[Review]

Ventilatory control at the onset of physical exercise in man

ヒトにおける運動開始時の換気調節

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Key words : ventilation, central command, afferent impulse, semicircular canals
キーワード：換気量、中枢性要因、求心性衝撃、半規管

Abstract

It is well known that pulmonary ventilation increase abruptly immediately after submaximal exercise for 10～20 sec (phase I). Then there are a brief plateau and ventilation increases slowly with time constant 60 ～ 70 sec (phase II) and reaches a new steady state (phase III) within 3～4 min. These changes in pulmonary ventilation during physical exercise in man are termed Phase I, Phase II and Phase III, as first defined by Whipp (1977). It has hitherto been reported that physiological background (mechanisms) of phase I response cannot be explained by humoral agents because of delay in transport. At present, the neurogenic factors of phase I are classified largely as central and peripheral stimuli, or as both.

要約

運動を開始と同時に換気量は10～20秒間かけて急増、一旦プラトーに達し、その後2～3分の間指数関数的に増加し、4～5分で定常状態に至り、運動を中止すると換気量は急減し、その後徐々に減少して安静レベルに戻るというそれぞれ3相の変化をすることはよく知られた事実である。Whipp（1977）は、これらをPhase I、Phase II、Phase IIIと名づけた。運動開始1呼吸目から観察される換気量のステップ状の急増（Phase I）の生理学的背景（メカニズム）は、化学的要因ではなく主として神経的要因であろうと考えられている。現在、Phase Iの神経的要因として中枢性ドライブ、末梢性ドライブおよびその両ドライブが挙げられている。

INTRODUCTION

Although it is well known that pulmonary ventilation increase abruptly immediately after exercise, the ventilatory response to submaximal exercise is divided into the three phases (Wasserman et al. 1977; Whipp 1981; Eldridge and Waldrop 1991) ; the first phase (Phase I), at the onset of exercise, usually occurs with the first breath (Dejours, 1964; D'angelo and Torrelli, 1971; Jensen et al. 1971; Ward 1979; Eldridge and Waldrop 1991). Then there is a brief plateau and ventilation increases slowly with time constant of 60 - 70 sec (Phase II) and reaches a new steady state (Phase III) within 3 - 4 min. On the other hand, a hasty decrement in ventilation can be observed immediately after exercise, followed by another brief plateau and then a decrease that is more or less exponential in form, until a new steady state level is reached near the initial resting ventilation as shown in Figure 1.

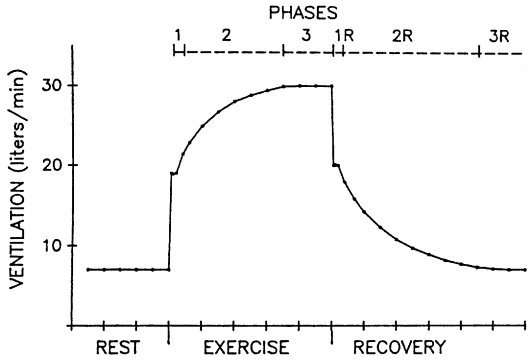

Figure 1 Idealized representation of ventilatory response during moderate exercise. There is a fast response at onset (phase 1), followed by a brief plateau, the a slow component rising over several minutes (phase 2) to the steady state (phase 3). Following offset of exercise, a rapid decrease (phase 1R) is followed by another brief plateau and then by a slowly declining ventilation (phase 2R) to the new steady state (phase 3R). (Eldridge and Waldrop, 1991)

The transition from rest to light or moderate intensity exercise is typically accompanied by an abrupt step-like increment in ventilation at the first exercise breath. In general, the initial rapid increase in pulmonary ventilation appearing at the onset of exercise is termed Phase I, as first defined by Whipp (1977). This phase I is observed during not only voluntary exercise and passive movement, but also during electrically induced muscle contraction. However, the responses at the onset of exercise are variable in magnitude, i.e., several authors performed a bicycle work from a background of light and mild exercises (Casaburi et al. 1978; Whipp et al. 1982; Browman and Wigertz 1971)

or from rest in supine (Karlsson et al. 1975; Weiler-Ravell et al. 1982) leads to a more gradual rise in ventilation. In addition, an abrupt changes in ventilation is observed in most but not all subjects (Craigg et al. 1963). It has hitherto been considered that phase I is influenced mainly by heredity and environment. Furthermore, the ventilatory responses at the onset of exercise seems to be variable in magnitude. That is, the phase I is influenced by various factors, such as posture (Karlson et al. 1975; Weiler-Ravell et al. 1982; Miyamura et al. 2001), exercise frequency (Casey et al. 1987; Kelsey and Duffin 1992), exercise limb (Ishida et al. 1994), age (Sato et al. 2000; Ishida et al. 2000) and physical training (Miyamura et al. 1997; Sato et al. 2004) as shown in Fig. 2.

Nevertheless many investigators have pursued the mechanisms of this phase I response, and their opinions as to its nature are still a matter of dispute. Since the changes in ventilation are so rapid during the transition from rest to exercise, phase I response cannot be explained by humoral agents because of delay in transport. In other

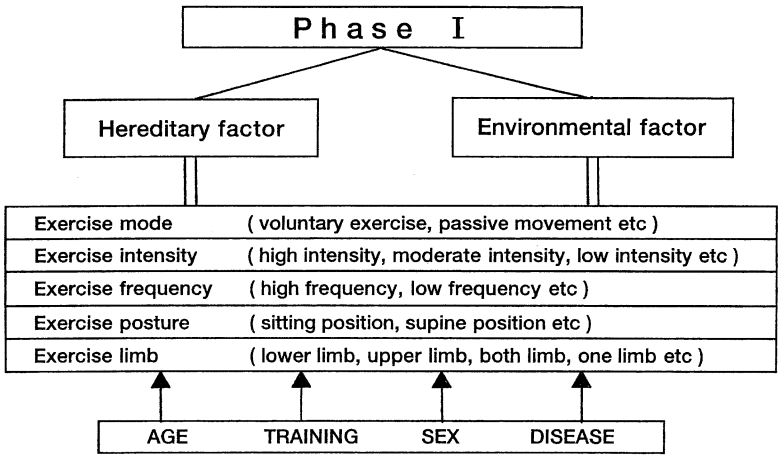

Figure 2 Various factors influence on ventilatory response at the onset of muscular exercise.

words, it could be variable to clarify the neural control of exercise hyperpnea by inquiring into the mechanism of phase I, even if it is a small quantity. At present, the causal factors of phase I are classified largely into three, i.e., central (descending) and peripheral (ascending) neurogenic stimuli, or both . This short review will focus on the respiratory control at the onset of exercise in healthy men based mainly on the data obtained in our experiments.

Ⅰ. CENTRAL COMMAND

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 debate. In 1888, Zuntz and Geppert described that the hyperpnea could 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 (1913) have observed rapid increment in both tidal volume and respiratory frequency immediately after bicycle exercise. They also observed dyspnea or low ventilatory response if the alveolar carbon dioxide tensions was reduced by voluntary hyperventilation before exercise. Since the increase of humoral factors such as CO_2 and lactic acid yield in the working muscle, they proposed that the rapid increase in ventilation may be due to the irradiation of impulses from the motor cortex to respiratory center. In addition, Morikawa et al. (1989) have investigated the circulatory and respiratory drives in the early phase of voluntary and passive exercise in healthy subjects and patients with traumatic spinal

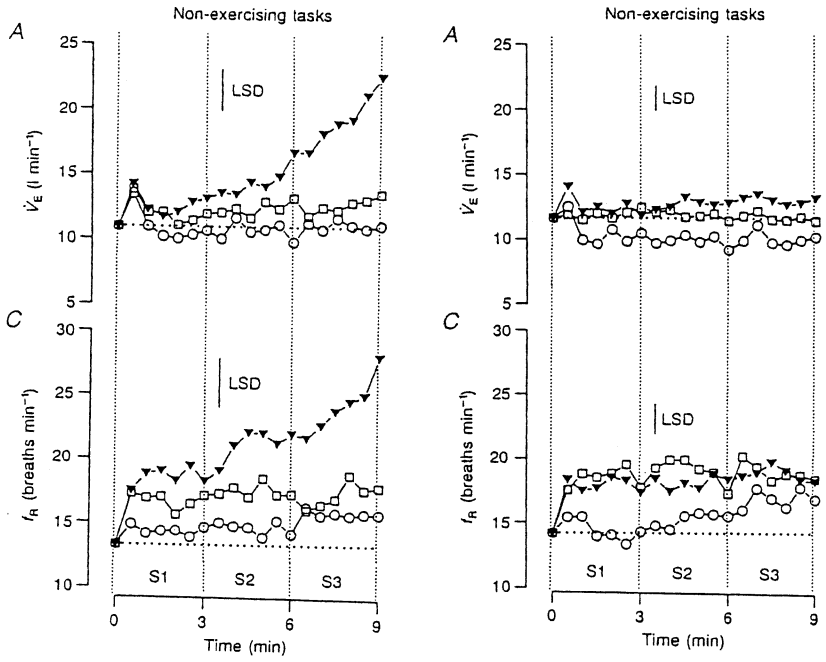

Figure 3 Mean changes of minute ventilation ($\dot{V}_E$) and respiratory frequency (fR) during imagined physical exercise (▼), visualizing letter (□) and the task with sounds of the treadmill only (○) in the athlete group (left panel) and non-athlete group (right panel), respectively. (Wuyam et al. 1995)

cord transection. They found that, in the healthy subjects, pulmonary ventilation ($\dot{V}E$) increased by 30% in passive movement, whereas $\dot{V}E$ in the patients did not change significantly. However, it was interesting to note that $\dot{V}E$ increased significantly when the patients make a great effort to perform the exercise consciously. More recently, imaged exercise produced an increase in ventilation especially in the athlete; pulmonary ventilation increases about 20% in the athlete group as compared with resting level, but not in the untrained group (Fig. 3). Thornton et al. (1999) also observed that resting ventilation increased twice when the athlete imaged the exercise. These results suggest that ventilatory response to the onset of exercise is to some extent related to the higher center activity.

On the other hand, Eldridge et al. (1981) and Di Marco et al. (1983) studied the relationships between respiration and exercise (locomotion) in anesthetized cats with

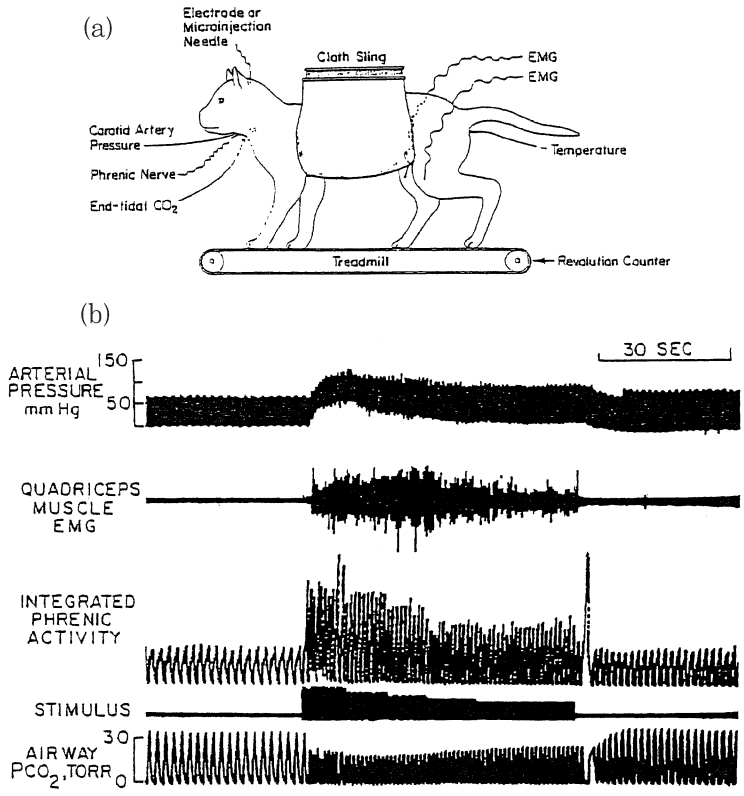

Figure 4 (a) Decorticate animal presentation used in experiments in which respiratory responses were studied during spontaneous locomotion and locomotion induced by stimulation in the diencephalon. The cat's head was held in a strereotaxic apparatus. Respiratory activity was determined from phrenic nerve recordings. (b) Example of locomotion induced by electrical stimulation of subthalamic locomotor region. (Eldridge et al. 1981)

intact brains and unanesthetized decorticated (hypothalamic) or decerebrated (mesencephalic) cats. They showed that hypothalamic stimulation elicited both locomotion and increased respiration; the magnitude of the integrated respiratory output is linearly related to the magnitude of the induced locomotor activity (Fig. 4). From these results, they suggested that command signals emanating from the hypothalamus provide the primary drive for changes of respiration during exercise. They also observed, however, that within the first one or two walking steps of spontaneous locomotor activity, the rate of rise of phrenic activity increased slightly while peak phrenic activity remained relatively constant; peak internal intercostal activity increased markedly while peak external activity and end-tidal carbon dioxide partial pressure ($PETCO_2$) decreased which were not observed in normal walking. In addition, a few investigators (Asmussen et al. 1943; Adams et al. 1984a; Adams et al. 1984b; Brice et al. 1988) claimed that exercise hyperpnea can occur in the absence of activation of the sub-hypothalamic locomotor center.

II. PERIPHERAL REFLEX

1) STIMULUS FROM THE CAROTID BODY

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 the 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, hypocapnia or hypercapnia. According to Dejours et al. (1960) 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 a evidence that phase I is neurogenic and that there are no interactions between neurogenic and chemical stimuli. And this consideration was developed into the rational basis for the well-known neuro-humoral theory of ventilatory control of exercise. Similar data were obtained later by Cunningham et al. (1966) whose conclusion was that chemical inputs do not interact immediately with neural stimuli, either centrally or peripherally. By contrast, Asmussen (1973) found that in the presence of chemical stimuli (both hypoxia

and hypercapnia), the 1st phase neurogenic ventilatory component at the onset of exercise was increased. In addition, Springer et al. (1989) reported that in both adults and children, breathing hypoxic mixtures (FIO_2=0.15) reduces phase I ventilatory response at exercise, while Nakazono and Miyamoto (1987) noted that hypoxia induces an overshoot of $\dot{V}E$ for 20-30 seconds after exercise onset.

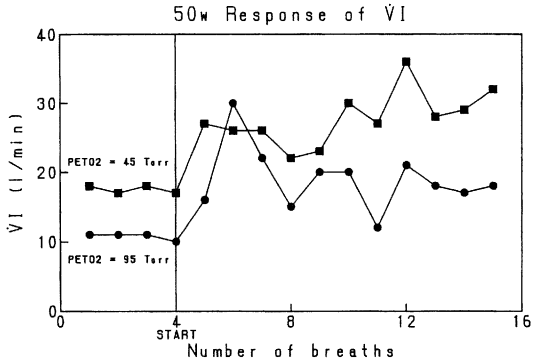

Figure 5 An example of inspiratory response in transition from rest to bicycle exercise with work rate of 50W in normoxic and hypoxic conditions. (Miyamura et al. 1990)

Figure 5 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 bicycle ergometer in normoxic ($FIO_2 = 0.21\%$) and hypoxic ($FIO_2 = 0.11$) conditions. Inspiratory minute volume ($\dot{V}I$) 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. From Fig. 6, 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. These results confirmed at different work loads, i.e., no statistical differences in the exercise $\dot{V}I$ and delta $\dot{V}I$ were found between hypoxia and normoxia both in 30 and 120 watts (Fig. 6). In addition, blood lactate levels were not increased by exercise in both normoxia and hypoxia conditions (Miyamura et al. 1992b).

Griffiths et al. (1986) observed that time constant of $\dot{V}E$ is shorter with a background of hypoxia. Springer et al. (1989) determined the time constant of pulmonary ventilation during submaximal bicycle exercise with constant pedaling frequency of 60rpm under hypoxic ($FIO_2 = 0.15$) and normoxic ($FIO_2 = 0.21$) conditions. They found that phase I

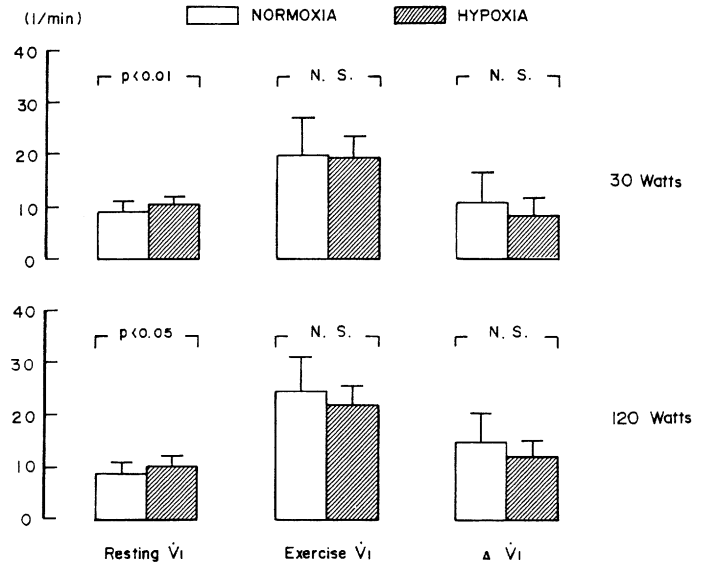

Figure 6 Comparison of resting $\dot{V}_I$, exercising $\dot{V}_I$ and delta $\dot{V}_I$ between normoxia and hypoxic conditions. (Miyamura et al. 1992b)

response decreased significantly during hypoxia in both children and adults as compared with the case for normoxia. The possible reasons for their specific findings remained obscure. However, whether or not phase I response is affected by hypoxia seems to be a matter of definition or length of duration of the phase I defined by the individual author. Therefore, Griffiths et al. and Springer et al. examined the effect of hypoxia on the phase I in terms of time constant estimated by fitting the data to the exponential model or $\dot{V}_E$ at 20 s expressed as percent change from resting to steady state level. Afterwards, phase I response is considered to last variously for 10 - 15 s (Whipp, 1981), 15 s (Wasserman et al. 1986; Grucza et al. 1990; Grassi et al. 1993), 15 - 20 s (Springer et al. 1989; Masuda et al. 1988), and 20 s (Linnarsson 1974; Cummin et al. 1986) among different investigators and still defined as the period where carbon dioxide and oxygen pressures in the mixed venous blood are maintained at the resting level. Since some subjects have low respiratory frequency (10 - 12 breaths/min), we have chosen the phase I response to be defined as the rapid change in ventilation occurring within 10 - 15 s (for 2 or 3 breaths), in which chemical substances may have not reached the peripheral chemoreceptors. According to this definition, we have evaluated the ventilatory response at the onset of exercise ($\triangle\dot{V}_I$). As described previously, $\triangle\dot{V}_I$ was not affected by hypocapnic hypoxia at the work rates of 30, 50 and 120 watts. These findings suggest that the neurogenic ventilatory drive at the onset of submaximal exercise at a work

load below the subject's anaerobic threshold may be independent of inspired O_2 pressure (PIO_2).

2) CARDIODYNAMIC THEORY

In 1974, Wasserman and colleagues (Jones et al. 1982; Weissman et al. 1982; Ward et al. 1983; Stremel and Rayne 1983) have proposed the so-called cardiodynamic theory because ventilation increased pari passu with an increase in cardiac output immediately after exercise. Cummin et al. (1986) described that the hypothesis of cardiodynamic hyperpnea considers a possible effect of increasing cardiac output ($\dot{Q}$) on ventilation ($\dot{V}_E$), since a tendency for $\dot{V}_E$ and $\dot{Q}$ responses was biphasic with an initial rise followed by a slight fall at the 14 s mark, and a subsequent rise, at all work loads of bicycle ergometer. However, Miyamoto et al. (1982) found that the magnititude of the initial response is much greater in $\dot{V}_E$ than $\dot{Q}$, i.e., up to the first 5 s, $\dot{V}_E$ increased 56% of its resting value, while $\dot{Q}$ increased by only 14%. (Fig. 7). They concluded that the

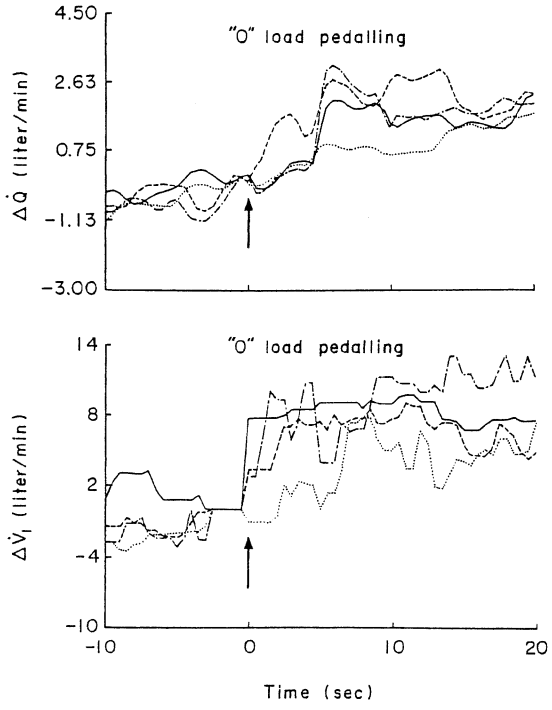

Figure 7 A comparison between the initial dynamics of cardiac output ($\dot{Q}$) and inspiratory ventilation ($\dot{V}_I$) in response to volitional ("0" load) pedaling. Arrows at 0 sec indicate the instants when the stimuli were given, and the ordinate is expressed in relative values from this point. (Miyamoto et al. 1988)

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 passive pedaling whereas cardiac output increased only gradually (Miyamoto et al. 1988). Miyamoto's conclusions concerning the cardiodynamic theory have been supported by several authors (Grucza et al. 1990; Adams et al. 1987; Fordyce et al. 1982; Concu 1988; Banner et al. 1988; Pokoroski et al. 1990). Recent findings made by simultaneous measurements of cardiac output and pulmonary ventilation at the onset of exercise are strongly against the concept that ventilation in phase I is causally liked to right ventricular output or right ventricular work (Ishida et al. 1993), while cardiodynamic theory may be valid in the latter of phase I or phase II and phase III as described by Morikawa et al. (1989) and Miyamoto et al. (1989).

Casaburi et al. (1989) have recently observed a rapid fall in oxygen saturation in the mixed venous blood (SVO_2) and a rise in carbon dioxide partial 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. From these results, they argued that these changes must be considered when interpreting ventilation and gas exchange immediately after exercise. However, how these changes in mixed venous blood related to cardiodynamic theory and the pathways and mechanisms important in mediating the early ventilatory response have not been clarified.

3) AFFERENT IMPULSES FROM WORKING MUSCLE

In 1932, Harrison et al. first concluded that exercise hyperpnea was controlled largely by afferent information from the exercising limbs. Afterwards, Comroe and Schmidt (1943) found that exercise hyperpnea by stimulation of the ventral spinal root was abolished after denervation or chordotomy in animals. These findings were confirmed by using the cross-circulation technique by Kao (1963). In addition, Morikawa et al. (1989) observed increment of ventilation during passive movement in the health subjects, but not in the patients of spinal cord transection (Fig. 8). The experiments of Senapati (1966), Kalia et al. (1972), McCloskey and Mitchell (1972), and Tibes (1977) all support the contention that stimulation of afferent neural pathways running in group III and IV fibers, which originate in the polymodal receptors in the muscles (Kumazawa and

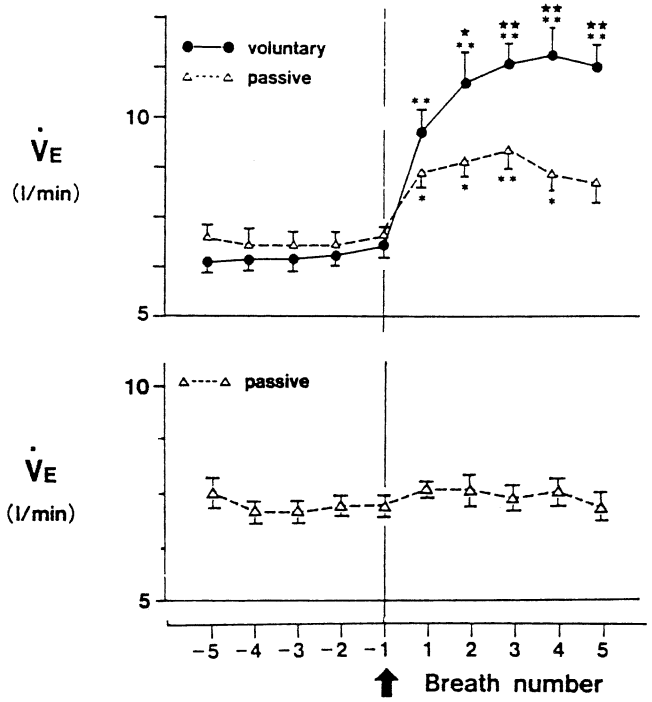

Figure 8 Sequential breath-by-breath changes in minute ventilation ($\dot{V}_E$) before and after onset of voluntary (●) and passive (△) exercise in healthy subjects (upper) and patients with spinal cord transection (lower). Arrow, point exercise started; vertical bars, SE. (Morikawa et al. 1989)

Mizumura 1977; Kaufman et al. 1982), can appreciably augment ventilation. Ingemann (1972) have determined the ventilation of the first (defined $\dot{V}_E$ 1 br.) and the average ventilation of the breaths during the first 20 s of exercise ($\dot{V}_E$ 20 s) for each subject during voluntary leg and arm work. They found the $\dot{V}_E$ 1 br and $\dot{V}_E$ 20 s were greater in the arm work than that in the leg work. Ishida et al. (1994) have confirmed significantly higher inspiratory minute ventilation ($\dot{V}_I$) during arm movement than that during leg movement, not only actively (voluntary) but also passively as shown in Fig. 9. These results suggested that afferent stimuli from moving limbs might be stronger in the upper than lower limbs if ventilation increased by only the stimulus through the group III and IV fibers. Nevertheless the numbers of receptors in the lower limbs are probably greater than that in upper limbs with respect to the amount of muscle mass; it is unclear why $\dot{V}_I$ during arm movement is higher than leg movement. It is possible to assume that the receptors of the arms may be more sensitive than those of the legs. However, further investigation will be necessary to confirm this assumption.

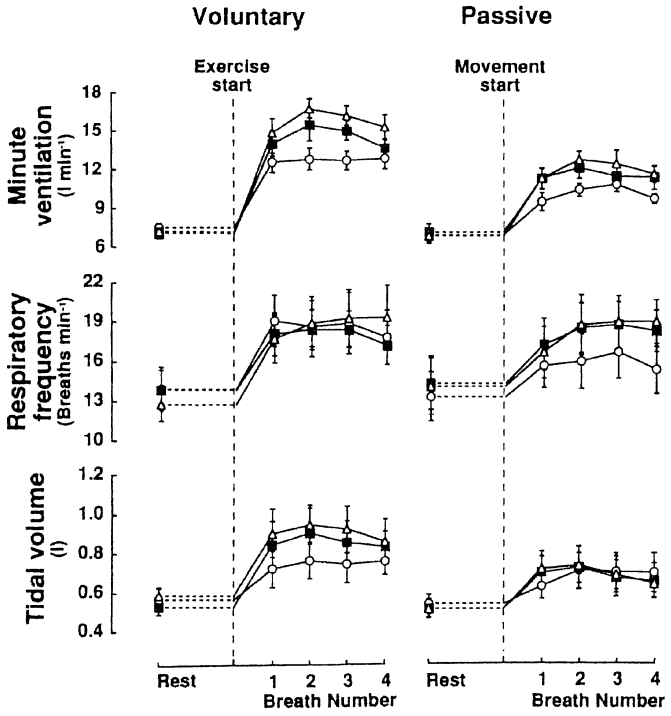

Figure 9 Mean and SE (n=7) of respiratory responses to voluntary exercise (left column) and passive movement (right column) by leg (○), arm (■) and combined arm and leg (△). From top, minute ventilation ($\dot{V}_I$), respiratory frequency (f) and tidal volume (V_T). Rest was the average of five breaths before the onset of exercise or movement. (Ishida et al. 1994)

Kaufman et al. (Kaufman et al. 1983; Kaufman and Rybicki 1987; Kaufman et al. 1988) reported that although both groups of III and IV muscle afferents contribute to cardiorespiratory reflex, group III fibers were likely to be stimulated by the mechanical effects of muscle contraction, whereas at least some group IV fibers were likely to be stimulated by the metabolic products due to muscular contraction (Fig. 10). At present, the specific stimuli that act mechanically and metabolically sensitive receptors have not been determined with certainty. Wildenthal et al. (1968) suggested the possibility that potassium can induce reflexes from the leg which may be functional during exercise. Although several authors reported that potassium of the working muscle might be an important factor regulating exercise hyperpnea (Hagberg et al. 1982; Tallarida et al. 1985; Thimm and Baum 1987), whether the increase of potassium leads to the critical depolarization and the generation of action potentials in afferent nerve fibers of group III and IV seems questionable (Rybicki et al. 1984).

Potassium appears to be a potent stimulus at the onset of contraction (Wildenthal et al. 1968; Hirche et al. 1980; Rybicki et al. 1984a; Rybicki et al. 1984b); other possibilities

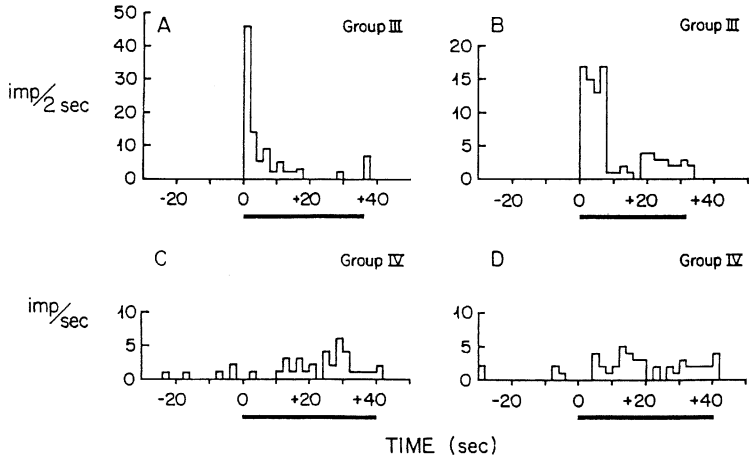

Figure 10 Discharge patterns of four thin fiber muscle afferents that responded to static contraction. Contraction period depicted by black bar. Group III fiber (A conduction velocity 17.8 m/s : A and 9.6 m/s : B) discharged vigorously at the onset of contraction, but hen its firing rate decreased even though muscle continued to contract. Group IV fiber (conduction velocity 1.3 m/s: C and 1.1 m/s: D) started to fire 4~10 s after onset of contraction and then gradually increased its firing rate during contraction period. (Kaufman et al. 1983)

include prostaglandins (Stebbins et al. 1986 a, 1986b), lactate (Rotto and Kaufman 1988), and ATP (Tibes 1980; Mitchell and Schmidt 1983; Stebbins and Longhurst 1986; Stebbins et al. 1986). Rotto and Kaufman (1988) reported that lactic acid and some cyclooxygenase products, such as prostaglandins and thromboxanes, are most likely to be responsible for metabolic stimulation of group III and IV fibers during muscular contraction. Furthermore, large myelinated (group I and II) fibers have also been implicated (Orani and Decandia 1990). From these results, further investigation seem necessary to clarify the mechanisms through peripheral stimulation. Adreani (1997) and Adeani and Kaufman (1998) have reported that group III and IV contribute cardiorespiratory responses even at very low level of work load.

The reviews written by Kaufman and Forster (1996) and Waldrop et al. (1996) seems to be available to understand the effect of peripheral reflex on ventilatory control.

4) STIMULUS FROM THE SEMICIRCULAR CANAL

Recently, stimulation of the vestibular system has been reported to elicit cardiovascular and respiratory changes (Biaggioni et al. 1998; Yates and Miller 1998). In support of this concept, Jauregui-Renaud et al. (2001) measured respiratory frequency during rotational stimuli by using a motorized rotating chair with acceleration in < 1s

to a constant rotational velocity of 60°/s on vertical axis, sustained for 1 min. They observed that stimulation of vertical semicircular canal increased breathing frequency in normal subjects but not vesibular-deficient patients. Monahan et al. (2002) have determined cardiorespiratory parameters such as inspiratory time, expiratory time, ventilation, heart rate, and mean blood pressure during seven various conditions (dynamic upright pitch, dynamic lateral pitch, dynamic head roll, dynamic yaw, dynamic yaw, dynamic chair rotation, static head down rotation, and static head rotation in the

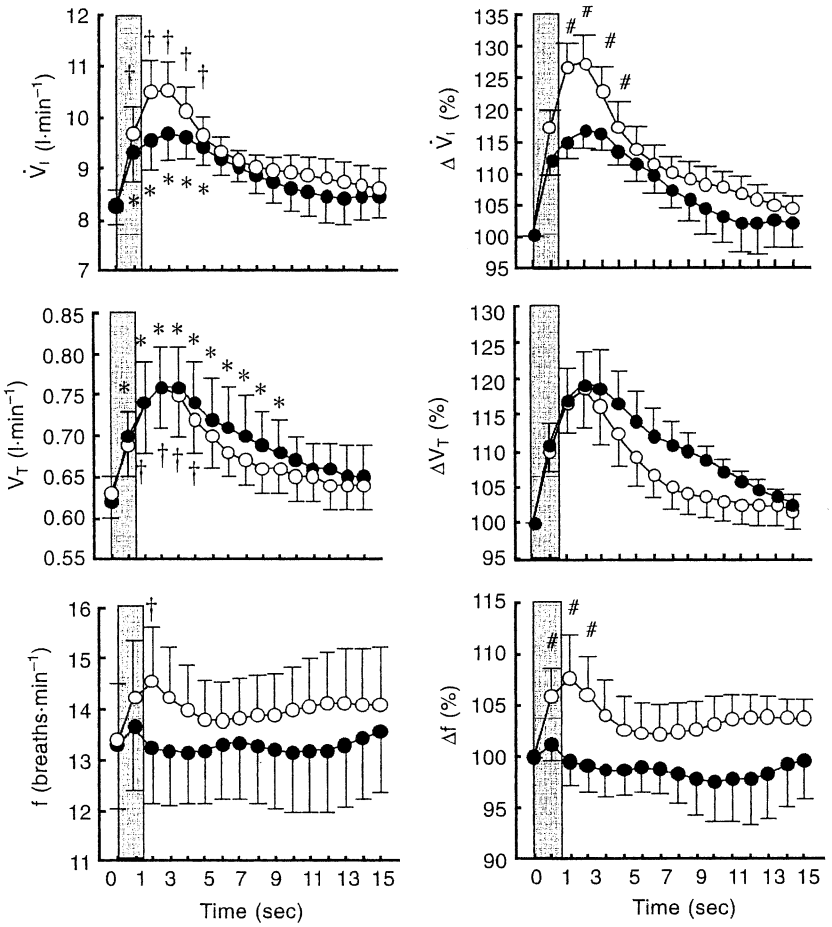

Figure 11 Absolute changes (left panel) and relative changes (right panel) in inspitatory minute volume ($\dot{V}_I$), tidal volume (V_T) and respiratory frequency (f) before, during and after chair rotation in left-turns (open circles) and right-turns (closed circles). Values in the right panel are absolute values that were converted by interpolation into values for each second. The percentage changes in inspiratory minute volume ($\triangle\dot{V}_I$), tidal volume ($\triangle V_T$) and respiratory frequency ($\triangle$f) in the right-turn and left-turn when the average of the values at rest was 100%. The turn period is shown with share area. Time 0 indicates the onset of rotation. Values are expressed as mean ($\pm$SE). The symbol * † indicate a significant difference ($p<0.05$) from rest. (Miyamura et al. 2004)

lateral decubitus position) in order to confirm the hypothesis that the activation of the semicircular canals would increase respiration in humans. They reported significant changes in respiratory frequency and minute ventilation from baseline during dynamic chair rotation for one minute. Because they did not indicate the results of respiratory parameters obtained by the breath-by-breath technique for 15 s from the start of chair rotation, however, it is unclear whether this horizontal vestibular activation produced functional alterations in phase I. In other words, it is important to emphasize that ventilatory and heart rate responses should be determined continuously with breath-by-breath and beat-by-beat techniques within 15 s rather than one minute total in order to clarify whether a horizontal semicircular canal stimulus is related to ventilatory response (phase I) at the onset of exercise. In our previous study (Miyamura et al. 2004, 2005), we found that inspiratory minute ventilation ($\dot{V}_I$) significantly increased immediately after chair rotation for very short time (1.5 s) in both the right- and left-turns (Fig. 11). From these results, it was suggested that the activation of horizontal semicircular canals is an important factor of ventilatory response at the onset of exercise with rotational movement in healthy subjects.

III. CENTRAL AND PERIPHERAL DRIVES

Kao et al. (1955) described that irradiation from motor cortex is not necessary exercise hyperpnea. Since Adams et al. (Adams et al. 1984a; Adams et al. 1984b) and Brice et al. (1988) also suggested that central mechanisms are not indispensable for the ventilatory response to exercise in humans, it is possible to assume that the phase I response is induced largely by afferents from the exercising muscle and this reflex hyperpnea may increase with an increase of amount of muscles involved in exercise. Figure 12 shows the comparison of average $\triangle\dot{V}_I$ in phase I response between one leg and both legs in passive or active movement. The $\triangle\dot{V}_I$ increased significantly in these four exercise tests. Average values of $\triangle\dot{V}_I$ in active and passive exercise were significantly higher in two legs than in one leg. Dejours et al. (1959) determined the ventilatory response to different types of repetitive movement consisting of flexion-extension of the lower legs from vertical to horizontal position in the supine position either passively or voluntarily at different frequencies. They found that delta expiratory volume ($\triangle\dot{V}_E$) increased almost linearly with increasing movement frequency when both

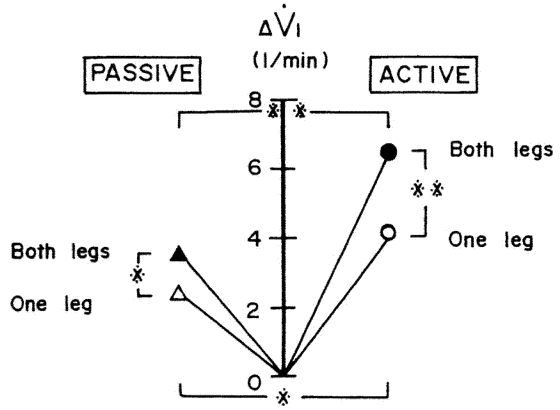

Figure 12 Comparison of average $\triangle\dot{V}_I$ between one leg and both legs in passive and active exercises. * indicates significant difference. (Miyamura et al. 1992)

lower legs were moved alternatively passively or voluntarily. As shown in Fig. 12, however, delta inspiratory volume ($\triangle\dot{V}_I$) with exercising of both legs was not double as compared with that of one leg in both passive and active exercise. These results indicate that ventilatory response in phase I may increase with increasing exercise frequency, but not proportionally to the amount of exercising muscle mass.

At present, it is difficult to clearly explain the mechanism for the above findings. As described previously, Adams et al. (1984) and Brice et al. (1988) claimed that central mechanisms are not necessary for the exercise hyperpnea in man. However, Eldridge et al. (1985) and Di Marco et al. (1983) suggested that command signals emanating from the hypothalamus provide the primary drive for respiratory and circulatory changes. Furthermore, Morikawa et al. (1989) observed a significant increase in ventilation when the patients with spinal cord transection made a great effort to perform exercise voluntarily. These results suggest that the cerebral cortex activity may be included at least during voluntary exercise in the awake condition in man.

On the other hand, Fink et al. (1963) have reported that subjects with bilateral subcortical cerebral dysfunction commonly had increased responsiveness both to carbon dioxide and to hypoxia. Hida et al. (1986) 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. They observed that ventilatory response during passive movement was higher in a deep anesthesia than that in a light one, while $\triangle\dot{V}_E$ obtained during passive exercise was almost the same as that during rhizotomy. Furthermore, it is of interest that in 4 out of 5 healthy subjects, average

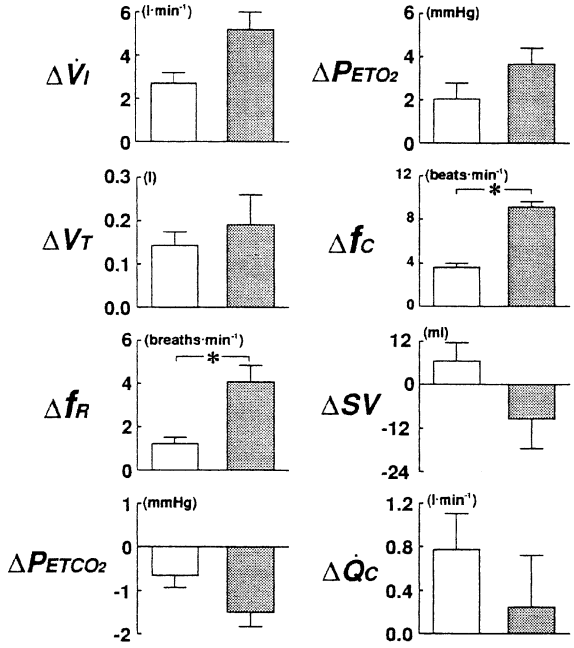

Figure 13 Comparison of the differences in phase I response between awake and sleep conditions. The delta values are calculated from mean response values minus pre-movemnt value. Open and hatched columns represent awake and sleep conditions, respectively. (Ishida et al. 1993)

$\triangle\dot{V}_I$ in passive exercise during sleep was more than double that while awake, though it was not statistically significant (Fig. 13). It is possible to speculate that the respiratory center may be inhibited by the higher center when awake but during deep anesthesia and/or sleep, such inhibition may disappear so that ventilation can increase considerably in response to afferent information from the moving limbs. In other words, there is some disinhibition during anesthesia or sleep, and the impulses from the central nervous system (CNS) and the brain stem reticular formation could provide two different types of information: facilitation and inhibition. It can be speculated that in an awake condition, larger $\triangle\dot{V}_I$ during active rather than during passive exercise may be due to the facilitatory influence from both the peripheral and central nervous system even if the central inhibition may have played a role. However, this assumption needs further investigation.

SUMMARY

When exercise starts, various cardiorespiratory adjustments take place for accomodating the greatly increased metabolic requirements. A rapid response in ventilation (phase I) may be at least useful for preventing oxygen deficiency and for increasing alveolar ventilation, oxygen tension, and oxygen uptake even if it is minimal. But why is the increasing tidal volume and respiratory frequency elicited so quickly at the onset of exercise? Does rapid ventilatory response play important roles as a trigger for surviving in exercising man?

It has hitherto been reported that phase I response is observed during not only voluntary and passive exercise, but also during electrically induced muscle contraction in man. In addition, it was observed that ventilation in phase I is not affected by hypoxia and is not causally liked to cardiac output. Although the mechanisms of ventilatory response at the onset of exercise in man have extensively explored by many investigators, they have still remained obscure. At present, the causal factors of phase I are classified

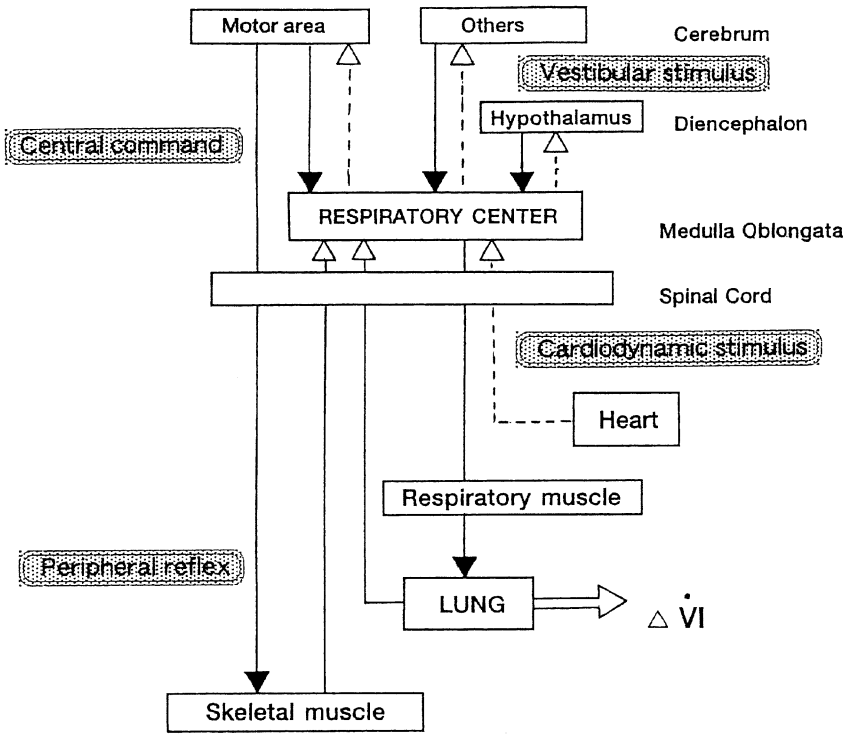

Figure 14 Schematic diagram of possible mechanisms of phase I.

as central and peripheral neurogenic stimulus, or as both (Fig. 14). In the awake condition, abrupt ventilatory increment immediately after voluntary and passive exercise in man could be attributed to the drives from the central command including cortical and hypothalamic activities as well as some peripheral afferent information through group III and IV fibers and/or semicircular canals. However, further investigations to clarify many unsolved problems with regard to phase I should be advanced in future.

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