Facial cooling-induced bradycardia does not slow pulmonary \(\text{VO}_2\) kinetics at the onset of high-intensity exercise

Masako Endo,¹ Shinko Tauchi,¹ Naoyuki Hayashi,² Shunsaku Koga,³ Harry B. Rossiter,⁴ and Yoshiyuki Fukuba¹

¹Department of Exercise Science and Physiology, School of Health Sciences, Hiroshima Prefectural Women’s University, Hiroshima 734-8558; ²Laboratory of Exercise Physiology, Faculty of Health and Sport Sciences, Osaka University, Toyonaka 560-0043; ³Laboratory for Applied Physiology, Kobe Design University, Kobe 651-2196, Japan; and ⁴Division of Physiology, Department of Medicine, University of California, San Diego, La Jolla, California 92033

Submitted 25 April 2003; accepted in final form 2 July 2003

Endo, Masako, Shinko Tauchi, Naoyuki Hayashi, Shunsaku Koga, Harry B. Rossiter, and Yoshiyuki Fukuba. Facial cooling-induced bradycardia does not slow pulmonary \(\text{VO}_2\) kinetics at the onset of high-intensity exercise. J Appl Physiol 95: 1623–1631, 2003. First published July 3, 2003; 10.1152/japplphysiol.00415.2003.—The mechanism(s) underlying the attenuation of the slow component of pulmonary \(\text{O}_2\) uptake (\(\text{VO}_2\)) by prior high-intensity exercise is (are) poorly understood but may be ascribed to either an intramuscular-metabolic or a circulatory modification resulting from “priming” exercise. We investigated the effects of altering the circulatory dynamics by delayed vagal withdrawal to the circulation induced by the cold face stimulation (CFS) on the \(\text{VO}_2\) kinetics during repeated bouts of heavy-intensity cycling exercise. Five healthy subjects (aged 21–43 yr) volunteered to participate in this study and initially performed two consecutive 6-min leg cycling exercise bouts (work rate: 50% of the difference between lactate threshold and maximal \(\text{VO}_2\)) separated by 6-min baseline rest without CFS as a control (N1 and N2). \(\text{CFS}\) was then applied separately, by gel-filled cold compresses to the face for 2-min spanning the rest-exercise transition, to each of the first bout (CFS1) or second bout (CFS2) of repeated heavy-intensity cycling exercise. In the control protocol, \(\text{CFS}\) responses in N2 showed a facilitated adaptation compared with those in N1, mainly attributable to the reduction of slow component. \(\text{CFS}\) application successfully slowed and delayed the heart rate (HR) kinetics (\(P < 0.05\)) on transition to exercise [HR time constant; N1: 55.6 ± 16.0 (SD) vs. CFS1: 69.0 ± 12.8 s and N2: 55.5 ± 11.8 vs. CFS2: 64.0 ± 17.5 s]; however, it did not affect the “primary” \(\text{VO}_2\) kinetics [\(\text{VO}_2\) time constant; N1: 23.7 ± 7.9 (SD) vs. CFS1: 20.9 ± 3.8 s, and N2: 23.3 ± 10.3 vs. CFS2: 17.4 ± 6.3 s]. In conclusion, increased vagal withdrawal delayed and slowed the circulatory response but did not alter the \(\text{VO}_2\) kinetics at the onset of supra-lactate threshold cycling exercise. As the facilitation of \(\text{VO}_2\) subsequent to prior heavy leg cycling exercise is not attenuated by slowing the central circulation, it seems unlikely that this facilitation is exclusively determined by a blood flow-related mechanism.

Vagal activation; oxygen uptake adjustment; heavy exercise

Pulmonary oxygen uptake (\(\text{VO}_2\)) during “moderate-intensity” square-wave cycling exercise [i.e., for work rates below the lactate threshold (LT)] approaches its steady state with an exponential time course (phase II) after a short delay (phase I) and attains a steady state (phase III) within 2–3 min in normal healthy individuals (e.g., see Whipp and Ward (53) for review). It has been suggested that the time constant (\(\tau\)) for phase II \(\text{VO}_2\) during moderate exercise reflects that of muscle \(\text{VO}_2\) (m\(\text{VO}_2\)) (17), and, because it is also closely related to intramuscular phosphocreatine concentration, “metabolic inertia” is thought to be its primary determinant (7, 35, 42). An alternative to this view argues that \(\text{VO}_2\) kinetics during moderate-intensity exercise is determined by a vascular limitation of \(\text{O}_2\) delivery (e.g., see Hughson (25) for review).

During “heavy-intensity” exercise (i.e., for supra-LT work rates), however, the \(\text{VO}_2\) response is more complex. The response consists of two main components: a fundamental phase II component, still well described by a single-exponential, and a subsequent delayed phase yielding a slowly developing supplemental rise in \(\text{VO}_2\), which has been termed “excess” \(\text{VO}_2\) or the \(\text{VO}_2\) “slow” component (52). Consequently, this delayed \(\text{VO}_2\) slow component supplements the expected increase in \(\text{VO}_2\), projected from the sub-LT \(\text{VO}_2\)-work rate relationship (e.g., Ref. 12).

Although the physiological determinant(s) of the \(\text{VO}_2\) response during square-wave exercise in the supra-LT domain is (are) still currently debated (e.g., Refs. 14, 27, 40, 48), it has been suggested that \(\text{O}_2\) delivery may be of a greater importance in modulating the \(\text{VO}_2\) kinetics during heavy-intensity exercise than during moderate-intensity work rates (13, 31, 53). Support for this notion is, in part, derived from the demonstration that the \(\text{VO}_2\) kinetics may be modulated (speeded) when heavy-intensity exercise (usually cycling) is preceded by a “priming” bout of identical intensity (13, 32, 44). For normal healthy subjects, such a modulation may only be brought about during exercise in the heavy-intensity domain and not in the moderate domain. It was proposed that this kinetic adjustment of

Address for reprint requests and other correspondence: Y. Fukuba, Dept. of Exercise Science and Physiology, School of Health Sciences, Hiroshima Prefectural Women’s Univ., 1-1-71, Ujina-higashi, Minami-ku, Hiroshima 734-8558, Japan (E-mail: fukuba@hirojo-u.ac.jp).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
Vo₂, seen on the transition to a second exercise bout, may be due to improved muscle perfusion consequent to the vasodilatory effects of the residual lactic academia still present at the onset of the second bout (13). More direct support for the circulatory limitation hypothesis is evident where central and/or peripheral circulation has been modified by postural manipulation (28), prior sprint exercise (47), administration of β-adrenergic blocker (25, 39), and hypoxic or hyperoxic air inspiration (32), the latter causing the mean response time of Vo₂ to be speeded in the heavy-intensity domain and not in the moderate-intensity domain. However, the alternative view, i.e., the metabolic inertia hypothesis, has also been supported by similar experimental manipulations, such as lower body negative pressure (55), and a reactive hyperemic maneuver (50), which had no effect on the Vo₂ kinetics. Therefore, it is currently not clear whether O₂ delivery to the exercising tissues is a critical determinant of the Vo₂ response dynamics during heavy intensity exercise.

It is well known that cold facial stimulation (CFS) induces a bradycardia through the trigeminal-vagal-cardiac pathways (e.g., Ref. 29). It is hypothesized, therefore, that CFS during the transition to a square-wave increase in cycle ergometer work rate would cause O₂ delivery to be delayed consequent to a delayed circulatory response via increased vagal tone. Although determination of O₂ delivery is technically challenging during cycle ergometry, and was not measured in the present study, CFS has been shown to lead to an immediate reflex bradycardia (19) followed by a sympathetically mediated vasoconstriction occurring after ~40 s of CFS (20). This increase in muscle sympathetic nerve activity (9) results in increased mean arterial pressure (e.g., Ref. 5) and a reduction of peripheral flow measured either in the finger, toe, and calf (19) or the limb (20) but not in the brain (5). As such, if the speeded Vo₂ response during the second exercise bout of a repeated-bout protocol (cf. Ref. 13) is predominantly due to a more rapid circulatory adaptation (and, therefore, O₂ delivery), then application of CFS at the onset of the second exercise bout would be expected to offset, or even delay, the adaptation of Vo₂. We, therefore, investigated the effects of delayed vagal withdrawal (via CFS) on the Vo₂ kinetics at the onset of heavy-intensity exercise, both before and after a heavy-intensity exercise bout.

METHODS

Subjects. Eight subjects volunteered for the study, were found to be in a good state of health by a physician, and gave informed consent to participate as approved by the ethics committee of the local institution (in accordance with the Declaration of Helsinki). Each subject underwent a series of preliminary CFS tests at rest, before performing the main protocol. During these preliminary tests, we found that two subjects could not tolerate the feeling of discomfort during CFS and another subject did not show a bradycardiac response. Therefore, five subjects [3 women and 2 men; age 28 ± 10 (SD) yr, height 168 ± 7 cm, weight 63 ± 13 kg] finally proceeded to the exercise protocols.

Exercise protocols. The subjects initially performed a ramp-incremental exercise test to their limit of tolerance, at a rate of 12 W/min (for the female subjects) or 16 W/min (for the male subjects), on an electromagnetically braked cycle ergometer (232c-XL, Combi) at 60 rpm. During the incremental exercise, ventilatory and gas-exchange parameters were measured breath by breath, and capillary blood was sampled every 2 min for blood lactate determination (see details below). The V-slope method (3) was used to determine the LT, with concomitant corroboration from the onset of systematic increases in the ventilatory equivalent for Vo₂ (minute ventilation/Vo₂) and end-tidal Pco₂, without a concomitant rise in the ventilatory equivalent for Co₂ output (minute ventilation/Co₂ output) or fall in end-tidal Pco₂ (51). Noninvasive determination of the LT was further corroborated in the profile of capillary blood lactate concentration. The work rate for the subsequent square-wave exercise was then set at Δ50%, where Δ is the difference between the work rates associated with LT and maximal Vo₂ from the incremental-ramp test (the delay time between work rate and Vo₂ was accounted for by the standard procedure; Refs. 36, 54).

The subjects then completed three different cycle ergometer exercise protocols in the upright position: two “repeated” bouts of a 6-min square-wave exercise separated by 6 min at rest and one “single” bout of 6-min square-wave exercise (Fig. 1). The protocols were preceded by 3 min of rest, and the work rate during the 6-min bouts was set at Δ50%. Subjects maintained a constant pedaling rate of 60 rpm throughout the exercise. For CFS, a soft gel-pack (14 × 30 cm) refrigerated to ~0–3°C was applied to the forehead and eyes [the most sensitive area for this reflex (29)] from 1 min before to 1 min after the onset of the exercise. A total duration of 2 min of CFS was chosen as being close to the limit of tolerance for most subjects (19). The subjects performed the first (N1) and second (N2) exercise bouts without CFS (control trial) (Fig.

Fig. 1. Schematic representation of the 3 experimental protocols. Control trial is a repeated-bout (1st bout, N1; 2nd bout, N2) square-wave exercise test separated by 6-min rest. Cold face stimulation (CFS) was applied either at the onset of a single-bout exercise (CFS1) or at the onset of the repeated exercise bout (bout 2: CFS2). CFS was applied from 1 min before to 1 min after the onset of exercise. Δ50%, 50% of the difference between lactate threshold and maximal O₂ uptake.

J Appl Physiol • VOL 95 • OCTOBER 2003 • www.jap.org
Effects of CFS and bout repetition. The initial broad description of the effects of CFS imposition revealed a significantly longer (\(P < 0.05\)) time delay of both the HR (Td) and \(\dot{V}O_2\) (both Td from the monoexponential fit, and Tdp) consistent with a significant slowing of central cardiac output and peripheral blood flow, independent of bout number. Time-averaged HR responses of a representative subject and group means are presented in Fig. 2. These data demonstrated a significantly slowed (i.e., longer \(\tau\) and delayed (i.e., longer Td) HR response mediated by CFS at the onset of both exercise bouts. The effect of the repeated bouts protocol (i.e., bout 1 vs. bout 2, independent of CFS) was also characterized by an alteration in the Td, as a reduction in Td of HR and \(\dot{V}O_2\). However, the predominant effects were manifest in an increase (\(P < 0.05\)) in the effective \(\dot{V}O_2\), and a reduction (\(P < 0.05\)) of \(A_2\) and \(\dot{V}O_2(6-3)\). After the establishment of significant (\(P < 0.05\)) alterations in the HR and \(\dot{V}O_2\) responses by CFS and the repeated-bouts protocol, the interaction of these effects was then explored in detail.

\(N1\) vs. \(N2\). An example of the \(\dot{V}O_2\) responses for a representative subject and the group means to the repeated-bout control protocol are superimposed in Fig. 3. The first bout of supra-LT leg cycling exercise induced an adaptation of the subsequent \(\dot{V}O_2\) response during the identical second exercise bout. Although monoexponential fitting (i.e., effective \(\tau\)) illustrated this difference in \(\dot{V}O_2\) kinetics between \(N1\) (43.8 ± 11.8 s) and \(N2\) (27.5 ± 8.0 s) (Table 1), double-exponential fitting demonstrated no difference in \(\tau\) (\(N1\): 23.7 ± 7.9 vs. \(N2\): 23.3 ± 10.3 s). Thus the predominant effect of the first bout was to significantly reduce the slow component (\(\Delta \dot{V}O_2(6-3)\), \(N1\): 145 ± 73 vs. \(N2\): 63 ± 25 ml/min; and \(A_2\), \(N1\): 298 ± 140 vs. \(N2\) 101 ± 31 ml/min). \(A_p\) was not significantly affected (\(N1\): 1,749 ± 533 vs. \(N2\): 1,830 ± 522 ml/min) by prior exercise but was manifest from a significantly increased baseline \(\dot{V}O_2\) during \(N2\) (365 ± 92 ml/min) compared with \(N1\) (260 ± 47 ml/min).

\(CFS1\) vs. \(N1\) and \(CFS2\) vs. \(N2\). As expected, HR was dramatically decreased during CFS manipulation at the onset of both the first and second bouts (Fig. 2). The residual plot (i.e., the difference of HR between the CFS and control protocols; Fig. 2, bottom) clearly demonstrated a large CFS-induced depression of HR. This substantial effect was maintained between ~30 s before and 60–90 s after exercise onset (e.g., average HR; \(N1\): 80.0 ± 7.0 vs. \(CFS1\): 71.8 ± 1.6 and \(N2\): 105.1 ± 9.7

\(J\) Appl Physiol • VOL 95 • OCTOBER 2003 • www.jap.org
vs. CFS2: 93.3 ± 12.4 beats/min at the onset of exercise; N1: 123.7 ± 14.5 vs. CFS1: 111.4 ± 8.2 and N2: 138.5 ± 12.6 vs. CFS2: 124.0 ± 11.9 beats/min at 30 s after onset). The HR kinetics (i.e., ΔHR) after the onset of exercise was significantly increased by CFS in both the first (N1: 55.6 ± 16.0 vs. CFS1: 69.0 ± 12.8 s) and second bouts (N2: 51.5 ± 11.8 vs. CFS2: 64.0 ± 17.5 s) (Table 2).

V̇O₂ responses (both from a representative subject and the group mean) during the first exercise bout after CFS manipulation (CFS1) is shown in Fig. 3 and superimposed with the control N1 response. Interestingly, the V̇O₂ response was unaffected by the CFS manipulation during the first bout as determined by all the quantitative variables derived from either empirical or monoexponential- and/or double-exponential fitting (Table 1). Surprisingly, however, there were also no changes in the dynamics of the V̇O₂ response during the second exercise bout (CFS2) compared with N2 (Fig. 3, Table 2). As such, CFS did not discernibly affect the effective τ or τₚ of V̇O₂ at the onset of supra-LT exercise despite the blunted HR responses.

Blood lactate concentrations just before the onset of exercise of bouts N1, N2, CFS1, and CFS2 were 0.9 ± 0.2, 5.1 ± 0.7, 1.0 ± 0.3 and 5.6 ± 0.8 meq/l, respectively. The prior exercise bout significantly increased blood lactate concentration; however, CFS during either the first or second exercise bouts had no further effect (i.e., no differences were observed between end-exercise N1 vs. CFS1 or N2 vs. CFS2). Also, blood lactate concentration accumulation (i.e., the difference of lactate concentration before, and after, the exercise

Fig. 2. Heart rate response at the onset of the 1st bout (top) and 2nd bout (bottom) with (thick lines) and without (thin lines) CFS application in a representative subject (A) and averaged group mean (B; i.e., from all subjects). Residuals show the difference between control and CFS application (plotted in the bottom of each panel as a dotted line). CFS application (i.e., disturbance of vagal withdrawal), therefore, clearly had a substantial effect on the dynamics of the central circulation.
bouts) was not significantly affected by the CFS manipulation (N1: 5.0 ± 0.6 vs. CFS1: 4.5 ± 1.2, and N2: 1.1 ± 0.6 vs. CFS2: 1.9 ± 0.9 meq/l).

**DISCUSSION**

The main finding of this study was that facial cooling-induced bradycardia at the onset of square-wave heavy-intensity leg cycling exercise had no discernible effect on pulmonary \( \dot{V}O_2 \) kinetics. This was the case during both the first transition, where blood flow is thought to be potentially limiting (e.g., Ref. 32), and also during the second, repeated bout, where a speeded limb blood flow has been suggested to mediate the speeding of the \( \dot{V}O_2 \) dynamics (e.g., Refs. 13, 47). In this study, the time course of HR was demonstrably slowed in response to an interruption of vagal withdrawal and increased sympathetic tone by CFS, both before and after the onset of exercise. Despite the substantially slower and delayed HR kinetics, the \( \dot{V}O_2 \) kinetic parameters estimated by mono- and double-exponential models were not significantly affected by the CFS manipulation in either heavy-intensity exercise bout. These findings are consistent with the notion that a reduction in the circulatory dynamics does not appear to play a central role in the adjustment of pulmonary \( \dot{V}O_2 \) during high-intensity leg cycling exercise (at least up to \( \Delta 50\% \)). This conclusion, however, assumes that blunting the circulatory response via CFS would be transmitted to the periphery as a significant reduction in muscle \( O_2 \) delivery. Each of these interpretations are addressed in turn.

**Does CFS limit limb blood flow?** During resting conditions, CFS manipulation is well known to induce an immediate and pronounced bradycardia coupled with a delayed rise in systemic blood pressure (e.g., Refs. 5, 45) and is commonly used to assess autonomic function (e.g., Ref. 19). The autonomic nervous system is one of the factors that can influence \( O_2 \) transport (25) because of its controlling influence on cardiac activity via the balance of sympathetic and parasympathetic tone. In this study, the CFS manipulation was applied for 2 min, around the onset of exercise, to activate vagal tone (via reflex centers located in the medullar region; Ref. 19) and induce a pronounced bradycardic response at rest before the onset of exercise and an attenuated tachycardia after the onset of exercise. This was clearly seen in our subjects (Fig. 2, Table 2). Whereas parasympathetic and sympathetic activity seem to be reciprocal, parasympathetic tone apparently does not affect vascular tone, because human arterioles show no evidence of parasympathetic innervation. Therefore, it is likely that the disturbance of vagal withdrawal mainly induces a negative effect on central circulatory acceleration (i.e., an attenuated increase of HR and cardiac output). However, CFS is also characterized by an increase in sympathetic nerve activity (which occurs after \( \sim 40 \) s; Refs. 19, 20). This delayed increase in sympathetic activity with CFS has been shown to reduce blood flow to the periphery and increase mean arterial pressure (5, 9, 19, 20, 45). It was expected, therefore, that prolonged (e.g., 2 min) CFS application through the onset of exercise would induce overall effects not dissimilar to interventions such as \( \beta \)-adrenergic blockade (e.g., Refs. 21, 24–26, 39). The actions of both propranolol and metoprolol limit maximal HR and reduce its steady-state value; however, it has not been consistently shown to slow the kinetics of the HR response (Hughson 24) showed no change in \( \tau \) HR, whereas Petersen et al. (39) showed only a small, 5-s slowing), which may limit \( O_2 \) delivery. Application of CFS in the study, on the other hand, slowed the \( \tau \) HR by \( >20\% \) (or \( \sim 13 \) s), providing potential for limiting \( O_2 \) delivery on transition to heavy exercise.

This substantial reduction in HR, both before and during the first minutes of exercise in the present study, resulted in a significantly increased \( T_d \) for HR, suggestive of an increased limb-to-lung transit time resulting from a slowed circulation. This circulatory delay was mirrored in the \( \dot{V}O_2 \) kinetics (either effective \( \tau \) or
Table 1. Pulmonary \( \dot{V}O_{2} \) response characteristics during N1, N2, CFS1, and CFS2

<table>
<thead>
<tr>
<th></th>
<th>N1</th>
<th>CFS1</th>
<th>N2</th>
<th>CFS2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>vs. N1</td>
<td>N2</td>
<td>CFS2</td>
<td>vs. N2</td>
</tr>
<tr>
<td>BL, ml/min</td>
<td>260 ± 47</td>
<td>275 ± 62</td>
<td>365 ± 92†</td>
<td>380 ± 90</td>
</tr>
<tr>
<td>( \Delta \dot{V}O_{2} ), ml/min</td>
<td>145 ± 73</td>
<td>133 ± 59</td>
<td>63 ± 25†</td>
<td>54 ± 36†</td>
</tr>
<tr>
<td>Mono-exponential fitting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;Effective&quot; ( \tau ), s</td>
<td>43.8 ± 11.8</td>
<td>38.7 ± 10.8</td>
<td>27.5 ± 8.0†</td>
<td>24.6 ± 12.1</td>
</tr>
<tr>
<td>Td, s</td>
<td>-4.8 ± 3.8</td>
<td>2.2 ± 8.1</td>
<td>4.2 ± 5.4</td>
<td>9.9 ± 7.0</td>
</tr>
<tr>
<td>A, ml/min</td>
<td>1,966 ± 575</td>
<td>1,945 ± 558</td>
<td>1,879 ± 506</td>
<td>1,883 ± 484</td>
</tr>
<tr>
<td>Double-exponential fitting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tdp, s</td>
<td>6.5 ± 7.1</td>
<td>12.9 ± 2.5</td>
<td>6.6 ± 8.8</td>
<td>14.0 ± 8.0</td>
</tr>
<tr>
<td>( \tau_{p} ), s</td>
<td>23.7 ± 7.9</td>
<td>20.9 ± 3.8</td>
<td>23.3 ± 10.3</td>
<td>17.4 ± 6.3</td>
</tr>
<tr>
<td>Ap, ml/min</td>
<td>1,749 ± 533</td>
<td>1,777 ± 550</td>
<td>1,830 ± 522</td>
<td>1,848 ± 479</td>
</tr>
<tr>
<td>Tds, s</td>
<td>102 ± 51</td>
<td>118 ± 29</td>
<td>147 ± 66</td>
<td>153 ± 51</td>
</tr>
<tr>
<td>A(_s), ml/min</td>
<td>298 ± 140</td>
<td>247 ± 99</td>
<td>101 ± 31†</td>
<td>68 ± 25</td>
</tr>
</tbody>
</table>

Values are means ± SD for 5 subjects. N1 and N2, 1st and 2nd exercise bouts during the "control" trial; CFS1 and CFS2, 1st and 2nd exercise bouts with the manipulation of cold face stimulation (CFS) (see the details in Fig. 1); BL, baseline \( \dot{V}O_{2} \) (\( \dot{V}O_{2} \) vs. N1 and N2, P < 0.05). *Significantly different from CFS1 or CFS2 to each trial indicated in the column, \( P < 0.05 \).

Table 2. Heart rate response characteristics during N1, N2, CFS1, and CFS2

<table>
<thead>
<tr>
<th></th>
<th>N1</th>
<th>CFS1</th>
<th>N2</th>
<th>CFS2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>vs. N1</td>
<td>N2</td>
<td>CFS2</td>
<td>vs. N2</td>
</tr>
<tr>
<td>BL, beats/min</td>
<td>68 ± 5</td>
<td>73 ± 6</td>
<td>95 ± 6†</td>
<td>100 ± 7</td>
</tr>
<tr>
<td>&quot;Effective&quot; ( \tau ), s</td>
<td>55.6 ± 16.0</td>
<td>69.0 ± 12.8</td>
<td>51.5 ± 11.8</td>
<td>64.0 ± 17.5</td>
</tr>
<tr>
<td>A, beats/min</td>
<td>98 ± 10</td>
<td>99 ± 11</td>
<td>80 ± 10†</td>
<td>79 ± 11</td>
</tr>
<tr>
<td>Td, s</td>
<td>-10.3 ± 2.2</td>
<td>-4.8 ± 4.7</td>
<td>-7.1 ± 2.9</td>
<td>3.1 ± 3.6</td>
</tr>
</tbody>
</table>

Values are means ± SD for 5 subjects. BL, baseline heart rate. *Significantly different from CFS1 or CFS2 to each trial indicated in the column, \( P < 0.05 \).

J Appl Physiol • VOL 95 • OCTOBER 2003 • www.jap.org
able to elicit a faster adjustment of muscle $V_{\dot{O}_2}$ (trapezius muscle that the Behnke et al. (4) have shown in the rat intact-spinosprint right position, these authors showed that a slowed was performed in the supine compared with the up-through, similar to the present study, though, similar to the present study, increased muscle blood can be facilitated $V_{\dot{O}_2}$ during the first exercise bout. Furthermore, recent studies (31, 38, 49) using handgrip exercise and single or repeated bouts (presumably in the heavy-intensity domain), demonstrated that m$V_{\dot{O}_2}$ and blood flow manifested similar adaptations of response. In other words, improved $O_2$ delivery speeded the m$V_{\dot{O}_2}$ response on-transition to the second bout of handgrip exercise after an identical conditioning bout, such that forearm m$V_{\dot{O}_2}$ during the first 30 s of the second bout of exercise was elevated compared with that in the first bout with a concomitant increase in blood flow to the forearm (31). However, because of the constraints of the experimental mode, the authors could not estimate the kinetic parameters of these changes. Furthermore, despite speeded $O_2$ kinetics at the onset of peak intensity exercise in the isolated canine gastrocnemius (16), a similar effect during exercise that elicited 60–70% of maximal $V_{\dot{O}_2}$ (15) was not found. In addition, Fukuba et al. (10) found no effect of a comparable systemic residual lactic acidosis (generated by exercising a different muscle group, i.e., arm) on subsequent $V_{\dot{O}_2}$ kinetics at the onset of heavy-intensity leg cycling exercise, despite the potential beneficial effects of peripheral vasodilatation and a rightward shift of $O_2$ dissociation curve (i.e., Bohr effect). It seems, therefore, that although the dynamics of cardiac output or blood flow is consistently faster than $V_{\dot{O}_2}$ at the onset of both moderate-intensity (8) and heavy-intensity exercise (e.g., Refs. 17, 33), this may not be the case during severe exercise (16, 47). Nevertheless these observations support the metabolic inertial hypothesis in determining the characteristics of the $V_{\dot{O}_2}$ response at the initial-onset. heavy-intensity exercise. However, an attenuating (not augmenting) manipulation applied at the onset of the second bout in the repeated-bouts protocol is, we believe, crucially important because, if the exercise itself were to reduce or remove an intramuscular “stenosis” that operates during the first exercise bout, it is possible that the elevated blood flow, apparent at the onset of the second bout, could play a role in the facilitation of the $V_{\dot{O}_2}$ response observed during N2. Therefore, our hypothesis, that the $V_{\dot{O}_2}$ response at the onset of the second bout of exercise would be suppressed by the attenuation $O_2$ delivery (i.e., by the CFS manipulation) was not supported by the results of the present study. Despite the delayed circulatory adaptation at exercise onset induced by CFS (Table 2, Figs. 2 and 4), there was no concomitant

![Fig. 4. Time-averaged group mean (n = 3) values of heart rate (top; in beats/min (bpm)) and femoral artery blood flow (bottom) responses to CFS application during the 1 min before the onset of first (A) and second (B) exercise bouts. Blood flow to the right leg was obtained by using simultaneous pulsed and echo Doppler ultrasound system with a 3.5-MHz probe (with an angle of insonation of 55–60°) to measure mean blood flow and femoral artery diameter from a site 2 cm distal to the inguinal ligament. CFS manipulation demonstrated that leg blood flow and heart rate showed a similar pattern of response during CFS.](image-url)
slowing of VO2 response at the onset of the second bout of heavy-intensity exercise (Table 1, Fig. 3).

The mechanism(s) underlying the facilitated VO2 response (manifest as either a speeding of the fundamental τp, a reduction in the slow component, or both) at the onset of the second exercise bout during repeated exercise, therefore, remain(s) to be elucidated. Rossiter et al. (44) have suggested that the VO2 slow component during the repeated-bouts protocol in humans was related to an intramuscular event linked to phospho-creatine degradation, which was in accord with the demonstration of Poole et al. (41) that ~80–90% of the pulmonary VO2 slow component could be accounted for by the associated increase in leg VO2. Consequently, the control of the VO2 slow component is commonly ascribed to factors related to the exercising limb, rather than to rest of the body. Therefore, we believe, mechanisms proposed to explain the facilitated VO2 in the second bout are more likely to be ascribed to an intramuscular event such as the pattern of motor unit recruitment and/or fatigue (1, 43); intracellular factors other than O2 availability (22), which may arise from either activation of the pyruvate dehydrogenase complex (23, 46); a relationship to the attenuation of the blood lactate increase (10, 13), or altered phosphate-mediated feedback control (44).

In summary, therefore, this study demonstrated that VO2 dynamics were not altered under conditions of increased vagal activity resulting from CFS manipulation before and after the onset of exercise despite a clearly delayed and slower HR response. Contrary to our hypothesis, the VO2 response during the second bout of repeated supra-LT cycling did not revert toward the response of the initial exercise bout, when a reduced circulatory dynamic was imposed via CFS. This suggests that the marked adaptation of VO2-kinetics during the second bout of supra-LT exercise may not be manifest by an O2 delivery-related mechanism. Rather, these data implicate mechanisms more proximally related to muscular ATP breakdown in mediating this phenomenon.

DISCLOSURES

This study was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan (nos. 10680048 and 12680048) and Uehara Memorial Life Science Foundation. H. B. Rossiter is an International Prize Traveling Fellow of the Wellcome Trust (United Kingdom) (no. 064898).

REFERENCES


EFFECTS OF VAGAL WITHDRAWAL ON VO2 KINETICS


