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Metabolic, ventilatory and cardiovascular responses to FES-cycling: A comparison to NMES and passive cycling

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Abstract.
BACKGROUND: Cyclergometry with functional electrical stimulation (FES-cycling) is a feasible method for rehabilitation. The concept is to promote exercise induced by depolarization of the motoneuron and muscular contraction.
OBJECTIVE: To measure acute physiological responses to FES-cycling.
METHODS: Retrospective study of data from ten healthy volunteers who performed FES-cycling, passive cycling and neuromuscular electrical stimulation (NMES) alone. Metabolic, ventilatory and cardiovascular parameters were analyzed.
RESULTS: Oxygen uptake enhanced 97 ± 15% during FES-cycling, with medium effect size compared to NMES and large effect size compared to passive cycling. Energy expenditure enhanced 102 ± 15% during FES-cycling, with medium effect size compared to NMES and large effect size compared to passive cycling. Minute ventilation enhanced 115 ± 26% during FES-cycling, with small effect size compared to NMES and medium effect size compared to passive cycling. Cardiac output enhanced 21 ± 4% during FES-cycling, with medium effect size compared to NMES and passive cycling. Arterial – mixed venous oxygen content difference enhanced 60 ± 8% during FES-cycling, with a medium effect size compared to NMES and large effect size compared to passive cycling.
CONCLUSIONS: FES-cycling enhances metabolic, ventilatory and cardiovascular demands and the physiological responses are higher than NMES and passive cycling.

Keywords: FES-cycling, exercise, oxygen uptake, NMES, electrical stimulation, cycling

1. Introduction

Functional electrical stimulation associated to cyclergometry (FES-cycling) is a feasible method for physical training and rehabilitation in adverse situations. The concept is to promote cyclergometry exercise induced by depolarization of the motoneuron and consequently all the physiological stages of

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Table 1
Anthropometric characteristics

Volunteer	Sex	Age (years)	Weight (kg)	Height (cm)
1	Male	57	74	185
2	Male	52	80	175
3	Male	35	79	181
4	Male	54	80	160
5	Male	32	78	171
6	Male	61	77	176
7	Male	21	63	178
8	Female	44	46	143
9	Female	26	47	160
10	Female	22	58	168

muscular contraction. It uses computer-driven electrical pulses delivered by transcutaneous electrodes, promoting muscle contractions independently on functionality of the physiological pathway [1].

The technology was originally developed over 30 years ago for patients with spinal cord injury [2], but has gained popularity in all situations in which patients cannot actively move their legs (especially in critically-ill patients). The use of FES-cycling for functional capacity improvement has been reported in several populations [3–6]. Mechanical power output produced during FES-cycling is lower than power output obtained in volitional cycling. However, the health benefits bestowed by FES-cycling are strongly related to the power output that can be generated [7].

Despite grater clinical use, acute metabolic, ventilatory and cardiovascular responses to FES-cycling have not been sufficiently described and are not completely understood. A possible superior effect compared to isolated FES-cycling components (passive cycling and NMES – neuromuscular electrical stimulation) also have not been sufficiently documented. Understanding the acute physiological responses to FES-cycling can be the key for more efficient rehabilitation prescription. It also can be important to avoid overtraining and minimize risk inherent to electrical stimulation.

Thus, the primary aim of this study was to measure acute physiological (metabolic, ventilatory and cardiovascular) responses to FES-cycling. The secondary aim was to compare these responses to isolated FES-cycling components.

2. Methods

2.1. Study design

A retrospective study was conducted with the data collected during the development of a FES-cycling equipment. Data from ten healthy volunteers were used (Table 1). The volunteers were placed in the supine position in a bed. They spent 2 minutes in rest and then performed 2 minutes of FES-cycling, 2 minutes of passive cycling and 2 minutes of NMES in a randomized order (randomization by sealed envelopes). They were allowed 5 minutes for recovery between each protocol. The study was approved by the Centro Universitário UNIESP Ethics Committee (CAAE 49243221.4.0000.5184, opinion number 4.838.409).

2.2. Data collection

The VO2000 (MedGraphics, St. Paul, MN, USA) was used for gas analysis and it was calibrated according to the manufacturer's instructions. Heart rate was captured by a transmitter belt placed on

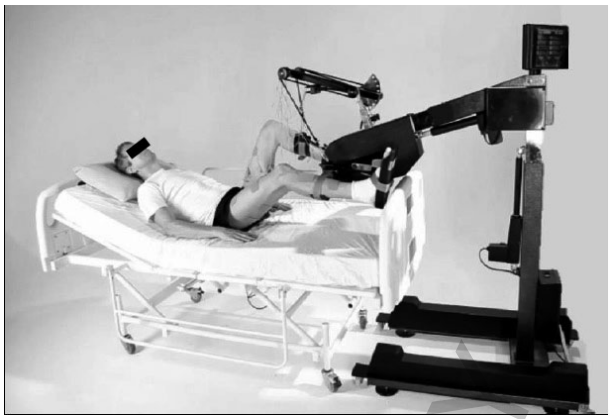

Fig. 1. MOBITRONICS® FES-cycling equipment.

the thorax (Polar T31, Oulu, Finland), connected by radio frequency to the gas analyzer. A 3-minute data collection was established. The time required for all volunteers to reach steady-state was 2 minute and 30 seconds (avoiding any possible anxiety bias). Data used for analysis was collected during the 30 seconds after steady-state. In addition, 5 minutes of recovery between each protocol was enough to return to baseline values. Furthermore, the following variables were used for analysis: oxygen uptake (VO_2); carbonic gas production (VCO_2); energy expenditure [8]; respiratory exchange ratio; minute ventilation; tidal volume; respiratory frequency; cardiac output [9]; arterial-mixed venous oxygen content difference (oxygen uptake divided by cardiac output) and oxygen pulse (oxygen uptake divided by heart rate).

2.3. FES-cycling protocol

Self-adhesive electrodes were placed bilaterally on the quadriceps (vastus lateralis and vastus medialis), hamstrings and tibialis anterior muscles. FES was set with 400 microseconds pulse width, 100 Hz frequency and 20–35 mA intensity. MOBITRONICS® FES-cycling equipment (INBRAMED, Porto Alegre, Brazil) was used to perform the protocol (Fig. 1). FES was triggered (ON) and stopped (OFF) by pedal position. There was a sensor to detect 360° pedal position. FES trigger/stop was set according to physiological joints (hip, knee and ankle) positions during cycling movement. An intensity of 20–35 mA was set because it was the greatest comfortably tolerated intensity. The cyclergometer was set on passive mode at 30 rotation per minute. The volunteers did not perform any voluntary effort. All the work was performed by the FES + cyclergometer.

2.4. NMES protocol

Self-adhesive electrodes (same electrodes of the FES-Cycling protocol) were placed bilaterally on the quadriceps (vastus lateralis and vastus medialis), hamstrings and tibialis anterior muscles. NMES was also set with 400 microseconds pulse width, 100 Hz frequency and 20–35 mA intensity (same intensity as the FES-cycling for each volunteer). STIMULUS-R equipment (HTM, Amparo, Brazil) was used to perform the protocol. NMES was set to promote the same contraction sequence and contraction time of the FES-cycling protocol. The hamstrings and tibialis anterior were activated in the opposite limb and vice versa during quadriceps activation in one limb. ON/OFF time was set at 1 second ON and 1 second OFF (30 rotation per minute in cyclergometer = 2 seconds duration in each rotation).

Table 2
FES-cycling acute physiological responses

Physiological parameter	Mean percentage change from rest	Mean absolute change from rest	p value
VO_2 (mL/min)	$\uparrow 97 \pm 15\%$	254 ± 36	0.0020
VCO_2(mL/min)	$\uparrow 121 \pm 18\%$	314 ± 41	0.0020
EE (watts)	$\uparrow 102 \pm 15\%$	94 ± 38	0.0020
RER	$\uparrow 13 \pm 18\%$	0.12 ± 0.05	0.0707
VE (L/min)	$\uparrow 115 \pm 26\%$	11 ± 3	0.0020
Vt (mL)	$\uparrow 46 \pm 20\%$	217 ± 102	0.0488
RF (breaths/min)	$\uparrow 56 \pm 9\%$	8 ± 1	< 0.0001
CO (L/min)	$\uparrow 21 \pm 4\%$	1.2 ± 0.2	0.0020
Ca-vO_2 (mL/100dL)	$\uparrow 60 \pm 8\%$	2.9 ± 1.2	0.0020
O_2 pulse (mL/beat)	$\uparrow 60 \pm 13\%$	2.2 ± 0.6	0.0054

VO_2: oxygen uptake; VCO_2: carbonic gas production, EE: energy expenditure, RER: respiratory exchange ratio, VE: minute ventilation, Vt: tidal volume, RF: respiratory frequency, CO: cardiac output, Ca-vO_2: arterial – mixed venous oxygen content difference and O_2 pulse: oxygen pulse.

2.5. Passive cycling protocol

Active muscle contraction was not allowed (the volunteers were instructed to be completely relaxed). MOBITRONICS® FES-cycling equipment (INBRAMED, Porto Alegre, Brazil) was also used, but FES was turned-off. The cyclergometer was set on passive mode at 30 rotations per minute. All of the work was only performed by the cyclergometer (without any voluntary effort).

2.6. Statistical analysis

Data normality was verified using the Shapiro-Wilk test. FES-cycling acute physiological responses were measured by the mean percentage change from rest. Differences between FES-cycling and rest were evaluated by paired t-test or Wilcoxon test (according to data normality). Ordinary one-way ANOVA with Tukey's multiple comparison test were used to evaluate intergroup differences for data with a Gaussian distribution. The Kruskal-Wallis test with Dunn's multiple comparisons test were used to evaluate intergroup differences for data without a Gaussian distribution. The post hoc achieved power of effect size was computed (effect size convention: trivial < 0.2; small > 0.2; medium > 0.5 and large > 0.8). A statistically significant value of $p \leqslant 0.05$ was set for all analyses. GraphPad Prism 7.0 and GPower 3.0.10 software programs were used. According to data normality distribution, data were presented as means $\pm$ standard deviations or as medians and interquartile ranges.

3. Results

3.1. Metabolic responses

VO_2 was enhanced during FES-cycling (538 ± 116 vs 285 ± 97 mL/min [rest], $p = 0.0020$) (Table 2). FES-cycling presented higher values for VO_2 than NMES and passive cycling ($p < 0.0001$, respectively). There was no statistically significant differences between NMES and passive cycling ($p = 0.1594$) (Fig. 2). FES-cycling presented a medium effect size compared to NMES and a large effect size compared to passive cycling (Table 3).

VCO_2 was enhanced during FES-cycling (591 ± 138 vs 277 ± 80 mL/min [rest], $p = 0.0020$) (Table 2). FES-cycling presented higher values for VCO_2 than NMES and passive cycling ($p = 0.0207$ and $p <$

Table 3
Effect size of FES-cycling

Physiological parameter	Compared to NMES effect size (power)	Compared to passive cycling effect size (power)
VO_2	0.74 (0.88)	0.82 (0.94)
VCO_2	0.49 (0.54)	0.85 (0.95)
EE	0.72 (0.86)	0.84 (0.95)
RER	0.41 (0.42)	0.63 (0.75)
VE	0.24 (0.17)	0.60 (0.72)
Vt	0.10 (0.07)	0.69 (0.84)
RF	0.31 (0.26)	0.41 (0.42)
CO	0.57 (0.67)	0.71 (0.85)
Ca-vO_2	0.73 (0.87)	0.83 (0.94)
O_2 pulse	0.93 (0.98)	1.08 (0.99)

VO_2: oxygen uptake; VCO_2: carbonic gas production, EE: energy expenditure, RER: respiratory exchange ratio, VE: minute ventilation, Vt: tidal volume, RF: respiratory frequency, CO: cardiac output, Ca-vO_2: arterial – mixed venous oxygen content difference and O_2 pulse: oxygen pulse.

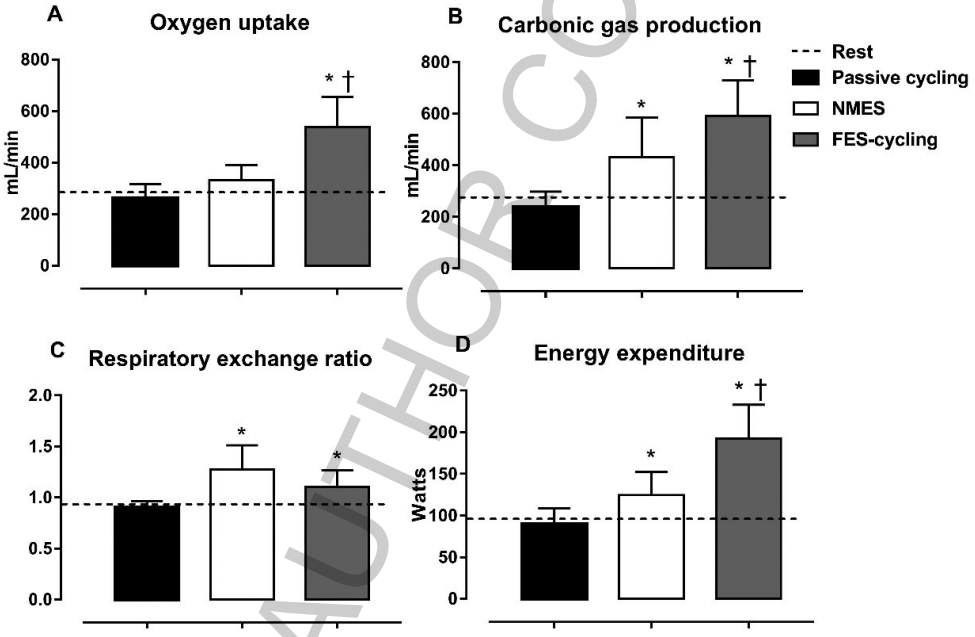

Fig. 2. Metabolic responses. $^{*}p < 0.05$ compared to rest. $^{\dagger}p < 0.05$ compared to NMES.

0.0001, respectively). There was a difference between NMES and passive cycling ($p = 0.0046$) (Fig. 2). FES-cycling presented a small effect size compared to NMES and a large effect size compared to passive cycling (Table 3).

Energy expenditure enhanced during FES-cycling (193 $\pm$ 40 vs 99 $\pm$ 10 watts [rest], $p = 0.0020$) (Table 2). FES-cycling presented higher values for energy expenditure than NMES and passive cycling ($p < 0.0001$, respectively). There was a difference between NMES and passive cycling ($p = 0.0432$) (Fig. 2). FES-cycling presented a medium effect size compared to NMES and a large effect size compared to passive cycling (Table 3).

Respiratory exchange ratio enhanced during FES-cycling (1.10 $\pm$ 0.16 vs. 0.98 $\pm$ 0.11 [rest], $p =$

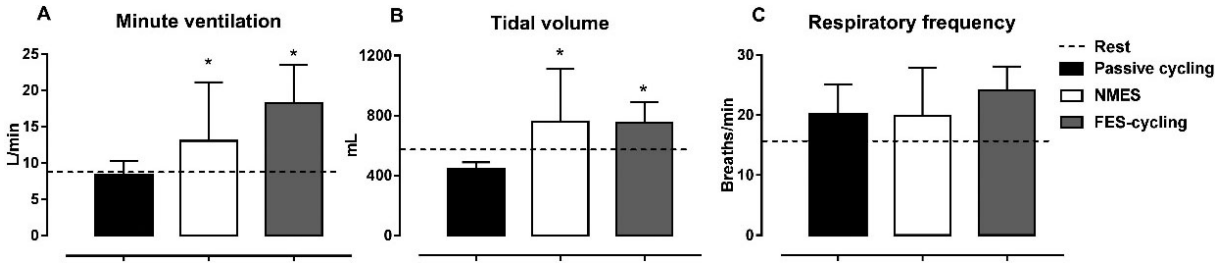

Fig. 3. Ventilatory responses. $^{*}p < 0.05$ compared to rest.

0.0707), however without statistical significance (Table 2). FES-cycling presented higher values for respiratory exchange ratio than passive cycling ($p = 0.0354$), without a statistically significant difference to NMES ($p = 0.0720$). There was a difference between NMES and passive cycling ($p = 0.0001$) (Fig. 2). FES-cycling presented a small effect size compared to NMES and a medium effect size compared to passive cycling (Table 3).

3.2. Ventilatory responses

Minute ventilation was enhanced during FES-cycling (20 ± 3 vs 9 ± 1 L/min [rest], $p = 0.0020$) (Table 2). FES-cycling presented higher values for minute ventilation than passive cycling ($p = 0.0006$), without a statistically significant difference to NMES ($p > 0.999$). There was difference between NMES and passive cycling ($p = 0.0075$) (Fig. 3). FES-cycling presented a small effect size compared to NMES and a medium effect size compared to passive cycling (Table 3).

Tidal volume was enhanced during FES-cycling (809 ± 84 vs 592 ± 53 mL/min [rest], $p = 0.0488$) (Table 2). FES-cycling presented higher values for tidal volume than passive cycling ($p = 0.0009$), without a statistically significant difference to NMES ($p > 0.9999$). There was difference between NMES and passive cycling ($p = 0.0002$) (Fig. 3). FES-cycling presented a trivial effect size compared to NMES and a medium effect size compared to passive cycling (Table 3).

Respiratory frequency was enhanced during FES-cycling (24 ± 4 vs 16 ± 5 breaths/min [rest], $p < 0.0001$) (Table 2). There was no statistically significant difference for respiratory frequency values compared to NMES and passive cycling ($p = 0.2652$ and $p = 0.2983$, respectively). There was no difference between NMES and passive cycling ($p = 0.9968$) (Fig. 3). FES-cycling presented a small effect size compared to NMES and passive cycling (Table 3).

3.3. Cardiovascular responses

Cardiac output enhanced during FES-cycling (6.6 ± 0.2 vs 5.5 ± 0.2 L/min [rest], $p = 0.0020$) (Table 2). FES-cycling presented higher values for cardiac output than passive cycling ($p = 0.0015$), without a statistically significant difference to NMES ($p = 0.0594$). There was no statistically significant difference between NMES and passive cycling ($p = 0.7553$) (Fig. 4). FES-cycling presented a medium effect size compared to NMES and passive cycling (Table 3).

Arterial-mixed venous oxygen content difference was enhanced during FES-cycling (8.0 ± 1.1 vs 5.1 ± 0.3 mL/100 dL [rest], $p = 0.0020$) (Table 2). FES-cycling presented higher values for arterial-mixed venous oxygen content difference than NMES and passive cycling ($p < 0.0001$, respectively). There was a difference between NMES and passive cycling ($p = 0.0479$) (Fig. 4). FES-cycling presented a medium effect size compared to NMES and a large effect size compared to passive cycling (Table 3).

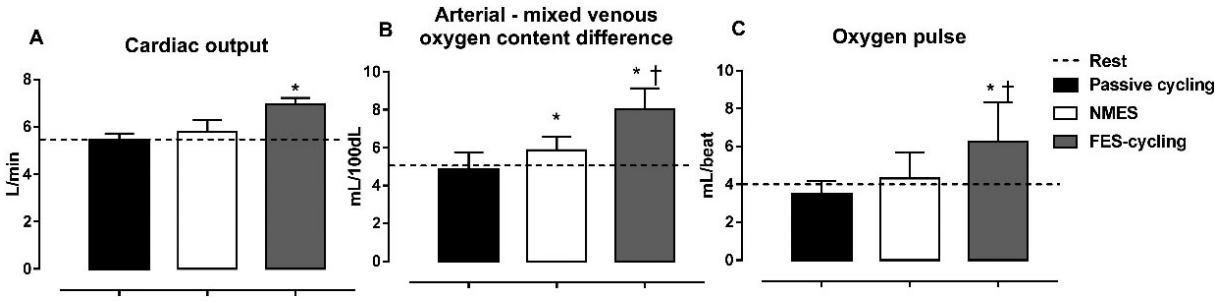

Fig. 4. Cardivascular responses. $^{*}p < 0.05$ compared to rest. $^{\dagger}p < 0.05$ compared to NMES.

Oxygen pulse was enhanced during FES-cycling (6.2 ± 2.1 vs 4.0 ± 1.5 mL/beat [rest], $p = 0.0054$) (Table 2). FES-cycling presented higher values for oxygen pulse than NMES and passive cycling ($p = 0.0202$ and $p = 0.0008$, respectively), without a statistically significant difference between NMES and passive cycling ($p = 0.4220$) (Fig. 4). FES-cycling presented a large effect size for NMES and passive cycling (Table 3).

4. Discussion

To summarize our main results, we have: 1) FES-cycling enhanced metabolic, ventilatory and cardiovascular demands; 2) the increase in physiological demands was reached due to an association of FES + cycling; 3) FES-cycling enhanced physiological demands more than NMES and passive cycling.

According to our knowledge, this is the first study to compare metabolic, ventilatory and cardiovascular FES-Cycling responses to isolated FES-Cycling components. The data presented in this study improves the knowledge about acute physiological responses to FES-cycling. This information is useful to guide a precise FES-cycling treatment in several pathological models, including critical ill (intensive care units patients), cardiopulmonary (chronic heart failure and chronic obstructive pulmonary disease) and neurological diseases (stroke and spinal cord injury).

4.1. Metabolic responses

FES-cycling reached a higher oxygen uptake probably because it generated higher external work. Duffel et al. [10] demonstrated that FES-cycling reaches 13% power output of maximal volitional cycling. Our data agrees with a study by Gojda et al. [1], which demonstrated a 138% enhancement in VO_2. Isometric muscle contraction produced by NMES only increases internal work. Tshe et al. [11] analyzed the ergogenic effects of NMES in a healthy population. The findings from their study suggest that acute NMES utilization does not evoke an acute ergogenic effect on VO_2. During passive cycling, VO_2 did not increase because the power output was lower than zero watts. Figoni et al. [12] reported that passive cycling produced insignificant increases in physiologic responses above the resting level in spinal cord injured subjects.

Contrary to physiological voluntary muscle contraction, functional electrical stimulation promotes type II fibers contraction prior to type I. The H^+ produced in cell as lactate must be immediately buffered upon its formation. However, because HCO_3^- is a volatile buffer, the resulting H_2CO_3 does not remain in the cell but leaves on its formation as CO_2, thereby removing H^+ from the intracellular environment [13]. This "extra" CO_2 is the main reason for higher CO_2 production during FES-cycling. NMES promoted

lower exercise intensity and probably lower type II fiber utilization occurred (as CO_2 production was numerically lower than FES-cycling). As no muscle contraction happened during passive cycling, lower VCO_2 values were expected.

As FES-cycling promotes external work, it produced higher energy expenditure than NMES. Respiratory exchange ratio suggests that the proportion of carbohydrate utilization in the bioenergetics and metabolic process during FES-cycling and NMES was higher than lipid utilization [14]. Contrary to our results, Tshe et al. [11] reported a respiratory exchange ratio lower than 1.0 during NMES utilization. This can be explained by differences in NMES protocols (much lower frequency and intensity than in the present study).

4.2. Ventilatory responses

The ventilatory response during exercise is closely related to the determinants of $PaCO_2$ (for example, muscular metabolic rate and respiratory center activation) [15]. As FES-cycling increased CO_2 production, central chemoreceptors and carotid bodies were activated [16]. Minute ventilation was increased due to an increase in tidal volume and respiratory frequency. As NMES also increased CO_2 production, a similar pattern of ventilatory responses was observed. Our data are in disagreement with Medrinal et al. [17], who reported that respiratory frequency increased without a tidal volume increase during FES-cycling in critically-ill patients. The reason is that these critically-ill patients were under controlled mechanical ventilation (impairing tidal volume enhance).

Stimulation of positions receptors and muscle spindles in the exercising muscles play a role in the genesis of ventilation enhancement. There was an immediate increase in minute ventilation at the start of exercise. This happened shortly after the onset of limb movement and before any consistent metabolic alteration. Another factor which must be taken into account is nociceptor activity. FES-cycling and NMES protocols were performed in the greatest comfortably tolerated intensity, but the role of pain in minute ventilation cannot be discarded.

4.3. Cardiovascular responses

Even without a statistically significant difference (borderline), cardiac output was numerically higher during FES-cycling than NMES. Medrinal et al. [17] demonstrated that FES-cycling enhanced cardiac output in critically-ill patients, but NMES did not. This data must be taken into consideration, and they tell us that it is not muscle contraction (promoted by electrical stimulation) alone which enhances cardiac output, but concentric muscle contraction against some resistance. A possible physiological explanation is that concentric muscle contraction against resistance causes compression of the vessels, followed by vasodilation and conductance improvement [18]. As no muscle contraction occurred during passive cycling, cardiovascular demand was lower.

FES-cycling increased arterial-mixed venous oxygen content difference, showing large oxygen extraction (superior to NMES). Once more, a possible physiological explanation is based on concentric muscle contraction against resistance. There is an intensification in oxygen release by hemoglobin due to greater accumulation of tissue metabolism co-products, as well increased heat production per unit of muscle (Bohr effect) [19]. Furthermore, there is greater vasodilation of arterioles which irrigates the active muscles with increase of muscular blood perfusion [20]. Gojda et al. [1] reported this, demonstrating a 165% increase in leg blood flow index during FES-cycling.

Oxygen pulse was higher during FES-cycling than NMES and passive cycling, showing an enhancement

in cardiovascular demand. It is reasonable to think that it increased stroke volume [21,22]. This can be attributed to higher muscle workload and exercise intensity.

The present study has some limitations. The volunteers were instructed to be completely relaxed and active muscle contraction was not allowed, however we didn't measure (by electromyography) if any slight and sporadic active muscle contraction was performed. Cardiac output and arterial-mixed venous oxygen content difference (oxygen extraction) values were obtained by mathematical equations based on VO_2 values and stroke volume was not measured. These cardiovascular variables can be directly measured by non-invasive gold standard methods (i.e. Impedance Cardiography and Near Infrared Spectroscopy). Unfortunately, these gold standard devices were not available for this study.

5. Conclusions

FES-cycling enhances metabolic, ventilatory and cardiovascular demands. The increase in physiological demands was probably reached due to external work produced by concentric muscle contraction during cyclergometry exercise. FES-cycling enhanced physiological demands more than NMES and passive cycling.

Conflict of interest

Murillo Frazão is a technical consultant at INBRAMED. Luis Augusto Werlang, Cássio Azevedo, Adelar Kunz and Maikel Peltz are employees of INBRAMED.

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