Myocardial Assistance by Grafting a New Bioartificial Upgraded Myocardium (MAGNUM Trial): Clinical Feasibility Study

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Background. **Cell transplantation for the regeneration of ischemic myocardium is limited by poor graft viability and low cell retention. In ischemic cardiomyopathy, the extracellular matrix is deeply altered; therefore, it could be important to associate a procedure aiming at regenerating myocardial cells and restoring the extracellular matrix function. We evaluated the feasibility and safety of intrainfarct cell therapy associated with a cell-seeded collagen scaffold grafted onto infarcted ventricles.**

Methods. **In 20 consecutive patients presenting with left ventricular postischemic myocardial scars and indication for coronary artery bypass graft surgery, bone marrow cells were implanted during surgery. In the last 10 patients, we added a collagen matrix seeded with bone marrow cells, placed onto the scar.**

Results. **There was no mortality and any related adverse events (follow-up 10 ± 3.5 months). New York Heart Association functional class improved in both groups from 2.3 ± 0.5 to 1.3 ± 0.5 (matrix, $p = 0.0002$) versus 2.4 ± 0.5 to 1.5 ± 0.5 (no matrix, $p = 0.001$). Left ventricular end-diastolic volume evolved from 142.4 ± 24.5 mL to 112.9 ± 27.3 mL (matrix, $p = 0.02$) versus 138.9 ± 36.1 mL to 148.7 ± 41 mL (no matrix, $p = 0.57$), left ventricular filling deceleration time improved significantly in the matrix group from 162 ± 7 ms to 198 ± 9 ms ($p = 0.01$) versus the no-matrix group (from 159 ± 5 ms to 167 ± 8 ms, $p = 0.07$). Scar area thickness progressed from 6 ± 1.4 to 9 mm ± 1.1 mm (matrix, $p = 0.005$) versus 5 ± 1.5 mm to 6 ± 0.8 mm (no matrix, $p = 0.09$). Ejection fraction improved in both groups, from 25.3% ± 7.3% to 32% ± 5.4% (matrix, $p = 0.03$) versus 27.2% ± 6.9% to 34.6% ± 7.3% (no matrix, $p = 0.031$).**

Conclusions. **This tissue-engineered approach is feasible and safe and appears to improve the efficiency of cellular cardiomyoplasty. The cell-seeded collagen matrix increases the thickness of the infarct scar with viable tissue and helps to normalize cardiac wall stress in injured regions, thus limiting ventricular remodeling and improving diastolic function.**

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Resident stem cells have been identified in the heart [1–5] as in many other organs, some of them with recognized proliferative activity, as skin [6] and blood [7] or others more static such as central nervous system components [8]. Cardiac stem cells have been isolated from human and murine hearts and have been characterized [9]. However, the evolution of patients makes it evident that, even in presence of native stem cells, the myocardium self-renewal is, at least, an insufficient mechanism to resolve the heart damage. In addition, migration of stem cells from extracardiac source is limited.

In contrast with some nonmammalian animals [10, 11], in humans, regeneration is reduced in favor of reparation and efficient wound healing with scar formation. This resolution should be a complex and multifactor process that includes not only muscle proliferation but also neoangiogenesis and electric and mechanical stabilization. A defective resolution results in temporary compensatory mechanisms that at some moment start a cascade that progresses to heart failure [12].

The objective of cellular cardiomyoplasty by stem cell implantation is to regenerate the myocardium [13–15]. Although some clinical studies showed functional benefits after stem cell therapy [16–18], until now isolated cellular cardiomyoplasty failed to clearly demonstrate improvements of ventricular function [19–21]. The main problem appears to be that cardiac effects of stem cell transplantation are limited by poor graft viability and by low cell retention into the treated area [22]. In ischemic disease, both the contracting cells (cardiomyocytes) and the extracellular matrix are pathologically modified. Therefore, it could be important to associate a procedure aiming at regenerating both myocardial cells and the extracellular matrix [23]. Preclinical investigations using tissue-engineering technologies showed that this approach may contribute to improve the efficiency of cellular therapy for organ regeneration [24–27]. Associating a

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cell-seeded matrix with cellular cardiomyoplasty in experimental ischemic hearts, we have demonstrated functional benefits over isolated cell therapy or matrix alone [28]. Other investigations demonstrated that collagen matrices enhance survival of transplanted cells and contribute to functional improvements and to the limitation of postischemic ventricular remodeling [29].

The goal of this clinical feasibility study was to evaluate the potential of a biodegradable three-dimensional collagen type I matrix seeded with bone marrow cells (BMC) and grafted onto the infarcted ventricle to support and regenerate postischemic lesions. Two groups of patients presenting with ischemic heart disease were compared: the first group was treated with intrainfarct injection of BMC; the second group was treated with intrainfarct injection of BMC associated with the implantation of a cell-loaded matrix placed onto the infarct scar.

Patients and Methods

Study Design

The study was a nonrandomized, controlled phase I clinical trial. Eligibility for inclusion was based on (1) systolic left ventricular (LV) dysfunction, as reflected by an echocardiographic LV ejection fraction (LVEF) of 35% or less; (2) a history of myocardial infarction with a residual akinetic and nonviable scar; and (3) an indication for concomitant single off-pump coronary artery bypass graft surgery (OP-CABG). These patients were free of angina symptoms, there was no indication of revascularization of other territories due to poor targets. The preoperative myocardial viability was assessed using thallium/sestamibi gated myocardial single-photon emission computed tomography (SPECT). Baseline evaluation was assessed within one week before surgery. We excluded patients who had cardiogenic shock or end-stage congestive heart failure, history of leukopenia or thrombocytopenia, evidence for malignant disease or terminal disease, patients under treatment with steroids or oncology drugs or immunologic suppression, renal insufficiency (serum creatinine >2.5 mg/dL) or known hepatic insufficiency, and stroke or major surgery during the last month.

Fig 1. Macroscopic view of the collagen type I, three-dimensional biodegradable matrix used for myocardial repair (size: 7 × 5 × 0.6 cm).

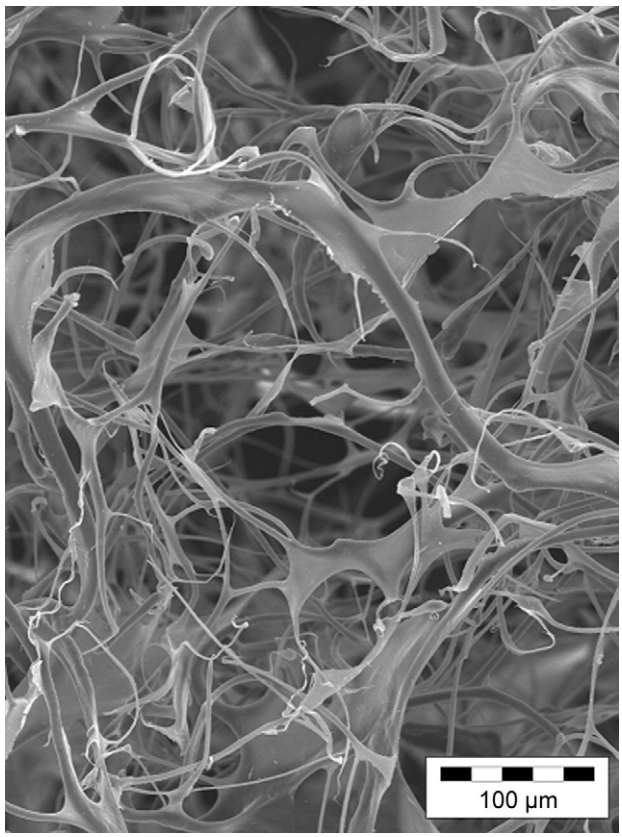

Fig 2. This image (scanning electron microscopy) shows the three-dimensional arrangement of collagen fibers of the matrix used to be seeded with bone marrow cells and grafted onto the left ventricular infarcted wall.

The procedures were performed in the Hospital Interzonal "Presidente Perón" of Avellaneda (Buenos Aires, Argentina) in collaboration with the surgical team of the Georges Pompidou European Hospital (Paris, France). The Institutional Review Board of the Hospital Interzonal "Presidente Perón" of Avellaneda approved this study, and informed written consent stating the experimental nature of the study was obtained from each patient before the procedure.

Patient Selection and Group Assignment

Two groups of patients were created. The first group (BMC) included 10 successive ischemic patients with indication for CABG and stem cell therapy; these 10 patients were the last of a series of 33 patients treated between January 2003 and May 2005 in the Department of

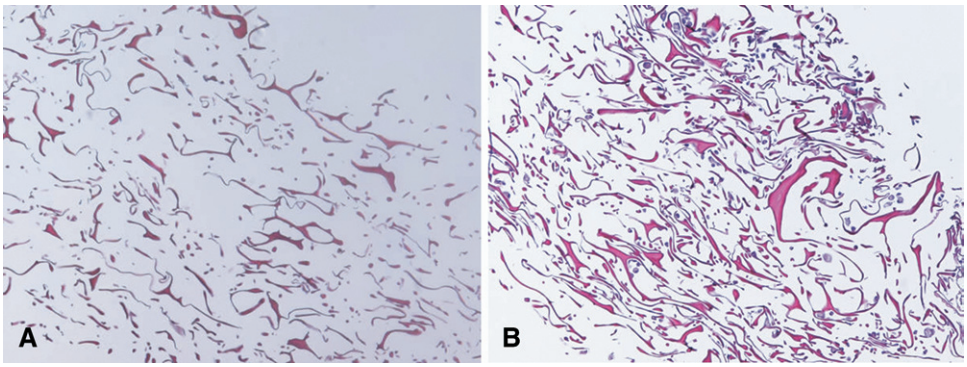

Fig 3. (A) Histologic study of the original collagen type I matrix. (Hematoxylin-eosin staining; original magnification ×100.) (B) Histologic study of the collagen matrix after cells seeding. (Hematoxylin-eosin staining; original magnification ×100.)

Cardiovascular Surgery of the Avellaneda Hospital (Argentina). The second group (BMC + matrix) included 10 successive ischemic patients with indication for CABG and stem cell therapy; in these 10 patients a cell-seeded collagen matrix was added to the previous treatment and were operated on since May 2005 in the same institution.

Bone Marrow Cells Isolation and Preparation

Four hours before the cardiac surgical procedure, bone marrow was aspirated from the ilium bone and processed to obtain mononuclear bone marrow cells. The cell suspension was loaded on Ficoll-Paque density gradient (specific gravity = 1.077 [Amersham Biosciences, Arlington Heights, Illinois]), and centrifuged for 20 minutes at 2,000*g*. Bone marrow cells were isolated from the layer between the Ficoll-Paque reagent and blond plasma, and washed two times in phosphate-buffered saline (PBS [Sigma, St. Louis, Missouri]). A suspension of mononuclear BMC was obtained (CD34+ 8%, AC133+ 3%) and diluted in autologous patient serum to perform intramyocardial injections and matrix seeding.

Collagen Matrix Preparation

Collagen matrix was prepared from a commercially available CE Mark collagen kit (Pangen 2; Urgo Laboratory, Chenove, France). This three-dimensional biodegradable matrix (size: 5 × 7 × 0.6 cm) was manufactured using a lyophilized nondenatured, native type I collagen (Fig 1). The matrix pores measured 50 to 100 μm (Fig 2). In the operating room, matrices were placed into a Petri dish; afterward, the cell suspension was seeded onto each matrix. To promote a regular distribution of BMC into the matrix pores, Petri dishes containing the collagen matrices were shaken continuously for 10 minutes at 120*g* using an Orbital Shaker (Stuart Scientific, Stone, Staffordshire, United Kingdom [Fig 3]). This procedure can be also performed using centrifugation (10 minutes at 900*g*) of the matrix and cells.

Surgical Procedures

After sternotomy, a single OP-CABG was performed using left interior mammary artery. At the end of surgery, the intrainfarct implantation of the autologous BMC was performed (250 ± 28 million cells), within and principally around the infarct, with a 25G × 40 mm retrobulbar ophthalmic needle, in all patients.

In the last 10 patients, a three-dimensional type I collagen matrix (size: 7 × 5 × 0.6 cm) seeded with the same number of BMC (250 ± 28 million cells) was added on the scarred area, covering the infarct and peri-infarct zones. It was fixed onto the epicardium by 6 single PDS sutures (6-0) and covered by a second noncellularized matrix (Fig 4). The number of BMC injected into the heart

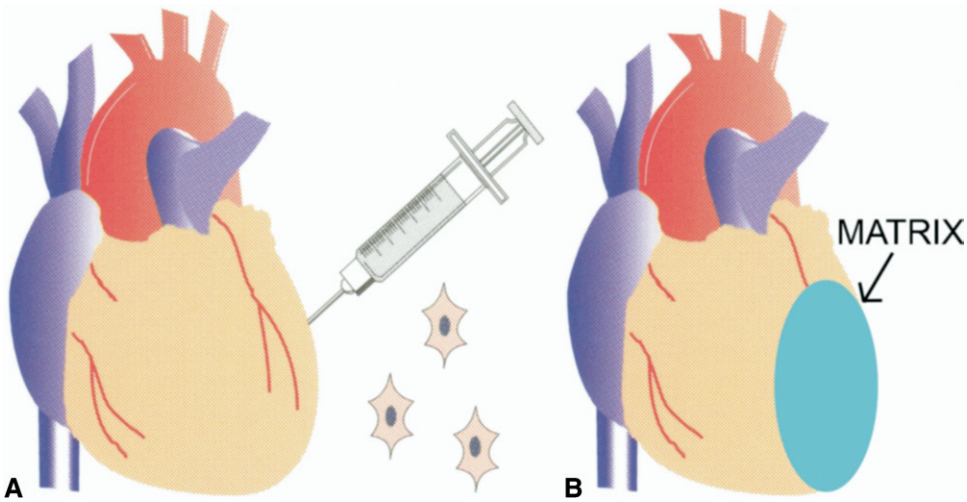

Fig 4. Surgical procedure associating the intrainfarct implantation of stem cells (A) followed by the fixation of a cell-seeded matrix onto the epicardial surface (B).

was selected according with our previous successful clinical experience with skeletal myoblast transplantation [30].

Assessment of Outcomes

The primary endpoints were feasibility and safety. Feasibility referred to the ability to perform bone marrow aspiration, BMC injections, matrix seeding, and surgical matrix implantation onto the epicardium.

We assessed safety on the basis of the following: development of major adverse cardiac events (death, new myocardial infarction, admittance to hospital due to aggravation of ischaemia, or heart failure); clinical status including dyspnea, chest pain; and detection of ventricular arrhythmias by 24-hour Holter electrocardiographic monitoring study.

After surgery, cardiac rhythm was monitored with continuous in-hospital telemetry. All patients underwent follow-up visits, 24-hour Holter recordings, and echocardiograms before hospital discharge at 1, 3, and 6 months, and at the end of follow-up.

The secondary endpoint was efficacy, which was primarily assessed by two-dimensional echocardiography. Global LVEF (%) was calculated from measurements of LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV; both in mL) using the biplane Simpson's rule, as ([LVEDV − LVESV]/LVEDV) × 100. Regional contractile function was assessed semiquantitatively after division of the left ventricle into 16 segments, as recommended by the American Society of Echocardiography [31]. Care was taken to optimize endocardial visualization on three parasternal short-axis views of the left ventricle (at the base, mid-ventricular level, and apex) and apical two-, three-, and four-chamber views. Segmental thickening of each segment was then visually evaluated and graded as dyskinetic, akinetic, severely hypokinetic, moderately hypokinetic, or normal. This assessment was performed within 1 week before surgery, not during episodes of cardiac failure, and at rest, before hospital discharge and at 3 months and at the end of follow-up. Echocardiographic measurement assessed changes in global and regional systolic function as well as in diastolic function. We made conventional Doppler measurements of early and late diastolic transmitral flow, the ratio between the two, and deceleration time. In addition to measurements of systolic and diastolic LV function, serial changes in LV segmental thickening were evaluated preoperatively and at the end of follow-up by echocardiography and SPECT Tc^{99m} sestamibi imaging. Image analysis was performed by two investigators, one of whom was blinded to the timing of echocardiography, and at the sites of cell injections and matrix implantation.

Statistics

Results were analyzed and reported as percentage or mean ± SD. The Student *t* test was used to compare the groups. A value of p less than 0.05 was considered to be statistically significant.

Table 1. Baseline Characteristics of Patients Enrolled in the Study

	Matrix Group (n = 10)	No-Matrix Group (n = 10)
Age[a] (years)	52.6	56.8
Male:female	10:0	8:2
Infarcted related artery (LAD:LCx:RCA)	7:3:0	8:2:0
LVEF[a] (%)	25.3 ± 7.3	27.2 ± 6.9
Body surface area (m^2)	1.83 ± 0.09	1.79 ± 0.08
NYHA class (II-III-IV)	7:3:0	6:4:0
Risk factors		
Hypertension	6	5
Diabetes mellitus	4	3
Hypercholesterolemia	6	7
Current cigarette smoking	4	6
Medication		
Aspirin	10	10
Statine	7	8
Beta-blocker	7	7
ACE inhibitor/AT-II receptor blocker	9	10

[a] Mean (SD).

Data are number of patients unless otherwise indicated.

ACE = angiotensin-converting enzyme; AT = angiotensin; LAD = left anterior descending artery; LCx = left circumflex artery; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RCA = right coronary artery.

Results

In this phase I nonrandomized trial, after consideration of inclusion and exclusion criteria, we enrolled 20 consecutive patients (90% male) presenting with chronic ischemic heart disease. The age of the infarcts was 8.2 ± 3.5 months (range, 3 to 25). The baseline characteristics were comparable in both groups (Table 1).

Bone marrow was aspirated from the posterior iliac crest during a brief general anesthesia with midazolam and etomidate; no bleeding complications at the harvest site were noted. On average, 200 to 250 mL were obtained for the no-matrix group and 350 to 400 mL for the matrix group. The increased bone marrow volume obtained for the matrix group patients was used to inject 50% of BMC into the infarct and 50% to be seeded into the matrix.

After sternotomy, a single OP-CABG was successfully performed in all patients, using the left interior mammary artery. At the end of surgery, the intrainfarct implantation of the autologous BMC (250 ± 28 million cells) was performed into well-exposed LV ischemic areas, permitting 12 ± 3 injections points within and around the infarct. Afterward, the cell-seeded matrix was positioned over the infarct and peri-infarct zones and surgically fixed (Fig 5). A second noncellular matrix was used to cover this area.

All patients had an uneventful recovery and were discharged from the intensive care unit 3.4 ± 2.6 days after surgery. Patients were discharged from the hospital at 11 ± 4 postoperative days. At a mean follow-up of 10 ±

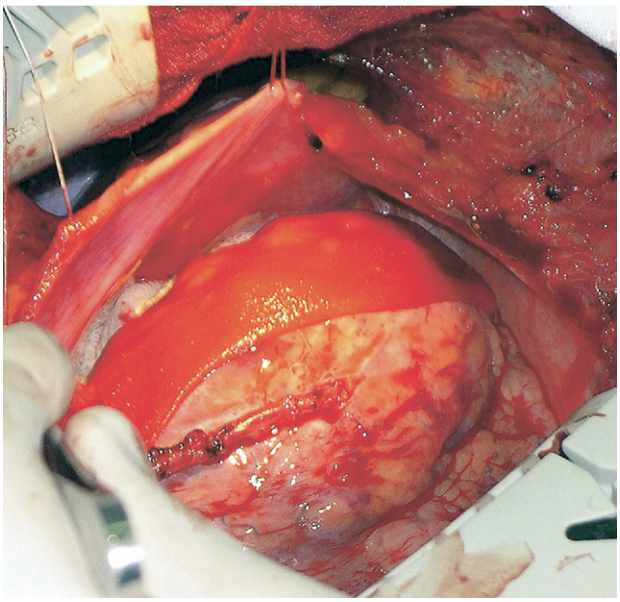

Fig 5. Clinical case showing the bone marrow cell–seeded collagen matrix grafted onto the heart, immediately after coronary artery bypass graft surgery and intrainfarct cell therapy.

3.5 months, without mortality and any related adverse events, no malignant cardiac arrhythmias were reported. No patient was lost to follow-up.

There were no differences between groups with respect to the number of premature ventricular complexes per hour and the occurrence of nonsustained ventricular tachycardias by Holter monitoring at 6 weeks, 3 months, 6 months, and at the end of follow-up. No sustained ventricular tachycardias was observed in either group.

New York Heart Association functional class improved in both groups from 2.3 ± 0.5 to 1.3 ± 0.5 (matrix, $p = 0.0002$) versus 2.4 ± 0.5 to 1.5 ± 0.5 (no matrix, $p = 0.001$).

Echocardiographic studies demonstrated that LVEF was comparable at baseline in both groups and that LVEF significantly increased in both groups at 10 ± 3.5 months of follow-up. There were no statistically significant differences between the treatment groups at baseline or at 10 ± 3.5 months of follow-up (Table 2).

Significant differences were observed at long term in the matrix-treated group concerning postischemic remodeling: LVEDV evolved from 142.4 ± 24.5 mL to 112.9 ± 27.3 mL (matrix, $p = 0.02$) versus 138.9 ± 36.1 mL to 148.7 ± 41 mL (no matrix, $p = 0.57$; Table 2).

Deceleration time improved in the matrix group from 162 ± 7 ms to 198 ± 9 ms ($p = 0.01$), but not enough in the no-matrix group (from 159 ± 5 ms to 167 ± 8 ms, $p = 0.07$). Scar area thickness progress from 6 ± 1.4 mm to 9 ± 1.1 mm (matrix, $p = 0.005$) versus 5 ± 1.5 mm to 6 ± 0.8 mm (no matrix, $p = 0.09$).

Blind radioisotopic analysis showed that 58% ± 9% of the cell-implanted segments versus 62% ± 5% of the cell-plus-matrix–treated segments improved their kinetics and viability ($p = 0.06$; Table 3, Fig 6).

Table 2. Myocardial Function Variables Assessed by Echocardiography

	Therapy Stratum		
	Matrix Group	BMC Group	*p* Value[a]
Ejection fraction			
Baseline (1 week before CABG) (%)	25.3 ± 7.3	27.2 ± 6.9	NS
10 ± 3.5 months (%)	32 ± 5.4	34.6 ± 7.3	NS
p value[b]	0.03	0.031	
Δ ejection fraction (% points)	6.7 ± 5.3	7.4 ± 7.5	NS
LVEDV			
Baseline (1 week before CABG) (%)	142.4 ± 24.5	138.9 ± 36.1	NS
10 ± 3.5 months (%)	112.9 ± 27.3	148.7 ± 41	0.033
p value[b]	0.02	NS	
Δ LVEDV (mL)	−29.5 ± 12.3	9.8 ± 12.1	<0.01
LVESV			
Baseline (1 week before CABG) (%)	117.8 ± 24.5	113.5 ± 33.3	NS
10 ± 3.5 months (%)	77.7 ± 23.5	99.1 ± 36.3	NS
p value[b]	0.001	NS	
Δ LVESV (mL)	−40.1 ± 10.1	−14.4 ± 14.9	0.003

[a] Between treatment groups. [b] Between baseline (1 week before CABG) and 10 ± 3.5 months follow-up by echocardiography.

Values represent mean ± SD.

BMC = bone marrow cell; CABG = coronary artery bypass graft surgery; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; NS = not significant.

Comment

This study attempts to demonstrate the feasibility and safety of simultaneous intramyocardial injection of BMC and fixation of a BMC-seeded matrix onto the epicardium of infarcted ventricles. The cardiac connective tissue is mainly composed of collagen, with smaller

Table 3. Single-Photon Emission Computed Tomography Radioisotopic Analysis of Myocardial Viability and Regional Left Ventricular Contractility in Bone Marrow Cell (BMC) Treated Patients (n = 10) and BMC Plus Matrix Treated Patients (n = 10)

Variable	Baseline	10 Months	*p* Value[a]
Nonviable segments			
BMC	74 ± 5.1	31 ± 2.4	0.001
BMC + matrix	76 ± 3.4	29 ± 3.1	0.001
Recuperated segments			
BMC		43 ± 3.7 (58% ± 9%)	
BMC + matrix		47 ± 3.2 (62% ± 5%)	

[a] Between baseline (1 week before CABG) and 10 ± 3.5 months follow-up; BMC group versus BMC + matrix-treated group ($p = 0.06$).

Values represent mean ± SD.

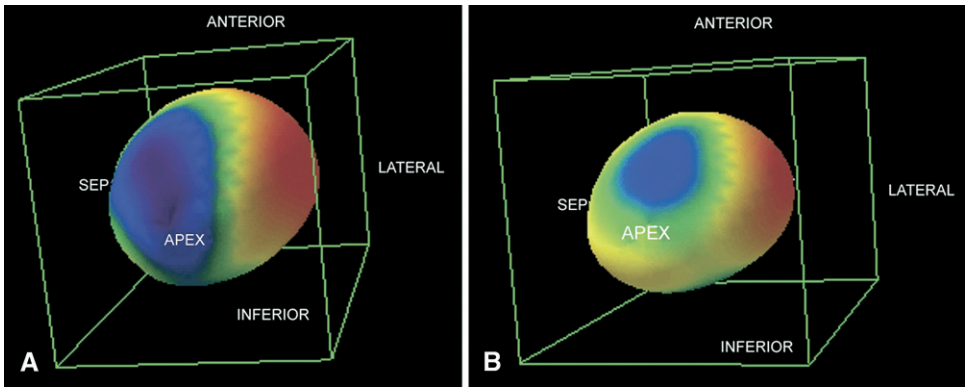

Fig 6. (A) Preoperative assessment of myocardial perfusion using single-photon emission computed tomography Tc^{99m} sestamibi imaging. The left ventricular anterolateroapical infarcted area is stained in blue (three-dimensional representation). (B) At 6 months' follow-up, the patient treated with stem cells associated with a cell-seeded collagen matrix shows a 62% reduction of the infarcted area (blue stain).

amounts of elastin, laminin, and fibronectin. There are two main types of collagen fibers in the normal adult heart, types I and III, produced by fibroblasts and myofibroblasts. Experimental observations have shown that in the process of ischemic heart disease, the myocardial extracellular matrix is deeply altered, the reserve of collagen type I, which is responsible for the structural support, can decrease, down from 80% to 40% after infarction [32]. Collagen fibers provide structural support and give the heart properties that include stiffness and resistance to deformation. In addition, they have shown an important role as a link between contractile elements of adjacent myocytes, carrying some information useful for cell function [23].

We designed this nonrandomized trial involving ischemic patients in which the first 10 were treated with BMC therapy and the next 10 patients were treated with a combined approach of BMC implant and fixation of a BMC-seeded collagen scaffold onto the epicardium. Our experimental studies [28] and others [24, 29] suggest that this combined approach may offer further benefits with respect to cell therapy alone. Thus, we tested whether these experimental procedures could be clinically upgraded so as to make them compatible with human use.

There were no perioperative complications related to bone marrow aspiration, BMC injections, or matrix seeding, and cellularized matrix surgical implantation onto the epicardium.

The number of BMC obtained by crest iliac aspiration was enough for both treatments. The cell matrix seeding procedures were easily carried out. After the OP-CABG and BMC intramyocardial injections, the cellularized matrix was placed in a few minutes onto the infarcted area without any technical problem.

The data of the present study demonstrate the feasibility of this combined approach in humans and provide a basis for ongoing studies and future developments. The presented data suggest that this therapeutic approach is safe; specifically, there was no evidence for an increased rate of proarrhythmic effects. In fact, there were no difference between both groups with respect of the number of premature ventricular complexes per hour and the occurrence of nonsustained ventricular tachycardias by Holter monitoring during follow-up. No sustained ventricular tachycardia was observed in either group.

Our phase I clinical study was not designed to assess efficacy of this combined treatment. In our opinion, the enhanced recovery of LV function must be considered with caution. In fact, the small number of patients analyzed does not allow us to draw definitive conclusions, and the improvement in symptoms and LVEF may also reflect efficacious CABG revascularization. Nevertheless, results suggest that this combined approach has an additional beneficial effect on LV remodelling when compared with cell therapy alone; the interaction effect of stem cells associated with the matrix appears to make heart repair more efficient.

The underlying mechanisms by which BMC-seeded matrix promote functional recovery after myocardial infarction are not clearly elucidated, but data derived from animal experimentations let us suppose that the use of a cellularized collagen matrix favors intramyocardial cell retention and creates a microatmosphere that promotes cell survival [24–29]. The enhanced recovery of LV function may be due to a significant reduction in the extent and magnitude of regional LV dysfunction between the infarct and peri-infarct areas. These cell-seeded biodegradable collagen scaffolds may be able to provide structural integrity within the body, and eventually it will break down, leaving the newly formed tissue that will take over the mechanical load; in this way the matrix seems to help normalize cardiac wall stress in injured regions [33–38]. Interestingly, we found the thickness of the infarcted wall to be significantly greater in the cell-seeded matrix group than in the cell therapy group. Such a finding suggests that the seeded grafts may improve cardiac function by minimizing adverse ventricular remodeling or wall thinning. A passive girdling effect of the cell-seeded collagen matrix generating a reduction of the ventricular wall stress and improving strain distribution and infarct scar elasticity could explain the functional benefits observed in the matrix group patients.

The reduction of the scar area assessed by radioisotopic studies (Fig 6) suggests that fibrotic tissue was replaced by living cells, resulting in improved myocardium elastic properties and compliance. This fact may explain the improvements in the diastolic filling time. In addition, no restrictive effects were observed in the treated areas; the collagen matrix (5 $\times$ 7 cm) only partially covers the pathologically dilated ventricles. It is

important to remark that this resorbable collagen matrix (Pangen) has high hemostatic capacity and is frequently indicated and used in our hospital and in other European centers as compresses for local hemostasis during cardiothoracic and abdominal surgical operations, when control of bleeding by ligaturing or other conventional means is ineffective or impractical. In cardiac use, long-term follow-up never demonstrated a restrictive process with impairment of diastolic function (ie, constrictive pericarditis).

Recent publications have highlighted the potential of BMC to promote paracrine effects in ischemic tissues (eg, secretion of angiogenic factors), and suggest that paracrine signaling, rather than cell incorporation, promotes functional recovery [39–42]. Transplanted BMC and matrix seeded cells may release growth factors that may preserve extracellular matrix and promote the recruitment of cardiac stem cells that would provide a new endogenous pool of contractile cells. In addition, transdifferentiation of BMC-derived hemopoietic stem cells to cardiomyocytes and potential cardiomyogenic properties of mesenchymal BMC can account for the beneficial effects of this new therapeutic procedure [43–46].

Limitations

A first limitation pertains to the semiquantitative approach used for assessing LV segmental function. Although two-dimensional echocardiography has become the technique of choice for direct visualization of endocardial motion and wall thickening, this assessment may still be confounded by contractile changes of the adjacent segments, as long as myocardial strain is not directly measured. The improved kinetics of the revascularized segments could therefore have skewed the grading of transplanted areas. We have used the LVEF as an index of systolic function, but one of the limitations of the LVEF is its load dependence, which confounds accurate assessment of LV systolic function. An alternative, strain and strain-rate images, could allow quantitative assessment of regional myocardial wall motion and may be more sensitive to regional myocardial ischemia.

The second limitation was the association with a CABG; thus, functional improvements can not be conclusively related to the cells and matrix. Another limitation is that this was a nonrandomized trial. In spite of this choice, our inclusion and exclusion criteria resulted in the enrollment of a relatively homogeneous patient population.

In conclusion, our data suggest that simultaneous autologous intramyocardial injection of mononuclear BMC and fixation of a cell-seeded matrix onto the epicardium is a feasible and safe procedure. This matrix seems to increase the thickness of the infarct scar with viable tissues and helps to normalize cardiac wall stress in injured regions. However, large randomized trials are required to show a beneficial effect not only on systolic and diastolic LV function, but also on clinical endpoints. Cardiac tissue engineering is emerging as a new therapeutic tool and extends even more the amazing possibilities of cell therapies in cardiology, becoming a promising way for the creation of a "bioartificial myocardium."

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