Cardiac bone marrow cell injection for chronic ischemic heart disease

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Chapter 8

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Effect of Intramyocardial Injection of Autologous Bone Marrow-derived Mononuclear Cells on Perfusion, Function and Viability in Patients with Drug-refractory Chronic Ischemia

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Abstract

Introduction: Intramyocardial injection of bone marrow cells has been proposed as a new therapeutic option for patients with chronic ischemic heart disease. We investigated whether autologous bone marrow-derived mononuclear cell injection into the myocardium of patients with drug-refractory ischemia reduces anginal symptoms, improves left ventricular (LV) function, increases myocardial perfusion and alters the extent of scar tissue.

Methods: In 25 patients (64±10 years, 21 male) with drug-refractory angina pectoris (Canadian Cardiovascular Society (CCS) class III-IV) despite optimized medical therapy and without options for conventional revascularization, bone marrow was aspirated from the iliac crest. Mononuclear cell injections were targeted at myocardial regions with stress-induced ischemia on Tc-99m tetrofosmin gated single photon emission computed tomography (SPECT). Anginal symptoms were reassessed at 3 and 6 months. At baseline and 3 months, Tc-99m tetrofosmin gated SPECT and F18-fluorodeoxyglucose (FDG) SPECT were performed to assess LV function, LV volumes, myocardial perfusion (stress and rest, 17-segment model) and the extent of scar tissue.

Results: CCS score improved from 3.4±0.6 at baseline to 2.3±0.6 at 3 months (P<0.01) and remained unchanged at 6 months (2.3±0.6; P<0.01 vs. baseline and P=NS vs. 3 months). Tc-99m tetrofosmin gated SPECT demonstrated an increased LV ejection fraction (47.6±13.5% vs. 54.1±16.9%; P<0.01) and a reduced LV end-systolic volume (81±68 ml vs. 75±70 ml; P<0.01). Segmental regional wall thickening increased from 34±12% to 39±17% at 3 months (P=0.01). The number of segments with stress-inducible ischemia per patient decreased from 4.6±3.2 to 2.0±2.6 (P<0.01). Both segmental stress and segmental rest score improved, although the improvement in stress score was more pronounced (decrease in stress score 0.22±0.20 vs. decrease in rest score 0.04±0.06; P<0.01). Myocardial perfusion improved in 53% of the injected segments and in 13% of the non-injected segments (P<0.01). The percentage of myocardial segments with some extent of scar remained unchanged at 3 months (13% vs. 12%; P=NS).

Conclusion: Autologous bone marrow-derived mononuclear cell injection in patients with drug-refractory angina and chronic ischemia improves anginal symptoms, increases LV function and predominantly enhances myocardial stress-perfusion in injected segments, whereas the extent of myocardial scar tissue remains unchanged.

Introduction

Bone marrow cell transplantation has been proposed as a new therapeutic option for patients with chronic ischemic heart disease. Previous studies demonstrated the safety of intramyocardial injection of autologous bone marrow-derived mononuclear cells.[1-4] Moreover, these initial studies suggested that bone marrow cell transplantation reduced anginal symptoms, enhanced myocardial perfusion and increased cardiac function.[1-4]

Although the potential mechanism of benefit from bone marrow cell transplantation has been evaluated in animal models,[5-10] few data are available in patients. It is hypothesized that bone marrow cells promote angiogenesis either through secretion of angiogenic cytokines[11] (resulting in a more or less generalized effect) or differentiation in endothelial and vascular smooth muscle cells[6,12] (resulting in a regional effect). Furthermore, it is unclear whether procedural-induced necrosis of ischemic myocardium or regeneration of myocardial tissue[9] (resulting in a reduced scar area and/or increased viability) contributes to the beneficial effects.

Nuclear imaging could potentially contribute in the evaluation of the benefit from bone marrow cell injection. Tc-99m tetrofosmin gated single photon emission computed tomography (SPECT) has a high sensitivity for the detection of myocardial ischemia,[13,14] and F18-fluorodeoxyglucose (F18-FDG) imaging is an excellent technique to differentiate viable myocardium from scar tissue, based on the assessment of cellular glucose utilization.[15,16]

The aim of the current study was to provide more insight into the mechanism of benefit from bone marrow cell transplantation in patients with chronic ischemia. Tc-99m tetrofosmin SPECT was used to evaluate changes in myocardial perfusion following cell transplantation and F18-FDG SPECT imaging was used to evaluate changes in scar tissue after cell transplantation.

Methods

Patients

The study population consisted of 25 consecutive "no-option" patients with chronic coronary artery disease and ischemia on nuclear (Tc-99m tetrofosmin gated SPECT) imaging. Patients had angina pectoris despite maximally tolerated medical therapy and were ineligible for percutaneous or surgical revascularization as assessed by coronary angiography. Ineligibility for surgical or percutaneous revascularization procedures was determined by an independent expert panel that reviewed the angiograms. The panel comprised 2 cardiovascular surgeons, 2 interventional cardiologists and a non-invasive cardiologist.

Exclusion criteria were acute myocardial infarction within 6 months of enrollment in the study, history of malignancy, renal dysfunction (serum creatinine >200 µmol/L), or

unexplained hematological or biochemical abnormalities. The local ethics committee approved the protocol and all patients gave informed consent.

Study Protocol

At baseline the severity of angina was graded according to the Canadian Cardiovascular Society (CCS) score. The Seattle Angina Questionnaire was used to assess quality of life. Within 2 weeks before bone marrow cell injection, Tc-99m tetrofosmin gated SPECT (to assess left ventricular (LV) function and myocardial perfusion) and F18-FDG imaging (to assess myocardial glucose utilization and detect viability and scar tissue) were performed. On the day of the injection procedure, bone marrow was aspired from the iliac crest under local anesthesia. Mononuclear cells were isolated by Ficoll density gradient. During isolation of mononuclear cells, patients underwent non-fluoroscopic LV electromechanical mapping with the NOGA system (NOGA star catheter, Biosense-Webster, Waterloo, Belgium). After completion of LV mapping, the mapping catheter was replaced by an injection catheter (Myostar catheter, Biosense-Webster). Autologous bone marrow-derived mononuclear cell injections were targeted at myocardial regions with stress-induced ischemia (on Tc-99m tetrofosmin SPECT). The injection catheter was prepared as described previously.[3] Before every injection of cells into the LV myocardium, the following criteria had to be met: unipolar voltage ≥6.9 mV (to identify viable myocardium within the treatment area), perpendicular position of the catheter to the myocardial wall, excellent loop stability (<4 mm), and presence of a premature ventricular contraction on extension of the needle into the myocardium. Subsequently, 8 to 13 intramyocardial injections of approximately 0.2 ml each were performed.

Immediately after the procedure, continuous heart rhythm monitoring was started for 2 days. Before discharge, 2D echocardiography was performed to exclude pericardial effusion. At 3 and 6 months, angina (CCS score), quality of life (Seattle Angina Questionnaire) and the occurrence of ventricular arrhythmia (24-hour Holter monitoring) were assessed. In addition, Tc-99m tetrofosmin gated SPECT and F18-FDG imaging were repeated at 3 months follow-up to reassess LV function, myocardial perfusion and myocardial viability (and scar tissue).

SPECT Imaging: Data Acquisition

A two-day stress-rest protocol was used the Tc-99m tetrofosmin SPECT examination. The stress protocol included a symptom-limited bicycle exercise test. Whenever possible, β-blockade agents and calcium antagonists were discontinued for 24 hours before Tc-99m-tetrofosmin SPECT. Test endpoints were physical exhaustion, angina pectoris, dyspnea, significant decrease in blood pressure (>10 mmHg), or achievement of maximal age-related heart rate. Blood pressure, heart rate and electrocardiogram (ECG) findings were monitored during the test. Tc-99m tetrofosmin (500 MBq) was injected intravenously at peak exercise, which was continued for another 1-2 minutes after tracer injection.

In patients unable to exercise, pharmacologic stress (intravenous administration of adenosine 0.14 mg/kg/min for 6 minutes, or dobutamine up to a maximum dose of 40 µg/kg/min in 15 minutes) was used. On the second day, resting images were obtained (using 500 MBq Tc-99m tetrofosmin) after the patient's daily dose of nitrates. The resting studies were acquired using ECG gating, for assessment of LV ejection fraction and LV volumes.[17] Stress and rest imaging were performed with the same medications and the same type of stressor at baseline and at 3 months follow-up. In particular, the use (and dosages) of β-blockers, calcium channel blockers and nitrates was unchanged at 3 months follow-up.

Imaging was performed using a triple-head SPECT camera (GCA 9300/HG, Toshiba Corp., Tokyo, Japan) equipped with low-energy general-purpose collimators. A 20% window was used around the 140-keV energy peak of Tc-99m. A total of 90 projections (step and smooth mode, 35 seconds per projection, total imaging time 23 minutes) were obtained over a 360° circular orbit. Data were stored in a 64x64 matrix. The raw scintigraphic data were reconstructed with filtered back projection using a Butter-worth filter (cut-off frequency at 0.26 cycles per pixel, of order 9). No attenuation correction was used.

SPECT Imaging: Data Analysis and Tissue Characterization

Additional reconstruction yielded standard long- and short-axis projections perpendicular to the heart axis. Reconstructed slices were 6 mm in all projections. The short-axis slices were displayed in polar map format, adjusted for peak myocardial activity (100%). The myocardium was divided into 17 segments, as previously proposed.[18]

The Tc-99m tetrofosmin SPECT images were analyzed by 2 experienced observers, who were unaware of the clinical information at the time of Tc-99m tetrofosmin SPECT image review. Quantitative assessment of LV function, LV end-diastolic and end-systolic volumes and wall thickening was performed using previously validated and automated software (quantitative gated SPECT, QGS, Cedars-Sinai Medical Center, Los Angeles, California, USA).[19] By estimating and displaying the endo- and epicardial surfaces, the LV end-systolic and LV end-diastolic volumes are calculated, and LV ejection fraction is derived. Intra- and interobserver reproducibility for LV ejection fraction (intercept=0.6, slope=0.01, r=1.00, mean difference=0.04±1.2% resp. intercept=2.1, slope=0.06, r=0.98, mean difference=0.81±3.9%) and LV end-systolic volume (intercept=1.7, slope=0.01, r=1.00, mean difference=0.8±3.6 ml resp. intercept=7.6, slope=0.04, r=0.98, mean difference=4.0±15.8 ml), and end-diastolic volume (intercept=2.7, slope=0.01, r=1.00, mean difference=1.1±4.5 ml resp. intercept=8.1, slope=0.04, r=0.99, mean difference=3.6±13.5 ml) was excellent.

Myocardial wall thickening was assessed as percentage increase (distance between endocardial and epicardial surfaces, normal to the midmyocardial surface) from end-diastole to end-systole.[19] Segmental wall thickening scores were summed and divided by 17 to yield the mean segmental wall thickening.

Myocardial perfusion was analyzed quantitatively (QGS-software) and segmental tracer

activity was categorized on a 4-point scale: 1= activity >75%; 2= tracer activity 50-75%; 3= tracer activity 25-50%; 4= tracer activity <25%. Perfusion defects on stress images were considered present when tracer activity was <75% of maximum. When significant fill-in (>10%) of perfusion defects was observed on the resting images, segments were classified as ischemic. Patients' segmental stress scores were summed and divided by 17 to yield the patients' segmental stress score.[20] Similarly, patients' segmental rest score was calculated. Intra- and interobserver agreement for segmental perfusion scores were 98% and 95% respectively.

F18-FDG Imaging: Data Acquisition

F18-FDG imaging, to evaluate myocardial glucose use, was performed on a separate day, after Acipimox administration (a nicotinic acid derivate, 500 mg, oral dose).[21] Acipimox enhances myocardial F18-FDG uptake by reducing the plasma level of free fatty acids.[22] After Acipimox administration, the patients received a low-fat, carbohydrate-rich meal. This small meal further enhances myocardial F18-FDG uptake by stimulating endogenous insulin release.[23] Sixty minutes after Acipimox administration, a blood sample was taken to assess plasma glucose levels. When plasma glucose was between 5 and 7 mmol/L, 185 MBq F18-FDG were injected at rest. Forty-five minutes thereafter, data acquisition was started. Metabolic imaging was performed at rest using the same SPECT system as described for perfusion imaging, and the system was equipped with commercially available 511 keV collimators. Data were acquired over 360° and stored in a 64x64, 16-bit matrix.

F18-FDG Imaging: Data Analysis

From the raw scintigraphic data, transaxial slices were reconstructed by filtered back projection using a Butterworth filter (cut-off frequency 0.17 cycles per pixel; order 8). Attenuation correction was not applied. Further reconstruction yielded standard short- and long-axis projections perpendicular to the heart axis. F18-FDG short-axis slides were displayed in polar map format, normalized to the maximum activity (set at 100%); the polar maps were divided into 17 segments.[18] The quantitatively analyzed segments were divided into 4 groups on the basis of the tracer activity: 1= normal tracer uptake (activity >75%), 2= mildly reduced tracer uptake (activity 50-75%), 3= moderately reduced tracer uptake (activity 25-50%) and 4= severely reduced tracer uptake (activity <25%). Patients' segmental F18-FDG scores were summed and divided by 17 to yield the patients' segmental F18-FDG score (indicating extent of reduced glucose use per patient, as a global indicator of extent of scar tissue per patient). All segments were subsequently evaluated for viability. Segments were considered as viable (normal) when normalized F18-FDG activity was greater then 75%; segments with tracer uptake <75% were considered to contain some extent of scar. Intra- and interobserver agreement for segmental assessment were 94% and 97% respectively.

Statistical Analysis

All continuous data are expressed as mean ± SD. Continuous variables were compared using the paired, two-tailed Student's t test. Differences between proportions were compared using the chi-square test. The intra- and interobserver reproducibility of LV ejection fraction and LV volumes was determined by linear regression analysis (Pearson correlation coefficient). For all tests, a P-value <0.05 was considered statistically significant.

Results

A total of 25 patients were included in this study (age 64±10 years; 21 male). The baseline clinical characteristics are summarized in **Table 1**. During the 6 months follow-up period, the type and dose of medications remained unchanged. Two patients did not tolerate ß-blockers because of chronic obstructive pulmonary disease. Another patient did not tolerate statins due to myalgia. All patients were ineligible for surgical revascularization or percutaneous coronary intervention as they had diffuse coronary artery disease with poor target vessels (small caliber).

Safety Data and Clinical Outcome

Patients received 10.3±1.8 (range 8 to 13) injections of approximately 0.2 ml each in 29 regions with stress-inducible ischemia (11 inferior, 7 lateral, 8 anterior, 3 septal). In 4

Table 1. Clinical characteristics of the study population (n=25)

Characteristic		
Age (years)	64±10	
Gender (Male)	21	(84 %)
Systemic hypertension	12	(48 %)
Diabetes mellitus	13	(52 %)
Insulin dependent	7	(28 %)
Non-insulin dependent	6	(24 %)
Hyperlipidemia	22	(88 %)
Smoking	2	(8 %)
Coronary artery disease in family	18	(72 %)
Body mass index	28±4	
Prior myocardial infarction	18	(72 %)
Prior percutaneous coronary intervention	19	(76 %)
Prior coronary artery bypass grafting	22	(88 %)
Current medication		
Nitrates	25	(100 %)
β-blockers	23	(92 %)
Calcium channel blockers	18	(72 %)
Statins	24	(96 %)
Angiotensin-converting enzyme inhibitors	19	(76 %)

Table 2. Stress test data

	Baseline	3 months	P-value
Level of stress achieved (Watt)	130±32	135±35	0.10
Heart rate at rest (bpm)	73±15	70±15	NS
SBP at rest (mmHg)	136±18	136±18	NS
DBP at rest (mmHg)	78±11	75±13	NS
Maximal heart rate at stress (bpm)	105±29	103±30	NS
Maximal SBP at stress (mmHg)	154±32	157±31	NS
Maximal DBP at stress (mmHg)	78±12	76±15	NS

bpm = beats per minute
DBP = diastolic blood pressure
SBP = systolic blood pressure

patients with more than 1 ischemic region, 2 different ischemic regions were injected (number of injections was equally distributed). With each intramyocardial injection 8.17±3x10^6 cells were injected. The total number of bone marrow-derived mononuclear cells in the injected suspension was 84.1±28.7x10^6.

Autologous bone marrow-derived mononuclear cell injection was safe: ventricular arrhythmia were not observed and no post-procedural pericardial effusion was detected on 2D echocardiography.

Mean CCS score improved from 3.4±0.6 at baseline to 2.3±0.6 at 3 months (P<0.01) and remained unchanged at 6 months (2.3±0.6; P<0.01 vs. baseline and P=NS vs. 3 months). Quality of life improved from 53±10% to 72±11% at 3 months (P<0.01) and 73±14% at 6 months (P<0.01).

Stress Test Data

Imaging was performed with the same medications and the same type of stressor (bicycle exercise test: n=11; adenosine: n=12; dobutamine: n=2) at baseline and at 3 months follow-up. Although there was a trend toward an increase in the level of stress achieved at 3 months follow-up, this did not reach statistical significance (130±32 Watt vs. 135±35 Watt; P=0.10). The maximal heart rate and maximal blood pressure were similar at baseline and at 3 months follow-up (**Table 2**). In the week before the baseline Tc-99m tetrofosmin SPECT study, patients experienced 17±27 episodes of angina, as compared to 5±8 episodes in the week before the 3 months follow-up Tc-99m tetrofosmin SPECT study (P=0.01).

Blood samples taken before each Tc-99m tetrofosmin SPECT study indicated that the plasma levels of total cholesterol (4.7±1.2 mmol/L vs. 4.8±1.3 mmol/L; P=NS) and C-reactive protein (5±5 mg/L vs. 5±4 mg/L; P=NS) remained unchanged. Also, body mass indices remained unchanged: 28±4 kg/m^2 at baseline vs. 28±4 kg/m^2 at 3 months follow-up (P=NS).

Left Ventricular Function and Volumes

Tc-99m tetrofosmin gated SPECT demonstrated a significant increase in LV ejection fraction

Table 3. Left ventricular ejection fraction and volumes as assessed by gated Tc-99m tetrofosmin SPECT

	Baseline	3 months	P-value
LV ejection fraction (%)	47.6±13.5	54.1±16.9	<0.01
LV end systolic volume (ml)	81±68	75±70	<0.01
LV end diastolic volume (ml)	137±80	139±82	NS

LV = left ventricular

from 47.6±13.5% at baseline to 54.1±16.9% at 3-months follow-up (P<0.01). LV end-systolic volume decreased (from 81±68 ml to 75±70 ml after 3 months; P<0.01), whereas LV end-diastolic volume remained unchanged (**Table 3**). Segmental regional wall thickening at rest increased from 34±12% at baseline to 39±17% at 3 months follow-up (P=0.01).

Myocardial Perfusion

At 3-months follow-up, the number of segments with stress-inducible ischemia per patient decreased from 4.6±3.2 to 2.0±2.6 (P<0.01). An example of resolution of inferior ischemia (baseline to 3 months follow-up) is shown in **Figure 1**. The segmental stress score per patient improved from 1.60±0.40 to 1.38±0.42 (P<0.01). Similarly, resting perfusion

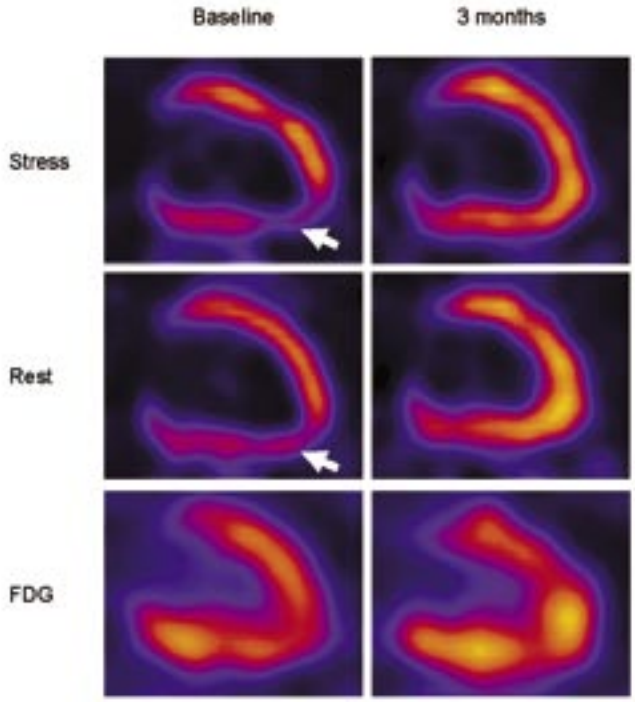

Figure 1
SPECT images (vertical long axis) from representative patient. Technetium-99m tetrofosmin SPECT shows stress-induced ischemia at baseline in the inferior wall (arrow). At 3 months follow-up, ischemia in the inferior wall has resolved. Metabolic imaging shows normal FDG uptake at baseline and 3 months follow-up in that region, indicating no scar formation after intramyocardial injection of bone marrow-derived mononuclear cells.

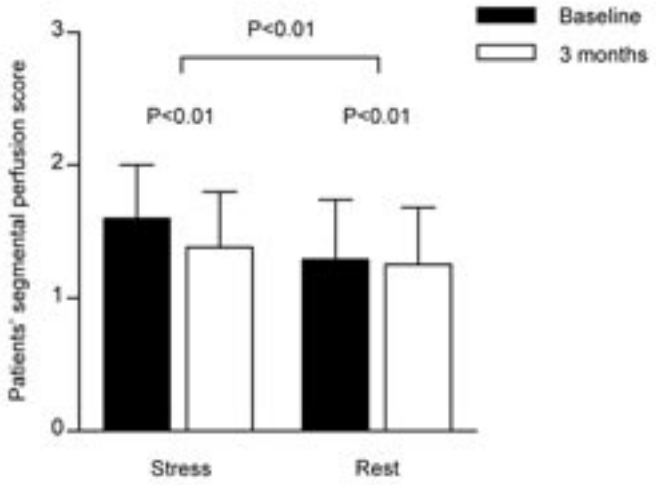

Figure 2
Patients' segmental stress and rest score improved significantly 3 months after autologous bone marrow-derived mononuclear cell injection. The magnitude of increase in stress score was significantly higher as observed for the rest score.

improved, as evidenced by a decrease in segmental rest score from 1.29±0.45 to 1.25±0.43 (P<0.01). The improvement in stress score was more pronounced than the improvement in rest score (**Figure 2**).

Perfusion and Function in Injected vs. Non-Injected Segments

In 25 patients, 257 injections were targeted at 91 myocardial segments (mean 3.6±1.4 injected segments per patient). Of the 91 injected segments, 48 segments increased at least 1 point in rest or stress perfusion (53%), whereas 45/334 (13%) of the non-injected segments improved (P<0.01; **Table 4**).

The stress score significantly improved in both injected and non-injected segments, although the improvement in injected segments was more pronounced (decrease in injected segments 0.42±0.39 vs. decrease in non-injected segments 0.14±0.18; P<0.01; **Figure 3**). There was a trend toward an improvement in rest score in injected (P=0.05) and in non-injected segments (P=0.06). The magnitude of the improvement in rest score was similar in injected and non-injected segments (injected segments 0.07±0.16 vs. non-injected segments 0.02±0.05; P=NS, **Figure 3**).

Regional wall thickening at rest increased in both injected segments (from 37±17% to

Table 4. Perfusion in injected and non-injected segments.

	Improved perfusion	No improved perfusion	P-value
Injected segments	48/91	43/91	<0.01
Non-injected segments	45/334	289/334	

Improved perfusion: ≥1 point increase in stress and/or rest perfusion

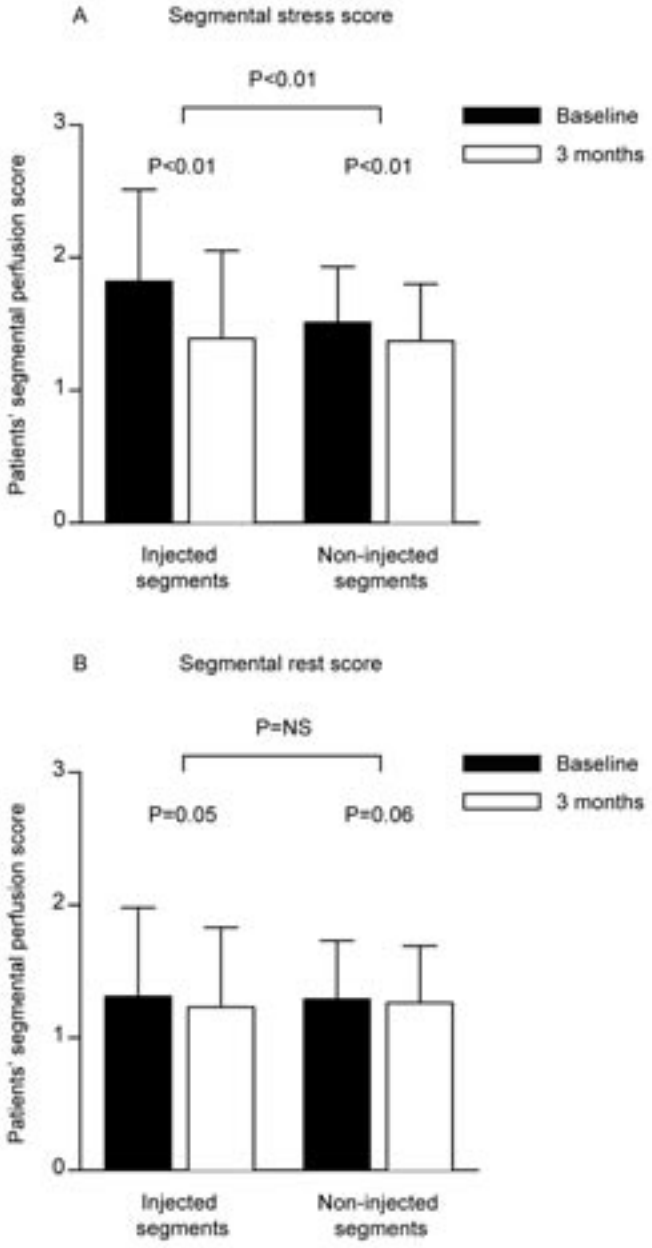

Figure 3
Patients' gated Tc-99m tetrofosmin SPECT segmental stress and rest scores in injected and in non-injected segments. (A) Patients' segmental stress score improved in injected and non-injected segments. The improvement in injected segments was more pronounced than the improvement in non-injected segments. (B) There was a trend toward improvement in rest score in injected and in non-injected segments. The magnitude of the improvement in rest score was similar in injected and non-injected segments.

42±22%; P=0.02) and in non-injected segments (from 33±12% to 38±17%; P=0.03). The magnitude of improvement was similar in injected and in non-injected segments (P=NS).

Viability

F18-FDG image quality was poor in 1 patient with diabetes mellitus and was subsequently excluded from analysis, leaving 408 segments for the final analysis. An example of F18-FDG imaging at baseline and at 3 months follow-up is shown in **Figure 1**. The amount of scar segments was similar at baseline and 3 months follow-up (55/408 (13%) vs. 48/408 (12%); P=NS). Patients' segmental F18-FDG score remained unchanged (1.20±0.3 at baseline vs. 1.18±0.3 at 3 months follow-up; P>0.05). The F18-FDG score improved in 10/408 segments (6/24 patients) whereas the F-18-FDG score decreased in 0/408 segments (0/24 patients).

DISCUSSION

The aim of the current study was to provide more insight into the mechanism of benefit from bone marrow cell transplantation in patients with chronic ischemia despite optimal pharmacological and non-pharmacological treatment. The findings of the current study can be summarized as follows:

1. A significant improvement in anginal symptoms and LV function was observed after autologous bone marrow cell transplantation.
2. Myocardial perfusion and function increased predominantly in injected segments but also, to some extent, in non-injected segments. The main improvement was detected in stress-perfusion, indicating relief of ischemia.
3. No increase in extent of scar tissue was observed after bone marrow cell transplantation.

Comparison to Previous Studies

Various studies have suggested a beneficial effect of bone marrow cell transplantation in patients with chronic ischemic heart disease.[1-4] Two studies described an improvement in anginal symptoms and myocardial perfusion in patients with severe angina pectoris.[1,2] In heart failure patients, an increase in LV function was described after 4 months follow-up.[3] The findings of our study are in line with these previously published clinical studies. Perin et al. demonstrated in 21 patients with ischemic heart failure that bone marrow cell transplantation improved myocardial perfusion but did not alter the percentage of scar tissue.[3,4] Similarly, a safety study in 8 patients with severe angina pectoris described a decrease in the area of hypoperfused myocardium assessed by magnetic resonance imaging.[1] However, both studies did not report whether the increase in perfusion occurred in injected areas only or in the entire left ventricle.[1,3,4] Only one safety study in 10 patients with severe angina reported an improved perfusion stress score (assessed by SPECT) within the injected territories, whereas rest score of these segments remained unchanged.[2]

In addition, a trend toward improvement in perfusion in the remote myocardium was observed, but the study population was too small to reach statistical significance.[2]

Mechanism of Benefit from Bone Marrow Cell Transplantation

The findings of our study are consistent with the hypothesis that bone marrow cells promote angiogenesis, resulting in increased myocardial perfusion and function. As improvement was observed both in injected and non-injected areas, differentiation of bone marrow cells in endothelial and vascular smooth muscle cells cannot solely explain the observed effects. The promotion of angiogenesis could be caused by the production of angiogenic cytokines and upregulation of endogenous cytokine expression, as previously proposed.[11]

The area of scar tissue remained unchanged after bone marrow cell injection. This finding indicates that procedural-induced necrosis or embolization of ischemic myocardium could not have contributed to the relief of angina. In addition, regeneration of cardiomyocytes did not result in resolution of scar tissue or an increase in viable tissue.

Study Limitations

This study was a prospective, observational study, without a control group or randomization procedure. As a consequence, a placebo effect from bone marrow cell transplantation cannot be ruled out. However, it should be emphasized that all scintigraphic studies were analyzed quantitatively using commercially available software. Large placebo-controlled, randomized trials with long-term follow-up should be performed to confirm the current findings. Furthermore, to clarify the precise cellular mechanism of action underlying the benefit of bone marrow cell injections, future clinical studies are warranted to track the trafficking of bone marrow cells in vivo over long periods of time. From a methodological point-of-view, it is important to emphasize that attenuation correction was not used in the SPECT studies, which may have influenced results to some extent.

Conclusions

In summary, intramyocardial bone marrow cell transplantation in patients with chronic ischemic heart disease was safe, improved anginal symptoms and increased LV function. Also, bone marrow cells appear to promote angiogenesis as evidenced by the improvement in perfusion in injected and non-injected segments. Scar formation was not observed. Additional randomized, placebo-controlled trials are warranted to further evaluate this approach of cell-based angiogenic therapy.

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