Relationship between tissue oxygen index in skeletal muscle and oxygen uptake at pulmonary level

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Key words

Oxygen tissue index, heart rate, oxygen uptake, cross correlation, oscillation

Abstract

We examined whether the relationship between muscle oxygen consumption and lung oxygen uptake is established by the intervention of cardiac pumping. Oxygen intake ($\dot{V}O_2$) and heart rate (HR) were determined breath-by-breath. The values were converted to 1-second values by a three-dimensional spine function. Tissue oxygen index (TOI) was determined per second from the vastus lateralis by using near-infrared spectroscopy. Exercise was performed for 10 seconds with an intensity of 70% of peak $\dot{V}O_2$. A rest period of 10 minutes after exercise was set before the exercise and a recovery period of 20 minutes was set after the exercise. All 1-second values during the test were processed with a low pass filter (<0.05 Hz). Cross-correlation of the processed values was obtained. $\dot{V}O_2$ rose during exercise and increased again during recovery. HR rose during exercise and declined during recovery. TOI decreased after exercise and increased during recovery. The maximum value of the cross-correlation between HR and $\dot{V}O_2$ was 0.712 ± 0.112. The minimum cross-correlation value between TOI and HR was -0.398 ± 0.225. Double of the time difference between the highest value and the lowest value of HR and $\dot{V}O_2$ or TOI and HR is the wavelength. It was 170 seconds (2.8 minutes). The results suggested that variation in TOI or its related substances in skeletal muscle (oscillation and level of the oscillation axis) is partly related to variation in cardiac pumping and that variation in the cardiac pump considerable affects variation of lung oxygen intake.

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INTRODUCTION

Aon et al. [1] have proposed the hypothesis that oxidative metabolism is synchronized by reactive oxygen species (ROS) among mitochondria. That is, NADH generated by the TCA cycle is converted to NAD by complex I in the electron transfer system. Oxygen is used in complex IV, but a part of it is produced as radical oxygen in complex III. This radical oxygen is an element that synchronizes the metabolism of other mitochondria. The evidence underlying this hypothesis is oscillatory phenomena of NADH, radical oxygen and mitochondrial inner membrane potential. It is thought that these oscillations synchronize the metabolism between mitochondria by mediating the production of ROS.

Iotte et al. [2, 3] found that creatine phosphate (CrP) oscillates in the re-synthesis process of CrP after human muscle activity. This phenomenon occurs due to the supply of ATP by oxidative phosphorylation. Therefore, oxygen consumption is estimated to oscillate. In other words, activation of the electron transfer system and creatine phosphate re-synthesis are thought to be coupled. Furthermore, when the results obtained by Aon et al. [1] are taken into consideration, it is thought that the micro synchronization between mitochondria is involved in the macro re-synthesis process of creatine phosphate.

Oscillation of the tissue oxygen index (TOI), which can be measured by using near-infrared spectroscopy has been determined in inactive muscles during exercise [4] and in the vastus lateralis during recovery from exercise [5]. As a result, we found that the frequency is very low. It was also shown by a model propose by Richard [6] that consumption of oxygen by complex IV oscillates. In other words, in order to maintain the dynamic homeostasis of ATP generated in complex V, it is thought that this oscillation occurs as ATP acts in a feedback manner on oxygen consumption [4,5].It was shown in a later study that oscillation of TOI at a very low frequency occurs during exercise [7]. Moreover, in that study, in addition to ATP feedback, it was suggested that interactions among biochemical substances in the TCA cycle cause oscillation of NADH and that the oscillation causes oscillation of oxygen consumption.

Oscillation of TOI is a phenomenon in skeletal muscle. This phenomenon does not only occur within skeletal muscle but also affects oscillations in organs except the skeletal muscle. Usuda [8] reported that there is coherence in the very low frequency band between TOI in the vastus lateralis and heart rate (HR) during recovery after a short intense exercise. He also reported that there is coherence in the very low frequency band between arterial oxygen saturation measured at the fingertip and TOI. These results suggest that when TOI is outputted from muscle, the TOI is inputted from the cardiorespiratory system (oscillation of oxygen supply) at the same time. In other words, oscillation of TOI is interrelated mainly with oscillation of the cardiorespiratory system. However, physiological significance of the relationship was not clarified in that study.

Oxygen consumption in skeletal muscle may regulate lung oxygen intake via cardiac

pumping. That is, the oscillation of TOI in skeletal muscle resonates with cardiac pumping, and then the oscillation of the cardiac pumping makes the resonance of lung oxygen intake. This may be a physiological significance of interrelations between oxidative metabolism and cardiorespiratory system. In this study, therefore, we examined whether the relationship between muscle oxygen consumption and lung oxygen uptake is established by the intervention of cardiac pumping.

METHODS

Subjects

Nine healthy males participated in this study. The means and standard deviations of ages, heights, body weights and peak oxygen uptake ($\dot{V}o_2$peak) levels of the subjects were 19.6 ± 1.4 years, 169.8 ± 5.6 cm, 63.7 ± 8.7 kg and 3.18 ± 0.52 l/min, respectively. Each subject signed a statement of informed consent following a full explanation regarding the nature of the experiment. The Ethics Committee of Hokkaido University Graduate School of Education approved the present study. This study was performed in accordance with the Declaration of Helsinki.

Experimental protocol

Each subject performed incremental ramp exercise until exhaustion on a cycle ergometer (Ergometer 232 CXL, Combi, Tokyo, Japan). After being in a resting state for 4 min, each subject performed constant-load exercise at 20 W for 4 min, and then incremental ramp exercise was increased by 20 W per one min until the subject could not maintain the revolution rate of pedaling (60 rpm). $\dot{V}o_2$peak was determined by the maximal value during the incremental ramp exercise. In this determination, data of $\dot{V}o_2$ for 20 s were used. On another day, each subject performed constant-load exercise: exercise with 70% of $\dot{V}o_2$peak determined by incremental ramp exercise for 10 sec. Each subject rested for 10 min before the exercise. The exercise was followed by a recovery period of 20 min. Before resting on the cycle ergometer seat prior to the exercise, each subject sat on a chair to attach electrodes on the subject's chest for monitoring heart rate (HR) and to attach photo probes on the subject's leg (vastus lateralis) for NIRS. Each subject was instructed to relax and to maintain cycle ergometer cranking in a horizontal position at rest and during recovery on the cycle ergometer,

Measurements and determinations

Blood samples (each 100 μl) were collected from warmed fingertips using a capillary tube. Each subject's hand was pre-warmed in 40-45 ℃ water while sitting on the chair prior to each test in order to arterialize capillary blood [9]. After the warming, the subject's hand was warmed by a heating glove at rest, during exercise and during recovery on the cycle

ergometer. It has been shown that such blood samples might not accurately reflect arterial O_2 pressure but can closely reflect arterial pH [9]. Samples were analyzed using a blood gas analyzer (i-STAT1, i-STAT, Abbott Point of Care Inc. IL, USA) to measure pH and lactate (La).

Data for respiration gas exchange were obtained using a respiratory gas analyzer by the breath-by-breath mode (AEROMONITOR AE-310S, Minato Medical Science CO., LTD., Osaka, Japan). Ventilation was measured by a hot-wire flow meter, and the flow meter was calibrated with a syringe of known volume (2 liters). O_2 and CO_2 concentrations were measured by a paramagnetic oxygen analyzer and photometric gas analyzer, respectively. The gas analyzer was calibrated by known standard gas (O_2: 15.13%, CO_2: 5.068%). Respiration gas exchange was measured continuously during rest, exercise, and recovery periods. HR was recorded using a heart rate monitor installed in the respiratory gas analyzer. $\dot{V}o_2$ and HR were obtained breath-by-breath. In incremental ramp exercise, breath-by-breath data were outputted as 20-s data.

TOI in the vastus lateralis was determined using a near-infrared spectroscopy (NIRS) system (NIRO200x, Hamamatsu Photonics, K. K. Hamamatsu, Japan). Although NIRO200x can determine oxygenation and deoxygenation by the Modified Beer-Lambert method, TOI determined by the SRS method was used in the present study. The NIRS probe consisted of a light source and an optical detector with a distance of 3.0 cm between the light source and detector. Triple-wavelength light (735, 810 and 850 nm) emitted from the light source penetrates tissue, where it is either absorbed or scattered, and some of the scattered light returns to the optical detector. The sampling frequency of TOI was 1 Hz. TOI was calculated from deoxygenation (HHb) and oxygenation (O_2Hb) determined by SRS using the following equation:

$TOI = O_2Hb/(HHb + O_2Hb)$.

Calculation and statistical analysis

In a previous study, in order to obtain 1-s data, breath-by-breath data obtained in repeated exercise with a time interval were converted to 1-s data in each exercise, and the data obtained in each exercise were averaged [10]. However, in this method, oscillation of the data obtained is eliminated by the averaging. A way to obtain second-by-second data from breath-by-breath data was developed in a recent study [11] but average data for four trials were also used. Therefore, in the final data obtained by these treatments, $\dot{V}o_2$ oscillation is cancelled. There is HR variability [12,13], which should affect oscillation of $\dot{V}o_2$. Therefore, in order to avoid this cancellation, breath-by-breath data for $\dot{V}o_2$ and HR were interpolated into 1-s data using a three-dimensional spine function for one trial data in the present study. However, there is also a problem in this method. Higher frequency of oscillation than respiration rate has no meaning.

In order to visualize the data of low frequency, a low pass filter was used for 1-sec $\dot{V}o_2$, 1-sec HR and 1sec TOI. Due to the filtering with treatment for removal of trend, TOI, HR and $\dot{V}o_2$ became values that were different from averages in whole data (Fig. 2). The pass

frequency was set below 0.05 Hz. By the processed data, cross correlations between HR and $\dot{V}o_2$ and between TOI and HR were obtained.

Results are presented as means ± standard deviations. Significant differences from resting values for blood samples were tested by Dunnett's method. The significant level was set at $p<0.05$.

RESULTS

Table 1 shows blood lactate levels and blood pH during rest periods and recovery periods after exercise. The exercise intensity was 70% $\dot{V}o_2$peak, but the exercise time is short. As a result, neither blood lactate nor blood pH was changed by the exercise.

Figure 1 shows representative examples of $\dot{V}o_2$, HR and TOI every second. $\dot{V}o_2$ rose sharply when the exercise started. After the exercise was stopped, $\dot{V}o_2$ temporarily decreased but it rose again and then declined. HR increased with the start of the exercise, decreased after the exercise, and returned to the resting level. TOI fell sharply and increased after the end of the exercise.

Figure 2 shows the results of processing the value of Figure 1 with a low pass filter (<0.05 Hz). $\dot{V}o_2$ increased at the onset of exercise and increased again after the end of exercise. HR increased at the beginning of exercise, decreased in the subsequent recovery period, and returned to the resting level. TOI decreased after starting exercise and exceeded the resting level during the recovery period. After that, it returned to the resting level. Slow oscillations of $\dot{V}o_2$, HR and TOI, were observed in the rest and recovery periods before and after exercise.

Figure 3 shows the cross correlations between TOI and HR and between HR and $\dot{V}o_2$. The minimum value of the cross correlation between TOI and HR was -0.398 ± 0.225 and the delay time was 9 seconds. The maximum value was 0.172 ± 0.081. The delay time between the lowest value and the highest value was 71 seconds. The maximum value of the cross correlation between HR and $\dot{V}o_2$ was 0.712 ± 0.112 and the delay time was 6 seconds. The minimum value was 0.597 ± 0.099. The delay time between the highest value and the lowest value was 82 seconds. The wavelength is twice of the delay time between the highest value and the lowest value of both cross correlations. Wavelengths between TOI and HR and between HR and $\dot{V}o_2$ were about 170 seconds (2.8 minutes). In terms of frequency, it is 0.0059 Hz.

Table 1

Blood lactate (La) and blood pH at rest and during recovery at 10 and 20 min in exercise with 70% of peak oxygen uptake for 10 seconds.

		Rest	Rec 5min	Rec 10 min	Rec 20 min
Blood La	Mean	1.26	1.39	1.29	1.28
	SD	0.31	0.34	0.35	0.35
Blood pH	Mean	7.39	7.37	7.39	7.39
	SD	0.02	0.01	0.02	0.03

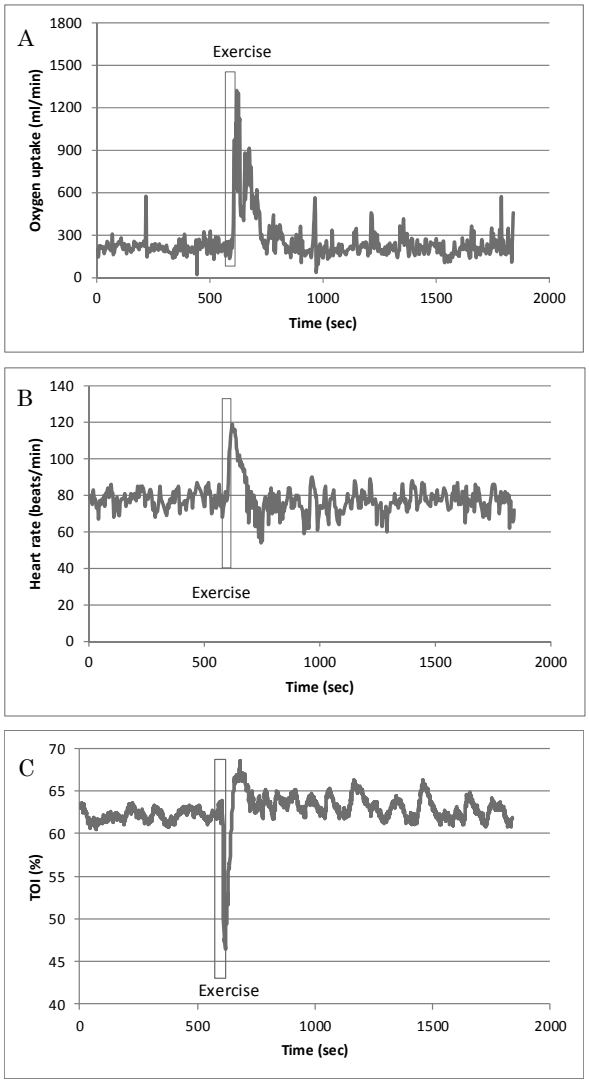

Figure 1

One-second data are shown. Oxygen uptake ($\dot{V}O_2$) rapidly increased during 10-sec exercise and then temporally decreased and again increased after the exercise (panel A). Heart rate (HR) rapidly increased during 10-sec exercise and then decreased (panel B). Tissue oxygen index (TOI) rapidly decreased during 10-sec exercise and then returned to the resting level (panel C). The oscillations in TOI, HR and $\dot{V}O_2$ can be seen.

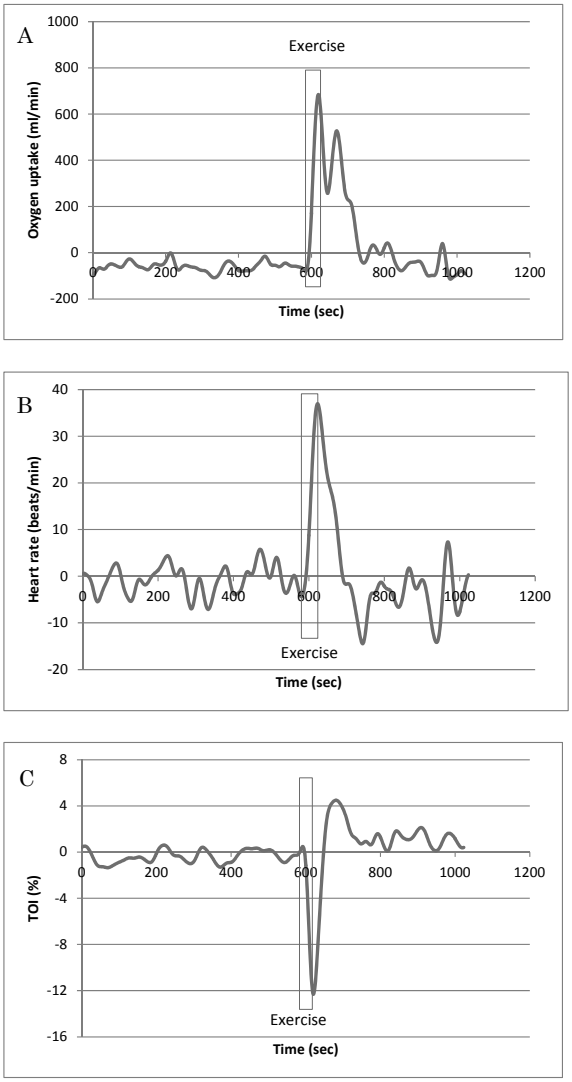

Figure 2

The data shown in Figure 1 were calculated by a low pass filter with 0.05 Hz. There were two peaks in $\dot{V}o_2$ and one peak in HR and TOI. There were also oscillations in $\dot{V}o_2$, HR and TOI. Due to filtering with treatment of removal for trend, $\dot{V}o_2$, HR and TOI became values that were different from averages of whole data.

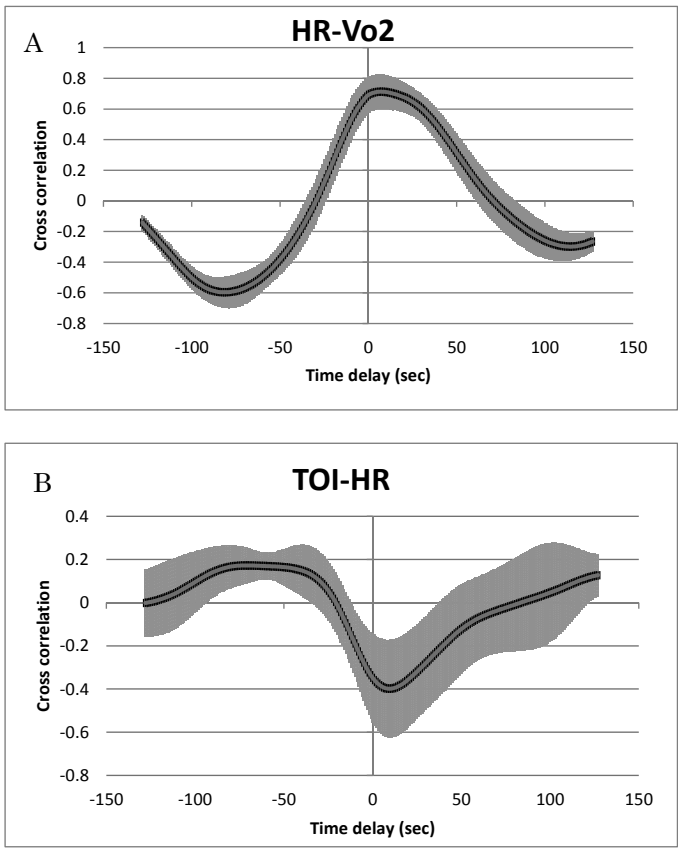

Figure 3

The data shown in Figure 2 after processing with a low pass filter with 0.05 Hz were used to obtain the correlations between $\dot{V}o_2$ and HR and between HR and TOI. There were high correlation coefficients.

DISCUSSION

Oxygen uptake increases with increasing cardiac output when impulsive-like exercise is started. After such exercise, the cardiac output falls. At that time, oxygen uptake in the lung increases again as venous blood oxygen that decreased in active muscles arrives with a delay in transport from the active muscles to the lungs. This phenomenon is a well-known event [14, 15, 16]. However, it is not generally known that oxygen uptake in the lung oscillates. This is due to the influence of oscillation of cardiac output on the oscillation of oxygen intake [16]. In skeletal muscle, oxygen concentration oscillates due to interactions among biochemical substances of the aerobic energy mechanism. Oscillation of oxygen uptake in the lung, of course, accompanies oscillation of oxygen supply. There is, therefore, a possibility that this oxygen supply affects oscillation of oxygen consumption in muscles.

We speculated that not only does the oscillation of oxygen supply induce oscillation of

oxygen consumption, but also that oxygen consumption itself oscillates. The reason for this speculation comes from the hypothesis based on experimental results [1] as mentioned in Introduction. Although there is no direct evidence that oxygen consumption oscillates, electrons in the electron transfer system can oscillate. Therefore, it is likely that oxygen consumption also oscillates.

The reason for using the low pass filter in this study is as follows. It is known that HR related to oxygen supply has a higher component [12, 13] than the frequency obtained in this study. This component was removed. In addition, only very low frequency components are extracted because oscillation caused by interactions among biochemical substances of the aerobic energy mechanism is very low frequency. The very low frequency has been reported as follows. The recovery process of creatine phosphate by oxidative phosphate after exercise oscillates at 0.002-0.025 Hz [2, 3]. Also, the frequency showing waves of TOI in skeletal muscle is 0.00339-0.0078 Hz [4, 5]. The frequency in this study is within the ranges in these reports.

As a property of the waves, there is an entrainment phenomenon. It was assumed in this study that the phenomenon occurs from TOI to HR and from HR to $\dot{V}o_2$. However, the cross correlation from TOI to HR was not so high. This may be due to muscle inhomogeneity [17]. That is, because the level of TOI varies from muscle to muscle, the level of the axis of oscillation is not a typical TOI level. Therefore, although the TOI level partly affected the HR level, the TOI imbalance in each muscle is thought to interrupt the relationship between TOI and HR. Nevertheless, it is thought that the frequency of TOI is the same regardless of the difference in the region because entrainment between TOI in each part and HR must be maintained. Alternatively, the oscillation of HR may be related to the oscillation of a biochemical substance related to TOI oscillation. If the oscillation has a phase difference with the oscillation of TOI, there would be a time delay of the oscillation of TOI and the oscillation of HR. For example, as shown in the appendix, there is a phase difference between oscillation of oxygen consumption and oscillation of TOI.

Thus, it is likely that oscillation leads to the entrainment phenomenon. However, changes in the levels of $\dot{V}o_2$, HR and TOI during exercise cannot be explained from this phenomenon of oscillation. Therefore, in addition to the entrainment phenomenon accompanying oscillation, it is thought that a decrease in TOI promotes an increase in HR, and an increase in HR causes an increase in $\dot{V}o_2$. That is, in this study, we assert that oscillation is the basis of propagation between organs and that the difference in the level of axial oscillation leads to a difference in the magnitude of axial level (see appendix).

It has been proved that partial restriction of blood flow in active muscle of the leg in light exercise and parasympathetic blockade by medication increases HR [18]. This suggests that muscle metaboreflex increases HR by sympathetic nerves, but no metabolites causing muscle metabolic reflex were identified in this study. Partial blood flow restricts oxygen supply, so the causative agent of muscle metaboreflex is a substance in relation to ischemia. Therefore, it can be a substance that oscillates in relation to oxygen concentration or

oxygen concentration. However, since there was no change in substances related to the glycolysis system in this study, it is though that there is no influence of HR on substances related to glycolysis system. Also, because the cross-correlation coefficient was moderate, we cannot simply assume that the cause of muscle metaboreflex is a substance related to TOI, especially during exercise. We must consider central commands [19] and muscle mechanical stimulation [20] during exercise.

The delay time of the maximum value of cross correlation between HR and $\dot{V}o_2$ was 6 seconds. There are two possibilities for the occurrence of this delay. One possibility is that an increase in cardiac output at the cardiac level causes a delay in the increase in blood flow at the lung capillary level. This may occur when blood is stored between the two. In this case, an increase in cardiac output of the heart does not directly lead to an increase in blood flow in pulmonary capillaries. The blood volume of blood vessels on the arterial side of the lung may increase during exercise. The other possibility is related to interpolating breath-by-breath data to 1-second intervals. This interpolation is mathematical and lacks accuracy within the breathing rate.

The delay time of cross correlation between TOI and HR was 9 seconds. If the heart rate was affected by oxygen concentration in the muscle tissue in response to the nervous system, such a delay would not have occurred. Therefore, there are two possible interpretations for the time delay. One is the possibility that the delay time was not accurately identified because the fluctuation range (SD) of the cross correlation is not small. The other is related to the fact that TOI is established by the balance between oxygen supply and oxygen consumption [21]. As shown in the present model, if there is a phase difference between oscillations of oxygen supply and oxygen consumption, TOI produces a time delay from oxygen consumption.

The present model shows that TOI has differences from oxygen consumption in phase difference and amplitude (see Figure 4 A). Therefore, care is needed in examination of oscillation of oxygen consumption from analysis of TOI. In this study, we also investigated the level of the axis of oscillation. We found that the axial level of TOI decreases when the increase in the axial level of oxygen consumption is greater than the rise in the level of axial oscillation of oxygen supply. Since the exercise in this study was performed for only 10 seconds, the influence of oscillation would have been small. The amplitude of oscillation was also small. Therefore, it seems that TOI decreases mainly due to the difference in the axis level.

The model assumes that the oscillation of energy metabolism in skeletal muscle is influenced by the oscillation of oxygen supply. In other words, this assumption implies that the phenomenon is circular. Therefore, the past oscillation of oxygen consumption affects the current oscillation, and the present oscillation affects the future oscillation. This is cycle relationship. We modeled this situation. It is also assumed that there is interaction between oscillation of oxygen consumption and oscillation of oxygen supply. These cases do not treat in conventional problem. In the previous studies, it has mainly been discussed whether

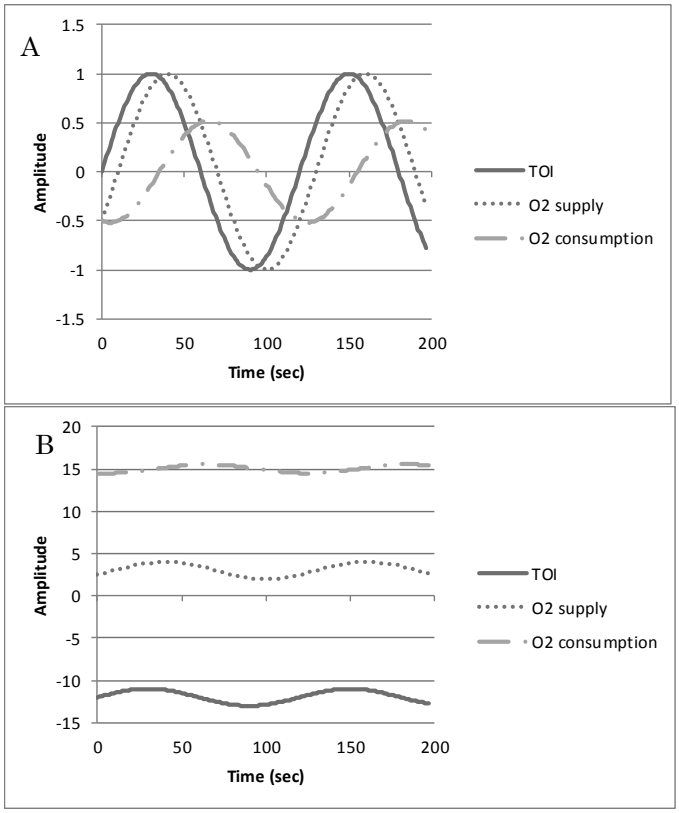

Figure 4

Explanation for tissue oxygen index (TOI) from oxygen consumption and oxygen supply. The model shows oscillation of oxygen consumption and oxygen supply with a time delay of 10 sec (A). The model also shows the effect of axis levels of oxygen consumption and oxygen supply on TOI (B).

the oxygen consumption in muscle is limited by oxygen transport system or the oxygen utilization system.

CONCLUSION

It is thought that the variation of TOI or its related substances in skeletal muscle (oscillation and level of the oscillation axis) is partly related to the variation of cardiac pumping, and the cardiac pump considerably affects oxygen uptake in the lung. Oscillation of TOI, HR, and $\dot{V}o_2$ is the basis of the entrainment phenomenon. It is thought that the level of the oscillation axis affects the level of each item. Oxygen consumption in skeletal muscle is not completely equivalent to oxygen intake in the lungs by the operation of cardiac pumping alone. The shortage is supplemented with a change in venous blood oxygen content. In the

supplementation of this deficiency, a time delay occurs.

Conflict of interest We declare no conflicts of interest.

APPENDIX: SIMPLE TOI MODEL

Aerobic energy metabolism in skeletal muscle oscillates by interaction of its biochemical substances. The oscillation is transmitted to the heart and lungs. It then recursively affects the oxygen dynamics in skeletal muscle as oscillation of oxygen supply. This idea is the basis of the model. The frequency of the oscillation is a reference value from the frequency of the re-synthesis process of creatine phosphate after exercise[2, 3] and the frequency of TOI [4, 5, 7]. In the present study, the wavelength was determined to be 2 minutes. Since oxygen supply is modeled as a cycle relationship from skeletal muscle, we also set the oxygen supply to the same wavelength as that of TOI. Since the TOI wavelength fluctuates by 1-2% (Fig. 2), the TOI amplitude was approximated to 2 in the present model.

It was assumed that the oxygen supply and TOI had a certain time delay (10 seconds) (A in Fig. 4). This comes from the following requirements. That is, oxygen consumption in skeletal muscle affects oscillation of the heart, and the influence reaches the lungs. As a result, the oxygen supply oscillates. This time difference is almost equal to zero because it is thought that the influence from the skeletal muscle to the heart is nervously propagated. Therefore, this time delay is calculated as the time delay from the heart to skeletal muscle due to blood circulation. When the delay time increases, the amplitude of oxygen consumption also increases. At the phase difference of 60 seconds, TOI amplitude becomes maximum.

TOI is assumed to be the difference between oxygen supply (O_2S) and oxygen consumption (O_2C). This is derived from the fact that TOI is conventionally determined by the balance between oxygen supply and oxygen consumption[21]. Also, if it is considered in an aquarium model, the following formula is easy to understand. That is, the amount of water flowing into the tank is O_2S and the amount of water flowing out is O_2C. Also, the water level or the amount of water in the aquarium is TOI.

$TOI = O_2S - O_2C.$

However, since the oscillation of TOI and O_2 supply can actually be determined, the above equation becomes as follows.

$O_2C = O_2S - TOI.$

If oxygen supply and TOI oscillate and there is a delay time between them, oxygen consumption oscillates as shown in Fig. 4 (A).

In this model, the case in which the axial level is increased by 15 for oxygen consumption and the oxygen level is increased by 3 was calculated (B in Fig. 4). In this case, TOI

decreases and oscillates. These numerical values are tentative. However, since the level of the axis of TOI actually decreases during exercise, it can be deduced that the change in the level of oxygen consumption is greater than the level of oxygen supply.

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骨格筋内の組織酸素指数と肺レベルの酸素摂取量との関係

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【要旨】 骨格筋レベルの酸素消費と肺レベルの酸素摂取との関係が，心臓ポンプ作用の介入によって確立されるかどうかを調べた。酸素摂取量（$\dot{V}o_2$）および心拍数（HR）は，3次元スパイン関数によって1秒値に変換された。近赤外分光法により，外側広筋から１秒ごとの組織酸素指数（TOI）を測定した。運動はピーク$\dot{V}o_2$の70％の強度で10秒間行った。その前後には，休憩10分と回復時間20分が設定された。試験中のすべての1秒値はローパスフィルタ（<0.05Hz）で処理されました。HRと$\dot{V}o_2$との間の相互相関の最大値は0.712±0.112であった。 TOIとHRとの間の最小相互相関値は，-0.398±0.225であった。骨格筋内のTOIまたはその関連物質の変動（振動軸および揺動軸のレベル）は，部分的に心臓ポンプ作用の変動に関連し，心臓ポンプ作用の変動は肺酸素摂取量の変動にかなり影響すると示唆された。

【キーワード】組織酸素指数，心拍数，酸素摂取量，相互相関，振動