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Correspondence

Endothelial progenitor cells mobilization after maximal exercise in patients with chronic heart failure

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Chronic heart failure (CHF) is a multifactorial clinical syndrome characterized by vascular endothelial dysfunction[1] and microcirculation abnormalities[2]. Exercise has been shown to improve exercise capacity[3] and stimulate the mobilization of endothelial progenitor cells (EPCs) that are involved in endothelial regeneration and neovascularization.[4,5] The effects of maximum exercise on EPCs in CHF remain under investigation. The purpose of the present study was to assess the effect of a symptom-limited maximal cardiopulmonary exercise testing (CPET) in the mobilization of EPCs in patients with CHF.

Forty-nine consecutive patients with stable CHF at optimal treatment and EF $\leq$ 49% underwent a ramp incremental symptom-limited maximal CPET on an electromagnetically braked cycle ergometer. This interventional clinical study was conducted in accordance with the Declaration of Helsinki and patients signed an informed consent form prior to their participation. CPET metabolic and ventilator parameters were measured and recorded breath by breath (Vmax 229, Sensor Medics, Anaheim, California, USA). Blood samples were drawn from a peripheral vein in EDTA tubes once before and once within the first 5 min after CPET. Four-color flow cytometry was performed within the first hour of the collection to identify and quantify 5 different cellular populations; 3 subgroups of EPCs ($CD34^+/CD45^-/CD133^+$, $CD34^+/CD45^-/CD133^+/VEGFR_2$, and $CD34^+/CD133^+/VEGFR_2$) and 2 subgroups of circulating endothelial cells (CECs) ($CD34^+/CD45^-/CD133^-$ and $CD34^+/CD45^-/CD133^-/VEGFR_2$).[6] The number of cellular populations was expressed as median (25th-75th percentiles) in absolute number of cells per 10^6 enucleated cells.

Demographic and exercise characteristics of patients are demonstrated in Table 1. All cellular populations increased after a symptom-limited maximal CPET ($p < 0.01$, Table 2). Power analysis for each circulating endothelial population was 0.99.

Our present study demonstrated that a single symptom-limited maximal CPET stimulates the mobilization of EPCs in patients with CHF (Fig. 1). In comparison with previous studies[7], we used a more specific and analytical EPCs quantification, and we showed that there is a significant EPCs mobilization after a symptom-limited maximal CPET in patients with CHF. During the last decades, both endothelial progenitor and CECs are being used as an index of the endothelium restoration potential, therefore reflecting the vascular endothelial function.[5] We have previously shown that neuromuscular electrical stimulation, an alternative modality of exercise

Table 1
Demographic and cardiopulmonary exercise testing characteristics of patients with chronic heart failure

Demographic characteristics	
Number of patients (N)	49
Gender (*Males/Females*)	41/8
Age (years)[a]	56 ± 10
Height (cm)[a]	175 ± 10
Weight (kg)[a]	90 ± 23
NYHA stage (class II/III)	34/15
EF (%)[a]	32 ± 8
Type of CHF	
Dilated cardiomyopathy [n (%)]	12 (25%)
Ischemic [n (%)]	29 (59%)
Other (valvulopathy, etc) [n (%)]	8 (16%)
Medication	
Diuretics [n (%)]	32 (65%)
ACE inhibitors [n (%)]	24 (49%)
ARBs [n (%)]	7 (14%)
b Blockers [n (%)]	48 (98%)
Aldosterone Antagonists [n (%)]	37 (76%)
Ca blockers [n (%)]	3 (6%)
Vasodilators [n (%)]	4 (8%)
Digoxin [n (%)]	3 (6%)
Amiodarone [n (%)]	8 (16%)
Cardiopulmonary exercise testing parameters	
Peak VO_2 (ml/kg/min)[a]	18.1 ± 4.4
Peak predicted VO_2 (%)[a]	63 ± 16
VE/VCO2[a] slope	34 ± 4
Peak WR (watts)[a]	96 ± 40
SBP at rest (mmHg)[a]	111 ± 10
DBP at rest (mmHg)[a]	73 ± 10
SBP at peak of exercise (mmHg)[a]	163 ± 12
DBP at peak of exercise (mmHg)[a]	91 ± 7
HR at rest (beats/min)[a]	78 ± 10
HR at peak of exercise (beats/min)[a]	177 ± 11

NYHA, New York Heart Association; **EF**, ejection fraction; **CHF**, chronic heart failure; **ACE**, angiotensin-converting enzyme; **ARB**, angiotensin II receptor blockers; **VO_2**, oxygen uptake; VE, minute ventilation; **VCO_2**, carbon dioxide output; **CPET,** cardiopulmonary exercise testing; **WR,** work rate; **SBP,** systolic blood pressure; **DBP,** diastolic blood pressure; and **HR,** heart rate.
[a] Values are expressed as mean ± SD.

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Table 2
Acute mobilization of circulating endothelial populations after a symptom-limited maximal cardiopulmonary exercise testing in patients with chronic heart failure

	Before CPET	After CPET	P value
$CD34^+/CD45^-/CD133^+$	48 (25 - 75)	90 (45 - 106)	< **0.001**
$CD34^+/CD45^-/CD133^+/VEGFR_2$	2 (1 - 4)	5 (3 - 8)	< **0.001**
$CD34^+/CD133^+/VEGFR_2$	11 (7 - 18)	14 (10 - 22)	< **0.01**
$CD34^+/CD45^-/CD133^-$	202 (151 - 312)	382 (252 - 608)	< **0.001**
$CD34^+/CD45^-/CD133^-/VEGFR_2$	1 (1 - 2)	3 (2 - 5)	< **0.001**

CPET, cardiopulmonary exercise testing.
Values of circulating endothelial populations are expressed as "*cells/10^6 enucleated cells.*"
Power analysis for each circulating endothelial population was 0.99.
The statistical significance was set at a p value &<0.05.

There is cumulative evidence from the international literature that EPCs hold high potential to ameliorate atherosclerotic pathogenesis and restore endothelial dysfunction in cardiac disorders.[10] Although there is some evidence that an exercise training program can improve EPCs and restore endothelial function in CHF patients[11], more randomized controlled trials are needed to investigate the beneficial effects of exercise on EPCs and its clinical and prognostic implications.

Conclusively, a single symptom-limited maximal CPET session stimulates the mobilization of EPCs in CHF patients.

Conflict of interest

The authors declare that they have no conflict of interest.

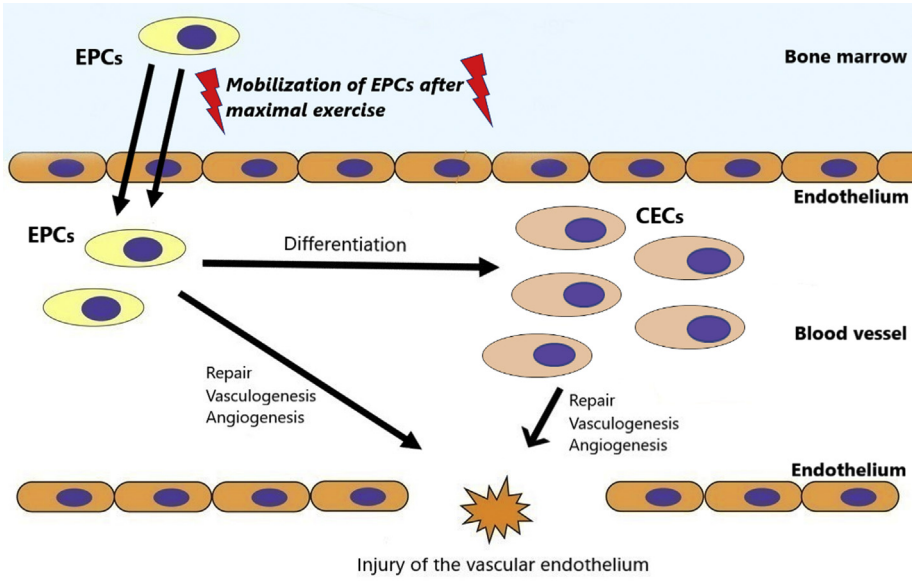

Figure 1. Mobilization of EPCs after a symptom-limited maximal cardiopulmonary exercise testing in patients with chronic heart failure.

training could stimulate the mobilization of EPCs in septic patients[8], confirming the acute exercise effects of the present study.

Shear stress and the ischemic/hypoxic stimulus could be suggested as potential triggering factors for EPCs release after maximum exercise.[9] Shear stress seems to upregulate the activity of endothelial nitric oxide (NO) synthase and increases the production of NO contributing to the amplified number and activity of EPCs.[9] The ischemic/hypoxic stimulus may relate to the upregulation of stromal cell-derived factor 1 and vascular endothelial growth factor (VEGF), which mediate processes to promote proliferative and migratory capacities of circulating EPCs.

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