The impact of aerobic fitness on arterial stiffness and adrenal cortex hormones in middle-aged and older adults

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Abstract. An increase in arterial stiffness with advance aging is a risk for cardiovascular disease. Cardiovascular dysfunction is associated with the imbalance of adrenal cortex hormones, especially with the cortisol/dehydroepiandrosterone sulfate (DHEAs) ratio. However, the impact of aerobic fitness on arterial stiffness and cortisol/DHEAs ratio is unclear. The aim of this study was to investigate the relationship between aerobic fitness, arterial stiffness, and cortisol/DHEAs ratio. A total of 198 middle-aged and older adults (aged 50–79 years old) participated in this study. The aerobic fitness evaluated by peak oxygen consumption (V\textsubscript{O2peak}), carotid-femoral pulse wave velocity (cfPWV) as an indicator of arterial stiffness, and serum cortisol and DHEAs and their ratio were measured. The subjects were divided into the lower (n = 100) and the higher (n = 98) aerobic fitness groups based on the median value of V\textsubscript{O2peak}. There were no significant differences in serum cortisol and DHEAs concentration alone between the lower and higher fitness groups. However, the cortisol/DHEAs ratio and cfPWV in the higher fitness group was smaller than in the lower fitness group (p < 0.05). The cortisol/DHEAs ratio was significantly correlated with cfPWV (r = 0.159, p < 0.05). These findings suggest that the cortisol/DHEAs ratio is associated with aerobic fitness and arterial stiffness in middle-aged and older adults.

Key words: Aerobic capacity, Arterial stiffness, Steroid, Aging

IT IS WELL ESTABLISHED that arterial stiffness increases with advancing age [1]. Stiffened artery lead to elevate systolic blood pressure and left ventricular after load, and decreased coronary perfusion [2, 3]. An increase in arterial stiffness is an independent risk factor for cardiovascular diseases [4]. Therefore, attenuating the increase in arterial stiffness is preferable in middle-aged and older adults. Previous studies imply that regular exercise and higher fitness reduce arterial stiffness [5], and exercise capacity is associated with arterial stiffness [6]. However, little is known about the underlying mediated the relationship between exercise and arterial stiffness.

Aging also affects the secretion of adrenal steroid hormones, a key component of stress response in the hypothalamic-pituitary-adrenal (HPA) axis [7]. Two hormones, cortisol and dehydroepiandrosterone (DHEA), are secretory signaling steroids released from the adrenal cortex of the zona fasciculata and the zona reticularis, respectively, and they have opposing actions that DHEA appears to act as a counterbalance to the negative implication of cortisol for health outcome [8]. It is well known that older adults have higher circulating cortisol and lower DHEA sulfate (DHEAs) levels, and the decline in DHEAs with age is termed as adrenopause [9, 10]. Elevated cortisol and reduced DHEAs are associated with blood pressure and cardiovascular function [11, 12], and DHEA replacement can improve arterial stiffness in elderly men and women [13]. Moreover, the imbalance of high cortisol and low DHEAs levels and consequent increase in the cortisol/DHEAs ratio is thought to be a
significant marker of health deterioration with age [14]. Additionally, the ratio of cortisol and DHEAs is associated with mental disorders, and cardiovascular diseases, as well as all-cause and cause-specific mortality [15, 16]. Recently, Heaney et al. [17] have reported that the cortisol/DHEAs ratio is lower in physically active individuals with high life-event stress. Taken together, it is plausible that adrenal hormones, especially the cortisol/DHEAs ratio, may be associated in higher fitness-related lower arterial stiffness. However, there has been no study investigating the association among aerobic fitness, adrenal cortex hormones, and arterial stiffness in a large number of samples.

The purpose of this study was to investigate the impact of aerobic fitness on adrenal hormones and arterial stiffness. Therefore, the present cross-sectional study examined associations between adrenal hormones including cortisol, DHEAs, and their ratio, the aerobic exercise capacity, and the arterial stiffness in a cohort of middle-aged and older adults. We hypothesize that aerobic fitness-related difference in arterial stiffness is associated with the level and ratio of cortisol and DHEAs.

**Materials and Methods**

**Subjects**

This study used a cross-sectional design and a total of 198 middle-aged and older healthy adults (81 men and 117 women, age 50–79 years) participated in this study. Subjects with a smoking habit, anti-hypertensive medication, hormone replacement therapy, cardiovascular, or cerebrovascular disease were excluded. All women were postmenopausal. All potential risks associated with the study were explained to the subjects, and written informed consent was provided by all participants. All procedures were reviewed and approved by the ethical committee of the University of Tsukuba, Japan.

**Procedures**

All experiments were conducted in the morning after a 12-hour overnight fast. Subjects abstained from alcohol and caffeine for at least 12 hours and did not exercise for at least 24 hours before the experiments. Measurements were performed in a quiet, temperature-controlled room (24–26°C). We measured arterial stiffness, hemodynamics, adrenal hormones, blood sample chemistry, and aerobic exercise fitness.

**Measurements**

Carotid-femoral pulse wave velocity (cPWV), indicative of arterial stiffness, was measured by a semi-automated vascular testing system in participant at a supine position. Briefly, left carotid and left femoral pressure waveforms were obtained by two applanation tonometry sensors incorporating an array of 15 transducers (Form PWV/ABI, Colin Medical Technology, Komaki, Japan). The distance between the left common carotid and left common femoral arterial recording sites was divided by the transit time to calculate cPWV. Brachial systolic blood pressure and diastolic blood pressure, and heart rate were measured with an electrocardiogram and oscillometric extremity cuff. Blood samples were collected from the antecubital vein after overnight fasting. cPWV and blood pressure measurements were taken at least three times that were recorded over a 30 s period.

Plasma and serum were collected and stored at –80°C, until they were used for specific assays. Serum cortisol, serum DHEAs concentration, plasma noradrenaline concentration, and plasma aldosterone concentration were determined using chemiluminescence immunoassay, chemiluminescence enzyme immunoassay, high-performance liquid chromatography, and radioimmunoassay, respectively. The intra-assay coefficient of variation was 2.23% for noradrenaline, 6.7% for aldosterone, 1.74% for DHEAs, and 2.51% for cortisol measurements. Serum total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglyceride, and plasma glucose were determined using the standard enzymatic technique, all by a commercial laboratory (LSI Medience Corporation Ltd., Tokyo, Japan).

Peak oxygen uptake (VO₂peak) was measured during the incremental exercise test on a bicycle ergometer (AEROBIKE 75XL III; Konami Wellness, Tokyo, Japan) with online computer-assisted circuit spirometer (AE300S; Minato Medical Science, Osaka, Japan). All subjects performed a symptom-limited cycling exercise test, which consisted of warm-up at 20 W for 2 minutes and followed by a 10 W increase per minute. We measured the average of oxygen uptake every 30 s during the exercise test until exhaustion or if one of the following criteria was met: clinical complaints of exhaustion by the participant, unable to maintain cadence (<50 rpm) for several seconds, or attainment of age-predicted maximal heart rate (208 – 0.7 × age) [18]. Heart rate was monitored continuously with an electrocardiogram. VO₂peak was defined as the highest value recorded during the test and used as an index of aerobic fitness.

**Statistical analyses**

All data are expressed as means ± standard deviation (SD). To assesses the effect of aerobic exercise fitness, the subjects were divided into the lower or a higher fitness groups based on the median value of a VO₂peak in each age group (over or under 65 years old) and sex (men or women). The analysis of normality was per-
formed with the Shapiro-Wilk test. The independent *t*-test or Mann-Whitney *U* test was used to evaluate group differences in continuous variables based on the result of the Shapiro-Wilk normality test. Pearson’s product correlation analysis was used to test the associations between cfPWV and adrenal hormone level after skewed variables were log-transformed and achieved normal distributions. All statistical data analyses were performed using SPSS software (Version24; IBM, Armonk, NY), and statistical significance was set a priori at *p* < 0.05 for all comparisons.

### Results

Table 1 shows the characteristics of the study participants. There were no significant differences in age, height, cholesterol, triglyceride, glucose, heart rate, or blood pressures between the lower and higher fitness groups. Weight and cfPWV in the higher fitness group was significantly smaller than that in the lower fitness group. *VO*₂peak in the higher fitness group was significantly higher than that in the lower fitness group. Table 2 shows the impact of aerobic fitness on adrenal hormones. Significant group differences were not found in noradrenaline, aldosterone, cortisol, and DHEAs concentration levels. However, the cortisol/DHEAs ratio in the higher fitness group was significantly smaller than that in the lower fitness group (0.088 ± 0.059 vs. 0.103 ± 0.058, *p* < 0.05) (Fig. 1). Furthermore, there was a significant positive correlation between the cortisol/DHEAs ratio and cfPWV (*r* = 0.159, *p* < 0.05) (Fig. 2).

### Discussion

This study evaluated aerobic fitness, arterial stiffness, and adrenal hormones in middle-aged and older adults. The salient findings of the present study were that the higher aerobic fitness group had lower arterial stiffness and cortisol/DHEAs ratio was correlated with arterial stiffness. Physiological response to various stresses in—

### Table 1 Characteristics and arterial stiffness in lower and higher aerobic fitness groups

|                      | All          | Lower fitness | Higher fitness |
|----------------------|--------------|---------------|----------------|
| *n* (men/women)      | 198 (81/117) | 100 (40/60)   | 98 (41/57)     |
| Age, years           | 63 ± 7       | 63 ± 7        | 63 ± 6         |
| Height, cm           | 161 ± 8      | 161 ± 8       | 161 ± 8        |
| Weight, kg           | 59 ± 9       | 60 ± 9        | 57 ± 9*        |
| Total cholesterol, mg/dL | 222 ± 34     | 222 ± 35      | 223 ± 33       |
| HDL cholesterol, mg/dL | 64 ± 16      | 63 ± 16       | 66 ± 15        |
| LDL cholesterol, mg/dL | 135 ± 31     | 135 ± 33      | 134 ± 28       |
| Triglyceride, mg/dL  | 98 ± 50      | 98 ± 51       | 98 ± 50        |
| Glucose, mg/dL       | 96 ± 16      | 98 ± 19       | 94 ± 11        |
| Heart rate, bpm      | 60 ± 7       | 61 ± 8        | 59 ± 7         |
| Systolic blood pressure, mmHg | 126 ± 15 | 127 ± 16 | 124 ± 14 |
| Diastolic blood pressure, mmHg | 77 ± 10 | 77 ± 10 | 76 ± 9  |
| cfPWV, cm/s          | 958 ± 178    | 985 ± 209     | 931 ± 136*     |
| *VO*₂peak, mL/min/kg | 23 ± 5       | 20 ± 3        | 26 ± 4*        |

Data are shown in Means ± SD. HDL, high density lipoprotein; LDL, low density lipoprotein; cfPWV, carotid-femoral pulse wave velocity. *p* < 0.05 vs. Lower fitness group.

### Table 2 Adrenal hormones in lower and higher aerobic fitness groups

|                      | All          | Lower fitness | Higher fitness |
|----------------------|--------------|---------------|----------------|
| Noradrenaline, ng/mL | 0.37 ± 0.18  | 0.36 ± 0.17   | 0.37 ± 0.19    |
| Aldosterone, pg/mL   | 132 ± 50     | 133 ± 50      | 131 ± 50       |
| DHEAs, μg/dL         | 124 ± 74     | 118 ± 73      | 130 ± 74       |
| Cortisol, μg/dL      | 9 ± 4        | 10 ± 4        | 9 ± 4          |

Data are shown in Means ± SD. DHEAs, dehydroepiandrosterone sulfate.
duces the activation of the endocrine system, such as the HPA axis, resulting in the secretion of cortisol and DHEA secreted from the adrenal cortex. It is well known that chronic high cortisol concentration reduces immune function and cognitive function [10]. In contrast, DHEA has an anti-glucocorticoid effect that regulates cortisol and then attenuates the increase in cortisol concentration [19]. Previous studies have demonstrated that the ratio of increased cortisol to decreased DHEAs with aging was associated with depression [20, 21]. Furthermore, a higher cortisol/DHEAs ratio was observed in patients with cardiovascular diseases [16]. In the present study, we found that the cortisol/DHEAs ratio was correlated with both VO_{2peak} and cfPWV in general healthy middle-aged and older populations. These results suggest that age-related deterioration in adrenal cortical hormone balance is associated with aerobic exercise capacity and arterial function.

Aerobic exercise fitness evaluated by VO_{2peak} is related to arterial function including its stiffness; thus, people who have undergo endurance training have more compliant artery than sedentary [22]. It has been reported that exercise training-related decrease in arterial stiffness is mediated by several physiologically active substances such as endothelin-1 and asymmetric dimethylarginie or steroid hormone such as testosterone [23-25]. These steroid hormones are founded to enhance endothelial function [26]. In this study, the ratio of cortisol to DHEAs was significantly different between aerobic fitness categories and was correlated with arterial stiffness rather than cortisol or DHEAs alone. These results suggested that fitness-related changes in arterial stiffness would be partly mediated by adrenal cortex hormones.

Physical and/or psychological stress increase the levels of both DHEA and cortisol. DHEA has an anti-glucocorticoid effect that suppresses the elevation of cortisol levels [27]. Over secretion of cortisol, as compared to that of DHEAs, seems to modulate adrenocortical and HPA activity and catabolic/anabolic balance [28]. Furthermore, the balance of two adrenal cortex hormones is higher in Alzheimer’s disease and ischemic stroke [29, 30]. In the present study, higher fitness level was associated with a lower cortisol/DHEAs ratio and cfPWV, and there was a weak but significant correlation between these two entities. The secretions of cortisol and DHEAs is complexly co-regulated by each other, and the balance between the two hormones has been usually considered to be an indicator of the health status [10]. In this regard, the interpretation of hormone ratio should be made cautiously, since the physiological mechanism underlying the effects of the hormone ratio is poorly understood [31]. It is possible that the analyses of such a hormone ratio can become a good marker of arterial stiffness and cardiovascular risks. However, further studies are warranted to understand the specific hormone ratio that can be indicative of a balance between adrenal hormones, and the underlying mechanisms that contribute to exercise fitness and vascular function.

There is a small but significant difference in the cortisol/DHEAs ratio between the higher and lower fitness groups (Fig. 1). Whether such a small difference is physiologically significant remains to be determined. However, it should be noted that a cohort-based study demonstrated that the cortisol/DHEAs level in hypertensive patient was significantly higher than normotensive peers, although such a difference was not so large (0.099 ± 0.082 vs. 0.086 ± 0.051, 13%) [32]. Moreover, another study reported that acute aerobic exercise decreased about 10% of cortisol/DHEAs level in healthy older adults [33]. Collectively, these findings suggest that

![Fig. 1](image1.png)  
Cortisol/DHEAs (dehydroepiandrosterone sulfate) ratio in lower and higher aerobic fitness group.

![Fig. 2](image2.png)  
The relationship between cortisol/DHEAs (dehydroepiandrosterone sulfate) ratio and cfPWV (carotid-femoral pulse wave velocity).
>10% deference in the cortisol/DHEAs levels may be associated with exercise-induced vascular adaptation.

The decrease in DHEAs with age is known to deteriorate cardiovascular health [11]. DHEA has a favorable effect on vascular function including nitric oxide synthase activation, endothelial cell proliferation, and endothelial-dependent dilation [34]. In this regard, a previous study on young adults reported that there is no difference in DHEAs concentrations between endurance-trained men with higher aerobic capacity and sedentary peers [35]. Similarly, in this study, no significant difference was evident in each concentration of DHEAs as well as noradrenaline, aldosterone, and cortisol alone between the higher and lower aerobic fitness groups in middle-aged and older adults. Thus, it is unlikely that aerobic exercise capacity is associated with the individual concentration of adrenal hormones. Taking together, the cortisol/DHEAs ratio may reflect exercise-related changes in arterial stiffness, which implicates the importance of assessing their balance. A potential benefit of assessing the cortisol and DHEAs as a ratio is that it captures the preferential production of one hormone over the other.

The findings of the current study have clinical implications. Increase in arterial stiffness with age is a strong risk factor for total cardiovascular events in general healthy populations [36]. In this regard, aerobic exercise fitness is known to have a favorable effect on the arterial aging [37]. Gando et al. [38] reported that higher aerobic fitness exhibited lower arterial stiffness progression after 2 years follow up. In accordance with the results of previous studies, our findings demonstrated that arterial stiffness was associated with aerobic fitness, and adrenal hormone levels, the cortisol/DHEAs ratio. These findings highlight the importance of the evaluating and the management of aerobic fitness and adrenal hormone balance in preventing cardiovascular disease.

The present study has some limitations. First, this study focused only on healthy middle-aged and older adults, and we observed a blunted effect of aerobic fitness on health-related outcomes such as the blood pressure and parameters of blood chemistry. The findings of this study did not include other populations, such as young adults or patients with mental disorders, hypertension, and diabetes mellitus. Second, DHEA (and DHEAs) is converted into androgens through androstenedione [39]. It has been also reported that arterial stiffness and endothelial function are associated with the level of testosterone in adult men [26, 40]. However, testosterone levels were not assessed in this study since testosterone is converted to estradiol in women, and testosterone level is very low in women than in men. Third, the study subjects were not analyzed separately each sex. It has been reported that in middle-aged and older populations the cortisol/DHEAs ratio was higher in women than in men [41]. Similarly, women in the present study had a higher cortisol/DHEAs ratio than men, although the impact of aerobic fitness was not different between men and women. These observations suggest that aerobic fitness is similarly associated with adrenal and arterial function in both men and women. Forth, the present study was a cross-sectional study that cannot determine the cause-effect relationship of aerobic exercise, the adrenal hormone ratio and arterial stiffness. Further studies are warranted to investigate the effects of regular exercise on the relation between adrenal hormones and arterial stiffness.

In conclusion, we demonstrated that the higher aerobic fitness group exhibited lower arterial stiffness and cortisol/DHEAs ratio in healthy middle-aged and older adults. Moreover, arterial stiffness correlated with the cortisol/DHEAs ratio. The results of the present study imply that the balance of adrenal cortical hormones is important for aerobic exercise-related decreases in arterial stiffness.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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