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## RESEARCH ARTICLE

## THE ACUTE EFFECT OF RESPIRATORY MUSCLE TRAINING ON MICROCIRCULATION IN PATIENTS WITH CHRONIC HEART FAILURE

Christina Katsoula<sup>1</sup>, Eleftherios Karatzanos<sup>1</sup>, Nikoleta Rovina<sup>2</sup>, Christina Routsis<sup>1</sup>, Ioannis Vasileiou<sup>1</sup>, Elektra Papadopoulou<sup>1</sup>, Alexandros Briasoulis<sup>3</sup>, Serafeim Nanas<sup>1</sup>, Ioannis Vasileiadis<sup>1</sup>

1. Clinical Ergospirometry, Exercise and Rehabilitation Laboratory, 1<sup>st</sup> Critical Care Department, Evangelismos Hospital, School of Medicine, National & Kapodistrian University of Athens, Greece
2. Intensive Care Unit, 1<sup>st</sup> Department of Respiratory Medicine, Sotiria Hospital, School of Medicine, National & Kapodistrian University of Athens, Greece
3. Department of Clinical Therapeutics, Alexandra Hospital, School of Medicine, National & Kapodistrian University of Athens, Greece

**Abstract**

**Background:** Patients with chronic heart failure (CHF) present microcirculation alterations and vascular endothelial dysfunction. Exercise training programs have been shown to improve the functional status of these patients, however less is known yet about the acute systemic effect of exercise on peripheral muscle microcirculation. The aim of the present study was to investigate the acute effect of a respiratory muscle exercise bout on the microcirculation of non-exercising muscles (systemic effect).

**Materials and Methods:** Thirty-four (30♂/4♀) stable CHF patients, with a mean age of 61.4±9.2 years, ejection fraction (EF): 33.9±7.8%, maximal inspiratory pressure (MIP): 78.2±27.1 cmH<sub>2</sub>O, VO<sub>2</sub>max: 17.5±4.05 ml/kg/min, VE/VCO<sub>2</sub> slope: 32.7±6.4 and a New York Heart Association classification (NYHA) ≥ II participated in the study. Microcirculatory assessment was performed at rest and immediately after the respiratory exercise program (5 sets/10 repetitions, training load: 60% of MIP). Basal tissue oxygen saturation (StO<sub>2</sub>), oxygen consumption rate (OCR) and reperfusion rate (RR) were measured utilizing near-infrared spectroscopy (NIRS) at the thenar muscle along with the vascular occlusion test (VOT).

**Results:** RR (%/min), following the release of vascular occlusion, as well as OCR (%/min) increased after the respiratory exercise program (from 3.4±1.6 to 3.9±1.7, p=0.007, and from 12.7±3.8 to 13.2±3.9, p=0.021 respectively), whereas the corresponding basal StO<sub>2</sub> values difference did not reach the level of statistical significance (from 85.5±6.4. to 84.7±6.2, p=0.065).

**Conclusions:** In the present study, concerning patients with CHF, after an acute respiratory exercise bout, dynamic microcirculatory indices assessed by NIRS in peripheral, non-exercising muscles, were significantly altered.

**Keywords:** Respiratory muscle training, microcirculation, chronic heart failure, acute exercise.

**Corresponding Author:** Ioannis Vasileiadis, M.D., Ph.D., Associate Professor of Internal Medicine and Critical Care, National and Kapodistrian University of Athens, School of Medicine, 1<sup>st</sup> Critical Care Department, Evangelismos Hospital, Ipsilantou 45-47, 10676, Athens, Greece, Tel: +30 6977644866, +302132043385, ORCID ID: 0000-0002-9529-9361, Email: [ioannisvmed@yahoo.gr](mailto:ioannisvmed@yahoo.gr), [ivasileiadis@med.uoa.gr](mailto:ivasileiadis@med.uoa.gr)

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## INTRODUCTION

Chronic heart failure (CHF) is defined as a complex clinical syndrome caused by structural or functional cardiac injury.<sup>1</sup> Patients with CHF present a wide range of symptoms, which comprise skeletal (and respiratory) muscle fatigue and dyspnea on exertion, leading to limited exercise capacity and impaired quality of life.<sup>2-3</sup> CHF is one of the most frequent causes of hospitalization and death worldwide. The prevalence of CHF is approximately 1–2% and increases to  $\geq 10\%$  among people over 70 years of age.<sup>4</sup> Endothelial dysfunction has been demonstrated in peripheral and coronary arteries in CHF patients, characterized e.g. by the inability of a vessel to dilate as a response to physiological stimuli.<sup>5-6</sup> Under normal conditions, the endothelium regulates the vascular tone, controlling, thereby, the blood flow to the tissues, participates in the production of new blood vessels, contributes to the balance between pro-inflammatory and anti-inflammatory mediators, and plays an essential role in the homeostasis and normal function of organs and systems.<sup>7</sup> Patients with CHF demonstrate skeletal muscle microcirculatory abnormalities which are associated with exercise intolerance and ventilatory inefficiency.<sup>8</sup>

It has been shown that exercise of specific muscle groups (even application of electrical muscle stimulation, EMS) can affect peripheral microcirculation, in other, non-exercising muscles, with beneficial effects on the vascular endothelium (systemic effect).<sup>9</sup> Near-infrared spectroscopy (NIRS) is a non-invasive method to assess tissue oxygenation. Light in the infrared region (700–1000 nm) passes through biological tissues; being differently absorbed by oxyhemoglobin and deoxyhemoglobin, enables assessment of tissue oxygen saturation (StO<sub>2</sub>). StO<sub>2</sub> accounts for the oxygenated hemoglobin found in arterioles, capillaries and venules.<sup>11</sup>

The vascular occlusion test (VOT) is used for the evaluation of dynamic microcirculatory indices, i.e., tissue oxygen consumption rate and reperfusion rate, the latter indicating the microvascular reactivity (endothelial function).<sup>12</sup>

Inspiratory muscle training is an alternative form of exercise that has been used in CHF patients, either supplementing the usual muscle training programs, or individually, with beneficial effects e.g. on echocardiographic parameters, quality of life, respiratory

and peripheral muscle strength,<sup>13-14</sup> nevertheless, there are insufficient data regarding the systemic effect of this form of exercise. We hypothesized that after an inspiratory muscle exercise bout in patients with CHF, microcirculation in remote, non-exercising muscles would be affected. The purpose of the study was to assess microcirculatory indices (using NIRS in combination with VOT) at the thenar, in patients with CHF, after an inspiratory muscle exercise bout.

## MATERIALS AND METHODS

Thirty-four CHF patients with reduced left ventricular ejection fraction (EF) were referred to our Exercise and Rehabilitation Laboratory from the outpatient heart failure units (Table 1). All patients were taking optimal medical treatment and were in stable condition. The New York Heart Association (NYHA) classification of patients according to their functional status was  $\geq$  II. Patients were excluded from the study if they had: valvular disease, uncontrolled arterial hypertension, pulmonary disease, severe peripheral vascular disorders, neuromuscular diseases as well as contraindications to performing a cardiopulmonary exercise testing (CPET) according to the American Thoracic Society-American College of Chest Physicians statement for CPET.<sup>15</sup> The study protocol was approved by the Evangelismos hospital Ethics Committee and all patients gave written informed consent in order to participate to the study. Inspiratory muscle strength, pulmonary function, peripheral muscle microcirculation as well as CPET parameters were evaluated.

### *Pulmonary Function*

Spirometric measurements were performed at seated position, according to the guidelines of the American Thoracic Society.<sup>16</sup> Forced expiratory volume in 1 s (FEV<sub>1</sub>) forced vital capacity (FVC) and the ratio FEV<sub>1</sub>/FVC were evaluated.

### *Inspiratory muscle function*

Maximal inspiratory pressure (MIP) was assessed using the Cosmed Quark machine. The MIP was measured at residual volume, according to Black and Hyatt.<sup>17</sup>

### *Cardiopulmonary exercise testing (CPET)*

Maximal functional capacity was evaluated with the patient performing CPET on a bicycle ergometer, utilizing a ramp incremental protocol. The duration of the test was estimated to be 8 to 12 minutes. Respiratory gas exchange was evaluated in each breath through a mouthpiece with a low resistance valve, in order to determine  $\text{VO}_2\text{max}$ ,  $\text{VO}_2\text{-slope}$  and other CPET parameters. The peak values for  $\text{VO}_2$  were evaluated as the average of the measurements done at the last 20 seconds of the exercise period, before the end of the test.<sup>10</sup> During CPET, heart rate and rhythm were monitored through a 12-lead electrocardiogram and hemoglobin saturation by a pulse oximeter. Non-invasive blood pressure measurements were taken every two minutes.

#### *Near-Infrared Spectroscopy*

Microcirculation in all patients was evaluated noninvasively by NIRS (InSpectra; Hutchinson Technology, Hutchinson, Minnesota) combined with a 3-minute VOT at the thenar muscle of each patient's upper limb. Ischemia (venous and arterial occlusion) was induced with inflating a pneumatic cuff that was placed above the elbow, to a pressure of 50 mm Hg above the patient's systolic blood pressure for 3 minutes.<sup>18-19</sup>  $\text{StO}_2$  was continuously recorded. All the curves were analyzed according to the InSpectra analysis program. The estimated parameters were:  $\text{StO}_2$  at baseline, oxygen consumption rate (OCR, %/min) as the first degree slope of hemoglobin desaturation (downslope) during the ischemic phase and the reperfusion rate (RR), which reflects microvascular reactivity (endothelial function), as the first-degree slope of the  $\text{StO}_2$  increase after the release of vascular occlusion (Figure 1).<sup>20</sup>

#### *Inspiratory exercise protocol*

Before the respiratory exercise, the patients were given a familiarization period, in which they were instructed how to breathe correctly/adequately. The respiratory exercise program was carried out at 60% of the current MIP measurement. The protocol included 50 breaths (5 sets/10 repetitions), with 5-10 s rest between the sets, using the hand-held POWERbreath KH2 machine. All the patients wore nose-clip during the exercise.

#### **Statistical analysis**

Statistical analysis was made with the SPSS version 25. All the variables are continuous variables and presented as mean  $\pm$  standard deviation. Normality of distribution was evaluated with

the Shapiro-Wilk test. P values  $<0.05$  were considered as statistically significant. Wilcoxon signed ranks test was used for the comparisons of the NIRS variables. The Spearman's  $r$  coefficient was used for correlations.

#### **RESULTS**

All the thirty-four patients completed the respiratory exercise protocol and no one reported any complaint or experienced discomfort during the ischemic phase of NIRS measurements. Respiratory exercise affected the peripheral muscle microcirculation (Table 2): RR (%/min) increased after the respiratory program, from  $3.4 \pm 1.6$  to  $3.9 \pm 1.7$ ,  $p = 0.007$ ; OCR (%/min) also significantly increased, from  $12.7 \pm 3.8$  to  $13.2 \pm 3.9$ ,  $p = 0.021$ ;  $\text{StO}_2$  values (%) did not significantly differ at rest and after the intervention ( $85.5 \pm 6.4$  vs.  $84.7 \pm 6.2$  respectively,  $p = 0.065$ ), although the recorded difference, i.e. reduction, approached the limits of statistical significance. Correlation analyses were also performed among: the percentage change of reperfusion rate, percentage change of occlusion slope, reperfusion rate pre-intervention, occlusion slope pre-intervention, MIP,  $\text{VO}_2\text{max}$ ,  $\text{VE}/\text{VCO}_2$  slope. From the correlation analysis, a significant correlation was found between the percentage change of reperfusion rate and the reperfusion rate pre-intervention,  $r = -0.45$  ( $p = 0.007$ ); No other correlations among the parameters were observed.

#### **DISCUSSION**

In this study we examined, in CHF patients, the variation of tissue oxygenation and microcirculatory alterations at the thenar muscle, induced by a single respiratory exercise bout. Specifically, after the respiratory exercise program, RR as well as OCR, assessed by NIRS combined with VOT, significantly increased. The results of the study are indicative of a systemic effect of *exercising exclusively the respiratory muscles*; this type of exercise appears to affect microcirculation in remote areas where muscles are not forcefully contracting to produce mechanical work. To our knowledge, there is currently no other study in the literature documenting this effect. The clinical significance of the observation is great as this systemic effect is, possibly, the pathophysiological basis for an expected beneficial effect of this type of exercise that will concern the whole organism. This finding may

lead to the use of this particular exercise method for specific therapeutic interventions.

To note, it has been shown that exercise training improves endothelial function, vascular reactivity and exercise capacity in CHF patients.<sup>21-23</sup>

Regarding the pathophysiology of the exercise effect on the circulatory system, it would be useful to briefly remark on. Under resting conditions, cardiac output and regional, peripheral blood flow are regulated, both through central control mechanisms and by local factors that determine the basic tone of the vascular smooth muscle, so that the blood supply meets the metabolic requirements of the tissues. During the acute exercise bout, muscle contraction increases the myocytes' needs for nutrients and oxygen. Thus, in the exercising muscles, an increase in blood flow occurs, in almost linear correlation with the increase in muscle oxygen consumption, so that, with an accompanying alteration of muscle oxygen extraction, these parameters (i.e.  $O_2$  delivery and  $O_2$  consumption) are matched. Changes in blood flow are induced by central control processes, which increase cardiac output, but also by local control of flow, mediated by vasoactive metabolites and mechanical stimuli - note that for the altered vascular reactivity an important role is played by the endothelium.<sup>24</sup>

Nevertheless, it seems that the exercise of individual muscle groups has, in addition to the local (i.e. in the region of the contracting muscles), a systemic effect on the microcirculation, in remote, non-exercising skeletal muscles. Thus, a systemic effect of bicycle ergometer exercise, during CPET, has been described, in which the imposition of a constantly increasing workload on the lower extremities, led to significant changes in microcirculatory indices, assessed at the thenar, in healthy subjects and CHF patients (to note, in the specific study, CHF patients presented an altered microcirculatory response compared to healthy subjects).<sup>9</sup> Also, in a study by Gerovasili et al,<sup>10</sup> a similar systemic effect on the microcirculation was found, by the application of electric muscular stimulation (EMS) to the lower limbs of critically ill patients, who cannot exercise actively; i.e. the OCR and RR, also assessed at the thenar of the patients, increased after the end of the EMS application.

The systemic effect of exercise could be attributed, among other

things, to the sympathetic nervous system activation,<sup>25</sup> but also to vasoactive and/or metabolically active factors that, possibly, being produced locally, in the exercising muscles, are transported by the circulation to all the tissues of the body. For example, Interleukin-6 is considered an energy sensor, produced by contracting muscles (myokine) and affects metabolism by increasing fat oxidation, muscle glucose uptake and glucose production from the liver.<sup>26-27</sup>

As for the post-exercise reduction in tissue oxygenation (although the observed difference approached but did not reach the level of statistical significance), few further comments would be useful. The  $StO_2$  value is determined by the balance between oxygen supply by the circulation and the tissue oxygen consumption rate. Therefore,  $StO_2$  reduction after the end of the respiratory exercise program, which seems to affect also the energy metabolism in distant tissues, could be attributed to a *slow metabolic recovery* (remaining "high" oxygen consumption with delayed return to the levels before the exercise effect) or/and to a *limited capacity of the circulatory system to locally increase blood flow*, alongside the increased energetic turnover. Both these two pathophysiological disorders and, overall, a mismatch between metabolic requirements and the response of the circulatory system to their alterations, characterize patients with CHF, being especially evident during exercise.<sup>28-29</sup> A similar finding, though with a significant difference in  $StO_2$  after the end of exercise (CPET), was also observed in the study by Tzani et al,<sup>9</sup> where, contrariwise, in healthy subjects the tissue oxygenation was preserved.

## CONCLUSIONS

A single respiratory exercise bout seems to affect microcirculatory indices assessed by NIRS combined with VOT, at the thenar muscle, in CHF patients, revealing a systemic effect of this type of exercise.

## Limitations

The rather small number of patients and the lack of a control group.

## Conflicts of interest

None declared.

### Funding

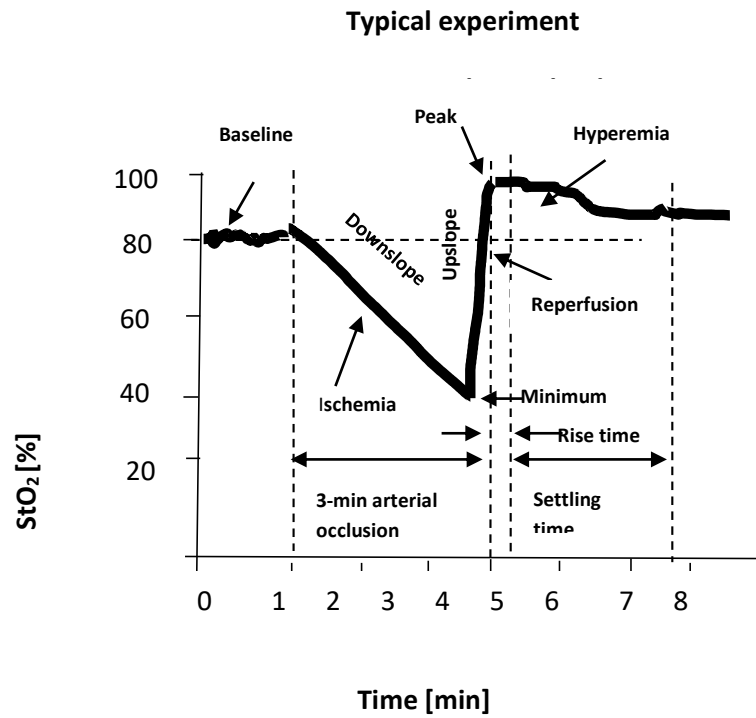
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## ANNEX

**FIGURE 1.** Vascular occlusion test-StO<sub>2</sub> derived into four phases: baseline, ischemia, reperfusion and hyperemia.



**TABLE 1.** Baseline characteristics of patients with chronic heart failure.

<b>N</b>	34
<b>Gender</b>	
• <b>Male</b>	30
• <b>Female</b>	4
<b>Age (years)</b>	61.4±9.2
<b>Weight (kg)</b>	88.2±18.2
<b>Height (cm)</b>	173.7±9.1
<b>EF (%)</b>	33.9±7.8
<b>MIP (cmH<sub>2</sub>O)</b>	78.2±27.1
<b>FEV<sub>1</sub> (%)</b>	82.9±16.0
<b>FVC (%)</b>	90.2±13.8
<b>FEV<sub>1</sub>/FVC</b>	95.7±11.1
<b>VO<sub>2</sub>max (ml/kg/min)</b>	17.5±4.0
<b>VE/VCO<sub>2</sub> slope</b>	32.7±6.4

**EF:** Ejection fraction, **MIP:** Maximal Inspiratory Pressure, **FEV<sub>1</sub>:** Forced expiratory volume at the end of the first second, **FVC:** Forced vital capacity, **VO<sub>2</sub>max:** Maximal oxygen consumption rate, **VE/VCO<sub>2</sub>:** Minute ventilation/Carbon dioxide production.

**TABLE 2.** Evaluation of microcirculatory indices at rest and after the exercise bout

<b>Parameters</b>	<b>Before</b>	<b>After</b>	<b>p</b>
<b>StO<sub>2</sub> (%)</b>	85.5± 6.4	84.7± 6.2	p= 0.065
<b>OCR (%/min)</b>	12.7± 3.8	13.2±3.9	p= 0.021
<b>RR (%/min)</b>	3.4 ± 1.56	3.9± 1.7	p= 0.007

**StO<sub>2</sub> (%):** Baseline tissue oxygen saturation, **OCR:** Oxygen consumption rate, **RR:** Reperfusion rate.