

Received: 2012.09.16
Accepted: 2013.02.08
Published: 2013.05.06

Nine-year follow-up of local implantation of autologous skeletal myoblasts in a patient with coronary heart disease

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCDEF **Dingguo Zhang***
BDE **Liansheng Wang***
AB **Fumin Zhang**
BF **Chunjian Li**
BF **Tiebing Zhu**
BF **Kejiang Cao**
BF **Wenzhu Ma**
ACG **Zhijian Yang**

Department of Cardiology, First Affiliated Hospital of Nanjing Medical University,
Nanjing, P.R. China

* Dingguo Zhang and Liansheng Wang play equal contribution for this manuscript
Zhijian Yang, e-mail: zhijianyangnj@yahoo.com.cn





Corresponding Author:

Patient: gender – Male, age – 63 year-old
Primary Diagnosis: Acute myocardial infarction
Co-existing Diseases: Hypertension
Medication: Aspirin • beta-blocker • captopril
Clinical Procedure: CABG • autologous skeletal myoblast transplantation • PCI
Specialty: Cardiology

Objective: Unusual or unexpected effect of treatment.
Background: Cell transplantation has been viewed as a promising strategy for end-stage heart failure, but long-term follow-up results are lacking.
Case Report: In December 2002 we began transplanting autologous skeletal myoblasts in one patient because of serious coronary heart disease. Here, we present the 9-year follow-up results of this patient. No ventricular tachyarrhythmias were detected after treatment. The patient had another myocardial infarction in April 2012 and was treated successful with PCI.
Conclusions: Autologous skeletal myoblast transplantation with bypass surgery is associated with improvement in cardiac function and lack of adverse effects in long-term follow-up, making it a promising therapy for patients with heart failure.

Key words: skeletal myoblast • cellular transplantation • ischemic heart disease • heart failure

Full-text PDF: <http://www.amjcaserep.com/download/index/idArt/883903>

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Background

Heart failure continues to be a major clinical problem despite advances in medical and surgical treatment of myocardial infarction in the acute phase and in the postinfarction period. It is estimated that more than 20 million people worldwide have had heart failure [1,2]. Although surgical and catheter-based revascularization of ischemic myocardium can restore blood flow, improve perfusion, reduce clinical symptoms, and augment function of viable myocardium, the viability of severely ischemic myocardium, necrotic myocardium, or both cannot be restored. In some patients, cardiac transplantation may be an option, but because of the organ shortage and need for immunosuppression therapy, its practical use is limited.

Cell therapy has recently emerged as a promising strategy for end-stage heart failure [3,4]. Many publications [5–8] have demonstrated the feasibility and efficacy of intramyocardial transplantation of autologous skeletal myoblasts for myocardial repair and functional improvement in experimental animals. The results of experimental studies encouraged Abraham et al. [9] to perform the first autologous skeletal myoblast transplantation in a patient, a survivor of myocardial infarction, during CABG. We investigated the safety of this treatment in a canine heart model. Echocardiographic evaluation of cardiac function, blood tests, and local histological findings of heart muscle did not demonstrate any evidence of systemic or local toxicity induced by this treatment in the acute or chronic phases. Therefore, starting in December 2002, we began a clinical trial in patients [10–12]. Here, we present the 9-year follow-up results of a patient who received autologous skeletal myoblast transplantation because of serious coronary heart disease. No ventricular tachyarrhythmias were detected after treatment. The patient had another myocardial infarction in April 2012 and was treated successfully with PCI. Our results demonstrate the safety and efficacy of this treatment in ischemic myocardial patients.

Case Report

In December 2002, a 63-year-old man with hypertension history was admitted with chest pain lasting more than 2 days to our hospital emergency department. He had no history of smoking or diabetes mellitus. He had been experiencing chest discomfort during slight exercise during the previous 3 months. Troponin T levels were 0.17 U/ml (normal <0.1 u/ml). An electrocardiogram (ECG) showed sinus rhythm with ST elevation over leads II, III, and aVF, revealing acute inferior myocardial infarction. He was admitted to the coronary care unit with a diagnosis of ST-elevation acute myocardial infarction and refractory heart failure (New York Heart Association class III). Echocardiographic left-ventricular mean ejection fraction (LVEF)

was 48%, with severe posterior wall hypokinesia. Coronary angiography was performed 7 days later, after medical treatment. Tight stenosis in the left main coronary artery, serious anterior trigeminal lesions (Figure 1A), and serious stenosis at the proximal right coronary artery (RCA) were detected (Figure 1B). These findings were a clear indication for myocardial revascularization. Because of the tight stenosis of multi-branches artery lesions, we decided to optimize the effects of bypass surgery by myoblast transplantation in his left ventricular posterior myocardium to improve heart function. This procedure was approved by our institutional review board. The patient received extensive information on the procedure and subsequently gave his written informed consent.

A skeletal muscle biopsy was obtained, and myoblasts were isolated and grown in *in vitro* cell culture, as previously described [1–3]. Three weeks after the biopsy sample was taken, the patient underwent CABG surgery. A saphenous vein (SV), divided into 3 parts, was grafted with the LAD, LCX, and posterior descending artery (PDA) of the RCA. The area of scar was then easily visualized on the left ventricular posterior wall. A total of 1.2×10^6 skeletal myoblast cells divided into 10 suspensions were injected into and around the scar area while the heart still under hypothermic cardioplegia. The needle holes were sealed with fibrin glue before reversal of hypothermic cardiac arrest. No bleeding occurred from the puncture sites. No ventricular tachyarrhythmias were detected after treatment with bypass surgery and skeletal myoblast implantation during the hospitalization period. The patient had an uneventful recovery and was discharged 9 days after surgery.

At 6-month follow-up, the patient's clinical status improved, and he had stable New York Association class II disease. He was prescribed aspirin, clopidogrel, beta-blocker, and captopril. There were no substantial arrhythmias on 24-h Holter recordings. Echocardiographic studies showed a slight (2%) increase of LVEF.

At 4-year follow-up, the patient felt no chest discomfort and lived successfully by himself. He was routinely taking aspirin, beta-blocker, and captopril. In April 11, 2012, he suddenly felt chest pain again and 10 days later he came to our hospital. Pathologic Q waves were determined in II, III, and aVF leads on ECG. Troponin T levels were slightly increased. Echocardiographic studies showed LVEF 57% with severe inferior wall hypokinesia and 24-h Holter monitoring found no ventricular tachyarrhythmias. CAG was performed and examination results showed the RCA was totally occluded (Figure 2A). A Runthrough® NS guidewire (Terumo Company, Europe) was easily and successfully annulated through the occlude RCA, which indicating the artery was recently occluded. After the occluded RCA was re-opened, 3.0×29mm and 3.0×18 mm Firebird 2™ sirolimus-eluting stents (Microport Company, China) were successfully implanted in the RCA (Figure 2B). No complications



Figure 1. Coronary angiography showing a significant lesion in left coronary artery (A) and RCA (B).

occurred during hospitalization. He remains free of angina symptoms and continues to do well at 3-month clinical follow-up. Dual antiplatelet therapy with aspirin and clopidogrel for at least 1 year was suggested.

Discussion

Myocardial infarction is the leading cause of death among people in industrialized nations. Although the heart has some ability to regenerate after infarction, myocardial restoration is inadequate. Consequently, cardiovascular investigators are currently exploring the use of stem cells, including skeletal myoblasts, adult bone marrow stem cells, and cardiac progenitor cells, as possible new regenerative treatments for patients with myocardial infarction and heart failure [4]. Skeletal myoblasts localize at the basal lamina of the adult skeletal muscle and maintain the regenerative potential of the muscle [5]. Because they

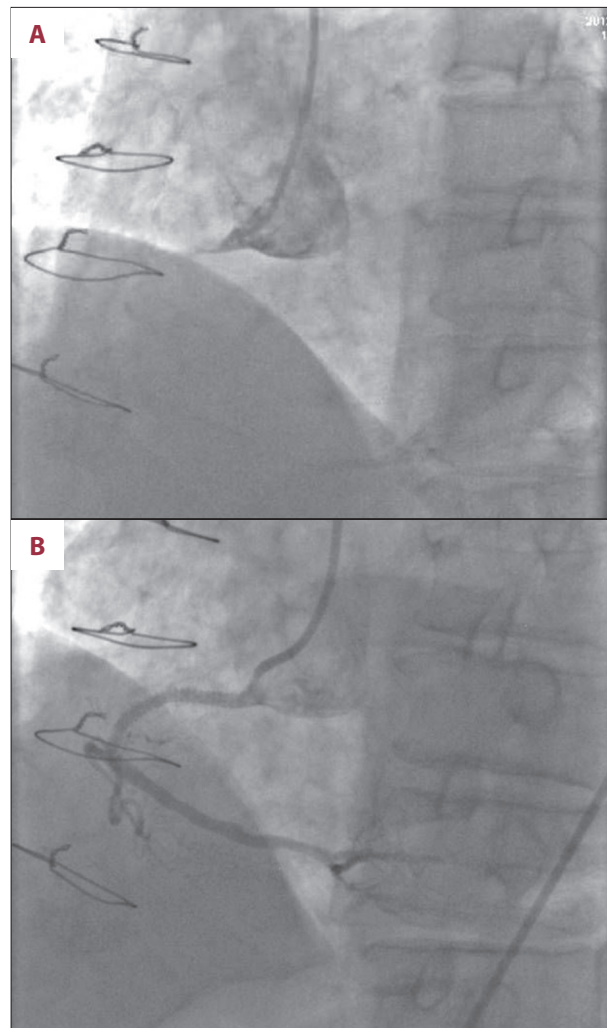


Figure 2. Coronary angiography before PTCA (A) and after stenting showing TIMI 3 flow and minimal residual stenosis in RCA (B).

are natural skeletal myocyte precursors, they have a relatively good proliferative potential under appropriate culture conditions, an advanced stage of differentiation accounting for a myogenic-restricted lineage commitment and high resistance to ischemia, and a capacity to differentiate into myocytes [6]. The possible use of autologous skeletal myoblast cells in clinical conditions is attractive because it avoids the need for immunosuppression, the shortage of donor tissue, and the ethical dilemmas associated with the use of embryonic cells. Very recent reports in patients with myocardial infarction have shown that autologous skeletal myoblasts can survive after transplantation and form viable grafts in heavily scarred human myocardial tissue, thus providing a proof of principle.

The feasibility and efficacy of intramyocardial transplantation of autologous skeletal myoblasts for myocardial repair and functional improvement in experimental animals has been

demonstrated [7]. The results of experimental studies encouraged Menasche et al. [8] to perform the first autologous skeletal myoblast transplantation in a patient, a survivor of myocardial infarction, during CABG. We investigated the safety of this treatment in a canine heart model. Echocardiographic evaluation of cardiac function, blood tests, and local histological findings of heart muscle did not demonstrate any evidence of systemic or local toxicity induced by this treatment in the acute or chronic phases. Therefore, we began a clinical trial of autologous skeletal myoblast transplantation for CAD patients, starting in December 2002 [1–3]. We believe this is the longest follow-up of patient with coronary heart disease who had received autologous skeletal myoblast transplantation. In this 9-year follow-up case study, we found that transplantation of autologous skeletal myoblast cells in patients with depressed LV function because of CAD improved significantly and remain remarkably stable over time, which is most likely because of cell transplantation.

Arrhythmic risk potentially represents a fundamental limitation of cell replacement therapy. Using a unique, state-of-the-art optical mapping system, Abraham MR et al. [9] examined the electrophysiological effects of skeletal myoblast integration within a 2-D array of cardiac myocytes. They found that

any electrically isolated cells introduced into the myocardium may increase arrhythmic risk. Arrhythmic risk has also been observed in human clinical trials. Although the baseline arrhythmic risk in these patients is high, potentially obscuring any effect of replacement cells, trials involving skeletal myoblasts show increased risk of malignant ventricular arrhythmias [10]. The risk seems highest early after transplantation. However, the mechanisms of these presumed arrhythmias still remain to be elucidated, complicated by the lack of appropriate preclinical models and the fact that the underlying heart failure itself predisposes patients to rhythm abnormalities. However, it is very interesting that no ventricular tachyarrhythmias were detected after treatment with bypass surgery and skeletal myoblast implant during 9-year follow-up in this patient.

Conclusions

In conclusion, our results suggest that autologous skeletal myoblast transplantation with bypass surgery is associated with improvement in cardiac function and lack of adverse effects, thus resulting in a promising therapy for patients with heart failure. We believe that these results warrant further clinical research, including randomized studies.

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