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

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Abstract

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

Keywords: myocardial infarction, chronic heart failure, bone marrow mononuclear cells, left ventricular remodeling, echocardiography

Introduction

It is well-known that the heart has a limited regenerative capacity and is not able to replace the cardiac cells once lost. Lost cardiac cells are replaced by fibroblasts and connective tissue with the remaining cardiac cells becoming hypertrophic, which may eventually lead to heart failure. The goal of the stem cell-based regenerative medicine is to create healthy, functional cardiac cells that are able to integrate in the injured heart and restore its function [1].

There are several trials about the grafting of stem cells, such as BOOST, TOPCASE-AMI, and ASTAMI trials and several stem cell types have been discovered in the past decade. In most of these trials the authors used bone marrow mononuclear cell (BMMNC) for transferring stem cells through percutaneous coronary intervention (PCI) catheter and selected patients with acute myocardial infarction. Outcome measurements to evaluate the efficacy of trials include clinical measures, echocardiog-

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raphy, magnetic resonance imaging (MRI), and single-photon emission computed tomography (SPECT). The effectiveness and safety of stem cell graft is well verified in these trials [2-13]. However, to our knowledge, patients with coronary artery bypass graft (CABG) combined with stem cells delivered through the graft vessels were not evaluated by echocardiography in the chronic phase.

During the past 12 years, it has become increasingly appreciated that myocardial infarcts, particularly large transmural infarcts, result in complex alterations in ventricular architecture involving both the infarcted and non-infarcted zones. These alterations, often referred as "ventricular remodeling," can profoundly affect the function of the ventricle and the patient's prognosis [14]. Most of patients with previous myocardial infarction and chronic heart failure undergo left ventricular (LV) remodeling. The aim of this study was to evaluate in patients with CABG combined with stem cells delivered through the graft vessels the improvement of left ventricular remodeling using echocardiography and to verify the effectiveness and safety of stem cell therapy in patients with previous myocardial infarction and chronic heart failure.

Material and methods

This study was a randomized, placebo-controlled trial of the effectiveness and safety of a CABG combined with stem cell (BMMNC) therapy in patients with previous myocardial infarction and chronic heart failure. The study was registered at Clinical Trials.gov (trial assigned number: NCT00395811).

Patient selection

The study was approved by the institution and hospital research Ethics Committees. All patients provided written informed consent.

Patients were eligible if they had met all the following conditions: 1) age <75 years; 2) at least 3 months since the last myocardial infarction; 3) planned CABG for triple-vessel disease and according to American Heart Association guidelines (indications for CABG in poor LV function) [15]; 4) no evidence of surviving myocardium in the infarct area, as shown by SPECT and left ventricular angiography; 5) LV ejection fraction<30% on MRI (chronic heart failure); 6) absence of LV aneurysm or valvular diseases requiring surgical intervention; 7) sinus rhythm without frequent ventricular arrhythmias, or history of malignant ventricular arrhythmias; 8) patients with cognitive abilities that agreed to participate in the entire study including the postoperative follow-up.

Patients were not eligible if they had any one of the following conditions: 1) acute myocardial infarction (<3 months); 2) cancer history; 3) mitral regurgitation, LV aneurysm, or intraventricular thrombus requiring concurrent surgery; 4) contraindications to cardiac MRI; 5) significant ventricular arrhythmias (sustained ventricular tachycardia) or atrial fibrillation; 6) primary hematologic diseases; 7) unexplained abnormality at laboratory baseline value; 8) history of other severe chronic diseases; 9) unwillingness to participate; 10) pregnant or lactating women.

Randomization

Patients were randomly allocated to one of the two groups: only CABG or CABG with BMMNC transplantation (CABG+BMMNC). The random table was generated by the SAS software version 9.13 (SAS Institute, Cary, North Carolina). After randomization, the study processes were performed blindly to the patients, participating surgeons, coordinators, and investigators who were responsible for patient assessment [15].

Preparation and transplantation of BMMNCs

Before CABG 60 ml of bone marrow was aspirated from the patient's iliac crest by an experienced hematologist and diluted with normal saline solution. The preparation of the BMMNC was accomplished as previously described [15]. The cells were counted under a light microscope, and the viability was assessed by trypan blue dye.

All surgery procedures were performed by 2 senior surgeons, with the same anesthetists and perfusionists. Standard techniques were adopted by a cardiopulmonary bypass, using cold antegrade cardioplegia, and moderate systemic hypothermia (28°C to 32°C). A left internal mammary artery graft was anastomosed to the left anterior descending coronary artery, and saphenous vein was used for other target vessels. A small bulldog clamp was used to keep the graft conduits filling. The blinded stem cells or placebo solution was injected via the saphenous vein bypass graft after distal anastomosis of the right coronary artery and left circumflex coronary artery. Each saphenous vein bypass graft area received 3 ml of solution and 4 ml of solution was injected through the distal left anterior descending coronary artery anastomosis right before completion of the distal left anterior descending artery bypass graft [15].

The harvested BMMNCs

The number of harvested BMMNCs ranged from 1.09 to 73×10^7 with an average of $13.28 \pm 9.41\times10^7$. The viability of BMMNCs was >98%. The BMMNCs have proliferative potential in vitro. The primary cell formed a clone at approximately 10 days and the time from primary passage to the first passage was 12 to 14 days. Microbiological examination showed no contamination of the culture.

Echocardiography

Echocardiography was performed in all patients before operation (2 to 3 days before surgery) and again 12 months after surgery.

Transthoracic echocardiography was performed using Philips IE 33 ultrasound systems (Philips Medical Systems, Irvine, California) with 2–4 MHz transducer and 3D phased-array transducer. The apical 3D full-volume data set was derived combining seven R wave–triggered subvolumes acquired from seven consecutive cardiac cycles during one breath hold. All imaging data were digitized and stored on a hard disk on the ultrasound machine and then transmitted to a personal computer for further analysis. The 3D data image analysis for LV volumes was performed offline using QLAB version 9.0 (Philips Medical Systems).

On B-mode transthoracic left ventricular long axis view anteroposterior end-diastolic (LVEDD) and end-systolic (LVESD) dimensions of left ventricle and the end-diastolic thicknesses of the interventricular septum and posterior wall were measured. The QLAB version 9.0 software automatically displayed the apical four-chamber and two-chamber views and the para-sternal short-axis view. Manual identification of mitral valve edges and LV apex with five reference points on both end-diastolic and end-systolic frames allowed the software to automatically identify the entire endocardial border in each frame; a manual correction of the endocardial contour was possible if needed. Consequently, a 3D model was generated, providing automatic quantification of end-diastolic (LVEDV) and end-systolic (LVESV) volumes [16] (fig 1). The volumes were subsequently indexed to body surface area (LVEDVI and LVESVI). LV mass was calculated using the following formula LVmass (g) = 0.8[1.04 (LVEDD +interventricular septal thickness + LV posterior wall thickness)^3- (LVEDD)^3] + 0.6 [17]. LV-mass was subsequently indexed to body surface area to obtain LV-massI. Color flow imaging provides a rapid and semiquantitative assessment of valvular mitral regurgitation severity [18]. The ratio between the length of the regurgitant jet and the superoinferior dimension of the left atrium (apical four-chamber view) corresponded to the severity of mitral regurgitation: score 0- no regurgitation; score 1- regurgitation with an length of ≤1/3; score 2- regurgitation length of > 1/3 and ≤1/2; score 3- regurgitation with an length of ≥1/2.

Reproducibility of echocardiographic measurements

Two observers independently assessed echocardiographic parameters. To test intraobserver variability, a single observer (Z.Q.) analyzed the data twice on occasions separated by an interval of 1 month. To test interobserver variability, a second observer (F.D.) analyzed the data without knowledge of the first observer's measures. Reproducibility was assessed as the mean percentage error (absolute difference divided by the mean of the two observations).

Statistical Analysis

Continuous variables were reported as mean±SD. The independent two sample t test analysis of variance was used to compare variables in CABG group and CABG+BMMNC group between the initial and follow-up data. To assess determinants of left ventricular remodeling, as a dependent variable we estimated crude ratios (ORs) with their 95% confidence intervals (CIs). Crude ORs were calculated using Chi-square tests. Chi-square tests were used for categorical variables. P values < 0.05 were considered to indicate statistical significance. All calculations were performed using SPSS version 16 for Windows (SPSS, Inc., Chicago, IL).

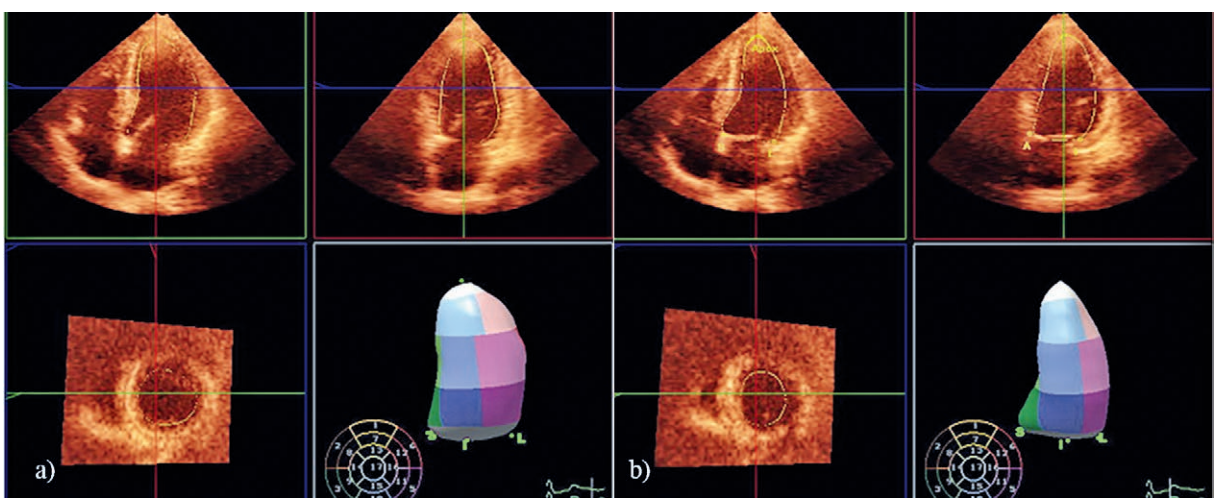

Fig 1. a) Apical 3D full-volume data set. Triplane is displayed. Para-sternal short-axis views are shown for completeness and to indicate the image plane position in the 3D images. End-diastolic volume of left ventricle is calculated and shown in the 3D imagings; b) Apical 3D full-volume data set. Triplane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

Results

Baseline characteristics

From January 2007 to August 2012, 45 patients were evaluated for eligibility. Three patients were excluded because their echocardiographic imagines did not reach the standard of further analysis due to the influence of the operation, aspiration, etc. The patients' number is different from the previous paper published by our group because of the previous echocardiographic study mainly focusing on 3D echocardiography and some patients have not total imaging of the further study needed [15]. From 60 patients that formed the initial group study (published results [15]), 15 were excluded due to the above causes. Of the 42 patients randomized (24 in CABG +BMMNC group and 18 in CABG group), there was a good balance between the 2 groups with respect to baseline characteristics (Table I). All patients except one (from CABG group died of heart failure 13 months after the operation) survived without serious complications and participated in the follow-up.

Intraoperative and early post-operative outcomes

The number of grafts per patient was 4±0.7 (ranging from 3 to 5 grafts) and the cardiopulmonary bypass time was 90±17 min (ranging from 61 to 103 min). Three patients were successfully assisted by intra-aortic balloon pump because of postoperative pulmonary capillary wedge pressure >20 mm Hg. One patient received for 7 days an LV assist device (BVS5000, Abiomed, Danvers, Massachusetts). The ventilation time was 22±32 h (ranging from 7 to 168 h) and the length of intensive care unit stay was 5±1 days (ranging from 1 to 36 days). No patients had serious complications, as defined previously.

Echocardiographic parameters

In CABG+BMMNC group the post-operative LVEDD, LVESD, LVEDV, LVESV, LVEDVI, LVESVI, LV-mass and LV-massI significantly improved comparing to preoperative status with exception of the mitral regurgitation score (Table II). In CABG group no significant differences were found when comparing the postoperative with preoperative parameters (Table III). Chi-square

Table I. Baseline Characteristics

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

Values are mean±SD or median (quartile). BSA=body surface area; BNP=B-type natriuretic peptide; CPB=cardiopulmonary bypass; ICU=intensive care unit; BMMNC=bone marrow mononuclear cell; CABG=coronary artery bypass graft; NYHA=New York Heart Association.

Table II. Echocardiographic parameters in CABG+BMMNC group

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

Values are mean±SD. Pre-surgen=before operation; 1 year later=12 months after surgery; LVEDD- end-diastolic dimension of left ventricle; LVESD- end-systolic dimension of left ventricle; LVEDV- end-diastolic volume of left ventricle; LVESV- end-systolic volume of left ventricle; LVEDVI- LVEDV indexed to body surface area; LVESVI LVESV indexed to body surface area; LV-mass- mass of left ventricle; LV-massI- LV-mass indexed to body surface area; MR score- score of mitral regurgitation.

Table III. Echocardiographic parameters in CABG group

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

Values are mean±SD. Pre-surgen=before operation; 1 year later=12 months after surgery; LVEDD- end-diastolic dimension of left ventricle; LVESD- end-systolic dimension of left ventricle; LVEDV- end-diastolic volume of left ventricle; LVESV- end-systolic volume of left ventricle; LVEDVI- LVEDV indexed to body surface area; LVESVI LVESV indexed to body surface area; LV-mass- mass of left ventricle; LV-massI- LV-mass indexed to body surface area; MR score- score of mitral regurgitation.

Table IV Factors predicting left ventricular remodeling in Chi-square tests

	Crude OR	95% CI	P value
LVEDD (mm)	2.06	1.67-5.61	0.000
LVESD (mm)	4.01	2.21-10.11	0.000
LVEDV (ml)	10.83	6.79-39.16	0.003
LVESV (ml)	11.39	6.45-32.51	0.001
LVEDVI (ml/m^2)	6.59	4.42-20.27	0.005
LVESVI (ml/m^2)	6.82	5.85-18.76	0.002
LV-mass (g)	8.61	6.36-36.65	0.008
LV-massI (g/m^2)	5.47	3.47-24.69	0.012
MR score	0.11	0.09-0.54	0.071

Crude OR=crude ratios; 95% CI=95% confidence intervals; LVEDD- end-diastolic dimension of left ventricle; LVESD- end-systolic dimension of left ventricle; LVEDV- end-diastolic volume of left ventricle; LVESV- end-systolic volume of left ventricle; LVEDVI- LVEDV indexed to body surface area; LVESVI LVESV indexed to body surface area; LV-mass- mass of left ventricle; LV-massI- LV-mass indexed to body surface area; MR score- score of mitral regurgitation.

tests confirmed that LVEDD, LVESD, LVEDV, LVESV, LVEDVI, LVESVI, LV-mass, LV-massI as determinants predicted left ventricular remodeling (Table IV).

Mean percentage error describing reproducibility of intraobserver variability: LVEDD 4.78%, LVESD 4.85%, LVEDV 4.23%, LVESV 4.18%, LV-mass 4.96%. Mean percentage error describing reproducibility of interobserver variability: LVEDD 4.67%, LVESD 4.92%, LVEDV 4.34%, LVESV 4.05%, LV-mass 5.09%.

Discussions

Repairing the injured body with its own tissue as a dream has captured human fascination for a long time. But the heart has a limited regenerative capacity. To deal with this problem, regenerative therapies of cardiovascular medicine are of major interest in ischemic heart disease [1]. Many trials of stem cells graft for ischemic heart disease have been performed over the past decade. Three delivered ways of stem cells have been used, i.e., PCI catheters, graft vessels, and injection in local myocardium. Using BMMNC, transferring stem cells through PCI catheter and selecting patients with acute myocardial infarction are popular in most of these trials. In the current study we focused on a new direction to discover the effectiveness and safety of BMMNC. We selected patients with chronic myocardial infarction (infarct time >3 months) and BMMNCs were delivered through graft vessels.

The effectiveness and safety of isolated CABG combined with BMMNCs delivered through a graft vessel for patients with previous myocardial infarction and chronic heart failure was verified by our previous study by clinical measures, MRI and SPECT [15]. In the current study, we focus on evaluating left ventricular function using echocardiography.

The prognosis of the patients bearing myocardial infarction is related to the cardiac mechanics and to the geometry of the left ventricle as well [19] and limiting the ventricular remodeling is one of the objectives for improving ventricular function and clinical outcome [14]. The LV function is an important part of the whole

heart function. Therefore, it is a hot spot in many studies. From echocardiography to MRI, B-mode imaging to strain and strain rate imaging, all kinds of measurements and parameters were used to evaluate left ventricular remodeling [16,20,21]. No matter how the evaluated measurements changed, B-mode imaging analysis is the basis of echocardiography. In this study, we measured LVEDD and LVESD on B-mode imaging, LVEDV and LVESV on 3D imaging, and mitral regurgitation on color flow imaging. LVEDVI, LVESVI, LV-mass, LV-massI, and mitral regurgitation score were derived from above parameters. Other parameters were derived from B-mode imaging and 3D imaging. LVEDD and LVESD are the most intuitional and handy parameters to evaluate the change of LV dimension at end-diastolic and end-systolic period. In the past LV volume was measured according to Simpson's rule on apical four-chamber view on 2D imaging. 2D imaging is often foreshortened, resulting in geometric inaccuracies when LV shape and function is assessed. Apical 3D full-volume data, reconstructed from 2D imaging dates at different angles and planes, is reliable in patients with good acoustic windows. The accuracy of evaluating LV volume is increased by 3D full-volume imaging, but some researchers regard that it could overestimate LV volume [22]. LV remodeling represents not only the increased LV dimension and volume but also LV hypertrophy. LV hypertrophy leads directly to higher left ventricular mass [23]. So an increased LV mass also indicates the degree of LV remodeling.

The weight of patients had large variations. Thus, patients' body surface area must be taken into account. We found that post-operative measured parameters significantly improved compared with those obtained prior to operation in CABG+BMMNC group but not in the CABG group and the explanation of this improvement is related to the BMMNC graft.

Revascularization procedures include percutaneous transluminal coronary angioplasty and CABG. The aim of revascularization is to recanalize the infarct-related artery. But the effectiveness of revascularization is just to reperfuse the infarct zone, not replace necrotic cardiac cells [24]. Lost cardiac cells are replaced by fibroblasts and connective tissue to form scar tissue. BMMNCs are stem cells aspirated from the patient's bone marrow can be transplanted directly, without cardiac cells differentiation in vitro before transplantation. BMMNCs have the ability to differentiate into non-hematopoietic cell types, such as the cardiac cells [1]. We suppose that BMMNCs differentiate into cardiac cells, replace scar tissue, and reconstruct LV wall structure due to the improvement of LV remodeling in patients of the CABG+BMMNC group.

Ischemic mitral regurgitation refers to mitral regurgitation that is primarily due to a pathologically dilated LV and mitral annulus or to regional disruptions of the LV and sub-valvular apparatus [25]. It is a common complication of myocardial infarction thought to result from leaflet tethering caused by displacement of the papillary muscles that occurs as the left ventricle remodeling [26]. Postoperative mitral regurgitation score was not significantly different from those prior to operation in both groups in this study. One of the excluding criteria when choosing patients was to exclude mitral regurgitation requiring concurrent surgery in order to avoid the confounding factor coming from other additional operations, such as mitral valvoplasty. Our enrolled patients had mild or no mitral regurgitation, this being probably the reason for no significant improvement of this parameter.

The limitation of this study is the small size of the sample. It is well known that the LV remodeling needs a long period of many physiopathological and anatomical changes. In a further study we will increase the sample size and discuss the role of the BMMNC graft for the improvement of left ventricular remodeling.

Conclusions

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

Conflict of interest: none

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