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ORIGINAL ARTICLE

Effects of exercise training and stem cell therapy on the left ventricle of infarcted rats

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KEYWORDS

Exercise;
Myocardial infarction;
Stem cells;
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Abstract

Introduction and Objectives: Stem cell therapy and aerobic exercise are non-pharmacological therapies following myocardial infarction. The aim of this study was to test whether aerobic exercise training enhances the benefits of mesenchymal stem cell (MSC) therapy on remodeling of the extracellular matrix and fetal gene expression in the left ventricle of infarcted rats.

Methods: Myocardial infarction was surgically induced in six-week old male Wistar rats. Animals were divided into four groups: sedentary control (SC) and sedentary and stem cell treated (SCMSC); exercised (EX) and exercised and stem cell treated (EXMSC). Bone marrow-derived MSCs were immediately transplanted via the tail vein (concentration: 1×10^6 cells). Exercise training (five days/week, 60 min/day; 60% of maximal running speed) started 24 hours after myocardial infarction and lasted for 12 weeks.

Results: Exercise capacity was higher in exercised than in sedentary groups. Animals in the SCMSC, EX and EXMSC groups exhibited better cardiac function than those in SC. Collagen content was lower in the SCMSC, EX and EXMSC groups than in SC and skeletal α -actin expression was lower in EX and EXMSC than in SC. The α/β -MHC ratio was higher in EX and EXMSC than in SC. The combination of therapies further reduced collagen content in the remote region of the infarct (~24%) and skeletal α -actin expression (~30%).

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PALAVRAS-CHAVE

Exercício;
Enfarte do miocárdio;
Células estromais;
Genes;
Colagénio

Conclusion: Aerobic exercise training appears to enhance the beneficial effects of stem cell therapy on remodeling of the extracellular matrix and fetal gene expression in the left ventricle of rats with moderate infarction.

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Influência do treinamento físico e da terapia com células-estromais sobre o ventrículo esquerdo de ratos enfartados

Resumo

Introdução e objetivos: Terapia com células estromais e exercício aeróbio são estratégias não farmacológicas no tratamento pós-enfarte do miocárdio. O objetivo foi testar se o treinamento aeróbio amplia os benefícios da terapia com células mesenquimais estromais (CME) na remodelagem da matriz extracelular e na expressão de genes fetais no ventrículo esquerdo de ratos enfartados.

Métodos: O enfarte do miocárdio foi induzido cirurgicamente em ratos com seis semanas de idade, divididos em quatro grupos: sedentário controle (SC) e tratado com CME (SCCME); exercício (EX) e exercício tratado com CME (EXCME). CME derivadas da medula óssea foram transplantadas através da veia caudal (concentração: 1×10^6 células). O treinamento aeróbio (5 dias/semana; 60 min/dia; 60% da velocidade máxima de corrida) iniciou 24 h após enfarte do miocárdio e durou 12 semanas.

Resultados: A capacidade de exercício foi maior nos grupos exercitados que nos sedentários. Os grupos SCCME, EX e EXCME apresentaram melhor função cardíaca do que o SC. O conteúdo de colagénio foi menor nos grupos SCCME, EX e EXCME que no SC. A expressão da α -actina esquelética foi menor nos grupos EX e EXCME, comparada à do SC. A razão miosina de cadeia pesada α/β foi maior nos grupos EX e EXCME, comparada à do SC. A combinação das terapias reduziu ainda mais o conteúdo de colagénio na região remota (~24%) e a expressão de α -actina esquelética (~30%).

Conclusão: O treinamento aeróbio parece potencializar os benefícios da terapia com células mesenquimais estromais na remodelagem da matriz extracelular do ventrículo esquerdo e expressão de genes fetais em ratos com enfarte moderado.

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Introduction

Left ventricular (LV) remodeling after myocardial infarction (MI) is one of the most common causes of heart failure (HF), and correlates directly with ventricular dysfunction and increased morbidity and mortality.¹ HF is characterized by cardiomyocyte death or hypertrophy, collagen accumulation and molecular changes, such as re-expression of fetal genes including skeletal α -actin and beta-myosin heavy chain (β -MHC) in the heart.² The use of non-pharmacological therapies is known to improve cardiac function, quality of life and survival rates in patients with post-infarction HF.^{3,4}

One such approach is mesenchymal stem cell (MSC) therapy. This therapy is associated with reduced myocardial infarct size, reduced LV wall thinning, antiapoptotic effects and attenuation of ventricular remodeling by antifibrotic action. Moreover, MSC therapy improves myocardial perfusion and preserves systolic and diastolic performance as well

as cardiac electrical viability and impulse propagation.⁵⁻⁸ Aerobic exercise training has also been shown to attenuate HF symptoms and to improve systolic and diastolic function and cellular contraction, as well as presenting a pattern of cardiac gene expression that is distinct from that of pathological cardiac adaptation.⁹⁻¹¹

The effects on infarcted hearts of combining MSC therapy and aerobic exercise training, however, are not yet clear.¹² Recently, our group showed that early exercise training and MSC therapy proved beneficial to LV morphology and function and to myocyte contractility in infarcted rats, although a beneficial effect of combining these therapies was not seen.¹³ Nevertheless, adaptations of the LV extracellular matrix and fetal gene re-expression to this combination of therapies have not been elucidated. Thus, the aim of this study was to test whether aerobic exercise training enhances the benefits of stem cell therapy on remodeling of the extracellular matrix and fetal gene expression in the left ventricle of infarcted rats.

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