

# Transcoronary stem cell delivery using physiological endothelium-targeting perfusion technique: the rationale and a pilot study involving a comparison with conventional over-the-wire balloon coronary occlusions in patients after recent myocardial infarction

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## Abstract

**Introduction:** Recent evidence shows poor efficacy of over-the-wire balloon catheter (OTW) coronary occlusive technique adopted widely for intracoronary bone marrow stem cell (BMSC) delivery. The waterfall effect of OTW-balloon inflation/deflation with reactive  $\geq 2$ -fold flow velocity increase might be partly responsible for poor BMSC retention.

**Aim:** To evaluate the safety, feasibility and tolerability of perfusion-infusion BMSC delivery with the facilitation of cell rolling in contact with the coronary endothelium (a pre-requisite for downstream transmigration).

**Methods:** We randomly assigned 11 patients (age 41-72 years) with first anterior myocardial infarction treated with PTCA+stent and LVEF  $\leq 45\%$  at 6-9 days to OTW in-stent occlusive (3 x 3 min.) BMSC delivery or cell infusion via a perfusion catheter with multiple side holes (SH-PC).

**Results:** OTW and SH-PC patients had a similar infarct size (mean peak CK 4361 vs 4717 U/L), LVEF (41.2% vs 40.3%), infused mononuclear cell number ( $2.99 \times 10^8$  range  $0.61-7.48 \times 10^8$  vs  $3.28 \times 10^8$  range  $1.64-4.39 \times 10^8$ ), CD 34+ number ( $1.79 \times 10^6$  vs  $1.62 \times 10^6$ ), cell viability (91.5% vs 91.8%) and clonogenicity (CFU assay). None of the SH-PC, but 67% of OTW patients, had ST-segment elevation with chest pain (and nsVT in one) that limited OTW occlusion tolerance to 50-110 sec. At 6 months  $\Delta$ LVEF in the OTW vs SH-PC patients was +4.2% (2-6) vs +8.8% (5-16) by MRI and +4.8 (2-7) vs +13.8% (2-24) by SPECT.

**Conclusions:** Our work indicates that the SH-PC technique can be used safely for intracoronary BMSC transplantation. Further research is needed to determine whether the putative advantages of physiological SH-PC delivery translate into enhanced BMSC homing.

**Key words:** stem cell therapy, transcoronary bone marrow stem cell transplantation, physiological stem cell delivery, endothelium-targeted stem cell delivery, myocardial infarction border zone regeneration

Kardiologia Polska 2006; 64: 489-498

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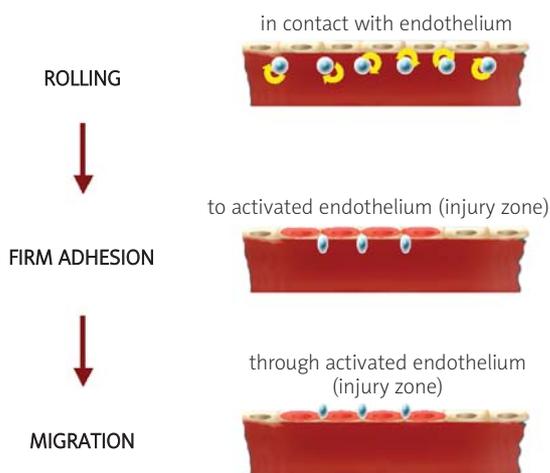
**Received:** 21 December 2005. **Accepted:** 15 February 2006.

*This work was partly supported by grant #PBZ-KBN-099/P05/2003 from the Polish Ministry of Education and Science*

*Parts of the study were presented at the Third Annual Meeting of the European Stem Cell Therapeutics Excellence Centre (STEC 2005) and the Transcatheter Cardiovascular Therapeutics (TCT 2005).*

## Introduction

Efficient delivery of bone marrow-derived stem cells (BMSC) to the recent infarct zone is fundamental for any effect of transcatheter BMSC therapy. Undisturbed cell rolling in contact with the endothelium is a first mandatory step in BMSC trafficking (Figure 1) [1, 2]. Endothelial BMSC rolling initiates multiple receptor-mediated cell-cell interactions (involving selectins, integrins and local chemokine stimulation) that mediate 'downstream' BMSC adhesion to the endothelium activated in the injury (border) zone and BMSC recruitment from coronary circulation [1-3]. Indeed, the key experimental evidence that intracoronary transplantation of BMSC after recent myocardial infarction (MI) can lead to BMSC endothelial trans-migration and homing in the injury area (with subsequent neovascularisation, reduction of apoptosis and potential new cardiomyocyte formation in the infarct border zone) was generated in small animal

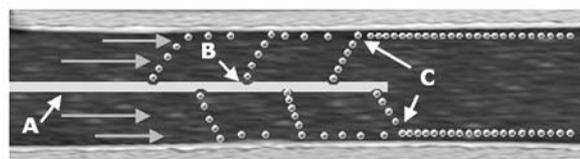


**Figure 1.** Three basic sequential mechanisms responsible for the trans-migration of stem cells to the target tissue. 1 – undisturbed rolling in contact with the endothelium (mediated by the laminar flow and stem cell surface selectins); 2 – adhesion to the activated endothelium (red), mediated by stem cell surface integrins, endothelial adhesion molecules, stem cell chemokine receptors (e.g. CXCR4 in a subpopulation of CD34<sup>+</sup> cells), and chemokines produced in the injury zone (e.g. SDF-1 for CXCR4<sup>+</sup> cells); 3 – trans-endothelial migration driven by the chemokine gradient and active stem cell cytoskeleton change. See the text for references

studies where cell delivery was performed without disturbing the normal coronary flow [4, 5].

Past and current translational human trials have been based on the use of over-the-wire balloon catheters (OTW) for intracoronary BMSC administration [6-13]. With OTW balloon inflation the cells are delivered through the catheter's distal tip positioned in the stent in the infarct-related artery while the epicardial and capillary flow is completely ceased (or, in some cases, reversed [14]) for usually 120-240 sec. Evidence shows that on balloon deflation there is an instantaneous reactive increase in epicardial and capillary flow velocity (with normal values exceeded  $\geq 2$ -fold) and a 20% increase in capillary diameter [15-17]. The *waterfall* effect of reactive hyperaemia can not only hamper the physiological rolling of BMSC in contact with the endothelium, but it can also cause a rapid undesired cell wash-out, greatly limiting the proportion of cells that can effectively interact with the endothelium and trans-migrate to the injury zone. Thus, circumstantial evidence suggests that non-occlusive, endothelium-targeted *physiological* BMSC delivery (Figure 2) might be superior to the *conventional* OTW technique by (I) enabling undisturbed physiological rolling in contact with the endothelium of a greater proportion of infused stem cells, and (II) avoiding cell wash-out with reactive hyperaemia.

The aim of our study was to test the use of an infusion-perfusion catheter with multiple side holes (SH-PC) for intracoronary endothelium-targeted BMSC delivery in patients after recent MI.



**Figure 2.** Schematic presentation of the rationale for the use of an infusion-perfusion catheter with multiple side holes (SH-PC) for endothelium-targeted bone marrow stem cell (BMSC) transcatheter transplantation. The catheter (A) is positioned centrally in the lumen of the infarct-related coronary artery, without significantly affecting the normal flow (grey arrows). Stem cell suspension is injected via the side holes (B) that direct the cells (C) towards the external layers of the laminar flow and the endothelium. This is anticipated to facilitate the BMSC rolling in contact with the endothelium – a step that is mandatory for BMSC downstream adhesion and trans-migration through the endothelial cells activated in the injury border zone

## Methods

### Patients

Subjects were eligible for inclusion in the study if they had: 1. the first acute ST-segment elevation anterior MI (infarct-related artery = left anterior descending, LAD) treated by primary angioplasty with stent implantation, 2. no revascularisation-requiring lesions in other epicardial arteries, 3. a creatinine kinase (CK) leak exceeding at least times the upper normal limit of activity, 4. significant anterior wall hypokinesia with left ventricular ejection fraction (EF) reduced to  $\leq 45\%$  at 6-9 days after MI. Patients were randomly assigned to intracoronary autologous BMSC delivery by the endothelium-targeted perfusion technique or the 'conventional' OTW-balloon occlusive method. The study was approved by the local Bio-Ethics Committee and all subjects gave their written informed consent.

### BMSC preparation

Bone marrow aspirates (60-85 mL) were obtained from the ilium in the morning of the day of cell transplantation. Bone marrow mononuclear cells were isolated by Ficoll-density gradient centrifugation and resuspended in heparinised saline. A flow cytometric analysis was performed for the presence of CD34<sup>+</sup> antigen. Cell viability (trypan blue) and clonogenicity (colony forming unit, CFU assay) were determined.

### The effect of transcatheter delivery on BMSC viability

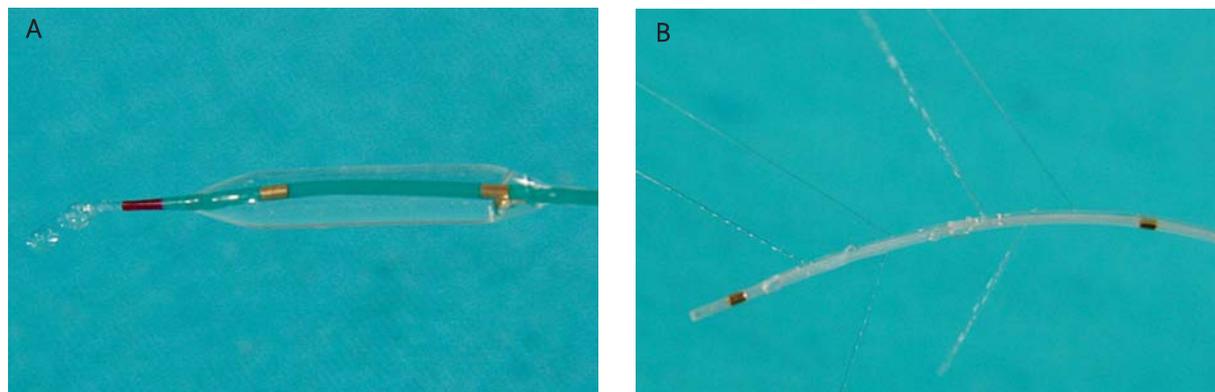
Potential loss of cell viability following OTW or SH-PC transcatheter passage was evaluated *ex vivo* in a system mimicking a coronary artery (n=3 tests for each catheter type; cell concentrations matching those used *in vivo*).

### Intracoronary BMSC application

After 6F sheath insertion into the femoral artery and heparinisation (100 U/kg), standard left ventriculography was performed with a pigtail catheter. A left coronary artery angiogram was obtained with a left Judkins catheter. Over a standard 0.014 J guidewire, either the OTW-balloon catheter (Figure 3A, nominal balloon diameter = stent diameter) or infusion-perfusion catheter with multiple side holes (Figure 3B) was advanced into the LAD stent. For OTW delivery, the guidewire was removed and the catheter's central lumen was used for cell injections (3.3 mL each) during in-stent occlusion (three times up to 3 min., total cell suspension volume of 10 mL) [6, 7]. Using SH-PC, cell suspension (50 mL) was administered via an infusion pump over 25 min. Following cell application, the left coronary angiogram was repeated to detect any potential epicardial or myocardial flow impairment.

### SPECT and MRI

In addition to clinical patient evaluation, the evolution of left ventricular perfusion and function were



**Figure 3.** Catheters for intracoronary cell delivery. A. Over-the-wire balloon catheter used universally for intracoronary stem cell delivery in past and current clinical trials. Flow cessation in the infarct-related artery is achieved by inflating the balloon in the stent implanted at primary PCI. During repeated balloon occlusions cell suspension is injected through the catheter's central lumen. Only a fraction of cells can interact with the endothelium, and lack of normal flow can greatly limit stem cell rolling in contact with the endothelium. Reactive hyperaemia on balloon deflation is associated with a waterfall effect; this is likely to contribute to undesired cell wash-out. B. Perfusion catheter with multiple side holes (SH-PC) applied in our study. In the absence of coronary occlusion, cell suspension is injected through multiple side holes that direct the cells towards the external layers of the normal laminar flow, facilitating stem cell rolling in contact with the endothelium (see also the schematic presentation in Figure 2)

followed by GSPECT and MRI (both performed 1-2 days prior to cell transplantation and at 6 months). In brief, Tc<sup>99m</sup> sestamibi images were acquired with an ECAM dual head camera (Siemens) and analysed according to the DICOM-Siemens protocol. MRI images were acquired on a Siemens Magnetom Sonata Class 1.5T scanner and EF was calculated using the commercially available Argus software provided by Siemens and implemented on the Leonardo workstation.

## Results

From June 2003 to January 2005 we included 11 patients (aged 41 to 72 years, mean age 59.6 years, 2 women). All the patients had a substantial myocardial injury, with peak CK activity 804–10765 U/L (mean 4522 U/L). Left ventricular EF prior to BMSC transplantation was 39.4% (range 27–44%) by MRI and 40.5% (range 25–45%) by GSPECT. The number of transplanted autologous bone marrow mononuclear cells was  $0.61 \times 10^8$  –  $7.48 \times 10^8$  (mean  $3.12 \times 10^8$ ) and included mesenchymal cells, CD 34<sup>+</sup> cells and endothelial progenitors [2, 3, 18]. The percentage of CD 34<sup>+</sup> cells was 0.23–1.56 (mean 0.66%). Cell viability was 89–95% (mean 91.6 %) and there were 49–310 (mean 160.6) per  $10^5$  colony forming unit cells. Table I shows the characteristics of the OTW and SH-PC groups separately.

Bench testing in a system that mimicked a coronary artery showed a loss of cell viability of 0.8% (range 0 – 2%) following passage through the OTW catheter and 0.6% (range 0 – 1%) for the SH-PC catheter. Thus, trans-catheter passage *per se* had a negligible effect on cell viability.

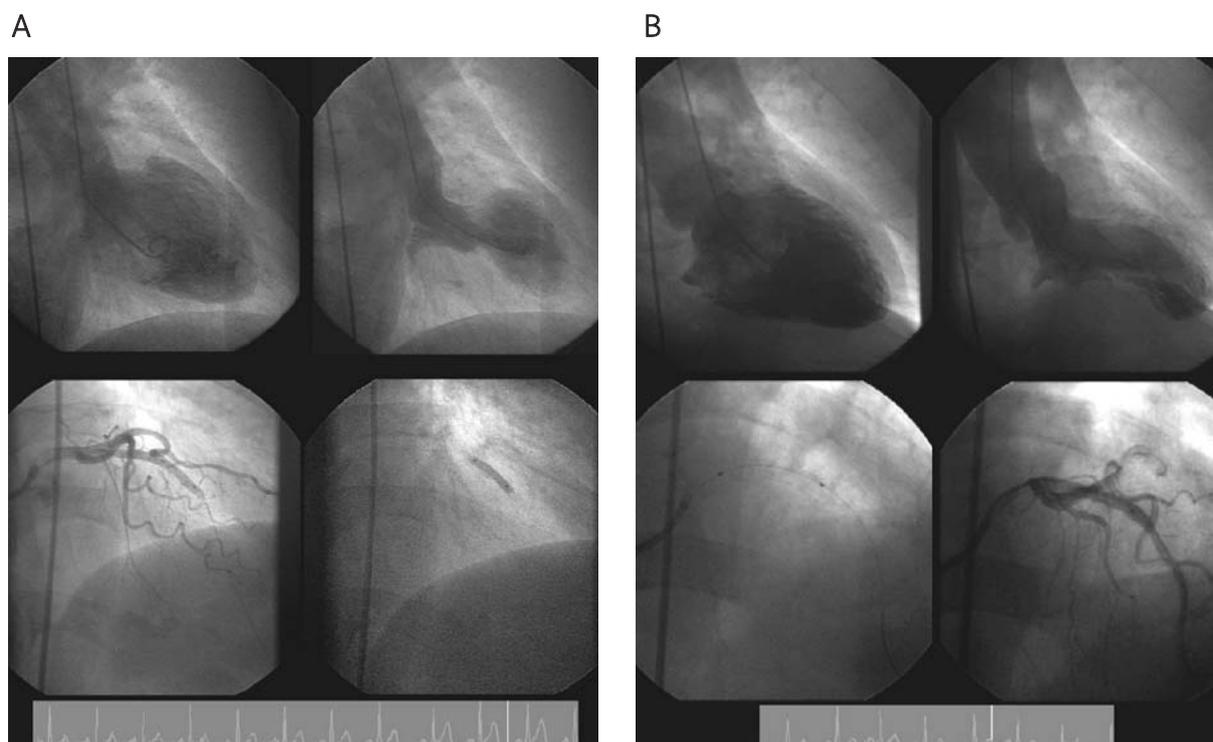
In the majority (67%) of OTW patients, cell administration time was limited by LAD occlusion

tolerance (average occlusion time of 68 sec., 81 sec. and 89 sec. for 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> occlusion). In one case (a 53-year-old man 7 days after anterior MI with peak CK 8236 U/L, EF 37%), the second OTW balloon inflation was associated with triggering of ventricular tachycardia at 47 sec.; this was preceded by anginal pain and ST-segment elevation. Maximal LAD occlusion time in the OTW group was 110 sec. In contrast with OTW cell delivery, patient tolerance of the non-occlusive SH-PC technique was excellent. With neither technique was there any post-procedural epicardial or tissue flow deterioration or troponin rise. No malignant ventricular arrhythmias were detected on Holter ECG monitoring on the first day after BMSC administration.

During clinical follow-up of 12.8 months (8–26 months) all patients were managed according to current standards. There was no death, MI or heart failure in functional class greater than NYHA II. There was no symptomatic restenosis in the infarct-related artery (LAD). However, two patients underwent coronary angiography due to angina recurrence with positive ECG stress test, and required angioplasty of the circumflex or marginal branch due to atherosclerosis progression. A pilot evaluation of left ventricular perfusion and contractility at 6 months after BMSC delivery showed  $\Delta$ EF of +4.2% (2-6) by MRI and +4.8 (2-7) by SPECT in the OTW patients, and +8.8% (5-16) by MRI and +13.8% (2-24) by SPECT in the SH-PC patients (Table I; the study not powered for statistical data evaluation). Figure 5 shows representative examples of MRI images and colour-coded SPECT images of myocardial perfusion and regional EF at baseline (prior to cell application) and 6 months after BMSC delivery.

**Table I.** Characteristics of the study groups and values of analysed parameters

Parameter	OTW group	SH-PC group
No. of patients [women]	6 [1]	5 [1]
Age [years] range	60.3 (41-68)	58.6 (53-72)
Peak CK (U/L) range	4361 (804-8617)	4717 (2279-1024)
<b>baseline</b> (5-9 days after MI)		
LVEF (GSPECT) range	41.2% (30-45)	40.3% (25-45)
LVEF (MRI) range	40.2% (29-44)	38.6% (27-43)
Mononuclear BM cells, n ( $\times 10^6$ ) range	2.99 (0.61-7.48)	3.28 (1.64-4.39)
CD 34 <sup>+</sup> , n ( $\times 10^6$ ) range	1.79 (0.30-3.44)	1.62 (0.48-4.32)
Cell viability (%) range	91.5 (89-95)	91.8 (89-95)
Cell clonogenicity (CFU-C / $10^5$ ) range	175.8 (56-310)	142.5 (49-246)
<b>at 6 months</b>		
$\Delta$ LVEF (GSPECT) range	+4.8% (2-7)	+13.8% (2-24)
$\Delta$ LVEF (MRI) range	+4.2% (2-6)	+8.8% (5-16)



**Figure 4.** Intracoronary administration of BMSC on angiography by the OTW-occlusive technique (A) and SH-PC (B). Top panels show LV gram prior to cell delivery (left – end-diastole, right – end-systole). The test injection of a contrast agent (A, bottom left) shows effective LAD in-stent occlusion. Following guide-wire removal, the central lumen of the catheter is used for cell injection, while normal flow is ceased. The ECG trace shows ST-segment elevation during cell injection. The infusion-perfusion technique (B) allows for BMSC delivery without disturbing normal coronary flow and without ECG signs or clinical symptoms of ischaemia

## Discussion

We have demonstrated the safety, feasibility and excellent tolerance of a non-occlusive endothelium-targeted delivery system employed for transcatheter transplantation of BMSC after recent MI. In contrast with the coronary-occlusive OTW technique that has been employed universally in human trials to date [6-13], cell delivery with the SH-PC catheter in our study occurs without disturbing the normal coronary flow (lack of coronary occlusion) and without any enhancement of undesired cell wash-out (lack of the *waterfall* effect of reactive hyperaemia). Thus, the infusion-perfusion technique is likely to limit the disruption of natural BMSC-endothelium interactions that are essential for downstream homing in the injury zone (Figure 1). Moreover, SH-PC delivery can facilitate cell rolling in contact with the endothelium, since cell infusion is directed towards the external layers of the undisturbed coronary flow (Figures 2, 3B). To increase the likelihood of endothelial contact following transcatheter cell passage with the SH-PC technique (multiple cell suspension exit sites), for SH-PC delivery the cells were suspended in a larger volume (50 ml) when compared

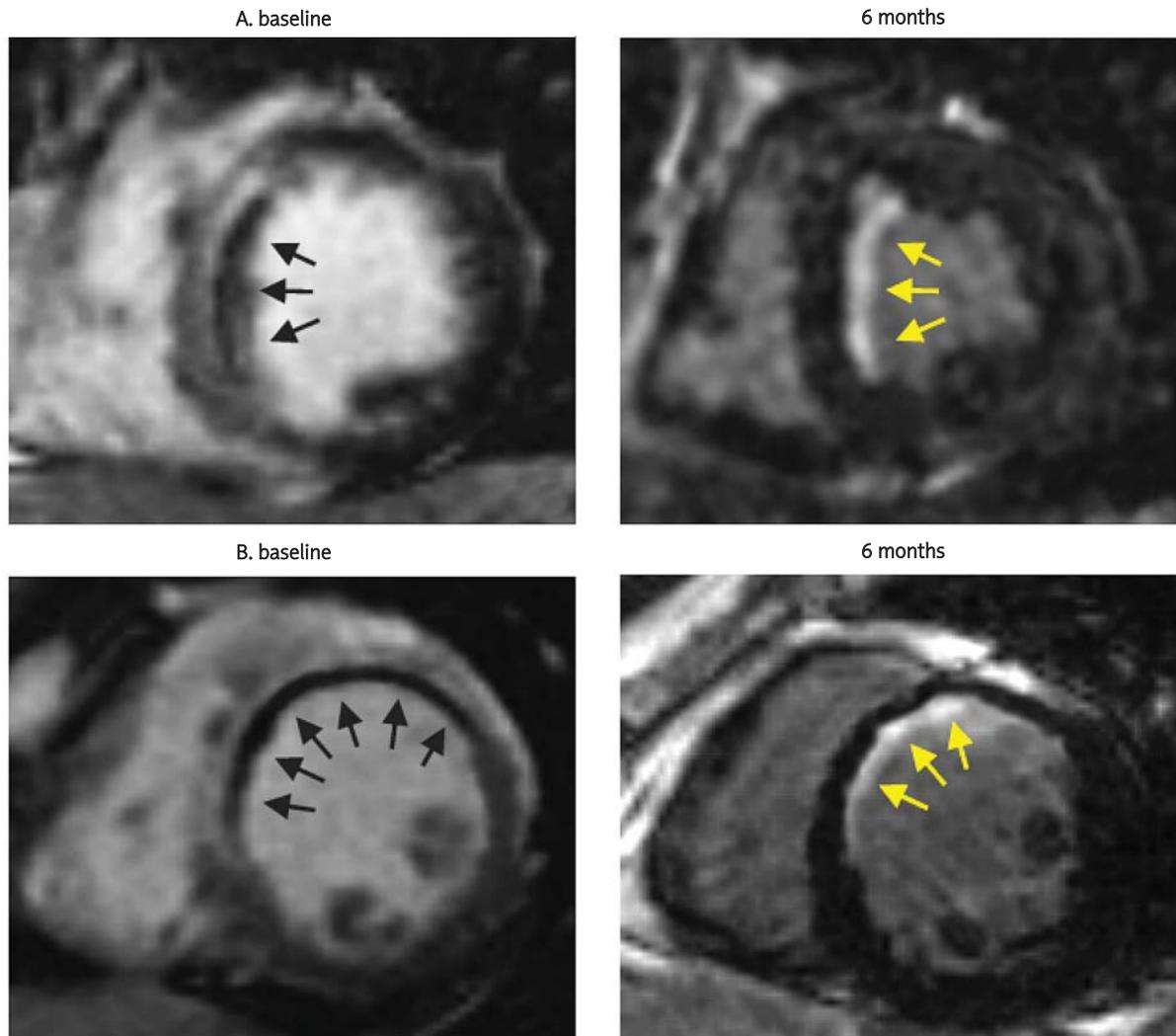
to the OTW mode (one exit site, cells suspended in 10 mL, as suggested originally by Assmus et al. [7]). Bench testing in a system that mimicked a human coronary artery, with cell concentrations matching those used *in vivo*, revealed that transcatheter passage had a negligible effect on cell viability (mean reduction of 0.8% for OTW and 0.6% for SH-PC).

The central role of the intracoronary delivery system in stem cell mediated myocardial regeneration strategies was recognised already in early experimental studies in small animals [5]. While an investigation of the intracoronary cell delivery system is clearly beyond the scope of the small animal model [5], translational human studies have focused on the issues of optimal transplantation timing, best cell type/population or cell number (unexpanded vs. expanded *ex vivo*) [3]. In contrast, the fundamental problem of optimising intracoronary stem cell delivery system in humans has not received similar attention.

The OTW technique has been adopted widely in human trials because it is readily available, familiar to most PCI operators and easy to use. Also, a common *expectation* has been that a coronary occlusion of

(usually) 120-240 sec. would be effective by allowing more time for interactions necessary for trans-endothelial migration and homing [6, 7, 11, 12]. Kuethe et al. [11] reported an average OTW-occlusion time of LAD of  $9.2 \pm 6.1$  min 'to prevent cell back-flow and to prolong

contact time for cellular migration'. Evidence indicates that in some patients already a 30 sec. balloon occlusion can be associated with epicardial flow reversal evidenced by Doppler wire measurement distal to the occlusion site [14]. The OTW LAD occlusions up to 10-minute duration



**Figure 5.** Examples of contrast magnetic resonance (gadolinium, short axis view, A and B) and gated single-photon emission computed tomographic  $^{99m}\text{Tc}$ -sestamibi (GSPECT, colour-coded polar map of regional perfusion and ejection fraction interpolated from 12 left ventricle cross-sectional slices; black=0%, pink=100%; C, D) myocardial images at baseline (5-9 days after anterior MI treated with primary PCI, left panel) and 6 months after intracoronary delivery of autologous BMSC (right panel). Images in A and C are from a patient in whom BMSC were delivered by the 'conventional' OTW technique, whereas images B and D are from a patient with SH-PC stem cell delivery. Black arrows in A and B indicate myocardial 'no-reflow' zone; yellow arrows represent the area of late enhancement (LE, scar) at 6 months. In the OTW patient (A), the extent of myocardial no-reflow correlates with LE, whereas in the SH-PC patient (B) only a part of the myocardial no-reflow zone forms the scar at 6 months. Also, note an apparently more prominent increase in the LAD-territory perfusion and regional ejection fraction in the SH-PC patient (D vs C). A potential link between the mode of stem cell delivery and the effect on the extent of myocardial damage by MRI and regional perfusion and ejection fraction by GSPECT requires further evaluation including studies of BMSC retention and long-term engraftment with both techniques

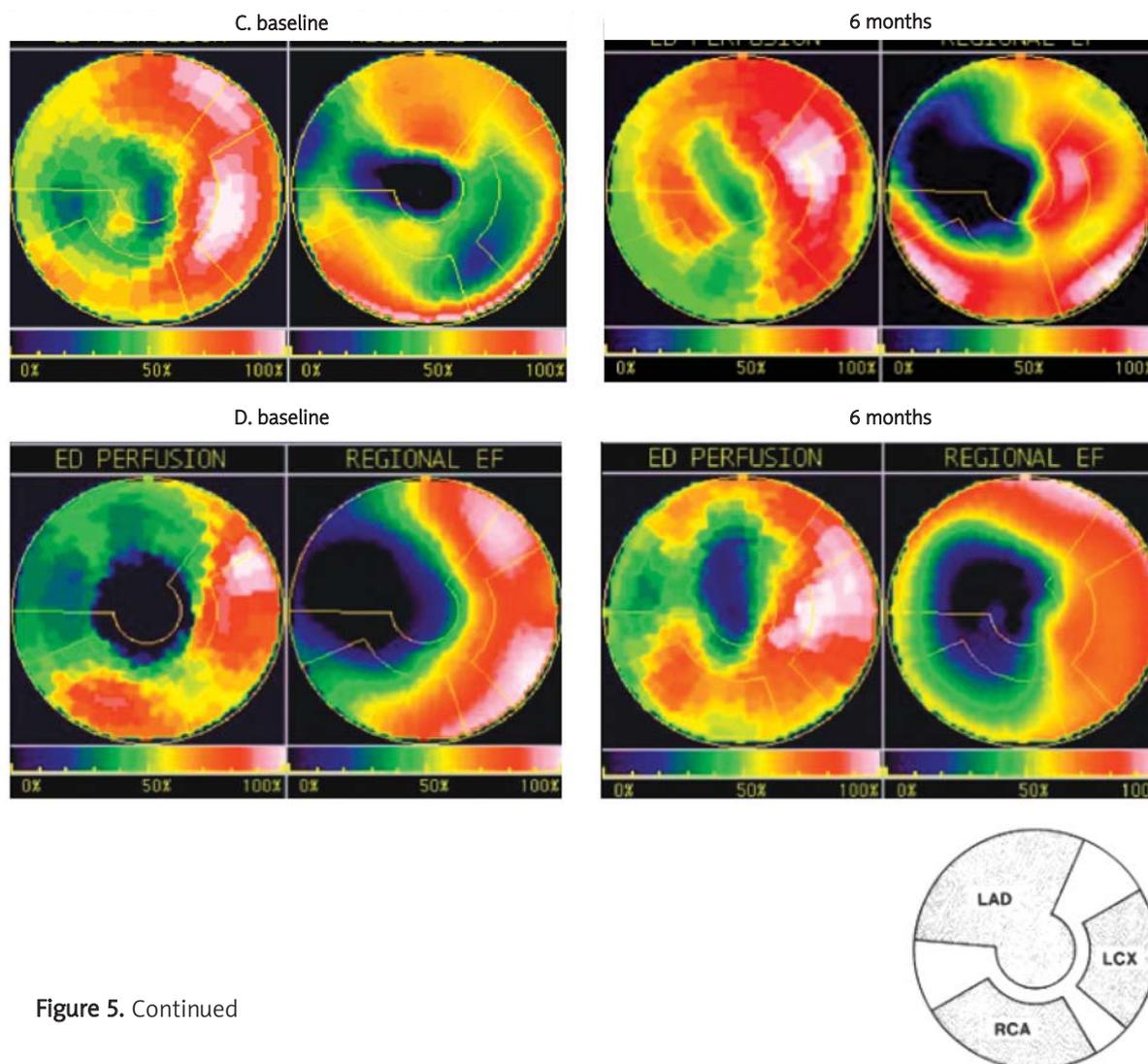


Figure 5. Continued

[6, 7, 9, 11, 12] are in contrast with our observation that cell injection time during OTW occlusion is usually limited by occlusion tolerance. Our data are consistent with prior work on coronary occlusion tolerance during PTCA [19]. In particular, average LAD occlusion tolerance in our study of patients with recent LAD-territory MI was 20-30% longer than that reported by Serruys and colleagues [19] in a study where the majority of patients had no prior MI. Moreover, the adverse provocation of ventricular tachycardia during cell delivery in an OTW patient suggests that the OTW technique may be associated with previously unreported safety concerns. This is not unexpected, since MI scar is well known to constitute an arrhythmic substrate, whereas OTW-occlusion induced ischaemia (evidenced by ST-segment elevation; see e.g. Figure 4A) can provide an arrhythmic trigger.

Cell injection through the distal tip of the OTW catheter in the centre of the vessel lumen is unlikely to

position the majority of cells adequately for endothelial rolling (*cf.* Figures 1, 3A), while the waterfall effect that follows OTW balloon deflation will further disrupt BMSC rolling and adhesion and can enhance cell wash-out rather than retention in the injury zone [15-17]. Indeed, recent evidence shows poor efficiency of OTW-mediated BMSC delivery in humans and in a large animal model of MI. For instance, in the pig model only  $2.6 \pm 0.3\%$   $^{111}\text{-Indium-oxinate}$  labelled mononuclear cells were retained in the heart one hour after OTW delivery [20]. Siminak et al. [21] used  $^{111}\text{-Indium-oxinate}$  to label  $\text{CD34}^+$  cells in man and found that only 1-11% of radioactivity was localised in the heart after 24 hours. A similar observation was made by Sousa et al. [22], who labelled unselected bone marrow mononuclear cells with  $^{99\text{m}}\text{technetium}$  ( $11 \pm 4\%$  radioactivity in the heart at 18 hours). This is consistent with  $^{18}\text{F-FDG}$  PET data indicating myocardial retention of only 1.3-2.6% of unselected bone-marrow

mononuclear cells [23] or 5.5% of CD34<sup>+</sup> cells [24] one hour after intracoronary OTW delivery. In four randomised controlled trials disclosed recently, the poor efficiency of OTW balloon-mediated intracoronary stem cell delivery in patients after recent MI is paralleled by only a modest effect (LVEF gain of 2.5% at 4 months [25]) or a lack of effect of BMSC therapy on LVEF ejection fraction at 4 months [26, 27] or 18 months [28]. One explanation for the discrepancy between the experimental evidence for the regenerative potential of BMSC in the MI border zone [3-5] and the poor efficiency of BMSC therapy in current randomised controlled trials [25-28] is the low myocardial cell retention/wash-out ratio with OTW balloon coronary occlusive delivery [20-24].

The SH-PC technique offers an attractive alternative to *conventional* OTW intracoronary stem cell delivery for the following reasons: 1. SH-PC is physiological – normal coronary circulation is maintained; 2. there is no reactive hyperaemia with doubled flow velocity and increased capillary diameter (both can reduce the probability of the cells' endothelial contact); 3. the cells are directed towards the external layers of the maintained laminar flow – this is likely to facilitate the endothelial contact required for rolling and subsequent adhesion/endothelial transmigration; 4. SH-PC delivery is safe and can be performed by every operator trained in routine angioplasty. Recent evidence that the transcatheter delivery of recombinant adenovirus via a perfusion-infusion catheter leads to a successful regional gene transfer in the animal [29] and human [30] heart further reinforces our concept of the use of the perfusion technique for regional BMSC delivery for myocardial repair. The putative advantages of the infusion-perfusion technique employed in our pilot study in man need to be further demonstrated in experiments involving quantification of myocardial BMSC retention following SH-PC coronary cell administration. Such work needs to precede the potential application of the SH-PC technique in larger clinical trials.

### Acknowledgement

Professor M. Z. Ratajczak (rationale for non-coronary occlusive, physiological stem cell delivery), Jagiellonian University Department of Transplantation.

Dr M. Krochin (patient recruitment and study execution), Jagiellonian University Dept. of Cardiac and Vascular Diseases.

Mr A. Kądziałski and Mr P. Banys (study logistics and technical support), Jagiellonian University Institute of Cardiology.

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## Przezwieńcowa transplantacja komórek macierzystych szpiku przy zastosowaniu nowej, fizjologicznej techniki perfuzyjnej. Podstawy teoretyczne i badanie pilotażowe obejmujące porównanie z konwencjonalną metodą okluzyjną u chorych po niedawnym zawale mięśnia serca

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### Streszczenie

Skuteczne dostarczenie komórek macierzystych szpiku (BMSC) w rejon uszkodzenia zawałowego jest wyjściowym warunkiem efektu klinicznego. Aktualne badania wykazują mierną skuteczność zaadaptowanej w ostatnich latach techniki okluzyjnej (*over-the-wire balloon*, OTW). Inflacje/deflacje cewnika OTW powodują *efekt wodospadu*, co może utrudniać retencję BMSC.

**Cel:** Określenie wykonalności, bezpieczeństwa i tolerancji nowej techniki perfuzyjnej z kierowaniem komórek na niezaburzone toczenie w kontakcie ze śródbłonkiem naczynia (pierwszy etap migracji do strefy uszkodzenia).

**Metodyka:** Jedenastu chorych (41–72 lata) z FW  $\leq 45\%$  6.–9. dnia po zawale serca ściany przedniej leczonym pierwotną angioplastyką wieńcową, zostało losowo przydzielonych do podania autologicznych BMSC: konwencjonalnie cewnikiem okluzyjnym OTW (3 x 3 min) albo cewnikiem perfuzyjnym z otworami bocznymi (SH-PC).

**Wyniki:** Chorzy grupy OTW i SH-PC byli podobni pod względem wielkości uszkodzenia zawałowego (średnie szczytowe CK 4361 vs 4717 U/L; FW 41,2% vs 40,3%), liczby podanych komórek mononuklearnych ( $0,61\text{--}7,48 \times 10^8$ , średnio  $2,99 \times 10^8$  vs  $1,64\text{--}4,39 \times 10^8$  średnio  $3,28 \times 10^8$ ), liczby komórek CD 34<sup>+</sup> ( $1,79 \times 10^6$  vs  $1,62 \times 10^6$ ), oraz żywotności (91,5% vs 91,8%) i klonogenności komórek. U 67% chorych OTW (natomiast u żadnego z chorych SH-PC) wystąpił ból stenokardialny z uniesieniem odcinka ST (ponadto 1 epizod częstoskurczu komorowego), ograniczając tolerancję okluzji tętnicy dozawałowej do 50–110 s. Po 6 mies. stwierdzono  $\Delta$ FW w grupie OTW vs SH-PC: +4,2% (2–6) vs +8,8% (5–16) w rezonansie magnetycznym i +4,8% (2–7) vs +13,8% (2–24) w SPECT (badanie pilotażowe, bez liczebności dostatecznej dla dokonania analizy statystycznej).

**Wnioski:** Przezwieńcowa podawanie BMSC przy zastosowaniu techniki perfuzyjnej SH-PC jest wykonalne, bezpiecznie i bardzo dobrze tolerowane. Konieczne są dalsze badania w celu ustalenia, czy teoretyczne zalety transplantacji komórek w sposób fizjologiczny przekładają się na zwiększony odsetek ich zadomowienia w strefie uszkodzenia zawałowego.

**Słowa kluczowe:** komórki macierzyste szpiku, terapia regeneracyjna mięśnia serca, fizjologiczna przezwieńcowa transplantacja komórek macierzystych, transplantacja kierowana na toczenie śródbłonkowe, leczenie komórkami macierzystymi

Kardiol Pol 2006; 64: 489-498

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**Praca wpłynęła:** 21.12.2005. **Zaakceptowana do druku:** 15.02.2006

Praca była częściowo finansowana przez grant KBN #PBZ-KBN-099/P05/2003.

Fragmety pracy były prezentowane na Third Annual Meeting of the European Stem Cell Therapeutics Excellence Centre (STEC 2005) oraz na Transcatheter Cardiovascular Therapeutics (TCT 2005).