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E-mail: jzus@zju.edu.cn

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Brain natriuretic peptide: A potential indicator of cardiomyogenesis after autologous mesenchymal stem cell transplantation?

LI Nan[1], WANG Jian-an[‡2]

([1]*Division of Clinical Pharmacology, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou 310016, China*)

([2]*Division of Cardiology, the Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310009, China*)

E-mail: nli_zum@yahoo.com.cn; Wang_jian_an@tom.com

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Abstract: We observed in a pilot study that there was a transient elevation of brain natriuretic peptide (BNP) level shortly after the transplantation in the patient with ischemic heart failure, which is unexplainable by the simultaneous increase of the cardiac output and six-minute walk distance. Similar findings were observed in the phase I trial. We postulated on the basis of the finding of Fukuda in vitro that this transient elevation of BNP level against the improvement of cardiac function and exercise capacity might indicate cardiomyogenesis in patients after mesenchymal stem cell transplantation. Further study is warranted to verify the hypothesis.

Key words: Mesenchymal stem cell transplantation, Brain natriuretic peptide, Cardiac function, Exercise capacity, Cardiomyogenesis

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Despite the evidence of autologous mesenchymal stem cells (MSCs) augmenting angiogenesis in ischemic area of myocardial infarction in animal model (Wang *et al*., 2004; Tang *et al*., 2004), the results of cardiomyogenesis are controversial and debatable. Currently, there are two methods to label the differentiation of MSCs into cardiomyocytes. The immunostaining of sarcomeric alpha-actinin and cardiac troponin T of infarct area were reportedly used to assess newly expressed cardiac muscle proteins (Shake *et al*., 2002). The magnetic resonance fluoroscopy could help to deliver MSCs into the infarcted area in swine model (Dick *et al*., 2003). Nevertheless, these biomarkers appeared not practical in human studies. In a pilot study of MSCs in ischemic heart failure patients, we observed that there was a transient elevation of brain natriuretic peptide (BNP) in one patient (with hypertension, atrial fibrillation, diabetes, and heart failure, NYHA III) at 1.5 months during follow-up (BNP: 341 vs 276 pg/ml), which did not parallel the improvement of symptoms, increase of six-minute walk distance (540 vs 495 m) and the metabolic gas exchange measurements (cardiac output: 3.0 vs 2.1 L/min; cardiac index: 1.7 vs 1.2; oxygen uptake: 0.302 vs 0.278 L/min). At the sixth month after transplantation the BNP level was lower than the baseline level before MSC transplantation (223 vs 276 pg/ml) and the end diastolic ventricular diameter was decreased (6.18 vs 7.59 cm). On the contrary, in a patient with prior ischemic heart failure, his BNP level was normal at baseline and had not increased after transplantation. Similarly, in a patient treated with optimal drug therapy (diuretics, digoxin, metoprolol, angiotensin receptor blocker, spironolactone, and statin) but without MSC transplantation, he presented gradual reduction of BNP during the follow up.

BNP is generally regarded as the prognostic factor in heart failure patients. It is a common knowledge that BNP is secreted after stimulus of ventricular myocardium stretch and ischemia (Li and Wang,

‡ Corresponding author

2005). However, Fukuda found that the MSCs may secret ANP (atrial natriuretic peptide) and BNP in vitro (Fukuda, 2002). We therefore postulated that if the MSCs differentiated into cardiomyocytes, they would have characteristics of cardiomyocytes, such as contraction and paracrine. The new cardiomyocytes would express BNP when they had stimulus from the infarcted tissue. The improvement of microcirculation, inhibition of fibrosis and prevention of further ventricular remodelling could be attributable to the paracrine of BNP (Fig.1).

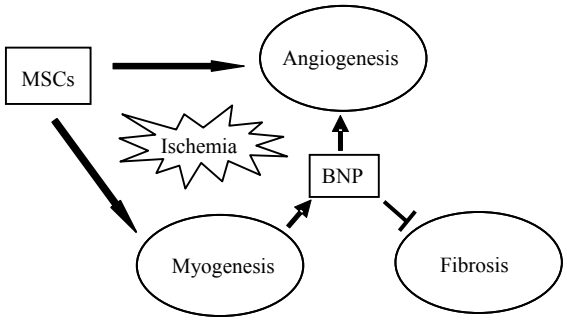

Fig.1 Illustration of the role of BNP in ventricular remodelling after autologous mesenchymal stem cell transplantation

Under this hypothesis, in a randomized clinical trial of MSCs transplantation compared to conventional drug therapy, a gradual reduction of BNP level should be expected in the drug group; meanwhile, a transient elevation of BNP level should be observed in MSCs group shortly after the transplantation. The delayed reduction of BNP in MSCs group should be the net outcome of the combined therapies.

In our phase I trial of mesenchymal stem cell transplantation (n=10, mean age=58, range from 36 to 72 years old, male:female=8:2), we found that during 6 months follow-up after stem cell transplantation, 4 patients had elevated serum BNP levels at the sixth month while their ejection fraction, six-minute walk distance and cardiac output values were improved compared to their corresponding baseline values. At the sixth month, the mean BNP level was not significantly changed compared to the baseline value (404.37±68.17 pg/ml vs 702.01±211.71 pg/ml, P=0.163); the mean left ventricular ejection fraction increased although the statistical analysis did not reach significant (38.83%±5.14% vs 31.45%±3.66%, P=0.059); and the mean cardiac output trended to increase compared to the baseline values before the transplantation (at rest: 3.10±0.29 L/min vs 2.21±0.23 L/min, P=0.063). The mean six-minute walk distances were significantly increased at the sixth month compared to the baseline values before the MSC transplantation (522.25±25.89 m vs 472.85±26.05 m, P=0.004). Data of 12 months follow-up of these patients were not available yet in this study.

It should be stressed that the survival and differentiation of stem cells into cardiomyocyte are not consistent with each other at a certain time spot as we expected. The labelling of biomarker in animal models indicating the emerging of those characteristic proteins of new cardiomyocytes varied around 2 weeks to 6 months. Even at the sixth month, these cardiomyocytes might not be completely matured (Dai *et al*., 2005).

Despite the importance, the ideal biomarker of engraftment of MSCs in vivo is lacking currently (Pittenger and Martin, 2004). In the autologous mesenchymal stem cell transplantation, because MSCs avoid autoimmune rejection, the transient elevation of BNP level observed along with the improvement of cardiac function and exercise capacity might indicate cardiomyogenesis after transplantation.

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