Effect of Endurance Exercise Training and Curcumin Intake on Central Arterial Hemodynamics in Postmenopausal Women: Pilot Study

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BACKGROUND
Lifestyle modification (i.e., regular physical activity and diet) is effective in preventing the age-related increase in cardiovascular disease risks. Potential therapeutic effects of curcumin (diferuloylmethane) have been confirmed on various diseases, including cancer and Alzheimer’s disease, but the effects of curcumin have not been tested on central arterial hemodynamics. The aim of this pilot study was to test the hypothesis that the regular endurance exercise combined with daily curcumin ingestion lowers the age-related increase in left ventricular (LV) afterload compared with either intervention alone in postmenopausal women using a randomized, double-blind, placebo-controlled, parallel manner.

METHODS
Forty-five women were randomly assigned to four interventions: “placebo ingestion” (n = 11), “curcumin ingestion” (n = 11), “exercise training with placebo ingestion” (n = 11), or “exercise training with curcumin ingestion” (n = 12). Curcumin or placebo pills (150 mg/day) were administered for 8 weeks. Aortic blood pressure (BP) and augmentation index (AIx), an index of LV afterload, were evaluated by pulse wave analysis from tonometrically measured radial arterial pressure waveforms.

RESULTS
There were no significant differences in baseline hemodynamic variables among four groups. After the interventions, brachial systolic BP (SBP) significantly decreased in both exercise-trained groups (P < 0.05 for both), whereas aortic SBP significantly decreased only in the combined-treatment (e.g., exercise and curcumin) group (P < 0.05). Heart rate (HR) corrected aortic AIx significantly decreases only in the combined-treatment group.

CONCLUSIONS
These findings suggest that regular endurance exercise combined with daily curcumin ingestion may reduce LV afterload to a greater extent than monotherapy with either intervention alone in postmenopausal women.

Keywords: aging; aortic blood pressure; blood pressure; cardiovascular disease risk; hypertension; lifestyle modification

Arterial pressure in the central region (e.g., aorta and carotid artery) is composed mainly of the incident wave from the heart and the reflected wave from periphery. Age-related aortic stiffening and impaired endothelial function may result in the early return (in late systole) of the augmented reflection wave from periphery and thereby increase left ventricular (LV) afterload. As the increase in LV afterload potentiates an increase in LV mass, an independent risk for heart failure and coronary heart disease mortality, central arterial hemodynamics has emerged as an important factor underlying the pathophysiology of cardiovascular disease. In this context, it should be noted that central arterial augmentation index (AIx), an index of LV afterload, increases with advancing age although it changes less with aging in older individuals and is higher in women than similar aged men at all ages. In turn, older women may exhibit the highest central arterial AIx among men and women at all ages.

The importance of lifestyle modification, especially regular physical activity, to prevent the age-related increase in cardiovascular disease risks has been endorsed by major health organizations. In typical clinical settings, however, dietary modifications are usually prescribed along with regular exercise. In this context, our research group reported that a dietary intervention (e.g., daily lactotripeptides ingestion) with regular endurance exercise training has additive beneficial effect on vascular function (i.e., endothelial function, central arterial compliance) compared with either exercise training or dietary treatment alone in postmenopausal women. Recently, potential therapeutic or

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preventive effects of curcumin (diferuloylmethane), a yellow pigment in the spice turmeric, have been confirmed on various diseases, including pancreatic cancer, colon cancer, and Alzheimer’s disease.\textsuperscript{13,14} These favorable effects seem to be associated with a wide range of beneficial properties of curcumin, including anti-inflammatory, antioxidant, chemopreventive, and chemotherapeutic activity presumably via multiple signaling pathways (i.e., survival pathways regulated by nuclear factor-κB, Akt, and growth factors; cytoprotective pathways; angiogenic pathways).\textsuperscript{13,14} Anti-inflammatory and antioxidant properties could potentially improve endothelial function and thereby attenuate the central wave reflection via the decrease in vascular tone. However, the effect on central arterial hemodynamics variables has never been addressed. Accordingly, the aim of this pilot study was to test the hypothesis that regular endurance exercise combined with daily curcumin ingestion improves central arterial hemodynamics (i.e., lowering LV afterload) to a greater extent than monotherapy with either intervention alone in postmenopausal women.

METHODS

Subjects. A randomized, double-blind, placebo-controlled, parallel design study was performed to test our hypothesis preliminarily. A total of 90 sedentary postmenopausal (e.g., more than 0.5 years since the last menses) women who were free of overt cardiovascular disease volunteered to participate. Thirty-four candidates who were taking cardiovascular-acting medications including hormone replacement therapy and smokers were excluded. Random assignment with mean age and brachial blood pressure (BP)-matching was done with the SORT function of Microsoft Excel. Fifty-six postmenopausal women were assigned randomly to one of the following interventions: “placebo ingestion” group (Pla), “curcumin ingestion” group (Cur), “exercise training with placebo ingestion” group (Ex+Pla), or “exercise training with curcumin ingestion” group (Ex+Cur). Final numbers of subjects who completed the intervention of exercise and/or curcumin intake and all measurements were 11 in Pla, 11 in Cur, 11 in Ex+Pla, and 12 in Ex+Cur, respectively (Figure 1). All subjects gave their written informed consent to participate. All procedures were reviewed and approved by the ethical committee of the University of Tsukuba.

Curcumin Ingestion. Curcumin or placebo was administered orally everyday for 8 weeks. Subjects in Cur and Ex+Cur groups ingested six pills of curcumin (per day), which consists 25 mg highly absorptive curcumin dispersed with colloidal nanoparticles\textsuperscript{15} (Theracurmin; Theravale, Tokyo, Japan) (total 150 mg/day). Likewise, Pla and Ex+Pla groups ingested six placebo pills (per day) which were of similar shape and color and made of an equivalent dose of starch (e.g., dextrin and maltose). Subjects were instructed to record the number of ingested pills in a notebook everyday and not to alter their dietary habit (other than placebo or curcumin ingestion) throughout the intervention period.

Exercise Intervention. Subjects in Ex+Pla and Ex+Cur groups underwent endurance exercise training 3–6 days/week for 8 weeks. The training program consists of supervised cycling exercise using electrically braked ergometer at the university 2–3 days/week and additional home-based walking exercise. Initially, subjects performed cycling or walking 25–30 min/day, 3–4 days/week at a relatively low intensity of exercise, e.g., 60% of their individually determined peak heart rate (HR) which was evaluated at the incremental cycle exercise test (see below). As their exercise tolerance improved, the intensity and duration of endurance exercise were increased to 40–45 min/day, 4–5 days/week, at an intensity of 70–75% of peak HR. HR during exercise training was evaluated by a digital pulse rate monitor (SM-66; Skynie, Tokyo, Japan). Adherence to the exercise prescription was documented through the use of a uniaxial electrical accelerometer (Lifecorder; KENZ, Nagoya, Japan) and physical activity logs as described previously.\textsuperscript{16} Subjects in Pla and Cur groups were instructed not to change their physical activity level.

Measurements. Blood biochemistry, arterial BP, HR, aortic pulse wave velocity (PWV), and peak oxygen consumption (VO\textsubscript{2peak}) were measured before and after 8 weeks of each intervention. Subjects abstained from caffeine and fasted for at least 12h before the experiment. Furthermore, subjects were studied 24h after their last exercise training session and/or the last curcumin ingestion to avoid the immediate (acute) effects of either stimulus. After 20–30 min of supine rest in a temperature-controlled dim room, cardiovascular function measurement followed blood sampling and aerobic capacity measurement were measured in each subject.
Blood samples. Fasting plasma concentrations of low-density lipoprotein and high-density lipoprotein cholesterol were determined by use of standard enzymatic techniques (e.g., direct method) (Cholesterol; Sekisui Medical, Tokyo, Japan; Determiner L HDL-C; Kyowa Medex, Tokyo, Japan) as we previously reported.17

Cardiovascular measures. HR, ejection duration (via electrocardiogram), and four extremities BP (oscillometric pressure sensor cuffs) were measured with a semiautomated device (Form PWV/ABI; Colin Medical Technology, Komaki, Japan). Recordings were made in triplicate with subjects in the supine position. Ankle-brachial BP index (ABI), a ratio between posterior-tibial and brachial arterial systolic BPs (SBPs), was evaluated to determine suspicious of peripheral arterial disease (ABI <0.9). None of subjects exhibited an ABI of <0.9, and were therefore allowed to participate in the protocol. Investigators who performed radial artery pressure waveforms recording with applanation tonometry and pressure waveform analysis were blinded to treatment (curcumin vs. placebo) and exercise. Radial arterial pressure waveforms were recorded by a validated applanation tonometry-based measurement device (Jentow; Colin Medical Technology) which was connected to an acquisition system (PowerLab 8/30; ADInstruments, Bella Vista, Australia) interfaced with a personal computer equipped with data acquisition software (LabChart 6; ADInstruments). Radial arterial pressure waveforms were calibrated with oscilometry-derived brachial BP and sampled at 1,000 Hz for off-line analysis. Stored radial arterial pressure waveforms were resampled at 128 Hz with data analysis software (AcqKnowledge; BIOPAC Systems, Santa Barbara, CA)18 and then transferred into aortic pressure waveforms with an arterial waveform analysis software involving a validated generalized transfer function (SphygmoCor software; AtCor Medical, Sydney, Australia).19 To quantify the magnitude of wave reflection from the periphery to the heart, augmented pressure (AP; peak pressure—pressure at the inflection point at systolic shoulder) was computed from synthesized aortic pressure waveforms. Aortic AIx was also calculated as AP divided by aortic pulse pressure.20 AP and AIx were normalized for HR at 75 beats per minute (bpm) (AP75 and AIx75, respectively). Aortic (carotid-femoral) PWV was calculated from the distance between two arterial recording sites divided by the transit time. Carotid and femoral arterial pulse waveforms were simultaneously recorded on the left common carotid and left common femoral arteries with a vascular testing device equipped with two applanation tonometry sensors (Form PWV/ABI; Colin Medical Technology). The transit time between carotid and femoral waveforms were automatically calculated with foot-to-foot method, as previously reported by our group.21 Arterial path length was assumed the straight distance between two recording sites, which was obtained in triplicate with a random-zero measurement.

Aerobic capacity. To evaluate VO2peak, all subjects underwent an incremental cycle exercise test (after 2 min at 40 W, with 20 W increases every 2 min). Criteria of the termination of exercise test were: (i) archiving the age-predicted maximal HR (220-age); (ii) Borg’s scale >19; (iii) respiratory equivalent >1.2; or (iv) not to keep the pedaling speed at >55 rpm. Oxygen consumption was measured with the metabolic cart throughout the exercise test.

Statistical analyses. Treatment compliance of exercise training was compared by unpaired t-test between Ex+Pla and Ex+Cur. Treatment compliance of pill intake was evaluated by two-way factorial analysis of variance (ANOVA). To determine the effect of each intervention on all outcome measures, repeated-measures ANOVA and two-way factorial ANOVA were used. Analysis of covariance was used to determine the effect of each intervention on changes in aortic AP, AP75, AIx, AIx75 after eliminating influences of the expected confounding factors (e.g., changes in brachial BP, body mass, or blood cholesterol). In the case of a significant F value, a post hoc test using the Fisher’s least significant difference test identified significant differences among mean values. All data are reported as means ± s.e.m. Statistical significance was set a priori at P < 0.05 for all comparisons.

RESULTS
There were no significant differences in treatment compliance for placebo or curcumin intake among four groups (94.7 ± 3.7% in Pla; 99.0 ± 0.6% in Ex+Pla; 99.4 ± 0.3% in Cur; 98.7 ± 0.8% in Ex+Cur). No one reported any adverse side effects of curcumin ingestion. Average training frequencies of supervised cycling exercise were comparable between two groups (2.4 ± 0.2 in Ex+Pla vs. 2.4 ± 0.1 days/week in Ex+Cur, P = 0.93). In addition, there were no significant differences in the average training frequencies of either walking exercise (2.6 ± 0.3 in Ex+Pla vs. 2.1 ± 0.4 days/week in Ex+Cur, P = 0.66) or entire training (5.0 ± 0.3 in Ex+Pla vs. 4.3 ± 0.4 days/week in Ex+Cur, P = 0.19) between two groups.

Table 1 shows selected physiological characteristics. There were no significant group-differences in any baseline variables except for body mass: Ex+Cur group was significantly heavier than Pla group. After the intervention, body mass and body mass index were decreased in Ex+Cur group (P < 0.05 for both). VO2peak increased after the intervention in Ex+Pla (P < 0.05) but not in the other groups. After the intervention, plasma levels of high-density lipoprotein cholesterol also increased in Ex+Pla (P < 0.05) but not in the other groups. Plasma level of low-density lipoprotein cholesterol did not change with the intervention in all groups. HR and ejection duration did not change with the intervention in all groups. After the intervention, brachial SBP decreased in Ex+Pla and Ex+Cur (P < 0.05 for both). In addition, Ex+Cur group demonstrated significant reductions in brachial mean arterial pressure and diastolic BP (P < 0.05 for both). Brachial pulse pressure did not change with the intervention in all groups.

Table 2 summarizes the response of aortic BP, central (e.g., aortic and carotid arterial) and peripheral (e.g., radial arterial) AIx, and aortic PWV to the intervention. There were no significant
Table 1 | Selected physiological characteristics

| Variables          | Time  | Pla (n = 11) | Cur (n = 11) | Ex+Pla (n = 11) | Ex+Cur (n = 12) |
|--------------------|-------|--------------|-------------|-----------------|-----------------|
| Age, years         | Before| 59 ± 2       | 61 ± 2      | 59 ± 2          | 60 ± 1          |
| Height, cm         | Before| 154 ± 2      | 155 ± 2     | 154 ± 1         | 157 ± 1         |
| Body mass, kg      | Before| 51.4 ± 2.0   | 55.0 ± 2.3  | 55.6 ± 2.7      | 58.2 ± 2.3**    |
|                    | After | 51.5 ± 1.9   | 55.4 ± 2.2  | 55.4 ± 2.6      | 57.6 ± 2.2*     |
| Body mass index, kg/m² | Before| 21.6 ± 0.8   | 23.0 ± 0.7  | 23.4 ± 1.0      | 23.7 ± 1.0      |
|                    | After | 21.7 ± 0.8   | 23.1 ± 0.7  | 23.3 ± 1.0      | 23.5 ± 0.9*     |
| Heart rate, beats/min | Before| 65.5 ± 2.6   | 60.3 ± 2.4  | 59.5 ± 1.6      | 60.6 ± 2.3      |
|                    | After | 64.0 ± 2.4   | 59.3 ± 2.1  | 58.5 ± 1.5      | 58.8 ± 1.7      |
| Brachial SBP, mm Hg | Before| 119 ± 3      | 120 ± 3     | 117 ± 3         | 119 ± 2         |
|                    | After | 117 ± 3      | 117 ± 3     | 113 ± 4*        | 114 ± 3*        |
| Brachial DBP, mm Hg | Before| 73 ± 3       | 71 ± 2      | 71 ± 2          | 72 ± 2          |
|                    | After | 71 ± 3       | 70 ± 2      | 69 ± 2          | 68 ± 2*         |
| Brachial MAP, mm Hg | Before| 92 ± 3       | 91 ± 2      | 89 ± 3          | 91 ± 3          |
|                    | After | 91 ± 3       | 90 ± 2      | 87 ± 3          | 86 ± 2*         |
| Brachial PP, mm Hg | Before| 47 ± 2       | 49 ± 2      | 46 ± 3          | 47 ± 1          |
|                    | After | 46 ± 2       | 47 ± 2      | 44 ± 3          | 46 ± 2          |
| VO₂ peak, ml/kg/min | Before| 22.0 ± 1.4   | 23.0 ± 0.9  | 24.4 ± 1.3      | 24.5 ± 1.4      |
|                    | After | 21.6 ± 0.9   | 22.0 ± 0.8  | 25.9 ± 1.2*     | 25.2 ± 1.4      |
| LDL cholesterol, mg/dl | Before| 127 ± 5      | 140 ± 8     | 138 ± 7         | 142 ± 6         |
|                    | After | 134 ± 5      | 152 ± 7     | 143 ± 5         | 149 ± 8         |
| HDL cholesterol, mg/dl | Before| 72 ± 5       | 63 ± 6      | 61 ± 3          | 68 ± 4          |
|                    | After | 71 ± 4       | 63 ± 5      | 69 ± 3*         | 71 ± 4          |

Data are mean ± s.e.m.
Cur: curcumin; DPP: diastolic blood pressure; Ex+Cur: exercise training+curcumin; Ex+Pla: exercise training+placebo; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAP: mean arterial pressure; Pla, placebo; PP, pulse pressure; SBP, systolic blood pressure; VO₂ peak, peak oxygen uptake.
*P < 0.05 vs. before intervention; **P < 0.05 vs. Pla group.

**DISCUSSION**

The salient findings of this pilot study are: (i) aortic SBP and HR-corrected aortic AP and AIx significantly decreased with the combined treatment of regular endurance exercise intervention and daily curcumin ingestion but did not change significantly with either regular endurance training or curcumin ingestion alone and (ii) the reduction in HR-corrected aortic AP and AIx with the combination of regular exercise training and curcumin ingestion was significantly larger than those of other groups even when the influences of confounding factors (i.e., mean arterial pressure, body weight, metabolic risks) were statistically excluded. Our findings may provide initial preliminary evidence that regular endurance exercise combined with daily curcumin ingestion may reduce LV afterload to a greater extent than monotherapy with either intervention alone in postmenopausal women.

In the present study, aortic and carotid AIx did not change across the intervention period, whereas aortic AIx corrected by HR decreased significantly with the combined treatment of regular endurance exercise training and daily curcumin ingestion. Although the concomitant change in HR was small (~2 bpm), it might mask the lowering effect on aortic AIx (non-adjusted value). On the other hand, in Ex+Pla group, aortic AIx did not change significantly even when it was corrected by HR. Tanaka et al. indicated in the cross-sectional study that endurance-trained (average 13 years of training experience) postmenopausal women have significantly lower carotid AIx compared with sedentary peers. A cause of this inconsistency is unclear but likely to be associated with the short duration of training intervention. Alternatively, it might
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be due to the small sample size. However, our findings suggest that the daily curcumin intake seems to have additive impact in lowering BP by regular endurance training in normotensive postmenopausal women.

We identified the attenuated magnitude of reflected wave (e.g., AP\textsubscript{75}) in Ex+Cur group, whereas aortic PWV and ejection duration, expected determinants of aortic AIx, did not change significantly throughout the intervention period. These results may suggest that the decreased aortic AIx may be attributed to the attenuation of the central wave reflection, although recently the notion that reflected waves are important contributors to augmenting central BP has been debated.\textsuperscript{23–26}

To determine the exact underlying mechanism(s), contribution of other possible factors (i.e., arterial reservoir pressure) has to be considered.

The results of the present pilot study suggest that in normotensive postmenopausal women the combined endurance exercise training and curcumin treatment may have more favorable effects on central arterial hemodynamic (i.e., lowering LV afterload) compared with either endurance exercise training or curcumin treatment alone.

**Study limitation**

There are several limitations to our current protocol. First, aortic BP was estimated from radial arterial waveform by applying general transfer function. The use of transfer functions to estimate central pressure from peripheral pressure has been a topic

| Variables | Time | Pla (n = 11) | Cur (n = 11) | Ex+Pla (n = 11) | Ex+Cur (n = 12) |
|-----------|------|-------------|-------------|----------------|----------------|
| Aortic SBP, mm Hg | Before | 114 ± 3 | 112 ± 3 | 113 ± 2 | 112 ± 2 |
| | After | 114 ± 3 | 109 ± 4 | 111 ± 2 | 107 ± 3* |
| Aortic DBP, mm Hg | Before | 73 ± 3 | 72 ± 2 | 72 ± 2 | 73 ± 2 |
| | After | 73 ± 3 | 70 ± 2 | 70 ± 2 | 69 ± 2* |
| Aortic PP, mm Hg | Before | 41 ± 2 | 40 ± 3 | 41 ± 2 | 40 ± 1 |
| | After | 40 ± 2 | 38 ± 3 | 41 ± 2 | 38 ± 2 |
| Aortic AP, mm Hg | Before | 14.1 ± 1.8 | 15.1 ± 1.7 | 13.7 ± 1.4 | 13.4 ± 0.9 |
| | After | 15.3 ± 1.4 | 15.3 ± 1.5 | 14.3 ± 1.0 | 10.5 ± 1.6 |
| Aortic AP\textsubscript{75}, mm Hg | Before | 10.3 ± 1.1 | 10.5 ± 1.4 | 9.5 ± 0.8 | 9.3 ± 0.6 |
| | After | 12.4 ± 1.1 | 11.1 ± 1.3 | 9.7 ± 0.7 | 6.5 ± 1.4* |
| Aortic AIx, % | Before | 35.0 ± 4.4 | 37.7 ± 2.3 | 33.2 ± 2.4 | 33.5 ± 1.6 |
| | After | 35.3 ± 4.9 | 39.5 ± 2.2 | 31.9 ± 3.4 | 27.9 ± 3.8 |
| Aortic AIx\textsubscript{75}, % | Before | 25.2 ± 2.5 | 26.0 ± 2.3 | 23.3 ± 1.9 | 23.2 ± 1.3 |
| | After | 30.5 ± 2.1 | 28.6 ± 1.9 | 23.8 ± 1.0 | 17.4 ± 3.4* |
| Carotid AIx, % | Before | 30.6 ± 4.9 | 26.9 ± 2.1 | 31.6 ± 1.8 | 26.5 ± 3.4 |
| | After | 31.8 ± 3.6 | 27.2 ± 1.5 | 28.4 ± 1.9 | 25.6 ± 3.4 |
| Radial AIx, % | Before | 105.0 ± 10.5 | 91.0 ± 2.4 | 98.2 ± 3.5 | 91.8 ± 3.1 |
| | After | 105.3 ± 6.4 | 91.0 ± 2.1 | 102.7 ± 4.2 | 83.3 ± 3.4**, ***|
| Aortic PWV, cm/s | Before | 990 ± 46 | 958 ± 24 | 987 ± 43 | 940 ± 33 |
| | After | 1,020 ± 55 | 937 ± 30 | 984 ± 37 | 940 ± 33 |

Data are mean ± s.e.m. AIx, augmentation index; AIx\textsubscript{75}, AIx normalized by HR at 75 bpm; AP, augmented pressure; AP\textsubscript{75}, AP normalized by HR at 75 bpm; bpm, beats per minute; Cur, curcumin; DBP, diastolic blood pressure; Ex+Cur, exercise training+curcumin; Ex+Pla, exercise training+placebo; HR, heart rate; MAP, mean arterial pressure; Pla, placebo; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure.

*P < 0.05 vs. before intervention; **P < 0.05 vs. Pla group; ***P < 0.05 vs. Ex+Pla group.

Figure 2 | Changes in aortic augmented pressure (AP\textsubscript{75}) and augmentation index (AIx\textsubscript{75}) normalized for heart rate at 75 bpm. Data are mean ± s.e.m. bpm, beats per minute; Cur, curcumin; Ex+Cur, exercise training+curcumin; Ex+Pla, exercise training+placebo; Pla, placebo.
of debate (i.e., existence of individual difference). Second, this pilot study has a small sample size because we rigorously screened candidates to determine the effect of primary prevention on age-related increase in BP in postmenopausal women. Thereby, statistical power provided by a post hoc power analysis was not always high enough (i.e., α >0.80). Future studies should be warranted in a larger sample size and different populations, such as elderly men and patients with hypertension. Third, we applied the combination of supervised cycling exercise and additional home-based walking exercise in order to maintain exercise training compliance of subjects, which is based on our experience of training intervention studies. Therefore, we might not control for cycling and walking training frequencies on each participant. Potential influence of divergent training compliance on trainability of aerobic capacity or changes in central arterial hemodynamics could not be completely ruled out.

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