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Resistance training-induced decreases in central arterial compliance is associated with increases in serum thromboxane B2 concentrations in young men

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Abstract Background: Reduction in central arterial compliance is an independent risk factor for cardiovascular disease, and is caused by high-intensity resistance training. The thromboxane has both potent vasoconstrictive and platelet aggregation effects, and is associated with cardiovascular diseases. However, whether thromboxane is involved in resistance training-induced decrease in central arterial compliance is unclear. The present study aimed to investigate relationships between circulating thromboxane levels and central arterial compliance in both cross-sectional and longitudinal (i.e., resistance training) designs.

Methods and results: First, in a cross-sectional study, we assessed association between circulating thromboxane concentrations and central arterial compliance in 63 young men, who showed significant negative correlation between those parameters. Second, in a longitudinal study, we examined effects of high-intensity resistance training on circulating thromboxane concentrations and central arterial compliance and relationship among changes from baseline in those parameters. Young sedentary men were assigned to control (n = 7) or training (n = 17) groups. Subjects in training group underwent four-week supervised high-intensity resistance training. Resistance training significantly elevated circulating thromboxane...
concentrations and decreased central arterial compliance; no significant change was observed in control group, and there was significant correlation between changes in those parameters. Conclusion: circulating thromboxane is possible mechanism explaining resistance training-induced decrease in central arterial compliance in young men.

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Introduction

The guidelines of the American College of Sports Medicine and the American Heart Association recommend moderate- to high-intensity resistance training because resistance training can elicit substantial increases in physical fitness and some health-related factors such as muscle strength, bone mineral density, and insulin sensitivity. In contrast, it has been reported that high-intensity resistance exercise and resistance training [≥75% one-repetition maximum (1RM)] decrease central arterial compliance (CAC).

Although low-intensity resistance exercise and resistance training increase arterial compliance, and moderate-intensity resistance training does not change arterial compliance. Moreover, a meta-analysis revealed that only high-intensity resistance training was significantly associated with a decrease in arterial compliance. It is possible that decreased arterial compliance with both acute and chronic resistance exercise is related to high-intensity and is not found in moderate- and low-intensity exercise. Deteriorated vascular function (i.e., decreased CAC) is an independent risk factor for future cardiovascular diseases. Thus, a decrease in CAC induced by resistance training may increase the future risk for cardiovascular diseases. However, the mechanisms underlying resistance training-induced decrease in CAC have not been clarified yet.

The arterial compliance is regulated by the composition of elastin and collagen (structural elements) and the vasoconstrictor tone exerted by smooth muscle cells (functional elements). The elastin/collagen composition of the arterial wall is a more slowly changing component that contributes to arterial compliance. As such, it is unlikely that this may be a physiological mechanism underlying decrease in arterial compliance induced by short-term resistance training. In contrast, the functional elements are regulated by some vasoconstrictive mediators. In particular, among vasoconstrictive mediators, thromboxane (TX) is produced from the platelets and has potent vasoconstrictory and platelet aggregation effects. The TX receptor exists on vascular smooth muscle cell. Thus, increased circulating TX concentrations are possibly associated with decreased arterial compliance. In contrast, high-intensity single bout of resistance exercise causes platelet aggregation, which strongly suggests that high-intensity resistance exercise may increase circulating TX concentrations. However, the effect of high-intensity resistance exercise on circulating TX concentrations has not been clarified yet. Moreover, whether increased circulating TX concentrations are associated with resistance training-induced decrease in arterial compliance is unclear.

Accordingly, the aim of the present study was to investigate whether circulating TX concentrations are related to arterial compliance and whether the resistance training-induced decrease in arterial compliance is associated with changes in circulating TX concentrations. We hypothesized that (a) circulating TX concentrations are associated with arterial compliance and (b) resistance training increases circulating TX concentrations, which is associated with a resistance training-induced decrease in arterial compliance. To test our hypothesis, in experiment 1, we examined the relationship between circulating TX concentrations and arterial compliance in a cross-sectional study in young men. In experiment 2, we investigated the effects of a four-week-long resistance training on circulating TX concentrations and arterial compliance in young men.

Materials and methods

Subjects

In experiment 1, 63 young men (age, 20–36 years) were enrolled in a cross-sectional study. In experiment 2, 24 young men (age, 20–35 years) were enrolled in a longitudinal study. Applicants for control and resistance training were recruited as each subject in control (n = 7) and training (n = 17) groups, respectively. All subjects were recruited from the local community through flyers, e-mails, and information sharing. None of the subjects had participated in any resistance or endurance training regularly. All subjects were non-smokers and cardiovascular disease-free, as indicated by their medical history. None of the subjects were taking cardiovascular medications. The subjects were instructed to maintain current eating behaviors for the duration of the intervention. The present study was conducted in accordance with the Declaration of Helsinki and was approved by the ethical committee of the University of Tsukuba. All subjects provided informed written consent.

Sample size estimation

The sample size was calculated based on the previous studies that circulating levels of vasoactive substances are associated with arterial compliance (experiment 1) and high-intensity resistance training decreases arterial compliance (experiment 2). Considering a power of 0.80 and an α level of 0.05, in experiment 1, a total sample size of 38 was found to be necessary by “bivariate normal model” using a general stand-alone power analysis program.
Resistance training and thromboxane

65

performed all image analyses. The diameter of the arterial ware (Image J, Maryland, USA). The same investigator uter images were analyzed by using image analysis soft-

was acquired 1 image of the cephalic portion of the common carotid artery

line.20 All repetitions of maximal strength test were

bicep curls. All subjects performed warm up exercise,

subject was tested before and after intervention using

In experiment 2, the maximal muscular strength of all

BPs.4,23 The daily coefficient of variation of carotid

measured the circulating TXB2 concentrations in

circulating TX concentrations

In experiment 2, a total sample size of 22 was

effects, special, main effects, and interactions” using a
general stand-alone power analysis program. We finally
decided to set a total sample size of 63 in experiment 1. Also, we finally decided to set the sizes of the control and training groups at 7 and 17 subjects, respectively, in experiment 2.

Experimental design

In experiment 1, characteristics of subjects, hemody-
namics, carotid arterial compliance, and circulating TX
concentrations were measured in all subjects. In experi-
ment 2, we measured hemodynamics, muscle strength,
carotid arterial compliance, and circulating TX concentra-
tions before and after the intervention for four weeks in all

Measurements

Before each test, subjects abstained from caffeine and

fasted for at least 12 h. All subjects were studied at least

48 h after they last exercised, to avoid acute effects of

exercise. All measurements were performed at constant

room temperature (23–25 °C), in a quiet room, after the

subjects had rested in a supine position for at least 15 min.

In experiment 2, the subjects were tested at the same time

of the day throughout the study period to avoid potential
diurnal variations.

Strength testing

In experiment 2, the maximal muscular strength of all

subjects was tested before and after intervention using

bicep curls. All subjects performed warm up exercise,

constituting 10 repetitions with 5 kg weights, and after-
wards, 1RM was obtained based on the established guide-
line.e20 All repetitions of maximal strength test were

performed in 3-s eccentric (lowering) and concentric (lift-
ing) phases. Subjects repeated the actions at approxi-
mately constant velocities and frequencies with the aid of a

metronome. Relative strength was calculated as follows:

Relative strength = 1RM/body mass. The day-to-day co-
efficients of variation were 1.0 ± 1.8% and 1.4 ± 1.4% for

1RM and relative strength, respectively.

Carotid arterial compliance

Common carotid artery echography immediately after

applanation of tonometrically obtained arterial pressure

from the carotid artery permits noninvasive determination

of dynamic carotid arterial compliance. The common ca-

rotid artery diameter was measured from the images
derived from an ultrasound machine (Logiq E; GE Health-
care, Tokyo, Japan) equipped with a high-resolution linear-
array transducer as previously described.4,21 A longitudinal

image of the cephalic portion of the common carotid artery

was acquired 1–2 cm distal to the carotid bulb. The com-
puter images were analyzed by using image analysis soft-
ware (Image J, Maryland, USA). The same investigator
performed all image analyses. The diameter of the arterial

lumen at minimal diastolic relaxation and maximal systolic

expansion was measured at three points per frame, and the

points were then averaged. Carotid arterial pressure

waveforms were obtained with arterial applanation tonometry using an array of 15 micro-piezoresistive trans-
ducers (form PWV/ABI; Colin Medical Technology, Komaki, Japan).22 These waveforms were calibrated by equating the
carotid mean arterial pressure, diastolic blood pressure
(BP) to the brachial mean arterial pressure, and diastolic

BP. Each parameter was averaged over 10–15 continuous
beats. Brachial BP was measured with the oscillometric

method using the automated polygraph apparatus (form

PWV/ABI; Colin Medical Technology, Komaki, Japan). Heart
rate was computed from ECG. Carotid arterial compliance

was calculated by using the equations: 

\[
\frac{1}{\text{stiffness index}} = \frac{L}{D^2},
\]

where L is the length of the carotid artery, and D is the

diameter of the carotid artery at diastole. The carotid

mean arterial pressure, diastolic blood pressure

(P1 – P0)/[(D1 – D0)/2], where D1 and D0 are the maximal

and minimum diameters, and P1 and P0 are the highest and

lowest BPs.4,23 The daily coefficient of variation of carotid

arterial compliance was 8.8% ± 2.7% in our laboratory. The

\(\text{stiffness index}\) is an index of

carotid arterial compliance adjusted for distending

pressure.4

Circulating TX concentrations

Each blood sample was placed in a chilled serum separator

tube and then centrifuged at 3000 × g for 15 min at 4 °C.

The serum samples were stored at −80 °C until the assay.

Among TXs, thromboxane-A2 (TXA2) has a potent vaso-

constrictory effect.16 However, TXA2 is metabolized to

thromboxane-B2 (TXB2), with a half-life of 30 s.14 Therefore,

we measured the circulating TXB2 concentrations in the

present study. Serum concentrations of TXB2 were

measured using an enzyme-linked immunoassay kit (Enzo

Life Sciences, New York, USA). The intra-assay coefficient

of variation of TXB2 was 3.1 ± 1.3%, as previously described

(TXB2, ADI-900-002, Enzo Life Sciences).

Body composition

Anthropometric measurements were taken with subjects’
barefoot and wearing only light clothing. Height was

measured to the nearest 0.1 cm using a stadiometer (AD-

6227R, A&D Co., Ltd., Tokyo, Japan). Body mass, body fat

percentage, and lean body mass were measured to the

nearest 0.1 kg on a calibrated digital scale (InBody 770,

InBody Japan, Tokyo, Japan) and adjusted for the esti-

mated clothing mass by subtracting 0.5 kg. Daily co-
efficients of variation for the two trials were 0.1% ± 0.1%,

0.2% ± 0.1%, 0.5% ± 0.2%, 3.4% ± 2.7%, and 0.4% ± 0.4% for

height, body mass, body mass index, body fat percentage,

and lean body mass, respectively.

Resistance training intervention

In experiment 2, the subjects in training group underwent

supervised resistance exercises thrice a week, during the

four-week-study. During the training session, the subjects

completed five sets of 10 repetitions of bicep curls at 75% of

1RM, with a 2-min inter-set rest period.19,25 We selected

bicep curls, which induce an increase in arterial stiffness

(i.e., decrease in arterial compliance) as well as whole-
body resistance training. All repetitions of the resistance training were performed in a 3-s eccentric (lowering) and concentric (lifting) phases. The subjects repeated the actions at approximately constant velocities and frequencies with the aid of a metronome. The loads were increased for the following exercise sessions when subjects were able to complete 10 repetitions in the third set. Each training session lasted for approximately 20 min. The resistance exercise was performed until concentric failure, afterward remaining sets were completed with the support of assistants. Except for routine activities during training, all other exercises (resistance training, anaerobic exercise, and aerobic exercise) were prohibited.

Statistical analysis

The Shapiro–Wilk test was used to evaluate the normality of distributions. Data were expressed as mean ± standard deviation unless indicated otherwise. In experiment 1, because serum TXB₂ concentrations were not a normal distribution, the relationship between carotid arterial compliance and serum TXB₂ concentrations was assessed by Spearman rank correlation coefficient (rs) analysis. It is worth noting that advancing age can elicit increased urinary TXB₂ concentrations and decreased carotid arterial compliance; therefore, the correlation was adjusted for age. In experiment 2, unpaired sample t-tests were used to examine differences between the groups on characteristics of subjects. A two-way analysis of variance with repeated measures was used to evaluate the interaction (group*time) on hemodynamics, muscle strength, carotid arterial compliance, and serum TXB₂ concentrations. When a significant interaction was detected, specific mean comparisons were performed to identify significant differences within each intervention. When a significant F values were obtained, a post-hoc test using the Bonferroni method was performed to identify the significant differences among the mean values. Moreover, we conducted the comparison of changes in arterial compliance and serum TXB₂ concentrations between groups using a non-parametric Mann–Whitney U test. Because changes in serum TXB₂ concentrations and arterial compliance were not a normal distribution, the relationship between the changes from baseline in serum TXB₂ concentrations and carotid arterial compliance in all subjects was assessed using Spearman rank correlation coefficient (rs) analysis. In addition, for the same reason described above, the correlation was adjusted for age. In all tests, a two-tailed P value < 0.05 was accepted as statistically significant. All statistical analyses were performed using SPSS Statistics version 24.0 for Windows (IBM SPSS Japan Inc., Japan).

Results

Experiment 1

We investigated whether serum TXB₂ concentrations are associated with carotid arterial compliance in young men. Table 1 shows the subjects’ characteristics, hemodynamics, carotid arterial compliance, and serum TXB₂ concentrations. We found a significant negative correlation between carotid arterial compliance and serum TXB₂ concentrations (Fig. 1, rs = -0.26, P < 0.05). After adjustment for age, serum TXB₂ concentrations were still significantly associated with carotid arterial compliance (partial rs = -0.25, P < 0.05).

Experiment 2

We investigated the effects of resistance training on serum TXB₂ concentrations and arterial compliance in young men. In the training group, subjects completed all training sessions (i.e., a total of 12 training sessions in four weeks). At the baseline, no significant differences were found in any of the parameters between the control and training groups (Tables 2 and 3, Fig. 2). In addition, no significant changes in arterial compliance and serum TXB₂ concentrations between groups were found using a non-parametric Mann–Whitney U test. Because changes in serum TXB₂ concentrations and arterial compliance were not a normal distribution, the relationship between the changes from baseline in serum TXB₂ concentrations and carotid arterial compliance in all subjects was assessed using Spearman rank correlation coefficient (rs) analysis. In addition, for the same reason described above, the correlation was adjusted for age. In all tests, a two-tailed P value < 0.05 was accepted as statistically significant. All statistical analyses were performed using SPSS Statistics version 24.0 for Windows (IBM SPSS Japan Inc., Japan).
interactions were observed in BPs (systolic BP, mean BP, and diastolic BP), heart rate, and carotid arterial distension between the control and training groups (Table 3); among these parameters, only carotid arterial distension was decreased after resistance training ($P < 0.05$). We found significant interactions in β-stiffness index, 1RM, and relative strength between the two groups (β-stiffness index: $F = 8.32, P < 0.01$; 1RM: $F = 38.19, P < 0.001$; relative strength: $F = 35.83, P < 0.001$; β-stiffness index, 1RM, and relative strength significantly increased after the four-week training (three parameters, $P < 0.001$).

After the intervention, we found a significant interaction on changes in carotid arterial compliance between the groups ($F = 8.70, P < 0.01$); carotid arterial compliance was significantly decreased after intervention in the training group (Fig. 2A, control: from 11 ± 2 to 11 ± 3 $10^{-2}$ mm$^2$/mmHg, N.S. training: from 12 ± 4 to 9 ± 2 $10^{-2}$ mm$^2$/mmHg, $P < 0.005$). Significant interaction on changes in serum TXB$_2$ concentrations was found between the control and training groups ($F = 4.76, P < 0.05$); serum TXB$_2$ concentrations were significantly increased only in the training group (Fig. 2B, control: from 31.7 ± 9.2 to 30.4 ± 7.8 ng/ml, N.S.; training: from 26.3 ± 9.9 to 34.4 ± 4.9 ng/ml, $P < 0.005$). Furthermore, the changes in carotid arterial compliance (decrease) and serum TXB$_2$ concentrations (increase) were significantly greater in the training group than in the control group (both, $P < 0.05$).

As shown in Fig. 3, we found a significant negative correlation between changes in serum TXB$_2$ concentrations and those in carotid arterial compliance before and after the intervention ($r_s = -0.56, P < 0.005$). In addition, the relationship between changes in serum TXB$_2$ concentrations and those in carotid arterial compliance remained significant after controlling for age (partial $r = -0.42, P < 0.05$).

### Discussion

The salient findings of the present study were as follows: First, in a cross-sectional study, a significant negative correlation was found between circulating TXB$_2$ concentrations and carotid arterial compliance in young men. Second, in a longitudinal study, the four-week resistance training significantly increased circulating TXB$_2$ concentrations, which was significantly associated with the resistance training-induced decrease in carotid arterial compliance in young men. Therefore, we suggest that the increases in circulating TXB$_2$ concentrations were partly involved in the decrease in CAC after the resistance training.

TXA$_2$ is produced from the platelets and has a potent vasoconstrictor effect. A previous study demonstrated that circulating concentrations of TXB$_2$ in subjects with high central BP are three-fold higher than that in subjects with low central BP. In addition, increasing urinary concentrations of TXB$_2$ have been reported to be associated with an increasing risk of cardiovascular events, particularly myocardial infarction and cardiovascular death. Thus, increased TXB$_2$ concentrations may be associated with deteriorated vascular functions, and cardiovascular disease. In our cross-sectional study, circulating TXB$_2$ concentrations were significantly negatively correlated with CAC in young men. Furthermore, after resistance training intervention, circulating TXB$_2$ concentrations were significantly elevated, arterial compliance was significantly decreased, and the changes in circulating TXB$_2$ concentrations were significantly negatively associated with a change in CAC in young men. In summary, our results suggest that the increased circulating TXB$_2$ concentrations participate, at least in part, in the mechanisms underlying resistance training-induced decrease in CAC, in young men.

The possible mechanisms underlying the resistance training-induced increases in circulating TXB$_2$ concentrations could be explained by the sympathetic nervous system. Inhibition of alpha-1 and alpha-2 adrenergic receptors has been reported to decrease circulating TXB$_2$ concentrations.
In addition, resistance training increases circulating norepinephrine concentrations, which increase alpha- and beta-adrenergic effects. Hence, the resistance training-induced increase in circulating norepinephrine concentrations possibly contributes to increased circulating TXB2 concentrations. However, further studies are necessary to elucidate the mechanisms underlying the increase in circulating TXB2 concentrations caused by resistance training.

In the present study, our data showed that increased circulating TXB2 concentrations induced by resistance training are significantly related to decreased CAC in young men. Several mechanisms can be proposed as follows: First, increased vasoconstrictor tone exerted by smooth muscle cells aggravates arterial compliance. TX is produced from the platelets and has potent vasoconstrictory and platelet aggregation effects. The TX receptor exists on vascular smooth muscle cell. Following the occupation of TX receptor on vascular smooth muscle cell, the contraction is elicited through coupling to either Gq/11 or, to a greater extent, G12/13 evokes the biosynthesis of inositol 1,4,5-trisphophate and activation of specific RhoA guanine nucleotide exchange factors that in turn activate Rho kinase. Such a contraction is significant because it is slow and lasting. Hence, increased circulating TXB2 concentrations induced by the resistance training possibly caused a direct decrease in CAC in the present study. Second, one animal study showed that TXA2 antagonist decreases the oxidative stress. A single bout of high-intensity eccentric exercise increases the oxidative stress in young men. Moreover, activation of oxidative stress provokes vasoconstriction in the central artery. Thus, oxidative stress possibly contributes to the relationship between changes in circulating TXB2 concentrations and CAC, which are induced by the resistance training. Future studies are necessary to test these hypotheses.

There are several noteworthy limitations of the present study that should be emphasized. First, the present study was not randomized control trial. Applicants for control and resistance training were recruited as each subject in control and training groups, respectively. Moreover, the sample size of the present study was small. However, the sample power in the present study was 0.81 for arterial compliance. This means that 81% of studies would be expected to yield a significant effect, rejecting the null hypothesis that the odds are 1.0, and suggesting that the present study has substantial statistical power. Further studies are necessary to investigate a randomized control trial of substantial statistical power. Second, the present study was not included women. Since female hormone (i.e., estrogen) influences arterial compliance, we recruited only men, which limits the generalizability of this study. Further studies are needed to examine this issue. Third, we adapted biceps curls as high-intensity resistance training used in previous study. However, bicep curls exercise is difficult to gain generalizability. Further interventional
studies are needed using whole-body resistance training. Fourth, the present study conducted arterial compliance analysis using calipers at three different points. A number of previous studies from our laboratory and others have reported that in exercise training intervention, arterial compliance has been conducted using calipers at three different points. Also, the daily coefficient of variation of arterial compliance was 6.8% in our laboratory, as well as 7.5% of coefficient of variation using wall tracking device for carotid artery distension. Thus, we believe that arterial compliance analysis using calipers at three different points has similar good repeatability to using wall tracking device.

In conclusion, the particularly novel findings in the present study are as follows: circulating TXB2 concentrations were significantly negatively correlated with CAC in a longitudinal study in young men. These findings suggest that the increases in circulating TXB2 concentrations partly contribute to the deterioration in CAC, resulting from resistance training in young men.

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Conflicts of interest

The authors declare no conflicts of interest, financial or otherwise.

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