

a simple reflection of changes in systemic (total) blood flow (17). However, there were no obvious group differences in the cardiac output and total peripheral resistance, and no significant relation was found between cardiac output and basal whole leg blood flow. Age-related reductions in basal whole leg blood flow are associated with tonically elevated muscular sympathetic nerve activity that would result in vasoconstriction (9). However, sympathetic nerve activity is reported to be higher, rather than lower, in resistance-trained older adults than in sedentary controls (26). Together, these findings do not support the hypothesis that changes in systemic blood flow and sympathetic nerve activity contributed to the preserved leg blood flow in resistance-trained men in the present study. Clearly, further studies are warranted to determine physiological mechanisms underlying effects of resistance exercise on arterial hemodynamics.

The present findings have potentially important clinical and physiological implications. It is widely accepted that resistance training in middle-aged and older adults increases power, reduces the difficulty of performing daily tasks, and promotes participation in spontaneous physical activity (6, 15). The present findings extend the beneficial influence of resistance training to vascular function in the aging human, contributing to the preservation of basal whole leg blood flow with age. The reduction in leg blood flow may limit peripheral glucose uptake and contribute to glucose intolerance and hyperinsulinemia in middle-aged and older adults (18). Additionally, it may also impair the clearance of atherogenic lipids and contribute to chronic dyslipidemia (5). Daily resistance training may contribute to the lower incidence of cardiovascular disease through its influence on basal leg blood flow.

Our laboratory has previously reported that the repeated increases in blood flow due to exercise training are associated with expansive arterial remodeling in the femoral artery (21). Our present results extend these previous reports in endurance-trained men to resistance training. In the present study, resistance-trained men had larger femoral arterial diameter compared with sedentary counterparts. Taken together, these results suggest that both aerobic and resistance exercise appear to cause arterial enlargement at the level of major conduit arteries. Although the cause-and-effect relation cannot be determined with our research design, it is plausible to hypothesize that the diameter of femoral artery enlarges over years to more easily accommodate the daily dose of high blood flow during repeated exercise sessions.

As illustrated in the present study as well as in other studies, age is an important factor for determining leg blood flow and hemodynamics. However, it should be noted that age explains only 10–20% of variance associated with leg blood flow. Thus many more aspects need to be critically analyzed in the future studies.

In summary, the age-associated reduction in basal whole leg blood flow did not occur in resistance-trained men, suggesting that daily weight training may prevent decreases in basal whole leg blood flow with advancing age. Importantly, preserved blood flow in resistance-trained men was independent of muscle mass. These results suggest that habitual resistance exercise may favorably influence leg perfusion and hemodynamics in the aging human.

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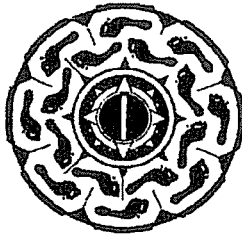
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# Effect of aging on carotid artery stiffness and baroreflex sensitivity during head-out water immersion in man

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## Abstract

To examine the possible age-related blood pressure (BP) deregulation in response to central hypervolemia, we measured spontaneous baroreflex sensitivity (SBRs), carotid arterial compliance (CC), and R-R interval coefficient of variation (RRICV) during basal and thermoneutral resting head-out-of-water immersion (HOWI) in 7 young (YG = 24.0 ± 0.8 years) and 6 middle-aged/older (OL = 59.3 ± 1.3 years) healthy men. Compared with basal conditions (YG = 19.6 ± 4.0 vs OL = 6.1 ± 1.5 ms/mmHg,  $P < 0.05$ ), SBRs remained higher in YG than OL during rest HOWI (YG = 23.6 ± 6.6 vs OL = 9.3 ± 2.1 ms/mmHg,  $P < 0.05$ ). The RRICV was significantly different between groups (YG = 6.5 ± 1.4 vs OL = 2.8 ± 0.4%,  $P < 0.05$ ) under HOWI. The OL group had no increase in CC, but a significant increase in systolic BP (basal = 115.3 ± 4.4 vs water = 129.3 ± 5.3 mmHg,  $P < 0.05$ ) under HOWI. In contrast, the YG group had a significant increase in CC (basal = 0.16 ± 0.01 vs water = 0.17 ± 0.02 mm<sup>2</sup>/mmHg,  $P < 0.05$ ) with no changes in systolic BP. SBRs was positively related to CC ( $r = 0.58$ ,  $P < 0.05$  for basal vs  $r = 0.62$ ,  $P < 0.05$  for water). Our data suggest that age-related vagal dysfunction and reduced CC may be associated with SBRs differences between YG and OL groups, and with BP elevation during HOWI in healthy older men.

## Key words

- Aging
- Baroreflex sensitivity
- Carotid compliance
- Water immersion
- Hypertension
- Vascular stiffness

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## Introduction

Orthostatic hypotension is prevalent with aging (1) and a proposed underlying mechanism is associated with impaired arterial baroreflex sensitivity (BRS; 2,3). It has been reported that in hypovolemic stress induced by head-up-tilt, the fluid shifts from the upper to the lower part of the body, unloading

cardiopulmonary and arterial baroreceptors. In contrast, head-out-of-water immersion (HOWI) results in a significant increase in cardiac filling accompanied by loading of cardiopulmonary and arterial baroreceptors (4). Arterial baroreceptors are sensory nerve endings that innervate large arteries (carotid sinuses and aortic arch) and appear to contribute importantly to the regulation of blood

pressure (BP) by the withdrawal of cardiac vagal tone (the immediate increase in heart rate (HR) determined by the acceleration of the electrocardiographic (ECG) R-R interval) during orthostatic challenge (5).

Age-related changes seem to provoke autonomic changes with impairment of vagal baroreflex and increases of baseline muscle sympathetic nerve activity (2). Shi et al. (6) demonstrated that age-related cardiac vagal dysfunction is associated with an attenuated response of BP regulation during hypovolemic stress. Their study showed that the elderly experienced orthostatic hypotension at the onset of orthostatic challenge because of a diminished HR response, but the increased vasoconstriction helped maintain their BP during a hypovolemic stress.

It has long been believed that aging leads to progressive structural and functional changes within the arterial walls, which are associated with increased vascular stiffness (7). In association with structural alterations, the elastic properties of the carotid arterial wall are reduced, blunting the baroreceptor response to increases in BP (8). Studies have revealed that the reduced carotid artery compliance (9,10) plays an important role in the age-associated decrease in cardiac BRS. On the other hand, studies (11,12) using hypovolemic circulatory stress have not detected changes in cardiovascular reflex responses with aging. Thus, the inconclusive findings concerning baroreflex responsiveness in young and older men, as well as its physiological consequences, provide a compelling rationale for the study of hemodynamic changes associated with BP regulation with advancing age.

The primary goal of the present study was to investigate age-related changes in cardiac autonomic control and elastic properties of the carotid artery related to BP regulation during resting hemodynamic stress. We used water immersion to load arterial and cardiopulmonary baroreceptors and hypothesized that: i) BP deregulation is prevalent in older adults and an underlying

mechanism may be the result of impaired BRS, and ii) age-related vagal dysfunction and elastic properties of the carotid artery could be related to BP changes and BRS responses during hemodynamic stress.

## Material and Methods

### Subjects

Thirteen healthy males, 7 young (YG,  $24 \pm 0.8$  years) and 6 middle-aged/older men (OL,  $59.3 \pm 1.3$  years), volunteered for the study. All signed an informed consent form released prior to participation. The experiments were carried out with the approval of the Ethics Committee of Kyoto University, Graduate School of Human and Environmental Studies. The subjects studied are normotensive (BP  $< 140/90$  mmHg) with no evidence of renal or cardiovascular disease as indicated on the basis of medical history and of a resting electrocardiogram.

### Experimental design

All of the experimental procedures were performed in two randomized sessions (resting basal conditions and during resting HOWI) on separate days at the same time each day. The following randomized measurements were made: anthropometric parameters, carotid artery diameter (CD), echocardiography measures, beat-to-beat HR, and BP. All measurements were made with the subject in the upright-seated position.

### Experimental procedures

All measurements were made with the subjects sitting on a chair under resting basal conditions (air temperature of  $27^{\circ}\text{C}$ ) and in a similar position during rest thermoneutral water immersion. An adjustable chair was placed in the swimming pool to adjust the water to heart level in all subjects evaluated. The subject, wearing only swim shorts, was

instrumented with cuffs around the left upper arm and right finger for the determination of brachial and peripheral arterial BP, respectively. Simultaneously, a beat-to-beat HR signal was recorded using a bipolar lead (CM5 lead). The noninvasive peripheral BP wave was recorded using an automatic sphygmomanometer (Finapres 2300, Ohmeda, Englewood, CO, USA) connected to a finger cuff containing a plethysmographic transducer. The noninvasive beat-to-beat BP recording device was fitted to the middle finger of the hand. The arm was placed at the level of the heart and adjusted for similar brachial BP values in all subjects under basal conditions and during rest HOWI. Then, the analog output of the ECG (with a band pass filter between 0.5 and 100 Hz) and BP signals were digitized via a 13-bit analog-to-digital converter (Trans Era Corporation, South Orem, UT, USA) at a sampling rate of 1 kHz. The beat-to-beat ECG and BP signals collected under basal conditions and during rest HOWI were stored on a computer hard disk for later analysis. To analyze spontaneous BRS (SBRS) and HR variability (HRV) the beat-to-beat ECG and BP signals were collected for 300 s.

Our beat-to-beat ECG and BP data collection procedures have been described in detail (13,14). The standard time domain analysis of HRV was performed by calculating the beat-to-beat ECG R-R interval coefficient of variation [ $RRICV = (R-R \text{ interval standard deviation} \times 100) / \text{mean R-R interval}$ ]. In addition, the systolic (SBP) and diastolic blood pressure (DBP) was measured at the 5th and 10th min in the left brachial artery with a standard sphygmomanometer. Arterial pulse pressure (PP) was calculated from arterial SBP minus DBP, and mean arterial blood pressure (MBP) was calculated from  $DBP + 1/3 PP$ .

#### Left ventricular vessel size

Subjects were studied under quiet resting

basal conditions while they were sitting on a chair and in a similar position during rest HOWI. Our procedures to measure left ventricular size have been described in detail elsewhere. Briefly, left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic ascending aortic diameter (LVESD) were measured by M-mode echocardiography with a model SSD 870 apparatus (Aloka, Tokyo, Japan) with the 2.5-MHz sector probe as previously reported (15). LVEDD and LVESD were measured during end respiration as an average of measurements from 3 M-mode pictures obtained from parasternal long axis views. All measurements were performed in a blind fashion and analyzed by the same investigator. Stroke volume (SV) was derived from measurements of LVEDD minus LVESD volumes. Cardiac output (CO) and total peripheral resistance were calculated from  $HR \times SV$  and  $MBP/CO$ , respectively, using brachial MBP and HR values obtained before the measurements of M-mode echocardiography, as described previously (16).

#### Carotid artery measurements

Subjects were studied in a sitting position under resting basal conditions and during rest HOWI. Common CD was measured from the images derived from an ultrasound machine (Shimadzu SSD 350, Tokyo, Japan) equipped with a high-resolution linear array transducer (7.5 MHz) as previously described by Miyachi et al. (17). A longitudinal image of the cephalic portion of the common carotid artery was acquired 1 to 2 cm proximal to the carotid bulb, with the transducer placed at a 90° angle to the vessel so that near and far wall interfaces were clearly discernible. These images were recorded using a VHS videocassette recorder and analyzed with computerized image analysis software (NIH Image). The same investigator who was blind to the group of the subjects performed all image analysis. Meas-

urements of maximal (systolic) and minimal (diastolic) lumen diameters from the media adventitia border of the near wall to the intima-lumen interface of the far wall were made for analysis. The  $\Delta$ CD was calculated using the difference between systolic ( $CD_{sys}$ ) minus diastolic ( $CD_{dia}$ ) CD. For the determination of arterial compliance under basal conditions and during rest HOWI, we used the combination of common CD with peripheral BP measurements obtained under basal conditions and during rest HOWI, respectively, using the following equation previously described (18):

$$\text{Arterial compliance} = [(CD1 - CD0)/CD0] / [2(P1 - P0)] \times \pi \times (CDO)^2$$

where arterial compliance is reported in  $mm^2/mmHg$ ; CD1 = maximal CD (mm); CD0 = minimal CD (mm); P1 = highest BP (mmHg); P0 = lowest BP (mmHg).

#### Spontaneous baroreflex sensitivity

##### The spontaneous baroreflex modulation

Table 1. Cardiovascular parameters at rest during basal conditions and during head-out water immersion of young and older subjects

	Young group		Older group	
	Basal	Water	Basal	Water
Heart rate (bpm)	53.4 ± 3.5	57.1 ± 3.1	62.9 ± 4.6	63.4 ± 5.6
RRICV (%)	4.8 ± 0.8	6.5 ± 1.4	2.3 ± 0.4	2.8 ± 0.4
Systolic BP (mmHg)	106.9 ± 2.5	105.9 ± 3.6	115.3 ± 4.4*	129.3 ± 5.3*
Diastolic BP (mmHg)	63.7 ± 2.4	58.4 ± 2.6	70.5 ± 4.6	72.0 ± 5.3*
Mean BP (mmHg)	78.0 ± 2.2	74.2 ± 2.1	85.7 ± 3.8	91.0 ± 4.6*
Pulse pressure (mmHg)	43.1 ± 2.1	47.4 ± 4.6	44.8 ± 5.0	57.3 ± 5.3*
LVESD (mm)	3.1 ± 0.1	3.1 ± 0.2	3.2 ± 0.2	3.2 ± 0.2
LVEDD (mm)	4.7 ± 0.1	4.9 ± 0.2	4.7 ± 0.2	4.9 ± 0.1
Cardiac output (l/min)	4.6 ± 0.2	5.2 ± 1.9*	4.6 ± 0.8	5.5 ± 1.1*
Stroke volume (ml)	80.3 ± 7.5	94.7 ± 3.7*	72.7 ± 7.5	85.7 ± 4.6*
TPR (mmHg per l/min)	17.3 ± 0.9	14.4 ± 2.2	20.4 ± 3	17.8 ± 2

Data are reported as means ± SEM. Young group (24 ± 0.8 years, N = 7), older group (59.3 ± 1.3 years, N = 6); RRICV = ECG R-R interval coefficient of variation; BP = blood pressure; LVESD = left ventricular end-systolic diameter; LVEDD = left ventricular end-diastolic diameter; TPR = total peripheral resistance. \*P < 0.05 basal vs water (two-way ANOVA).

of HR was assessed using the sequence method. Details of this analysis have been previously described (19). Briefly, sequences of three or more consecutive beats, characterized by either a progressive rise in SBP and lengthening of R-R interval (+RR/+SBP sequences) or by a progressive decrease in SBP and shortening of the ECG R-R interval (-RR/-SBP sequences) with a correlation higher than 0.80 were identified. A linear regression was applied to each sequence and the mean individual slope of the significant SBP/R-R interval relationship obtained by averaging all slopes computed within the test period was calculated and taken as a measure of the SBRS.

#### Statistical analysis

Data are reported as means ± SEM. The unpaired Student *t*-test was used to assess statistical differences in anthropometric characteristics. Two-way analysis of variance for repeated measures was used to analyze differences between conditions (basal condition; water) and groups (YG; OL). When a significant effect was found, the Scheffé test for multiple comparisons was applied for condition and group. An alpha level of 0.05 was used to determine statistical significance. The relationships between SBRS and CD measured during rest HOWI were determined by linear regression analysis. The correlation coefficient (*r*) was calculated for the product-moment equation. All calculations were performed using the Statistica statistical program (version 5.0 for windows; StatSoft Inc., Tulsa, OK, USA).

#### Results

There was a significant difference in age between the YG and OL groups ( $24.0 \pm 0.8$  vs  $59.3 \pm 1.3$  years,  $P < 0.01$ ), but no significant difference in height ( $171.5 \pm 1.4$  vs  $169.0 \pm 2.9$  cm,  $P > 0.05$ ), weight ( $71.1 \pm 4.6$  vs  $68.9 \pm 4.1$  kg,  $P > 0.05$ ), or body fat



percentage ( $22.0 \pm 3.0$  vs  $20.6 \pm 1.6\%$ ,  $P > 0.05$ ).

**Cardiovascular responses**

The cardiovascular responses obtained for the two groups under the two conditions are shown in Table 1. No significant differences were detected in HR, LVESD, or LVEDD between groups between the basal condition and resting HOWI. There were no differences in RRICV between groups under basal conditions, but RRICV was significantly different between the YG and OL groups during resting HOWI. The SV and CO were significantly increased while total peripheral resistance was slightly decreased in both groups during rest HOWI compared with basal conditions, with no significant differences between groups. The YG group showed no increase in resting SBP or PP while the OL group showed a significant increase in SBP and PP during rest HOWI. There was a significant increase in SBP between groups during rest HOWI. The DBP and MBP in the YG group showed a slight decrease in response to resting HOWI, while the OL group showed a slight increase. We found a significant difference in DBP and MBP between groups during rest HOWI.

**Spontaneous baroreflex sensitivity**

The SBRS group data, CD and carotid artery compliance for both groups under the two conditions are shown in Table 2. SBRS was significant higher in the YG than in the OL group under basal conditions. Upon resting HOWI, the SBRS was significantly different between the YG and OL groups.

**Carotid artery diameter and compliance**

Under basal conditions, the  $CD_{dia}$  was greater while the  $\Delta CD$  was smaller in the OL group compared with the YG group. YG

subjects had significant increases in  $CD_{dia}$  and  $CD_{sys}$  in response to resting HOWI, leading to a significant difference in  $\Delta CD$  compared with the OL group. On the other hand, OL individuals showed no significant changes in  $CD_{dia}$  and  $CD_{sys}$  diameters in response to resting HOWI. Arterial compliance was significantly higher in the YG than in the OL group under basal conditions and was consistently higher in the YG group during rest HOWI.

The relation between SBRS and elastic

Table 2: Spontaneous baroreflex sensitivity, carotid artery diameters, carotid arterial compliance during basal conditions and during head-out water immersion of young and older groups at rest are summarized:

	Young group		Older group	
	Basal	Water	Basal	Water
SBRS (ms/mmHg)	$19.60 \pm 4.5$	$23.60 \pm 6.6$	$6.10 \pm 1.5$	$9.30 \pm 2.1^*$
$CD_{sys}$ (mm)	$6.64 \pm 0.2$	$7.16 \pm 0.1^*$	$7.09 \pm 0.2$	$7.21 \pm 0.3$
$CD_{dia}$ (mm)	$5.95 \pm 0.2^*$	$6.41 \pm 0.1^*$	$6.63 \pm 0.2$	$6.76 \pm 0.2$
$\Delta CD$ (mm)	$0.69 \pm 0.1$	$0.75 \pm 0.1$	$0.46 \pm 0.1$	$0.46 \pm 0.1^*$
Compliance (mm <sup>3</sup> /mmHg)	$0.16 \pm 0.01^*$	$0.17 \pm 0.02$	$0.12 \pm 0.02$	$0.10 \pm 0.02^*$

Data are reported as means  $\pm$  SEM. Young group ( $24 \pm 0.6$  years,  $N = 7$ ), older group ( $59.3 \pm 1.3$  years,  $N = 6$ ); SBRS = spontaneous baroreflex sensitivity;  $CD_{dia}$  = diastolic carotid artery diameter;  $CD_{sys}$  = systolic carotid artery diameter;  $\Delta CD$  = difference between  $CD_{sys}$  and  $CD_{dia}$ . \* $P < 0.05$  (and vs water); † $P < 0.05$  young vs older during basal conditions; \* $P < 0.05$  young vs older in water (two-way ANOVA).

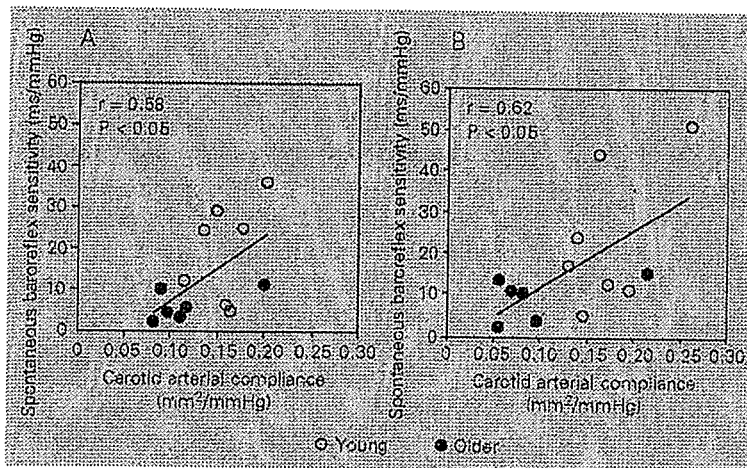


Figure 1. Scatter plots of spontaneous baroreflex sensitivity and carotid arterial compliance in all subjects during basal conditions (A), and during rest head-out water immersion (B). Correlation coefficients were determined by the method of Pearson.

properties of the carotid artery was determined in all subjects under basal conditions and during rest hypervolemic circulatory stress (Figure 1). BRS was positively related to carotid arterial compliance ( $r = 0.58$ ,  $P < 0.05$ ) under basal conditions and a significant association also was present during rest HOWI ( $r = 0.62$ ,  $P < 0.05$ ).

### Discussion

The goal of this study was to investigate age-related changes in cardiac autonomic control and elastic properties of the carotid artery related to BRS and BP regulation during resting hemodynamic stress. The new findings of this study are that the age-related vagal dysfunction and the elastic properties of the carotid artery may be related to SBRS differences between YG and OL groups, as was also the case for BP elevation during HOWI in healthy older men.

During rest HOWI, the RRICV, a measure of HRV, was significantly higher in the YG group, indicating a greater reflex action shifting the cardiovascular autonomic modulation toward the prevalence of parasympathetic activity. On the other hand, BP was significantly elevated in OL subjects with a lack of buffering vagal autonomic modulation during rest HOWI. These findings agree with previous studies suggesting that age-related vagal deficiencies may contribute to BP deregulation (6), which would reduce neural transduction of stretch into vagal outflow (associated with central autonomic integration, vagal outflow and sinoatrial node responsiveness) and blunt baroreflex responses (20).

In the present study, the SBRS was significantly higher in the YG than in the OL group under basal conditions. Upon resting HOWI, the SBRS was significantly different between OL and YG groups. Reduced BRS is associated with potentially adverse changes in BP control including an increase in arterial BP variability (21-24). On the other hand, HOWI is a powerful stressor used to assess

autonomic nervous modulation as it relates to BP control. In the present study, our HOWI procedures stimulated arterial baroreceptors because PP and RRICV increased in the OL and YG groups, respectively. Since SBRS is based on analysis of spontaneous BP and HR fluctuations allowing us to assess the cardiac BRS as it operates in response to BP variations, in the present study, we chose the SBRS technique for analysis of cardiac BRS during rest HOWI.

It is well documented that a complex interaction exists between cardiac baroreflexes and arterial baroreflexes (25). Shi et al. (26) reported that an increase in central venous pressure due to lower body positive pressure (LBPP) or volume expansion diminished the carotid BRS. Potts et al. (27) reported that the baroreflex gain in HR was decreased by LBPP but was not affected by volume expansion in humans. For instance, one could predict that SBRS would be reduced during rest HOWI due to the increased firing of the cardiopulmonary and arterial baroreceptors, as seen in LBPP experiments. The discrepancy between the present and previous results using LBPP in YG groups may be due to the activation of intramuscular mechanoreceptors during LBPP, which has been reported to modulate the sympathetic nervous system (28).

It has been reported that leg venous compliance may have important implications for arterial BP regulation during orthostatic stress in men (29). A previous study (12) reported that the reduced cardiovascular reflex response found in the elderly during orthostatic stress seems to be caused by a reduced capacitance in the legs with age and a concomitantly smaller central hypovolemic stimulus rather than a reduced efficiency of the reflex response. In the present study, to avoid the influence of peripheral venous compliance on central blood volume, we used the sitting position during all measurements. Our results showed that both the YG and OL groups demonstrated an increase in



SV to a similar extent during rest HOWI. Furthermore, the SV and CO increased in both groups without significant differences between them. Thus, our interventional stimulus using rest HOWI during the sitting position might have increased central blood volume in YG, as well as in OL subjects and loading baroreceptors to a similar extent.

Analysis of static measures of carotid hemodynamic indicated that  $CD_{dia}$  was greater in the OL compared with the YG group values at basal conditions. Also, the OL group showed a smaller  $\Delta CD$  during the cardiac cycle reflecting the loss of arterial wall distensibility in older adults. These changes between YG and OL are consistent with findings of previous studies showing the main modifications of the physical properties of large arteries in human vascular aging: an increase in arterial diameter (30) and a decreased distensibility (9). Despite increased  $CD_{dia}$  at baseline, OL subjects showed no changes in carotid diameters with resting HOWI, but a significant increase in peripheral SBP and PP during HOWI. On the other hand, the YG group had a significant increase in  $CD_{dia}$  and  $CD_{sys}$  diameters and peripheral MBP decreased by 4 mmHg. During rest HOWI, the MBP in the OL group increased by 5 mmHg as compared to basal conditions. We found significant differences in MBP and DBP during resting HOWI between groups. Previous study (31) showed that transmural arterial pressure was linearly related to changes in carotid diameter. In patients after endarterectomy, those with increased carotid sinus diameter had greater carotid sinus nerve activity and lower post-operative BP (32). Thus, in the present study, the significant increase in carotid diameters in YG group during resting hypervolemic stress, may contribute to maintain stable the BP. On the other hand, the absence of changes in carotid diameters in OL group may reflect the large arterial rigidity with advancing age which tends to increase SBP and PP during rest hypervolemic stress. The reduction in

BP obtained during rest HOWI in the YG group is in line with the previous study (33) measuring BP invasively during rest HOWI in young subjects.

Hunt et al. (20), and more recently Komet et al. (34) suggested that assessment of variation in parameters derived from CD might serve as an appropriate index of arterial baroreceptor stimulus and resulting afferent activity. Recently, published papers, argue for an important role of arterial compliance in contributing to age-associated declines in baroreflex function (9,35,36). The evaluation of carotid arterial compliance has also been reported to be an important tool for cardiovascular prognosis (including isolated systolic hypertension, left ventricular hypertrophy, congestive heart failure, and orthostatic and postprandial hypotension) in older adults (7,37-39). In the present study, the carotid arterial compliance was higher in YG subjects on basal conditions and consistently higher during rest hemodynamic stress. Furthermore, we demonstrated a positive correlation with carotid arterial compliance during basal conditions as well as under resting hypervolemic stress.

Since SBP changes are sensed by arterial baroreceptors located in the carotid sinus, the stiffening of this vessel might lead to less afferent firing for a given change in arterial pressure, which would reduce baroreceptor afferent responsiveness. Age-related vagal deficiencies may also reduce neural transduction of stretch into vagal outflow and blunt baroreflex responses. These structural and neural changes may contribute for SBRS differences between YG and OL groups, as well as BP deregulation during rest hypervolemic stress.

#### Limitation of this study

In the present study, all BP measurements were made in the periphery, which may not reflect changes that occur in the vascular regions of interest (i.e., carotid ar-

tery). Furthermore, with advancing age, the amplification of the pressure wave between central and peripheral arteries is reduced so carotid and brachial SBP become similar in older adults (40). Another arterial BRS to control muscle sympathetic nerve activity and cardiopulmonary BRS were not analyzed.

The present study provides fundamental evidence that BP deregulation is prevalent in older adults during rest hemodynamic stress.

Age-related vagal dysfunction, as well as the elastic properties of the carotid artery, may contribute to SBRS differences between YG and OL groups, as well as BP elevation during rest central hypervolemia in healthy older men. Thus, the neural and structural adaptations appear to be components of fundamental importance for cardiovascular homeostasis during rest HOWI in healthy humans.

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## スポーツ用サプリメントの有効性と有害性

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スポーツ用サプリメントは、競技成績やスポーツパフォーマンスを向上させ、試合や激しい練習で消費し不足する可能性がある栄養素を効率的に補うために用いられる。現在ではさまざまなスポーツ用サプリメントが市場に出回っており、トップアスリートからスポーツ愛好家まで幅広い人々に用いられている。エビデンスに基づき有効性が認められているサプリメントは、たんぱく質、炭水化物、重炭酸塩、クレアチン、カフェインであり、その数は多いとはいえない。単にその有効性のみならず、安全性、合法性と倫理性に照らし合わせ、適切に用いられるべきである。もし、本人が使用するべきか否か判断できない場合には、スポーツ科学に精通した科学者、医師、管理栄養士などの助言を仰ぐべきである。

### はじめに

スポーツ用サプリメントは、①食品と同様の栄養成分を含み、便利さ、実用性、おいしさを組み合わせて具体的な必要を満たすもの、いわゆる栄養補助食品と、②一般に食物よりずっと多量の栄養成分を含み、特別な栄養ニーズを満たすというより薬理的・生理学的作用を通じて機能補助または運動能力強化特性を持つもの、すなわちエルゴジェニックの二つの形態で市場に出回っており、比較的容易に購入することができる。

栄養補助食品は、表1に示す通り、清涼飲料水やスナック菓子などとほとんど区別がつかない形態や価格で市場に出回っている。アスリートやスポーツ愛好家だけでなく、運動習慣のない人もその味覚に魅かれたり、あるいは過剰に特定の効用を謳った広告などの影響を受け、摂取している場合が多い。栄養補助食品は基本的に食品なので、製品の広告やコマーシャルに謳われているほどの効果は期待できない。その一方で、副作用な

どの好ましくない影響もほとんどないので、安全性の面からは補助食品の摂取を強く否定する理由はない。

エルゴジェニックは運動能力強化特性を持つものとして売られており、表2の通り、筋量増加、成長ホルモン増産、脂肪減少、免疫機能、エネルギー産生、疲労回復などが効能として主張されている。しかし、これらの製品によって運動能力が向上することはまれである。仮に効果があると評価されているものでも、個人によって効果の程度は異なるかもしれない。また、そのような製品を不適切に使用して効果を低下させることもあるだろう。さらに、国際オリンピック委員会 (IOC) や世界アンチ・ドーピング機構 (WADA) の定める規則<sup>1)</sup>により、「ドーピング」と考えられることもある。もしエルゴジェニック製品の使用を考えているならば、その有効性、安全性、合法性、適切な1回当たり摂取量についての最新情報を提供できるスポーツ科学者やスポーツドクターの専門的なアドバイスを求める必要がある。

アスリートやスポーツ愛好家がサプリメントを

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表1. スポーツ用栄養補助食品の製品形態

スポーツ栄養補助食品	含有物	使用方法
スポーツ・ドリンク	炭水化物 6~7% / ナトリウム 10~25 mmol/l	運動中の水分・炭水化物供給 / 運動後の水分・グリコーゲン回復
液状補助食	炭水化物 50~70% / たんぱく質 10~25% / ビタミン・ミネラル強化 / 液体でも粉末でもとれる	体重増加を助ける凝縮されたエネルギー供給源 / 運動後食欲がない場合に特に適した回復用スナック
炭水化物ローダー・パウダー	グルコース・ポリマー(ブドウ糖重合体)として炭水化物 100%	レース前にグリコーゲン蓄積を最大化するために / 運動後のグリコーゲン・レベルの回復
炭水化物ゼリー	袋当たり炭水化物 20~30 g / 各種添加物(アミノ酸, 鉄分, カフェイン, ガラナ, ビタミンC・Eなど)	凝縮された炭水化物供給源 / いつでも摂取できる
ビタミン・ミネラルのサプリメント	各ビタミンの食事からの推奨摂取量の全量を満たす / また特別なビタミン・ミネラルの大量摂取	エネルギー消費が少ない人 / 食事制限中や食品品質の保証がない国でレースする場合 / 欠乏症と診断された場合の治療
スポーツ・バー	炭水化物 40~50 g / プロテイン 10+g / ビタミン・ミネラル	凝縮された炭水化物供給源 / いつでも摂取できる

用いる理由は二つある。① 競技成績やスポーツパフォーマンスを向上させること、② 試合や激しい練習で消費し不足する可能性がある栄養素を効率的に補うことである。現在では、トップアスリートのみならず、一般スポーツ愛好家、ひいては習慣的にスポーツをしていない人であっても、少なくともスポーツドリンクなどの栄養補助食品を飲食した経験はあると思われる。このように、スポーツ用サプリメントの使用は、あらゆるレベルのスポーツマンに広がっているが、サプリメント、特にエルゴジェニックを使用すべきか否かについては、以下の三つの点を十分に考慮する必要がある。

- 1) 有効か：期待されたパフォーマンス向上が見込めるか？
- 2) 安全か：心身を障害するような作用はないか？
- 3) 合法的かつ倫理的か：ドーピングに相当しないか？ 個人の倫理観に抵触していないか？

以上三つの点のうち、どれか一つでも問題がある場合にはスポーツ用サプリメントの使用を控えるなければならない。

### スポーツ用サプリメントの有効性

スポーツ用サプリメントが有効か否かについて

判断する材料には以下の3点がある。① 製品の広告や雑誌・インターネットの記事、② アスリート個人の経験と証言、③ 研究による考察である<sup>2)</sup>。結論から先にいえば、③ 研究による考察のみが信頼できる判断材料とって良い。

1. 製品の広告や雑誌・インターネットの記事  
 栄養補助食品やエルゴジェニックを製造している企業は、利益を生むことが目的なので、製品による利益を追求するあまり本当の効果と懸け離れた効能を謳った広告を行う可能性がある。広告によるごまかしの手法の代表として、実験計画や精度が不十分な研究による発見、スポーツ団体のお墨付きや推薦、特許の申請があげられるが、そのいずれも製品の有効性を示すものではない。また、インターネットなどの規制のかけにくい媒体に真実と異なる記事を掲載し、製品の広告をリンクさせる手法なども近年頻繁に用いられている。

### 2. アスリート個人の経験と証言

一流アスリートをキャラクターに登用して販売促進を行う会社もある。アスリート自身は、この製品を使ってパフォーマンスが向上したとはいわないとしても、それをみた消費者(特にそのアスリートに憧憬を抱いている者)は、通常は効果があるのではという印象を受けやすい。また、実際にそれを自分で試してみたところ、試合で調子が良くなったと感じるかもしれない。このような個人的体験は“プラセボ効果”によるところが大き

表2 エルゴジェニックスの効能とその科学的根拠

分類と品目	効能	科学的根拠
<b>栄養学的エルゴジェニックス</b>		
水分補給	心循環機能低下予防, 体温調節, 脱水予防	あり
炭水化物サプリメント	高強度運動のエネルギー源の補給	あり
プロテイン	筋量増加, 筋力増強, 栄養バランスの保持	あり
アルギニン, リジン, オルニチン	筋量増加, 体脂肪率減少	なし
BCAA's, グルタミン	成長ホルモンの増産, 筋肉の成長を刺激, 疲労軽減, 耐久能力, 免疫能力の向上	なし
アスパラギン酸塩	遊離脂肪酸の利用高進とグリコーゲン節約	なし
抗酸化物 (例: ビタミン A・C・E)	練習による筋肉の酸化損傷を軽減する	不明
葉酸	DNA 合成の補酵素で赤血球増加に関与	なし
鉄分	エネルギー利用とたんぱく質合成向上, ヘモグロビン合成	なし
マグネシウム	筋量増加, 筋力増強	なし
カルシウム	筋収縮の円滑化やエネルギー代謝にかかわる酵素の活性化	なし
ホウ酸	テストステロン上昇に伴う筋量増加と脂肪量減少	なし
クロム	血糖を低下させ, インスリン感受性を高め, 糖代謝を活発化	なし
リン酸塩	代謝に重要な役割を持ち, エネルギー代謝を活性化し, 赤血球数を増加させる	不明
HMB	筋肉の損傷とたんぱく質の破壊を抑制し, 筋肉増強を促進する	不明
朝鮮人参	スタミナ補給	なし
<b>生理学的エルゴジェニックス</b>		
重炭酸ナトリウム	乳酸蓄積を緩衝し, ミドルパワー競技での持久力を保持	あり
クレアチン	繰り返し行われる集中度の高い練習による疲労回復を促進する	あり
コエンザイム Q10	高強度運動によるフリーラジカルによる細胞ダメージを防ぐ	なし
コリン塩, レシチン	神経伝達物質の増加を補助	なし
グリセロール (アミノ酸の一つ)	強力な水分補強剤で練習前の摂取により水分不足を減らし体温維持効果がある	不明
カルニチン	遊離脂肪酸の利用高進とグリコーゲン節約	なし
<b>薬理的エルゴジェニックス</b>		
カフェイン	脂肪代謝を促進, 神経系統を刺激, 集中度の高い練習と耐久能力を強化する	あり
アルコール	鎮静剤として心理ストレスの緩和作用	なし

い。このような場合には、製品の意図しない効果も併せて発揮される場合がある。真に有効なサプリメントは、それが意図した通りのパフォーマンス向上効果だけがみられるはずである。

### 3. 研究による考察

スポーツ用サプリメントの有効性を確認するためには“適切な”研究成果の集積が必要である。“適切な”研究とは、以下の条件が整っているものと考えて良いであろう。正当な原理や学問的背景、適切な被験者群、スポーツパフォーマンスや生理学的指標の適切な評価、十分な習熟試行と研究への慣れ、プラセボを用いた無作為割り付け介入、二重盲検、テストや評価環境の制御、適切な統計

処理といった条件である。

研究の成果は、審査済み論文として学術誌に掲載されている。情報源としては、① 個別研究、② 権威ある専門家による総説、③ 統計学を駆使したメタ解析の三つであるが、後者ほどエビデンスレベルが高いとあって良い。

### スポーツ用サプリメントの分類と利用法

スポーツ用エルゴジェニックスは、① 通常の食品にも含まれる栄養素からなる栄養学的エルゴジェニックス、② 自然な生理機能を高進する働きを持つ生理学的エルゴジェニックス、③ ホルモンや神経伝



表3 スポーツ用サプリメントの機能と分類

サプリメントの機能	分類		
	栄養学的	生理学的	薬理的
<b>身体パワー増加のためのサプリメント</b>			
筋量増加	たんぱく質・アミノ酸	成長ホルモン	アナボリックステロイド
代謝高進	ビタミン類	カルニチン	興奮薬
エネルギー供給の増加	炭水化物	クレアチン	アルコール
エネルギー源運搬の向上	鉄	血液	カフェイン
蓄積物質の中和	抗酸化物	重炭酸ナトリウム	抗消炎薬
<b>精神力向上のためのサプリメント</b>			
興奮を誘発	アミノ酸	コリン	アンフェタミン
鎮静に導く	ビタミンB	重炭酸ナトリウム	鎮痛薬
<b>バイオメカニクスの効率を高めるサプリメント</b>			
体重や筋量の増加	たんぱく質・アミノ酸	クレアチン	アナボリックステロイド
体重や脂肪の減少	クロム	成長ホルモン	利尿薬

違物質と同様に作用するように設計された薬理的エルゴジェニックの三つに分類される。

スポーツのパフォーマンスを高めるためには、

① 身体的パワーの向上、② 精神力の向上、③ バイオメカニクスの効率の向上の三つの機序が重要であるが、真に有効なサプリメントは予想される機序によって意図した通りにパフォーマンス向上に寄与する。

表2と3にサプリメントの分類と、どの機序に基づいて作用するのか示した。

### 有効なスポーツ用サプリメントの実際

表2に各サプリメントの有効性に関するエビデンスの有無について示した<sup>3-7)</sup>。多くのサプリメントの中で、意図通りの運動パフォーマンス向上が期待できるというエビデンスが十分に得られているのは、① たんぱく質、② 炭水化物、③ 炭酸水素ナトリウム、④ カフェイン、⑤ クレアチンである。

1) たんぱく質は筋などの体を構成する材料であるが、激しいトレーニングを行っているアスリートでは体重1kg 1日当たり1.5~2.0gの摂取が必要で、これは一般人の1.5~2倍に相当するため、一般人と同じ質の食事を摂る場合には相当な食事量を摂取する必要がある。プロテインパウダーのような形態のたんぱく質サプリメントは、アミノ酸がバランスよく配合されており、正しい食事とトレーニングとの組み合わせで、筋量や筋

力の増加が期待できる。

2) 炭水化物は、原則として食事により摂取されることが望ましいが、試合前や試合の合間などにエネルギーを手早く補給する必要がある場合には、炭水化物サプリメントなどを利用すると良い。特に長時間の試合や、もしくは複数の試合が繰り返されることによるエネルギー枯渇を防ぐことや、炭水化物ローディングによる筋グリコーゲンの増加などに有用であり、粘り強さを引き出すことができる。

3) 重炭酸ナトリウムは、血中乳酸の増加に伴う血液のアシドーシスを抑制し、45秒~6分間続く、中・長距離走のような運動のパフォーマンスを高める。

4) クレアチンサプリメントの摂取は筋中のクレアチン量を増加させ、クレアチンリン酸の再合成を容易にする。したがって、短時間、反復、高強度の競技のパフォーマンスの向上に有用である。

5) カフェインは、有効と考えられる五つのサプリメントの中で唯一これまでドーピング規則により記載されている物質であった(2005年1月1日以降除外された)。しかし、コーヒーでカップ7杯以上を摂取しないと陽性と判定されなかったが、それ以下のカフェイン摂取でも、覚醒状態を保ち、交感神経興奮ならびに遊離脂肪酸の利用を高める効果により、特に長時間運動のパフォーマンスを向上させるのに有効である可能性がある。

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## スポーツ用サプリメントの安全性

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生体に影響を及ぼす物質は、すべて過剰に摂取すれば毒となると考えて良い。すなわちサプリメント、特にエルゴジェニックは過剰に摂取し、用法を誤れば健康上のリスクとなる可能性が高い。健康を害するサプリメントをアスリートやスポーツ愛好家がわざわざ摂取するとは考えられないが、一部のアスリートにとっては、スポーツでの成功の方が健康を害するリスクよりも優先される場合がある。

サプリメントの効果に関する研究はかなり多いが、サプリメントを長期にわたり摂取したことによる健康被害に関する科学的データはほとんどない。動物実験や健康被害を体験した人の症例研究が散見されるのみである。人を対象としたスポーツ用サプリメントの副作用に関する研究は、研究倫理上、実施が困難である。したがって、アスリートがスポーツ用サプリメントを正当に、もしくは過剰に摂取したことによる健康被害を漏れなく収集し、データベースとしてまとめて、公表していく他にエビデンスを集積できないであろう。独立行政法人 国立健康・栄養研究所では、「健康食品」の安全性・有効性情報を収集し、広くデータベースとして公開している。このようなデータベースがスポーツ用サプリメントに関しても構築され、公開され、継続的に情報収集がなされることで、スポーツ用サプリメントの安全性や危険性に関するエビデンスの集積が期待できる。

サプリメントの有効性の項目でエビデンスに基づき有効とされたものでも、好ましくない作用がみられる場合もある。例えば、カフェインに対する感受性の高い個人では摂取により血圧が上昇し、イライラ感を感じたりする。

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## ・スポーツ用サプリメントの合法性と倫理性

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ここでいう合法性とは、スポーツ用サプリメントがドーピングに当たるか否かという問題である。ドーピングとは、「競技パフォーマンスを人工的かつ不正な方法で向上させる意志を持って、身

体に異質な物質を投与あるいは服用すること、あるいは生理的物質であっても異常な量を摂取したり、異常な経路で体内に入れること」と国際オリンピック委員会により定義されている。このような行為にスポーツ用サプリメントの摂取（特に過剰な）が相当するか否かという点である。

ドーピング物質に指定されていない合法的サプリメントでも（例えばクレアチンや重炭酸ナトリウムのような）、通常の食事で摂取されるよりもかなり多く、サプリメントを用いて意図的に摂取し、スポーツパフォーマンスが高まった場合、ドーピング規則を犯していることになるのであろうか。法的には恐らくシロであるが、アンチドーピングの精神からすると倫理的問題はあるといえるかもしれない。このような場合には、アスリート個人の倫理観が、サプリメント使用の可否を決定する要因となる。

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## おわりに

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スポーツ用サプリメント、特にエルゴジェニックの使用に当たっては、その有効性、安全性、合法性ならびに倫理性に基づいた個人の判断による適切な使用が求められる。自らの判断によって使用の可否が判断できない場合、スポーツ医科学に精通した医師や管理栄養士の指導を仰ぐことが必要である。

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## Experimental Physiology

## Variations in carotid arterial compliance during the menstrual cycle in young women

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The effect of menstrual cycle phase on arterial elasticity is controversial. In 10 healthy women ( $20.6 \pm 1.5$  years old, mean  $\pm$  s.d.), we investigated the variations in central and peripheral arterial elasticity, blood pressure (carotid and brachial), carotid intima-media thickness (IMT), and serum oestradiol and progesterone concentrations at five points in the menstrual cycle (menstrual, M; follicular, F; ovulatory, O; early luteal, EL; and late luteal, LL). Carotid arterial compliance (simultaneous ultrasound and applanation tonometry) varied cyclically, with significant increases from the values seen in M ( $0.164 \pm 0.036$  mm<sup>2</sup> mmHg<sup>-1</sup>) and F ( $0.171 \pm 0.029$  mm<sup>2</sup> mmHg<sup>-1</sup>) to that seen in the O phase ( $0.184 \pm 0.029$  mm<sup>2</sup> mmHg<sup>-1</sup>). Sharp declines were observed in the EL ( $0.150 \pm 0.033$  mm<sup>2</sup> mmHg<sup>-1</sup>) and LL phases ( $0.147 \pm 0.026$  mm<sup>2</sup> mmHg<sup>-1</sup>;  $F = 8.51$ ,  $P < 0.05$ ). Pulse wave velocity in the leg (i.e. peripheral arterial stiffness) did not exhibit any significant changes. Fluctuations in carotid arterial elasticity correlated with the balance between oestradiol and progesterone concentrations. No significant changes were found in carotid and brachial blood pressures, carotid artery lumen diameter, or IMT throughout the menstrual cycle. These data provide evidence that the elastic properties of central, but not peripheral, arteries fluctuate significantly with the phases of the menstrual cycle.

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Arterial compliance reflects the ability of an artery to expand and recoil during cardiac contraction and relaxation, stabilizing the fluctuations in arterial pressure and blood flow (Nichols & O'Rourke, 1998). Reductions in central arterial compliance impair this buffering function, contributing to elevations in systolic blood pressure, development of left ventricular hypertrophy, and reductions in arterial baroreflex sensitivity (O'Rourke, 1990; Tanaka *et al.* 1998; Monahan *et al.* 2001). Since lower central arterial compliance is associated with increased mortality in patients with end-stage renal failure and essential hypertension (Blacher *et al.* 1999), prevention and treatment of decreased central arterial compliance are important.

Many studies have reported that hormone replacement therapy (HRT) effectively prevents and, in some cases, reverses the decreases in central arterial compliance seen in postmenopausal women (McGrath *et al.* 1998; Bui *et al.* 2002). McGrath *et al.* (1998) reported that carotid arterial distensibility in women with oestrogen treatment alone was greater than that in women with oestrogen plus progestin treatment. In addition, several reports could not identify any increases in arterial compliance in women receiving oestrogen and progesterone (Westendorp *et al.* 2000; Teede *et al.* 2001). These results suggest that progesterone seems to counteract the effects of oestrogen on arterial elasticity.

The effects of the menstrual cycle on arterial compliance also have never been conclusive. One study showed that carotid and femoral arterial distensibility and compliance did not change significantly during the menstrual cycle (Willekes *et al.* 1997). In contrast, it was reported that systemic arterial compliance, but not aortic pulse wave velocity increases in the late follicular phase and decreases after ovulation during the menstrual cycle (Williams *et al.* 2001). Changes in radial artery compliance were similar (Giannattasio *et al.* 1999). This discrepancy may be derived from differences in the evaluation of arterial elasticity and/or the method of identifying the menstrual cycle phase. In these two studies, however, measurements of arterial compliance around the time ovulation were not done even though blood oestradiol concentrations increase sharply prior to ovulation. Therefore, we decided to divide the menstrual cycle into phases in order to examine changes in the arterial elasticity in detail.

From previous studies, we hypothesized that carotid arterial compliance changes significantly during the menstrual cycle, probably in a manner that is synchronized with the balance between serum oestrogen and progesterone. To address this aim comprehensively, we determined the changes in central and peripheral arterial compliance and stiffness at five hormonal time points during the normal menstrual cycle in healthy young women.

## Methods

### Subjects

Ten healthy sedentary or recreationally active young women, ranging in age from 18 to 24 years old ( $20.6 \pm 1.5$  years old, mean  $\pm$  s.d.), were examined. All subjects were normotensive, non-diabetic and non-smokers who did not take any form of oral contraception. Seven of the subjects jogged daily ( $1\text{--}2$  h  $\text{day}^{-1}$ , 3 or 4 days  $\text{week}^{-1}$ ) and three subjects were sedentary women. All subjects had regular menstrual cycles ranging between 25 and 32 days (mean, 28.3 days) in length for at least two menstrual cycles before experimentation. All subjects gave their written informed consent prior to participation. All procedures were approved by the Ethics Committee of the University of Tsukuba and conformed with the Declaration of Helsinki.

### Study protocol

The changes in central and peripheral blood pressure, carotid arterial elasticities (carotid arterial compliance, distensibility coefficient and the  $\beta$ -stiffness index), peripheral arterial stiffness (pulse wave velocity in the leg), and serum ovarian hormone (oestradiol and

progesterone) concentrations were measured in five phases of the subject's menstrual cycles: menstrual phase (M; 2–4 days after the beginning of menstruation); follicular phase (F; the middle day between the day of measurement in the M phase and the predicted day of ovulation), ovulatory phase (O; the 3 day period beginning 2 days prior ovulation), early luteal phase (EL; 4–7 days after ovulation), and late luteal phase (LL; 11–13 days after ovulation). The day of ovulation was predicted on the basis of previous menstrual cycle length and the time of menstruation, using the assumption that the luteal phase duration was 14 days. Timing of ovulation was determined from the body temperature and a urinary ovulation kit (Rohto pharmaceutical Co., Ltd, Osaka, Japan). Subjects were enrolled randomly at different phases in the menstrual cycle to prevent examiner bias. To avoid potential diurnal variations, subjects were always tested at the same time of day (between 9.00 am and noon). Subjects fasted, abstaining from caffeine, for at least 12 h prior to each test. All haemodynamic and hormonal measurements were initiated by placing the subject in the supine position. Individuals were then fitted with an electrocardiogram and brachial blood pressure device. After a 20 min rest, brachial blood pressure, heart rate, pulse wave velocity of a peripheral (leg) artery, carotid arterial compliance, distensibility coefficient (DC) and the  $\beta$ -stiffness index (assessed by ultrasound imaging and applanation tonometry) were measured. After another 15 min rest, blood was drawn for hormonal measurements.

### Measurements

We combined ultrasound imaging of the common carotid artery with simultaneous applanation tonometry to obtain arterial pressure from the contralateral carotid artery. This technique permits the non-invasive determination of arterial compliance (Miyachi *et al.* 2004). Carotid artery diameter was measured from ultrasound images obtained using a high-resolution linear-array transducer. A longitudinal image of the cephalic portion of the common carotid artery was acquired 1–2 cm proximal to the carotid bulb. Computer images were digitized using a media converter and analysed using image analysis software (NIH image 1.62). The minimal and maximal lumen diameters were determined by scrolling through images acquired at 33 ms intervals. Both diameters measured the distance from the media–adventitia border of the near wall to the intima–lumen interface of the far wall. All image analyses were performed by a single investigator, who was blinded to the menstrual phase assignments.

Pressure waveforms and amplitudes were obtained from the common carotid artery using a pencil-type

probe that incorporated a high-fidelity strain-gauge transducer (SPT-301, Millar Instruments, Houston, TX, USA; Miyachi *et al.* 2004). Since baseline carotid blood pressure levels are subjected to hold-down force, the pressure signals obtained by tonometry were calibrated by equating the carotid mean arterial and diastolic blood pressures to the values determined for the brachial artery as described by Armentano *et al.* (1995). Carotid arterial compliance, DC and the  $\beta$ -stiffness index were calculated from the equation:  $(D_1^2\pi - D_0^2\pi)/[2(P_1 - P_0)]$ ,  $[(D_1^2\pi - D_0^2\pi)/D_0^2\pi]/[2(P_1 - P_0)]$  and  $\log(P_1/P_0)/[(D_1 - D_0)/D_0]$ , respectively, where  $D_1$  and  $D_0$  are the maximum and minimum diameters of the vessel and  $P_1$  and  $P_0$  are the maximal and minimal blood pressures. As previously reported (Miyachi *et al.* 2004), the day-to-day coefficients of variation were  $2 \pm 1$ ,  $7 \pm 3$  and  $5 \pm 2\%$  for carotid artery diameter, pulse pressure and arterial compliance, respectively.

Carotid artery intima-media thickness (IMT) was measured from ultrasound images obtained using a high-resolution linear array transducer as described by Miyachi *et al.* (2004). Ultrasound images were digitized using a video frame grabber and analysed using computerized image analysis software (NIH image 1.62). At least 10 IMT measurements were obtained at each segment; the mean values were used for analysis. Day-to-day coefficient of variation was  $3 \pm 1\%$  for measurement of the carotid IMT (Miyachi *et al.* 2003).

Heart rate, brachial blood pressure, and the pulse wave velocity of a leg artery (leg PWV) during resting in the supine position were measured in triplicate using a semi-automated device (form PWV/ABI, Colin Medical Technology, Komaki, Japan). Brachial blood pressures were measured by the oscilometric method as previously described (Sugawara *et al.* 2005). To measure leg PWV, we simultaneously recorded pressure waveforms at the femoral and posterior-tibial arteries. Femoral arterial pressure waveforms were acquired by two multi-element tonometry sensors attached manually to the left femoral artery. Posterior-tibial arterial pressure waveforms were recorded by a cuff that was connected to a plethysmographic sensor wrapped around the left ankle. PWVs were calculated by dividing the distance between the two arterial recording sites by the time delay between the proximal and distal 'foot' waveforms as we have previously reported (Sugawara *et al.* 2004). Day-to-day coefficient of variation was  $2.3 \pm 0.6\%$  for measurement of the leg PWV (Sugawara *et al.* 2004).

To measure serum oestradiol and progesterone concentrations in each menstrual phase, a 5 ml fasting blood sample was taken from the antecubital vein. Blood was centrifuged at 3000 r.p.m. (2000g) for 15 min. All serum samples were distributed into appropriate preservative tubes and stored at  $-80^\circ\text{C}$  until analysis. Serum oestradiol and progesterone concentrations were

measured by radioimmunoassay (Abraham *et al.* 1972) using commercially available kits. To minimize intra-assay variability, all samples were analysed together; intra-assay variability was  $< 5\%$ . Body composition was determined using the previously described bioelectric impedance method (Houtkooper *et al.* 1992).

### Statistical analysis

We performed *a priori* sample size calculation and it was decided that the number of subjects is sufficient, and our data were normally distributed. Differences across menstrual cycle phases in the parameters other than carotid arterial elastic properties were assessed by one-way analysis of variance (ANOVA) with repeated measures. For significant *F* values in ANOVA, a *post hoc* test using the Newman-Keuls method was used to identify significant differences between the mean values. We analysed for changes in arterial elastic properties (arterial compliance, distensibility coefficient and  $\beta$ -stiffness index), with brachial mean arterial pressure as covariates (ANCOVA), because blood pressure level is a key determinant of arterial elasticity. Pearson's correlation and regression analyses were performed to determine the relationship between variables of interest. The level of significance was set at  $P < 0.05$ . All data are presented as the means  $\pm$  s.d.

### Results

The 10 women examined were nulliparous, exhibiting an average menstrual cycle length of  $28 \pm 3$  days. Body weight, percentage fat and serum ovarian hormone measurements are detailed in Table 1. Measured serum oestradiol and progesterone concentrations were consistent with the predicted cycle phases of the subjects. Serum oestradiol concentrations were higher during the O and EL phases than in the other menstrual phases ( $P < 0.05$ ). Serum progesterone concentrations were significantly higher in the EL phase in comparison with the other phases ( $P < 0.05$ ). Determination of the ratio of oestradiol to progesterone (E:P ratio) is another method for identifying periods in which oestradiol is the predominant hormone. The E:P ratio was significantly higher in the O phase than in the other phases ( $P < 0.05$ ). The value of this ratio was higher in the F phase than in either the EL or LL phases ( $P < 0.05$ ). Body weight and percentage fat did not change significantly over the five phases of the menstrual cycle.

Mean values for heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and pulse pressure did not change significantly throughout the menstrual cycle (Table 2).

The carotid arterial compliance changed cyclically, increasing from M and F into the O phase and decreasing

Table 1. Physiological characteristics of subjects

Variables	M	F	O	EL	LL
Age (years)	20.6 ± 1.5	—	—	—	—
Height (cm)	158.3 ± 5.7	—	—	—	—
Weight (kg)	53.4 ± 4.9	53.4 ± 4.6	53.4 ± 4.7	53.3 ± 4.8	52.9 ± 5.2
Percentage fat (%)	26.5 ± 3.8	27.1 ± 3.7	26.6 ± 3.8	26.8 ± 3.8	26.7 ± 3.8
Oestradiol (pg ml <sup>-1</sup> )	36 ± 24	48 ± 17	142 ± 74*	132 ± 48*	67 ± 37
Progesterone (ng ml <sup>-1</sup> )	0.7 ± 0.3	0.5 ± 0.2	0.8 ± 0.6	10.5 ± 7.35†	3.9 ± 2.9
E:P ratio	52 ± 21	83 ± 12†	190 ± 121†	16 ± 9	24 ± 20

Value are means ± s.d. M, menstrual phase; F, follicular phase; O, ovulatory phase; EL, early luteal phase; LL, late luteal phase phase; and E:P ratio, oestradiol:progesterone ratio. \* $P < 0.05$  vs. M, F and LL phases; † $P < 0.05$  vs. EL and LL phases; ‡ $P < 0.05$  vs. the other four phases.

Table 2. Changes in haemodynamic indices during the menstrual cycle

Variables	M	F	O	EL	LL
Heart rate (beats min <sup>-1</sup> )	54 ± 7	53 ± 6	56 ± 7	54 ± 7	58 ± 6
Brachial SBP (mmHg)	104 ± 9	102 ± 7	103 ± 9	101 ± 7	103 ± 8
Brachial DBP (mmHg)	62 ± 3	59 ± 5	61 ± 8	60 ± 4	60 ± 8
Brachial MAP (mmHg)	78 ± 6	75 ± 5	77 ± 7	74 ± 5	77 ± 7
Brachial PP (mmHg)	42 ± 9	43 ± 6	41 ± 7	41 ± 5	43 ± 7
Carotid SBP (mmHg)	96 ± 6	96 ± 7	94 ± 7	95 ± 8	97 ± 8
Carotid PP (mmHg)	36 ± 7	38 ± 6	37 ± 4	39 ± 5	38 ± 3
Carotid diameter (mm)	5.44 ± 0.28	5.57 ± 0.28	5.47 ± 0.30	5.55 ± 0.30	5.56 ± 0.25
Carotid IMT (mm)	0.47 ± 0.02	0.46 ± 0.05	0.47 ± 0.04	0.47 ± 0.04	0.47 ± 0.04
Carotid arterial DC × 10 <sup>-3</sup> (kPa <sup>-1</sup> )	54.0 ± 14.6*	53.8 ± 12.9*	59.4 ± 13.7*	47.0 ± 11.8	45.6 ± 8.7
β-Stiffness index (a.u.)	4.2 ± 1.4	4.2 ± 1.0	3.8 ± 0.9*	4.9 ± 1.4	4.7 ± 0.7
Leg PWV (cm s <sup>-1</sup> )	816 ± 98	813 ± 92	782 ± 123	785 ± 79	833 ± 88

Values are means ± s.d. M, menstrual phase; F, follicular phase; O, ovulatory phase; EL, early luteal phase; LL, late luteal phase; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; carotid diameter, diastolic lumen diameter; IMT, intima-media thickness; PWV, pulse wave velocity; and DC, distensibility coefficient.

\* $P < 0.05$  vs. EL and LL phases.

sharply in the EL and LL phase ( $F = 8.51$ ,  $P < 0.05$ ; Fig. 1). *Post hoc* comparisons demonstrated that O phase values were significantly higher than those obtained for the M, EL or LL phases ( $P < 0.05$ ). F phase values were significantly higher than those from either the EL or LL phases ( $P < 0.05$ ). The change of carotid arterial DC was similar to that of carotid arterial compliance ( $F = 8.75$ ,  $P < 0.05$ ; Table 2). In general, qualitatively similar, inversely related changes were obtained using the carotid artery  $\beta$ -stiffness index ( $F = 4.03$ ,  $P < 0.05$ ; Table 2); *post hoc* comparisons indicated that O phase values were significantly lower those obtained during EL and LL phases ( $P < 0.05$ ). Leg PWVs did not change significantly throughout the menstrual cycle (Table 2).

No changes could be observed in the carotid arterial diastolic lumen diameter (minimum diameter), IMT, carotid systolic blood pressure or pulse pressure during the menstrual cycle (Table 2).

Across all subjects, carotid arterial compliance ( $r = 0.42$ ,  $P < 0.05$ ; Fig. 2), carotid arterial DC ( $r = 0.48$ ,  $P < 0.05$ ) and the carotid artery  $\beta$ -stiffness index ( $r = -0.39$ ,  $P < 0.05$ ) correlated significantly with the

E:P ratio. No other variables were significantly related to measurements of any carotid arterial elastic properties or leg PWV.

## Discussion

We explored the complex relationship between variations in ovarian hormones and the elastic properties of central and peripheral arteries at five distinct time points throughout the menstrual cycle. Interestingly, central (carotid) arterial compliance, but not peripheral arterial stiffness, fluctuated significantly over the course of the menstrual cycle; carotid arterial compliance increased from the menstrual phase into the ovulatory phase, declining sharply in the luteal phases. The fluctuation in carotid arterial compliance was synchronized with the changes in the balance of oestradiol and progesterone concentrations. These results indicate that central, but not peripheral, arterial elastic properties are influenced by menstrual cycle phase, suggesting that the changes in ovarian hormone concentrations may regulate the elastic properties of central elastic arteries.