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Original article

Coronary Flow Reserve and Ventricular Function Following Regenerative Treatment in Patients With Revascularized Acute Anterior Myocardial Infarction

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A B S T R A C T

Introduction and objectives: Bone marrow stem cells may reconstruct infarcted myocardium through distinct mechanisms. However, little is known on the relationship between recovery of muscular and microvascular function after regenerative treatments. Our objective was to analyze the relationship between changes in left ventricular and microvascular function in patients with anterior acute myocardial infarction receiving regenerative treatment.

Methods: We performed a pooled analysis of 2 clinical trials and a pilot study evaluating stem cell therapy in 88 patients with revascularized acute anterior myocardial infarction. Coronary flow reserve and left ventricular function were analyzed with identical methods in all patients. Patients treated with regenerative treatment received intracoronary bone–marrow-derived mononuclear cell transplant (n = 40), subcutaneous administration of granulocyte colony-stimulating factor (n = 14), or a combination of both (n = 10). A control group of 24 patients was treated with conventional revascularization.

Results: Mean ejection fraction increased from 37% ± 8% to 46% ± 12%, ($P < .05$). Mean coronary flow reserve increased from 1.6 ± 0.5 to 2.3 ± 0.9 ($P < .05$). However, there was no correlation between parameters of left ventricular function and microvascular parameters at follow-up.

Conclusions: Left ventricular function shows favorable changes after regenerative treatment of infarction. However, no correlation was found between changes in microvascular and myocardial function after regenerative therapy.

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Reserva coronaria y función ventricular izquierda tras la terapia regenerativa en pacientes con infarto anterior agudo revascularizado

Palabras clave:
Infarto agudo de miocardio
Células madre
Reserva coronaria

R E S U M E N

Introducción y objetivos: Las células madre de médula ósea pueden regenerar el miocardio infartado por distintos mecanismos. La relación entre la recuperación de la función muscular y microvascular después del tratamiento regenerativo ha sido poco estudiada. El objetivo es analizar la relación entre los cambios en función ventricular y función microvascular en pacientes con infarto agudo que reciben la terapia.

Métodos: Se analizó a 88 pacientes con infarto anterior revascularizado incluidos en 2 ensayos clínicos y 1 estudio piloto que evaluaban la eficacia de la terapia celular. El estudio de la reserva coronaria y la función ventricular se analizaron con la misma metodología en todos ellos. Se administraron células mononucleares derivadas de médula ósea autóloga (n = 40), factor estimulante de colonias granulocíticas (n = 14) o la combinación de ambos (n = 10). Hubo un grupo control (n = 24) que solo recibió revascularización convencional.

Resultados: La media de fracción de eyección se incrementó del 37 ± 8% al 46 ± 12% (p < 0,05). La media de incremento de la reserva de flujo coronario fue de 1,6 ± 0,5 a 2,3 ± 0,9 (p < 0,05). No hubo correlación entre los parámetros de función muscular y los parámetros de función microvascular al seguimiento.

Conclusiones: Hay cambios favorables en el miocardio tras el tratamiento con terapia regenerativa después de un infarto, aunque no se ha encontrado correlación entre los cambios de función muscular y microvascular.

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Abbreviations

ABM-MNCs: autologous bone marrow-derived mononuclear cells
CFR: coronary flow reserve
G-CSF: granulocyte colony-stimulating factor

INTRODUCTION

Coronary flow reserve (CFR) is the capacity of the heart to increase coronary flow and to self-regulate and maintain a constant source of oxygen to the myocardium, meeting its needs continuously. Patients with depressed left ventricular systolic function are known to have impaired microvascular function, even in the absence of significant stenosis in the epicardial coronary arteries.[1] However, following acute myocardial infarction, microvascular function is further impaired and changes to the coronary microcirculation on the first day after primary angioplasty are related to the degree of ejection fraction recovery within 6 months after the procedure.[2]

For more than a decade, regenerative therapy has been used as adjunct therapy for heart failure, particularly in cases of ischemic origin, with promising results.[3–15]

To our knowledge, there has been only limited study of the relationship between the changes in myocardial function and microvascular function–as evaluated by CFR following stem cell administration. In our study, this association was investigated in a series of patients who received autologous bone marrow-derived mononuclear cells (ABM-MNCs) administered after successful percutaneous revascularization of an anterior myocardial infarction.

METHODS

Study Design

The study was designed as a pooled analysis of 2 clinical trials[16,17] and 1 pilot study assessing the efficacy of regenerative therapy in patients with a revascularized anterior myocardial infarction.

Study Inclusion and Exclusion Criteria

The inclusion criteria were as follows: *a)* depressed left ventricular function (< 45%), and *b)* patients with acute anterior myocardial infarction and early reperfusion of the anterior interventricular artery by intravenous fibrinolysis or by percutaneous coronary intervention and subsequent stent implantation in this artery. The exclusion criteria were as follows: *a)* age > 80 years; *b)* hematologic disease; *c)* malignant neoplasms or relevant systemic diseases; and *d)* mechanical complications of the infarction or cardiogenic shock.

Procedure

All participants underwent hemodynamic study of both left ventricular function and microvascular function at baseline and at 3 months. The patients received ABM-MNCs (n = 40), granulocyte colony-stimulating factor (G-CSF) (n = 14), or a combination of both (n = 10). A control group (n = 24) was treated by revascularization alone.

Regenerative Therapy Protocol

Intracoronary Extraction and Infusion of Autologous Bone Marrow-derived Mononuclear cells

The study protocol has been previously published.[16] Patients who received ABM-MNCs underwent a second catheterization 5 to 12 days after the acute infarction (7 ± 2 days) with intracoronary infusion of the cell broth in the anterior interventricular artery. Autologous bone marrow had been collected by a hematologist 4 hours earlier. The patient's bone marrow was collected by repeat aspirations from the posterior iliac crest under local anesthesia (approximate volume, 100 mL). Processing consisted only of eliminating plasma, erythrocytes, and granulocytes, and only mononuclear cells were obtained. The procedure was performed by Ficoll-Hypaque density-gradient ultracentrifugation of 1.077 g/mL, in a COBE-2991 semiautomatic cell processor, and the cells were finally resuspended in 10 mL of 0.9% sodium chloride with 1% heparin without preservatives. Following filtration through a 150-μ filter, the cells were then concentrated in a syringe for the anterior interventricular artery. Samples were collected for cell counts, viability, and microbiologic monitoring, as well as for research purposes. The final cell suspension was taken to the Interventional Cardiology Unit for immediate administration by catheterization. All handling was done under strictly sterile conditions below a laminar flow hood located in the cell therapy laboratory.

Of the 88 patients selected who agreed to the protocol and signed the informed consent form, 50 received the proposed treatment: ABM-MNCs. The mean ABM-MNC dose administered was 22×10^6 $CD34^+$. Selective infusion in the anterior interventricular artery (for 2-4 minutes) was performed using a balloon catheter placed in the proximal segment (in the implanted stent) by continuous infusion and with the balloon inflated. The balloon size was determined by vessel size, thus achieving flow pooling conditions to encourage cell nesting and avoid systemic loss. The patients were then transferred to the ward for continuous 24-hour monitoring for possible arrhythmic events, and peak creatine kinase and troponin plasma concentrations were determined to detect any myocardial injury.

Granulocytic-colony Stimulating Factor Mobilization

The 24 patients who received 10 days of subcutaneous administration of recombinant G-CSF (Neupogen; Amgen, Thousand Oaks, California, United States) started treatment on day 5 postinfarction at a dose of 5 μg/kg every 12 hours. On days 0, 3, 5, and 10 of administration, peripheral blood samples were collected to determine white blood cell and circulating $CD34^+$ counts, as well as $CD34^+$ immunophenotype derivatives, using 3-color immunofluorescence cytometry to count $CD34^+$ and stem cells present in peripheral blood.

Diagnostic and Therapeutic Catheterizations

In all 88 patients, angiography was performed using the same method at baseline, before infusion, and at 3 months postinfarction. Each ventriculogram (30° right anterior oblique view) attempted to obtain sinus and postextrasystolic beats to study left ventricular contractile reserve. The calculations and measurements were performed in the hospital laboratory, where 2 angiography operators traced the end-diastolic and end-systolic silhouettes using the CASS system. Ventricular volumes and ventricular function were both obtained, and regional motility was also analyzed. The method described by Sheehan FH[18] was used to study asynergy by dividing the superimposed silhouettes into

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100 radii of systolic wall shortening, from end-diastole to end-systole, and the abnormal contraction segment was defined as the percentage of radii that showed akinesia or dyskinesia. The degree of functional recoverability or gain obtained at follow-up was calculated as the functional difference obtained at this follow-up less the baseline value. These parameters were evaluated from the sinus and postextrasystole beats and from left ventricular filling pressure.

Measurement of Flow Velocity and Coronary Flow Reserve

Flow velocities and coronary reserve in the anterior interventricular artery were assessed using an invasive method, measured after intracoronary adenosine injection. The FloMap system (Cardiometrics, Mountain View, California, United States) was used. A 0.014-inch Doppler guidewire was introduced, with the tip placed in the proximal third of the epicardial course of the artery, and flow velocities were recorded continuously. Flow velocity was measured at baseline and after administration of an intracoronary bolus of 60 μg of adenosine in the anterior interventricular artery; CFR was calculated as the ratio between peak flow velocity during peak adenosine effect and baseline flow velocity. Variables were analyzed for the pooled series and by groups. Flow velocities, CFR, and CFR gain (assessed by calculating CFR at 3 months less CFR at baseline) were included. Coronary reserve studies were performed before cell infusion and at 3 months.

Statistical Analysis

Continuous variables are expressed as the mean ± standard deviation, and categorical variables as percentage. The mean values of the quantitative variables between the groups established were compared by analyzing variance. The Pearson correlation coefficient (R) was used to obtain linear correlations. The study population showed a normal distribution, according to the Lilliefors-corrected Kolmogorov-Smirnov test. All data were analyzed using the SPSS commercial package (version 15.0), and a value of $P < .05$ was considered statistically significant.

RESULTS

Most patients included were men (88%) with a mean age of 55.3 ± 10.4 years. In the pooled series, 16% of the patients were diabetic, 47% were smokers, 64% had hypertension, and 73% had elevated low-density lipoprotein cholesterol levels (> 135 mg/dL). The percutaneous coronary intervention was primary in 9% of patients, rescue in 14%, and delayed in the remainder. There were no significant differences in baseline characteristics between the groups in terms of ventricular volumes or regional contractility abnormalities or in those obtained by ventriculography in sinus or postextrasystolic beats, except for sinus and postextrasystolic baseline ejection fraction, which was lower in the group treated with ABM-MNCs + G-CSF. Likewise, there were no differences in terms of flow velocities or baseline CFR value. Table 1 lists the clinical, myocardial function, and microvascular function data at baseline. Table 2 shows the changes obtained in muscular function at 3 months of follow-up, in both the pooled series and by groups. Overall, ejection fraction and regional contractility improved, with a reduction in abnormal contraction segments, as well as a decrease in affected radii at 3 months. No significant changes were found by groups in ventricular volumes, except in left ventricular end-diastolic volume in the G-CSF group, which showed significant growth at follow-up with no changes in ejection fraction. Table 3 lists the baseline and follow-up data for microvascular parameters in the pooled series and by groups, where CFR improved (overall mean CFR increased from 1.6 ± 0.5 to 2.3 ± 0.9; $P < .001$). In addition, peak velocity decreased

Table 1
Clinical Baseline and Ventricular and Microvascular Function Data According to Treatment Group

	ABM-MNCs (n = 40)	G-CSF (n = 14)	ABM-MNCs + G-CSF (n = 10)	Control (n = 24)	P*
Age, y	54.2 ± 10.5	53.7 ± 8.2	56.9 ± 11.2	57.3 ± 11.4	NS
Sex, men	36 (90)	12 (86)	8 (80)	21 (88)	NS
Smoking	21 (53)	8 (57)	3 (30)	9 (38)	NS
HTN	23 (58)	10 (71)	7 (70)	16 (67)	NS
Hyperlipidemia	27 (68)	10 (71)	9 (90)	18 (75)	NS
Diabetes mellitus	7 (18)	2 (14)	3 (30)	2 (8)	NS
Primary PCI	5 (13)	1 (7)	1 (10)	1 (4)	NS
Rescue PCI	9 (23)	1 (7)	1 (10)	1 (4)	NS
Delayed PCI	26 (65)	12 (86)	8 (80)	22 (92)	NS
TIMI III flow	40 (100)	14 (100)	10 (100)	24 (100)	NS
LVEF, %	35.9 ± 6.7	40.2 ± 6.9	30.0 ± 5.5	39.3 ± 8.7	.003
PE LVEF, %	48.1 ± 8.4	51.9 ± 9.1	41.1 ± 7.0	48.5 ± 10.9	.047
LVEDD, mL/m^2	125.7 ± 40.3	142.1 ± 25.1	143.8 ± 56.8	136.9 ± 32.1	NS
LVESD, mL/m^2	79.2 ± 26.3	83.8 ± 17.9	101.1 ± 43.8	82.9 ± 22.5	NS
Abnormal contraction segments, %	32.0 ± 14.0	31.3 ± 15.3	34.0 ± 12.3	29.1 ± 13.9	NS
Radii affected, %	52.1 ± 12.5	44.9 ± 14.0	53.8 ± 9.5	47.6 ± 8.9	NS
LVEDP, mmHg	25.6 ± 8.7	27.5 ± 10.2	25.9 ± 11.4	28.3 ± 9.2	NS
CFR	1.7 ± 0.6	1.4 ± 0.3	1.5 ± 0.5	1.7 ± 0.4	NS
VP, cm/s	25 ± 11	22 ± 7	34 ± 23	31 ± 16	NS
Adenosine VP, cm/s	40 ± 17	33 ± 12	46 ± 21	52 ± 28	NS

ABM-MNCs, autologous bone marrow-derived mononuclear cells; adenosine VP, peak coronary flow velocity after administration of intracoronary adenosine; CFR, coronary flow reserve; G-CSF, granulocyte colony-stimulating factor; HTN, hypertension; LVEDD, left ventricular end-diastolic volume; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic volume; NS, nonsignificant; PCI, percutaneous coronary intervention; PE, postextrasystolic; TIMI, Thrombolysis in Myocardial Infarction; VP, peak coronary flow velocity.
Unless otherwise specified, the data are expressed as No. (%) or mean ± SD.
* Statistical significance, $P < .05$.

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Table 2
Changes in Ventricular Function Parameters at Follow-up in the Pooled Series and According to Treatment Group

Groups	LVEF, %	P*	PE LVEF, %	P*	LVEDD, mL/m	P*	LVESD, mL/m^2)	P*	Abnormal contraction segments, %	P*	RA, %	P*	LVEDP, mmHg	P*
ABM-MNCs (n = 40)														
Baseline	36 ± 7	.0001	49 ± 9	.0001	126 ± 42	NS	79 ± 27	NS	31 ± 14	.0001	52 ± 12	.0001	25 ± 9	.028
Third month	49 ± 13		59 ± 14		128 ± 50		69 ± 36		12 ± 13		35 ± 20		22 ± 9	
G-CSF (n = 14)														
Baseline	40 ± 7	NS	53 ± 9	NS	142 ± 25	NS	84 ± 18	NS	31 ± 15	.012	45 ± 14	NS	28 ± 10	NS
Third month	45 ± 15		57 ± 15		178 ± 43		103 ± 50		22 ± 16		37 ± 23		25 ± 11	
ABM-MNCs + G-CSF (n = 10)														
Baseline	30 ± 5	.006	41 ± 7	.025	144 ± 57	NS	101 ± 44	NS	34 ± 12	.025	54 ± 10	NS	26 ± 11	NS
Third month	38 ± 10		51 ± 13		145 ± 35		90 ± 30		23 ± 14		46 ± 15		21 ± 11	
Control (n = 24)														
Baseline	39 ± 9	.002	49 ± 11	.002	137 ± 33	NS	83 ± 23	NS	29 ± 14	.004	48 ± 9	.001	28 ± 9	.018
Third month	47 ± 10		58 ± 11		142 ± 36		76 ± 29		19 ± 12		33 ± 19		23 ± 8	
Total (n = 88)														
Baseline	37 ± 8	< .001	49 ± 10	< .001	134 ± 39	< .001	83 ± 28	< .001	31 ± 14	< .001	50 ± 12	< .001	27 ± 9	< 0.001
Third month	46 ± 12		57 ± 13		142 ± 47		79 ± 38		18 ± 14		36 ± 20		23 ± 9	

ABM-MNCs, autologous bone marrow-derived mononuclear cells; G-CSF, granulocyte colony -stimulating factor; LVEDD, left ventricular end-diastolic volume; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic volume; NS, nonsignificant; PE, postextrasystolic; RA, radii affected (akinetic/dyskinetic).
* Statistical significance, $P < .05$.

and postadenosine peak velocity increased in the pooled series, whereas no statistically significant differences were observed by groups. Table 4 shows a new comparative study of muscular function gain–both global and segmental–and microvascular function gain at 3 months between the various treatment groups. Whereas the pooled series achieved significant gain in ejection fraction (9.1 ± 11.1% and 8.8 ± 12.3%; $P < .001$) observed by invasive ventriculography in sinus and postextrasystolic beat, respectively, there were no significant differences between the groups. However, this gain showed some tendency to be larger in the experimental group. The mean CFR gain in the pooled series was 0.87 ± 0.87 ($P < .001$), although there were no differences between the groups. Table 5, Table 6, Table 7, and Table 8 show the correlations obtained between the gains in angiographic parameters and microvascular parameters in the groups treated with ABM-MNCs, ABM-MNCs + G-CSF, G-CSF, and the control group, respectively. No statistically significant correlations were observed between global or segmental function gain compared with the gain in CFR or peak coronary flow velocities. There were no adverse events related to the therapy administered or the procedure used.

DISCUSSION

CFR indicates the capacity to increase baseline coronary flow after maximum hyperemia and is considered an indicator of the state of coronary circulation.[19] This is impaired particularly in patients with significant coronary disease,[20] and is not regained immediately after percutaneous revascularization.[21–24] Some

Table 3
Changes in Microvascular Function Parameters at Follow-up in the Pooled Series and According to Treatment Group

Groups	CFR	P*	VP, cm/s	P*	Adenosine VP, cm/s	P*
ABM-MNCs (n = 40)						
Baseline	1.7 ± 0.5	.0001	26 ± 11	.036	41 ± 17	.016
Third month	2.6 ± 0.7		21 ± 9		52 ± 18	
G-CSF (n = 14)						
Baseline	1.4 ± 0.3	.0001	22 ± 7	NS	33 ± 12	.012
Third month	2.4 ± 0.6		23 ± 10		54 ± 22	
ABM-MNCs + G-CSF (n = 10)						
Baseline	1.5 ± 0.5	.001	34 ± 23	NS	46 ± 21	.008
Third month	2.5 ± 0.8		27 ± 9		62 ± 12	
Control (n = 24)						
Baseline	1.7 ± 0.4	.002	30 ± 15	NS	51 ± 28	NS
Third month	2.6 ± 0.9		26 ± 16		53 ± 14	
Total (n = 88)						
Baseline	1.6 ± 0.5	< .001	27 ± 12	< .05	43 ± 21	< 0.001
Third month	2.3 ± 0.9		23 ± 11		55 ± 18	

ABM-MNCs, autologous bone marrow-derived mononuclear cells; adenosine VP, peak coronary flow velocity after administration of intracoronary adenosine; CFR, coronary flow reserve; G-CSF, granulocyte colony-stimulating factor; NS, nonsignificant; VP, peak coronary flow velocity.
* Statistical significance, $P < .05$.

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Table 4
Ventricular and Microvascular Function Gain According to Treatment Group at Follow-up

	ABM-MNCs (n = 40)	G-CSF (n = 14)	ABM-MNCs + G-CSF (n = 10)	Control (n = 24)	P[a]
LVEF gain,[b] %	12.3 ± 11.1	4.6 ± 13.1	8.2 ± 7.3	7.3 ± 2.1	NS
PE LVEF gain,[c] %	9.8 ± 11.9	3.9 ± 13.4	10.0 ± 11.8	9.7 ± 12.8	NS
Abnormal contraction segment gain,[d] %	16.0 ± 17.9	9.3 ± 11.9	10.5 ± 10.4	13.0 ± 17.4	NS
RA gain,[e] %	18.4 ± 17.8	8.2 ± 15.4	7.8 ± 14.3	10.3 ± 19.9	NS
CFR gain[f]	0.9 ± 0.8	0.9 ± 0.6	0.9 ± 0.6	0.8 ± 1.1	NS
VP gain,[g] cm/s	3.2 ± 13.4	0.7 ± 13.4	9.2 ± 12.2	5.5 ± 15.8	NS
Adenosine VP gain,[h] cm/s	10.5 ± 21.1	20.8 ± 25.4	15.8 ± 14.7	2.4 ± 29.9	NS

ABM-MNCs, autologous bone marrow-derived mononuclear cells; CFR, coronary flow reserve; G-CSF, granulocyte colony-stimulating factor; LVEF, left ventricular ejection fraction; NS, nonsignificant; PE, postextrasystolic; RA, radii affected (akinetic/dyskinetic); VP, peak coronary flow velocity.
[a] Statistical significance, $P < .05$.
[b] LVEF at 3 months less LVEF at baseline.
[c] PE LVEF at 3 months less PE LVEF at baseline.
[d] Abnormal contraction segments at 3 months less abnormal contraction segments at baseline.
[e] RA at 3 months less RA in baseline study.
[f] CFR at 3 months less CFR at baseline.
[g] Peak coronary flow velocity at 3 months less peak coronary flow velocity at baseline.
[h] Peak coronary flow velocity after intracoronary adenosine at 3 months less peak coronary flow velocity after intracoronary adenosine at baseline.

Table 5
Correlations Between Ventricular and Microvascular Function Gains in the Group Treated With Autologous Bone Marrow Mononuclear Cells*

	CFR Gain	P	VP Gain	P	Adenosine VP Gain	P
LVEF gain	r = 0.05	NS	r = 0.24	NS	r = −0.17	NS
Abnormal contraction segment gain	r = 0.07	NS	r = 0.13	NS	r = 0.06	NS
RA gain	r = 0.13	NS	r = 0.20	NS	r = −0.01	NS

Adenosine VP, peak coronary flow velocity after administration of intracoronary adenosine; CFR, coronary flow reserve; LVEF, left ventricular ejection fraction; NS, nonsignificant; RA, radii affected (akinetic/dyskinetic); VP, peak coronary flow velocity.
* Gain: 3-month value less baseline value.

Table 6
Correlations Between Ventricular and Microvascular Function Gains in the Group Treated with Autologous Bone Marrow Mononuclear Cells Plus Granulocyte Colony-stimulating Factor*

	CFR Gain	P	VP Gain	P	Adenosine VP Gain	P
LVEF gain	r = −0.10	NS	r = 0.63	NS	r = 0.22	NS
Abnormal contraction segment gain	r = −0.48	NS	r = 0.01	NS	r = −0.33	NS
RA gain	r = −0.24	NS	r = 0.59	NS	r = 0.04	NS

Adenosine VP, peak coronary flow velocity after administration of intracoronary adenosine; CFR, coronary flow reserve; LVEF, left ventricular ejection fraction; NS, nonsignificant; RA, radii affected (akinetic/dyskinetic); VP, peak coronary flow velocity.
* Gain: 3-month value less baseline value.

Table 7
Correlations Between Ventricular and Microvascular Function Gains in the Group Treated with Granulocyte Colony-stimulating Factor*

	CFR Gain	P	VP Gain	P	Adenosine VP Gain	P
LVEF gain	r = −0.03	NS	r = 0.26	NS	r = 0.36	NS
Abnormal contraction segment gain	r = 0.14	NS	r = 0.54	NS	r = 0.51	NS
RA gain	r = 0.25	NS	r = 0.13	NS	r = 0.52	NS

Adenosine VP, peak coronary flow velocity after administration of intracoronary adenosine; CFR, coronary flow reserve; LVEF, left ventricular ejection fraction; NS, nonsignificant; RA, radii affected (akinetic/dyskinetic); VP, peak coronary flow velocity.
* Gain: 3-month value less baseline value.

Table 8
Correlations Between Ventricular and Microvascular Function Gains in the Control Group*

	CFR Gain	P	VP Gain	P	Adenosine VP Gain	P
LVEF gain	r = −0.07	NS	r = 0.26	NS	r = 0.09	NS
Abnormal contraction segment gain	r = −0.04	NS	r = 0.22	NS	r = 0.21	NS
RA gain	r = −0.13	NS	r = −0.10	NS	r = −0.25	NS

Adenosine VP, peak coronary flow velocity after administration of intracoronary adenosine; CFR, coronary flow reserve; LVEF, left ventricular ejection fraction; NS, nonsignificant; RA, radii affected (akinetic/dyskinetic); VP, peak coronary flow velocity.
* Gain: 3-month value less baseline value.

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authors have also reported that participants with depressed ejection fraction after acute infarction have lower CFR, whereas participants with preserved ejection fraction have significantly higher CFR.[2,25]

The precise mechanism leading to improvement or worsening of CFR after an acute infarction treated by angioplasty is unclear, although microvascular dysfunction is known to be closely related to recovery of left ventricular function.[26–28] It has been postulated that coronary reserve behaves as an independent predictive factor of response to adverse remodeling after angioplasty[29–32]; thus, participants with adverse remodeling during follow-up had low acute-phase CFR. This could be explained because microvascular integrity is essential for a favorable outcome after a reperfused infarction. Our series found no correlation between CFR and ventricular function, perhaps because patients began with a large anterior infarction with depressed ejection fraction and–although the group was rather homogeneous in terms of baseline characteristics–there were statistically significant differences between groups in baseline ejection fraction (obtained in both sinus and postextrasystolic beats), which was lower in the group treated with ABM-MNCs + G-CSF.

Various studies have shown that intracoronary ABM-MNC infusion may have a beneficial effect on remodeling, ventricular function, and reperfusion after infarction.[5–8,12–16] Although questions have been raised regarding the benefits of stem cell mobilization by G-CSF in patients with infarction and left ventricular function recovery, in our experience, participants who received G-CSF did not differ from the control group in terms of an improvement in ventricular function.[16]

Only a few studies have investigated CFR in patients receiving regenerative therapy after a myocardial infarction,[16,17] and only a few authors have found an improvement in CFR after stem cell administration.[6,33,34] One study also observed a correlation between circulating stem cell levels after an infarction and the degree of coronary reserve recoverability.[35] Our series showed improvement in both muscular and microvascular function. Additionally, among other findings, postadenosine peak velocity was increased at 3 months of follow-up, possibly due to greater vasoconstriction of the coronary microvasculature in the acute phase of infarction which, along with a probable process of distal microembolization, indicates that appropriate vasodilation does not occur after adenosine use, unlike what takes place during follow-up.

However, to our knowledge, there has been limited study of the relationship between the changes in left ventricular function and those observed in coronary reserve after the use of regenerative therapy in acute myocardial infarction.[36] Our series showed no statistically significant correlations between ventricular function parameters and CFR gain in either the control group or the experimental groups treated with ABM-MNCs or G-CSF. Nevertheless, because the sample was small in each group, the results should be interpreted with caution. Generally speaking, the tendency in ejection fraction gain was larger in the ABM-MNC-treated group than in the control group, particularly when compared with the group treated with G-CSF.[16]

Various mechanisms have been postulated to encourage cardiac regeneration–such as transdifferentiation or fusion with resident cells–thus explaining the improvement in myocardial function after stem cell use in myocardial infarction. However, the paracrine effect[37] (induced by stem cells infused in the myocardium due to the release of cytokines and growth factors) may be what causes essential pleiotropic effects–not only in terms of neoangiogenesis, but also by direct stimulation of resident stem cells–to promote differentiation and cardiomyocyte proliferation and to reduce the inflammatory response and fibrosis that develop after infarction-related heart damage. Likewise, it seems logical to add the unquestionable contribution of early revascularization of the culprit artery along with optimal drug therapy of known effectiveness, which both contribute to counteracting adverse remodeling.

Limitations

The main limitations of this study include the single-site design, heterogeneous sample, and short follow-up period. Hence, the results obtained should be interpreted with caution. The study was not randomized and this, together with the limitations of pooled analyses, may account for the lack of statistical significance in the correlations established and in ventricular function and CFR gain between treatment groups.

CONCLUSIONS

The favorable changes observed in left ventricular function after regenerative therapy in patients with acute anterior infarction do not correlate with the improvement in coronary reserve. The precise mechanism of action used by stem cells is only partially understood. Specifically designed studies should be conducted to clarify these mechanisms and thus optimize therapy and improve the therapeutic outcome of patients with acute myocardial infarction.

CONFLICTS OF INTEREST

None declared.

WHAT IS KNOWN ABOUT THE TOPIC?

– Various studies have established the apparent relationship between changes in microvascular function and myocardial function following acute myocardial infarction revascularization and have also found that CFR is a predictor of short- to mid-term recoverability of cardiac function. However, the changes seen in CFR after ABM-MNC infusion in ischemic patients vary widely, and there is no consensus on the true benefit of this technique, unlike the improvement in myocardial function, where studies are more conclusive and generally show it to be a beneficial therapy.

WHAT DOES THIS STUDY ADD?

– This study evaluates whether or not the improvement in coronary microcirculation after regenerative therapy one of the theoretical mechanisms of action influences the degree of myocardial functional recovery. No correlation was found between the improvement obtained in the various muscular function parameters and the improvement in CFR, although the lack of statistical significance may be due to an insufficient sample, to the type of analysis used, to the short follow-up, or to the fact that ventricular function was considerably depressed at baseline, a factor that also influences the degree of CFR recoverability.

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