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[Minireview]

Initial change in ventilation at the start of exercise in man

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Introduction

Although it is well known that pulmonary ventilation increases after exercise, the ventilatory response to submaximal exercise is divided into the three phases[18,58,62]; the first phase (Phae I), at the onset of exercise, usually occurs with the first breath[11,14,25,43,54]. Then there is a brief plateau and ventilation increases slowly with a time constant of 60—70 sec (Phase II) and reaches a new steady state level (Phase III) in 3—4 min during submaximal exercise in which lactic acid does not increase more than at the resting level. On the other hand, a hasty decrement in ventilation can be observed immediately at the end of exercise, followed by another brief plateau and then a decrease that is more or less exponential in form, until a new resting steady-state level is reached near the initial resting ventilation as shown in Fig. 1.

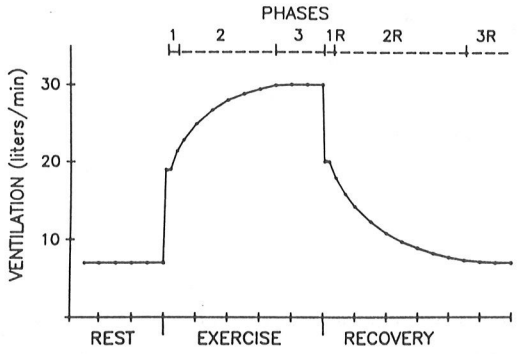

Fig. 1 An idealized representation of ventilatory response during moderate exercise. (Eldridge and Waldrop (1991)[18])

The transition from rest to light or moderate intensity exercise is typically accompanied by an abrupt increase in ventilation at the first exercise breath. In general, the initial rapid increase in ventilation appearing at the onset of exercise has been referred to as phase I[59]. This phase I is observed during not only voluntary and passive movement, but also during electrically induced muscle contraction. It has been reported that phase I hyperpnea is observed when the subject performs exercise from rest to 100 watts, but not from 0 watt to 100 watts[63], and that phase I hyperpnea was markedly attenuated by prior moderate hyperventilation[55]. However, Jensen et al.[25] reported that when care is taken to eliminate outside factors, a rapid ventilatory response on the start of exercise is seen which is not due to conditioning, and that the magnitude of rapid response may increase in the process of learning.

The present paper gives a brief review of phase I during submaximal exercise in man based mainly on the data obtained in our laboratory.

1. Effect of acute hypoxia on ventilatory response at the onset of submaximal exercise

The mechanisms of exercise hyperpnea, particularly of its early stage (2—3 initial breaths or phase I), have been and still are a matter for

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debate. Nerve endings located in the carotid bodies are known to be stimulated by an increase in CO_2 pressure ($PaCO_2$) and hydrogen ions (H^+) and by a decrease in O_2 pressure (PaO_2) in the arterial blood. It is possible to assume that activation of the carotid body by changes in blood gases or pH might explain the increased ventilation observed during exercise. However, an unresolved problem is whether the amplitude of the initial ventilatory response at the onset of exercise may be affected by chemical stimuli, such as hypoxia, hypo-or hypercapnia. According to Dejours et al.[13], the early hyperventilatory response to exercise is not affected by changes of inspired CO_2 pressure ($PICO_2$) and O_2 pressure (PIO_2). These results were considered as evidence that phase I is neurogenic and that there are no interactions between neurogenic and chemical stimuli, and represent one of the standpoints of the well-known neuro-humoral theory of ventilatory control of exercise. Similar data were obtained later by Cunningham et al.[10] whose conclusion was that chemical inputs do not interact immediately with neural stimuli, either centrally or peripherally. By contrast, Asmussen[3] found that in the presence of existing chemical stimuli (both hypoxia and hypercapnia, or a combination of the two), the first neurogenic ventilatory component at the onset of exercise increased. More recently, Springer et al.[49] reported that in both adults and children, breathing hypoxic mixtures (FIO_2=0.15) reduces phase I ventilatory response at exercise. In addition, Nakazono and Miyamoto[41] noted that hypoxia induces an overshoot of $\dot{V}_E$ 20–30 seconds after exercise. Fig. 2 shows typical examples of breath-by-breath inspiratory ventilatory response at the onset of exercise when the subject performed 50 watt rectangular loads on a cycle ergometer in normoxic (FIO_2=0.21) and hypoxic (FIO_2=0.11)

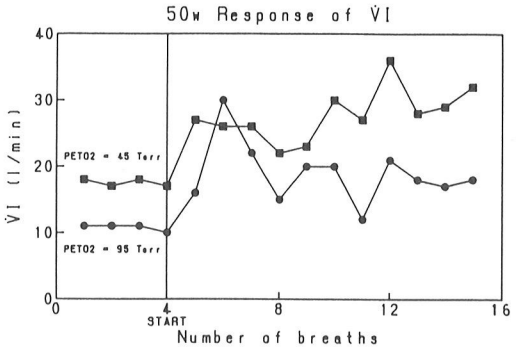

Fig. 2 An example of inspiratory response in transition from rest to exercise in normoxic and hypoxic conditions. (Miyamura et al. (1990)[37])

conditions. Inspiratory minute ventilation ($\dot{V}_I$) increased immediately in response to the exercise stimulus. Similar results were obtained in expiratory minute ventilation ($\dot{V}_E$), with a pattern similar for both experimental conditions. After a sudden initial increase (2–3 breaths, 1st phase), both $\dot{V}_I$ and $\dot{V}_E$ kept increasing at a somewhat slower rate over about 20–30 sec (2nd phase). The latter change was more pronounced in hypoxia. From Fig. 3, it appears that the average resting $\dot{V}_I$ was significantly higher in hypoxia than in normoxia. However, no statistical differences in exercise $\dot{V}_I$ and delta $\dot{V}_I$, which are calculated as the differences between the mean of the first and second breath after the onset of exercise and the mean of 4 breaths preceding exercise, were found between hypoxia and normoxia.

Our findings are in agreement with those of Dejours et al.[13], Cunningham et al.[10] and Nakazono and Miyamoto[41], but not with those of Asmussen[3], Griffiths et al.[21] and Springer et al.[49]. The reasons for these discrepancies might be related to various factors such as the subject's age, inspired oxygen concentration, work load etc. Concerning the last factor, it has been observed

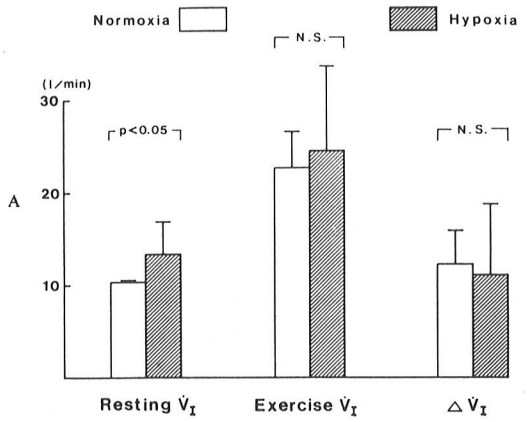

Fig. 3 Comparison of average inspiratory volume between normoxia and hypoxia. (Miyamura et al. (1990)[37])

that ventilatory response at the onset of exercise increases with increasing work load[9] or movement frequency.[12] Thus, it is possible to hypothesize that the effects of acute hypoxia on pulmonary ventilation at the onset of submaximal exercise at the different work load may differ even if the exercise was performed below the anaerobic threshold (AT).

Fig. 4 shows the comparison of resting $\dot{V}_I$, exercise $\dot{V}_I$ and delta $\dot{V}_I$ between 30 and 120 watts both in normoxia (N) and hypoxia (H) conditions. As shown in Fig. 4, there were no significant differences in the resting $\dot{V}_I$ between 30 watt and 120 watts during N and H, while exercise $\dot{V}_I$ and delta $\dot{V}_I$ were significantly ($p < 0.05$) higher in 120 watts than in 30 watts. On the other hand,

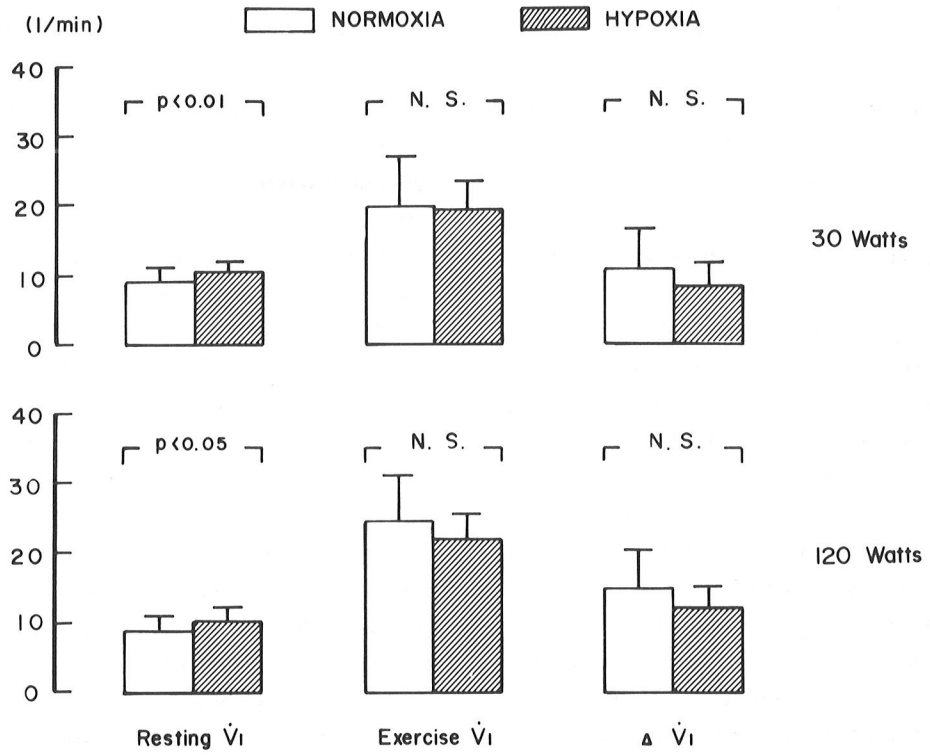

Fig. 4 Comparison of resting $\dot{V}_I$, exercising $\dot{V}_I$ and delta $\dot{V}_I$ between normoxic and hypoxic conditions. (Miyamura et al. (1992)[39])

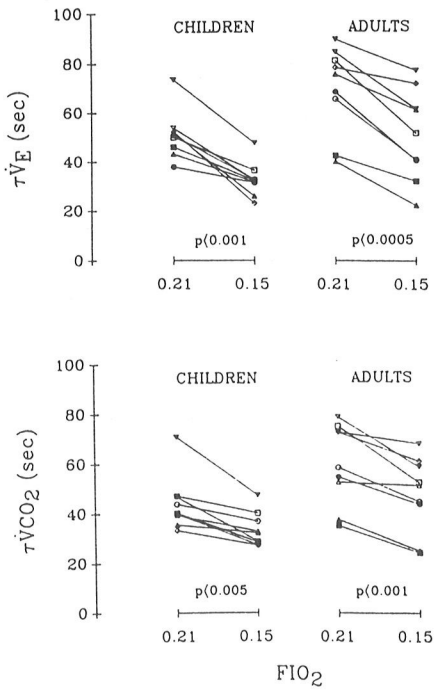

Fig. 5 Effect of hypoxia on $\dot{V}_E$ and $\dot{V}CO_2$ responses to exercise in children and adults. (Springer et al. (1989)[49])

resting $\dot{V}_I$ was significantly ($p<0.05$) higher in the H than in the N both in 30 and 120 watts as shown in Fig. 5. The average values of resting ratio of tidal volume to inspiratory time (V_T/T_I) are similar to those of resting $\dot{V}_I$. In contrast with resting $\dot{V}_I$ and V_T/T_I, the average values of resting end-tidal CO_2 pressure ($PETCO_2$) were significantly lower in H (36.2 ± 2.2 torr) as compared with N (38.9 ± 3.0 torr). However, no statistical differences in the exercise $\dot{V}_I$ and delta $\dot{V}_I$ were found between H and N both in 30 and 120 watts. Blood lactate levels did not increase during 30 and 120 watts exercise in both N and H conditions as compared with rest. Moreover, no significant difference was found in the blood lactate between N and H conditions.

Asmussen[3] has reported that in the presence of existing chemical stimuli-e.g. in hypercapnia, hypoxia, or a combination of the two, the fast neurogenic component is very pronounced. Springer et al.[49] determined the time constant of the pulmonary ventilation during submaximal bicycle exercise at a constant pedaling frequency of 60 rpm under hypoxic (FIO_2=0.15) and normoxic (FIO_2=0.21) conditions. They found that phase I response of ventilation to exercise decreased significantly during hypoxia in both the children and adults as compared with the case for normoxia (Fig. 5). In contrast to the above authors, Cunningham et al.[10] have described that the increase in ventilation during the first inspiratory - expiratory cycle in exercise is independent of the prevailing levels of hypercapnia, hypoxia and hyperoxia at lower levels of ventilation and work. Wasserman et al.[57] also reported that the phase I response of exercise hyperpnea was not altered in carotid body resection subjects. As shown in Fig. 3 and 4, no statistically significant differences in the initial ventilatory responses to exercise at 30, 50 and 120 watts rectangular loads on cycle ergometer were found between eucapnic normoxia and hypocapnic hypoxia.

The reasons for these discrepancies cannot be explained on the physiological grounds. However, whether or not ventilatory response at the onset of exercise is affected by hypoxia seems to be closely related to the definition or time of the so-called phase I. Therefore, the early phase ventilatory response might be defined as the response during the initial period in which mixed venous blood is still maintained with resting $PETCO_2$ and end-tidal O_2 pressure ($PETO_2$) for 10—15 sec[62], 15 sec[59], 15—20 sec[32,49] and 20 sec.[9] Since cardiac output is considered to increase immediately after exercise[2,9,48] and since some subjects have low respiratory frequency

(10−12 breaths/min), it is possible to assume that the phase I could be defined as a rapid change in ventilation occurring within about 10 seconds (2 or 3 breaths) immediately after exercise, in which chemical substance has not reached the peripheral chemoreceptors. According to the above assumption, we have evaluated the ventilatory response at the onset of exercise (delta $\dot{V}_I$). As shown in Fig. 3 and 4, delta $\dot{V}_I$ was not affected by hypocapnic hypoxia at the work loads of 30, 50 and 120 watts. In addition, blood lactate levels were not increased by exercise in both N and H conditions. These findings suggest that the neurogenic ventilatory drive at the onset of submximal exercise at a work load below the subject's anaerobic threshold is independent from inspired O_2 pressure (PIO_2).

2. Ventilatory response to active and passive exercise

Zuntz and Geppert[64] described that the hyperpnea could not be accounted for by arterial gas levels in the neural center and postulated the following: the brain above the primary respiratory control regions in the medulla and pons produces a command signal capable of driving not only locomotion but also respiration. Krogh and Lindhard[30] have observed a rapid increment both of tidal volume and frequency of respiration immediately after bicycle exercise. Since the increase of breathing after the onset of exercise was too rapid to be explained by a humoral factor such as CO_2 and lactate yield in the working muscle, they proposed that the rapid increase in ventilation at the onset of exercise may be due to the irradiation of impulses from the motor cortex to the respiratory center. However, the pathways and mechanisms mediating the early rapid ventilatory response have not been confirmed.

Casaburi et al.[5] have recently observed a rapid fall in O_2 saturation in the mixed venous blood (SVO_2) and a rise in CO_2 pressure in the mixed venous blood ($PVCO_2$), well in advance of the arrival of blood produced by exercising legs at the onset of exercise. However, Cerretelli et al.[6] concluded that the ventilatory control at the onset of exercise appears to be independent of changes of CO_2 pressure and/or flow in the lungs because no statistical significant difference in delta $\dot{V}_I$ was found between sedentary controls and heart transplant recipients. Although they described that these changes must be considered when interpreting ventilation and gas exchange immediately after exercise, the pathways and mechanisms important in mediating the early ventilatory response have not been clarified. Miyamoto et al.[35] have reported that close synchronization between the ventilation and cardiac output responses at an initial period of transitions from rest to exercise and from exercise to rest seems to support the concept of cardiodynamic hyperpnea proposed first by Wasserman's groups[26,56,60,61]. However, Miyamoto et al.[36] also concluded that the cardiodynamic process could be ruled out as the origin of the initial ventilatory response, and instead, other neurogenic mechanisms mediated either centrally or peripherally, should be considered since a sudden increase in ventilation was observed immediately after the onset of the volitional and passive pedaling whereas cardiac output increased only gradually (Fig. 6). Miyamoto's conclusions concerning the cardiodynamic theory have been supported by several authors.[2,8,20,22,24,44]

On the other hand, Comroe and Schmidt[7] found that exercise hyperpnea by the stimulation of the ventral spinal root was abolished after denervation or chordotomy in animals. These findings were confirmed using the cross circulation by

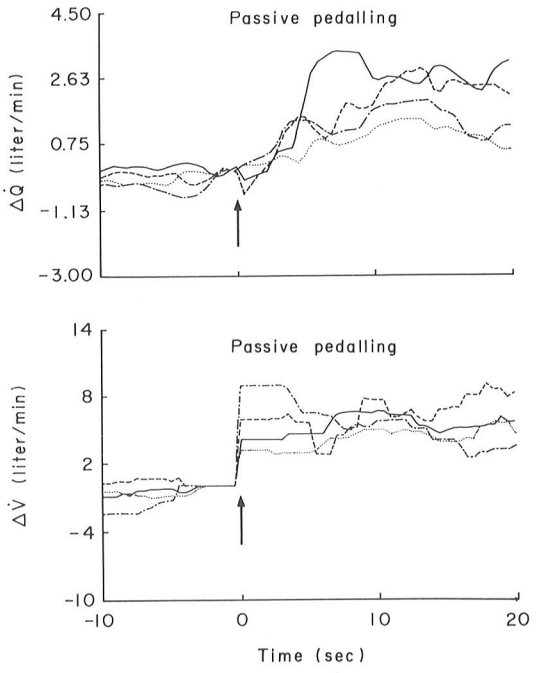

Fig. 6 A comparison between the initial dynamics of cardiac output ($\dot{Q}$) and inspiratory ventilation ($\dot{V}_I$) in response to passive pedaling. Arrows at 0 sec indicate the instants when the stimuli were given, and the ordinate is expressed in relative values from this point. (Miyamoto et al. (1988)[36])

Kao[28]. The experiments of Senapati[47], Kalia et al.[27], McCloskey and Mitchell[43], and Tibes[52] all support the contention that stimulation of afferents running in group III and IV, which terminate in the polymodal receptors in the muscles,[29,31] can appreciably stimulate ventilation. The specific stimuli that activate metabolically sensitive receptors have not been determined with certainty. Potassium appears to be potent at the onset of contraction[45,46]; other possibilities include prostaglandins, bradykinin, lactate, and ATP.[34,50,51,53] More recently, large myelinated (group I and II) fibers have also been implicated.[42] Since Adams et al.[1] and Brice et al.[4] suggested that central mechanisms are not necessary for the ventilatory response to exercise in humans, it is possible to assume that the phase I is induced largely by afferents from the exercising muscle and this reflex hyperpnea may increase addititively when the amount of muscle exercised is increased.

Fig. 7 shows the comparison of average delta $\dot{V}_I$ between one leg and both legs or passive and active exercise. The delta $\dot{V}_I$ increased significantly ($p<0.05$–0.01) in the four exerciser test. i.e., the average values and standard deviations of delta $\dot{V}_I$ were 4.22 ± 1.63 ℓ/min for the active exercise with one leg and 4.46 ± 1.80 ℓ/min for the active exercise with two legs. Average values of delta $\dot{V}_I$ in active exercise were significantly ($p<0.01$) higher in the two-leg exercise than in those for one leg. The average values and standard deviations of delta $\dot{V}_I$ were 2.46 ± 1.12 ℓ/min for passive exercise with one leg and 3.44 ± 1.55 ℓ/min for the passive exercise with two legs. Average values of delta $\dot{V}_I$ in passive exercise were significantly ($p<0.05$) higher in two legs than in one leg. Dejours et al.[12] have determined the ventilatory response to different types of repetitive movement consisting of

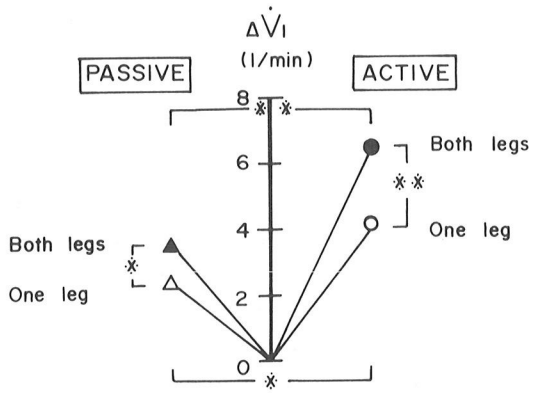

Fig. 7 Comparison of average delta $\dot{V}_I$ between one leg and both legs or passive and active exercise. * indicates significant difference (*$p<0.05$, **$p<0.01$). (Miyamura et al. (1992)[38])

flexion-extension of the lower legs from a vertical to horizontal position in the supine position either passively or voluntarily at different frequencies. They found that delta expiratory volume (delta $\dot{V}_E$) increased almost linearly with increasing movement frequency when both lower legs of the subjects were moved alternatively with passively or voluntarily. In our study, however, delta inspiratory volume (delta $\dot{V}_I$) obtained at the onset of simultaneous exercise with both legs was not double as compared with one leg in both passive and active exercise (Fig. 7). These results indicate that ventilatory response in phase I may increase with increasing exercise frequency, but not according to the amount of exercised muscle.

At present, it is very difficult to explain why phase I does not increase additively when the amount of muscle exercised is increased. As described previously, Adams et al.[1] suggested that central mechanisms are not necessary for the ventilatory response to exercise in man. However, Eldridge et al.[16, 17] and DiMarco et al.[15] have observed ventilatory response to electrical stimulation of the subthalamic locomotor region or mesencephalic locomotor region. They suggest that command signals emanating from the hypothalamus provide the primary drive for changes of respiration and circulation during exercise. Furthermore, Morikawa et al.[49] compared the ventilatory and circulatory responses during voluntary and passive exercise in healthy subjects and patients with traumatic spinal cord transection. They observed a significant increase in ventilation when the patients made a great effort to perform exercise voluntary, but not passively. These results suggest that the cerebrum higher center exists within the ventilatory response during exercise.

On the other hand, Fink et al.[19] have reported that subjects with bilateral subcortical cerebral

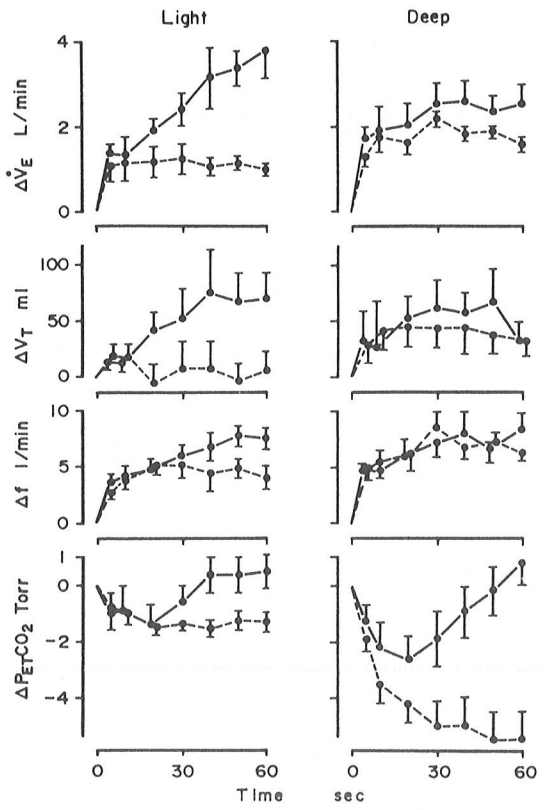

Fig. 8 Time course of mean transitional changes in minute ventilation ($\dot{V}_E$), tidal volume (V_T), breathing frequency (f), and end-tidal CO_2 tension ($PETCO_2$) at onset of electrically induced muscle contraction (solid line) and passive movement (dotted line) in 7 lightly (left) and deeply (right) anaesthetized dogs without rhizotomy. (Hida et al. (1986)[23])

dysfunction commonly had increased responsiveness both to carbon dioxide and to hypoxia. Hida et al.[23] compared minute ventilation, tidal volume, breathing frequency, and end-tidal CO_2 tension at the onset of passive movement in lightly and deeply anesthetized dogs without rhizotomy (Fig. 8). They observed that ventilatory response during passive movement was higher in a deep anesthesia than that in a light one, while delta $\dot{V}_E$ obtained during passive exercise is

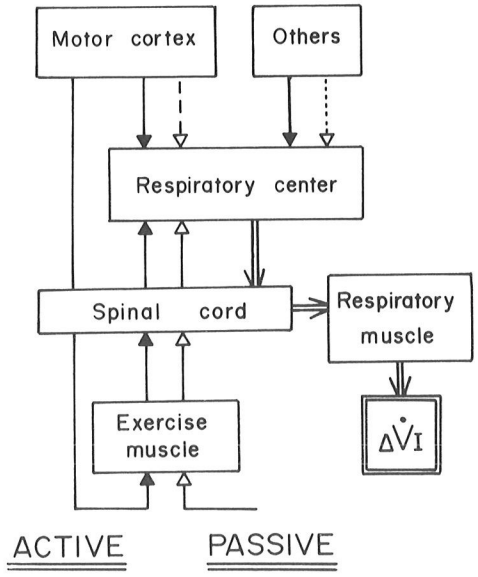

Fig. 9 Schematic diagram of neural mechanisms in the phase I during passive and active movement. See discussion in text.

almost the same as that during rhizotomy. We found recently, furthermore, that in the 4 out of 5 healthy subjects average delta $\dot{V}_I$ estimated at the onset of passive exercise during sleep was more than double that while awake, but it was not statistically significant.[24] These results suggest that there is some disinhibition during anesthesia or sleep, and that the impulses from the cerebral cortex to the so-called central nervous system such as the brain stem reticular formation which will influence the respiratory center, could be divided into 2 types: facilitation and inhibition. It is possible to assume, therefore, that in an awake condition higher delta $\dot{V}_I$ during active exercise than that during passive exercise may be due to the stimulation of facilitation from the peripheral and central nervous system even if the central inhibition may have augmented more or less as shown in Fig. 9. In other words, non-additive ventilatory response to the passive and active exercise during wakefulness may be the result of integration of facilitation from the afferent impulse and inhibition and facilitation from the central nervous system. However, this possibility needs further investigation.

In summary, the transition from rest to exercise is typically accompanied by an abrupt increase in ventilation at the first exercise breath. The initial rapid increase in ventilation appearing at the onset of exercise has been referred to as phase I. This phase I is observed during not only voluntary and passive movement, but also during electrically-induced muscle contraction in human subjects. Although a rapid increase in ventilation could be mediated by changes in blood gas and/or so-called central command, the precise mechanisms of phase I are still unknown at this time. At present, however, phase I is considered mainly due to the stimulation of afferent impulses in group III and IV, which terminate in polymodal receptors in the muscle, since the increase of ventilation at the onset of exercise is too rapid to be explained by a humoral factor such as CO_2 and lactate yield in the working muscle.

Finally, it might be of interest to consider the physiological meaning of phase I., i.e., why the ventilation should increase so rapidly at the onset of exercise. It is likely that a rapid increase in ventilation will at least be useful to a decrement of oxygen deficit or increase of oxygen transport or energy production through the increase of aleveolar ventialtion, alveolar O_2 tension and pulmonary diffusing capacity even if it is of a small quantity. In other words, phase I may probably play an important role as a trigger for starting exercise or in survival.

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