



EDITORIAL COMMENT

Combining mesenchymal stem cell therapy and exercise training in myocardial infarction: The perfect symbiosis?☆



Terapêutica combinada de células estaminais mesenquimatosas e exercício físico no enfarte agudo do miocárdio: uma simbiose perfeita?

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Available online 25 November 2019

Myocardial infarction (MI) remains one of the leading causes of morbidity and mortality worldwide.¹ Following MI, the injured myocardium is replaced by fibrotic tissue, resulting in reduced contractility and ventricular remodeling that can lead to the development of heart failure.²

The classical view of the human heart as a postmitotic organ incapable of self-regeneration has been overturned, largely by a study by Quaini et al. in the *New England Journal of Medicine* in 2002 that identified cardiac cells with the Y chromosome in hearts from female donors transplanted into male recipients.³ This landmark study demonstrated cardiac regeneration in adults by showing that stem cells can migrate from the host to the transplanted heart, where they develop into cardiac cells.^{3,4}

Various studies over the last two decades have produced promising results concerning the ability of stem cells to promote cardiac regeneration, in both animal models and clinical trials.^{5–7}

Mesenchymal stem cells (MSCs) are non-hematopoietic adult stem cells produced in bone marrow that are capable

of self-renewal, proliferation and multidifferentiation in a suitable environment. They can differentiate into a limited number of cell types of the mesodermal lineage, including osteoblasts, chondrocytes, adipocytes, myocytes, endothelial cells and marrow stroma.⁸ MSCs can be isolated from bone marrow, as well as adipose tissue, the placenta, umbilical cord blood, and Wharton's jelly.^{9–11} They have been the subject of more studies and clinical trials than any other stem cells,¹² due to advantages such as ease of collection, expansion and genetic modification in vitro and their low immunogenicity and tumorigenicity.^{12,13}

It has been shown that MSCs are capable of engrafting in host tissue, where they differentiate into vascular endothelial cells (direct action) and, more importantly, stimulate recruitment of other, endogenous stem cells (paracrine action).¹³ Their action has various beneficial cardiac effects, including increased perfusion, reduced fibrosis and inflammation, improved left ventricular (LV) regional and global contraction, and decreased LV end-systolic volume, resulting in improved LV function following MI.^{6,14–16}

The benefits of MSC therapy in MI have been explored in phase I and II clinical trials and the results are promising. A meta-analysis published in 2017 of 34 trials enrolling 2307 patients with MI showed that those who received transplanted MSCs presented significant improvements in LV systolic function and decreased LV volumes.⁵ Another meta-analysis, including 1938 patients with ST-elevation MI in 28 clinical trials, showed that the improvement in LV systolic

☆ Please cite this article as: António N. Terapêutica combinada de células estaminais mesenquimatosas e exercício físico no enfarte agudo do miocárdio: uma simbiose perfeita? Rev Port Cardiol. 2019;38:657–659.

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function associated with MSC therapy was maintained in the long term.⁷

However, despite the promising results of initial studies on stem cell therapy in MI patients, various problems still stand in the way of fulfillment of their therapeutic potential. One is the low rate of adhesion, retention, differentiation and survival of these cells in a hostile ischemic environment.⁶ Previous studies indicate that only about 3 % of transplanted MSCs appear in the marginal area of the infarct within 24 hours of systemic administration,¹³ and that fewer than 1 % survive for more than one week.¹⁷ Furthermore, the improvement in LV systolic function associated with MSC therapy in patients with MI is only modest.¹⁸

It is thus important to develop strategies to improve the microenvironment of the host myocardium in order to enhance the survival and function of transplanted MSCs.

The cardiovascular benefits of aerobic exercise have been amply demonstrated. Regular exercise reduces the incidence of coronary events and also improves survival after MI.^{19,20} The cardioprotection afforded by exercise in MI can be explained not only by reductions in conventional risk factors such as dyslipidemia and hypertension, but also by improved endothelial function and through ischemic preconditioning.¹⁹

In the article by de Freitas et al. published in this issue of the *Journal*,²¹ the authors demonstrate that a combination of exercise training and MSC therapy has a synergistic effect on extracellular matrix remodeling and LV function in infarcted rats. This suggests that exercise training may be a way to make the ischemic microenvironment more favorable to the action of MSCs in MI.

This animal model compared four groups of rats with induced MI: sedentary rats treated with autologous MSCs (obtained from bone marrow and administered intravenously); rats that underwent a 12-week exercise program beginning 24 hours after MI; rats that underwent the exercise program and were also treated with MSCs; and sedentary control rats.²¹ The authors found that in the three treatment groups – exercised, MSC treated, and exercised and MSC treated – infarct size was smaller and LV systolic function was better than in the control group, and that the reduction in infarct size was greater in the group that received the two therapies in combination. They also observed that exercise training was associated with reductions in collagen content and α -actin expression and an increased α/β myosin heavy chain ratio in the left ventricle, especially when combined with MSC therapy. These effects may explain the additional improvement in cardiac function with exercise training.

The mechanisms by which MSCs enhance cardiac repair are not fully understood. Recent research questions whether the cells have any direct action and suggests that their mode of action is basically paracrine.²² The study by de Freitas et al. supports the idea that the benefit from MSC therapy derives exclusively from their indirect action, since these cells were not detected in the hearts of rats transplanted with the same dose of MSCs and euthanized 18 hours after MI. The improvement in cardiac function observed even though no MSCs were retained indicates that their therapeutic effect results from their stimulation of endogenous repair processes via paracrine signaling. Previous studies have demonstrated that MSCs release various paracrine cytokines, including stromal cell-derived factor 1, vascular

endothelial growth factor, hepatocyte growth factor, insulin-like growth factor, microRNAs, and exosomes.¹³ Through release of these soluble factors, MSCs exert a powerful proangiogenic effect, stimulating the action of endogenous cardiac stem cells; they also have anti-inflammatory and antifibrotic effects by inhibiting fibroblast proliferation and reducing collagen deposition, thereby stabilizing the extracellular matrix.¹³ In the study by de Freitas et al., the authors showed that collagen content in the left ventricle was lower both in animals treated with MSCs and in those undergoing exercise training, and was further reduced in those receiving the two therapies in combination.

Stem cell therapy is an approach worth exploring to minimize cell loss and ventricular remodeling following MI. However, although the safety of this therapy has been confirmed in humans, its therapeutic effect in isolation has so far been modest. Combining it with exercise training may, through synergistic effects, succeed in amplifying the benefit of MSC therapy in preventing adverse ventricular remodeling and progression to heart failure.

Conflicts of interest

The authors have no conflicts of interest to declare.

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