“Sense of effort” and M1 activity with special reference to resistance exercise with vascular occlusion

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Abstract  Low-to-moderate intensity resistance exercise with vascular occlusion induces increased muscle mass and strength, comparable to that after conventional heavy resistance training. Also, participants feel as if they require greater force (effort) to lift a weight when undergoing resistance exercise following vascular occlusion. Vascular occlusion of the proximal upper arm increased perceived magnitude of exerted hand-grip force without causing any accompanying changes either in electromyographic or efferent/afferent activity of the median nerve. There was also no effect on motor evoked potentials in the hand following resting-state transcranial magnetic stimulation (TMS) over the primary motor cortex (M1). Moreover, low-frequency, repetitive transcranial magnetic stimulation (lf-rTMS) over the left primary somatosensory cortex did not significantly affect estimations of right-hand grip force exertion. Thus, the primary factor responsible for the overestimation of force exertion with increased voluntary effort (“sense of effort”) during occlusion was the central signal related to motor command size. Brain imaging studies show that vascular occlusion increases M1 activity during force exertion, which may be related to functions of motor-related cortical areas, e.g., supplementary motor area, as sources of excitatory input to M1. M1 suppression by lf-rTMS during force exertion causes participants’ sense of effort and force perception to increase. This mechanism may also operate during muscular contraction with vascular occlusion. It is easy to imagine perceiving maximal effort when we consciously try to produce maximal force; however, does M1 activity become maximal at that point in time? In this study, the liberation of potential muscular strength, focusing on the motor system state before awareness of motor intention, is looked at.

Keywords: force exertion with occlusion, force perception, efference copy, primary motor cortex, motor system state, potential muscular strength

Introduction

Skeletal muscles can adapt themselves to exercise stimuli with varied changes in their mechanical and metabolic properties. These changes have been shown to be specific to the type of exercise stimuli: intense resistance exercises generally cause increases in muscular size and strength\(^1\), whereas exercise with much smaller loads (endurance exercise) results in an increase in muscle oxidative capacity without considerable increase in muscular size\(^2\). However, Takarada et al.\(^3\) have previously shown that low-intensity resistance exercise combined with vascular occlusion induces a marked hypertrophy and concomitant increase in strength, even if the exercise load is much lower than that expected to induce muscular hypertrophy.

Also, participants require more voluntary effort to exert muscular force to lift a weight when undergoing resistance exercise following vascular occlusion\(^4\). Why does such a subjective experience of willed effort, namely the feeling of exerting a certain amount of effort to energize the body, happen? We know that an action is always carried out with a certain amount of effort, or even imagined, and we also already know a certain amount of the effort that the action demands, independent of and antecedent to all experience. This implicit knowledge suggests that the subjective experience of willed effort is probably the key component of the feeling of initiating an action, and an important element of the sense of volition.

In this article, the production of the conscious feeling of effort during muscular contraction with vascular occlusion will be discussed from the perspective of the concept of sense of effort closely linked to notions such as consciousness, will and self, with the physiology of resistance exercise with vascular occlusion in mind. Also, the liberation of potential muscular strength, focusing on motor system state before the awareness of willed motor effort, is explored.
Mechanisms for resistance exercise with vascular occlusion

The mechanisms underlying the effect of externally applied occlusive stimulus have been interpreted as follows: 1) additional larger motor unit recruitment\(^3\)^,\(^5\),\(^6\), 2) stimulated secretions of growth hormone and norepinephrine\(^5\),\(^6\), 3) an acute increase in circulating IGF-1 levels\(^5\),\(^7\),\(^8\), 4) an increase in IGF-1 expressed in skeletal muscle and mechanogrowth factor (MGF, a splice variant of IGF-1)\(^9\), and a decrease in myostatin\(^10\), and 5) moderate production of reactive oxygen species\(^11\) including nitric oxide (NO) that may promote tissue growth\(^10\). It should be noted that NO regulates the expression of cyclooxygenase 2 (COX-2) in skeletal muscle\(^12\); and prostaglandins of the COX-2 pathway including prostaglandin E2 (PGE2) and prostaglandin F2alpha (PGF\(_{2\alpha}\)) have functions of mechanotransduction and control of protein synthesis and degradation\(^13\). PGF\(_{2\alpha}\) may regulate hypertrophy of skeletal muscle by activating both cell fusion and protein synthesis\(^14\). Taken together, it is reasonable to deduce that long-term exercise training combined with vascular occlusion would increase muscular strength, with concomitant muscle hypertrophy, and improve vasodilatation. This idea is reinforced by the recent results of a low-intensity cycle exercise with vascular occlusion that showed the promotion of GH secretion through acute hypoxia and accumulation of metabolites (Fig. 1), and NO production (Fig. 2B) through enhanced post-exercise hyperemia\(^6\).

Sense of effort during force exertion with vascular occlusion

As mentioned above, repetitive muscular contractions combined with vascular occlusion increase the electrical activity of muscles with the additional recruitment of fast-twitch fibers\(^3\),\(^5\),\(^6\), resulting in participants reporting the need to exert more effort to maintain the same force level. This result is not peculiar to resistance exercise with vascular occlusion, which often occurs in normal daily activities. For example, when the muscles supporting the weight of an item become fatigued, we know that we need to exert more effort to maintain the same level of output force with an increase in the perception of our

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**Fig. 1** Changes in plasma concentrations of lactate (A), noradrenaline (B), and growth hormone (C) after cycle exercises with (CEO, filled square) and without occlusion (CE, open square), and only occlusion without any exercise stimulus (OO, open circle)\(^6\). Means ± SE were plotted. Rest: before session, 0: immediately after session. *\(p < 0.05\), ANOVA with Tukey’s method for multiple comparison.
voluntary muscular force. It has long been known that the primary responsible factor for the overestimation of perceived force exertion during such muscle fatigue is the centrally generated motor command rather than factors in the peripheral nerves and/or muscles. The authors used the term “sense of effort” to describe the increase in voluntary effort required to support weights in a fatigued condition. Also, they consider that this feeling of effort emanates from the sense of effort, which is intrinsically linked to the size of the motor command controlling the muscular contraction. Moreover, another previous study has shown that participants required more voluntary effort to exert a predetermined handgrip force level, with overestimation of perceived handgrip-force exertion during muscular contraction with vascular occlusion of the proximal portion of the right upper arm from the beginning of a given task. This is the first objective evidence of the effects of muscular contractions combined with vascular occlusion on sense of effort.

The primary motor cortex (M1) is the final cortical stage of the motor execution program, and a specific level of M1 output is associated with the amount of force generated by a muscle. Thus, it is reasonable to assume that M1 is the source of the centrally originating motor command associated with sense of effort from a neurophysiological point of view. The N20 of somatosensory evoked potentials (SEPs) and nerve action potential at Erb’s point were unaffected by tourniquet-induced transient occlusion of the brachial artery at the proximal end of the upper arm, and the maximum motor response to median nerve stimuli at the axilla was also unchanged. This previous study suggests that the tourniquet-induced transient occlusion of the brachial artery does not seriously affect median nerve function. Moreover, such a transient vascular occlusion had no effect on motor evoked potentials (MEPs) in a hand muscle following transcranial magnetic stimulation (TMS) over M1 during the resting state. Furthermore, low-frequency, repetitive transcranial magnetic stimulation (lf-rTMS) over the primary somatosensory cortex in the left hemisphere did not significantly affect participants’ estimations of right-hand grip force exertion by an after-mentioned force-matching task (Fig. 3C). These facts suggest that the primary factor responsible for the overestimation of force exertion with an increase in voluntary effort during occlusion was the centrally generated motor command, as hypothesized by McCloskey et al. and McCloskey.

Indeed, an fMRI study showed that the activity of M1 correlated with the perceived magnitude of exerted handgrip forces both with and without a tourniquet-induced arterial occlusion, and the M1 neuronal activity (Fig. 4) and force perception were significantly larger with the arterial occlusion than without it at all predetermined target force levels (20%, 40%, 60%, and 80% maximal voluntary contraction [MVC]). Moreover, a TMS study showed that the amplitudes of MEPs in a hand muscle, when applying TMS over M1, were enhanced with such an arterial occlusion, suggesting that a transient vascular occlusion increases the excitability of M1 during force exertion (Fig. 5). However, because increased M1 output is associated with stronger input from other motor regions, such as premotor cortex and the supplementary motor area (SMA), the sense of effort with an increase in force perception may be related to either an increase in M1 output itself or an increase in input to M1.

### Sense of effort and M1 activity

To differentiate these two alternative possibilities, we examined how suppression of M1 activity by If-rTMS...
Fig. 4 Effects of arterial occlusion on fMRI-measured activation of the primary cortex (M1). The fMRI-measured activations of M1 were shown as relative BOLD signal changes. All values of exerted handgrip force were normalized to those during the maximal voluntary contraction (MVC) in each participant. All values are shown as means ± SE (n = 9). *Statistically significant difference between values in handgrip contraction with and without arterial occlusion at four different predetermined target forces (A two-factorial [condition X control, occluded] ANOVA with repeated-measures design, at the 1% level of significance; F (1, 7) = 46.4, p < 0.01). M1 activity increased in proportion to exerted muscular forces both in the occluded and control conditions. However, the M1 activity was significantly larger in the occluded condition than in the control at all target forces.

Fig. 3 Effects of lf-rTMS on force perception. Results of M1 (A), sham (B), and SI (C) stimulation of the left hemisphere. (A–C) Average handgrip force at each target-force level (20%, 40%, 60%, and 80% of MVC) for the indicator (left) hand. Horizontal axes: Average handgrip force at each target-force level for the reference (right) hand. Error bars denote the SE. Note that at three force levels (20%, 40%, and 60% of MVC), the force exerted by the indicator (left) hand in post-rTMS sessions was significantly greater than at pre- and recover-rTMS periods (ANOVA, *P < 0.01). No significant differences were found under other conditions.
influences sense of effort by using a force-matching task to quantify the sensation of effort. In the force-matching task, force was applied to one hand (the reference: right hand) and participants tried to exert the same amount with the other (the indicator: left hand). The relationship between the level of force applied to the reference hand and that exerted by the indicator hand gives an objective indication of the sensation of effort in the reference hand (Fig. 6). Exerting more force than that applied to the reference hand (i.e., overestimating the force) reflects a greater sense of effort. The lf-rTMS over the M1 in the left hemisphere approximately 11 min (600 pulses) resulted in a 42% reduction in MEPs (Fig. 7). Again, as mentioned earlier, the amount of force generated by a muscle is associated with a specific level of M1 output. Thus, if M1 is suppressed, it needs to receive stronger input to generate the amount of output required for the same amount of force. Therefore, if the sense of effort needed to generate a particular amount of force changes after experimental manipulation, this result suggests that the neuronal input to M1 is involved in creating the sense of effort, rather than a purely internal increase in M1 activity. The results showed that suppression of M1 by lf-rTMS during a force-matching task caused participants’ sense of effort to increase, as evidenced by the overestimation of exerted force (Fig. 3A). In fact, participants commented that they experienced a stronger feeling of effort. Thus, the M1 suppression by lf-rTMS was compensated by function of motor-related cortical areas as the source of excitatory input to M1, rather than a purely internal increase of activity in M1 alone. In other words, compensatory neural mechanisms that increase M1 activity may play an important role in producing the sense of effort. Such a mechanism may also work in sense of effort with an increase in voluntary force perception during muscular contractions with vascular occlusion. Although we cannot dismiss the
possibility that peripheral feedback, such as somatic sensation, might allow the modulation and calibration of the central signal of effort in muscular contraction with vascular occlusion, a question remains: why does the activity in motor centers located upstream of M1 increase? Is it enough for neuronal excitability of the motor centers to produce force perception?

Motor system state and potential muscular strength

Although it is easy to imagine that we will perceive the maximal effort when we produce muscular force with a conscious feeling of exerting the maximal amount of effort, does the M1 activity become maximal at that moment? Human maximal voluntary force involves both neural and morphological factors. All morphological factors being equal, maximal voluntary force is usually limited by the participant’s capacity to activate motor units. In fact, the activation of muscle fibers may be inhibited in about half of any given group of participants even when they are asked to exert force with maximal volition. Ikai and Steinhaus proposed that maximal voluntary force is limited by psychological inhibiting factors, based on experimental results showing that such force was enhanced by manipulations such as the sound of a gunshot or a shout during maximal exertion efforts. These results indicate that force exertion in the motor system is relatively inhibited, and that there is a latent ability for producing additional force hidden in ordinary force exertion.

Next, how can such latent ability for exerting force be aroused? In daily life, we usually have the feeling that we are the authors of the actions we take, that the decisions we make and the corresponding movements we perform are consciously initiated and controlled. However, Libet et al. showed that a participant’s readiness potential, a change in electroencephalography (EEG) activity over the motor cortex, began more than 350 ms before the participant became aware of the decision to act. Moreover, several cortical regions, such as the precuneus and the frontopolar cortex, activated for the classification of the outcome of their decision ~2 to 3 seconds before they became aware of the decision to act, in other words, before the decision to move entered awareness; and thereafter, the SMA determined the timing of that decision. These experiments provide clear evidence suggesting that a voluntary action might be initiated unconsciously and that movement selection always precedes awareness, while consciousness of intention comes afterward, which also fits with the model considering free will as a perception.

Taken together, if the excitability of an already acting M1 can be enhanced before awareness of motor intention, namely, before a corollary of the prepared motor signal involved in intended effort in the SMA is sent to the parietal cortex, we would be able to exert maximal voluntary force without the above neural or psychological inhibiting factors. In other words, we would be able to extract our latent potential for muscular force exertion.

The following two experiments were designed based on this idea. Concerning the subliminal priming study, subliminal priming with motivational reward actually altered the background state of the motor system, resulting in an increase in hand-grip force level of maximum voluntary contraction by about 7% in the absence of consciousness. The affective-motivational effect on the motor system
by the subliminal priming words with positive reward enhanced the maximal level of voluntary force exertion; in other words, a latent ability for force exertion could be aroused. For the hypnotic study, it is significant that hypnotic suggestion-enhanced M1 activity before awareness of action intention could be recognized in relation to the activated precuneus region that is associated with mental imagery and self-representation through the perspective of time of the above-mentioned voluntary initiation of action and the associated brain regions such as the precuneus, the frontopolar cortex, SMA, and M1.

Currently, research regarding the effect of a system other than the reward-linked dopaminergic system, such as the noradrenergic system, on the motor system and motor action by using the above subliminal priming stimuli, is being undertaken to reveal the neural or psychological inhibiting factors of human maximal voluntary force. As far as a sense of effort is concerned, a subject of future investigation is to examine the role of the neural mechanism for production of force perception.

Conflict of Interests

The author declare that there is no conflict of interests regarding the publication of this article.
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