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Response of External Inspiration to the Movements Induced by Transcutaneous Spinal Cord Stimulation

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Abstract—The dynamic of the parameters of lung ventilation and gas exchange have been studied in 10 young male subjects during involuntary stepping movements induced by transcutaneous spinal cord electrical stimulation applied in the projection of T_{11}–T_{12} vertebrae and during voluntary stepping movements. It has been found that the transcutaneous spinal cord stimulation inducing stepping movements leads to an increase in breathing frequency and a reduction in tidal volume. These effects may be mediated by some neurogenic factors associated with muscular activity during stepping movements, the activation of abdominal expiratory muscles, and the interaction between the stepping pattern and breathing generators.

Keywords: respiration, human, transcutaneous electrical spinal cord stimulation, induced involuntary stepping movements, lung ventilation, gas exchange

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Researchers in experimental physiology and rehabilitation of patients with locomotor pathologies are now actively using noninvasive (transcutaneous) electrical spinal cord stimulation (tESCS) for the activation of stepping pattern generators [1, 2].

The spinal cord segments subjected to electrical stimulation contain, apart from the locomotor neuronal networks, spinal centers for the regulation of autonomic functions. Since the threshold of excitation of the autonomic centers of the spinal cord (SC) is below the threshold of motor neurons [3], electrical stimulation correcting somatic locomotion is, in fact, always accompanied by responses of autonomic system [4].

For example, some authors report that epidural electrical stimulation of the cervical spinal cord increases cerebral blood flow. When the T_2–T_3 spinal cord segments are stimulated, inspiratory muscles are activated [5–8]. Epidural stimulation at the level of the T_5–T_8 spinal cord segments accelerates the emptying of the stomach and reduces the time for food to pass through the upper compartments of the gastrointestinal tract [9]. Epidural electrical stimulation of the T_9, T_{11} and L_1 spinal cord segments induced contractions of abdominal muscles and an increase in the expiratory air flow [10]. Epidural electrical stimulation of lumbar spinal cord segments causes vasodilation in arteries of the lower limbs [3, 11]. However, the behavior of the autonomic system in response to tESCS has remained almost entirely unknown.

Therefore, the objective of this study was to investigate the effect of tESCS, which activates the locomotor function, on spontaneous humans lung ventilation.

The respiratory system cannot only respond directly to the effect of stimulation of the spinal cord segments representing the respiratory control system; they can also be activated by stimulation-induced stepping movements triggering the neurogenic mechanisms of breathing control [12, 13] in the case of electrical stimulation parameters sufficient to activate the spinal stepping pattern generators used. Therefore, we compared the breathing parameters during movements induced by spinal cord stimulation with those obtained at the execution of voluntary stepping movements.

METHODS

The group of subjects consisted of ten male students and employees of the Velikie Luki State Academy of Physical Culture and Sports who were familiar with the experimental situation and participated earlier in the study of the effect of transcutaneous electrical stimulation of the spinal cord on the locomotor function (body mass index was 23.3 ± 0.19 kg/m^2, the mean age was 35.2 ± 2.36 years). In accordance with

Table 1. Parameters of external respiration, gas exchange and locomotor activity during the execution of voluntary stepping movements and movements induced by tESCS

Parameters[1]	Movements	Recording conditions				
		initial	start	$p_{1-2}<$	gradual	$p_{2-3}<$
		1	2		3	
VE, L/min	Voluntary	7.9 ± 0.68[2]	9.7 ± 0.73	0.01	10.0 ± 0.73	–
	Induced	8.6 ± 0.79	9.7 ± 0.88	0.05	9.7 ± 0.78	–
VT, L	Voluntary	0.62 ± 0.048	0.67 ± 0.052*[3]	–	0.69 ± 0.044**[3]	–
	Induced	0.66 ± 0.066	0.57 ± 0.042	0.05	0.57 ± 0.034	–
Rf, cycle/min	Voluntary	13.2 ± 0.95	14.8 ± 0.62*	–	14.7 ± 0.43**	
	Induced	13.7 ± 1.07	17.8 ± 1.63	0.01	17.1 ± 0.83	–
Ti, s	Voluntary	2.24 ± 0.244	1.83 ± 0.090	0.05	1.80 ± 0.045*	
	Induced	2.14 ± 0.163	1.64 ± 0.119	0.01	1.66 ± 0.061	–
Te, s	Voluntary	2.70 ± 0.231	2.36 ± 0.113*	–	2.41 ± 0.084**	
	Induced	2.59 ± 0.217	2.05 ± 0.204	0.01	1.97 ± 0.114	–
VO_2, mL/min	Voluntary	293 ± 25.3	373 ± 30.6	0.01	394 ± 30.1	–
	Induced	319 ± 27.8	358 ± 29.3	0.01	353 ± 27.0	–
$PetO_2$, mmHg	Voluntary	104.6 ± 1.36	103.2 ± 1.53	0.05	101.0 ± 1.36**	0.05
	Induced	104.4 ± 1.34	105.1 ± 1.03	–	105.5 ± 0.80	–
$PetCO_2$, mmHg	Voluntary	34.3 ± 0.54	35.2 ± 0.84*	0.05	35.9 ± 0.64**	0.05
	Induced	34.4 ± 0.63	33.9 ± 0.63	–	33.9 ± 0.57	–
SpO_2, %	Voluntary	97.5 ± 0.31	97.4 ± 0.31	–	97.4 ± 0.31	–
	Induced	97.5 ± 0.27	97.5 ± 0.34	–	97.5 ± 0.40	–
RQ	Voluntary	0.77 ± 0.026	0.76 ± 0.021	–	0.74 ± 0.018	–
	Induced	0.78 ± 0.018	0.77 ± 0.017	–	0.77 ± 0.016	–
A, m	Voluntary	–	1.43 ± 0.075*	–	1.57 ± 0.091*	0.05
	Induced	–	0.61 ± 0.220	–	0.84 ± 0.286	0.05
F, Hz	Voluntary	–	0.46 ± 0.013*	–	0.48 ± 0.019*	–
	Induced	–	0.39 ± 0.018	–	0.37 ± 0.036	–
F, J	Voluntary	–	16.65 ± 2.385*	–	19.54 ± 3.555*	–
	Induced	–	4.18 ± 2.192	–	6.98 ± 4.224	–

[1]See the designations under the "Methods". [2]Arithmetic mean ± error of arithmetic mean. [3]Significance of differences between the parameters recorded during the execution of voluntary movements and during tESCS: ** $p < 0.01$, * $p < 0.05$.

the requirements of the Helsinki Declaration, the subjects were informed about the content of the study and all kinds of applied interventions.

To minimize the gravity effects and facilitate the performance of stepping movements, the subjects were in a horizontal position lying on their side with legs hung on independent swing-suspensions [14].

The subjects were spontaneously breathe through masks. The lung ventilation and gas exchange parameters were recorded by a Cosmed Quark Cardiopulmonary Exercise Testing (CPET) system including a turbine sensor for measuring the air flow, a photoelectric oxygenometer, an infrared carbon dioxide sensor, and a paramagnetic oxygen sensor. The results were automatically processed, and we determined the minute volume of lung ventilation (*VE*, L/min), tidal volume (*VT*, L), breathing frequency (*Rf*, cycles/min), inspiration time (*Ti*, s), expiration time (*Te*, s), minute volume of oxygen consumption (VO_2, mL/min), respiratory quotient (*RQ*), alveolar partial pressure oxygen ($PetO_2$, mmHg), alveolar partial pressure of carbon dioxide ($PetCO_2$, mmHg), arterial blood oxygenation (SpO_2, %).

The procedure of tESCS was performed using BiokinES-5 stimulator (OOO Cosyma) [15]. The cathode was placed between the T_{11} and T_{12} vertebrae, while two anodes were placed symmetrically above the crests of iliac bones, and the applied frequency of stimulation was 30 Hz. The stimulation intensity was individually selected, with the current power being increased

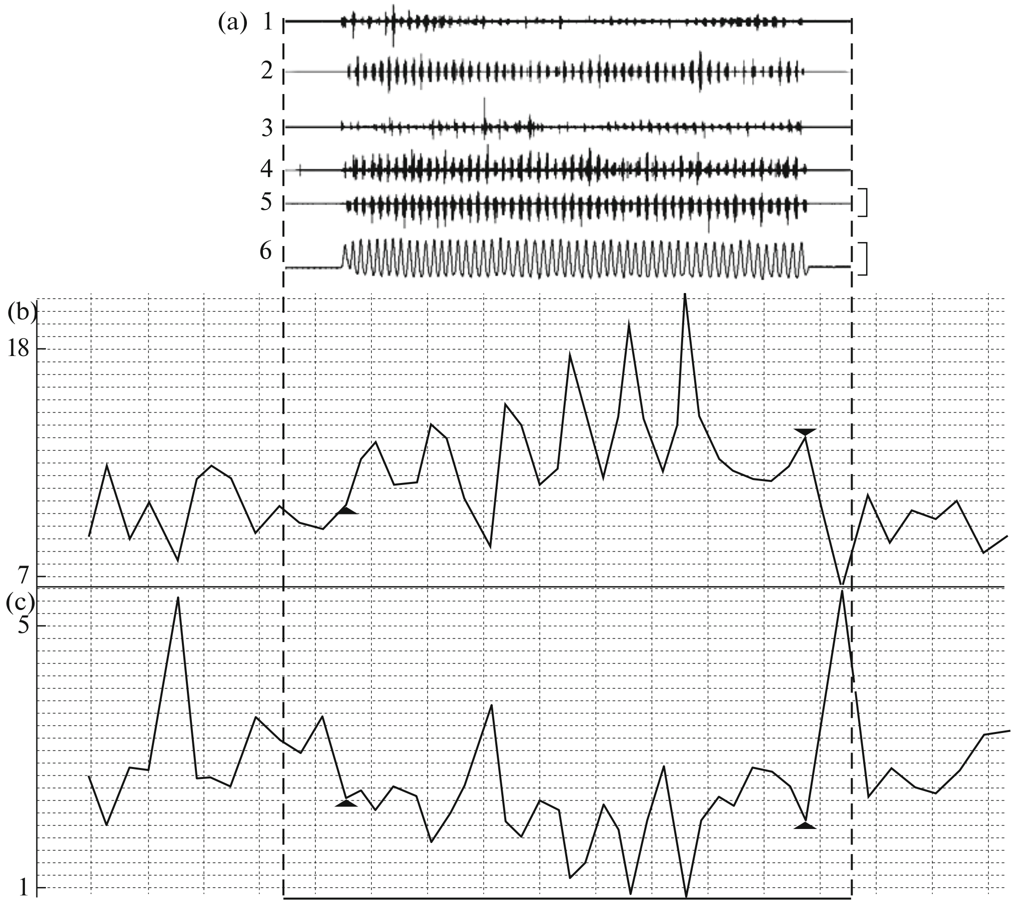

Fig. 1. Response of the respiratory system to voluntary movements of the lower extremities. (a) EMG of the right leg muscles (m. tibialis, 1; m. gastrocnemius, 2; m. biceps, 3; m. rectus, 4; m. vastus lat., 5; scale is 210 mV) and an angular change in the knee joint (6, scale is 95 angle deg.); the duration of recordis 150 s; (b) breathing frequency, cycles/min; (c) duration of expiration time, seconds. In Figs. 1b and 1c, markers point to the commands "Start movements" and "Stop movements". The subject was D.G.

up to the value initiating a motor response while avoiding painful sensations; as a result, the stimulus intensities varied within the 30–150 mA range. The detail execution of tESCS was described previously [1].

The leg movements of the subjects were controlled using a Qualisys motion capture video system (Sweden). The electrical activity of muscles was recorded as described previously [1]. As a result of the analysis of movements, we determined the step cycle amplitude (*A*, m) and the frequency of stepping movements (*f*, Hz), as well as the force developed in stepping (*F*, J), taking individual anthropometric characteristics of the subjects into account.

For the control response of the respiratory system to stepping movements, prior to each study session, the lung ventilation and gas exchange parameters were recorded in the initial state of resting (1 min) and during voluntary performance of stepping movements (2 min) under the experimenter's control.

After a complete recovery by subjects of respiratory parameters to the initial level (respiration was monitored), we investigated responses from the respiratory and locomotion systems to transcutaneous electrical stimulation of the lumber spinal cord enlargement. The lung ventilation and gas exchange parameters were recorded for 1 min during the initial posture of resting and 2 min of stimulation.

The analysis of motor and respiratory responses included values of parameters recorded under the state of resting (1); during the start response to the stimulation, i.e., during the first five respiratory cycles from the onset of stimulation (2); and within the post-start period of gradual increase in performance (3), i.e., from the onset of the sixth respiratory cycle to the end of stimulation.

The arithmetic mean and the error of the arithmetic mean were estimated under a statistical analysis of the results. The significance of differences between the parameters was evaluated by the nonparametric Wilcoxon test [16].

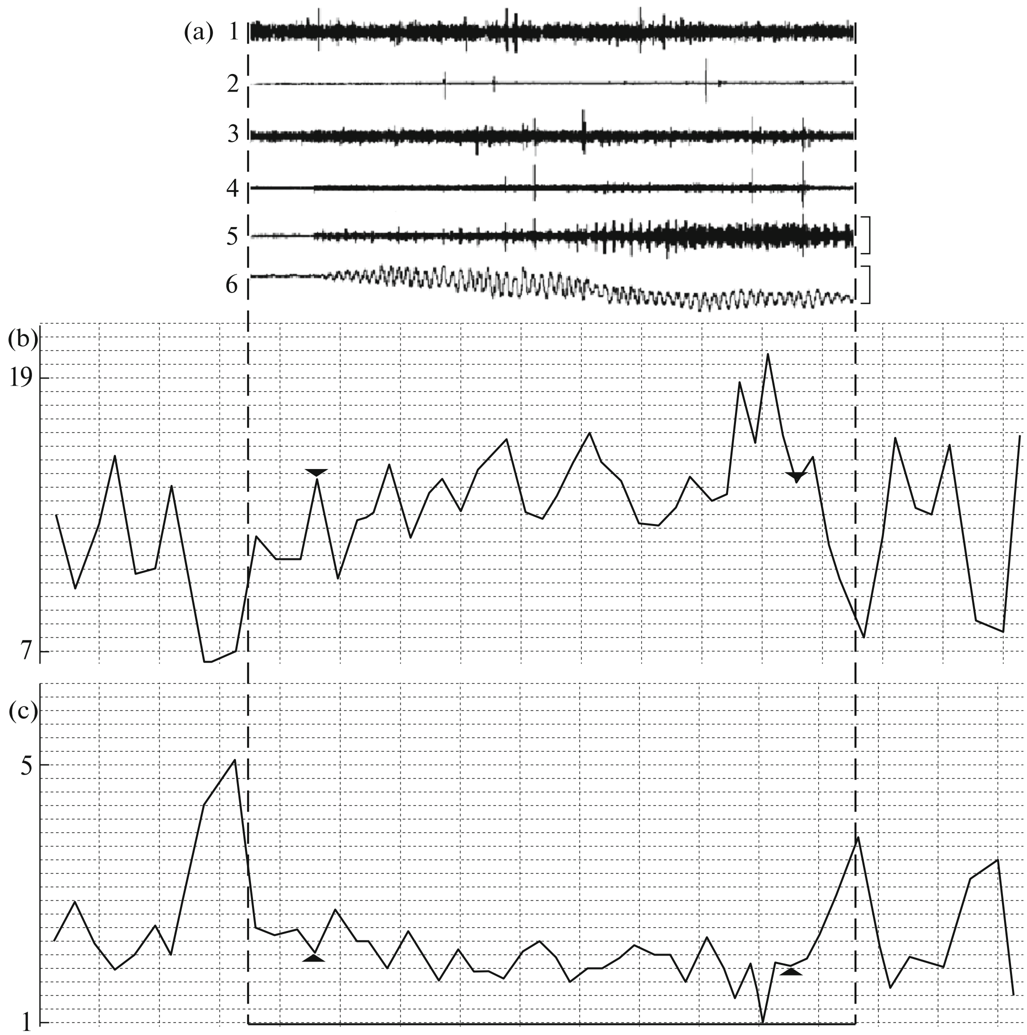

Fig. 2. Response of the respiratory and locomotor systems to tESCS. For designations, see Fig. 1, except for 5, scale is 200 mV; 6, scale is 10 angle deg.

RESULTS

The parameters of lung ventilation in the initial resting state of subjects in a side-lying position did not encompass the normal variability limits (Table 1). The minute volume of lung ventilation prior to the spinal cord stimulation was insignificantly higher (by 0.6 ± 0.53 L/min) compared with that before the performance of voluntary movements. The greater prior-to-stimulation ventilation of the lungs was caused by a slightly higher (by 0.4 ± 0.72 cycle/min) breathing frequency, at the expense of the proportionately shorter inspiration and expiration time (Table 1). The level of oxygen consumption prior to the stimulation was also only 26 ± 19.1 mL/min higher than before voluntary movements. These insignificant differences between the breathing indicators prior to the initiation of voluntary movements and electrical stimulation may be caused by some anxiety of subjects anticipating the onset of electrical stimulation.

The start response from the respiratory system to the execution of voluntary stepping movements was manifested in a significant extension of the lung ventilation volume by 1.8 ± 0.46 L/min ($p < 0.01$), at the expense of synchronous, albeit insignificant, increases of tidal volume (by 0.05 ± 0.041 L) and frequency (by 1.6 ± 0.63 cycle/min) (Fig. 1b). The breathing frequency increased, first of all, at the expense of a significantly reduced inspiration time (by 0.42 ± 0.179 s). The alveolar partial pressure of oxygen slightly decreased in the majority of subjects, while the carbon dioxide pressure increased (Table 1). The oxygen consumption significantly grew (by 81 ± 22.5 mL/min). The respiratory quotient and arterial blood oxygenation degree at the onset of voluntary movements remained actually almost unchanged (Table 1).

The observed motor and respiratory responses to the spinal cord stimulation showed various degrees of expressiveness throughout subjects (Table 1, Fig. 2).

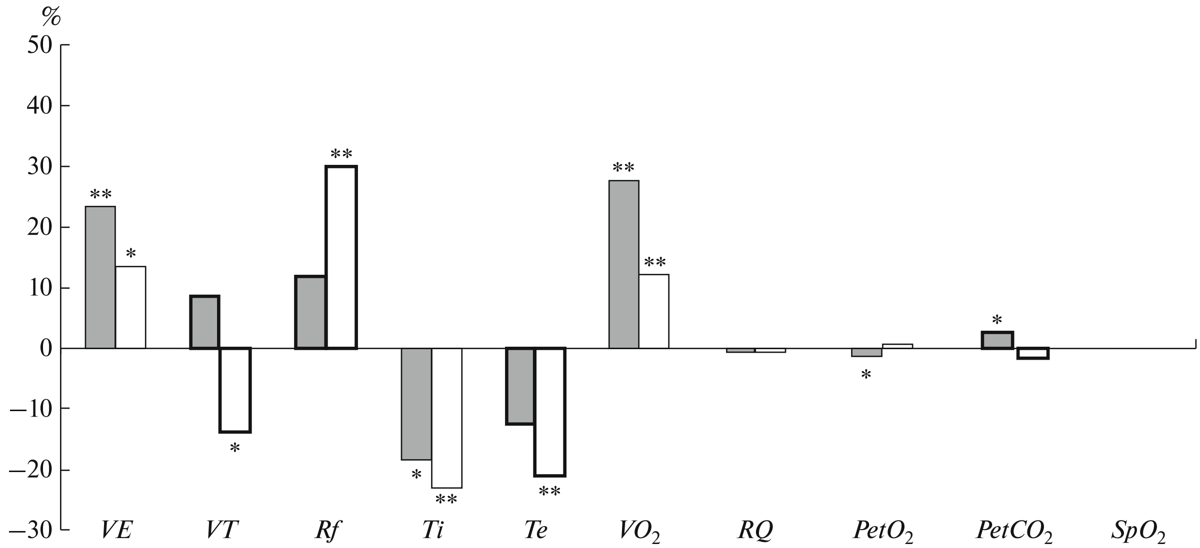

Fig. 3. Changes of the parameters of lung ventilation and gas exchange during the start response to the execution of voluntary movements (grey bars) and transcutaneous spinal cord stimulation (white bars), in percent of their initial value. See the designations under the "Methods". The significance of changes of the parameters relative to initial values: ** $p < 0.01$, * $p < 0.05$. The significance of differences between the responses to the execution of voluntary movements and to the stimulation is designated by outlining the columns with a thick line ($p < 0.05$).

According to the data obtained earlier under analogous conditions [1], stimulation at the level of the T_{11}–T_{12} vertebrae at a frequency of 30 Hz caused involuntary stepping movements. The amplitude and rate of induced movements was significantly less than those of voluntary movements (Table 1, Figs. 1a, 2a).

The start response from the respiratory system to the spinal cord stimulation and the induced movements manifested in a sharp and significant breathing frequency growth (by 4.1 ± 0.95 cycle/min) at the expense of a synchronous reduction in inspiration and expiration time (Table 1, Figs. 2b, 2c). The tidal volume decreased by 0.09 ± 0.035 L ($p < 0.05$), at the expense of which lung ventilation significantly increased only by 1.2 ± 0.42 L/min. The oxygen consumption significantly grew by 39 ± 11.1 mL/min ($p < 0.01$).

The respiratory quotient and gas exchange indicators at the onset of stimulation have actually remained almost unchanged (Table 1).

A significant increase in the amplitude of movements, in average, by 0.13 ± 0.066 m, was observed during voluntary stepping movements, however, by the end of the second minute the amplitude of voluntary movements decreased by 0.2 ± 0.18 m compared to the initial one. Initially, the rate of movements also slightly increased, but it decreased to the initial values by the end of the second minute.

The response from the respiratory system to the execution of voluntary steppng movements developed in a classical manner [17, 18]; however, due to a low intensity of movements being performed under the conditions of outer support, the expressiveness of the response was low, and we can discuss only some trends. For example, a gradual increase was observed in the lung ventilation at the expense of deeper breathing against a gradual decrease in its frequency. The decrease in breathing frequency developed, mainly, at the expense of a gradual increase in the expiration time.

Changes in the gas exchange indicators demonstrated a hypoventilatory dynamics. For example, an increase by 21 ± 10.8 mL/min of the oxygen consumption was observed during a gradual increase in the performance. The majority of subjects experienced a decrease in the partial oxygen pressure and an increase in the alveolar partial pressure of carbon dioxide. The respiratory quotient gradually decreased and reached the value of 0.73 ± 0.016 by the end of the second minute of exercise performance.

The dynamics of amplitude variations in the stimulation-induced movements almost entirely coincided with the dynamics for the amplitude of voluntary movements. A significant increase by 0.21 ± 0.142 m on the start response was observed in the amplitude of the induced movements without changes in their rates.

The response from the respiratory system to the stimulation was characterized by stability in the lung ventilation and gas exchange parameters. However, we can note some, although insignificant, trends. For example, antiphase and mutually compensated changes were observed in in tidal volume and frequency. It is interesting that a decrease in breathing frequency occurred exclusively at the expense of an

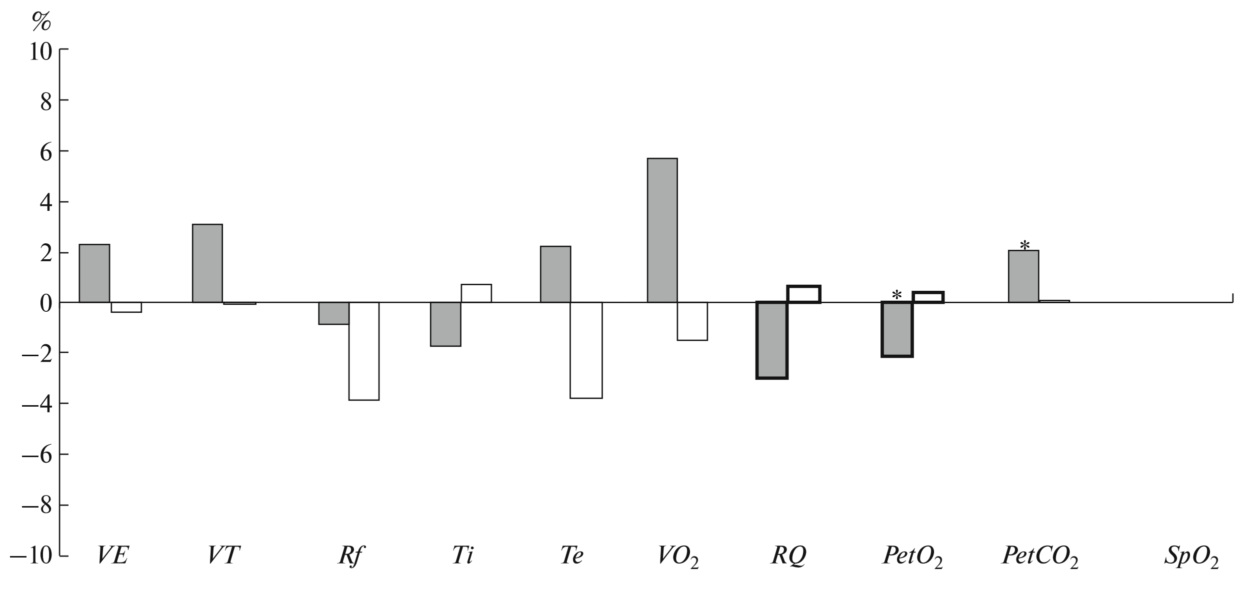

Fig. 4. Changes of the parameters of lung ventilation and gas exchange during the period of gradual increase in response to the execution of voluntary movements (grey bars) and transcutaneous spinal cord stimulation (white bars), in percent of their initial value during the start response period. For designations, see Fig. 3.

increase in the inspiration time, whereas the expiration time continued to decrease (Table 1).

The trend towards a reduction in oxygen consumption against the start response was also observed during stimulation. This resulted in the arterial blood oxygenation, which insignificantly increased against the unchanged lung ventilation by the end of the stimulation period (by 0.3 ± 0.16% relative to the onset of stimulation).

DISCUSSION

Comparative analysis of the response developed by the external breathing system to stepping movements induced by spinal cord stimulation and the voluntary stepping movements has revealed opposite directions in the start changes in tidal volume (Fig. 3). For example, whereas the tidal volume during electrical stimulation significantly decreased, it increased, although insignificantly, during the execution of voluntary movements, becoming significantly greater than during stimulation. The direct activation of motoneurons of the external and internal oblique, transverse and straight abdominal muscles, which are located in the stimulated spinal cord segments, can be considered as a cause for the reduced respiratory volume during electrical stimulation . These muscles are auxiliary expiratory abdominal muscles [19] and, respectively, can counteract the shortening of the major inspiratory diaphragm-muscle and restrain the realization of inspiration.

In addition, the start response from the respiratory system to the movements induced by stimulation of the spinal cord differed from the response to the voluntary movements in a significantly higher growth of breathing frequency at the expense of a more expressed reduction of the expiration time (Figs. 1–3). The mentioned differences may probably be caused by accelerated expiration at the expense of direct activation of motoneurons of the auxiliary expiratory muscles located in the stimulated spinal segments [19, 20].

The partial pressure of alveolar carbon dioxide at the start response to the stimulation was significantly lower than at the onset of voluntary movements (Fig. 3). This fact can be explained by the suggestion that stepping movements induced by electrical stimulation were characterized by a significantly lower force than voluntary ones, whereas both kinds of movements were performed with the same intensity of lung ventilation (Table 1). However, the cause of the discussed phenomena may be hidden by noncorrespondence between ventilation and perfusion of the lungs under the spinal cord stimulation conditions.

Comparative analysis of the dynamics of respiratory parameters has shown a higher level of stability in the movements induced by the spinal cord stimulation than during voluntary movements (Fig. 4). For example, during electrical stimulation , in contrast to voluntary movements, there were no increase in the oxygen consumption, minute lung ventilation and tidal volume, as well as the respiratory quotient or the partial pressure of alveolar oxygen associated with the humoral reflexive component in the regulation of respiration during muscular activity [17]. The expiration time continued its decrease during the manifestation of the movements induced by spinal stimulation, whereas the duration of expiration slightly increased during the performance of voluntary movements.

The indicated specific patterns in the behavior of the respiratory system during tESCS resulted rather from the activation of abdominal muscles. Therefore, a high activity of the abdominal expiratory muscles, which manifests itself in accelerating expiration and restraining inspiration are supported for the entire period of electrical stimulation .

We have previously shown the efficiency of spinal stimulation for the locomotor rehabilitation of patients after a spinal cord trauma [2, 21, 22, etc.]. The results obtained by this study demonstrate a new possibility for the application of this method in clinical practice. Respiratory complications in humans with a high level of spinal cord injuries are known to be the main cause of mortality: the paralysis of abdominal muscles leads to inefficiency of cough, and as a result, mucus is accumulated in respiratory airways and seal these ways [23]. One recently suggested solution for this problem included the abdominal muscle training [24] and the electrical stimulation of these muscles [25] or epidural electrical spinal cord stimulation ([26]. The obtained data on the spinal cord stimulation leading to the fast activation of abdominal muscles during the first respiratory cycles give us grounds to believe that the noninvasive stimulation of the lumber spinal cord enlargement can potentially be used, in particular, for augmenting cough in patients with spinal injuries. However, this needs further and specialized research.

CONCLUSIONS

Thus, we can suggest that the tESCS aimed at activating locomotor functions affects the spontaneous lungs ventilation through changes in the neurogenic factors associated with the muscular activity arising during stepping movements [27], the activation of the abdominal expiratory muscles, and the interaction between the stepping and respiratory generators [13].

The respiratory effect of stimulation is primarily expressed in an instant increase in breathing frequency due to a reduced time for expiration and in a less depth of tidal volume to the counteraction of the activated expiratory muscles to the contraction of the diaphragm, and it is preserved during the entire period of stimulation. Since the intensity of movements induced by the spinal cord stimulation was considerably less than the intensity of voluntary stepping movements, the former were manifested involving fewer number of motor units and did not cause any significant metabolic disturbances. As a result, the effects of humoral and neurogenic regulations of breathing triggered by backward sensory control during the movements induced by spinal stimulation appeared to be significantly less expressed than during the execution of voluntary movements.

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