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博士論文

**Increasing Cerebral Oxyhemoglobin by Ankle Exercise:  
An Attempt at Preventing Symptoms of Orthostatic Hypotension**

足関節運動による脳内酸素化ヘモグロビンの増加  
— 起立性低血圧を予防するための試み —

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**Increasing Cerebral Oxyhemoglobin by Ankle Exercise:  
An Attempt at Preventing Symptoms of Orthostatic Hypotension**

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# 和文概要

頻度や程度の差はあるが、多くの人が、しゃがんだ姿勢から急に立ち上がった場合などに、立ちくらみを経験している。この立ちくらみは、姿勢を変える時に、重力の影響を受けて循環血液の分布が変動することが原因で生じる。これは、起立性低血圧として、よく知られた症状である。起立時だけでなくベッド上での体位変換においてもこのような症状が生じる場合がある。特に、圧受容器反射の機能が低下している高齢者や、自律神経障害を伴う疾患（糖尿病、パーキンソン病など）の患者は、体位変換時に大幅な血圧低下を示すことがある。血圧の低下に付随した脳虚血の程度によっては、めまいやもうろう感、失神などが生じる場合もある。またこれらの症状は転倒の原因にもなることから、これに対処するための看護介入が求められている。

この起立性低血圧の症状を予防するための看護的な介入として、スクワットなどが有効だと報告されている。しかしこれらの方法は、主に長時間立位をとった後に起こる血圧低下への対処方法であり、体位変換直後に起こる症状の予防には適さない。体位変換直後の症状を予防するためには、体位変換の前から、事前に症状を予測し対応できるような介入が求められる。

下肢の筋は、筋ポンプとして循環動態の調節に重要な役割を担っている。足関節運動（背底屈運動）は、下肢の静脈血の流速を上げる効果的な方法であることが証明されている。この足関節運動を体位変換前に実施し、下肢の静脈血を押し出すことで静脈還流を増加できれば、体位変換後の脳循環の変動を軽減できる可能性がある。しかし、足関節運動が、脳循環にまで効果を示すかどうかは明らかにされていない。

この論文の目的は、足関節運動の脳循環への効果を検証することである。この目的を達成するために、第2章では、仰臥位で足関節運動を行い、前額部の酸素化ヘモグロビン濃度(OxyHb)の変化を確認した。第3章では、仰臥位で足関節運動を行った後に、実際に体位変換を実施し、運動の効果を検討した。

第2章では、17名の高齢女性が研究に参加した。参加者は、仰臥位で足関節の背底屈運動を1分間実施した。心拍数、血圧と前額部のOxyHbを測定した。運動の種類は、能動的と受動的運動の2条件であった。足関節運動は、能動的、受動的運動の両者ともに、前額部のOxyHbを有意に上昇させることが明らかになった ( $p < 0.05$ )。

第3章では、健康な成人と高齢者11名を対象に、3条件（能動的／受動的足関節運動および、コントロール）を比較した。参加者は、仰臥位で能動的、受動的な足関節運動を1分間実施した後、端座位に体位を変換された。体位変換はギャッチベッドを用い受動的に実施した。

加えてコントロールとして足関節運動を行わない場合も実施した。これらの条件で脈拍数、血圧、前額部の OxyHb を測定した。体位変換開始時から 90 秒間の OxyHb の平均値を比較したところ、受動的運動とコントロール（運動なし）の間に有意な差は確認されなかったが、能動的運動は、受動的運動およびコントロールよりも OxyHb が有意に高いことが確認された ( $p < 0.05$ )。この結果から、能動的な足関節運動は、体位変換を行った際の初期の OxyHb の低下を緩和する効果を持ちうることが示唆された。

本研究の結果を解釈する上でいくつかの限界がある。前額部の OxyHb が維持されたことと、起立性低血圧の症状が予防できることを同様に考えることはできない。足関節運動を実際の症状緩和に結び付けるためには、より効果的な運動の強さや運動の継続時間を検討すること、足関節運動を行った場合の症状の変化について確認するなど、さらなる研究が必要である。これらの限界はあるものの、本研究によって足関節運動（特に能動的運動）が起立性低血圧の症状緩和に効果があると考ええる一つの根拠を示すことができたと考えられる。

体位変換は、患者の活動を拡大することにつながる重要な看護介入である。一方で、体位変換によって循環血液の分布が変動することも事実である。体位変換によって引き起こされる循環動態の変動を懸念して、看護師は保守的な介入方法を選択する傾向があるとも考えられる。患者の体位の変換に関して、これまでの看護介入は、体位変換後の循環動態の変動に対応するか、あるいは、変動を起こすような体位変換を避ける、という内容に限られていた。足関節運動が看護介入法として確立されれば、より積極的に患者の活動を拡大できるような看護を展開することが可能になると考えられる。

# Abstract

Standing up quickly sometimes results in a transient lightheadedness. This is a common symptom for most people. The main cause of lightheadedness is the blood distribution changes induced by the gravity effect. A similar phenomenon sometimes occurs when nurses change a patient's posture, even if this is carried out on a bed. The cardiovascular system promptly adjusts the blood distribution; therefore, severe hemodynamic fluctuation is usually not observed. However, elderly people with lower baroreceptor sensitivity and patients with dysfunctions of the autonomic nervous system (e.g., diabetic mellitus, Parkinson's disease) have problems when they stand up. This phenomenon is known as "orthostatic hypotension (OH)." The OH is sometimes accompanied by symptoms such as dizziness, faintness and syncope, depending on the degree of cerebral hypoperfusion. Furthermore, these symptoms could cause falling. Thus nursing intervention is required to prevent OH.

To prevent this phenomenon, some physical counter-maneuvers such as squatting have been proposed as nursing interventions. However, these maneuvers address symptoms that occur after standing for a long time and do not seem to be effective in preventing the hypotension experienced in the early phase after postural change. Prior intervention is required to prevent the symptoms that occur immediately after postural change.

The skeletal muscle pump plays an important role in adjusting hemodynamics. Ankle exercise (i.e., ankle plantar flexion and dorsiflexion movements) has been proven to be an effective intervention to increase venous velocity. If ankle exercise performed in a supine position is proven to have the effect of maintaining cerebral hemodynamics, it can prevent the symptoms of the early phase after postural change. However, the role of ankle exercises in cerebral hemodynamics has been less well established.

The goal of this dissertation is to confirm the efficacy of ankle exercises for cerebral hemodynamics. To achieve this goal, the first study, with an experiment, was conducted to identify the effect of active and passive ankle exercises on the cerebral oxyhemoglobin (OxyHb) in a supine position (Chapter 2). Following the results of the first experiment, the

second experiment studied the effect of ankle exercises on postural changes (Chapter 3).

In the first study, discussed in Chapter 2, there were seventeen elderly women who participated. The participants repeated ankle plantar flexion and dorsiflexion movements for 60 s. Heart rate, blood pressure, and cerebral OxyHb levels were recorded in a supine position. Two types of exercises were used, active movement and passive movement. Both active and passive ankle exercises could increase cerebral OxyHb ( $p < 0.05$ ).

Eleven healthy adults and elderlies participated in the experiment in Chapter 3. Three conditions (active/passive ankle exercise, and control condition) were examined for each participant. The participants performed ankle exercise for 60 s before postural change. The postural change was conducted passively by using the electric motor of a hospital bed. Additionally, as a control condition, data was taken without ankle exercise. Pulse rate, blood pressure, and cerebral OxyHb levels were recorded in a supine position. No significant difference was observed between passive exercise and the control condition. Conversely, active ankle exercise demonstrated significantly higher cerebral OxyHb than passive exercise and the control during and after postural change ( $p < 0.05$ ). From the results in Chapter 3, active ankle exercise which was performed before postural change has the possibility of attenuating the initial changes in cerebral OxyHb.

There are some limitations to be observed when interpreting this study. The demonstration that there is an effect of maintaining cerebral OxyHb does not fully support the idea that such exercise will improve the symptoms of OH. Further studies on such aspects as changing the degree of the exercise, or its duration, and confirming the improvement of symptoms may answer this question. In spite of these limitations, the author believes that this study provides some evidence for considering that ankle exercise (especially active ankle exercise) can prevent symptoms of OH.

Postural change is an important nursing intervention for expanding the patient's mobilization. On the other hand, it is a fact that postural change has the possibility of inducing changes in blood distribution. Nurses may tend to avoid postural change when they foresee the likelihood of hemodynamic instability after postural change. If ankle exercises before postural change are validated as a nursing intervention, we can expect them to expand the

mobility of patients.

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## List of Abbreviations

ANOVA	Analysis of variance
BP	Blood pressure
CBF	Cerebral blood flow
CBF-V	Cerebral blood flow velocity
CBV	Cerebral blood volume
CO	Cardiac output
CT	Computed tomography
DBP	Diastolic blood pressure
fNIRS	Functional near infrared spectroscopy
HHb	Deoxyhemoglobin concentration
HR	Heart rate
MAP	Mean arterial blood pressure
NIRS	Near infrared spectroscopy
OH	Orthostatic hypotension
OxyHb	Oxyhemoglobin concentration
PET	Positron emission tomography
PR	Pulse rate
rCBF	Regional cerebral blood flows
rOEF	Regional oxygen extraction fraction
SBP	Systolic blood pressure
SPECT	Single photon emission computed tomography
SE	Standard error
SV	Stroke volume
TCD	Transcranial Doppler
tHb	Total hemoglobin
TPR	Total peripheral resistance
Xe-CT	Xenon 133 computed tomography
$\eta G^2$	Generalized eta squared

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# **Chapter 1**

## **Backgrounds**

## **1.1 Physiological Background**

### *1.1.1 Cardiovascular responses to postural change*

Human beings acquired upright posture and bipedalism in the process of evolution. Upright posture and bipedalism brought great advantages to humans because it allowed them to acquire large brains and to use their upper extremities freely. However, having evolved in the limited environment of the planet Earth, humans sometimes experienced a trade-off when a change took place in their physical makeup.

To develop bipedalism from quadrupedalism, the human skeleton had to change dramatically. Quadrupedalism puts the center of gravity at or near the point that is central to the four legs (near the center of the torso), but it is located between two legs with bipedalism. The human pelvis changed its shape to support the abdominal viscera and to maintain balance during bipedal locomotion. In exchange, the size of the human birth canal was reduced, while the fetus has a big brain (Lovejoy, 1988). Childbirth in humans is very difficult compared to that of other animals. A human is prone to lumbar pain, hernias, hemorrhoids and varices; these diseases are rarely observed in the quadrupedal animals, including, of course, the other primates that are our relatives. These diseases are attributed to maintaining an upright posture against the pull of gravity.

The human cardiovascular system also faced the challenges of regulating the circulation during various movements. Compared with apes, humans have larger brains, which require more blood. The human brain accounts for only 2% of the body mass, but it needs about 14% of the resting cardiac outputs. In addition, the grey matter has a very high rate of oxidative metabolism (about 7 ml O<sub>2</sub>/min/100g), which causes a loss of consciousness after a few seconds of cerebral ischemia (Levick, 2010, p.294). Even worse, the human brain is located above the heart; considering the hydrostatic aspect, this is a very disadvantageous position for the brain. The human cardiovascular system has to pump blood upward to sustain this expensive organ. Of course, there are many enormous animals that have longer necks than do humans: giraffes, for example. The brain of a giraffe is about 2 m above its heart. Therefore, giraffes have a unique problem in the adjustment of circulation. They have powerful hearts and very high blood pressure. Moreover, they have extremely muscular

arterioles and very tight skin and fascia in their extremities (Hargens, Millard, Pettersson, & Johansen, 1987; Rowell, 1993, pp. 1–36). These physical characteristics maintain a giraffe's cerebral circulation over a distance greater than the 2 m that separate the heart and brain. However, the human body is completely different from that of a giraffe, so the human cardiovascular system is forced to use other strategies to adjust their circulation.

The principal mechanism underlying the adjustment for movement and postural changes is a system of adaptation to gravity. Thus, the postural effect on circulation has more impact when the movement is greater in a vertical direction. When a human being moves from a supine to upright posture, blood is immediately shifted from the thorax to the lower part of the body. The amount of blood thus affected is about 500 to 700 ml (8 to 10 ml/kg) (Smith, & Kampine, 1990, p. 97). The walls of the veins contain little elastic tissue, creating a large capacity for holding blood. Humans have large legs compared to those of other animals; this allows the shifted blood to pool in the veins of the lower limbs. This blood pooling in the veins leads reduction in venous return to the heart. As a result, the cardiac output decreases (Frank-Starling mechanism), and subsequently, the mean arterial blood pressure (MAP) falls. If there is an extreme decrease in MAP, an adequate cerebral blood pressure cannot be maintained, causing syncope (Costanzo, 2014, pp. 174–184).

When people stand up, severe hypotension usually does not occur because an immediately compensatory response works to adjust the shift in blood volume. The baroreceptor reflex plays an important role in these adjustments. The baroreceptors are mechanoreceptors located in the carotid sinus. The baroreceptor senses a drop in the MAP by the degree of stretching in the blood vessel walls and sends signals to the medullary vasomotor center. The vasomotor center directs an increase in sympathetic activity to the heart and blood vessels. Simultaneously, orders from the vasomotor center decrease parasympathetic activity to the heart. As a result, the heart rate (HR), total peripheral resistance (TPR) and venoconstriction are increased; then the MAP goes back to normal (Pocock, & Richards, 2006, pp. 262–310). This prompt response by the baroreceptor works on the circulation to facilitate dynamic postural changes in humans.

The skeletal muscle pump is another mechanism that acts quickly to adjust the

circulation in humans. In upright humans, the skeletal muscles of the lower extremities soon begin rhythmic cycles of reflex contraction and relaxation. This muscle contraction and relaxation are due to the unconscious swaying motion of the body while standing. Rhythmic cycles of muscle contraction help squeeze the pooled blood from the lower extremities, aiding it in returning to the heart so that the blood pressure (BP) is maintained at an adequate level (Smith, & Kampine, 1990, pp. 99–107). Because of this compensatory mechanism, the leg muscles are considered to be a “second heart.”

### *1.1.2 Hypotension is induced by postural change*

The hemodynamics changes associated with changes in posture are a very natural response. Normally, a postural change does not have a serious effect on blood pressure in healthy people. However, some people have symptoms of hypotension such as dizziness, syncope, and falling, when they change their posture because their cardiovascular system cannot act immediately to maintain the BP. These symptoms are often observed when such people stand up; therefore, this condition is known as “orthostatic hypotension (OH).” The consensus definition of OH is a reduction of systolic blood pressure (SBP) of at least 20 mmHg or a reduction of diastolic blood pressure (DBP) of at least 10 mmHg within 3 min of erect standing (The Consensus Committee of the American Autonomic Society and the American Academy of Neurology, 1996). OH can be divided into subclasses. Initial OH occurs immediately after standing (within 30s) and many healthy people are familiar with the symptoms of initial OH (Wieling, Krediet, van Dijk, Linzer, & Tschakovsky, 2007). Delayed OH produces symptoms within 3 to 30 min of standing (Gibbons, & Freeman, 2006; Streeten, & Anderson, 1992). As for a hospital situation, it is considered that initial OH is a situation more frequently encountered by nurses because patients rarely maintain a standing posture for 30min.

OH is observed in all age groups. However, the prevalence of OH increases with age (Lipsitz, 1989; Masaki, et al., 1998) because baroreceptor sensitivity decreases with aging (Rutan, et al., 1992). The prevalence of OH in the community-dwelling elderly is reported to be 6 to 34 %, depending on the methodology used and differences in population (Hiitola,



Enlund, Kettunen, Sulkava, & Hartikainen, 2009; Kobayashi, & Yamada, 2012; Luukinen, Koski, Laippala, & Kivelä, 1999; Matsubayashi, et al., 1997). In hospitalized elderly people, OH is a relatively common condition. The prevalence is over 50% in patients attending geriatric clinics (Poon, & Braun, 2005) and those admitted to acute care hospitals (Gorelik, et al., 2005; Shibao, Grijalva, Raj, Biaggioni, & Griffin, 2007; Weiss, Grossman, Belosoesky, & Grinblat, 2002; Vloet, Pel-Little, Jansen, & Jansen, 2005).

OH may result from neurogenic and nonneurogenic conditions. Diabetes mellitus (Van Hateren, et al., 2012; Wu, Yang, Lu, Wu, & Chang, 2008) and Parkinson's disease (Allcock, Ulliyart, Kenny, & Burn, 2004; Senard, et al., 1997; Velseboer, de Haan, Wieling, Goldstein, & de Bie, 2011) are well-known causes of neurogenic OH. Nonneurogenic factors, such as cardiac impairment, reduced intravascular volume and vasodilation are related to OH. Some drugs may cause OH. Antihypertensives, diuretics and vasodilators are recognized as causes of OH (Hajjar, 2005; Kamaruzzaman, Watt, Carson, & Ebrahim, 2010). There is a significant relationship between OH and the number of drugs being taken (Poon, & Braun, 2005). Especially for hospitalized patients, bed rest is one of the problems associated with OH. Within 24 to 48 hours, bed rest results in a decrease in plasma volume (Creditor, 1993; Fortney, Hyatt, Davis, & Vogel, 1991; Olson, 1967/1990). Bed rest can also lead to baroreceptor dysfunction. The signs of orthostatic intolerance begin to appear within 3 to 4 days after bed rest (Convertino, Hung, Goldwater, & DeBusk, 1982; Greenleaf, & Kozlowski, 1982). These physical complications related to bed rest can cause OH by themselves. Baroreceptor sensitivity decreases with aging; in addition, the elderly usually have multiple medical problems and take several drugs. Because of these factors, OH in the elderly population tends to have multiple causes. Some studies have been reported that in the elderly, OH is associated with difficulty walking (Rutan, et al., 1992), cognitive impairment (Mehrabian, et al., 2010), and falling (Allan, Ballard, Rowan, & Kenny, 2009; Gangavati, et al., 2011; Ooi, Hossain, & Lipsitz, 2000; Rutan, et al., 1992). Preventing and treating OH is one of the important challenges in improving the quality of life for the elderly.

## **1.2 Postural Change as Nursing Intervention**

### *1.2.1 Nursing problems in postural changes*

At the end of the day, humans go to their beds to rest. Rest and sleep are essential functions. For patients, being in a supine position on a bed has some benefits because it requires less oxygen consumption than other positions (e.g., a sitting position) (Jones, & Dean, 2004). The benefits of rest were emphasized as treatment in the 19th century. Bed rest was strongly recommended for diseases such as myocardial infarction and after orthopedic surgery (Allen, Glasziou, & Del Mar, 1999). However, it is very unnatural for humans to continue bed rest for a long time because usually they lie down only while they are asleep. Prolonged bed rest sometimes does severe harm. Many previous studies have revealed negative effects of bed rest and recommend the early initiation of patient mobilization (Perme, & Chandrashekar, 2009; Stiller, & Phillips, 2003; Timmerman, 2007).

Bed rest leads to many complications such as pneumonia (Drakulovic, et al., 1999), pressure ulcers (Lahmann, Kottner, Dassen, & Tannen, 2012), deep venous thrombosis (Cook, et al., 2000), and joint contracture (Clavet, Hébert, Fergusson, Doucette, & Trudel, 2008). When patients cannot move by themselves or their movements are restricted by some medical problem and treatment, nurses regularly change their patients' posture. However, as discussed in an earlier part of this chapter, carrying out postural change for patients means that the patient's blood is more or less shifted by the effect of gravity, even if the body does not move much. Therefore postural changes in patients can result in potential adverse hemodynamic effects, such as reduced cardiac output, hypotension, and arrhythmia (Evans, 1994).

Leaving the hospital bed and standing up on his/her own feet is the first step in a patient's return to daily life. On the other hand, difficulties can easily be predicted when nurses promote early mobilization in critically ill and elderly patients because those patients sometimes experience hemodynamic instability that includes OH (Bundgaard-Nielsen, et al., 2009; Feldstein, & Weder, 2012; Jans, Bundgaard-Nielsen, Solgaard, Johansson, & Kehlet, 2012). It is reported that a patient's hemodynamics instability can complicate a nurse's attempts at early mobilization that includes postural change (Garzon-serrano et al., 2011; Haines, Skinner, & Berney, 2013). Thus, nurses observe the patient's BP carefully when they

carry out postural change, especially the first one (Nagaya, Fujimoto, & Kobayashi, 2014). Postural change is a basic nursing care, but that does not mean it is easy. Nurses are required to have the ability to assess whether the patient's circulatory system can tolerate a change in posture. In addition, postural change can become more effective means of care if a way is proposed to actively promote an adjustment in hemodynamics in order to expand mobilization.

### *1.2.2 Treatments for orthostatic hypotension*

OH can be induced by a variety of factors, sometimes by multiple ones at the same time. Therefore, some different approaches have been proposed for managing each factor. As a pharmacological approach, the European Federation of Neurological Societies recommends fludrocortisone and midodrine to manage OH (Moya, et al., 2009). In Japan, the guidelines for the diagnosis and management of syncope recommend fludrocortisone, erythropoietin, midodrine hydrochloride, and etilefrine hydrochloride (Inoue, et al., 2012). The effectiveness of pharmacological and nonpharmacological approaches to OH has been confirmed through previous studies. The important and difficult issue in OH symptom management is how to treat the condition without excessive supine hypertension. Therefore, a nonpharmacological approach, which would have no adverse effects, is considered to be a better first line defense.

If OH is primarily caused by hypovolemia, then oral giving salt and adequate amounts of water is a safe approach because it can expand plasma volume (El-Sayed, & Hainsworth, 1996). In Japan, if patients do not have hypertension, 10 g of salt and 2 to 3 L of water per day are recommended (Inoue, et al., 2012).

For patients with autonomic failure, drinking about 500 ml of water at room temperature improves their condition in less than 5 min (Shannon et al., 2002). Drinking water can raise sympathetic activity and increase the BP. After drinking 500ml of water, the BP increases and this effect is sustained for more than 60 min (Jordan, Shannon, Grogan, Biaggioni, & Robertson, 1999; Jordan et al., 2000).

Some nonpharmacological approaches work to return pooling blood from the legs to the heart. Compression garments or tightly fitting body stockings are useful for treating OH

because they can reduce the venous capacitance bed (Podoleanu, & Maggi, 2006). However, it is difficult for elderly patients to put on tightly fitting stockings by themselves. In addition, patients have to wear the stockings all the time if they want to reduce the symptoms of OH.

Leg-crossing and squatting are representative examples of physical counter maneuvers (Figure 1.1.). Leg-crossing can contribute to the mechanical compression of veins in the lower extremities by stimulating the muscles. This stimulus reduces venous capacity and increases the TPR (Ten Harkel, van Lieshout, & Wieling, 1994). Consequently, the increased venous return raises the mean blood pressure to a high enough level to maintain cerebral blood flow (CBF) (Van Lieshout, ten Harkel, & Wieling, 1992). Squatting has the same effect as leg-crossing. To bend the legs can increase muscle tone, which promotes venous return. In addition, in a squat posture, the distance between the legs and the heart is shorter than when upright posture: therefore, it is considered a more advantageous posture for the heart when we consider the hydrostatic involved. Leg-crossing and squatting are easy and economical approaches because they do not need special aids like compression garments or salt tablets, or even a glass of water. However, if patients want to prevent orthostatic symptoms they have to perform these maneuvers before the BP falls. It is difficult for elderly patients to always do these maneuvers with the appropriate timing, especially in cases in which OH occurs immediately after a patient stands up.

Ankle exercises in the supine position have been proven to be an effective intervention to increase venous velocity by squeezing accumulated blood from the lower part of the body (Kwon, Jung, Kim, Cho, & Yi, 2003; Sochart, & Hardinge, 1999; Stein, et al., 2009). Studies have been conducted on ankle exercises for preventing deep vein thrombosis. Ankle exercises are simple to execute, even for elderly patients. Therefore, if this intervention is proven to be effective in preventing postural change-induced hypotension, particularly OH, it could be particularly helpful for elderly people.



**Figure 1.1. Examples of physical counter maneuvers**

*The pictures show examples of physical counter maneuvers recommended to patients with orthostatic hypotension. Physical counter maneuvers using muscle contractions of lower limbs. These maneuvers can help maintain blood pressure to compensate for continued orthostatic stress.*

### **1.3 Methodological Background**

#### *1.3.1 Measurement of cerebral hemodynamics*

The primary function of the cardiovascular system is to carry blood to cells throughout the body. It transports nutrients and oxygen to the cells and takes away waste products. The most important destination for the blood is the brain because it is very susceptible to hypoxemia. It is no wonder that researchers' interests are directed toward cerebral hemodynamic changes when they discuss how postural change effects cardiovascular system.

Several devices have been developed to estimate cerebral hemodynamics. The main techniques are positron emission tomography (PET), single photon emission computed tomography (SPECT), Xenon 133 computed tomography (Xe-CT), transcranial Doppler (TCD), and near infrared spectroscopy (NIRS) (Dhar, & Diringer, 2014, pp. 20–36). PET can provide information on the cerebral blood flow (CBF), cerebral blood volume (CBV),

regional oxygen extraction fraction (rOEF), and glucose metabolism. This information can be obtained by injecting a radioisotope into the body (Buzung, 2011, pp. 311–342). SPECT can also measure the CBF. Like PET, SPECT uses radioactive tracer materials and scanners. Nonradioactive Xenon is used as a contrast material to measure the CBF for Xe-CT. Xenon gas dissolves in blood and can pass through the blood-brain barrier. The concentration of Xenon in the brain is quantitated and visualized by computed tomography (CT) (Wintermark, et al., 2005). These three techniques can be used to detect and provide significant information about diseases, such as cerebrovascular disease, Alzheimer's disease, Parkinson's disease, and brain tumors. However, the physical burden on the patients is not negligible, as specific tracers are needed to measure the CBF. In addition, patients must lie completely still while the tracers circulate throughout the body and also during the subsequent scan. Therefore, these techniques are not suitable for measuring the CBF changes of postural change. When the focus is placed on studies of postural change and OH, there are only a few devices that researchers can use: TCD and NIRS for example.

TCD and NIRS are used to measure different aspect of cerebral hemodynamics. TCD uses 2MHz ultrasound to insonate the basal cerebral arteries (Aaslid, Markwalder, & Nornes, 1982). The TCD method measures changes in the velocity of the cerebral blood flow (CBF-V) and vessel pulsatility. NIRS, on the other hand, measures changes in cerebral oxygenation in the cerebral cortical tissue, using near infrared light. Although these techniques are different, previous studies have revealed that both CBF-V and cerebral oxygenation showed similar changes with orthostatic stress (Kim, Bogert, Immink, Harms, Colier, & van Lieshout, 2011; Krakow, Ries, Daffertshofer, & Hennerici, 2000; Madsen, et al., 1998). From these studies, it can be concluded that both techniques are suitable for studies of postural change. However, TCD requires advanced techniques to create accurate images. In addition, insonation of the middle cerebral artery is inadequate or impossible in 5–20% of all patients (White, et al., 2001). These obstacles sometimes limit the usefulness of TCD for researchers. It is considered that NIRS may be the better technique for measuring the cerebral hemodynamics associated with postural changes.

### 1.3.2 Principles of near infrared spectroscopy

NIRS is one of the major continuous and noninvasive methods available for measuring cerebral hemodynamics (Figure 1.2.). In 1977, Jöbsis (1977) reported that in vivo hemoglobin can be detected by using near infrared. Visible light (wavelength 390–700 nm) does not penetrate biological tissue. However, near infrared light (wavelength 700–1,000 nm) can penetrate biological tissue because biological tissue has an optical window for specific wavelengths. Near infrared light is absorbed by chromophores (oxyhemoglobin, deoxyhemoglobin and myoglobin). The absorption spectra of oxyhemoglobin (OxyHb) and deoxyhemoglobin (HHb) are different. These two absorption spectra cross at a wavelength of about 800 nm (Figure 1.3.). The optical intensity of near infrared that penetrates biological tissue changes with the oxygen status of hemoglobin. NIRS measures the optical intensity changes between emission and detection probes. By calculating this change in optical intensity, NIRS shows us the change in concentration of OxyHb and HHb. (Yamashita, & Niwayama. 2013, pp. 1–19). The relationship between total hemoglobin (tHb) measured by NIRS and CBF measured by PET revealed a significant correlation when NIRS assumed a penetration depth of 0.9 cm into the brain (Hock, et.al., 1997). According to this result, NIRS is considered capable of measuring phenomenon occurring in the cerebral cortex when the optical probes are attached to the scalp.

The application of NIRS has been expanded to various fields. Simultaneously, there have been some discussions about how researchers interpret the information from NIRS. Depending on the researchers' interests, information from NIRS has been widely applied to explain various parameters such as CBF, cerebral oxygenation, and cerebral function.

In infants, the data obtained by NIRS showed a significant correlation with CBF as determined by <sup>133</sup> Xenon clearance (Bucher, Edwards, Lipp, & Duc, 1993). In healthy subjects, OxyHb and tHb measured by NIRS are correlated with changes in regional cerebral blood flow (rCBF) detected by PET (Hoshi, & Tamura, 1993). These results have led to NIRS' being considered an acceptable monitor of CBF.

Doctors have been interested in using NIRS in clinical setting. Oxygen exchange in the brain is essential for patients receiving intensive care and/or surgery; therefore, NIRS has

been used as a helpful real time monitor to observe the cerebral oxygenation (Talpahewa, Ascione, Angelini, & Lovell, 2003). NIRS is widely used to a monitor of cerebral oxygenation from newborns to adults (Munro, Walker, & Barfield, 2004; Wyatt, 1993; Zweifel, et al., 2010).

NIRS also has been used as a method of measuring the brain responses associated with various stimuli (Tanida, Sakatani, Takano, & Tagai, 2004; Tsunetsugu, Miyazaki, & Sato, 2005; Tsunetsugu, Miyazaki, & Sato, 2006). Putting probes on the surface of the skull, NIRS measures the concentration changes in OxyHb and HHb that are evoked by nervous activities. These signals can be used to interpret the cerebral functions of each area of the brain. The development of functional NIRS (fNIRS) has allowed researchers to detect activities of the whole brain noninvasively. fNIRS has been used to understand human cerebral function by giving specific tasks to the subjects (e.g. doing arithmetic, speaking, driving) (Dieler, Tupak, & Fallgatter, 2012; Tanida, Sakatani, Takano, & Tagai, 2004; Walter, et al., 2001).

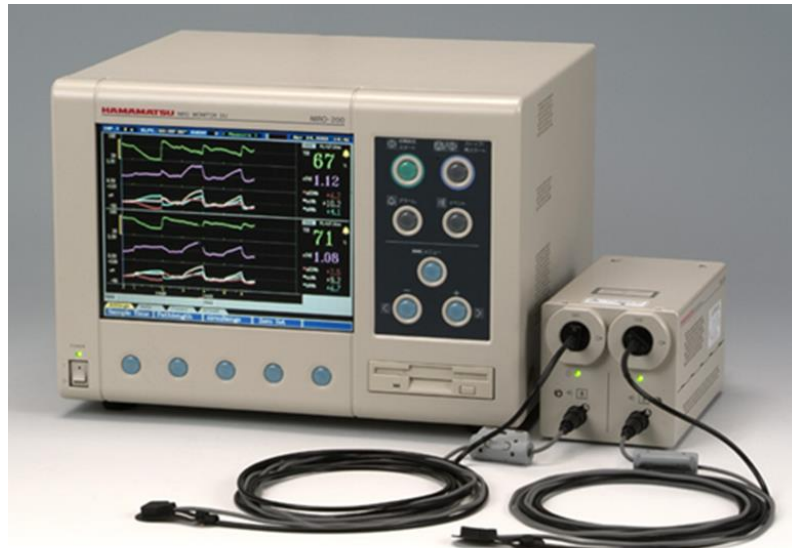
Applications of NIRS are not confined to the task of estimating the brain condition. NIRS allows the measurement of changes in the concentration of OxyHb and HHb where an oxygen transfer to tissues takes place within the reach of the near infrared. NIRS allows taking measurements of a natural condition because fiber optics is well-suited to any posture or movement. These strong advantages of NIRS have been utilized in various types of research on the human body (Truijen, et al., 2012).

NIRS is also used in studies of the effect of orthostatic stress on hemodynamic changes. Previous studies have shown that orthostatic stress causes a significant reduction in frontal cortical oxygenation in patients with autonomic failure (Hunt, et al., 2006) and healthy elderly people (Edlow, et al., 2010; Mehagnoul-Schipper, Vloet, Colier, Hoefnagels, & Jansen, et al., 2000; Mehagnoul-Schipper, Colier, & Jansen, 2001). Measuring the cerebral hemodynamics of children is relatively easy with NIRS. Several studies have estimated orthostatic effects on the cerebral hemodynamics of children who have orthostatic dysregulation (Kim, et al., 2009; Tanaka, Matsushima, Tamai, & Kajimoto, 2002).

In this way, NIRS is a very useful apparatus for measuring the cerebral oxygenation changes related with postural changes. However, it has some limitations, as do other



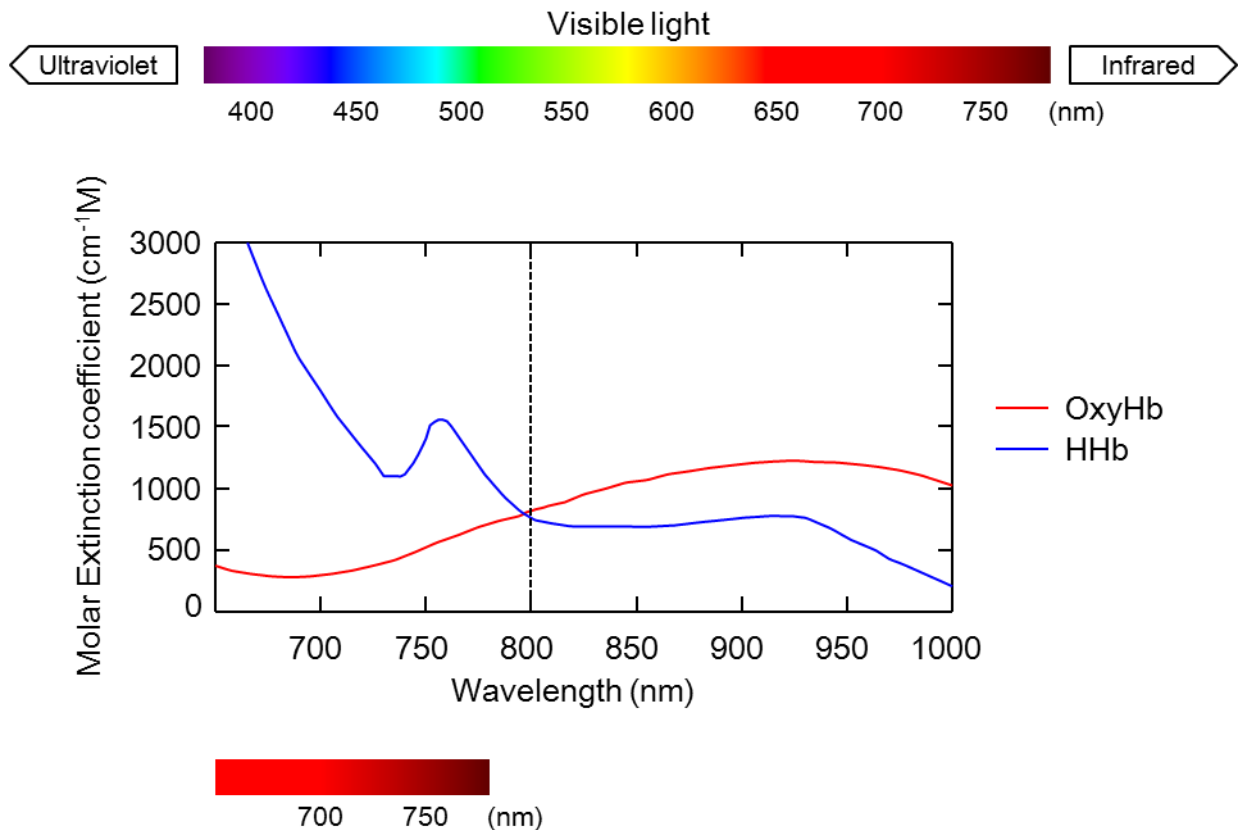
techniques. The data provided by NIRS have to do with changes in concentration. NIRS displays the divergence of values from the point that researchers have set to zero. In other words, the data obtained from NIRS depend on the time when zero is set. If this limitation is not well understood, the analysis and discussion of research can become misleading.



**Figure 1.2. Near infrared spectroscopy**

**(NIRO-200; Hamamatsu Photonics, Shizuoka, Japan)**

*The figure shows an example of near infrared spectroscopy (NIRS). The basic NIRS has one set of optodes (emission and detection). By increasing the number of optodes, NIRS can measure the values of different body regions simultaneously. The optode is attached to human body with double-stick tape. NIRO-200 is dual optods NIRS. The picture is NIRO-200 which is manufactured by Hamamatsu photonics.*



**Figure 1.3. Absorption spectra of oxyhemoglobin and deoxyhemoglobin**

*This figure was drawn using the data which were taken from on the Oregon medical Laser Center website:*

*(<http://omlc.ogi.edu/spectra/hemoglobin/summary.html>).*

*The figure shows the absorption spectra of oxyhemoglobin (OxyHb) and deoxyhemoglobin (HHb) in the near infrared region of the spectrum. The wavelength of visible light is from about 390 to 700 nm. Light with wavelengths shorter than visible light (but longer than X-ray) is ultraviolet. Infrared has a longer wavelength than visible light. OxyHb and HHb have different absorption spectra that cross at about 800 nm. This wavelength region falls within near infrared portion of the spectrum. Therefore, we can use the near infrared to measure the oxygenation level of human body because it can detect the differences between OxyHb and HHb.*

## **1.4 Aims of This Dissertation**

Previous studies have revealed that physical counter-maneuvers can help to maintain blood pressure by increasing venous return. Physical counter-maneuvers are easy approaches for various patients. However, these maneuvers do not seem to be effective in preventing the hypotension that occurs in the early phase after postural change. There are some patients who experienced symptoms immediately after postural change. Nurses sometimes face and have to treat these situations. Ankle plantar flexion and dorsiflexion movements have been proven to be an effective intervention to increase venous velocity. However, the question has remained unanswered as to whether this simple exercise can attenuate the impact of postural change on cerebral hemodynamics. If ankle exercise is confirmed as having an effect similar to physical counter-maneuvers, this exercise may be able to contribute to nursing. The main purpose of this dissertation is to confirm the efficacy of ankle exercise for cerebral oxygenation.

## **1.5 Overview of This Dissertation**

The dissertation consists of four chapters. This chapter is an overview of the current status of knowledge regarding physiological responses to postural changes, nursing interventions or treatments, and methodological backgrounds.

Following this introductory chapter, the relationship between ankle exercises and cerebral oxygenation in the supine position is studied in Chapter 2. Both active and passive ankle exercises increased cerebral blood oxygenation in the supine position.

In Chapter 3, the evaluation of the efficacy of ankle exercises is focused on the cerebral oxygenation changes induced by postural changes. Active ankle exercise resulted in significantly higher cerebral OxyHb than passive ankle exercise and the control condition during and after postural change.

In the final chapter, Chapter 4, the findings of Chapter 2 and 3 are discussed together. The strengths and limitations of this dissertation are mentioned. The contributions of this dissertation to nursing and suggestions for the direction of further research are described in Chapter 4.

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## **Chapter 2**

### **Ankle Exercise Increases Cerebral Blood Oxygenation in the Elderly**

## **2.1 Introduction**

It has been reported that several non-pharmacological approaches can prevent orthostatic hypotension (OH) because it promotes venous return from legs to the heart. However, some approaches, such as leg-crossing or squatting, are not easy for elderly people to perform immediately, when they expect symptoms to occur. Moreover, these maneuvers must be performed in the correct way. For example, intentional muscular tonus is needed for leg-crossing; it does not work by simply the legs. In addition, the main targets of these maneuvers are symptoms seen during standing; therefore, it seems that they are not suitable for the early phase of postural change.

Active ankle exercises have been proven to be an effective intervention to increase venous velocity by squeezing accumulated blood from the lower part of the body (Kwon, Jung, Kim, Cho, & Yi, 2003; Sochart, & Hardinge, 1999; Stein et al., 2009). Ankle exercises are simple to execute, even for elderly patients. Therefore, if this exercise is proven to be effective in maintaining cerebral hemodynamics, it can be presumed that it may develop into a new intervention for preventing the symptoms related to postural changes. In addition, if the beneficial effect of passive ankle exercise can be demonstrated, it can be useful for immobilized patients because nurses will be able to enhance cerebral hemodynamics as a result of passive exercise. However, little attention has been given to the effects of active/passive ankle exercises on changes in cerebral oxygenation.

The aim of Chapter 2 is to reveal whether cerebral oxygenation is increased by active or passive ankle exercise.

## **2.2 Methods**

### **2.2.1 Participants**

Community-dwelling elderly volunteers based on the following criteria were recruited: (i) age 65 years and older and (ii) absence of cardiac arrhythmias and/or impaired motor function. They voluntarily chose to participate in this study; therefore, there were no participants who refused the experiments. The study consisted of 17 elderly women, aged 69 to 83 years (74 years on average), living in the community. Their mean height, weight, and

body mass index were  $150.2 \pm 4.3$  cm,  $52.9 \pm 5.7$  kg, and  $23.4 \pm 2.2$  kg/m<sup>2</sup>, respectively. The clinical characteristics of participants are presented in Table 2.1. Seven participants were hypertensive and 4 had diabetes mellitus. Data were gathered from the participants' own reports based on physician diagnoses. Data on antihypertensive medications were taken from the notebook that recorded each participant's medication history. Prior to the study, the participants were instructed to abstain from alcohol for 12 hours, not to eat a meal within 90 min of testing, and to get enough sleep. Participants with cardiac arrhythmias and/or impaired motor function were excluded.

**Table 2.1. Characteristics of 17 participants**

	n
Hypertension	7
Antihypertensive medication use:	10
Angiotensin converting enzyme inhibitors	4
Angiotensin receptor blockers	1
Beta blockers	1
Calcium channel blockers	6
Diuretics	1
Cardiovascular disease	2
Diabetes mellitus	4

*The number of medicines is illustrated as the total number.*

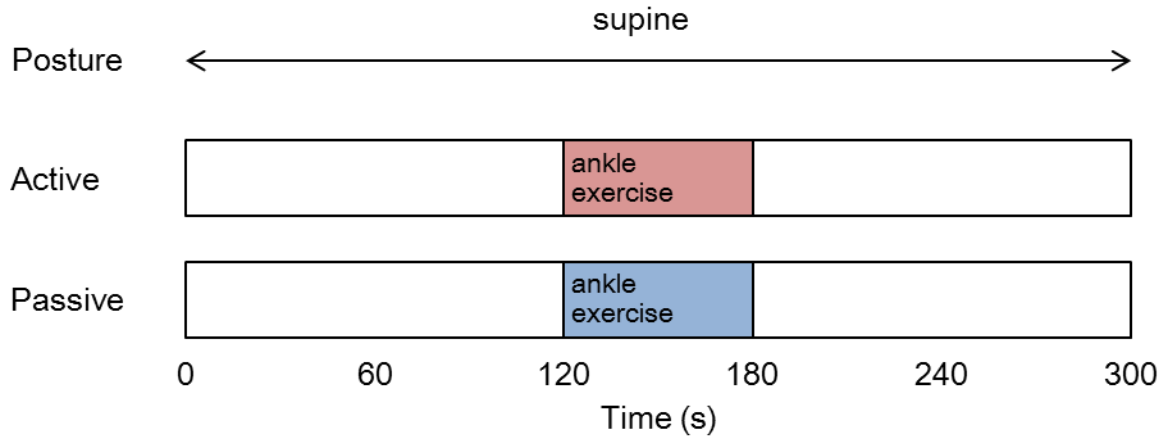
*Some of the antihypertensive medications are overlapped in individual participant.*

### 2.2.2 Experimental procedures

The experiments were conducted from November to December 2012. To maintain stable environmental conditions, the experiments were conducted in a climatic chamber. The room temperature was maintained at 25°C with 50% relative humidity. Before the

measurements, the experimental protocols were explained in detail to the participants. Before the measurements, the experimental protocols were explained in detail to the participants. In addition, the participants practiced the ankle exercises with the researcher.

Figure 2.1. shows the experimental procedures. After a 120 s rest in the supine position, each participant performed active or passive ankle exercises. For active ankle exercise, the participants alternately performed plantar flexion and dorsiflexion movements of the ankle joint for 60 s. For passive ankle exercise, the researcher moved the participant's ankle in a manner similar to that described for active exercise. The pace of ankle movements was 60 times/min for both active and passive exercises. The manner of exercise was determined by referring to previous studies (McNally, Cooke, & Mollan, 1997; Stein et al. 2009). As for the duration of exercise, MacNally et al. reported that their participants could not perform active ankle exercise for longer than 120 s because of fatigue or discomfort. They also revealed that 60 s of active exercise produced a significant increase in venous outflow (McNally, Cooke, & Mollan, 1997). Based on their result, 60 s of ankle exercise was thought reasonable and simple to apply as a nursing intervention. The participants were given oral instructions by researcher to start/stop the exercise. To control the experimental conditions, the researcher kept silent during the measurements, except for giving start/stop signals. After the exercise, the participants rested for 120 s. The aim of Chapter 2 was to estimate the early changes in cerebral OxyHb after ankle exercise. Therefore, the measurement periods were set after ankle exercise to 120 s. Throughout the experiments, including the exercise period, the participants lay supine on a bed. Each participant was evaluated under two experimental conditions (active/passive ankle exercise). To avoid carryover effect, the order of the conditions was varied in a balanced manner for the different participants.



**Figure 2.1. Schematic representation of the experimental protocol (Chapter 2)**

*The ankle exercises began at 120 s. The physiological responses were monitored throughout the experiment.*

### 2.2.3 Measuring physiological responses

To estimate cerebral hemodynamics, continuous changes in the oxyhemoglobin (OxyHb) were measured. The recent development of near infrared spectroscopy (NIRS) has enabled us to continuously estimate cerebral blood oxygenation. OxyHb was measured by NIRS (NIRO-120; Hamamatsu Photonics, Shizuoka, Japan) at a sampling rate of 2 Hz. OxyHb is expressed in micromolar ( $\mu\text{M}$ ). An optode was placed on the left side of the participant's forehead during the experiment. The left side of forehead was selected as the measurement region because previous studies using NIRS did not show any difference between the right and left forehead during moderate exercise (Subudhi, Miramon, Granger, & Roach, 2009). Prior to measurement, the OxyHb of each subject was recorded for 180 s to obtain a baseline value.

Heart rate (HR) and systolic and diastolic blood pressures (SBP and DBP, respectively) were monitored by BP-608 Evolution II (Omron Colin, Tokyo, Japan), which continuously captured these cardiovascular signals. BP-608 Evolution II can measure beat-by-beat BP noninvasively, using tonometry methods. The principle of tonometry is based on the compressing and partial flattening of a superficial artery against bone. For that reason, the radial arteries usually are selected as target vessels because they have the radius bone just below them. The pressure transducer is placed above the radial artery and supplies pressure to

partially flatten the artery. In this way circumferential pressures can be translated into blood pressure values in terms of blood pressure by the transducer (Salvi, 2012, p. 110; Weiss, Spahn, Rahmig, Rohling, & Pasch, 1996).

The mean arterial blood pressure (MAP) was calculated by adding one-third of the pulse pressure to DBP. HR and MAP recordings were linearly interpolated into 2-Hz equidistant signals to synchronize with the NIRS recording.

#### 2.2.4 *Statistical analysis*

The physiological signals (HR, MAP, and OxyHb) of the 17 participants were assembled to indicate an average continuous response to the exercises. Moreover, the signals before and after exercise were individually averaged for 60 s for two-way repeated measures analysis of variance (ANOVA). Hereinafter, the factor related to the type of exercise (active or passive) is expressed as the TYPE factor and the factor related to time (before or after) is expressed as the TIME factor. The statistical significance was set at  $p < 0.05$ . Generalized eta squared ( $\eta G^2$ ) values were presented as the effect size of each factor. As  $\eta G^2$  values can be interpreted in the same manner as  $\eta^2$  values,  $\eta G^2$  values of 0.01, 0.059, and 0.138 were interpreted as small, medium, and large effects, respectively (Cohen, 1998). Statistical tests were performed by R 3.0.3 for Windows.

#### 2.2.5 *Ethical considerations*

The participants were told the purpose and methods of this study and were informed that they could refuse to participate or withdraw from it at any time. Informed consent was obtained in writing from all participants. The Ethics Committee of Nagoya University Graduate School of Medicine, Japan, approved the study protocol (No. 2012-0182). Before the start of the experiment, we checked participants' physical conditions (such as the presence of knee pain) carefully. Participants could take breaks between each measurement at which they were asked whether they wanted to discontinue the measurements.



## 2.3 Results

All the participants completed the experimental protocol. Figure 2.2. demonstrates the time course of the HR responses to active and passive ankle exercises. With the active ankle exercise, HR was markedly elevated during active exercise (120–180 s). HR shifted from increasing to decreasing at the end of the exercise. For 60 s following active exercise, HR was headed down toward the baseline level. Passive exercise did not change HR throughout the experimental period.

Figure 2.3. illustrates the time-course response of MAP to active and passive ankle exercises. MAP increased only during active exercise. In contrast, in passive ankle exercise, there was no change in MAP accompanying plantar flexion and dorsiflexion ankle movements.

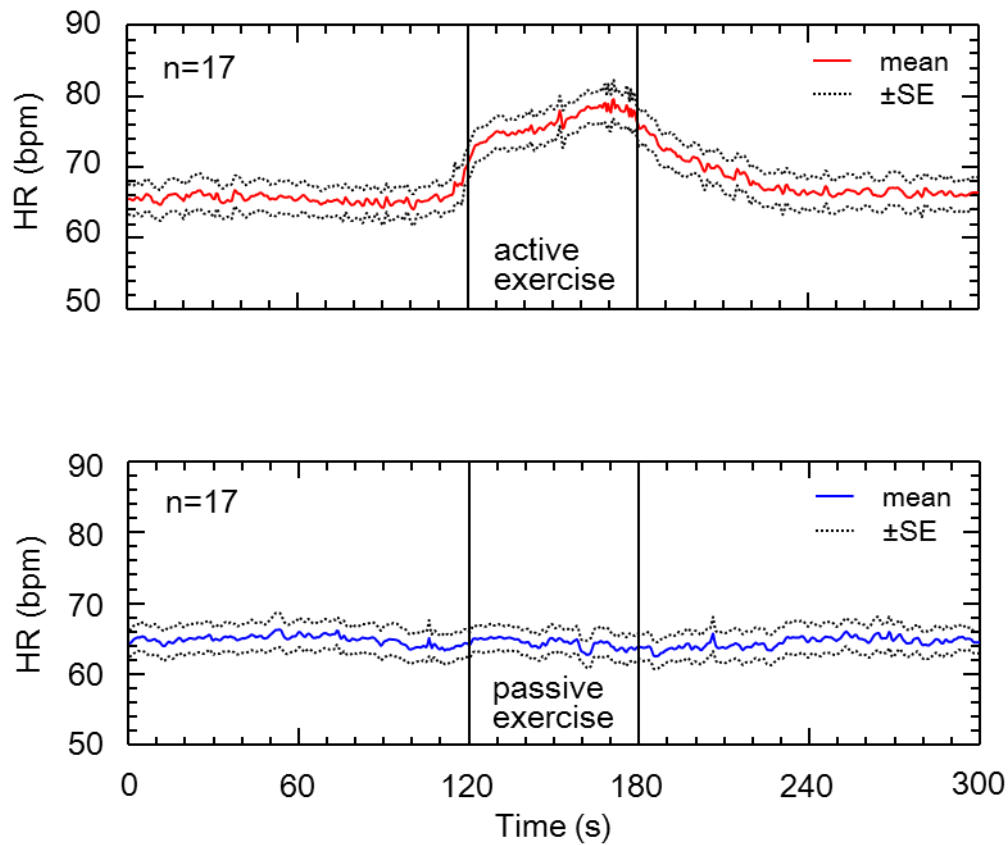
Figure 2.4. shows the time-course response of cerebral oxygenation to ankle exercise in the supine position. A progressive rise in OxyHb measured at the forehead was demonstrated during both active and passive exercises. Upon the completion of active exercise, OxyHb immediately decreased, thereafter did not show marked changes, and it maintained a high level in comparison with the pre-exercise values. Passive exercise had the same tendency as active exercise, while it was being performed. OxyHb showed a gradual decrease after passive exercise.

Figure 2.5. shows the effects of the various exercises on the 60 s averages of HR, MAP, and OxyHb. In Figure 2.5., the data of before exercise was obtained from 60 s to 120 s and the data of after exercise was obtained from 180 s to 240 s. The results of two-way ANOVA are summarized in Table 2.2. HR and MAP showed different tendencies depending on the type of exercise. For HR, the TYPE factor and TIME factor were significant ( $p < 0.01$ ,  $\eta G^2 = 0.035$  and  $p < 0.01$ ,  $\eta G^2 = 0.011$ , respectively). In addition, a significant interaction ( $p < 0.01$ ,  $\eta G^2 = 0.020$ ) was observed in the case of HR. For MAP, neither the TYPE factor nor the TIME factor showed statistical significance. There was a significant interaction effect in case of MAP ( $p < 0.01$ ,  $\eta G^2 = 0.009$ ).

On the other hand, active and passive exercises showed parallel responses with regard to OxyHb. For OxyHb, no significant effect was observed for the TYPE factor and a

significant interaction effect was observed for the TIME factor ( $p < 0.05$ ,  $\eta G^2 = 0.153$ ). ANOVA did not show an interaction effect in case of OxyHb.

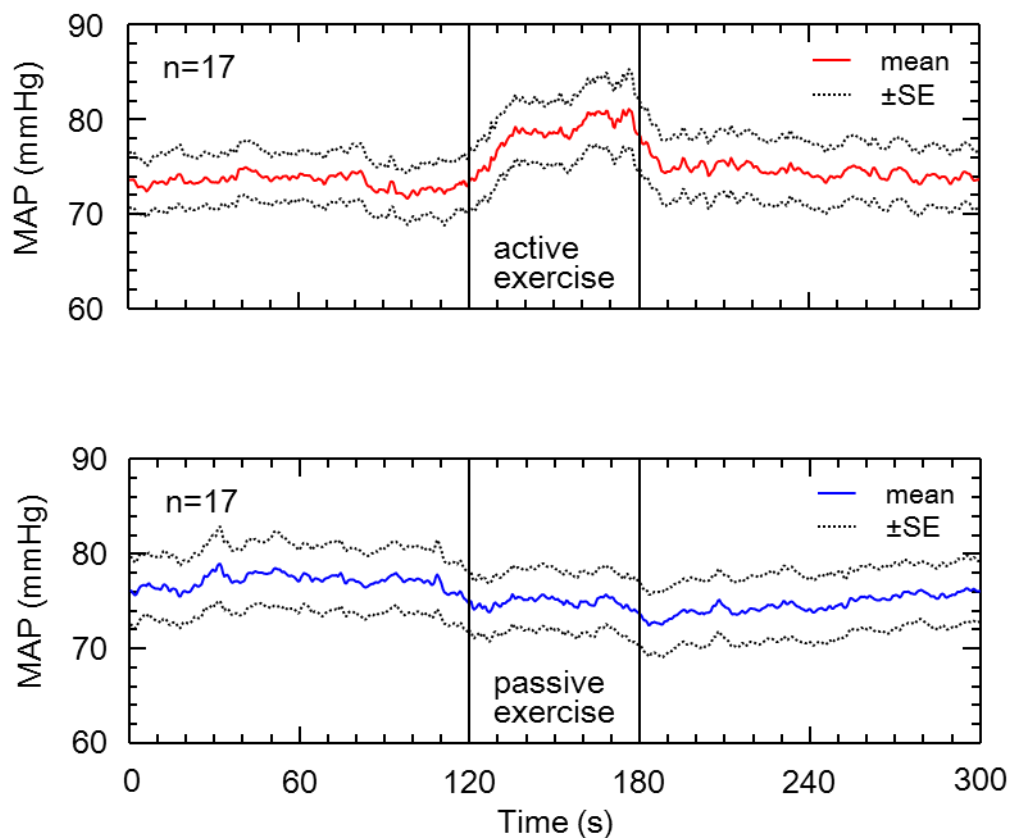
In summary, active and passive ankle exercises showed different effects on HR and MAP; however, both increased OxyHb levels at the forehead.



**Figure 2.2. Heart rate responses to active and passive ankle exercises (n = 17)**

Data are given as a mean  $\pm$  standard error (SE). A solid line indicates the mean heart rate (HR). A dashed line indicates the SE.

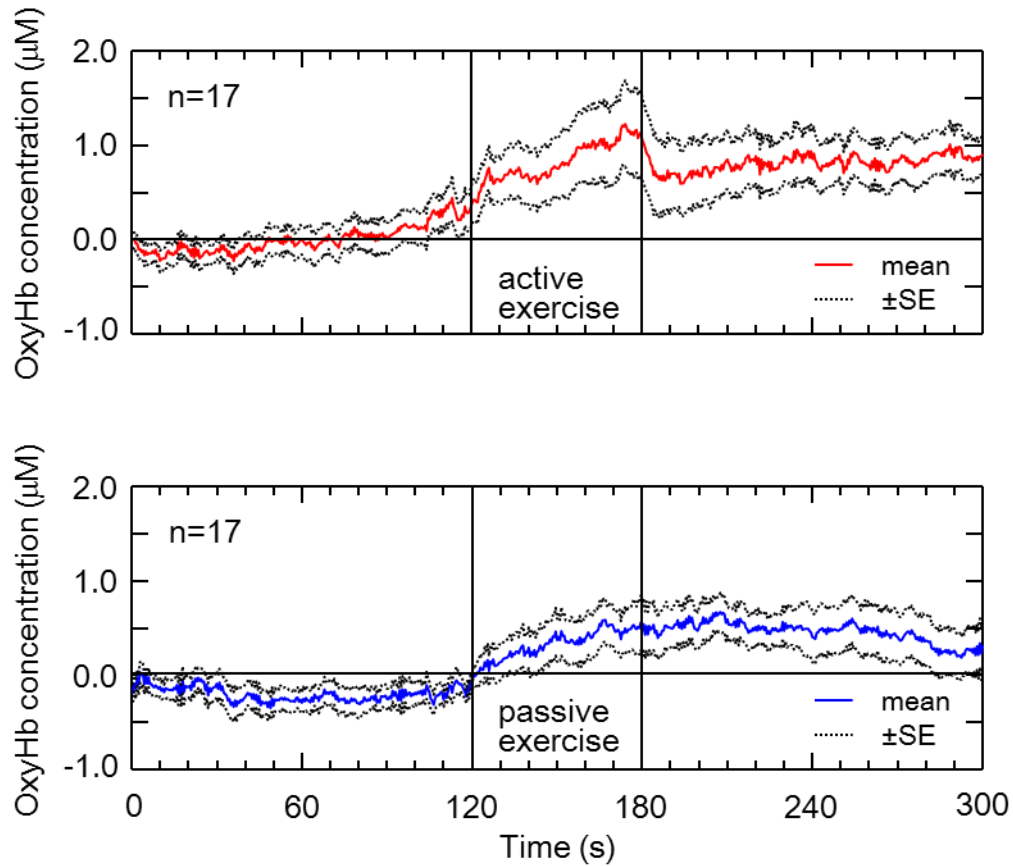
HR was markedly elevated during active exercise (120–180 s). The increase in HR shifted to a decrease at the end of the exercise. For the next 60 s after active exercise, HR decreased toward the baseline level. HR did not change with passive exercise throughout the experimental period.



**Figure 2.3. Mean arterial blood pressure responses to active and passive ankle exercises (n = 17)**

*Data are given as a mean  $\pm$  standard error (SE). A solid line indicates the mean arterial blood pressure (MAP). A dashed line indicates the SE.*

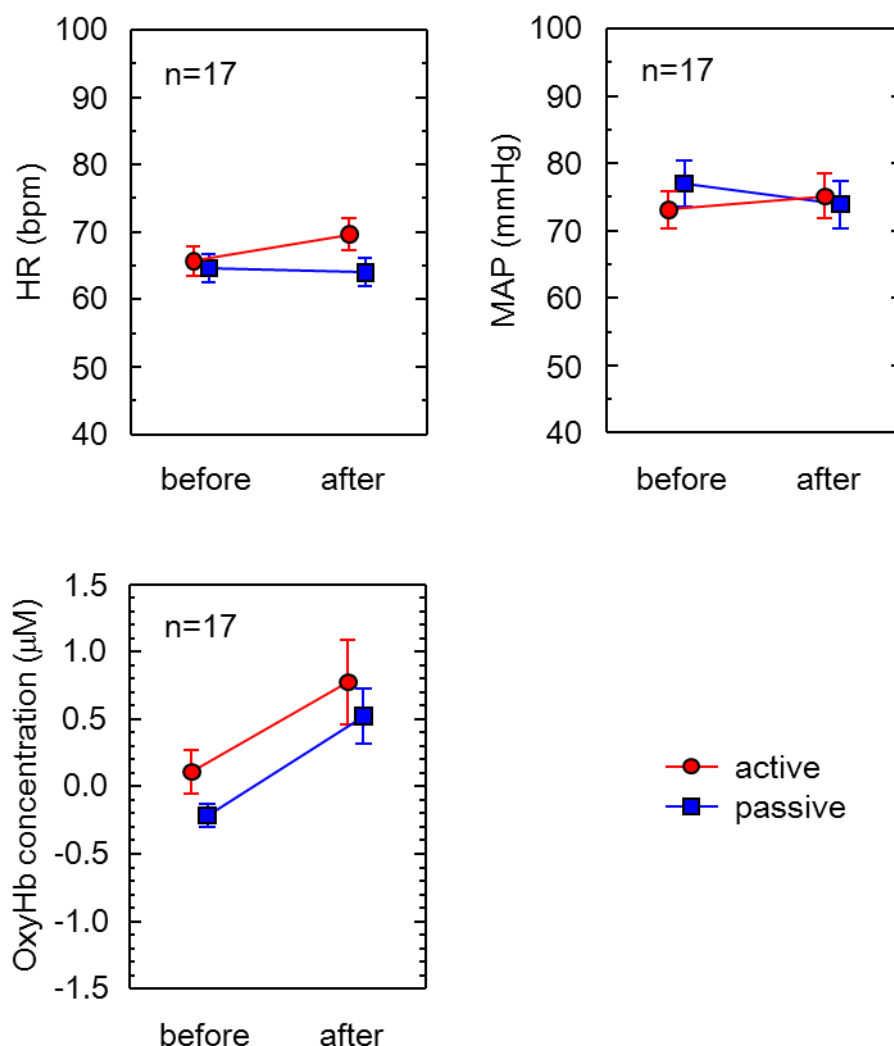
*MAP increased only during active exercise, while passive ankle exercise did not show any effect on MAP.*



**Figure 2.4. Oxyhemoglobin responses to active and passive ankle exercises (n = 17)**

*Data are given as a mean  $\pm$  standard error (SE). A solid line indicates the mean oxyhemoglobin (OxyHb). A dashed line indicates the SE.*

*A progressive rise in OxyHb measured at the forehead was demonstrated during both active and passive exercises. After the exercise finished, OxyHb immediately decreased in the active exercise phase; however, it maintained a high level in comparison with the values from before the exercise. In the passive exercise phase, OxyHb showed a gradual decrease after exercise.*



**Figure 2.5. Effects of active and passive ankle exercises on 60 s averages of heart rate, mean arterial blood pressure, and oxyhemoglobin (n = 17)**

*Circles: mean values of active ankle exercise; squares: mean values of passive ankle exercise; error bars: standard error of the mean.*

*Before: each value represents the mean value from 60 s to 120 s. After: each value represents the mean value from 180 s to 240 s.*

*HR and MAP showed different tendencies depending on the type of exercise. Both active and passive exercises increased oxyhemoglobin (OxyHb) measured at the forehead, and the slope of the change was also similar.*

**Table 2.2. Results of ANOVA for effects of the TYPE factor and TIME factor on ankle exercises**

factor	HR (bpm)		MAP (mmHg)		OxyHb concentration ( $\mu$ M)	
	<i>p</i>	$\eta_G^2$	<i>p</i>	$\eta_G^2$	<i>p</i>	$\eta_G^2$
TYPE	<0.01**	0.035	<0.56**	0.003	0.13	<0.030
TIME	<0.01**	0.011	<0.54**	0.001	<0.05*	<0.153
TYPE*TIME	<0.01**	0.020	<0.01**	0.009	0.78	<0.001

*The factor related to the type of exercise (active or passive) is expressed as the TYPE factor.*

*The factor related to time (before or after) is expressed as the TIME factor.*

*\*:  $p < 0.05$ ; \*\*:  $p < 0.01$*

*$\eta_G^2$  : effect size for each factor*

## 2.4 Discussion

### 2.4.1 Responses of HR and MAP to ankle exercises

Previous studies have reported that cardiovascular responses to exercise depend on the type of exercise. Active limb exercise increased blood pressure significantly; however, this increase was not observed during passive exercise (Doering, et al., 1998). Active elbow exercise was found to increase HR; however, passive elbow exercise did not show the same effect (Sato, Moriyama, & Sadamoto, 2009). Liang et al. (Liang, Nakamoto, Mochizuki, & Matsukawa, 2011) compared voluntary and involuntary exercises. They defined voluntary exercises as those performed by the participants and involuntary exercises as those evoked by electrical muscle stimulation. HR and MAP increased with voluntary ankle dorsiflexion. There were no significant changes in HR and MAP with involuntary exercise. In this study, increases in HR and MAP over time occurred only during active exercise and not passive exercise. These results are in line with those of previous studies (Doering, et al., 1998; Liang, Nakamoto, Mochizuki, & Matsukawa, 2011; Sato, Moriyama, & Sadamoto, 2009). The difference in the response between active and passive exercise could be attributed to a

difference in the workload of the exercise.

#### 2.4.2 *Responses of cerebral hemodynamics to ankle exercises*

Ankle movements increase blood velocity to the popliteal (Stein et al., 2009) and femoral veins (Kwon, Jung, Kim, Cho, & Yi, 2003; Sochart, & Hardinge, 1999). Leg muscle contractions lead to mechanical compression of the venous vascular beds. As a result, cardiac filling pressure and cardiac output increase, ultimately leading to an increase in cerebral perfusion (France, France, & Patterson, 2006). Plantar and dorsiflexion ankle movements involve movements of the anterior tibialis, gastrocnemius, and soleus muscles. These muscles are considered to act as skeletal muscle pumps when there are ankle movements, and they increase OxyHb measured at the forehead. With regard to different types of exercise (e.g., example, hand or lower limb), previous studies have reported that both active and passive exercises affect cerebral blood velocity (Doering, et al, 1998; Matteis, et al., 2001). These previous results agree with the findings of our study, which were based on measurements performed by NIRS. Both active and passive ankle exercises appear to produce similar types of mechanical stimuli, although differences in intensity exist. Thus, stimuli from either active or passive ankle exercise could contribute to an increase in cerebral oxygenation.

NIRS has been used as a method of measuring the brain functions associated with exercise. It has been reported that OxyHb is elevated by motor imagery (Naseer, & Hong, 2013). In our study, the value of OxyHb before exercise seemed to be different between active and passive exercise (Figure 2.5.). This difference in OxyHb may represent brain activity that was evoked by motor imagery in the participant's mind in preparation for active exercise. However, motor imagery effects were considered relatively small compared with that of ankle exercise because the effect of motor imagery is short-lived (Naseer, & Hong, 2013).

Postural change causes some degree of lowered blood pressure because fluids in the body shift under the influence of gravity. Usually, activation of the baroreceptor reflex controls HR and total peripheral resistance (TPR) to maintain adequate pressure (Costanzo, 2014, pp. 174–184). However, baroreceptors need a little time to work. Gravitational fluid shifts also affect cerebral circulation. Therefore, some people experience lightheadedness or



dizziness when baroreceptor reflection cannot fully compensate for changes in cerebral circulation. This phenomenon has been documented in studies using NIRS. Previous studies have shown a significant decline in the frontal cortical blood oxygenation of patients with autonomic failure (Hunt, et al; 2006) and healthy elderly people (Mehagnoul-Schipper, Vloet, Colier, Hoefnagels, & Jansen, 2001) when they stand up. From these results, it is considered that maintaining cerebral oxygenation is essential for preventing symptoms associated with postural change.

Galizia et al. (Galizia, et al., 2013) have revealed that supine leg exercises are effective in mitigating the initial drop in blood pressure in people with orthostatic hypotension; however, their study did not investigate cerebral oxygenation. This experiment confirmed that ankle exercise in the supine position can increase OxyHb measured at the forehead and that it lasts at least 1 min after exercise. Hemodynamic changes following postural changes commonly occur in a short period immediately after moving (Imholz, Settels, van der Meiracker, Wesseling, & Wieling, 1990; Sprangers, Wesseling, Imholz, Imholz, & Wieling, 1991; Wieling, Harms, Kortz, & Linzer, 2001). The increased duration of the change in OxyHb evoked by ankle exercise is considered to allow sufficient time for the initial change in hemodynamics induced by postural changes. Therefore, the results of the experiments in Chapter 2 (Figure 2.4, 2.5) indicated that ankle exercises may be useful for preventing symptoms associated with postural change.

## **2.5 Conclusions**

Chapter 2 investigated the effects of ankle exercise on HR, MAP, and OxyHb in the supine position. The physiological response of OxyHb to ankle exercise was different from that of the other cardiovascular functions. Both active and passive ankle exercises increased cerebral blood oxygenation, although the other cardiovascular functions showed no response to passive exercise.

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## **Chapter 3**

# **Ankle Exercise Increases Cerebral Blood Oxygenation During and After Postural Change**

### **3.1 Introduction**

The previous study reported in Chapter 2 revealed that ankle exercises have the significant effects of increasing cerebral oxygenation. In addition, this increased cerebral oxygenation was sustained for at least 1 min. One minute might be sufficient for postural change even in the actual clinical situations. If postural change is carried out after ankle exercise, it may attenuate a reduction in cerebral oxyhemoglobin (OxyHb) induced by orthostatic change. Therefore, it was hypothesized that ankle exercises before postural change can prevent symptoms of orthostatic hypotension (OH).

The experiment reported in Chapter 2 demonstrated that ankle exercises led to a significant increase in cerebral oxygenation. However, the conclusion was discussed as applied to the limited condition of supine posture. A further examination was required to establish the effect of ankle exercise on postural changes. Therefore, in this chapter, to estimate the efficacy of ankle exercises performed in a supine position, the experiment was conducted with a postural change from supine to sitting.

A transient shifting of blood from the upper to the lower part of the body occurs after postural change. This blood shift causes a decrease in venous return and sometimes induces hypotension. Two regulating mechanisms play significant roles in immediately adjusting this phenomenon. The first is the baroreceptor reflex; the second is the skeletal muscle pump. The baroreceptor reflex plays a part in increasing the heart rate and the total peripheral resistance (TPR). The skeletal muscle pump helps squeeze pooled blood from the lower extremities to increase the venous return. As for the baroreceptor reflex, it has been reported that the sensitivity of the baroreceptor decreases with aging (Rutan, et al., 1992). Previous studies have demonstrated that physical training improves baroreceptor sensitivity (La Rovere, Bersano, Gnemmi, Specchia, & Schwartz, 2002; Loimaala, et al., 2003; Monahan, et al., 2000; Somers, Conway, Johnston, & Sleight, 1991). However, the physical training requires sometime to have an effect. When a prompt effect is desired, it is considered that using the skeletal muscle mechanism is a more efficient way to prevent symptoms during the early phase of a postural change.

## **3.2 Methods**

### *3.2.1 Participants*

The study consisted of 11 participants (5 male, 6 female), age  $46.2 \pm 12.9$  (range 31 – 74) years. Their mean height, weight, and body mass index were  $160.6 \pm 10.2$  cm,  $57.6 \pm 8.8$  kg, and  $22.1 \pm 2.5$  kg/m<sup>2</sup>, respectively. One of the participants was hypertensive and using antihypertensive medications (angiotensin converting enzyme inhibitors and beta blocker). Prior to the study, the participants were instructed to abstain from alcohol for 12 h, not to eat a meal within 90 min, and to get enough sleep. Due to safety considerations, participants were recruited from a relatively younger generation than those in Chapter 2. At the same time, the younger generation was considered more suitable for collecting accurate data. In the experiments in Chapter 2, obtaining stable NIRS baseline data took a little time. It was thought that a participant's mental condition could potentially affect OxyHb because some elderly people seemed to be made nervous by an unusual circumstance such as the use of a climatic chamber.

### *3.2.2 Experimental procedures*

The experiments were conducted from September to October 2014. All data collection was conducted in a climatic chamber. The room temperature was maintained at 25°C with 50% relative humidity.

Figure 3.1. shows the experimental protocol of Chapter 3. After a 120 s rest in the supine position, each participant performed active or passive ankle movements for 60 s in the same manner as in the experiment in Chapter 2. After the exercise was finished, the participants changed their posture from supine to sitting. They held a sitting position for 60 s, and then each protocol ended. The postural change was conducted passively. First, using the electric motor of a hospital bed, the participant's position was changed from supine to the high Fowler's position. Then the researcher turned the participant's body 90 degrees to a sitting position (sitting on the edge of a bed without leaning against the mattress). This sequence of postural changes took about 30 s. Additionally, as a control condition, the data was taken without ankle exercise (resting quietly for 180 s in the supine position before

postural change). In this way, each participant was evaluated under three experimental conditions (active and passive exercise and control), and the order of the conditions was varied in a balanced manner for the different participants.

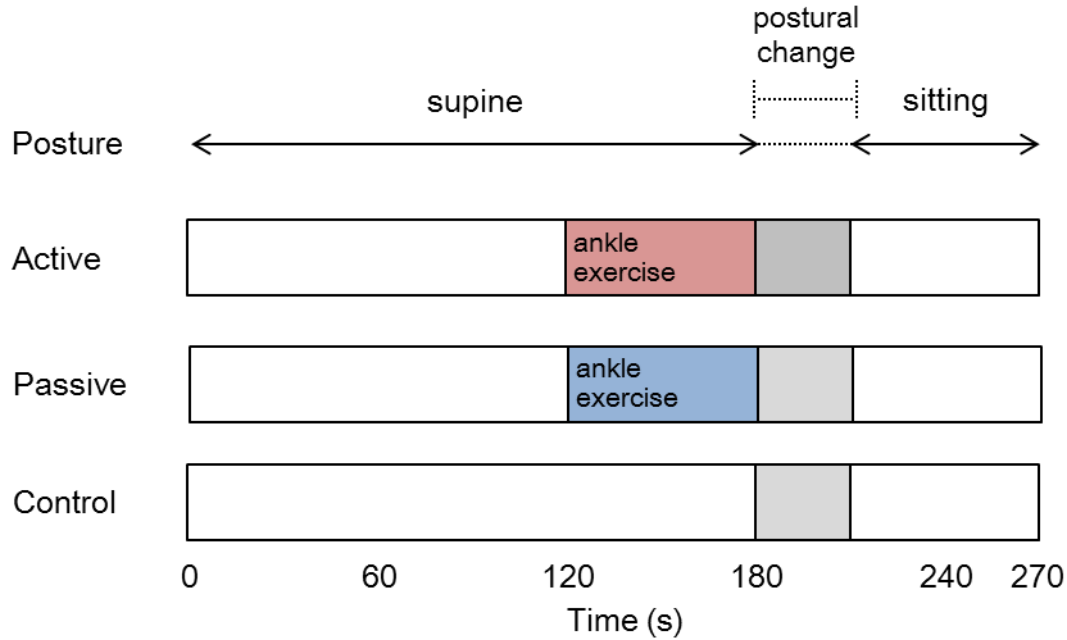


Figure 3.1. **Schematic representation of the experimental protocol (Chapter 3)**

### 3.2.3 Measuring physiological responses

Cerebral blood oxygenation was measured by NIRS (Near infrared spectroscopy) (NIRO-200; Hamamatsu Photonics, Shizuoka, Japan) at a sampling rate of 2 Hz. NIRO-200 is a device for near infrared spectroscopy with dual optodes. The optodes were placed on the right and left sides of the forehead during the experiment. The baseline value of OxyHb was obtained from start to 60 s. The pulse rate (PR) and systolic and diastolic blood pressures (SBP and DBP, respectively) were monitored by HEM-7130 (Omron Colin, Tokyo, Japan). PR and BP were measured twice for each condition; at 60 s after the experiment started and again immediately after the completion of the postural change. In the preliminary experiment, it was difficult to obtain accurate continuous blood pressure readings because, even though the arm being used for the measurement was held in position by a bandage, its position could be affected by body movements and change. Therefore, the blood pressure was measured intermittently. To obtain the stable data, each condition was repeated twice. However, due to

the necessity to avoid a carry-over effect, none of the conditions was repeated twice in a row. The mean arterial blood pressure (MAP) was calculated by adding one-third of the pulse pressure to DBP.

#### 3.2.4 Statistical analysis

When the cerebral functions are estimated by NIRS, usually the data from the two optodes is analyzed separately because the right and left hemispheres provide different functions. However, the purpose of this study is to measure changes in OxyHb induced by postural change; therefore, in order to discuss the two hemispheres in an equal manner, the data from the NIRS's right and left optodes were averaged together.

The pair of physiological signals (PR, MAP, and OxyHb) in each condition was averaged for analysis. Additionally, the OxyHb values for 11 participants were assembled to indicate an average continuous response to the exercises. PR and MAP data between the supine and sitting positions were tested by paired t test. One-way repeated measures analysis of variance (ANOVA) was used to estimate the effect of the different kinds of exercises. When the one-way ANOVA was significant, the differences between exercises were examined using Holm methods.

The statistical significance was set at  $p < 0.05$ . Generalized eta squared ( $\eta G^2$ ) values were presented as the effect size of each factor. As  $\eta G^2$  values can be interpreted in the same manner as  $\eta^2$  values,  $\eta G^2$  values of 0.01, 0.059, and 0.138 were interpreted as small, medium, and large effects, respectively (Cohen, 1988). Statistical tests were performed by R 3.0.3 for Windows.

#### 3.2.5 Ethical considerations

The participants were told the purpose and methods of this study and were informed that they could refuse to participate or withdraw from the study at any time. The Ethics Committee of Nagoya University Graduate School of Medicine, Japan, approved the study protocol (No. 2012-0182).



### 3.3 Results

Table 3.1. describes PR and MAP responses to postural change. MAP showed a significant increase under all three conditions (active;  $p < 0.001$ , passive;  $p = 0.002$ , control;  $p = 0.003$ ), from supine to sitting. PR also increased under all conditions; however, it did not show a significant difference for any of the conditions (active;  $p = 0.07$ , passive;  $p = 0.30$ , control;  $p = 0.11$ ).

Figure 3.2. shows PR and MAP for each condition observed after postural change. PR and MAP were recorded immediately following postural change. No significant difference in PR for the three conditions was observed after postural change ( $p = 0.07$ ,  $\eta G^2 = 0.024$ ). MAP showed a significant difference in the one-way repeated measures analysis of variance (ANOVA) ( $p < 0.05$ ,  $\eta G^2 = 0.035$ ). A Holm analysis indicated that active ankle exercise resulted in a significantly greater MAP than passive ankle exercise after postural change ( $p < 0.05$ ), but not in the case of the control condition.

Figure 3.3. shows the cerebral oxygenation responses to postural change following each ankle exercise (active, passive, control) carried out in a supine position. OxyHb continually increased during active exercise. In contrast the control condition showed little change from the baseline. In terms of duration of the exercise in Figure 3.3., passive exercise did not have as strong an impact on the increase in OxyHb as did active exercise. In all three conditions OxyHb began to decline and reached its lowest level at approximately 24–26 s after postural change. The increase of OxyHb brought about by ankle exercise did not diminish with the cessation of movement; this effect seemed sustainable until the influence of postural change eclipsed the effect of ankle exercise. During and after postural change, the level of OxyHb induced by active ankle exercise seemed to remain at a higher level in comparison with passive and control conditions.

Figure 3.4. shows the effect of three kinds of ankle exercise on cerebral OxyHb. The data from 160 to 180 seconds (20 s before the end of exercise) were analyzed. ANOVA showed a significant difference in OxyHb, depending on the type exercise ( $p < 0.01$ ,  $\eta G^2 = 0.379$ ). Holm methods revealed that active ankle exercise increased OxyHb more significantly than the passive ( $p < 0.01$ ) and control conditions ( $p < 0.05$ ). In addition, the level of OxyHb

induced by passive ankle exercise was significantly higher than under the control condition ( $p < 0.05$ ).

Figure 3.5. shows the changes in OxyHb brought about by each condition observed after postural change. OxyHb was analyzed for an average of 90 s (180–270 s) as typical during and after postural change. ANOVA showed a significant effect on OxyHb by different kinds of exercise during and after postural change ( $p < 0.01$ ,  $\eta G^2 = 0.059$ ). A Holm post hoc analysis revealed that active ankle exercise increased OxyHb more significantly than the passive or control conditions ( $p < 0.05$ ) did. However, there was no significant difference between the effect of passive ankle exercise and that of the control condition ( $p = 0.53$ ).

**Table 3.1. Pulse rate and mean arterial blood pressure response to postural change from supine to sitting (n = 11)**

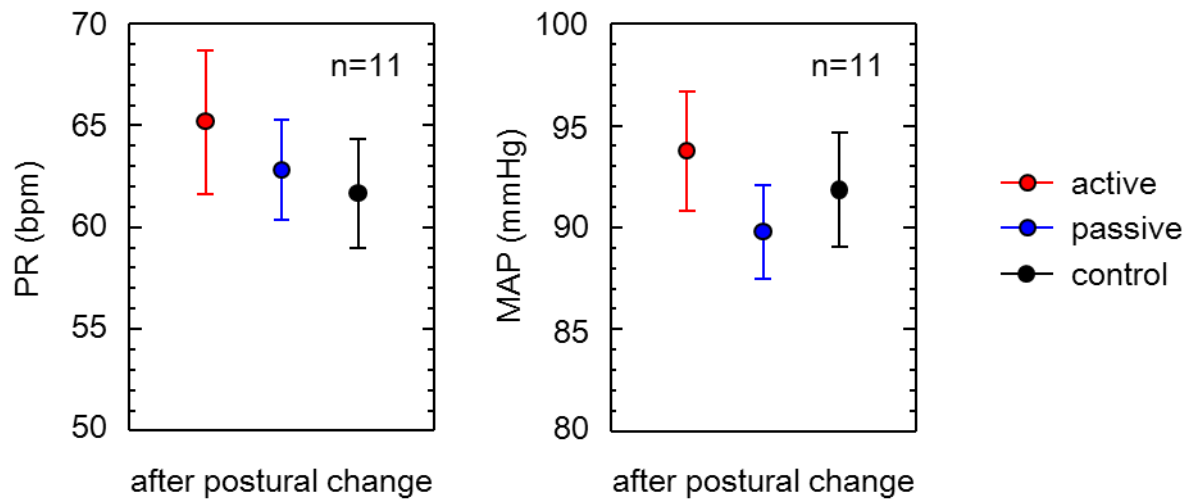
	PR (bpm)		MAP (mmHg)	
	supine	sitting	supine	sitting
Active	61.23 ± 2.41	65.18 ± 3.53	87.35 ± 2.98	93.76 ± 2.94**
Passive	61.45 ± 1.86	62.82 ± 2.44	85.30 ± 2.34	89.79 ± 2.31**
Control	59.27 ± 1.81	61.68 ± 2.69	86.62 ± 2.85	91.85 ± 2.82**

*Results are expressed as a mean ± standard error (SE).*

*Supine: each value was measured in supine position before an ankle exercise.*

*Sitting: each value was measured in sitting position after an ankle exercise.*

*Significant changes between supine and sitting are indicated by \* ( $p < 0.05$ ) and \*\* ( $p < 0.01$ ).*

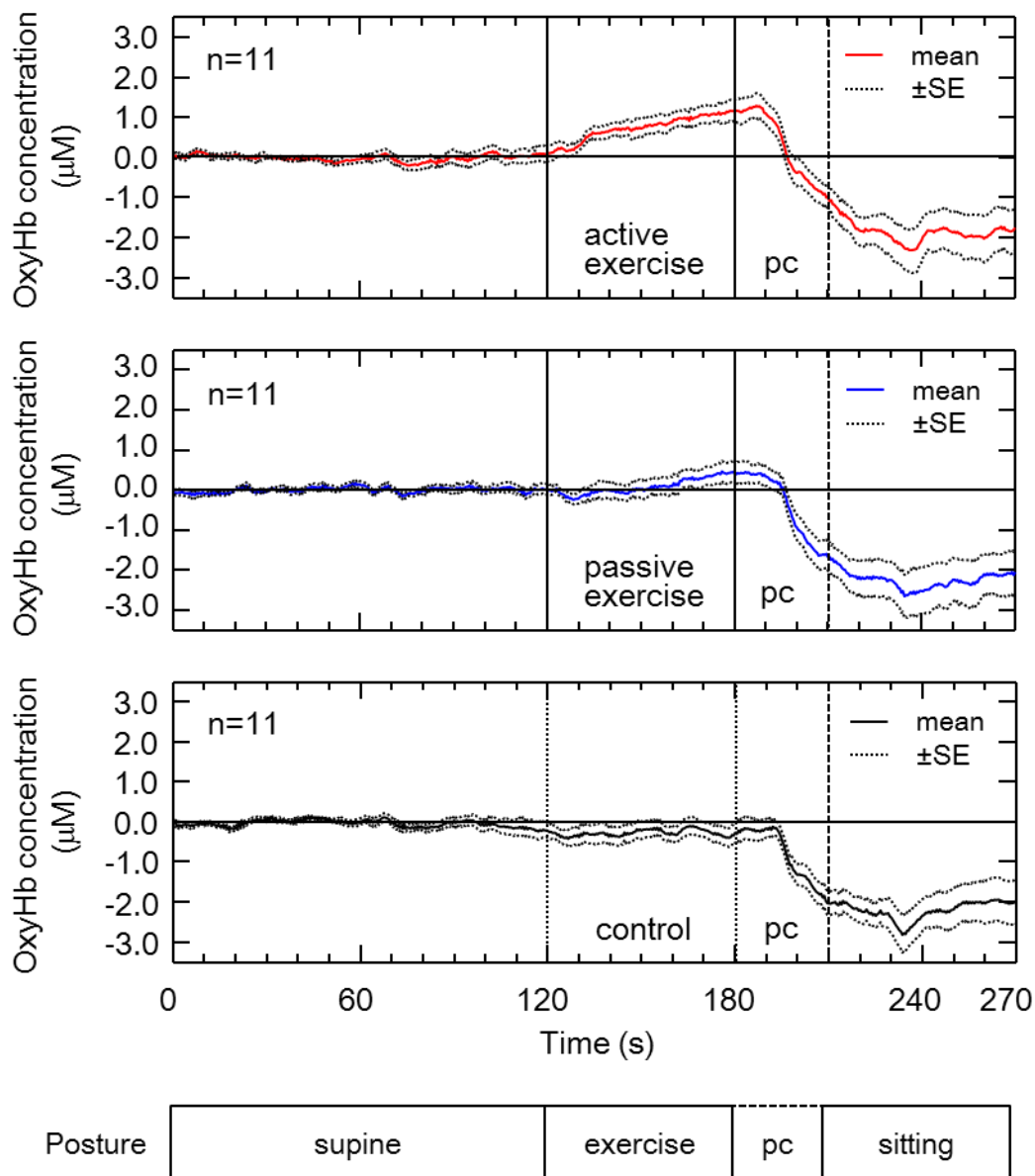


**Figure 3.2. Pulse rate and mean arterial blood pressure response to postural change following ankle exercises (n = 11)**

*The data were given as a mean  $\pm$  standard error (SE).*

*Each value was measured in sitting position after postural change. In active and passive condition, participants performed active or passive ankle movements before a postural change.*

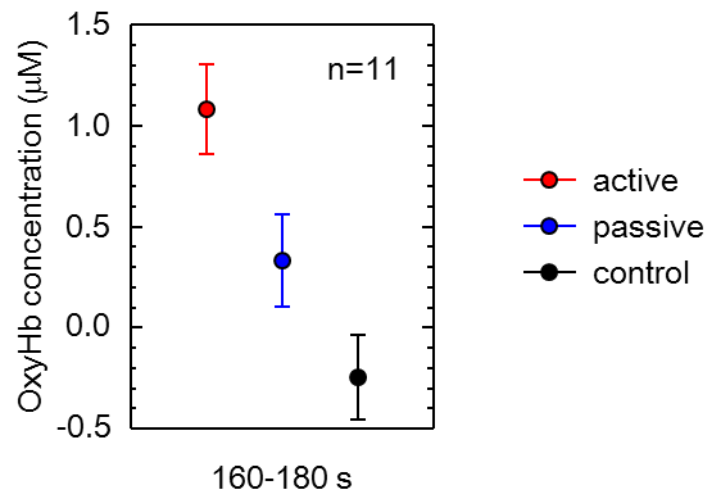
*No significant difference in PR for the three conditions was observed after postural change. ANOVA showed a significant effect on MAP by different kinds of exercise after postural change. Active ankle exercise demonstrated a significantly greater MAP than passive ankle exercise after postural change. Vertical bars represent standard errors from mean.*



**Figure 3.3. Oxyhemoglobin responses to ankle exercises and postural change (n = 11)**

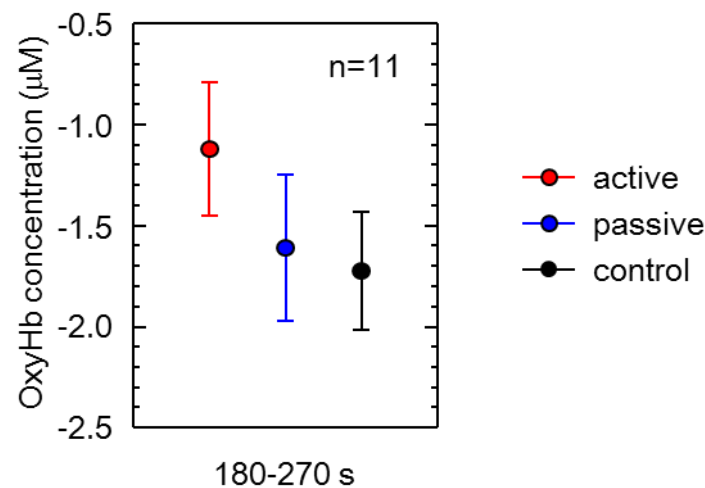
Data are given as a mean  $\pm$  standard error (SE). A solid line indicates the mean oxyhemoglobin (OxyHb). A dashed line indicates the SE.

The top figure illustrated OxyHb responses to active ankle exercise. The middle is passive ankle exercise, and bottom is the control condition respectively. The postural changes were conducted passively from supine to sitting position. Each postural change took about 30 s and it is represented as “pc” in each figure. Active ankle exercise escalated OxyHb gradually from just onset of exercise. On the other hand, passive exercise did not show the effect for a while. Passive exercise increased OxyHb after the exercise lasted approximately 30 s. During and after postural change, active ankle exercise could maintain higher level of OxyHb in comparison with passive and control conditions.



**Figure 3.4. Oxyhemoglobin during each ankle exercises (n = 11)**

*Results are averaged 20 s during each ankle exercise. Error bars are standard error of the mean. Both active and passive ankle exercise resulted in an increase in OxyHb compared with the control condition. In addition, active ankle exercise produced significant increase in OxyHb when compared with the passive exercise.*



**Figure 3.5. Oxyhemoglobin response to postural change following ankle exercises**  
(n = 11)

*The data were given as a mean  $\pm$  standard error (SE).*

*The OxyHb responses to each ankle exercise during and after postural change. Active ankle exercise showed significantly difference from passive and control conditions. There was no significant difference between passive and control.*

### 3.4 Discussion

#### 3.4.1 Differences in the effect on OxyHb of different ankle exercises

It is generally accepted that cerebral blood flow (CBF) is independent of changes in MAP within a range from 60 to 150 mmHg (Lassen, 1959). Because of this, normal exercises are considered to have little effect on CBF since it is not to be expected that MAP would deviate from the 60 to 150 mmHg range during exercise. Some studies have shown that exercise has no effect on CBF (Globus, et al., 1983; Madsen, et al., 1993), which is in line with Lassen's concept. Conversely, other researchers have had different views about the regulation of cerebral hemodynamics during exercise, and there are some studies demonstrating changes in cerebral hemodynamics during exercise (Doering, et al, 1998; Matteis, et al., 2001; Salvadego, et al., 2011). There is, therefore, still controversy as to whether physical exercise affects cerebral hemodynamics.

In terms of the effect of exercise on cerebral oxygenation, previous studies have demonstrated that OxyHb increases with the intensity of exercise unless the work rates reach the fatigue level (Ide, Horn, & Secher, 1999; Timinkul, et al., 2008; Salvadego, et al., 2011).

In this study, ankle exercises showed an effect similar to that found in previous studies. In the supine position, active ankle exercise increased OxyHb significantly more than did the passive and control conditions. These differences in the results can be explained by differences in the intensity of each exercise. Active exercise involves muscle contractions and relaxations. In contrast, muscles are not activated by passive exercise. To meet the muscle demand induced by active exercise, the cardiovascular system adjusted its hemodynamics by increasing HR, SV (stroke volume) and TPR. As a consequence, it is considered that these responses increased cerebral OxyHb because the changes in CO (cardiac output) and MAP are associated with the changes in cerebral hemodynamics (Lind-Holst et al., 2011; Ogoh et al., 2005). It can be presumed that the extent of the influence of exercise on the cardiovascular system led to significant difference between active and passive exercise. However, this explains only the results that were observed for active and passive exercises. This experiment also showed a significant difference between passive exercise and control condition. Passive exercise does not involve muscle activity, but external stimulus (passive movements) can lead to mechanical compressions. The ankle joints were moved rhythmically, in turn, this moved the lower limb muscles (e.g., gastrocnemius, soleus), and compressed the internal vessels, and, blood was extracted toward upper body. This process contributed to an increase in the cerebral OxyHb. The combination of exercise intensity and mechanical compression to vessels was possible for the different effect on cerebral OxyHb in the supine position.

#### *3.4.2 The effect of ankle exercise to postural change*

Of the three conditions (active, passive, control), active ankle exercise showed significantly higher OxyHb than the others during and after postural change. On the other hand, no significant difference was detected between passive exercise and the control condition. Sympathetic nerve activity can explain why there are different results were obtained for increase of OxyHb, depending on the exercise. One of the effects of ankle exercise is to squeeze blood from the lower limbs (Kwon, Jung, Kim, Cho, & Yi, 2003; Sochart, & Hardinge, 1999; Stein et al., 2009). This can increase venous return; however, venous return is just one aspect of hemodynamics regulation. The effect of ankle exercise will

be offset if the returned blood shifts again toward lower limbs due to postural change, without redistributing to the brain. The venous system serves as a blood reservoir for the circulation because the veins contain more than 60% of total blood in the circulatory system (Hall, 2010, p. 175). In counteracting the reduction in OxyHb related with postural change, the way in which the cardiovascular system regulates vascular constriction becomes important. The sympathetic nervous system plays an important role in this regulation. It is easy to assume that the activation of the sympathetic nerve by active exercise is greater than in the case of passive exercise, and, of course greater than for the control. In the period after postural change, the reason why active ankle exercise could maintain OxyHb higher than control condition (without exercise) is considered to be the fact that the skeletal muscle pump worked efficiently and higher activity of the sympathetic nerve regulated the hemodynamics appropriately.

Passive ankle exercise did not show an influence on cerebral OxyHb similar to that of active exercise after postural change. This result was different from what was hypothesized. Judging from the results for the supine position, passive ankle exercise undeniably increases cerebral OxyHb. However, the effect of passive ankle exercise proposed in this experiment may be insufficient to prevent postural hemodynamic reduction. On this point, modified passive ankle exercise may be effective for postural change. Figure 3.3. shows that, compared with active ankle exercise, the effects of passive ankle exercise may take longer to appear. Extending the period or changing the interval and intensity of passive exercise has the possibility of maintaining cerebral OxyHb after postural change.

In this study, the period of after postural change was defined as 210 to 240 s. This means the analysis was done in approximately the first minute after the onset of postural change. The initial OH was observed immediately after standing (within 30 s) (Wieling, Harms, Kortz, & Linzer, 2001; Wieling, Krediet, van Dijk, Linzer, & Tschakovsky, 2007). Therefore it can be presumed that active ankle exercise performed in supine position has the effect to attenuating the reduction in cerebral OxyHb in the initial period of postural change. However, this study has been discussed under several limitations. The symptoms of OH were not adopted as indicators in this experiment. For safety considerations, limitations were



placed on the postures taken during the experiment. MAP showed a significant increase after postural change including the control condition (Table 3.1.). This result indicates that the participants' autonomic nerves were able to regulate their cardiovascular systems well in response to postural changes from supine to sitting. Previous studies have reported that continuous measurement showed temporarily drops in blood pressure caused by postural change and that the pressure recovered within 30 sec. Sometimes the blood pressure not only recovers to a baseline level, but reactively goes on to overshoot (Bundgaard-Nielsen et al., 2009; Imholz, Settels, van der Meiracker, Wesseling, & Wieling, 1990; Thomas, et al., 2009). Thus, taking previous results into account, it seems right to presume that the data for MAP after postural change represent points of recovery from the postural stress.

The demonstration of the maintenance of cerebral OxyHb in this experiment cannot be taken to indicate the complete prevention of symptoms. These limitations mean that this experiment will not have immediate utility as a practical intervention in nursing. However, this study makes a contribution to nursing in that it demonstrates the possibility of a clinical application of ankle exercise by revealing the relationship between ankle exercise and cerebral OxyHb changes related to postural change.

### **3.5 Conclusions**

Chapter 3 investigated the effects of ankle exercise performed prior to postural change. No significant difference was observed between passive ankle exercise and the control condition. In contrast, active ankle exercise demonstrated significantly higher cerebral OxyHb than passive ankle exercise and control condition during and after postural change.

### 3.6 References

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## **Chapter 4**

### **General Discussion**

The main focus of this dissertation has been the question as to whether ankle exercises could attenuate the cerebral oxygen reduction induced by postural changes.

First, in Chapter 2, the effects of ankle exercise to cerebral oxyhemoglobin (OxyHb) were evaluated for both active and passive exercise. The study in Chapter 2 demonstrated that both active and passive ankle exercises in a supine position can contribute to an increase in cerebral oxygenation in elderly individuals ( $n = 17$ ). This effect of increased OxyHb lasted at least 1 min after exercise. In comparison with passive ankle exercise, active ankle exercise had a greater tendency to increase OxyHb, but there was no significant difference between active and passive exercise.

The study in Chapter 3 investigated the effect of ankle exercises performed prior to postural change (from supine to sitting). Eleven healthy adults participated in the experiment in Chapter 3. The experimental conditions were constructed by active exercise, passive exercise and control (no exercise). OxyHb was analyzed using averages between 180 to 270 s as representative values during and after postural change. Of three conditions (active/passive/control), active ankle exercise showed significantly higher OxyHb than the others during and after postural change. In contrast, no significant difference was detected between passive exercise and the control condition.

When interpreting the results of Chapter 2 and Chapter 3 together, the existence of some methodological differences between the two experiments should be considered. The first to be noticed is the baseline characteristics of the participants. The participants in Chapter 2 were seventeen elderly women; in contrast to that, there were eleven adults (5 male, 6 female) in Chapter 3. There were more participants in Chapter 2 than in Chapter 3. In addition, these two experiments were conducted with different sex ratios. The second factor to be considered is the differences in the design of the specific experiments. In Chapter 3, dual optodes NIRS (near infrared spectroscopy) was used. It allowed the simultaneous measurement of the right and left hemispheres. Additionally, measurements were repeated twice for each condition. On the other hand, in Chapter 2, one-optode NIRS was used to measure OxyHb, therefore the data in Chapter 2 reflect only the left hemisphere. To the best of my knowledge, there has been no study revealing that hemispheric difference in the OxyHb response to postural change.

In addition, measurements were made only once for each condition. Thus, the sample size of the experiment in Chapter 3 is smaller than that in Chapter 2, but the statistical power of NIRS measurement in Chapter 3 is considered greater than that in Chapter 2. This interpretation is supported by a comparison of the figures from each experiment. The each time series graph of NIRS in Chapter 3 (Figure 3.3.) has more stable baseline measured before the onset of exercise than does the one in Chapter 2 (Figure 2.4.).

The results in Chapter 2 showed that active ankle exercise has a stronger OxyHb-increasing effect than passive exercise; however, it did not demonstrate a significant difference between active and passive exercise. In contrast, the results in Chapter 3 revealed that the changes in OxyHb during ankle exercise (active/passive) reached a higher level than they did under the control condition. In addition, active ankle exercise resulted in more a significant elevation of OxyHb, than did passive exercise. These partial discrepancies in the results might be attributed to statistical power differences in the two studies, rather than age and gender differences in the participants.

The results in Chapter 3 came from an analysis of data from healthy adults from 31 to 74 years old. The participants of Chapter 3 were people who were relatively younger than those in Chapter 2; this was due to safety considerations. To avoid the occurrence of adverse effects associated with postural change, it was considered suitable to recruit a younger generation for the experiment in Chapter 3. Chapter 3 revealed that active ankle exercise increases OxyHb more than passive exercise does. However, the question has remained unanswered as to whether a similar result can be obtained in elderly participants. Nevertheless, the experiment in Chapter 2 demonstrated that ankle exercise has the effect of increasing OxyHb in elderly participants when there is no postural change. These results indicate that active ankle exercise in elderly individuals have the possibility of increasing OxyHb in the same way as it did for the participants in Chapter 3. A further study focusing on the elderly would answer this question.

The present study estimated OxyHb by using NIRS. As mentioned in Chapter 1, the OxyHb data from NIRS was measured as an indicator of cerebral blood flow in previous studies. Therefore, the results of this dissertation can be interpreted as demonstrating that

ankle exercises had the effect of attenuating the reduction of cerebral blood flow induced by postural change. However, it should be noted that the results reached in this dissertation do not ensure complete prevention of clinical symptoms. The reduction of cerebral blood flow leads to symptoms, but this fact does not fully support the idea that improving the reduction in cerebral blood flow would mean the prevention of symptoms. Confirming the prevention of symptoms associated with postural change is beyond the scope of this study.

The differing effects of active ankle exercise in OxyHb during and after postural change are statistically significant; however, the effect size of it was medium. There is room for discussion as to whether or not ankle exercises have a strong enough effect when applied in clinical situations. Further studies on such aspects as changing the degree of the exercise or its duration may answer this question. Additionally, in the experiment reported in Chapter 3, passive ankle exercise did not show a significant effect in preventing the decrease in OxyHb associated with postural change. On this point, modified ankle exercise may be effective for postural change because the elevation in OxyHb was also observed with passive ankle exercise, as reported in Chapter 2. If passive exercise is confirmed as having an effect similar to that of active exercise, the range of application of this intervention will be expanded because there are many patients who cannot perform active ankle exercise due to cognitive or physical disorders.

As mentioned above, further studies will be required to validate ankle exercises as a nursing intervention for preventing the symptoms induced by postural change. However, the present study has demonstrated that such exercise contributes to the improvement of the cerebral blood flow after postural change. The author hopes that patients will benefit from practical interventions stemming from the findings of the present study.

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## **Appendices**

**Appendix A: Individual data of heart rate, mean blood pressure, and oxyhemoglobin  
before and after ankle exercises (Chapter 2)**

*Before: each value represents the mean value from 60 s to 120 s. After: each value represents the mean value from 180 s to 240 s in experiment of Chapter 2.*

Participant	P1_active		P2_active		P3_active		P4_active		P5_active	
	before	after	before	after	before	after	before	after	before	after
HR (bpm)	76.04	77.58	70.37	75.34	68.75	71.34	53.69	56.34	66.93	73.34
MAP (mmHg)	78.44	78.29	56.20	56.98	67.33	66.41	63.68	58.79	80.66	86.44
OxyHb ( $\mu$ M)	0.39	-0.68	-0.06	0.45	-1.35	0.14	-0.65	-0.41	-0.46	-0.05

Participant	P6_active		P7_active		P8_active		P9_active		P10_active	
	before	after	before	after	before	after	before	after	before	after
HR (bpm)	77.61	85.35	64.72	66.34	61.25	62.66	53.01	57.86	50.84	54.43
MAP (mmHg)	101.6	115.71	88.65	90.00	83.28	81.86	75.72	69.52	70.01	74.36
OxyHb ( $\mu$ M)	0.07	-0.32	1.02	0.10	-0.69	-0.17	0.76	3.05	0.37	0.38

Participant	P11_active		P12_active		P13_active		P14_active		P15_active	
	before	after	before	after	before	after	before	after	before	after
HR (bpm)	59.83	62.03	63.32	70.92	60.78	67.06	66.60	69.66	83.12	88.59
MAP (mmHg)	67.20	66.04	64.46	65.12	70.07	69.44	77.89	72.15	70.15	75.20
OxyHb ( $\mu$ M)	0.26	0.09	0.73	1.24	-0.53	3.10	0.45	2.84	0.46	0.38

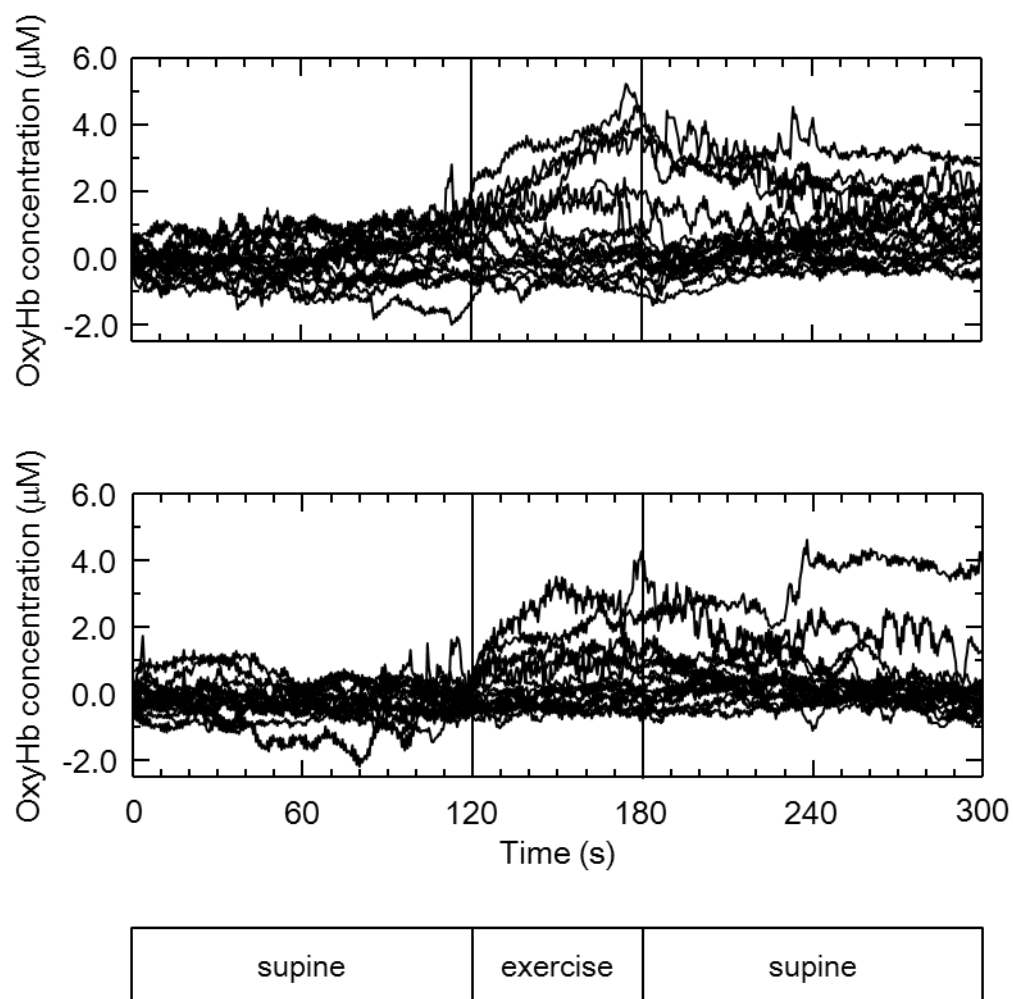
Participant	P16_active		P17_active	
	before	after	before	after
HR (bpm)	66.12	68.48	70.05	77.23
MAP (mmHg)	69.16	80.56	58.83	69.82
OxyHb ( $\mu$ M)	1.02	2.61	0.032	0.46

Participant	P1_passive		P2_passive		P3_passive		P4_passive		P5_passive	
	before	after	before	after	before	after	before	after	before	after
HR (bpm)	68.32	67.09	67.46	66.38	67.23	68.50	55.57	54.24	68.09	68.29
MAP (mmHg)	93.93	89.94	55.27	53.72	86.48	78.93	68.07	60.38	71.69	71.48
OxyHb ( $\mu$ M)	0.25	-0.27	-0.19	-0.07	-0.59	0.45	-0.39	-0.47	0.03	0.27

Participant	P6_passive		P7_passive		P8_passive		P9_passive		P10_passive	
	before	after	before	after	before	after	before	after	before	after
HR (bpm)	78.39	79.25	63.52	63.90	60.33	59.78	52.94	51.03	48.92	48.97
MAP (mmHg)	111.08	111.00	85.38	83.15	74.39	71.73	89.07	84.38	82.13	85.23
OxyHb ( $\mu$ M)	0.36	0.19	0.02	0.13	-0.70	0.71	-0.06	2.05	0.22	0.36

Participant	P11_passive		P12_passive		P13_passive		P14_passive		P15_passive	
	before	after	before	after	before	after	before	after	before	after
HR (bpm)	56.26	57.21	65.79	63.90	60.58	62.44	67.29	64.59	80.84	80.84
MAP (mmHg)	66.36	63.94	67.43	63.23	70.75	67.05	61.00	57.59	85.11	80.74
OxyHb ( $\mu$ M)	-0.67	0.13	-0.90	1.12	-0.2	2.71	-0.20	-0.30	-0.03	0.44

Participant	P16_passive		P17_passive	
	before	after	before	after
HR (bpm)	66.86	63.18	70.52	69.08
MAP (mmHg)	81.24	75.25	59.94	58.71
OxyHb ( $\mu$ M)	-0.48	0.32	-0.14	1.09



**Appendix B: Individual data of oxyhemoglobin in the experiment of Chapter 2**

### Appendix C: Individual data of pulse rate, mean blood pressure, and oxyhemoglobin before and after postural change (Chapter 3)

*Before: PR and MAP showed each value before ankle exercise (supine position), oxyhemoglobin showed the mean value from 30s to 120 s in experiment. After: PR and MAP showed each value after postural change (sitting position), oxyhemoglobin showed the mean value from 180 s to 240 s in experiment.*

Participant	P1_active		P2_active		P3_active		P4_active		P5_active	
	before	after	before	after	before	after	before	after	before	after
PR (bpm)	63.0	68.5	61.5	59.5	73.0	71.5	66.0	69.0	66.5	71.0
MAP (mmHg)	97.33	106.17	98.83	103.33	98.17	99.67	84.83	91.17	82.5	92.67
OxyHb ( $\mu$ M)	0.09	0.04	-0.26	0.11	0.11	-3.01	0.03	-0.91	0.32	-1.76

Participant	P6_active		P7_active		P8_active		P9_active		P10_active	
	before	after	before	after	before	after	before	after	before	after
PR (bpm)	60.5	60.0	55.0	60.0	72.0	94.0	48.0	52.5	51.5	54.0
MAP (mmHg)	76.17	81.83	85.33	93	85.5	85.17	82.83	94	70	77.33
OxyHb ( $\mu$ M)	-0.05	-0.90	-0.15	-0.49	0.46	-1.36	-0.16	-1.44	-0.69	0.17

Participant	P11_active	
	before	after
PR (bpm)	56.5	57.0
MAP (mmHg)	99.33	107
OxyHb ( $\mu$ M)	0.05	-2.79

Participant	P1_passive		P2_passive		P3_passive		P4_passive		P5_passive	
	before	after	before	after	before	after	before	after	before	after
PR (bpm)	62.5	65.0	67.5	67.0	66.5	65.5	66.0	67.0	64.5	61.0
MAP (mmHg)	97.17	102.33	87.00	89.17	93.83	96.17	87.67	91.5	81.33	85.5
OxyHb ( $\mu$ M)	0.027	-0.80	-0.04	-0.01	0.00	-3.16	0.19	-1.07	0.22	-2.52

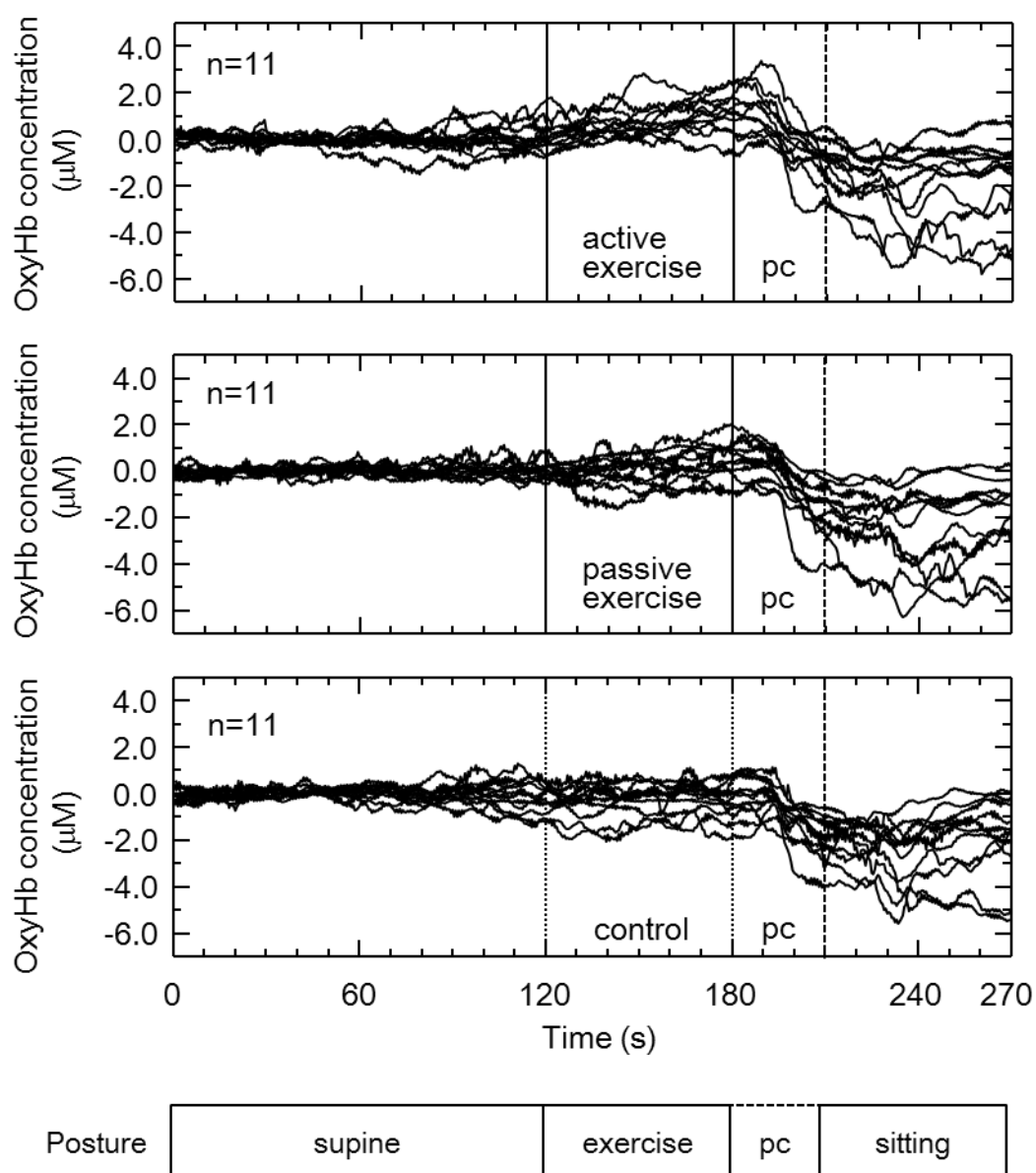
Participant	P6_passive		P7_passive		P8_passive		P9_passive		P10_passive	
	before	after	before	after	before	after	before	after	before	after
PR (bpm)	58.5	57.5	57.5	58.0	68.5	81.0	48.0	49.5	56.0	56.0
MAP (mmHg)	76.17	82.83	84.00	86.83	85.00	81.83	82.5	91.33	70.67	79.00
OxyHb ( $\mu$ M)	-0.16	-1.29	0.00	0.01	0.07	-2.18	0.22	-2.08	-0.06	-0.97

Participant	P11_passive	
	before	after
PR (bpm)	60.5	63.5
MAP (mmHg)	93.00	101.17
OxyHb ( $\mu$ M)	-0.20	-3.63

Participant	P1_control		P2_control		P3_control		P4_control		P5_control	
	before	after	before	after	before	after	before	after	before	after
PR (bpm)	64.5	65.5	55.5	59.5	68.5	67.0	63.5	69.0	60.0	60.0
MAP (mmHg)	98.50	97.00	95.33	93.67	97.00	106.17	86.83	94.83	81.33	83.17
OxyHb ( $\mu$ M)	0.18	-0.90	0.01	-0.45	0.00	-3.11	-0.14	-1.67	0.15	-2.62

Participant	P6_control		P7_control		P8_control		P9_control		P10_control	
	before	after	before	after	before	after	before	after	before	after
PR (bpm)	58.0	57.5	55.0	55.5	67.0	81.5	49.0	47.5	54.5	55.5
MAP (mmHg)	76.17	83.50	81.33	88.33	84.83	85.33	84.33	91.83	69.83	78.67
OxyHb ( $\mu$ M)	0.13	-0.50	-0.15	-1.23	0.00	-2.45	0.25	-1.41	-0.31	-1.50

Participant	P11_control	
	before	after
PR (bpm)	56.5	60.0
MAP (mmHg)	97.33	107.83
OxyHb ( $\mu$ M)	-0.43	-3.16



#### Appendix D: Individual data of oxyhemoglobin in the experiment of Chapter 3

*The top figure illustrated oxyhemoglobin (OxyHb) responses to active ankle exercise. The middle is passive ankle exercise, and bottom is the control condition respectively. Each postural change is represented as “pc” in figures.*