Neural blockade during exercise augments central command’s contribution to carotid baroreflex resetting


1Department of Integrative Physiology and Cardiovascular Research Institute, University of North Texas Health Science Center, Fort Worth, Texas 76107; and 2Copenhagen Muscle Research Center, Department of Anesthesia, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Received 29 July 1999; accepted in final form 3 October 2000

Neural blockade during exercise augments central command's contribution to carotid baroreflex resetting. Am J Physiol Heart Circ Physiol 280: H1635–H1644, 2001.—This investigation was designed to determine central command’s role on carotid baroreflex (CBR) resetting during exercise. Nine volunteer subjects performed static and rhythmic handgrip exercise at 30 and 40% maximal voluntary contraction (MVC), respectively, before and after partial axillary neural blockade. Stimulus-response curves were developed using the neck pressure–neck suction technique and a rapid pulse train protocol (+40 to −80 Torr). Regional anesthesia resulted in a significant reduction in MVC. Heart rate (HR) and ratings of perceived exertion (RPE) were used as indexes of central command and were elevated during exercise at control force intensity after induced muscle weakness. The CBR function curves were reset vertically with a minimal lateral shift during control exercise and exhibited a further parallel resetting during exercise with neural blockade. The operating point was progressively reset to coincide with the centering point of the CBR curve. These data suggest that central command was a primary mechanism in the resetting of the CBR during exercise. However, it appeared that central command modulated the carotid-cardiac reflex proportionately more than the carotid-vasomotor reflex.

Blood pressure; anesthesia; paralysis; cardiovascular control regulation during exercise and was progressively reset with increasing intensity of exercise. This was confirmed for moderate- to high-intensity exercise by Papelier et al. (18) and the recent work of Norton et al. (16). Norton and colleagues provided data that defined two additional characteristics of the CBR: 1) the CBR was progressively reset proportional to the exercise intensity, even to maximal exercise, and 2) the operating point (OP) was progressively relocated toward the threshold pressure of the reflex and away from the centering point (CP) (16). Also, Norton et al. (17) documented that the CBR control of HR and MAP was progressively reset during prolonged steady-state exercise as muscle fatigue increased along with a similar relocation of the OP in direct relation to increasing indexes of central command.

Potential mechanisms for the resetting of the CBR include the feedforward central signals (i.e., central command) that activate in parallel the cardiovascular and motor responses to exercise (13, 21) and the feedback from muscle reflexes due to chemical and mechanical signals (i.e., exercise pressor reflex) (13, 21, 22). Rowell and O’Leary (22) proposed a model of the sympathetic control arm of the arterial baroreflex at the onset of exercise. The OP of the baroreflex was relocated laterally rightward. This relocation was influenced by the increasing descending influence of central command on the baroreceptor centers in the brain stem, so that the reflex would operate around the increased arterial pressure induced by exercise. They further proposed that activation from muscle reflexes would increase sympathetic nerve activity and result in a vertical shift that would not alter the prevailing OP pressure. In combination, this central neural integration would result in the parallel upward and rightward resetting that has been described by Potts et al. (20) and Norton et al. (16) for HR and MAP. While the effect of augmented central command on cardiovascular control during static and dynamic exercise has been characterized (6, 7, 13, 15, 25), major questions remain as to the proportion of the CBR resetting mechanism that may be attributed to central command via vagal or sympathetic influences of the CBR.
The purpose of this investigation was to examine the effect of increased central command on CBR control of HR and MAP during static and rhythmic static handgrip exercise. We hypothesized that the increased central effort and motor recruitment (central command) required to maintain a constant tension during a condition of induced muscle weakness by axillary blockade would augment HR and MAP responses during exercise. We further hypothesized, on the basis of the model of Rowell and O'Leary of arterial baroreflex resetting (22), that the increasing central command would reset the CBR horizontally during exercise to a higher operating arterial pressure.

METHODS

Subjects. Nine healthy male volunteer subjects were studied during static (isometric hold) and rhythmic static (repeat- ed isometric hold-relax) handgrip exercise before and after partial axillary neural blockade. The group values (means ± SE) for age, height, and weight were 24.6 ± 0.5 yr, 182.9 ± 2.9 cm, and 74.5 ± 2.4 kg, respectively. All volunteer subjects were informed of protocols and potential risks involved with the experiment. All procedures and protocols were approved by the Ethical Committee of Copenhagen, Denmark (01-008/98), and subjects provided written consent.

Instrumentation. On morning arrival at the laboratory, the subjects were placed in a semirecumbent position with the head end of the table elevated to ~60°. Handgrip exercise was conducted with each subject’s dominant arm. A strain-gauge grip dynamometer was lowered from an overhead support, and the subject’s exercising arm was supported to remain in a natural relaxed position. A measuring bridge (Caspersen & Nielsen, Copenhagen, Denmark) converted contraction force to an electrical current displayed on a metered panel on a scale of 0–100. The instrument calibration was set to produce a displayed output of ~60 (scale 0–100) when a contraction force above that which could be generated with unilateral handgrip was applied. This initial calibration was maintained for all experiments and used to calibrate the data acquisition system for the measurement of contraction force in arbitrary units (AU). The displayed panel output served as visual feedback to the subject for the maintenance of the prescribed force production.

For all studies the subjects were instrumented with standard electrocardiogram (ECG) electrodes. HR was calculated beat-to-beat (R-R intervals) and output to an ECG/pressure monitor (Dialogue 2000) interfaced with the computer data acquisition system. Arterial pressure was measured using a 2-in., 19-gauge Teflon arterial cannula (Ohmeda) placed in the brachial artery of the nondominant arm. The arterial pressure waveform was transduced utilizing a sterile, disposable pressure transducer (model PX-260, Baxter) and the ECG/pressure monitor. The pressure monitor output included systolic arterial pressure, diastolic arterial pressure, and MAP. The arterial pressure transducer was positioned and calibrated at heart level of the midaxillary region and kept patent by a continuous drip saline infusion (3 ml/h).

Axillary anesthesia was introduced through a 19-gauge catheter placed in the perivascular space at the lateral border of the pectoral muscle. After the control exercise protocol was completed, a total dose of 30 ml of 2% lidocaine (Xylocaine, Astra) was infused into the axillary catheter. In addition, 3 ml of 2% lidocaine were injected as a radial block at the level of the elbow to ensure partial neural blockade of all forearm musculature. Subjects rested for 15–20 min to allow for the activation of the anesthesia. Presence of partial neuromuscular blockade was verified by a reduction of handgrip maximal voluntary contraction (MVC) of >25% from control values. In addition, sensory attenuation was established by the elimination of cutaneous sensory pain detection (pin prick).

Exercise protocol. The exercise protocol consisted of static and rhythmic exercise before and after axillary partial neural blockade. Before the beginning of each exercise bout, the subject conducted three MVC attempts that were recorded and averaged to determine the exercise workload. The static exercise trials consisted of 3 min of handgrip exercise at 30% of the subject's control MVC. The rhythmic exercise trials consisted of 7 min of exercise at a rate of 0.5 Hz (1 s of contraction followed by 1 s of relaxation) paced by a metronome. The workload for the rhythmic exercise was 40% of the subject's control MVC. Ratings of perceived exertion (RPE) were taken at the end of minute 3 during static exercise and at the end of minutes 3 and 7 during rhythmic exercise using the Borg scale of perceived exertion (range 6–20).

The experimental protocol utilized the following exercise order: control static followed by a 30-min recovery period and control rhythmic followed by a 1-h break. During the break the axillary and radial neural blocks were applied. After the determination of muscular weakness, each subject repeated three maximal contractions. The workload for exercise with the partial blockade was maintained at the same absolute tension used for the control condition. Therefore, the resulting muscular weakness coupled with the maintenance of the same control workload values resulted in the subjects working at a higher percentage of their MVC under blockade. The exercise protocol was repeated beginning with the blocked static trial followed by a 30-min recovery period. Before the blocked rhythmic exercise trial, the subject completed three additional MVC attempts to establish the extent of blockade remaining. HR and MAP data were collected continuously throughout the experiment, and CBR stimulus-response curves were collected starting after minute 1 or 3 of exercise for static or rhythmic static exercise, respectively.

CBR function. To evaluate the CBR control of HR and MAP at rest and during exercise, the neck pressure-neck suction (NP-NS) technique was utilized. Pressure stimuli were applied through a cushioned malleable lead collar that was modified from the design previously described by Eckberg et al. (4) and placed around the anterior two-thirds of the neck. Graded levels of pressure between +40 and −80 Torr were generated by a variable pressure source and controlled by two-way solenoid valves (model 8215B, Asco, Florham Park, NJ). The external neck chamber pressure applied to the carotid sinus region was measured by a pressure transducer (model DP45, Validyne Engineering, Northridge, CA). To minimize the respiratory-related modulation of HR and MAP, all CBR perturbations were conducted during an end-expiratory breath held initiated by the subject. The total duration of breath hold varied between 10 and 15 s. Previously, we identified no alteration in the arterial blood gases during the breath hold at dynamic exercise intensities of 50% of maximal O₂ consumption (V̇O₂max) (20). The baroreflex protocol was a rapid pulse train that was comprised of 12 pulses of 300- to 500-ms duration. Each pulse was computer controlled to deliver the manually set NP-NS pulse to the carotid sinus precisely 50 ms after the R wave of the ECG. The intensity of each pulse in the pressure profile was manually set and began with four pulses of +40 Torr followed by three pulses of decreasing positive pressure to 0 Torr. This was followed by five pulses of increasing negative pressure from 0 to −80 Torr in approximately −20-Torr increments. After each pres-
sure pulse, the neck chamber was vented to atmospheric pressure by computer control to create a pulsatile stimulus. Three to four rapid pulse trains were collected during each collection period with 0.5–1 min of recovery between pulse trains.

The beat-to-beat responses of HR and MAP were recorded along with the chamber pressure measured within the neck collar. The chamber pressure was used to calculate an estimated CSP. Previously, the CSP has been estimated by subtracting the measured neck chamber pressure (ChP) from the prestimulus MAP (CSP = MAP − ChP). The CBR stimulus-response curve was defined as the nine-beat data period corresponding to the last four positive-pressure pulses and the five negative-pressure stimuli. The nine-beat HR and MAP responses that best represent the peak reflex response range were selected and aligned with the calculated CSP to complete the stimulus-response data set.

Data analyses. Carotid-cardiac (HR) and carotid-vasomotor (MAP) function at rest and during exercise were individually fit for each subject to the four-parameter logistic function described by Chen and Chang (2) and the calculated G max, CSP thr and CSP sat for all subjects within an experimental condition were averaged to provide group mean data values.

To generate the CBR response curves representing the group data, the parameters A 1–A 4 and the calculated G max, CSP thr and CSP sat for all subjects within an experimental condition were averaged to provide group mean data values. These data were then applied to the Kent logistic model (9) to generate the resulting group curve. The OP was defined as the prestimulus CSP, which is equal to prestimulus MAP, for the carotid-cardiac and carotid-vasomotor reflexes.

Statistical analyses. Comparison of CBR parameters (G max, CSP thr and CSP sat, CP, OP, Rng, R min) and cardiovascular variables (HR and MAP) were analyzed using a repeated-measures two-way ANOVA. If significance was found, a Student-Newman-Keuls post hoc test was employed. Values are means ± SE. The α-level of P < 0.05 was considered significant. Analyses were conducted using JMP IN statistical software for Windows (SAS Institute, Cary, NC).

RESULTS

Workload and MVC. After the administration of axillary and radial blockade, the subjects reported parasthesia on dorsal and ventral sides of the forearm. The force produced during a maximal handgrip attempt (MVC) and recorded from the handgrip dynamometer visual readout was reduced from the control value of 39.9 ± 2.0 to 23.3 ± 2.3 AU during the blocked static exercise bout and 20.1 ± 3.5 AU for the blocked rhythmic trial (P < 0.05). This represents an ~40% reduction in maximal strength due to the neural blockade. The control MVC results were used to calculate the 30% static and 40% rhythmic workloads. This calculation resulted in exercise workloads of 11.3 ± 0.8 AU for static exercise and 15.2 ± 1.3 AU for the rhythmic handgrip exercise. After partial neural blockade, the subjects attempted to maintain the same handgrip tension loads as during the control exercise. These workloads, while equal in absolute work produced, resulted in an increased percentage of the reduced maximal workload (MVC) after partial neural blockade. Calculated workloads after blockade were calculated as 61.2 ± 6.8 and 57.0 ± 6.5% of maximal contraction during static and rhythmic static exercise, respectively.

Cardiovascular response to exercise. Although there was a small increase in resting HR and MAP after administration of the partial neural blockade, the difference was not significant. The HR responses at rest and during the 3 min of static exercise before and after neural blockade are shown in Fig. 1A. The HR response to static exercise was increased with neural blockade compared with control throughout the exercise period (P < 0.05). The greatest increase in HR took place between minutes 1 and 2 of exercise for the control bout, with no further significant increase between minutes 2 and 3. The increased effort required during the exercise with neural blockade resulted in the most rapid increase in HR during the initial minute of exercise with blockade. This increased effort also resulted in a trend to increase HR at minutes 2 and 3; however, the change in HR over minute 3 was not significant.

The HR responses at rest and during the 7 min of rhythmic exercise before and after neural blockade are shown in Fig. 2A. During the control condition, there was a minimal increase in HR until minutes 3–5, where HR increased and remained at a steady state to the completion of the exercise bout. During exercise under the effect of neural blockade, HR was elevated compared with the control exercise bout throughout the 7-min period (P < 0.05). HR increased rapidly during minute 1 of exercise, remained at a steady state until minute 3, and then increased with a tachycardic pattern similar to that seen in the control condition. HR remained at a steady state from minute 4 of exercise to completion in control and neural blockade exercise bouts.
The MAP response to static exercise is shown in Fig. 1B. The MAP response during control and neural blockade exercise increased linearly throughout exercise. There was a significant increase in MAP during exercise with partial neural blockade compared with control. Rhythmic exercise MAP responses are shown in Fig. 2B. Control exercise arterial pressure increased progressively during the first 3 min of exercise, with minimal and nonsignificant further increases through minute 7. The MAP response during the axillary blocked condition resulted in a rapid increase compared with control followed by an apparent plateau that remained above the control values for the duration of exercise (P < 0.05). The MAP remained at steady state for both exercise conditions from minute 3 to the completion of the rhythmic exercise bout.

There was a significant increase in all exercise RPE values after axillary blockade administration (P < 0.05; Table 1). The static exercise RPE at 3 min increased from ~12 (subject description from Borg scale between fairly light and somewhat hard) during control exercise to ~15 (subject description as hard) under partial neural blockade (P < 0.05). During minute 3 of rhythmic exercise, subjects reported an increased RPE from ~10 (below fairly light) to ~13 (somewhat hard) due to the effect of neural blockade (P < 0.05). The perceived exertion was increased further by the completion of minute 7 of rhythmic exercise from a rating of ~12 during control conditions to ~15 with exercise under neural blockade (P < 0.05). These data indicate that the application of partial neural blockade significantly increased the subjects’ central perceived exertion to maintain the same absolute amount of force production, thus supporting an increase in central command.

Because of the extent of muscle weakness induced by the neural blockade, one subject during blocked static exercise and three subjects during blocked rhythmic exercise could not maintain the same absolute tension as during control and, therefore, were working at 100% MVC during the exercise with neural blockade. Although these subjects were exercising at maximal effort, their HR responses and reported RPE values did not disproportionately affect the group values pre-

Table 1. RPE during exercise

<table>
<thead>
<tr>
<th></th>
<th>Static Minute 3</th>
<th>Rhythmic Minute 3</th>
<th>Rhythmic Minute 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>12.3 ± 0.7</td>
<td>10.2 ± 0.6</td>
<td>12.0 ± 0.6†</td>
</tr>
<tr>
<td>Partial blockade</td>
<td>15.1 ± 0.8*</td>
<td>12.9 ± 1.0*</td>
<td>15.2 ± 0.8*†</td>
</tr>
</tbody>
</table>

Values are means ± SE of ratings of perceived exertion (RPE) utilizing the Borg scale (6–20) during static (30% maximal voluntary contraction (MVC)) and rhythmic static (40% MVC) exercise during control and partial neural blockade in 9 healthy subjects. RPE values were measured after minute 3 of static exercise and after minutes 3 and 7 during rhythmic exercise. *Significant difference between control and partial neural blockade exercise; †difference between minutes 7 and 3 of rhythmic exercise (P < 0.05).
sented in Table 1. All subjects reported increased HR and RPE values during exercise with neural blockade compared with control exercise values.

**CBR control of HR.** The stimulus-response curves for the CBR control of HR are shown in Fig. 3A for static exercise and Fig. 4A for rhythmic exercise, indicating rest, control exercise, and partial axillary blockade exercise. The logistic parameters ($A_1$–$A_4$) for the carotid-cardiac baroreflex are summarized in Table 2. The responses for static and rhythmic exercise were similar and were as follows: the HR response range ($A_1$, Rng) increased from rest to control exercise ($P < 0.05$). During static exercise with neural blockade, $A_1$ increased further but was not significantly different from control exercise. There was no difference in the calculated slope ($A_2$) of the stimulus-response curve during any condition or trial. Compared with the resting value, the CSP at the CP ($A_3$) was increased during control exercise and increased further after axillary blockade ($P < 0.05$). The maximal reflex bradycardia, or minimum HR response ($A_4$, $R_{min}$) elicited by the CBR in response to the higher-intensity negative pressure pulses, increased to higher HR values progressively from rest to control exercise to blocked exercise ($P < 0.05$).
Central command and carotid baroreflex resetting

The major finding of the present investigation was that central command was an important and direct mechanism in the resetting of CBR during exercise. The findings further suggest that the increase in the central command’s influence on the cardiovascular system during exercise results in an upward and rightward shift along with a relocation of the HR at the OP pressure in the carotid-cardiac stimulus-response curve. In addition, the resultant reflex function curves suggest that central command may modulate the carotid-cardiac limb of the CBR differently from the carotid-vasomotor limb.

Effect of partial neural blockade on central command during exercise. Various techniques have been utilized to increase the efferent activity attributed to central command during exercise. In several investigations the neuromuscular blocking agents tubocurarine and vecuronium (11, 15, 23) were used. However, the use of this type of drug protocols had no impact on the influence ofafferent information from the working muscle. Hence, although there was a selective augmentation of central command through muscular weakness and the need for increased motor recruitment to maintain a constant work rate, there remained a functional integration of muscular afferent and efferent input on cardiovascular regulation.

In a classical study by Goodwin et al. (7), central command was manipulated by utilizing a tendon vibration stimulus to selectively increase agonist or antagonist muscle spindle activation. Although this novel technique was productive in altering central command, there remained unanswered questions as to the full effect of reflex activation and afferent feedback from

Table 2. Logistic model parameters describing CBR control of HR and MAP

<table>
<thead>
<tr>
<th></th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
<th>A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid-cardiac baroreflex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control rest</td>
<td>16.9 ± 2.2</td>
<td>0.24 ± 0.08</td>
<td>87.7 ± 3.2</td>
<td>44.0 ± 2.7</td>
</tr>
<tr>
<td>Control static</td>
<td>22.5 ± 1.5†</td>
<td>0.14 ± 0.02</td>
<td>100.9 ± 3.3†</td>
<td>50.1 ± 1.7†</td>
</tr>
<tr>
<td>Blocked static</td>
<td>26.9 ± 2.3</td>
<td>0.14 ± 0.01</td>
<td>112.9 ± 4.4†</td>
<td>56.0 ± 1.8†</td>
</tr>
<tr>
<td>Control rhythmic</td>
<td>29.6 ± 1.8†</td>
<td>0.12 ± 0.01</td>
<td>100.0 ± 2.5†</td>
<td>48.8 ± 1.7†</td>
</tr>
<tr>
<td>Blocked rhythmic</td>
<td>26.3 ± 2.0</td>
<td>0.13 ± 0.01</td>
<td>106.5 ± 2.5†</td>
<td>59.0 ± 2.5†</td>
</tr>
</tbody>
</table>

Values are means ± SE, A1, range (maximum–minimum); A2, gain coefficient; A3, carotid sinus pressure at midpoint of A1; A4, minimal response. CBR, carotid baroreflex; HR, heart rate; MAP, mean arterial pressure. *Significantly different between conditions (control vs. partial neural blockade), P < 0.05. †Significantly different from resting control condition, P < 0.05.

The stimulus-response variables that were calculated from the above logistic parameters are presented in Table 3. During static and rhythmic control exercise, CSPthr and CSPsat were reset to higher CSP values than at rest. Exercise after axillary blockade resulted in a further shift of CSPthr and CSPsat to higher values (P < 0.05). Gmax was similar between experimental conditions and exercise protocols (P > 0.05).

CBR control of MAP. The stimulus-response curves for the CBR control of MAP are shown in Fig. 3B for static exercise and Fig. 4B for rhythmic exercise, at rest, and exercise before and after axillary neural blockade. The carotid-vasomotor reflex curves were shifted upward during exercise, illustrating the presor response and CBR resetting associated with exercise. The logistic parameters (A1–A4) for the carotid-vasomotor baroreflex are summarized in Table 2. The MAP response range (A1–A4) was not different between rest and control static exercise. There was a small increase in MAP response range during control rhythmic exercise and after axillary blockade in static and rhythmic exercise compared with the control resting value. Neural blockade also increased Rng during static exercise with axillary blockade compared with the control static exercise trial. The CP (A3) and Rmin (A4) were increased during control exercise (static and rhythmic) compared with resting values. The resetting of the CBR function curve during exercise after neural blockade resulted in a further increase in CP and Rmin compared with control static and rhythmic exercise (P < 0.05).

The stimulus-response variables that were calculated for the carotid-vasomotor reflex are presented in Table 4. The maximal gain of the CBR control of MAP was less than that of HR, but as seen in the carotid-cardiac reflex, Gmax was not different between experimental conditions or exercise protocols. There was an increase in CSPthr and CSPsat with control static and rhythmic exercise compared with rest. With the exception of the increased CSPsat value during static exercise, there were no significant increases in CSPthr and CSPsat with exercise after neural blockade.

DISCUSSION

The major finding of the present investigation was that central command was an important and direct mechanism in the resetting of CBR during exercise. The findings further suggest that the increase in the central command’s influence on the cardiovascular system during exercise results in an upward and rightward shift along with a relocation of the HR at the OP pressure in the carotid-cardiac stimulus-response curve. In addition, the resultant reflex function curves suggest that central command may modulate the carotid-cardiac limb of the CBR differently from the carotid-vasomotor limb.

Effect of partial neural blockade on central command during exercise. Various techniques have been utilized to increase the efferent activity attributed to central command during exercise. In several investigations the neuromuscular blocking agents tubocurarine and vecuronium (11, 15, 23) were used. However, the use of this type of drug protocols had no impact on the influence of afferent information from the working muscle. Hence, although there was a selective augmentation of central command through muscular weakness and the need for increased motor recruitment to maintain a constant work rate, there remained a functional integration of muscular afferent and efferent input on cardiovascular regulation.

In a classical study by Goodwin et al. (7), central command was manipulated by utilizing a tendon vibration stimulus to selectively increase agonist or antagonist muscle spindle activation. Although this novel technique was productive in altering central command, there remained unanswered questions as to the full effect of reflex activation and afferent feedback from
skeletal muscle by tendon vibration. In the present investigation, muscular weakness was developed with the application of regional anesthesia to the axillary and radial region. This technique, which was similar to epidural anesthesia used for investigation of lower body exercise, created a weakness in MVC of the forearm similar to that induced by curare but also blocked or attenuated afferent exercise pressor feedback from the working muscle.

Elevations in HR, electromyographic (EMG) activity, RPE, and to some degree VO₂ are commonly used to evaluate the degree of central command activation. With the application of neuronal blockade as in the present investigation, EMG activity and VO₂ are not acceptable indicators of central command because of an “uncoupling” of the myoneural integration. With curare, the blockade effect occurs at the motor end plate with inhibition of muscular contraction by competition with ACh activation of a skeletal muscle action potential. Therefore, the nerve pathway from cortical activation to skeletal muscle would be intact. EMG activity would remain an appropriate indicator of the quantity of central cortical-generated motor unit activation and recruitment (central command) due to the absence of interference between cortical activation and the signal termination at the motor end plate. However, with axillary neuronal blockade utilized in the present investigation, the efferent motor nerve was anesthetized far proximal to the motor end plate of the active skeletal muscle, so that action potentials due to the increased motor unit recruitment by central command would be effectively conducted only as far as the site of anesthesia. Neuronal depolarization could not continue distal to this point; therefore, EMG activity recorded at the working muscle would not fully represent the amount of centrally activated motor unit recruitment. Additionally, VO₂ may not be an accurate indicator in any protocol of muscular blockade due to the potential alterations in muscle fiber type recruitment or altered metabolic substrate utilization. Therefore, in the present study, HR, MAP, and RPE were utilized as indicators of altered central command.

Effect of partial neural blockade on cardiovascular response to exercise. During static and dynamic exercise with increasing workload, central command and afferent information emanating from the working skeletal muscle are continually increased and are thought to be integrated to derive the final end organ and systemic responses. In the present experiment, control exercise responses, including HR, MAP, and CBR function, would have been the result of integrated efferent (central command) and afferent (mechanical and chemical) receptor information. However, the application of axillary blockade resulted in a reduction in the subject’s ability to maximally contract and also attenuated afferent feedback from the working muscle. To maintain the same absolute force during static and rhythmic exercise under the effects of axillary anesthesia, the subjects would be required to increase the actual number of motor units centrally recruited, and this exercise effort resulted in the subjects working at a greater percentage of their maximal ability after neural blockade. The exercising HR response and the increase in RPE during static and rhythmic exercise after neural blockade indicated an increase in central command. Therefore, by selectively increasing central command, we assume to have produced an effect similar to an increase in exercise workload on the feedforward efferent autonomic arm of the reflex, even though the absolute force or tension of the muscle was maintained or reduced. The increase in central command was accomplished simultaneously with attenuation of the feedback afferent information from exercising muscle, thus strengthening the assumption that the observed cardiovascular changes were due to the efferent central command effect.

The results indicated that HR and MAP responses during neural blockade exercise were increased compared with control. These data are in contrast to those in previous investigations (10, 14) in which cardiovascular responses during static exercise were reduced under neural blockade and in which it was concluded that afferent information from the working muscle was important in the HR response during exercise. However, the use of maximal-intensity static exercise for brief 4-s contractions (10) or the use of a leg extension exercise at a lower intensity (10% MVC) (15) and time period (2 min) than used in the exercise protocol of the present investigation indicates differences in central integration between central command and afferent information that were dependent on muscle mass, absolute tension, time under tension, or percentage of maximal ability. It appears that central command and the exercise pressor reflex can be redundant mechanisms and that, within the central nervous system, neural occlusion may be operative. We suggest that when muscular weakness induces a disproportion between an increase in central command and constant or de-

Table 4. Derived variables describing the stimulus-response relationship for CBR control of MAP

<table>
<thead>
<tr>
<th></th>
<th>Control Rest</th>
<th>Control Static</th>
<th>Blocked Static</th>
<th>Control Rhythmic</th>
<th>Blocked Rhythmic</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSPᶜᵃᵖ, mmHg</td>
<td>62.7 ± 3.3</td>
<td>80.2 ± 3.6†</td>
<td>85.7 ± 4.1†</td>
<td>76.7 ± 2.9†</td>
<td>82.0 ± 3.2†</td>
</tr>
<tr>
<td>CSPᶜᵃᵖ, mmHg</td>
<td>109.1 ± 3.9</td>
<td>124.9 ± 4.8†</td>
<td>138.6 ± 4.5‡</td>
<td>127.7 ± 3.4†</td>
<td>132.1 ± 3.7†</td>
</tr>
<tr>
<td>MAPᶜᵃᵖ, mmHg</td>
<td>85.6 ± 4.8</td>
<td>99.61 ± 3.7†</td>
<td>107.3 ± 4.5‡</td>
<td>99.3 ± 0.7†</td>
<td>109.3 ± 0.7†‡</td>
</tr>
<tr>
<td>MAPᶜᵃᵖ, mmHg</td>
<td>86.1 ± 2.4</td>
<td>103.1 ± 4.0†</td>
<td>112.7 ± 4.0‡</td>
<td>102.8 ± 2.7†</td>
<td>108.6 ± 3.2†‡</td>
</tr>
<tr>
<td>Gᵐᵃˣ, mmHg/mmHg</td>
<td>−0.46 ± 0.09</td>
<td>−0.50 ± 0.05</td>
<td>−0.56 ± 0.04</td>
<td>−0.53 ± 0.05</td>
<td>−0.52 ± 0.06</td>
</tr>
</tbody>
</table>

Values are means ± SE. MAPᶜᵃᵖ, MAP at operating point of reflex (prestimulus); MAPᶜᵃᵖ, MAP at centering point of reflex (Aᵢ). †Significantly different from resting control condition, P < 0.05. ‡Significantly different between conditions (control vs. partial neural blockade), P < 0.05.
creasing muscle tension or exercise duration, the increased signal arising from central command determines the magnitude of the cardiovascular responses and the subsequent relocation of the CBR (i.e., resetting).

Central command and CBR resetting. Potts and colleagues (20) described the resetting of the CBR curve during mild exercise as a parallel upward and rightward shift with increases in threshold and saturation pressures without a change in reflex gain or sensitivity. Work by Norton et al. (16) and Papelier et al. (19) indicate that this parallel resetting of carotid-cardiac and carotid-vasomotor function continues to increase in proportion to the intensity of exercise, even to maximal exercise intensities. However, the findings of the present investigation emphasized the specific role of increasing central command in affecting the resetting of the carotid-cardiac and vasomotor reflexes.

Several hypotheses have been proposed that implicate alterations of central command and afferent muscle reflexes in the modulation of CBR resetting (3, 22). Rowell and O’Leary (22) proposed that at the onset of exercise, by increasing the descending influence of central command on the baroreceptor centers in the brainstem, the OP of the baroreflex control of sympathetic neural activity was relocated laterally rightward. Such a resetting would alter the reflex to operate around the increased arterial pressure induced by the exercise. They further proposed in the model of sympathetic reflex control by the CBR that activation from muscle reflexes would increase sympathetic nerve activity and result in a vertical shift that would not alter the OP. When combined, these two mechanisms would result in the parallel upward and rightward resetting (16, 20). However, the proposed model did not consider the vagal regulatory control of the baroreflex, especially with respect to the carotid-cardiac baroreflex. Although the individual contributions from central command and muscle reflexes may not be discernable in the results described by Potts et al. (20), Norton et al. (17) recently found that the carotid-cardiac reflex was classically reset at the onset of exercise and was further reset over time during prolonged dynamic exercise up to 1 h at a constant work rate. Thus we suggest that muscle fatigue with prolonged exercise or an increase in exercise intensity requires the recruitment of additional motor units by central command and results in similar patterns of CBR resetting. However, Papelier et al. (19) and Iellamo et al. (8) raised the possibility that an activated metaboreflex may also be operative in increasing sympathetic nerve activity and, therefore, may interact with the resetting of the carotid-cardiac reflex at a time when vagal input to the reflex resetting is reduced.

In the present investigation, the OP of the carotid-cardiac baroreflex was linearly reset from rest to control exercise and further reset with increased central command during neural blockade exercise in static and rhythmic exercise paradigms. With each progressive resetting, the OP (defined as the prestimulus CSP or MAP) was shifted congruently with the location of the resetting of the CP (point of G_max or equal ability to buffer hypotensive or hypertensive stimuli) of the reflex. There was no mathematical difference between the OP and the CP between control and neural blockade exercise in static or rhythmic exercise trials (Table 4).

The importance of this observation was that if the position of a reset OP (prevailing MAP) remained in a constant relationship to the position of the reset CP, then the ability of the CBR to buffer a hypotensive or hypertensive alteration to CSP was not altered with the CBR resetting. This is in contrast to the findings of previous research with intact efferent (central command) and afferent (exercise pressor) integration (17–18, 21), which reported a progressive divergence of the OP away from the CP and toward the threshold with increased exercise intensity or muscular fatigue. This would indicate a reduced ability of the CBR to buffer a hypotensive insult. The data from the present experiment demonstrate the possibility that central command has only a minimal role in the relocation of the OP during CBR resetting.

The location of the prestimulus HR at the OP and CP of the carotid-cardiac baroreflex increased with static and rhythmic exercise-induced resetting, as would be expected. However, the difference between the location of the prevailing HR at the OP and the prevailing HR at the CP of the carotid-cardiac baroreflex was increased further with the application of partial neural blockade with static and rhythmic exercise at the same absolute workload as control exercise (Table 3). The observation of this divergent pattern of HR location at the OP and CP with increasing central command suggests that the resetting of the HR location on the carotid-cardiac baroreflex was determined by the intensity of the central command independent of the position of the OP, which was minimally affected by increased central command. This divergent relationship observed in a graph of the carotid-cardiac baroreflex (HR vs. MAP) would not be seen in the carotid-vasomotor reflex, because plotting MAP vs. MAP as all shifts in prestimulus CSP or MAP would be reflected on the dependent and independent variable axes. However, the difference between the relocation of the HR at the OP pressure in relation to the CP and the relocation of the MAP OP in relation to the CP suggests that the effects of the central command on the carotid-cardiac reflex are via the differential parasympathetic control of the HR rather than the sympathetic arm of the reflex.

Differences in central command effects on carotid-cardiac and carotid-vasomotor response curves. The progressive resetting of the carotid-cardiac baroreflex response curve during static and rhythmic exercise with neural blockade occurred with the same characteristic increase in threshold and saturation pressures and unaltered gain described by previous investigations (17, 21) utilizing progressive increases in exercise intensity. In the present investigation, this occurred with the attenuation of an afferent feedback influence. The resetting of the carotid-vasomotor
baroreflex curves displayed the same progressive increase in saturation and threshold from rest to control exercise. However, only the saturation of the carotid-vasomotor during static exercise resulted in further increases after partial neural blockade. These data confirm the previous suggestion that, in forearm exercise, central command was a primary driving influence for carotid-cardiac and carotid-vasomotor baroreflex resetting and that afferent information from muscle reflexes would play a minor or unnecessary role.

Whether the information from central command and muscle reflexes is integrated differently in the cardiovascular control areas of the brain stem for the control of HR and MAP responses has been studied previously. Multiple investigations (5, 14, 24) have indicated that, in leg exercise, afferent feedback information was important in determining the blood pressure response to exercise. By combining this information with the carotid-vasomotor reflex response curves presented here, we suggest that the central integration centers of the brain stem modulate CBR control of HR and MAP differently.

A criticism of using NP-NS to analyze a carotid cardiac and carotid vasomotor end organ response to changes in CSP is that the technique is limited to examination of the vagal limb of the autonomic nervous system with limited sympathetic influence. While it is accepted that vagal alteration is the primary mechanism for the fast cardiac response to carotid sinus stimulation, it has been suggested that the CBR-controlled alterations in MAP would be derived primarily from changes in cardiac output, with a minimal impact of true sympathetic alterations in vasomotor tone. Figure 5 indicates the typical beat-to-beat changes in HR and MAP with a rapid pulse CBR stimulus from 40 to −80 Torr. The beat-to-beat alteration in carotid sinus stimulation can be seen in Fig. 5C, while Fig. 5D is a time series analog sample of the pulsatile NP-NS stimulus. The peak tachycardic HR response (Fig. 5B) occurs by the third or fourth pressure pulse. Pulsatile changes in CSP result in rapid changes in HR response, with the peak bradycardic response occurring at approximately −60 to −80 Torr NP-NS stimuli. If the measured MAP or vasomotor...
response was simply a hemodynamic alteration from changes in cardiac output driven by the carotid-cardiac reflex response, then the peak increase and decrease in MAP would occur within one cardiac cycle of the peak HR response as a result of the beat-to-beat change in cardiac output. However, it can be observed in Fig. 5a that the peak changes in MAP occur not within one, but in three to four, cardiac cycles after the peak HR response (dotted lines) and, actually, at HR values that approximate prestimulus values. Therefore, although vasomotor end organ response was not measured directly, these data support the idea that there were actual peripheral vascular resistance changes that contribute to alteration in MAP from CBR stimulation and were independent of the carotid-cardiac responses.

The hypothetical model presented by Rowell and O’Leary (22) predicted a rightward lateral shift in the stimulus-response curve with an increase in central command and minimal vertical resetting due to the limited muscle reflex feedback. In contrast to this model, the present data suggest that central command predominantly controls the degree of vertical resetting with a minimal rightward shift of the curve.

In summary, the results of this investigation support the concepts that 1) central command was a primary mechanism in the active resetting of the CBR during handgrip exercise; 2) the carotid-cardiac and carotid-vasomotor reflexes were reset upward and rightward, with a selective increase in central command during static and rhythmic static exercise; 3) the reset carotid-cardiac baroreflex with neural blockade was similar to the resetting that occurs with increased; exercise intensity, in that there was no change in gain, and yet the threshold and saturation were increased; and 4) unlike the model of classic CBR resetting, where the OP is relocated toward the threshold pressure and away from the CP during exercise, selective activation of increased central command significantly altered the prestimulus HR with minimal effects on the resetting of the OP pressure away from the CP.

The authors thank Rita Welch-O’Connor, Paul Fadel, and Michael Williams for laboratory support and Lisa Marquez for secretarial support. The authors also thank the subjects for their interest and cooperation.

This study was supported in part by Danish National Research Foundation Grant 504-14 (Copenhagen, Denmark).

This research was submitted in fulfillment of the requirements for the degree of Doctor of Philosophy for R. G. Querry, as submitted to the University of North Texas Health Science Center.

REFERENCES