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Pulmonary Oxygen Uptake Kinetics in Nonsteady State

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Abstract. The body does not always achieve a steady state and is more often kept in a nonsteady state. It is important not only in terms of physiological anthropology but also in its application to rehabilitation and training to clarify whether oxygen transport or utilization is the limiting factor in oxygen uptake in the nonsteady state. Hypotheses concerning the limiting factor in oxygen uptake have their own rationales, and it is still controversial as to which is actually responsible. The limiting factor in oxygen uptake may vary according to exercise conditions. Under certain conditions, oxygen transport would be responsible for limiting the oxygen uptake, and under others, oxygen utilization or both oxygen transport and utilization would be responsible. These conditions differ according to the type of exercise (e.g. step exercise vs. cycling, leg vs. arm exercise, and dynamic vs. static exercise), posture, recruited muscle fibers, and other experimental conditions. Considering that oxygen uptake is regulated by coupling among respiration, circulation, and metabolism, it may be possible that interactions among these functions vary in a complicated manner according to exercise conditions, which may require a different limiting factor in regulating oxygen uptake.

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The steady state is achieved as the coupling among respiration, circulation, and metabolism is regulated appropriately and the balance between oxygen supply and demand is established. In such a state, aerobic energy is utilized enabling exercise to be sustained for a considerably long time.

In physical activity in daily life, however, the intensity and pattern of the activity vary with time, which results in a delay in responses of respiration, circulation, and metabolism. This means that the body does not always achieve a steady state and is more often kept in a nonsteady state. It will therefore be useful to clarify nonsteady state conditions, i.e. transient response, of respiration, circulation, and metabolism, at the onset of exercise, during recovery, or during transitions where exercise intensity changes, because it seems that only when physical response during both steady- and nonsteady-state exercise are understood can physiological features and functional regulation be grasped more accurately and more profoundly.

The capacity for oxygen uptake is determined by oxygen transport, which consists mainly of the respiratory and circulatory systems, and oxygen utilization (oxidative capacity). If either of these functions does not operate adequately, aerobic metabolic processes will fail to work properly. Anaerobic metabolic process will then follow to counterbalance this. In such a case, it will take longer to achieve the steady state or such a state may not be reached at all, which makes it impossible to sustain exercise for a long time. It is important not only in terms of physiological anthropology but also in its application to rehabilitation and training to clarify whether oxygen transport or utilization is the limiting factor in oxygen uptake in the nonsteady state.

At the beginning of exercise, oxygen uptake remains in a nonsteady state. The changing pattern of oxygen uptake is divided into two phases, namely phase 1 (the initial phase) which continues for 15 - 20 seconds immediately after the onset of exercise, followed by phase 2 (Whipp et al., 1982; Whipp 1994). In phase 2, the responses of ventilation, carbon dioxide output, and oxygen uptake change monoexponentially, and the steady state is finally attained in exercise of moderate or lower intensity. Moderate exercise is defined as exercise in which oxygen uptake is at an anaerobic threshold (AT) or lower.

It has been a matter of some controversy as to

which is the limiting factor in oxygen uptake, oxygen transport or oxygen utilization. The hypothesis that oxygen transport is the limiting factor is based on the fact that when oxygen transport response is delayed due to hypoxia, lying in a supine position, or depressed cardiac function, the oxygen uptake response is delayed in the lungs (Hughson, 1990; Hughson et al., 1993). Provided that oxygen is supplied adequately to active muscles, and thus oxygen transport does not act as the limiting factor, the time constant, which expresses the speed of response of oxygen consumption in active muscles, does not change even when the exercise intensity is changed (dynamic linearity) (Mahler, 1985). However, if oxygen supply to the muscles is not evenly distributed, causing local hypoxia, oxygen transport can be the limiting factor. Dynamic linearity cannot therefore be established between responses of muscle oxygen consumption and pulmonary oxygen uptake. For example, it is believed that oxygen uptake response is delayed due to a delay in the response of cardiac output if baseline exercise intensity is higher even when intensity changes in the same manner (Hughson and Morrissey, 1982, 1983; Inman et al., 1987).

The hypothesis that oxygen utilization is the limiting factor is also convincing. Barstow et al. (1991, 1993) and Whipp and Ward (1990) demonstrated that dynamic linearity exists in the responses not only of active muscles but also the lungs, and that experimentally increased blood flow does not increase oxygen uptake. They also showed that, during cycling in a sitting position, oxygen transport is not the limiting factor in oxygen uptake, based on the results of earlier studies which demonstrated that cardiac output or muscle blood flow respond faster than pulmonary oxygen uptake (Pendergast et al., 1980; Miyamoto et al., 1982). Cerretelli et al. (1979) and Di Prampero et al. (1989) also assumed that it is the oxygen utilization that limits the response of oxygen uptake.

Both hypotheses concerning the limiting factor in oxygen uptake have their own rationales, and it is still controversial as to which is actually responsible. The authors would like to propose the following. The limiting factor in oxygen uptake varies according to exercise conditions. Under certain conditions, oxygen transport is responsible for limiting the oxygen uptake, and under others, oxygen utilization or both oxygen transport and utilization are responsible. These conditions differ according to the type of exercise (e.g. step exercise vs. cycling, leg vs. arm exercise, and dynamic vs. static exercise), posture, recruited muscle fibers, and other experimental conditions.

In our study of the regulation of oxygen uptake during arm cranking exercise (Koga et al., 1996), response of oxygen uptake was delayed compared to that during leg cycling exercise (Fig. 1). Cardiac output

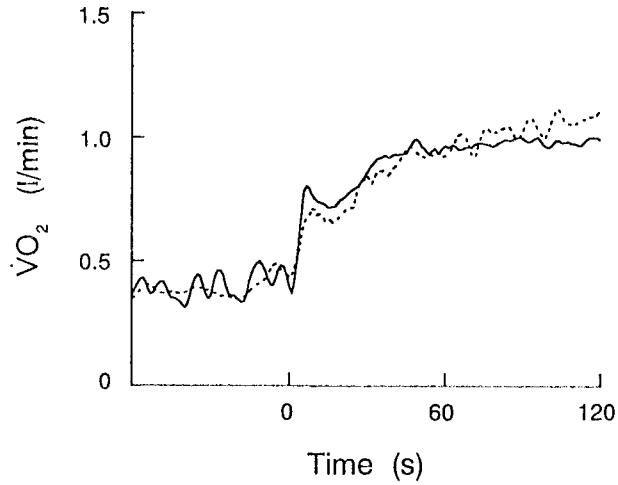

Fig. 1 Breath-by-breath $\dot{V}o_2$ response of one subject to transition between rest and exercise in leg and arm exercise. Dashed line, arm exercise; solid line, leg exercise. The increase in $\dot{V}o_2$ was less in the arm than in the leg exercise.

response was delayed even further than oxygen uptake response. Arm exercise induced more isometric muscle contractions than leg exercise for torso stabilization. In arm exercise, therefore, blood flow is prone to be occluded, and muscle pump activity is low. Due to the reduction of muscle blood flow, oxygen transport is delayed, which, it is believed, acts as the limiting factor in oxygen uptake. Arm muscles, however, have a higher proportion of fast twitch fibers compared to leg muscles. Fast twitch fibers have lower oxygen utilization, which may be responsible for the delayed oxygen uptake during arm exercise. If leg muscles are cooled before starting exercise, oxygen uptake response is slower than when the muscles are kept at normal temperature (Koga et al., 1993) (Fig. 2). This may be due to delayed oxygen transport caused by decreased muscle blood flow or due to the shift to the left of the oxy-hemoglobin dissociation curve, or it may be due to depressed metabolism caused by cooling the muscles (Q_{10} effect), reduced enzyme activity, or greater recruitment of fast twitch fibers than at normal temperature. It is known that the time constant for response of fast twitch fibers is slower than for slow twitch fibers. Cochrane and Hughson (1992) recently demonstrated in a simulation that very slight changes in blood flow distribution and in an oxy-hemoglobin dissociation curve at the beginning of exercise may induce a different regulation of oxygen uptake, indicating that the balance between oxygen transport and demand is very delicate. Considering that oxygen uptake is regulated by coupling among respiration, circulation, and metabolism, it may be possible that interactions among these functions vary in a complicated manner according to exercise conditions, which may require a different limiting factor in regulating

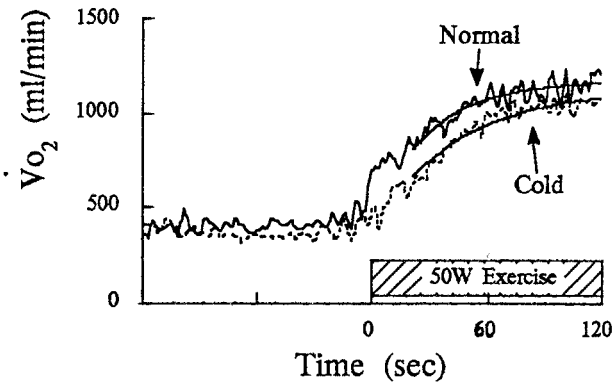

Fig. 2 Breath-by-breath $\dot{V}o_2$ response of one subject to transition between rest and exercise in the lowered and the normal muscle temperature. Dashed line, the lowered muscle temperature; solid line, the normal muscle temperature. The increase in $\dot{V}o_2$ was markedly less in the lowered than in the normal muscle temperature.

oxygen uptake.

In order to clarify the limiting factor in oxygen uptake at the onset of exercise, it is important to confirm that the time constant for oxygen consumption in active muscles corresponds to that of oxygen uptake in the lungs and that dynamic linearity is attained. If it can be confirmed that the time constant for oxygen uptake in the lungs corresponds to that of active muscles, and if dynamic linearity is established, this will indirectly prove that limitation is not caused by oxygen transport in the regulation of oxygen uptake. Current evidence indicates that the time constant for oxygen consumption estimated from a reduction in creatine phosphate in active muscles, which is measured by nuclear magnetic resonance (NMR) (Barstow et al., 1994a; Binzoni et al., 1992; Marsh et al., 1993; Yoshida and Watari, 1993), the time constant for oxygen consumption obtained from blood flow in active limbs and arteriovenous oxygen differences (Grassi et al., 1996), and the time constant for oxygen uptake in the lungs measured breath-by-breath seem to correspond with each other (Barstow, 1994b). The establishment of dynamic linearity has thus been confirmed. Caution is needed in interpreting the NMR data, because they were obtained from leg extension and flexion exercise and not from exercise of a large muscle group such as when cycling.

From this evidence, it can be said that the limiting factor in oxygen uptake is not oxygen transport but oxygen utilization at the beginning of cycling in a sitting position, which is a standard type of exercise. However, if, under certain exercise conditions, uneven blood distribution in the muscles results in local hypoxia (Whipp et al., 1995), or if the regulation of oxygen transport is delayed under conditions such as hypoxia, lying in a supine position, or depressed cardiac function, transient anaerobic metabolic processes take place, which could result in early lactate production and delayed oxygen uptake.

The above argument should consider the accuracy and resolution of the techniques used. The response of oxygen uptake in the lungs is vulnerable to the influence of irregular respiration and contains noise. An alveolar gas-exchange technique has therefore been adopted, which corrects gas store at every breath to minimize any variation in gas exchange values (Beaver et al., 1981). Furthermore, the interpretation of response kinetics, dynamic linearity in particular, may differ according to different models which approximate the response of oxygen uptake mathematically (Barstow et al., 1991, 1993). The reliability of methods to detect responses of nonsteady-state cardiac output and muscle blood flow has been controversial (Hughson, 1990). Thus, it remains unclear how oxygen uptake response is regulated at the beginning of exercise of a moderate intensity, especially whether the limiting factor is oxygen transport or utilization. This will be elucidated by repeating, alternately, a study of both exercise under a standard condition (rest or unloaded exercise as a baseline followed by cycling in a sitting position) and exercise under other conditions, and by simulation.

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