P value
LVEDD (mm)	60.96±5.26	52.29±5.94	0.000
LVESD (mm)	46.70±5.77	37.86±6.47	0.000
LVEDV (ml)	196.17±41.26	145.38±40.81	0.000
LVESV (ml)	126.04±28.22	82.04±34.02	0.000
LVEDVI (ml/m2)	108.14±20.94	80.72±22.59	0.000
LVESVI (ml/m2)	69.47±14.52	45.62±19.13	0.000
LV-mass (g)	267.25±67.97	222.88±60.44	0.021
LV-massI (g/m2)	147.37±35.33	123.53±32.45	0.019
MR score	1.42±0.65	1.04±0.71	0.061

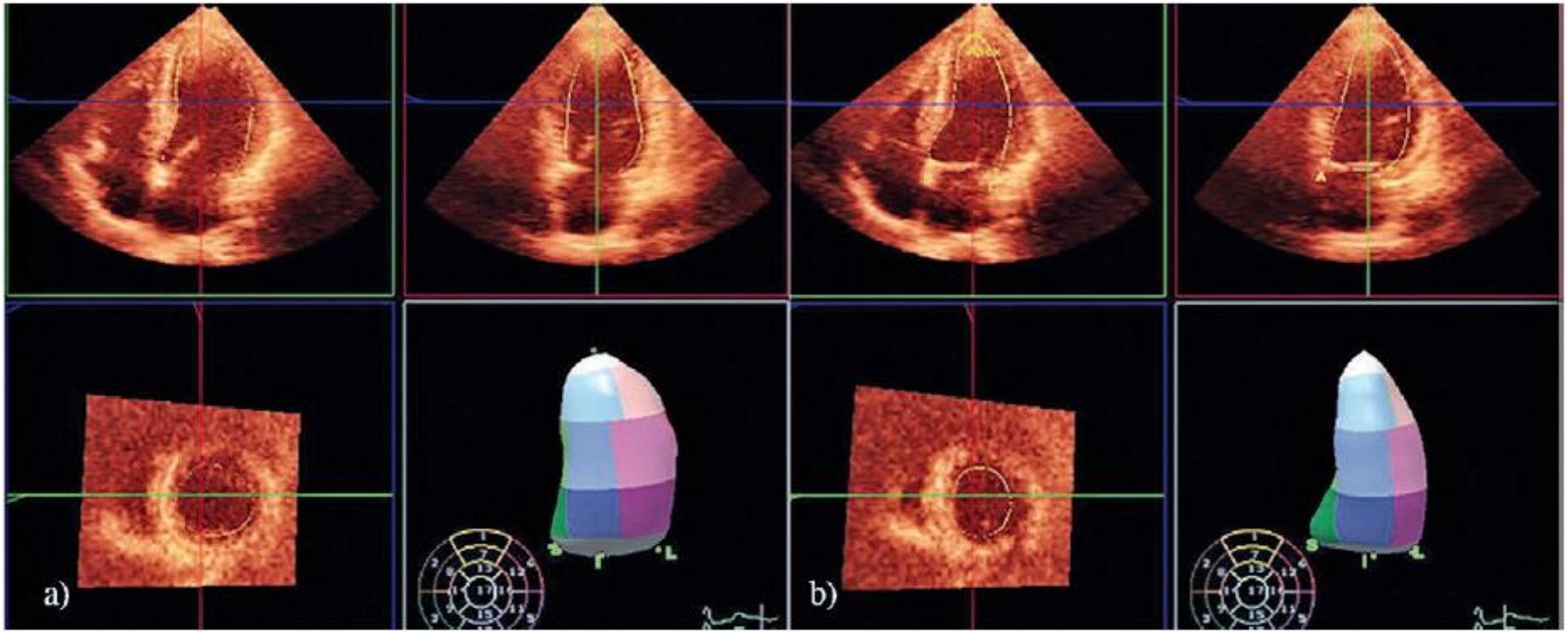


Fig 1. a) Apical 3D full-volume data set. Triplane is displayed. Para-sternal short-axis views are shown for completeness and to indicate the image plane position in the 3D images. End-diastolic volume of left ventricle is calculated and shown in the 3D imagings; b) Apical 3D full-volume data set. Triplane is displayed. Para-sternal short-axis views are shown for completeness and to indicate the image plane position in the 3D images. LVESV is calculated and shown in the 3D imagings.

Med Ultrason 2015, Vol. 17, no. 2, 160-166
DOI: 10.11152/mu.2013.2066.172.effbm

Conclusions

The effectiveness of isolated CABG combined with BMMNC delivered through graft vessels in improvement of the LV remodeling of patients with previous myocardial infarction and chronic heart failure was verified in this study. The improvement of LV remodeling in CABG+BMMNC group was better than in the CABG group and this improvement can by verified by using echocardiography.

Conflict of interest: none

European Heart Journal (2009) **30**, 662–670
doi:10.1093/eurheartj/ehn532

CLINICAL RESEARCH
Coronary heart disease

Improved regional function after autologous bone marrow-derived stem cell transfer in patients with acute myocardial infarction: a randomized, double-blind strain rate imaging study

Aims To investigate whether intracoronary transfer of bone marrow progenitor cells (BMPCs) early after reperfusion of an acute myocardial infarction improves regional myocardial function in a randomized double-blind, placebo-controlled strain rate imaging study.

Methods and results Regional myocardial deformation was measured using velocity-derived strain rate imaging in 67 STEMI patients randomized 1:1 to intracoronary infusion of BMPC ($n = 33$) or placebo ($n = 34$). Myocardial segments were grouped into infarct ($n = 232$), border ($n = 250$), and remote ($n = 526$) based on MRI-delayed enhancement and the perfusion territory of the infarct-related vessel.

Four months after revascularization and progenitor cell/placebo transfer, regional myocardial deformation (rate) improved significantly more in the infarct segments of BMPC patients (treatment effect on end-systolic strain: $-3.7 \pm 1.0\%$, $P = 0.0003$; peak-systolic strain rate: $-0.20 \pm 0.07\ s^{-1}$, $P = 0.0035$). These findings were confirmed by a significantly greater improvement of longitudinal mitral valve ring displacement in the infarct walls of BMPC patients (treatment effect: 0.93 mm, $P = 0.034$).

Conclusion Intracoronary infusion of BMPC early after reperfusion of a STEMI improves recuperation of regional myocardial function at 4 months' follow-up. Quantitative assessment of regional systolic function might be more sensitive than global LV ejection fraction for the evaluation of BMPC therapy after STEMI.

Keywords Stem cell therapy • Regional myocardial function • Strain rate imaging • Acute myocardial infarction

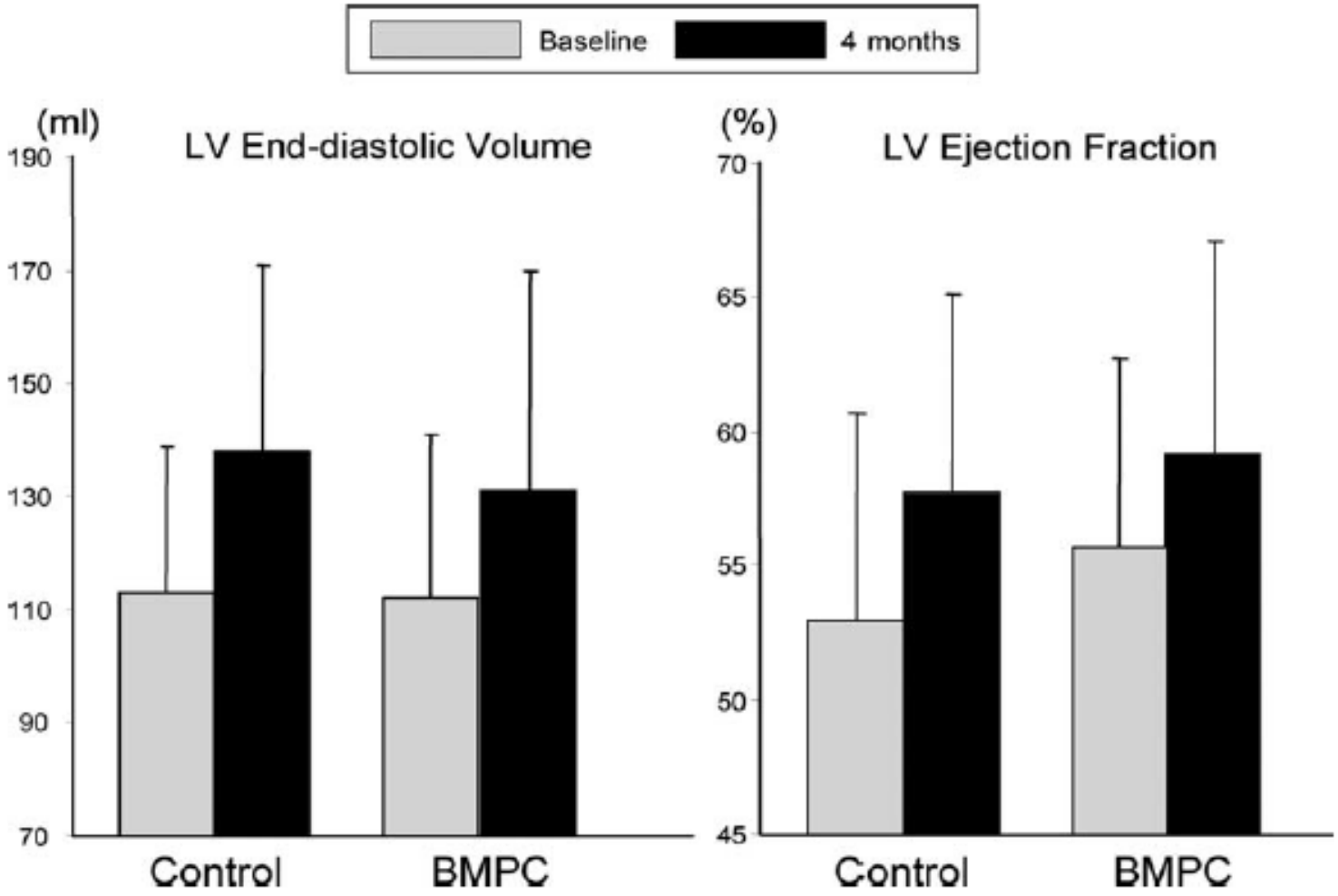


Figure 3 LV end-diastolic volume (mL) and LV ejection fraction (%) by ultrasound modified Simpson's method at baseline and at 4 months' follow-up in patients treated with bone-marrow progenitor cells (BMPCs) and in controls. Data are mean ± SD.

Clinical Track

Autologous Mesenchymal Stem Cells Produce Concordant Improvements in Regional Function, Tissue Perfusion, and Fibrotic Burden When Administered to Patients Undergoing Coronary Artery Bypass Grafting

The Prospective Randomized Study of Mesenchymal Stem Cell Therapy in Patients Undergoing Cardiac Surgery (PROMETHEUS) Trial

Vasileios Karantalis, Darcy L. DiFede, Gary Gerstenblith, Si Pham, James Symes,

Clinical Trial Registration: Circ Res. **2014;114:1302-1310**

- Preclinical studies provide evidence that bone marrow stem cells contribute to cardiac function and reverse remodeling after ischemic damage acting both locally and remotely (possibly through paracrine mechanisms.

- In studies to date, investigators have either infused or injected bone marrow–derived cells in areas that were undergoing revascularization

- ***Here, we test the hypothesis that intramyocardial injections of autologous MSCs delivered to segments of myocardium not receiving surgical revascularization improve regional cardiac structure and function*.**

- *Methods and Results:* patients were injected with autologous **MSCs into akinetic/hypokinetic myocardial territories not receiving bypass graft** for clinical reasons.

- MRI was used to measure scar, perfusion, wall thickness, and contractility at baseline, at 3, 6, and 18 months and to compare structural and functional recovery in regions that received MSC injections alone, revascularization alone, or neither.

- After 18 months, subjects receiving MSCs exhibited **increased LV ejection fraction (+9.4±1.7%, *P*=0.0002)** and decreased scar mass (−47.5±8.1%; *P*<0.0001) compared with baseline.

- MSC-injected segments had concordant reduction in scar size, perfusion, and contractile improvement (concordant score: 2.93±0.07), whereas revascularized (0.5±0.21) and nontreated segments (−0.07±0.34) demonstrated nonconcordant changes (*P*<0.0001 versus injected segments).

European Heart Journal (2014) **35**, 1263–1274
doi:10.1093/eurheartj/ehu007

CLINICAL RESEARCH
Stem cells

Autologous CD133^{+} bone marrow cells and bypass grafting for regeneration of ischaemic myocardium: the Cardio133 trial†

[5]Berlin-Brandenburg Center for Regenerative Therapies, Berlin 13353, Germany

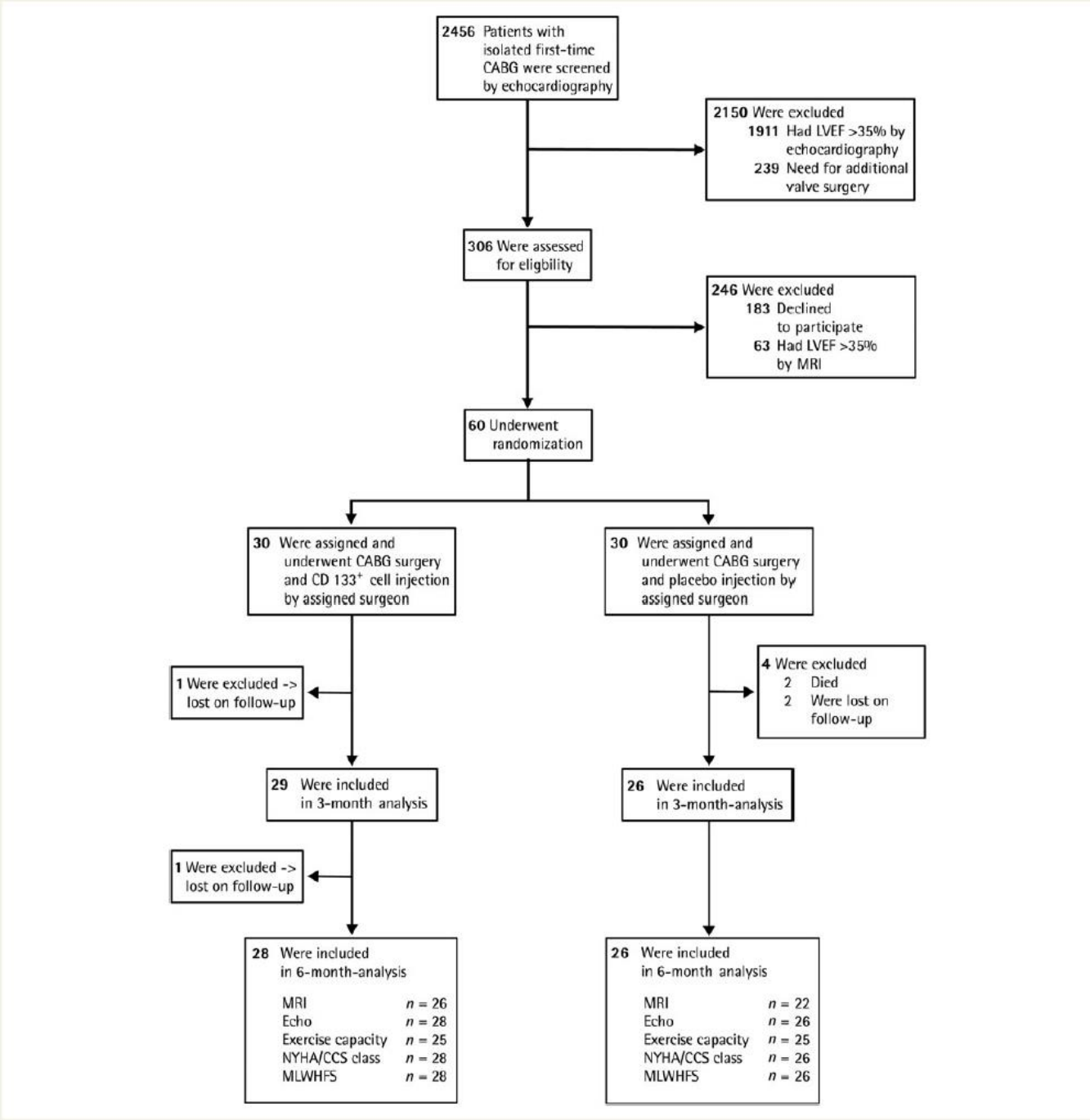
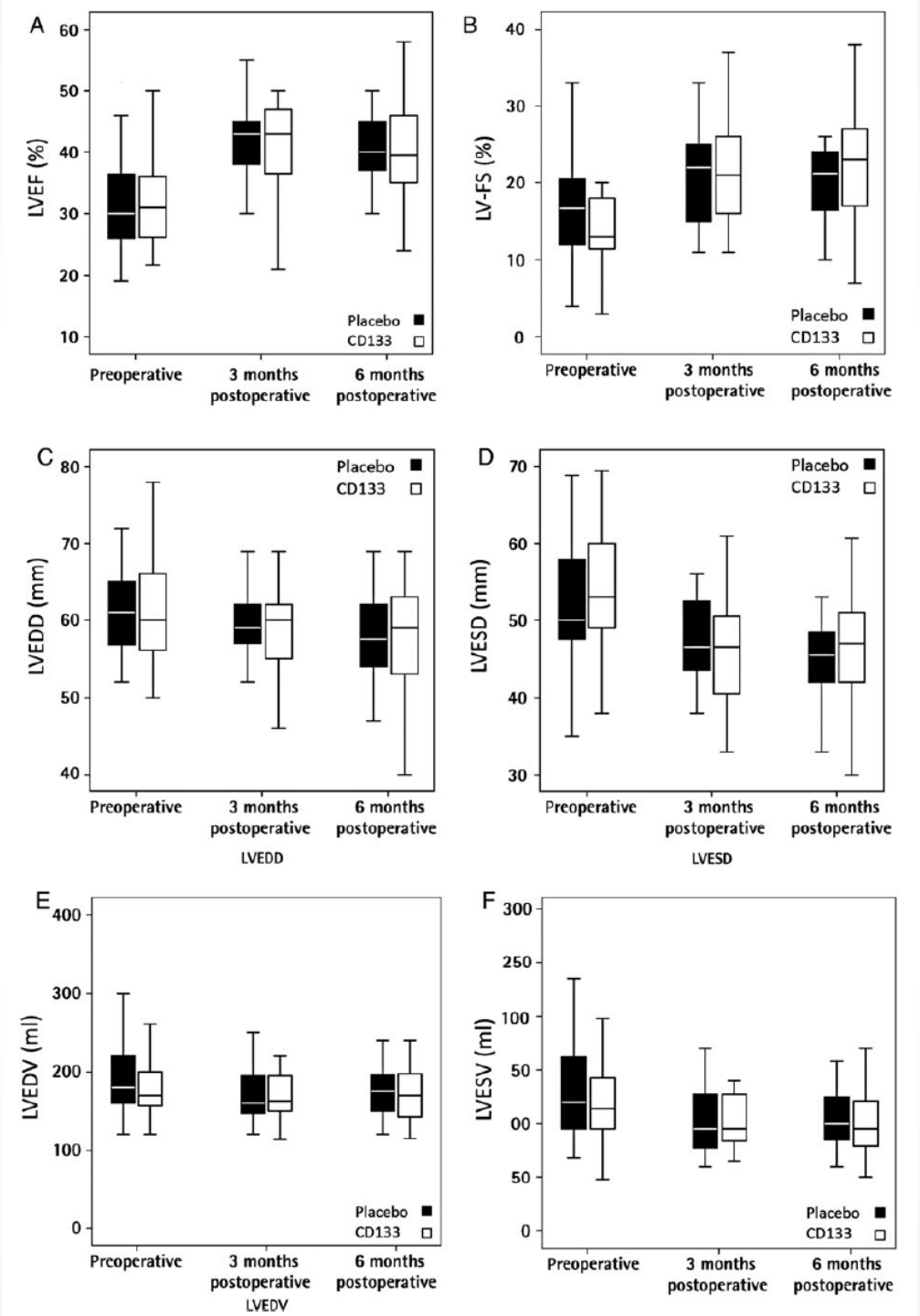
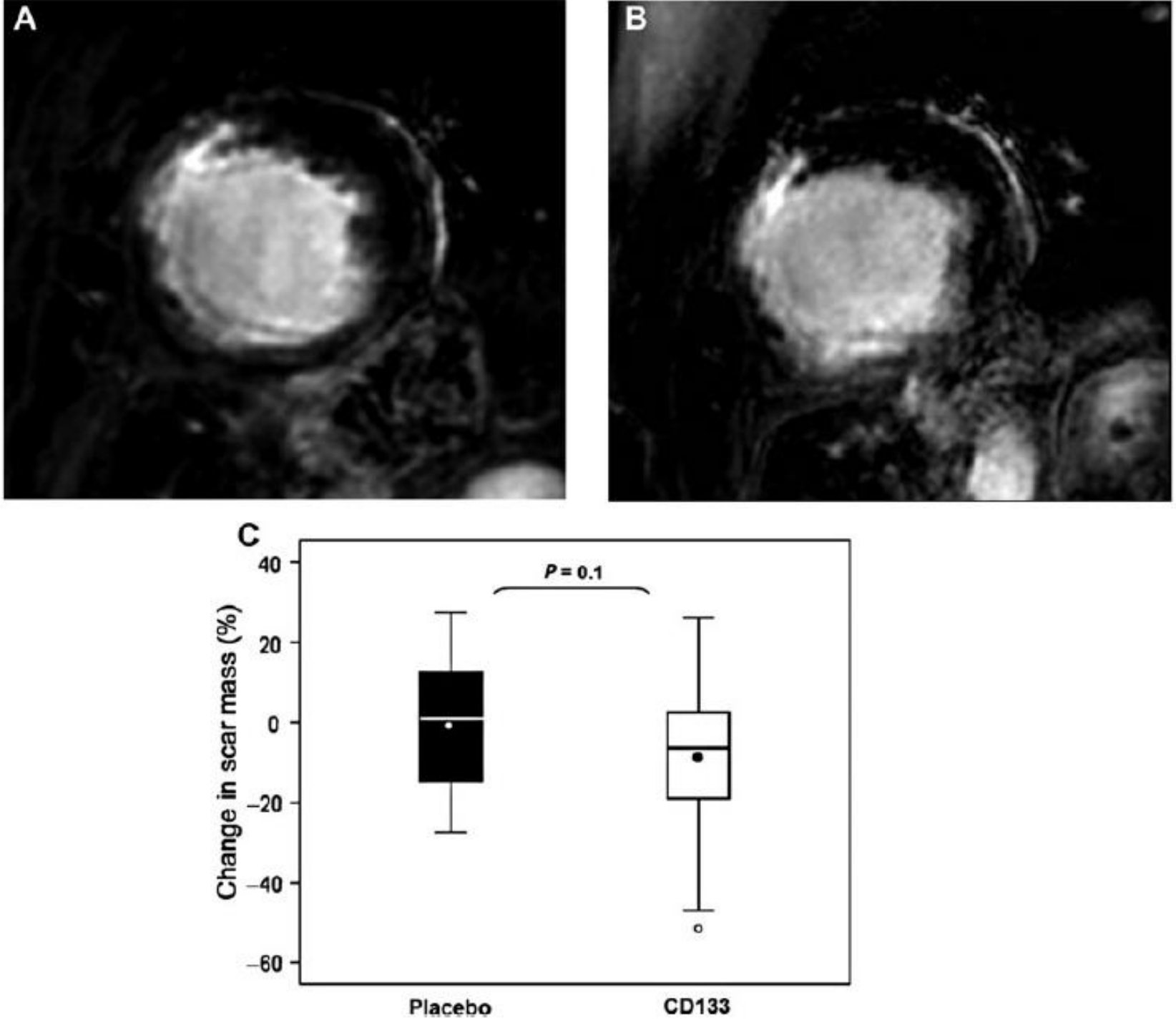


Figure 1 Study design: Consort flow chart of the CARDIO133 trial.


A
LVEF (%)
60
50
40
30
20
10
Placebo
CD133
Preoperative
3 months postoperative
6 months postoperative
B
LV-FS (%)
40
30
20
10
0
Placebo
CD133
Preoperative
3 months postoperative
6 months postoperative
C
LVEDD (mm)
80
70
60
50
40
Placebo
CD133
Preoperative
3 months postoperative
6 months postoperative
LVEDD
D
LVESD (mm)
70
60
50
40
30
Placebo
CD133
Preoperative
3 months postoperative
6 months postoperative
LVESD
E
LVEDV (ml)
400
300
200
100
0
Placebo
CD133
Preoperative
3 months postoperative
6 months postoperative
LVEDV
F
LVESV (ml)
300
250
100
50
0
Placebo
CD133
Preoperative
3 months postoperative
6 months postoperative


A
B
C
40
20
0
−20
−40
−60
Change in scar mass (%)
P = 0.1
Placebo
CD133

European Heart Journal (2014) **35**, 1263–1274
doi:10.1093/eurheartj/ehu007

Conclusion Although there may be some improvements in scar size and regional perfusion, intra-myocardial injection of $CD133^+$ BMC has no effect on global LV function and clinical symptoms. Improvements in regional myocardial function are only detectable in patients with posterior infarction, probably because the interventricular septum after anterior infarction is not accessible by trans-epicardial injection.

BMJ

BMJ 2014;348:g2688 doi: 10.1136/bmj.g2688 (Published 29 April 2014)

RESEARCH

Discrepancies in autologous bone marrow stem cell trials and enhancement of ejection fraction (DAMASCENE): weighted regression and meta-analysis

Conclusions Avoiding discrepancies is difficult but is important because discrepancy count is related to effect size. The mechanism is unknown but should be explored in the design of future trials because in the five trials without discrepancies the effect of bone marrow stem cell therapy on ejection fraction is zero.

Kardiologia Polska 2013; 71, 5: 485–492; DOI: 10.5603/KP.2013.0095 ISSN 0022–9032

ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

The combined use of transmyocardial laser revascularisation and intramyocardial injection of bone-marrow derived stem cells in patients with end-stage coronary artery disease: one year follow-up

Methods: Five male patients (age 49–78 years) with end-stage diffuse CAD, severe angina (CCS III/IV) despite intensive medical therapy and disqualified from prior coronary artery bypass grafting (CABG) or percutaneous coronary intervention were included. After heart exposure, at sites where CABG was impossible, TMLR was performed with the Holmium: YAG laser combined with injection of 1 mL of bone marrow concentrate into the border zone of a laser channel using a Phoenix handpiece.

Results: No deaths in the follow-up period were observed. All patients were in I CCS Class. One year after the procedure, left ventricular (LV) segments treated by BMLR tended to demonstrate stronger myocardial thickening compared to baseline ($53.0 \pm 7.5\%$ vs. $45.0 \pm 9.5\%$; $p = 0.06$). Using late gadolinium-enhanced imaging, new myocardial infarction was found after one year only in one LV segment treated by BMLR. The BMLR treated regions in the remaining subjects, as well as regions subtended by left internal thoracic artery in two subjects, did not show new myocardial infarction areas. In contrast, all subjects who underwent only BMLR procedure revealed new and/or more extensive myocardial infarct in regions not treated by BMLR.

Conclusions: Intramyocardial delivery of bone marrow stem-cells together with laser therapy is a safe procedure, with improvement in quality of life during follow-up. One year after the procedure, myocardial regions where BMLR was performed tended to demonstrate stronger myocardial thickening observed in cardiac magnetic resonance imaging.

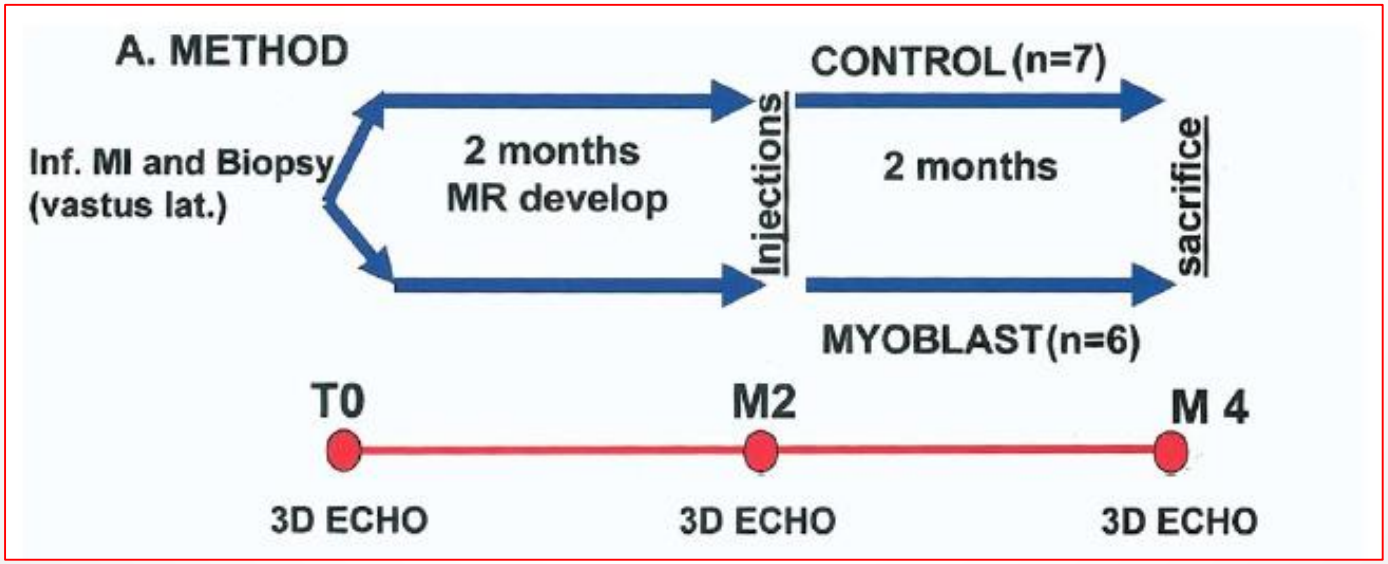
Journal of the American College of Cardiology
© 2006 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 47, No. 10, 2006
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2005.12.063

Autologous Myoblast Transplantation for Chronic Ischemic Mitral Regurgitation

Emmanuel Messas, MD, MSc,*†‡§ Alain Bel, MD,*†‡§ Miguel Cortes Morichetti, MD,†‡§ Claire Carrion, PhD,‖ Marc D. Handschumacher, BS,¶ Séverine Peyrard, BS,# Jean Thomas Vilquin, PhD,‖ Michel Desnos, MD,*†‡§ Patrice Bruneval, MD,*§** Alain Carpentier, MD, PhD, FACC,*†‡§ Philippe Menasché, MD, PhD,*†‡§ Robert A. Levine, MD,¶ Albert A. Hagège, MD, PhD†‡§

Paris, France; and Boston, Massachusetts



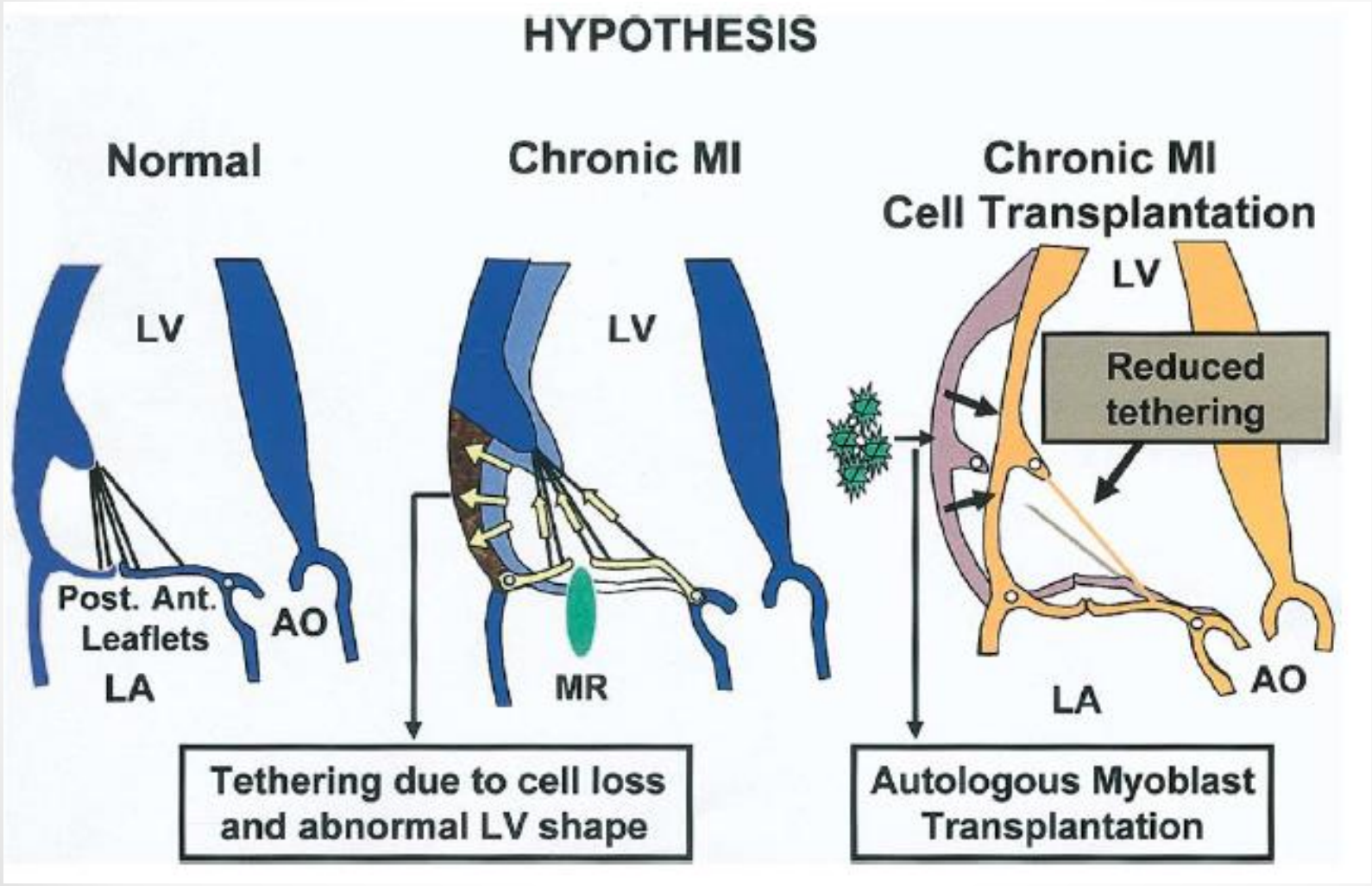
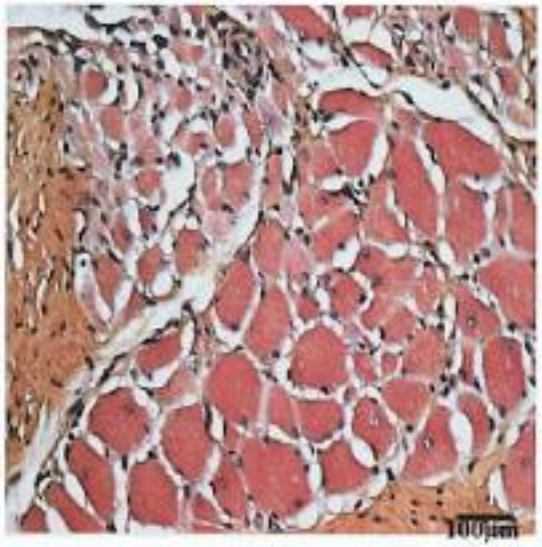

HYPOTHESIS
Normal
Chronic MI
Chronic MI
Cell Transplantation
LV
LV
LV
Post. Ant.
Leaflets
AO
LA
MR
Reduced
tethering
LA
AO
Tethering due to cell loss
and abnormal LV shape
Autologous Myoblast
Transplantation

Table 1. Echocardiographic Measurements

	Baseline		Chronic MI		Sacrifice	
	Control	Cell Transplantation	Control	Cell Transplantation	Control	Cell Transplantation
HR	99.5 ± 1.6	99.1 ± 2.7	103.1 ± 3.4	100.6 ± 3.6	109.7 ± 2.9	100.8 ± 4.9
EDV(ml)	32.01 ± 0.5	32.2 ± 1.6	63.4 ± 3.1*	62.6 ± 5.1*	111.0 ± 3.8†	102.3 ± 5.1†
ESV(ml)	10.5 ± 0.33	11.8 ± 0.5	39.1 ± 1.7*	39.7 ± 3.1*	75.4 ± 4.1†	63 ± 2.9†
EF	0.67 ± 0.01	0.63 ± 0.02	.38 ± 0.02*	.36 ± 0.02*	.33 ± 0.01	.38 ± 0.01
WMS indexed	0.0 ± 0.0	0.0 ± 0.0	1.25 ± 0.08*	1.19 ± 0.05*	1.39 ± 0.11†	.94 ± 0.13†
Tethering dist (cm)	2.48 ± 0.03	2.5 ± 0.05	3.07 ± 0.05*	2.9 ± 0.06*	3.5 ± 1.1†	2.51 ± 0.04†
MAA (cm^2)	5.8 ± 0.04	5.8 ± 0.19	6.8 ± 0.19*	6.3 ± 0.12*	7.2 ± 0.12†	6.6 ± 0.18†
MRSV (ml)	1.14 ± 0.2	1.33 ± 0.41	7.2 ± 0.59*	5.8 ± 0.59*	13.1 ± 0.77†	4 ± 0.51†
RF%	5.4 ± 0.9	6.3 ± 1.8	30 ± 0.5*	27.4 ± 4.8*	36 ± 1	10.5 ± 1.6†

All two-way ANOVAs but one (heart rate) were significant $p < 0.05$. Significant changes $p < 0.025$ (Bonferroni corrected) are indicated for the two-way comparisons: *Baseline

A. Transversal



B. Longitudinal

CONCLUSIONS Autologous skeletal myoblast transplantation attenuates mild-to-moderate chronic ischemic MR, which otherwise is progressive, by decreasing tethering distance and improving EF and wall motion score, thereby enhancing valve coaptation. These data shed additional light on the mechanism by which skeletal myoblast transplantation may be cardioprotective. (J Am

doi:10.1510/icvts.2010.245936

INTERACTIVE
CARDIOVASCULAR AND
THORACIC SURGERY

www.icvts.org

Tra ...ation

retrospective studies showed no effect on long-term mortality in patients affected by severe MR and considerable left ventricular dysfunction undergoing mitral valve repair [5]. These results reflect the etiology of ischemic MR which is secondary to ventricular dysfunction and indicate that myocardial factors form fundamental determinants regarding the outcomes of patients with cardiomyopathy undergoing mitral valve surgery. Mitral valve repair without addressing myocardial remodelling processes most likely results only in a temporary reduction of the MR grade [4]. Therefore, patients with ischemic MR offering no option to address the underlying pathology by revascularisation pro-

European Heart Journal (2011) **32**, 2830–2840
doi:10.1093/eurheartj/ehr059

BASIC SCIENCE

Injectable living marrow stromal cell-based autologous tissue engineered heart valves: *first experiences with a one-step intervention in primates*

Aims A living heart valve with regeneration capacity based on autologous cells and minimally invasive implantation technology would represent a substantial improvement upon contemporary heart valve prostheses. This study investigates the feasibility of injectable, marrow stromal cell-based, autologous, living tissue engineered heart valves (TEHV) generated and implanted in a one-step intervention in non-human primates.

Methods

Scaffold fabrication

Isolation of primate bone marrow-derived mononuclear cells

Phenotyping of bone marrow-derived mononuclear cells

Bone marrow-derived mononuclear cell seeding and characterization

Tissue engineered heart valves implantation and *in vivo* functionality

Minimally invasive delivery: the transapical implantation of tissue engineered heart valves

The transapical implantations were successful in all animals. Of all six animals five valves were deployed in the orthotopic valvular

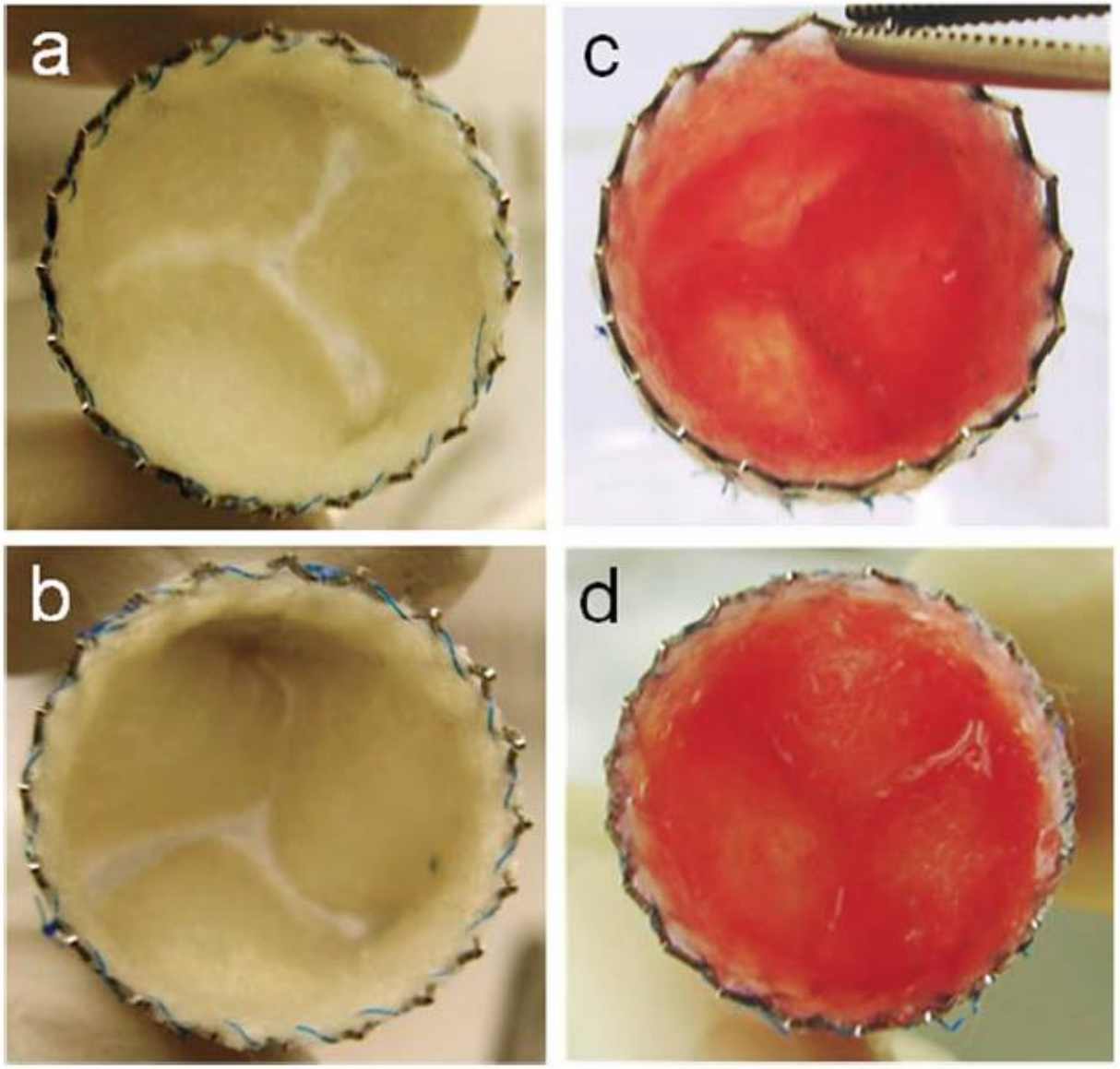
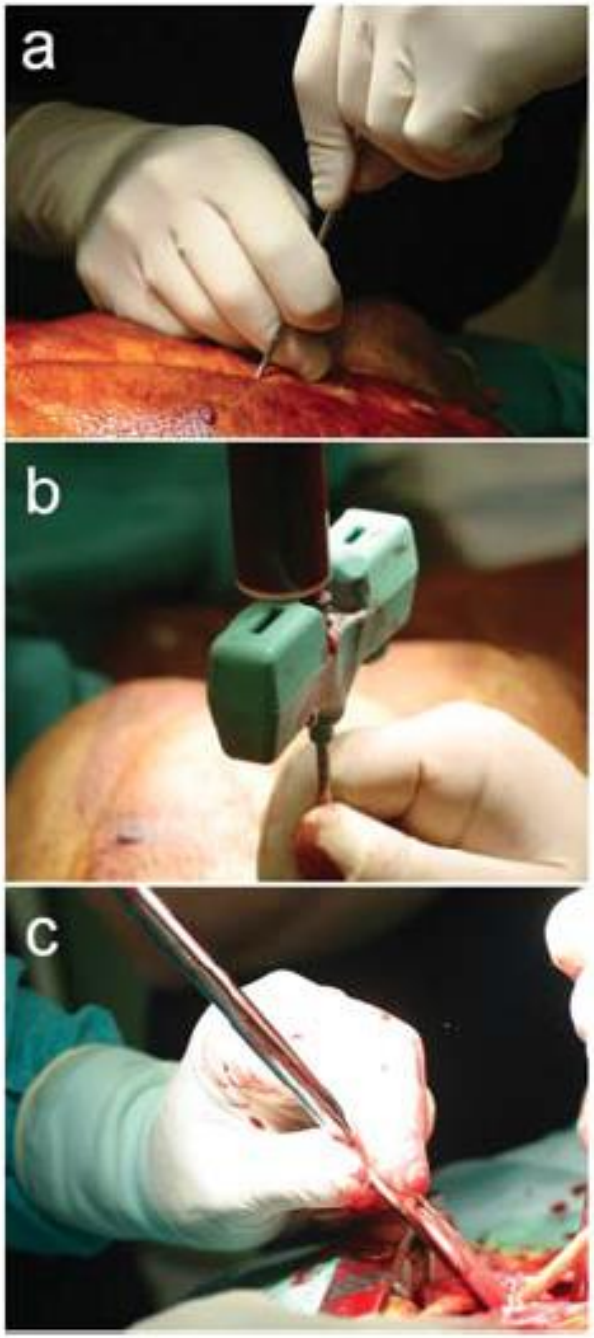


Figure 2 Bone marrow-derived tissue engineered heart valves. After isolation of bone marrow-derived mononuclear cells, stented polyglycolic acid scaffold matrices (*A* and *B*) were seeded with cells using fibrin as a cell carrier (*C* and *D*).


a
b
c
d
b
a
c
d
e

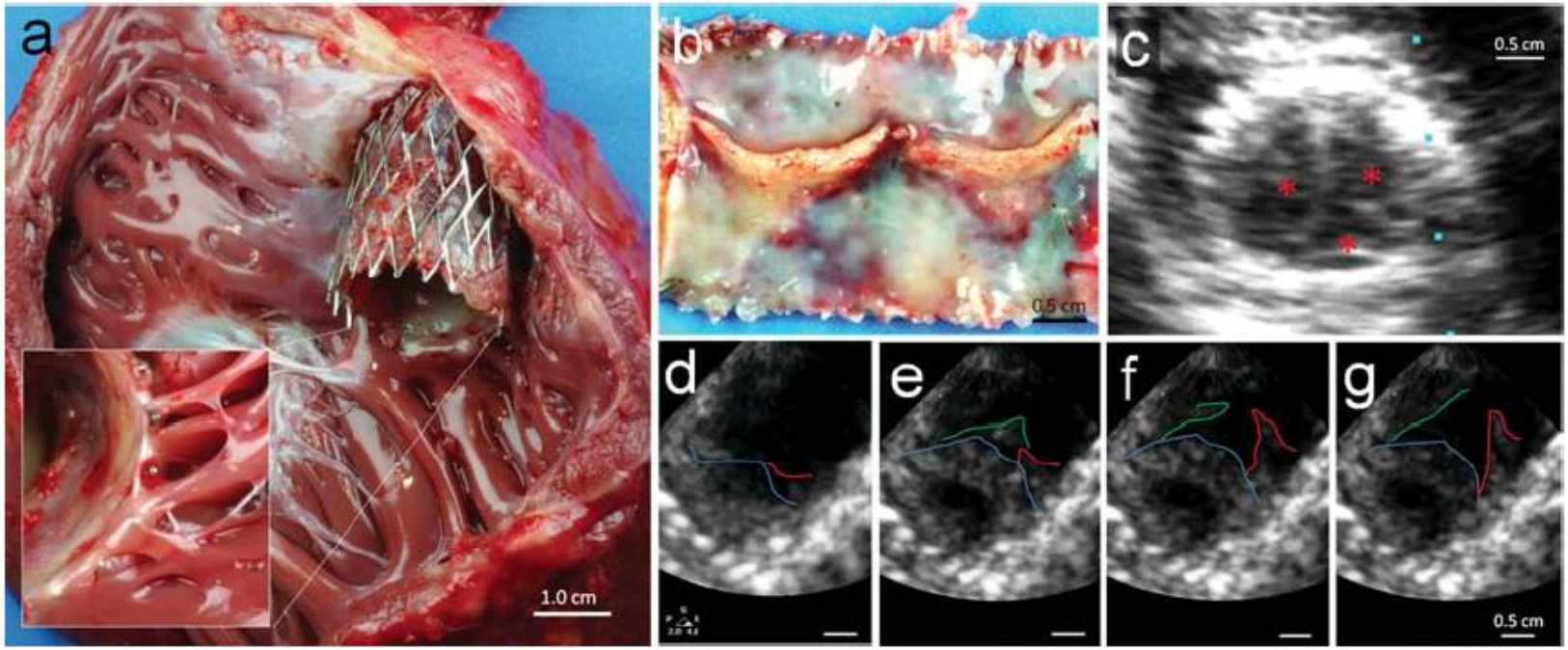


Figure 4 Explant analysis of tissue engineered heart valves. After 4 weeks *in vivo* the stented constructs were well integrated into the adjacent tissue (*A*). Orthotopical tissue engineered heart valves (*B*) presented with a cusp-like leaflet structure, with shorter leaflets than native controls. In a final transoesophageal echocardiography-assessment the leaflet co-aptation (*C*; asterisk indicates leaflets) as well as opening movements of all three leaflets could be visualized (*D*–*G*).

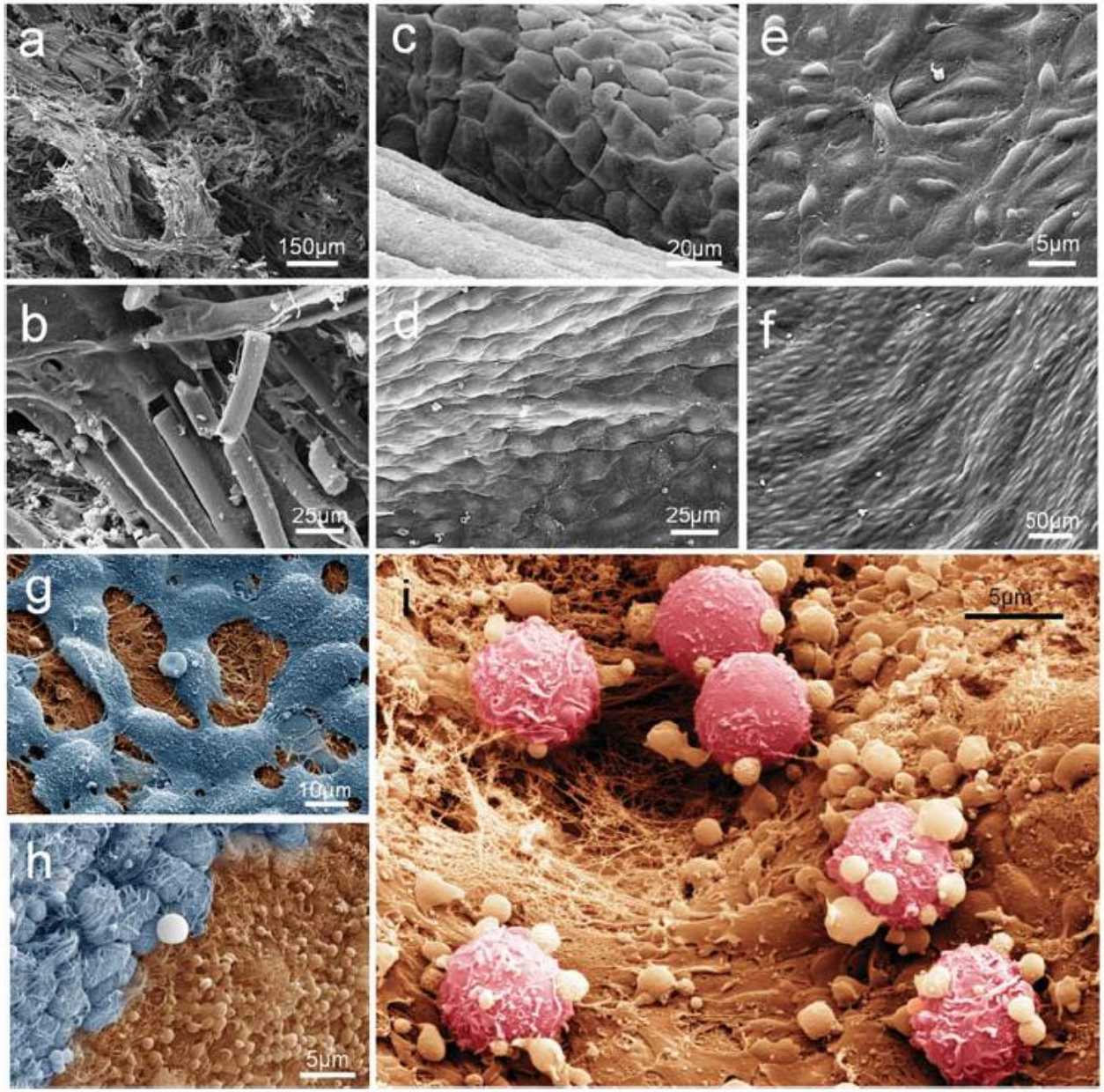


Figure 5 Scanning electron microscopy of the polyglycolic acid–poly-4-hydroxybutyrate scaffold (*A* and *B*), primate (*C*), and human (*D*) control leaflets. In most areas the surface of the 4 week explants showed confluent (*E* and *F*) or initial (*G*) endothelial coverage. In some areas the surface remodelling was still evident involving thrombocyte attachment (*H*) and leucocyte attraction (*I*).

Conclusions

These first results of combining minimally invasive valve replacement procedures with heart valve tissue engineering in a single intervention in a preclinical primate model are promising and demonstrate the feasibility of using BMCs for the fabrication of TEHV. Moreover, utilizing the body's natural abilities to regenerate TEHV *in vivo*, may greatly simplify, and improve the clinical feasibility of the autologous cell-based TEHV approach. Such autologous and living heart valves with repair and regeneration capacities may represent the next generation of transcatheter and transapical heart valves overcoming the time limitations of the currently used bioprosthetic valves suggesting their future clinical application also beyond elderly patients.

International Journal of Nanomedicine

Dovepress

open access to scientific and medical research

Original Article

Expression of *COLLAGEN* 1 and *ELASTIN* Genes in Mitral Valvular Interstitial Cells within Microfiber Reinforced Hydrogel

Maryam Eslami, M.D, Ph.D.[1, 2, 3*], Gholamreza Javadi, Ph.D.[1*], Nasser Agdami, Ph.D.[4], Mohammad Ali Shokrgozar, Ph.D.[5]

1. Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran
2. Department of Genetics,Tehran Medical Sciences Branch, Islamic Azad University, Tehran, Iran
3. Applied Biotechnology Research Center, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, Iran
4. Department of Stem Cells and Developmental Biology, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran
5. Cell Bank Division, Pasteur Institute of Iran (IPI), Tehran, Iran

J Tissue Eng Regen Med. 2016 Jan 22. doi: 10.1002/term.2127. [Epub ahead of print]

Engineering natural heart valves: possibilities and challenges.

Namiri M1,2, Ashtiani MK1, Mashinchian O1, Hasani-Sadrabadi MM1,3, Mahmoudi M4,5,6, Aghdami N1, Baharvand H1,2.

During the past three decades, tissue engineering-based approaches have shown tremendous potential to overcome these limitations by the development of a **biodegradable scaffold**, which provides biomechanical and biochemical properties of the native tissue. Among various scaffolds employed for tissue engineering, the decellularized heart valve (DHV) has attracted much attention, due to its native structure as well as comparable haemodynamic characteristics. Although the human DHV has shown optimal properties for valve replacement, the limitation of valve donors in terms of time and size is their main clinical issue. In this regard, xenogenic DHV can be a promising candidate for heart valve replacement. Xenogenic DHVs have similar composition to human valves, which will overcome the need for human DHVs. **The main concern regarding xenogeneic DHV replacement is the immunological reaction and calcification following implantation, weak mechanical properties and insufficient recellularization capacity**.

Hindawi Publishing Corporation
Stem Cells International
Volume 2016, Article ID 7168797, 11 pages
http://dx.doi.org/10.1155/2016/7168797

Review Article

Improving Cell Engraftment in Cardiac Stem Cell Therapy

Myocardial infarction (MI) affects millions of people worldwide. MI causes massive cardiac cell death and heart function decrease. However, heart tissue cannot effectively regenerate by itself. While stem cell therapy has been considered an effective approach for regeneration, the efficacy of cardiac stem cell therapy remains low due to inferior cell engraftment in the infarcted region. This is mainly a result of low cell retention in the tissue and poor cell survival under ischemic, immune rejection and inflammatory conditions. Various approaches have been explored to improve cell engraftment: increase of cell retention using biomaterials as cell carriers; augmentation of cell survival under ischemic conditions by preconditioning cells, genetic modification of cells, and controlled release of growth factors and oxygen; and enhancement of cell survival by protecting cells from excessive inflammation and immune surveillance. In this paper, we review current progress, advantages, disadvantages, and potential solutions of these approaches.

Int. J. Mol. Sci. **2015**, *16*, 597-627; doi:10.3390/ijms16010597

OPEN ACCESS
International Journal of
Molecular Sciences
ISSN 1422-0067
www.mdpi.com/journal/ijms

Review

Accelerating *in Situ* Endothelialisation of Cardiovascular Bypass Grafts

Ee Teng Goh [1,2], Eleanor Wong [1,2], Yasmin Farhatnia [1], Aaron Tan [1,2,3] and Alexander M. Seifalian [1,4,*]

REVIEW

Luminal Surface Engineering, 'Micro and Nanopatterning': Potential for Self Endothelialising Vascular Grafts?

D.S.T. Chong [a,b], B. Lindsey [a], M.J. Dalby [c], N. Gadegaard [d], A.M. Seifalian [b], G. Hamilton [a,b,*]

[a] Department of Vascular Surgery, Royal Free London NHS Foundation Trust, London, UK
[b] Centre for Nanotechnology and Regenerative Medicine, Division of Surgery and Interventional Science, University College London, London, UK
[c] Centre for Cell Engineering, University of Glasgow, Glasgow, UK
[d] Division of Biomedical Engineering, School of Engineering, University of Glasgow, Glasgow, UK

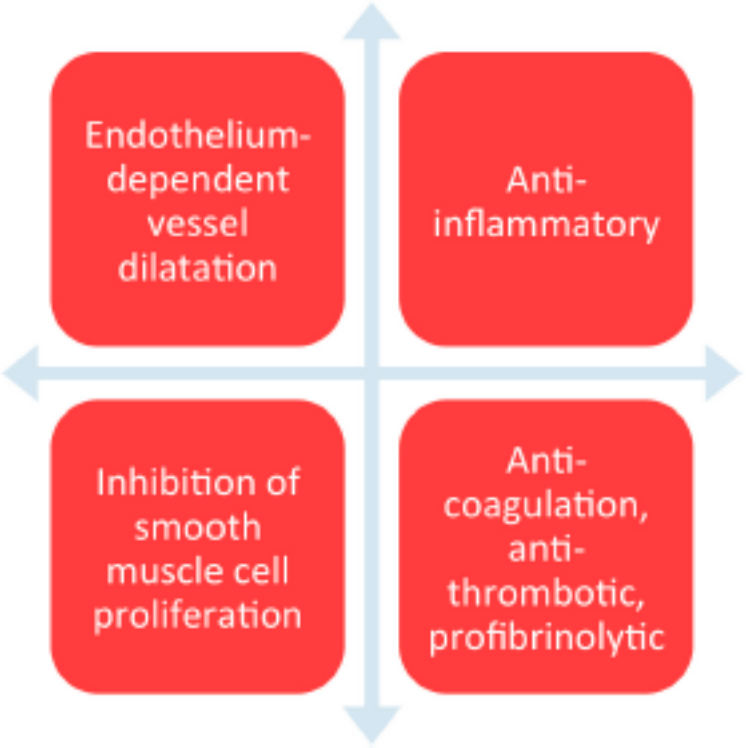


Figure 1. Shows the different functions of endothelium.

Abstract: The patency of synthetic cardiovascular grafts in the long run is synonymous with their ability to inhibit the processes of intimal hyperplasia, thrombosis and calcification. In the human body, the endothelium of blood vessels exhibits characteristics that inhibit such processes. As such it is not surprising that research in tissue engineering is directed towards replicating the functionality of the natural endothelium in cardiovascular grafts. This can be done either by seeding the endothelium within the lumen of the grafts prior to implantation or by designing the graft such that *in situ* endothelialisation takes place after implantation. Due to certain difficulties identified with *in vitro* endothelialisation, *in situ* endothelialisation, which will be the focus of this article, has garnered interest in the last years. To promote *in situ* endothelialisation, the following aspects can be taken into account: (1) Endothelial progenital cell mobilization, adhesion and proliferation; (2) Regulating differentiation of progenitor cells to mature endothelium; (3) Preventing thrombogenesis and inflammation during endothelialisation. This article aims to review and compile recent developments to

Ann Thorac Surg. 2012 May ; 93(5): 1524–1533. doi:10.1016/j.athoracsur.2012.01.063.

Stem Cells in Thoracic Aortic Aneurysms and Dissections: Potential Contributors to Aortic Repair

Ying H. Shen, MD, PhD[1,2], **Xiaoqing Hu, MD**[1,2], **Sili Zou, MD**[1,2], **Darrell Wu, MD**[1,2,3], **Joseph S. Coselli, MD**[1,3], and **Scott A. LeMaire, MD**[1,2,3]

[1]Texas Heart Institute at St. Luke's Episcopal Hospital, 6770 Bertner Ave., Houston, TX 77030

Comment

Multipotent SCs are known to play an important role in arterial remodeling after injury. The presence of circulating endothelial progenitor cells has been previously reported in a murine model of abdominal aortic aneurysms [15], in patients with abdominal aortic aneurysms [16], and, recently, in patients with ascending aortic aneurysms [17]. In this study, we have shown that SCs are abundant in two other forms of aortic disease: descending TAA and chronic TAD. Specifically, we found that there were significantly more STRO-1+ cells, c-kit+ cells, and CD34+ cells and in the media and adventitia of aortic tissue from TAA and TAD patients than in control aortic tissue. Furthermore, subsets of STRO-1+ cells, c-kit+ cells, and CD34+ cells appeared to differentiate into SMCs and fibroblasts, and a large number of STRO-1+ cells exhibited differentiation into macrophages. The presence of multipotent SCs at sites of aneurysm and dissection formation that can further differentiate into SMCs suggests the existence of an active repair process involving SCs.

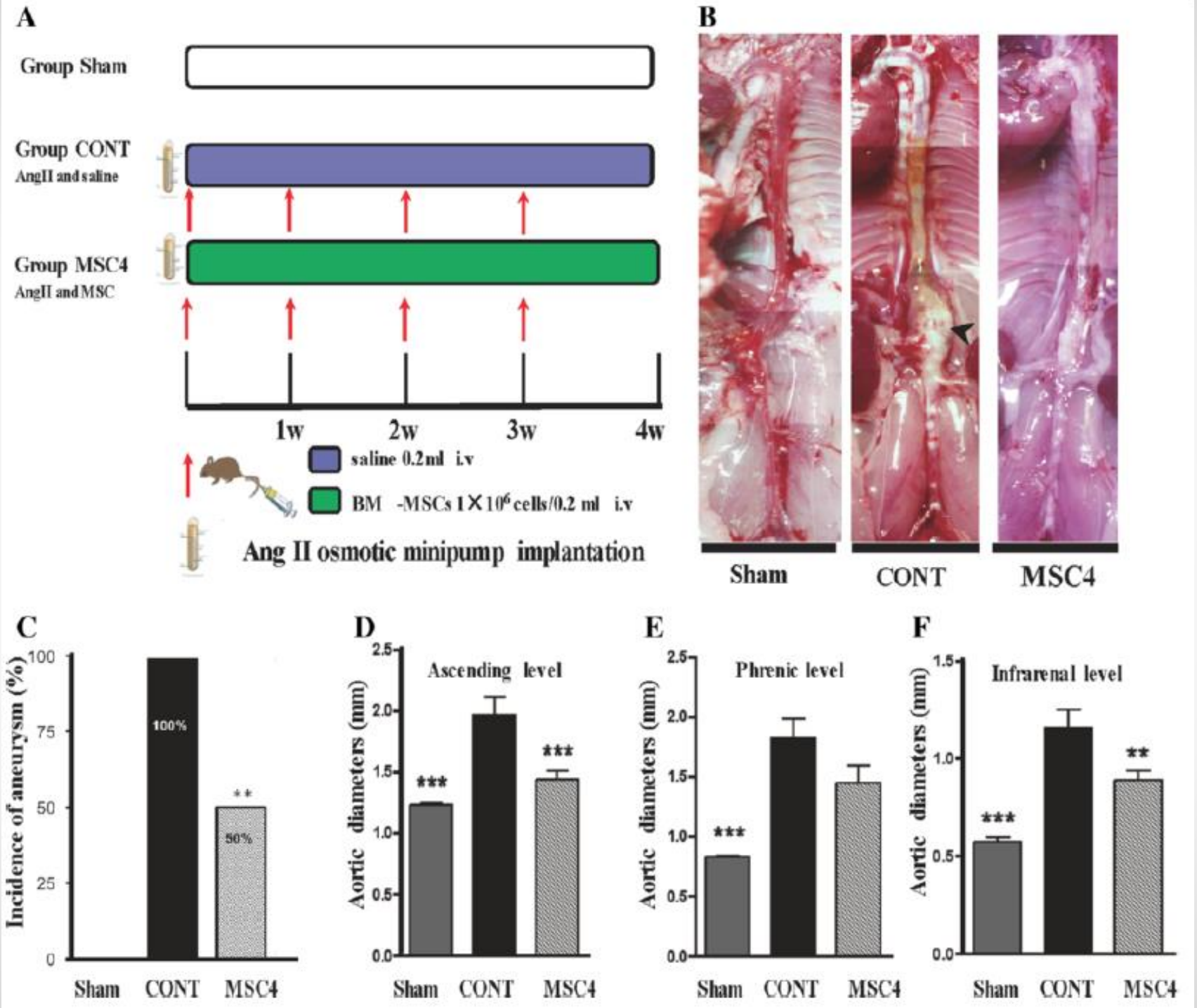
Fu et al. Journal of Translational Medicine 2013, 11:175
http://www.translational-medicine.com/content/11/1/175

JOURNAL OF TRANSLATIONAL MEDICINE

RESEARCH Open Access

Intravenous administration of mesenchymal stem cells prevents angiotensin II-induced aortic aneurysm formation in apolipoprotein E-deficient mouse

Xian-ming Fu†, Aika Yamawaki-Ogata†, Hideki Oshima, Yuichi Ueda, Akihiko Usui and Yuji Narita*


A
Group Sham
Group CONT
AngII and saline
Group MSC4
AngII and MSC
1w
2w
3w
4w
saline 0.2ml i.v
BM -MSCs 1×10^6 cells/0.2 ml i.v
Ang II osmotic minipump implantation
B
Sham
CONT
MSC4
C
Incidence of aneurysm (%)
100
75
50
25
0
100%
**
50%
Sham
CONT
MSC4
D
Ascending level
Aortic diameters (mm)
2.5
2.0
1.5
1.0
0.5
0.0
***
***
Sham
CONT
MSC4
E
Phrenic level
Aortic diameters (mm)
2.5
2.0
1.5
1.0
0.5
0.0
***
Sham
CONT
MSC4
F
Infrarenal level
Aortic diameters (mm)
1.5
1.0
0.5
0.0
***
**
Sham
CONT
MSC4

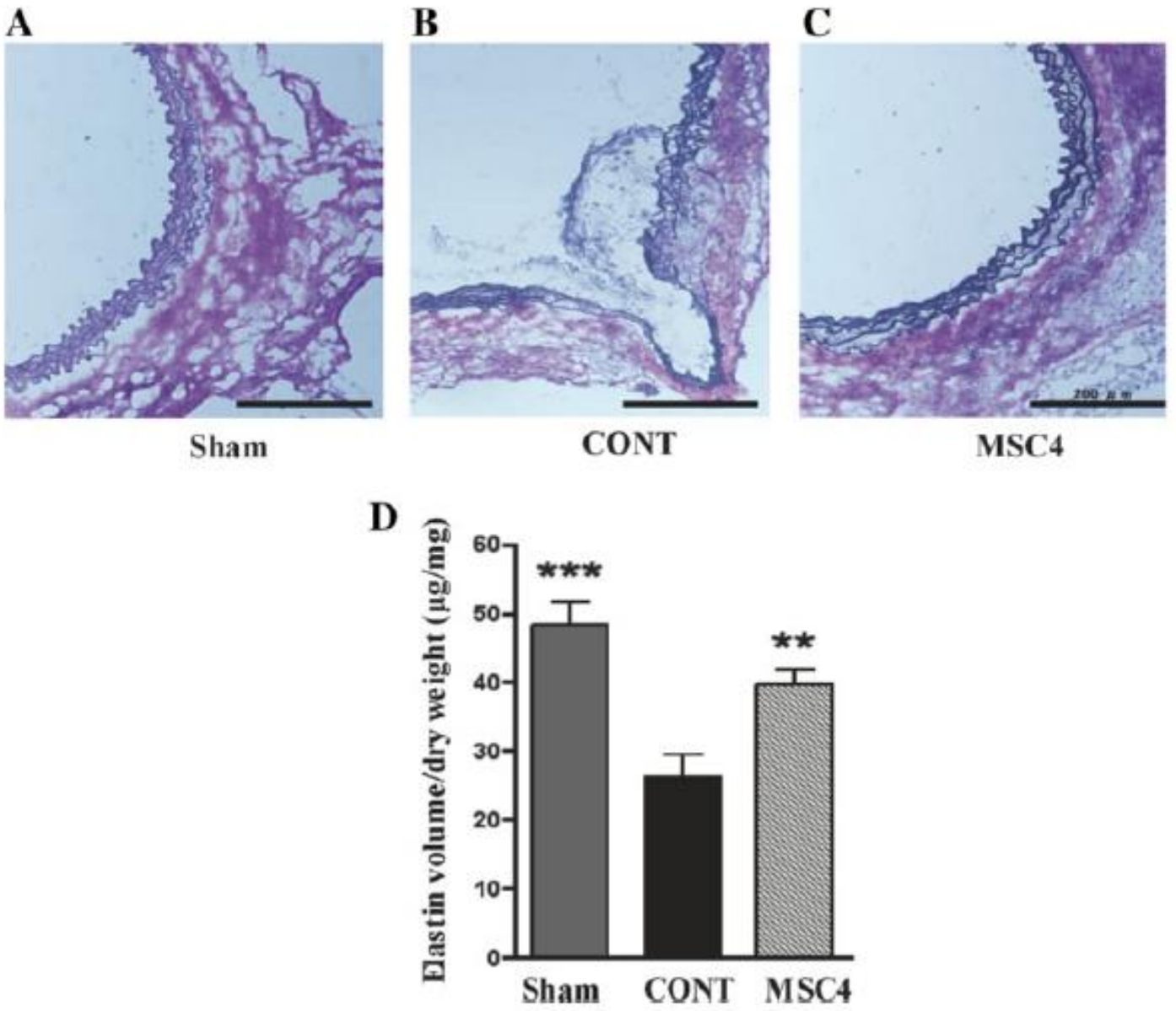


Figure 2 Multiple intravenous administrations of BM-MSCs attenuated aortic elastin degradation in apoE$^{-/-}$ mice. A) EVG staining shows normal wavy elastic lamina structure in group Sham, and **B)** disruption of elastic lamina and aneurysm formation in group CONT. **C)** Administration of BM-MSCs maintained wavy structure of the elastic lamellae. Scale bar = 200 µm. **D)** Measurement of elastin volume of aortic tissues showed a significant decrease in group CONT compared with group Sham, but preservation in group MSC4. Data are presented as means ± SEM (n =10-12) $^{**}P<0.01$, $^{***}P<0.001$ vs. group CONT, assessed by one-way ANOVA.

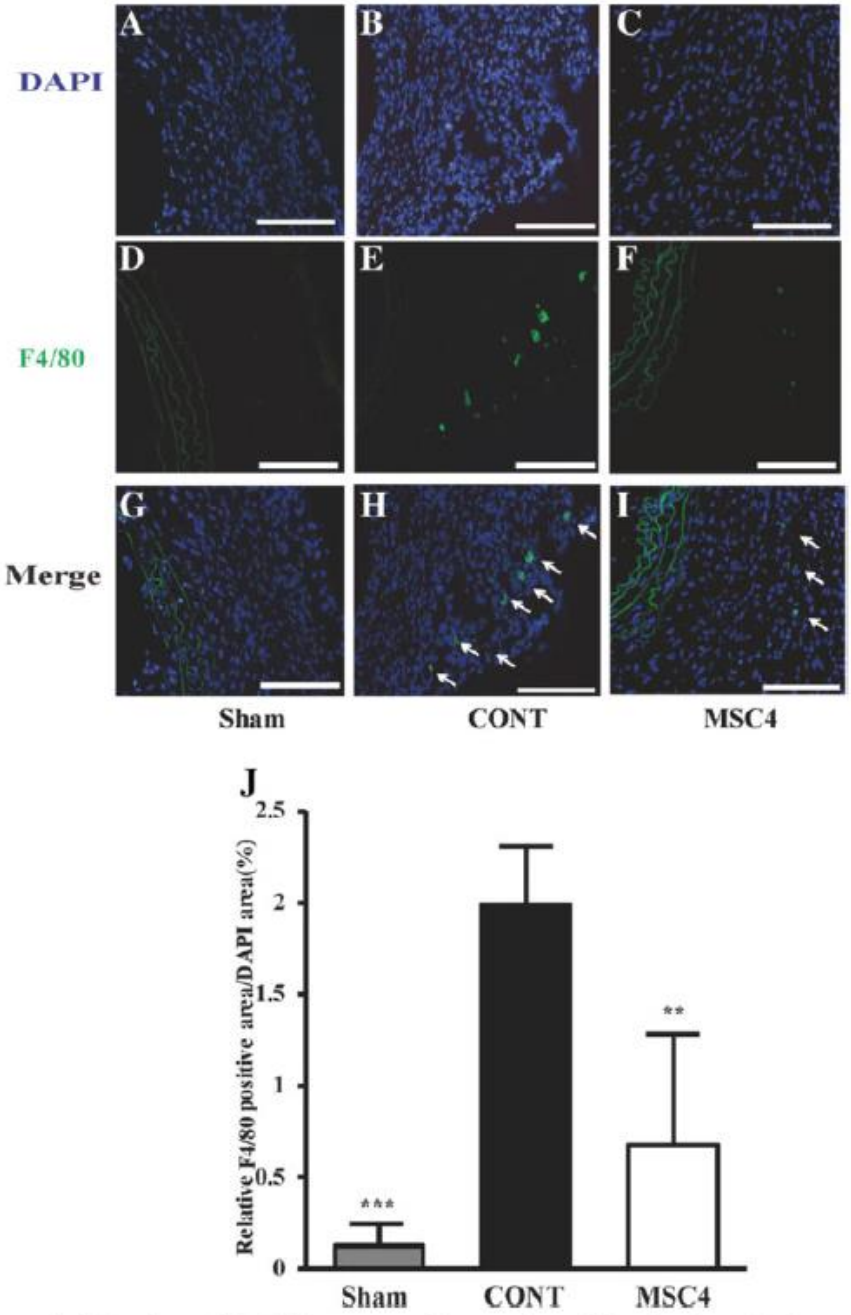


Figure 3 Multiple intravenous administrations of BM-MSCs suppressed macrophage infiltration in aortic tissues. A-I) Representative F4/80 immunofluorescence stained sections of suprarenal aortas from Sham, CONT, and MSC4 groups. Arrowheads indicated F4/80 macrophages. Scale bars=100 μm. **J)** Quantitation of F4/80- positive macrophages area as a ratio of the DAPI staining area. Data are presented as means ± SEM (n =10-12) $^{**}P<0.01$, $^{***}P<0.001$ vs. group CONT, assessed by one-way ANOVA.

Fu *et al. Journal of Translational Medicine* 2013, **11**:175
http://www.translational-medicine.com/content/11/1/175

JOURNAL OF TRANSLATIONAL MEDICINE

Conclusions

Multiple intravenous administrations of BM-MSCs were effective to suppress inflammatory reactions in Ang II-infused apoE$^{-/-}$ mice, and inhibit the development of AAs. It may therefore serve as a new therapeutic strategy for patients with AA.

Biomaterials. 2015 Dec;73:175-84. doi: 10.1016/j.biomaterials.2015.09.016. Epub 2015 Sep 11.

6-month aortic valve implantation of an off-the-shelf tissue-engineered valve in sheep..

Departments of Biomedical Engineering, University of Minnesota, United States.

The high pressure gradients and dynamic flow across the aortic valve leaflets require engineering a tissue that has the strength and compliance to withstand high mechanical demand without compromising normal hemodynamics. A long-term preclinical evaluation of an off-the-shelf tissue-engineered aortic valve in the sheep model is presented here. The valves were made from a tube of decellularized cell-produced matrix mounted on a frame. The engineered matrix is primarily composed of collagen, with strength and organization comparable to native valve leaflets. In vitro testing showed excellent hemodynamic performance with low regurgitation, low systolic pressure gradient, and large orifice area. The implanted valves showed large-scale leaflet motion and maintained effective orifice area throughout the duration of the 6-month implant, with no calcification. After 24 weeks implantation (over 17 million cycles), the valves showed no change in tensile mechanical properties. In addition, histology and DNA quantitation showed repopulation of the engineered matrix with interstitial-like cells and endothelialization.

J Artif Organs. 2007;10(1):29-35. Epub 2007 Mar 23.

Minimally immunogenic decellularized porcine valve provides in situ recellularization as a stentless bioprosthetic valve.

Iwai S1, Torikai K, Coppin CM, Sawa Y

To overcome these obstacles, we have developed a minimally immunogenic tissue-engineered valve that consists of an unfixed, decellularized porcine valve scaffold capable of being spontaneously revitalized in vivo after implantation. Porcine aortic root tissue was decellularized using detergents such as sodium lauryl sulfate and Triton X-100. The porcine valve was treated very gently and plenty of time was allowed for constituents to diffuse in and out of the matrix. In a preliminary study, a piece of decellularized porcine valve tissue was implanted into the rat subdermal space for 14 and 60 days and the structural integrity and calcification were evaluated. As an in vivo valve replacement model, the decellularized porcine valve was implanted in the pulmonary valve position in dogs and functional and histological evaluation was performed after 1, 2, and 6 months. Histological examination showed that the newly developed detergent treatment effectively removed cellular debris from the porcine aortic tissue. Decellularized porcine valve tissue implanted subdermally in rats showed minimal inflammatory cell infiltration and calcification. In the valve replacement model, spontaneous reendothelialization and repopulation of the medial cells were observed within 2 months, and good valve function without regurgitation was observed by echocardiography up to 6 months.

Biointerphases
A Journal of Biomaterials and Biological Interfaces

Novel heart valve prosthesis with self-endothelialization potential made of modified polyhedral oligomeric silsesquioxane-nanocomposite material

Hossein Ghanbari, Dina Radenkovic, Sayed Mahdi Marashi, Shirin Parsno, Nima Roohpour, Gaetano Burriesci, and Alexander M. Seifalian

(Received 1 October 2015; accepted 11 December 2015; published 13 January 2016)

In the cardiovascular system, the endothelial layer provides a natural antithrombogenic surface on the inner portion of the heart and associated vessels. For a synthetic material therefore, the ability to attract and retain endothelial or endothelial progenitor cells (EPCs), ultimately creating a single endothelial layer on its surface, is of prime importance. The authors have developed a nanocomposite polymer, based on a combination of polyhedral oligomeric silsesquioxane nanoparticles and polycarbonate urea urethane (POSS-PCU), which is biocompatible and has been used in human for the world's first synthetic trachea, tear duct, and bypass graft. In this study, the authors modified the surface of this casted nanocomposite by grafting fibronectin derived bioactive peptides [glycine-arginine-glycine-aspartic acid-glycine (GRGDG) and lauric acid conjugated GRGDG (GRGDG-LA)] to enhance the endothelialization for using heart valves leaflets from circulating EPCs. Human peripheral blood mononuclear cells were separated using Ficoll–Paque centrifugation, with harvested EPCs purified using CD34 microbead labeling and magnetic-activated cell sorting. Cells were seeded onto 96 well plates coated with POSS-PCU, GRGDG/GRGDG-LA modified POSS-PCU and PCU polymers, for a period of 21 days. Cells

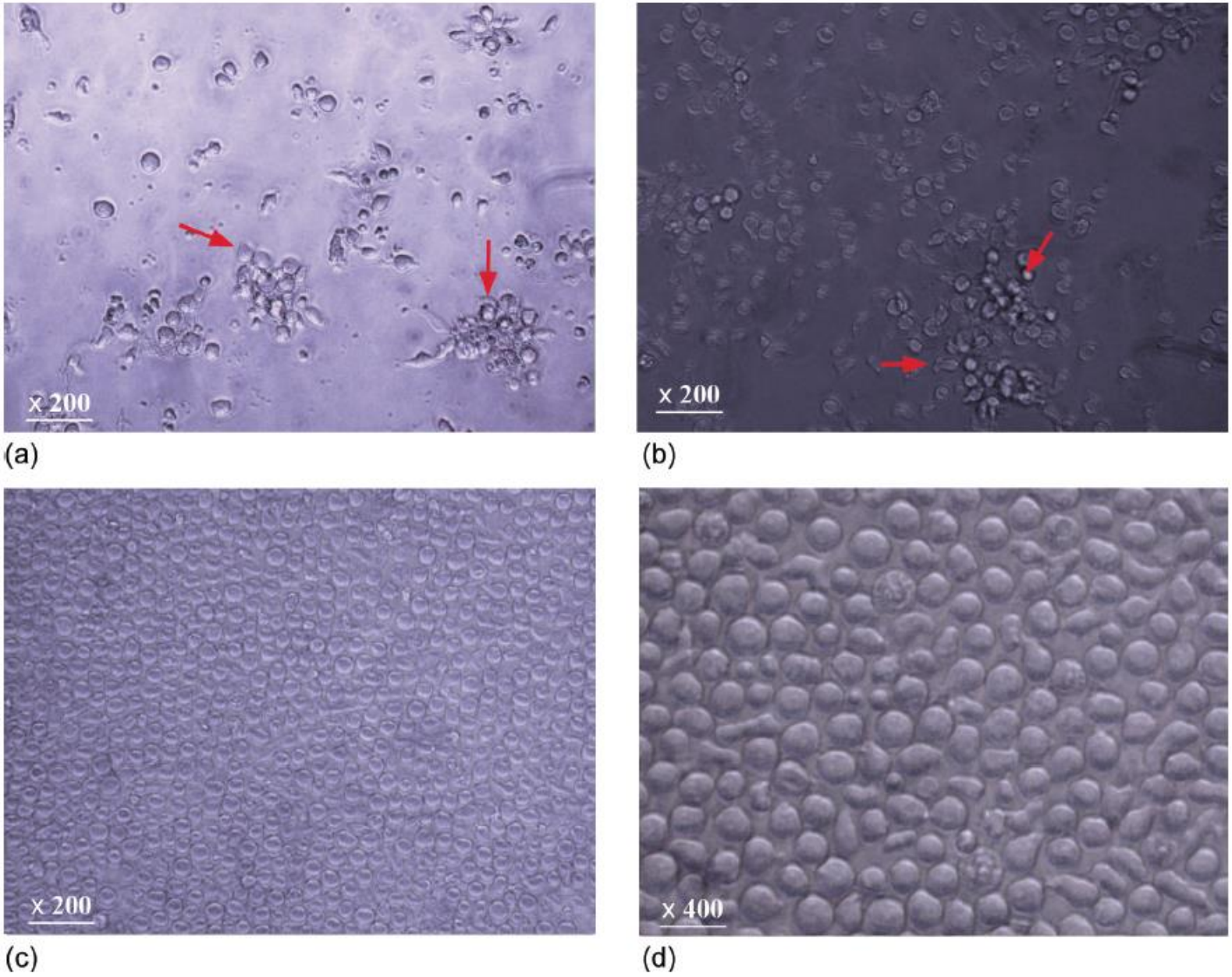


FIG. 6. Live microscopy images of the isolated cells cultured on POSS-PCU nanocomposite samples. Colonies of EPC (marked with arrows) undergoing proliferation resulted in an increased cell population over time of culture as shown on day 7 (a) and day 14 (b). The cells underwent morphological changes during the culture and spindle-shaped morphology of early EPCs on day 7 (a) was dominated by cobble stone-shaped confluent layer at day 21 (c), characteristic morphology of the endothelial cells. (d) Higher magnification of confluent layer of EC on day 21.

Biointerphases
A Journal of Biomaterials and Biological Interfaces

Novel heart valve prosthesis with self-endothelialization potential made of modified polyhedral oligomeric silsesquioxane-nanocomposite material

Hossein Ghanbari, Dina Radenkovic, Sayed Mahdi Marashi, Shirin Parsno, Nima Roohpour, Gaetano Burriesci, and Alexander M. Seifalian

V. CONCLUSIONS

In an *in vitro* setting, EPCs were extracted from adult peripheral blood and umbilical cord blood and cultured on the POSS-PCU nanocomposite in comparison with PCU, GRGDG, and GRGDG-LA modified polymers. EPCs' proliferation and differentiation was noticed over the time of culture. The POSS-PCU nanocomposite revealed an enhanced cell affinity and capability to provide a cell friendly environment for EPC proliferation and differentiation. According to the results, this nanocomposite material can be used for the development of synthetic leaflet heart valves, but modification with suitable peptides could result in superior in-situ endothelialization capability.

Crit Rev Biotechnol. 2015 Jul 15:1-11. [Epub ahead of print]

Hearts beating through decellularized scaffolds: whole-organ engineering for cardiac regeneration and transplantation.

Zia S1, Mozafari M, Natasha G, Tan A, Cui Z, Seifalian AM

Abstract

Whole-organ decellularization and tissue engineering approaches have made significant inroads during recent years. If proven to be successful and clinically viable, it is highly likely that this field would be poised to revolutionize organ transplantation surgery. In particular, whole-heart decellularization has captured the attention and imagination of the scientific community. This technique allows for the generation of a complex three-dimensional (3D) extracellular matrix scaffold, with the preservation of the intrinsic 3D basket-weave macroarchitecture of the heart itself. The decellularized scaffold can then be recellularized by seeding it with cells and incubating it in perfusion bioreactors in order to create functional organ constructs for transplantation. Indeed, research into this strategy of whole-heart tissue engineering has consequently emerged from the pages of science fiction into a proof-of-concept laboratory undertaking. This review presents current trends and advances, and critically appraises the concepts involved in various approaches to whole-heart decellularization and tissue engineering.

European Heart Journal Advance Access published May 19, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv189

EHJ BRIEF COMMUNICATION
Heart failure/cardiomyopathy

Human embryonic stem cell-derived cardiac progenitors for severe heart failure treatment: first clinical case report

tive applications, and based on the epicardial delivery of a cell-loaded patch. Several studies have documented the superiority of this patch-based approach over intramyocardial injections with regard to cell retention, survival,[22] and, ultimately, preservation of heart function.[21] Our choice of encaging the *Isl-1*$^{+}$ cardiac

Figure 1 Intraoperative view of the progenitor cell-loaded fibrin patch that has been slid into the pocket between an autologous pericardial flap and the epicardial surface of the infarct area.

H. Oh, M.D., Ph.D.

STEM CELL THERAPIES IN PATIENTS WITH SINGLE VENTRICLE PHYSIOLOGY

Suguru Tarui, M.D.[a]; Shunji Sano, M.D., Ph.D.[a]; Hidemasa Oh, M.D., Ph.D.[b]

[a]*Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan;*
[b]*Okayama University Hospital, Okayama, Japan*

Abstr
Single
conge
patien
trials u
term i
ability
heart

Cardiac stem cell therapies for congenital heart diseases

Shuta Ishigami, Shunji Sano, Hidemasa Oh

Future Cardiol. 2012 Mar;8(2):161-9. doi: 10.2217/fca.12.13.

Potential for stem cell use in congenital heart disease.

Pincott ES1, Burch M.

CASE REPORTS: CONGENITAL

Regenerative therapy for hypoplastic left heart syndrome: First report of intraoperative intramyocardial injection of autologous umbilical-cord blood–derived cells

Harold M. Burkhart, MD,[a] Muhammad Yasir Qureshi, MBBS,[b] Susana Cantero Peral, MD,[c,d] Patrick W. O'Leary, MD,[b] Timothy M. Olson, MD,[b] Frank Cetta, MD,[b] and Timothy J. Nelson, MD, PhD,[b,c,d,e,f] the Wanek Program Clinical Pipeline Group, Rochester, Minn

The case study involves an HLHS newborn whose umbilical cord blood was collected at birth. The umbilical cord blood was then processed to achieve mononuclear cells and preserved at below zero temperatures until the time of delivery. At four days old, the infant underwent the Stage I Norwood procedure, allowing the right ventricle to pump blood to the lungs and the body. Then, at four months old, the patient underwent Stage II surgery, also known as the Glenn procedure, and the stem cells were injected into the baby's right ventricle. During the one and three month follow ups, the child's right ventricle function had improved.

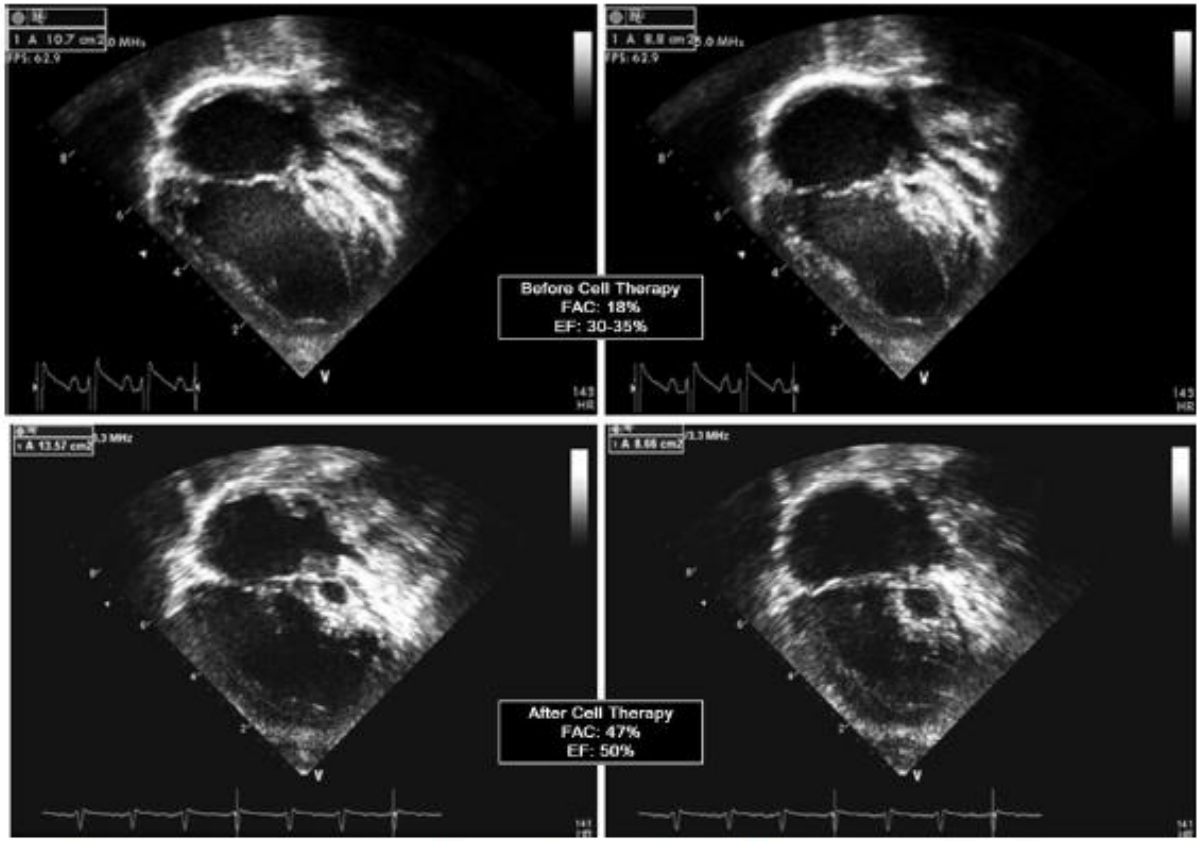


FIGURE 1. Apical views of echocardiogram performed before (*top panels*) and 3 months after (*bottom panels*) intramyocardial injection of umbilical-cord blood–derived stem cells. Images show improvement in right ventricular function, with an increase in the ejection fraction from 30%-35% to 50%. *FAC*, Fractional area change; *EF*, ejection fraction.