

Effects of curcumin intake and aerobic exercise training on arterial compliance in postmenopausal women

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1 **Effects of curcumin intake and aerobic exercise training on arterial compliance in**
2 **postmenopausal women**

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21 **Running title:** Curcumin, exercise, and arterial compliance
22

1 **Abstract**

2

3 **Background:** Reduction in arterial compliance with aging increases the risk of
4 cardiovascular disease. Lifestyle modification, particularly aerobic exercise and dietary
5 modification, has a favorable effect on vascular aging. Curcumin, a major component of
6 turmeric, is an anti-inflammatory agent. Therefore, it is plausible to hypothesize that
7 curcumin improves arterial compliance. We investigated the effects of curcumin ingestion
8 alone and in combination with aerobic exercise training on arterial compliance in
9 postmenopausal women.

10 **Methods:** A total of 51 postmenopausal women were assigned to 4 groups: placebo,
11 curcumin, exercise and placebo (Ex + placebo), and exercise and curcumin (Ex + curcumin).
12 Curcumin or placebo was ingested orally for 8 weeks. The exercise groups underwent
13 moderate aerobic exercise training for 8 weeks.

14 **Results:** Carotid arterial compliance increased significantly in the curcumin, Ex + placebo,
15 and Ex + curcumin groups, whereas no such changes were observed in the placebo control
16 group. The magnitude of increases in carotid arterial compliance was the greatest in the Ex +
17 curcumin group.

18 **Conclusion:** We concluded that curcumin ingestion improves carotid arterial compliance and
19 that the combination of curcumin and aerobic exercise training was more efficacious in
20 increasing central arterial compliance than either of these treatments alone in postmenopausal
21 women.

22

23 **Keywords:** arterial stiffness, lifestyle modification, physical activity, turmeric

24

1 Introduction

2 The large elastic arteries, such as the common carotid artery and the aorta, have the
3 ability to buffer and cushion oscillation in blood pressure and blood flow.¹ This compliant
4 function of central arteries decreases with advancing age.²⁻³ Reduction in central arterial
5 elasticity is an independent risk factor for cardiovascular disease.⁴ In addition, although
6 arterial compliance in premenopausal women is greater than in age-matched men, this
7 difference is lost in postmenopausal years,⁵⁻⁶ which suggests that postmenopausal women are
8 at a higher risk of cardiovascular disease.⁷⁻⁸ We have previously demonstrated that regular
9 aerobic exercise is clinically efficacious in preventing and treating decreased arterial
10 compliance.⁹⁻¹⁰ Thus, it is therefore preferable to treat or prevent a decrease in arterial
11 compliance without pharmacological therapies, e.g., lifestyle modification including exercise
12 and/or diet.

13
14 Recent studies suggest that impairment of the arterial elastic properties is associated
15 with chronic inflammatory disorders.¹¹⁻¹² Vlachopoulos et al.¹³ reported that acute systemic
16 inflammation leads to deterioration of the central artery. Therefore, it is plausible that central
17 arterial compliance improves with the aid of an anti-inflammatory agent. Curcumin is a
18 polyphenolic molecule extracted from turmeric.¹⁴ Curcumin regulates various biochemical
19 and molecular pathway by modulating several molecular targets, including transcription
20 factors, cytokines, enzymes, and gene regulating cell proliferation and apoptosis.¹⁵ As a
21 result, curcumin has been shown to exert anti-inflammatory activity by binding to directly to
22 pro-inflammatory molecules.¹⁵ Furthermore, it has been reported that curcumin may have
23 protective effects against cardiovascular disease.¹⁶ However, the effect of curcumin ingestion
24 on arterial compliance is unknown. Furthermore, although it is well known that aerobic
25 exercise improves arterial compliance,^{3,9,10} the combined effect of exercise training and
26 curcumin on arterial compliance has never been investigated.

27
28 The purpose of this study was to determine effects of curcumin ingestion alone and

1 in combination with aerobic exercise training on central arterial compliance in
2 postmenopausal women. We hypothesized that curcumin ingestion increases arterial
3 compliance and the combination of curcumin and exercise training is more efficacious in
4 increasing arterial compliance than either treatment alone. To test these hypotheses, we used
5 a placebo-controlled study involving apparently healthy postmenopausal women.

6 7 **Methods**

8 **Subjects.**

9 A total of 51 healthy, sedentary postmenopausal women volunteered to participate. Subjects
10 were assigned randomly to one of the following intervention groups: placebo group (n = 12),
11 curcumin group (n = 12), exercise training with placebo group (Ex + placebo; n = 13), and
12 exercise training with curcumin group (Ex + curcumin; n = 14). Subjects were nonsmokers,
13 nonobese, and free of cardiovascular disease as assessed by medical history. None of the
14 subjects were taking cardiovascular-acting medications. All subjects gave their written
15 informed consent to participate. All procedures were reviewed and approved by the ethical
16 committee of the University of Tsukuba.

17 18 **Experimental design.**

19 All experiments proceeded in the morning after a 12-h overnight fast. Subjects abstained
20 from alcohol and caffeine for at least 12 h and did not exercise for at least 24 h before
21 beginning the experiment to avoid the potential acute effects of exercise. Measurements were
22 taken in a quiet, temperature-controlled room (24–26°C). After a resting period of at least 20
23 min, carotid arterial compliance, intima-media thickness (IMT), arterial blood pressure, and
24 blood biochemistry were determined. After these measurements, peak oxygen consumption
25 ($\dot{V}O_{2\text{peak}}$) was measured during incremental cycle ergometer exercise. These parameters were
26 measured before and after each intervention.

27 28 **Curcumin ingestion.**

1 Subjects in the curcumin and Ex + curcumin groups ingested 150 mg of curcumin
2 (Theracurumin, Theravalues Corporation, Tokyo) per day divided into 6 capsules. The
3 capsule with only starch (e.g., dextrin and maltose) was used as a placebo. Each subjects in
4 the placebo and Ex + placebo groups ingested 6 placebo capsules. Curcumin or placebo was
5 administered orally for 8 weeks. All subjects were instructed not to alter their dietary habits
6 during the intervention period.

7 8 **Exercise intervention.**

9 Subjects in the Ex + placebo and Ex + curcumin groups underwent aerobic exercise training
10 more than 3 days per week (2–3 supervised sessions and additional home-based training) for
11 8 weeks as previously described.¹⁰ Initially, subjects performed cycling and walking 30
12 min/day at a relatively low intensity (60% of their individually determined maximal heart rate,
13 which was evaluated by the maximal cycle exercise test). As their exercise tolerance
14 improved, the intensity and time of aerobic exercise were increased to 40–60 min/day at an
15 intensity of 70–75 % of the maximal heart rate. Heart rate during exercise was evaluated by a
16 digital pulse rate monitor (SM-66; Skynie, Tokyo, Japan). Subjects recorded their actual
17 exercise and any additional physical activity on diary basis. Adherence to the exercise
18 prescription was documented through the use of a uniaxial electrical accerometer (Lifecorder;
19 KENZ, Nagoya, Japan) and physical activity logs as described previously.¹⁷ Subjects in the
20 placebo and curcumin groups were instructed not to change their level of physical activity.

21 22 **Measurements**

23 ***Carotid Arterial Compliance.*** Carotid arterial compliance was determined using a
24 combination of ultrasound imaging and simultaneous applanation tonometry of the common
25 carotid artery. The common carotid artery was imaged B-mode using ultrasound (En Visor;
26 Koinklijke Philips Electronics, Eindhoven, The Netherland) equipped with a high-resolution
27 linear-array transducer (7.5 Hz). Diameters were measured from the intima of the far wall to
28 the media-adventitia of the near wall. Pulsatile changes in the common carotid artery

1 diameter were analyzed 1 to 2 cm proximal to the bifurcation. Carotid arterial pressure
 2 waveforms were obtained with arterial applanation tonometry incorporating an array of 15
 3 micropiezoresistive transducers (FormPWV/ABI; Colin Medical Technology, Komaki,
 4 Japan),¹⁸ and were calibrated by equating the carotid mean arterial and diastolic blood
 5 pressure to the brachial mean arterial and diastolic blood pressure. The arterial lumen
 6 diameter at minimal diastolic relaxation and maximal systolic expansion of the vessel was
 7 measured at 3 points per frame and then averaged. Each parameter was averaged over 10–15
 8 continuous beats and statistically analyzed. Arterial compliance was obtained using the
 9 following equation:

$$10 \quad [(D1 - D0)/D0]/[2(P1 - P0)\pi D0]$$

11 where D1 and D0 are the maximal and minimum arterial diameters, and P1 and P0 are the
 12 highest and lowest blood pressures respectively. In addition to arterial compliance, the
 13 β -stiffness index was analyzed using the following equation:

$$14 \quad \ln(P1/P0)/[(D1 - D0)/D0]$$

15 The β -stiffness index provided an index of arterial compliance adjusted for distending
 16 pressure.¹⁹

17

18 ***Carotid Artery Intima-Media Thickness.*** Carotid artery IMT was measured from the images
 19 derived from the same ultrasound machine (En Visor; Koinklijke Philips Electronics,
 20 Eindhoven, The Netherland) as previously described.²⁰ Carotid IMT was defined as distance
 21 from the leading edge of the lumen-intima interface. Lumen diameter was defined as the
 22 distance between the lumen and intima, and a near-wall boundary, corresponding to the
 23 interface of the adventitia and media. These measurements were made at end diastole. At
 24 least 10 measurements of IMT were taken at each segment, and the mean values were used
 25 for analysis.

26

27 ***Blood Chemistry.*** A blood sample was collected from the antecubital vein after overnight
 28 fasting. Serum concentrations of cholesterol and triglyceride were determined using standard

1 enzymatic techniques.

2

3 **Peak Oxygen Consumption.** $\dot{V}O_{2\text{peak}}$ was measured during incremental cycle ergometer
4 exercise by using online computer-assisted circuit spirometry (AE280; Minato Medical
5 Science, Osaka, Japan). All subjects underwent an incremental exercise test (after 2 min at 40
6 W, with 20 W increases every 2 min) until volitional exhaustion. $\dot{V}O_{2\text{peak}}$ was defined at the
7 highest value recorded during the test. Heart rate and rating of perceived exertion²¹ were
8 measured throughout the exercise, and the total exercise duration required to reach
9 exhaustion was recorded.

10

11 **Statistical analyses**

12 To determine the effect of each intervention on all outcome measures, repeated measures
13 analysis of variance was used. When indicated by a significant main effect on intervention,
14 specific mean comparisons were performed to identify significant within each intervention. In
15 the case of a significant F-value, a post-hoc test (the Bonferroni test) was used to identify
16 significant differences among mean values. All data are reported as means \pm SE. Statistical
17 significant was set a priori at $P < 0.05$ for all comparisons.

18

19 **Results**

20 In the exercise groups (Ex + placebo and Ex + curcumin), the average frequency and
21 time of the exercise training were similar. The average frequency of the exercise training was
22 4.7 ± 0.3 days/week (Ex + placebo) and 4.9 ± 0.3 days/week (Ex + curcumin) ($p=0.776$), and
23 the average time of the exercise training was 43.0 ± 1.6 min/day (Ex + placebo) and $49.5 \pm$
24 3.8 min/day (Ex + curcumin) ($p=0.136$). There were no significant differences in
25 compliance/adherence to the placebo and curcumin ingestion regimen between the 4 groups
26 ($95\% \pm 3\%$ in placebo; $99\% \pm 1\%$ in curcumin; $98\% \pm 1\%$ in Ex + placebo; $98\% \pm 1\%$ in Ex
27 + curcumin).

28

1 Table 1 shows the baseline characteristics of the study participants. Before the
2 intervention, there were no significant differences in any of the variables among groups.
3 Body weight and body mass index decreased in the Ex + curcumin group ($P < 0.05$).
4 High-density lipoprotein cholesterol increased significantly after the intervention in the Ex +
5 placebo group ($P < 0.05$). There were no significant changes in low-density lipoprotein
6 cholesterol and triglyceride level with any of the intervention. Absolute and relative $\dot{V}O_{2peak}$
7 in the exercise groups (both Ex + placebo and Ex + curcumin groups) increased significantly
8 after the intervention ($P < 0.05$).

9
10 As shown in Table 2, there were no statistically significant differences in the
11 baseline hemodynamic parameters at rest among the groups before intervention. Heart rate
12 did not change in any of the group. After 8 weeks of intervention, brachial and carotid systolic
13 blood pressure decreased in the curcumin, Ex + placebo, and Ex + curcumin groups ($P <$
14 0.05). Brachial diastolic blood pressure significantly decreased in the Ex + curcumin group (P
15 < 0.05). Brachial pulse pressure significantly decreased in the Ex + placebo group ($P < 0.05$).
16 IMT did not change before and after each intervention in all groups. Carotid pulse pressure
17 and β -stiffness index significantly decreased in the Ex + placebo and Ex + curcumin groups
18 ($P < 0.05$).

19
20 There was no significant difference in the baseline carotid arterial compliance
21 among the groups (Fig. 1). After 8 weeks of intervention, carotid arterial compliance
22 increased significantly in the curcumin, Ex + placebo, and Ex + curcumin groups. There was
23 no significant change in carotid arterial compliance in the placebo control group. The percent
24 change in carotid arterial compliance was significantly greater in the Ex + curcumin group
25 than in the placebo group (Fig. 2). On the other hand, the percent change in the curcumin
26 group or the Ex + placebo group statistically did not differ compared with the placebo group
27 (Fig. 2).

1 **Discussion**

2 The main findings of the present investigation were as follows. A regular ingestion
3 of curcumin significantly increased carotid arterial compliance in postmenopausal women.
4 The magnitude of improvement by curcumin was similar to that of exercise training alone.
5 Moreover, the combination of exercise training and curcumin ingestion led to a greater
6 improvement in arterial compliance compared to that achieved with either treatment alone.
7 These results suggest that a combination of exercise and curcumin can have a strong positive
8 effect on arterial compliance.

9
10 Curcumin is a perennial herb that is widely cultivated in Asia and is commonly used
11 as a spice to add flavor and yellow, coloring to food. Curcumin is known to
12 anti-inflammatory effects in addition to acting as an anti-carcinogenic and neuroprotective
13 agent.²²⁻²⁴ To our knowledge, the effects of curcumin on arterial compliance have never been
14 studied. In the present study, we revealed for the first time that central arterial compliance
15 increased after 8 weeks of the curcumin ingestion in postmenopausal women. Furthermore,
16 the magnitude of improvement achieved by curcumin treatment was comparable to that
17 obtained with exercise treatment ($10.1\% \pm 4.5\%$ vs. $10.0\% \pm 3.6\%$). This finding suggests
18 that the favorable effect of curcumin can be a primary therapeutic approach for
19 cardiovascular disease in postmenopausal women.

20
21 In our previous study, we investigated the effect of exercise training and curcumin
22 ingestion on central arterial hemodynamics, i.e., wave reflection and central blood pressure.²⁵
23 Wave reflection and central blood pressure were not improved by exercise training alone or
24 curcumin ingestion alone. These parameters improved in the combined exercise training with
25 curcumin ingestion. On the other hand, the present study investigated the effect of curcumin
26 on arterial compliance. We demonstrated for the first time that curcumin ingestion alone
27 increased arterial compliance. In addition, the magnitude of increase in carotid arterial
28 compliance was the greatest in the Ex + curcumin group among 4 groups. Therefore, these

1 results suggest that the combination of exercise and curcumin may more effectively increase
2 arterial compliance than either treatment alone, although curcumin ingestion alone or exercise
3 training alone increased arterial compliance.

4
5 The mechanism responsible for the curcumin ingestion induced improvement in
6 arterial compliance is unclear in this study. Arterial elastic property is associated with
7 inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α).¹² Curcumin exerts
8 anti-inflammatory effects by inhibiting the expression of cytokines including TNF- α .²⁶
9 Therefore, the effect of curcumin on arterial compliance may be mediated by suppression of
10 inflammation via downregulating of TNF- α . However, we did not measure any inflammatory
11 cytokines in this study. Further studies are warranted to clarify the mechanism underlying the
12 effect of curcumin on arterial compliance.

13
14 Most measures of arterial compliance are somewhat dependent on arterial pressure.
15 It is possible that the improvement in the arterial compliance by our treatment of curcumin
16 ingestion and exercise training may be mediated by the corresponding changes in arterial
17 blood pressure. To address this possibility, we calculated the β -stiffness index of arterial
18 compliance adjusted for distending pressure. The results indicated that improvement in
19 arterial compliance after the exercise intervention remained statistically significant even
20 when the data were expressed as the β -stiffness index. However, the change in the β -stiffness
21 index after curcumin intervention did not attain statistical significance. Thus, the
22 improvement in arterial compliance with curcumin may be effected partly by the
23 epiphenomenon of blood pressure change.

24
25 We observed that the greatest change in arterial compliance was achieved with a
26 combination of curcumin ingestion and exercise training. This result may be attributable to
27 physiological mechanism by which exercise training and curcumin increase arterial
28 compliance. Aerobic exercise training results in a decrease in of endothelin-1 production²⁷

1 and α -adrenergic vasoconstrictor tone.²⁸ To the best of our knowledge, there have been no
2 reports that curcumin positively influence these mechanisms. Therefore, curcumin and
3 exercise training are likely to have different physiological mechanisms to improve the elastic
4 property of the large artery. This may be the reason why combining exercise training with
5 curcumin ingestion appears more effective than a single intervention.

6
7 It is unclear that body weight and BMI decrease only in the Ex + curcumin group.
8 Little is known to the effect of curcumin on body composition. An animal study suggests that
9 curcumin increases fatty acid oxidation and reduces fatty acid esterification, resulting in
10 catabolism in adipose tissue and body weight reduction in obese mice.²⁹ However, our
11 present study was not observed weight and BMI reduction by curcumin supplementation
12 alone in postmenopausal women. Exercise training alone also did not decrease body weight
13 and BMI. On the other hand, the combination of exercise training with curcumin ingestion
14 decreases body weight and BMI. It is possible that fatty acid oxidation is promoted by the
15 combination of curcumin ingestion and exercise training in postmenopausal women.

16
17 In conclusion, the present study demonstrated that curcumin ingestion alone
18 increases arterial compliance in postmenopausal women and that combining curcumin
19 ingestion with aerobic exercise training more effectively increases arterial compliance than
20 curcumin ingestion or aerobic exercise training alone. Regular curcumin ingestion and
21 aerobic exercise may be effective lifestyle modifications for minimizing and reversing the
22 loss of carotid arterial compliance with advancing age in women.

23 24 25 **Acknowledgments**

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1 **Conflict of interest**

2 We have no financial, consultant, institutional and other relationships that might lead
3 to bias or a conflict of interest.

4

5

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1 **Figure legends**

2 **Figure.1** Carotid arterial compliance before and after intervention. Data are expressed
3 as mean \pm SE. *P < 0.05 before vs. after intervention.

4

5 **Figure.2** Percent changes in arterial compliance in response to intervention. Data are
6 expressed as mean \pm SE. *P < 0.05 placebo vs. exercise + curcumin (Ex + curcumin).

7

8

Table 1. Selected subject characteristics

		Placebo	Curcumin	Ex+placebo	Ex+Curcumin
Age, years	Before	58 ± 1	60 ± 2	59 ± 2	60 ± 1
Height, cm	Before	156 ± 2	155 ± 2	154 ± 1	157 ± 1
Weight, kg	Before	52.1 ± 1.9	52.6 ± 2.5	52.2 ± 1.5	56.6 ± 1.8
	After	52.3 ± 1.8	52.7 ± 2.5	52.1 ± 1.5	55.6 ± 1.5*
Body mass index, kg/m ²	Before	21.5 ± 0.8	21.9 ± 0.7	22.1 ± 0.5	23.2 ± 1.8
	After	21.6 ± 0.7	22.0 ± 0.7	22.1 ± 0.6	22.7 ± 0.8*
HDL cholesterol, mmol/L	Before	1.73 ± 0.11	1.58 ± 0.13	1.69 ± 0.07	1.78 ± 0.10
	After	1.81 ± 0.12	1.61 ± 0.13	1.85 ± 0.08*	1.89 ± 0.12
LDL cholesterol, mmol/L	Before	3.45 ± 0.12	3.65 ± 0.21	3.56 ± 0.19	3.64 ± 0.15
	After	3.42 ± 0.10	3.98 ± 0.20	3.57 ± 0.18	3.74 ± 0.19
Triglyceride, mmol/L	Before	1.15 ± 0.15	1.66 ± 0.29	1.16 ± 0.11	1.15 ± 0.13
	After	1.24 ± 0.15	1.56 ± 0.32	0.99 ± 0.12	1.16 ± 0.18
$\dot{V}O_{2peak}$, ml/min	Before	1312 ± 78	1179 ± 58	1282 ± 66	1390 ± 79
	After	1221 ± 56	1175 ± 62	1394 ± 73*	1474 ± 82*
$\dot{V}O_{2peak}$, ml/kg/min	Before	25.6 ± 2.0	22.6 ± 0.9	24.7 ± 1.2	24.5 ± 1.2
	After	23.5 ± 1.2	22.4 ± 0.8	26.9 ± 1.4*	26.5 ± 1.2*

Values are means ± SE. HDL; high density lipoprotein, LDL; low density lipoprotein, $\dot{V}O_{2peak}$; peak oxygen consumption. *P < 0.05 vs. before intervention.

Table 2. Hemodynamic parameter before and after intervention

		Placebo	Curcumin	Ex + placebo	Ex + Curcumin
Heart rate, beats/min	Before	64 ± 3	61 ± 2	59 ± 1	60 ± 2
	After	62 ± 2	59 ± 2	57 ± 1	57 ± 1
Brachial SBP, mmHg	Before	114 ± 4	123 ± 5	112 ± 3	118 ± 4
	After	114 ± 4	119 ± 4*	108 ± 3*	113 ± 4*
Brachial DBP, mmHg	Before	71 ± 3	72 ± 4	69 ± 2	71 ± 3
	After	71 ± 3	69 ± 3	68 ± 2	67 ± 3*
Brachial PP, mmHg	Before	42 ± 2	51 ± 2	43 ± 3	47 ± 2
	After	43 ± 2	50 ± 2	40 ± 2*	45 ± 2
Caroid SBP, mmHg	Before	103 ± 3	112 ± 5	103 ± 3	107 ± 4
	After	104 ± 3	108 ± 4*	99 ± 3*	102 ± 4*
Carotid PP, mmHg	Before	32 ± 2	40 ± 2	34 ± 3	37 ± 2
	After	33 ± 2	39 ± 2	32 ± 2*	35 ± 2*
IMT, mm	Before	0.53 ± 0.01	0.55 ± 0.03	0.55 ± 0.03	0.52 ± 0.02
	After	0.53 ± 0.01	0.55 ± 0.03	0.54 ± 0.03	0.52 ± 0.02
β-stiffness, U	Before	7.6 ± 0.4	7.8 ± 0.6	8.3 ± 0.6	8.0 ± 0.5
	After	7.9 ± 0.4	7.4 ± 0.4	7.5 ± 0.5*	7.2 ± 0.4*

Values are means ± SE. SBP; systolic blood pressure, DBP; diastolic blood pressure, PP; pulse pressure, IMT; intima-media thickness. *P < 0.05 vs. before intervention.

Figure 1

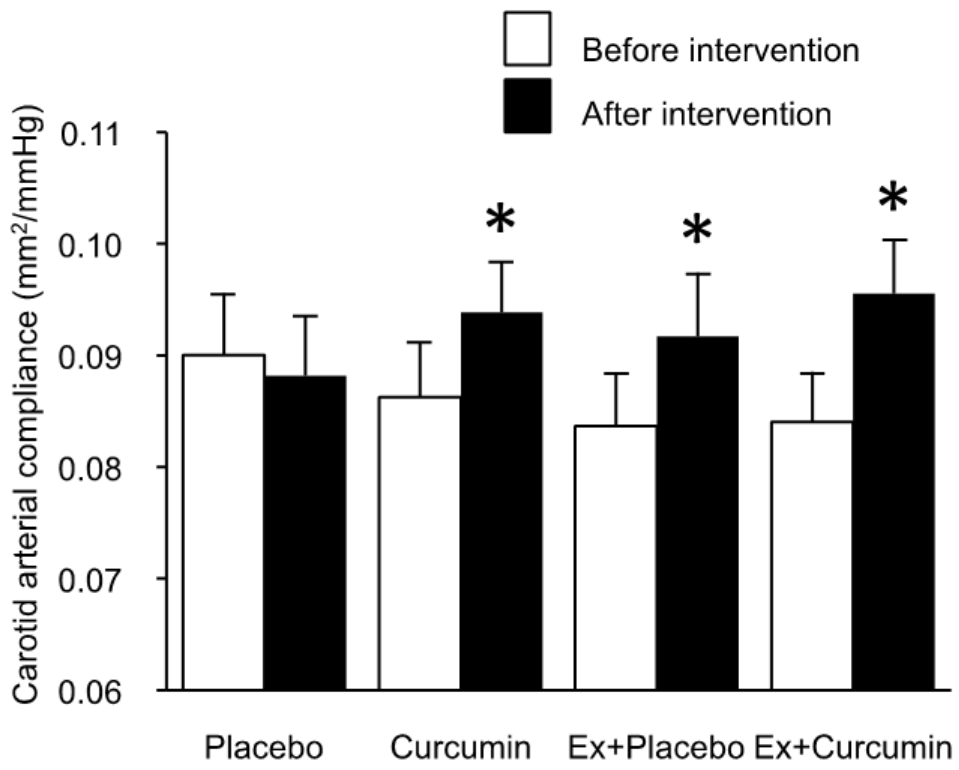


Figure 2

