Venous occlusion to the lower limb attenuates vasoconstriction in the nonexercised limb during posthandgrip muscle ischemia

K. Tokizawa,1 M. Mizuno,1 Y. Nakamura,2 and I. Muraoka2

1Graduate School of Human Sciences and 2School of Sport Sciences, Waseda University, Saitama 359-1192, Japan

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Tokizawa, K., M. Mizuno, Y. Nakamura, and I. Muraoka. Venous occlusion to the lower limb attenuates vasoconstriction in the nonexercised limb during posthandgrip muscle ischemia. J Appl Physiol 96: 981–984, 2004.—We investigated the effects of increases in calf volume on cardiovascular responses during handgrip (HG) exercise and post-HG exercise muscle ischemia (PEMI). Seven subjects completed two trials: one control (no occlusion) and one venous occlusion (VO) session. Both trials included a baseline measurement followed by 15 min of rest (REST), 2 min of HG, and 2 min of PEMY. VO was applied at 100 mmHg via cuffs placed around both distal thighs during REST, HG, and PEMY. Mean arterial pressure, heart rate, forearm blood flow (FBF) in the nonexercised arm, and forearm vascular resistance (FVR) in the nonexercised arm (FVR) were measured. During REST and HG, there were no significant differences between trials in all parameters. During PEMY in the control trial, mean arterial pressure and FVR were significantly greater and FBF was significantly lower than baseline values (P < 0.05 for each). In contrast, in the VO trial, FBF and FVR responses were different from control responses. In the VO trial, FBF was significantly greater than in the control trial (4.7 ± 0.5 vs. 2.5 ± 0.3 ml·100 ml−2·min−1, P < 0.05) and FVR was significantly lower (28.0 ± 4.8 vs. 49.1 ± 4.6 units, respectively, P < 0.05). These results indicate that increases in vascular resistance in the nonexercised limb induced by activation of the muscle chemoreflex can be attenuated by increases in calf volume.

calf volume; blood flow; vascular resistance; muscle chemoreflex

FEEDBACK MECHANISMS via the afferent nerves arising from muscle play an important role in cardiovascular and ventilatory control. Chemical and mechanical stimulation of muscle group III and IV afferents elicits increases in blood pressure and muscle sympathetic nerve activity (MSNA) (22). In animal studies, it was reported that arterial occlusion of a peripheral limb induces a decrease in minute ventilation, whereas venous occlusion (VO) induces an increase (11, 13). A population of group III and IV afferent nerves responds to the mechanical distension of the venular structures in muscle (10). It has been hypothesized that blood volume in the peripheral venular system mediates the ventilatory effects of vascular impediment through stimulation of the muscle group III and IV afferent nerves (9). Although this hypothesis might also apply to cardiovascular control, the mechanisms by which blood volume in the peripheral venular system affects the cardiovascular response have not been fully identified.

Ray et al. (20) demonstrated that light dynamic handgrip (HG) elicited an attenuation of MSNA when performed during contralateral post-HG muscle ischemia; however, light rhythmic HG does not affect MSNA. They suggested that the attenuation of chemoreceptor-mediated increases in MSNA appeared to be the result of mechanosensitive muscle afferent activation. If an increase in blood volume in the peripheral venular system activates the group III and IV afferent nerves, VO should elicit an attenuation of sympathoexcitation during postexercise muscle ischemia (PEMI).

The purpose of the present study was to determine the effect of increases in blood volume in the peripheral venular system on cardiovascular response. To evaluate this problem, we measured forearm blood flow (FBF) and vascular resistance (FVR) in the nonexercised, contralateral forearm during dynamic HG exercise and during PEMI when VO was applied on the nonexercised lower limb. We presumed that application of VO would attenuate vasoconstriction during PEMI.

METHODS

Subjects. Seven men volunteered to participate in the study, which was approved by the local ethics committee; all work conformed with the Declaration of Helsinki. The age, height, and weight of the subjects were as follows (means ± SD): 23.9 ± 1.4 yr, 170.7 ± 3.3 cm, and 67.8 ± 9.1 kg, respectively. Before the experiment, the subjects were informed of all aspects of the study, and each signed an informed consent document.

Procedures. Maximal voluntary HG contraction was assessed in the right hand using an HG dynamometer. The average of three attempts was taken as the subject’s maximal voluntary contraction. On separate days after the preliminary test, the subjects performed two trials on different days in a random order: one control trial and one trial during VO. Both trials included a baseline measurement with the subject in a supine position followed by a 15-min rest period (REST), 2 min of HG exercise, and 2 min of PEMI. In both trials, the subject remained in a supine position with the knee joint flexed to 90° without both feet flat on the floor (Fig. 1). HG was performed as a dynamic contraction at 40% of maximal voluntary contraction (20.4 ± 2.8 kg) with the right hand. The contraction-relaxation duty cycle consisted of 4 s of contraction and 2 s of relaxation, which was timed with a calibrated metronome. PEMI was applied using a cuff placed around the upper right arm and inflated to 200 mmHg during the last contraction. VO was applied for 15 min before HG by inflation of the cuffs placed around both distal thighs to 100 mmHg during REST, HG, and PEMI.

Measurements. Blood pressure was measured with a finger cuff using an optomechanical photoplethysmographic method (2300 Finapres, Ohmeda, Englewood, CO). The monitoring finger cuff was placed around the middle finger of the left hand and supported at the heart level. Heart rate (HR) was determined using standard ECG leads (model CEC-8108, Nihon Kohden, Tokyo, Japan). FBF in the nonexercised arm was measured by VO plethysmography (31) using a mercury-in-Silastic strain gauge (model EC-5R, Hokanson, Bellevue, WA).

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Wa). The strain gauge was placed around the largest area of the left forearm. The arm was supported at the level of the heart, and a VO pressure of 60 mmHg was used. FBF was measured at 5-min intervals at REST and at 30-s intervals in HG and PEMI. FBF was calculated from the rate of increase of forearm volume during VO and expressed as milliliters per minute per 100 ml of forearm volume. FVR in the nonexercised arm was calculated by dividing mean blood pressure by FBF.

On a separate day from the exercise tests, changes in calf volume during two trials were measured noninvasively using strain gauge plethysmography (model EC-5R, Hokanson) at the maximal calf circumference. Mercury-in-Silastic strain gauges were calibrated to determine changes in limb volume relative to baseline in a supine position. After sufficient rest, the calves were lowered in the vertical plane maximally over the edge of the table without (control) or with VO for 19 min, while the change in calf volume was recorded.

Statistics. A repeated-measures two-way analysis of variance, with main effects of trial and time, was employed to determine significant differences. If a significant $F$ value was observed, Fisher’s post hoc test was used to locate the differences. Statistical significance was accepted at $P < 0.05$. Values are means ± SE.

RESULTS

Changes of calf volume in the VO trial increased progressively and reached a steady state within 9 min of initiation of VO; this resulted in an increase of $5.8 \pm 0.9\%$ compared with the control trial. In the VO trial, there were no significant differences in changes of calf volume during the periods corresponding to the final 2-min rest, HG, and PEMI.

Mean arterial pressure (MAP) and HR responses in both trials are shown in Fig. 2. In both trials, MAP and HR were significantly increased during HG, and MAP was maintained at a significantly higher level during PEMI. No significant differences in these responses were observed between trials during REST, HG, and PEMI. FBF and FVR responses in both trials are shown in Fig. 3. During REST, there were no significant differences between trials in both parameters. During HG, FBF at 30 s was significantly greater than the baseline value in the VO trial ($P < 0.05$). There were no significant differences between trials in both parameters during HG. During PEMI in the control trial, FBF was significantly lower than the baseline value ($2.5 \pm 0.3$ vs. $3.7 \pm 0.1$ ml·100 ml⁻¹·min⁻¹) and FVR was significantly greater than the baseline value ($49.1 \pm 4.6$ vs. $24.6 \pm 1.0$ units). In contrast, during PEMI in the VO trial, FBF and FVR were similar to the preexercise baseline and differed significantly from the responses observed in the control trial. During PEMI, FBF was significantly greater in the VO than in the control trial ($4.7 \pm 0.5$ vs. $3.5 \pm 0.3$ ml·100 ml⁻¹·min⁻¹) and FVR was significantly lower ($28.0 \pm 4.8$ vs. $49.1 \pm 4.6$ units), except for 3.5 min after the onset of exercise ($P = 0.058$).

DISCUSSION

The major new finding from the present study is that, in the control condition during PEMI, the FVR of the contralateral, resting forearm was increased above baseline levels; the increase in FVR was not seen with occlusion of the lower limbs in VO. This suggests that an increase in calf volume attenuates vasoconstriction in the nonexercised limb.

First used by Alam and Smirk (1), PEMI is a maneuver that causes accumulation of metabolites in the exercised limb as a result of external cuff pressure. Although central command and the muscle mechanoreflex are absent during PEMI, Alam and Smirk observed an increase in blood pressure, which suggested that peripheral metabolic changes are related to cardiovascular control. Thereafter, many researchers investigated the muscle chemoreflex by which chemosensitive afferent input alters cardiovascular responses during application of PEMI. Limb pH falls below baseline levels during PEMI after dynamic (6) and static (28) HG exercise. Sinoway et al. (28) confirmed a significant elevation of calf vascular resistance, indicating an association between forearm cellular acidosis and calf vasoconstriction. Contralateral FVR also increased and FBF de-

![Fig. 1. Schematic representation of experimental paradigm. Two trials were performed by subjects lying in a supine position with the knee joint flexed to 90°. Thigh cuffs were inflated to 100 mmHg in the venous occlusion (VO) trial. HG: handgrip; PEMI: postexercise muscle ischemia; MVC: maximal voluntary contraction.](http://jap.physiology.org/)

![Fig. 2. Changes in mean arterial pressure (MAP) and heart rate (HR) during rest, HG, and PEMI in each control and VO trial. There were no significant differences between trials. bpm, Beats/min.](http://jap.physiology.org/)
creased during post-HG muscle ischemia (23). With regard to the role of the autonomic nervous system, MSNA is activated in the arm and leg during PEMI (17, 30). These studies suggest that PEMI-induced accumulation of metabolites in the exercised limb and activated MSNA elicit vasoconstriction in the nonexercised limb, resulting in elevated vascular resistance and decreased blood flow in the nonexercised limb during PEMI.

In the present study, results in the control trial during PEMI are consistent with results from previous studies showing that MAP and FVR were significantly greater and FBF was significantly lower than baseline values. Therefore, we suggest that the PEMI model used in the present study fully induces MSNA and arterial and cardiopulmonary baroreceptors. However, during PEMI the augmentation in FVR and the reduction in FBF were not elicited by application of VO in the lower limb. This is likely from the reduction of venous return by application of VO. We cannot completely exclude the possibility that the cardiopulmonary baroreflex could operate in the VO trial. However, two considerations lead us to believe that the cardiopulmonary baroreflex is not the main determinant of an attenuated increase in FVR during PEMI, as observed in the present study. 1) Under a reduced central venous pressure by lower body negative pressure, FVR significantly increases (5). However, in the present study, increased FVR during PEMI was attenuated in the VO trial. 2) Although HG and/or PEMI were performed under a lower body negative pressure-induced reduction in central venous pressure, no difference was observed in FVR and MSNA compared with HG and PEMI alone (2, 24–26).

Human and animal studies support the hypothesis that increased blood volume in the peripheral venular system is related to an increase in ventilation. In human studies, a depression of minute ventilation occurs when arterial occlusion is applied after muscular exercise (12, 14, 21). In animal studies, application of arterial occlusion or VO by inflatable balloons placed at the abdominal aorta or vena cava induces conflicting ventilatory responses: arterial occlusion decreases ventilation, whereas VO increases it (11, 13). Moreover, venous distension by VO increases discharge of group III and IV afferent nerves (10), the nerve endings of which are close to the venula (29). On the basis of these previous studies, it has been suggested that blood volume in the peripheral venular system could mediate the ventilatory effects of vascular impediment through stimulation of the muscle group III and IV afferent nerves (9). Although the efferent pathway is regulated differently from ventilatory control, cardiovascular control is also mediated by group III and IV afferent input from muscle. Therefore, attenuation of the increased FVR during PEMI observed in the present study could arise from venous distension.

Ray et al. (20) demonstrated that MSNA is inhibited by addition of contralateral rhythmic HG during PEMI. Because this response disappeared with sensory nerve blockade of the contralateral arm, they concluded that attenuation of chemoreceptor-mediated increases in MSNA resulted from input from mechanosensitive muscle afferents. Furthermore, Legramante et al. (16) reported that repetitive-twitch contraction of rabbit triceps surae muscles evokes a reflex depressor response. In contrast to mechanical stimulation to muscle, the present study involved stimulation to blood vessels by increasing blood volume. Mechanical muscle stimulation (15) and peripheral venous stimulation (10) activate discharge of muscle afferents. Therefore, an increase in discharge by afferents in response to mechanical stimulation may attenuate chemoreceptor-mediated increases in MSNA.

During HG, no effect of VO on cardiovascular responses was observed. Unlike PEMI, central command and the muscle mechanoreflex engage during exercise. Central command (27) and mechanosensitive muscle afferents (20) act to oppose metaboreceptor-mediated vasoconstriction. The effect of VO on FVR observed during PEMI would be counteracted by these
factors during Pemi. There was a failure to observe lower MAP during Pemi with VO when FVR decreased. It is possible that sympathetic outflow to other vascular beds may have increased and that attenuation of the increased FVR elicited by VO may not have been of sufficient magnitude to change MAP.

We recognize that there are potential limitations in the design of our study. Foremost, we were unable to distinguish between vascular and interstitial contributions to the overall volume change. Although cuff pressure is a good index of intravascular pressure in humans (8), a detailed analysis of interstitial volume would be speculative. Changes in volume in the exercising limb are related to the cardiovascular responses to exercise, indicating that augmentation of interstitial volume affects afferent nerves (3, 4, 18, 19). In our study, however, VO was applied to the nonexercised limb. Therefore, we can only speculate on the effect of increases in interstitial volume with VO on the cardiovascular response in the present study. Similarly, we were unable to accurately quantify mental stress, which causes forearm vasodilatation (7). Thigh cuffs are more obvious to the subjects during Pemi, which eliminates central volitional factors. Finally, the present study speculated on the role of cardiopulmonary baroreflex in the VO trial. Reduction of venous return could be induced by application of VO, but direct measurement of central venous pressure was not performed. Whether there is an effect of the VO intervention on central venous pressure remains to be solved. To clarify the above issues, the additional experiment might be required to measure some variables of central circulation and sympathetic outflow.

In conclusion, FVR was not augmented during Pemi by application of VO to the lower limb. This result indicated that an increase in calf volume induced by VO could attenuate metaboreceptor-mediated vasoconstriction in the nonexercised limb during Pemi.

REFERENCES