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 to a greater extent than monotherapy 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*

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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.[1] As the increase in LV afterload potentiates an increase in LV mass,[2] an independent risk for heart failure and coronary heart disease mortality,[3] central arterial hemodynamics has emerged as an important factor underlying the pathophysiology of cardiovascular disease.[2,4–6] 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[7,8] and is higher in women than similar aged men at all ages.[8] 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.[9,10] 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.[11,12] 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.[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).[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 hemodynamic 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[15] (Theracurumin; Theravalues, 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.

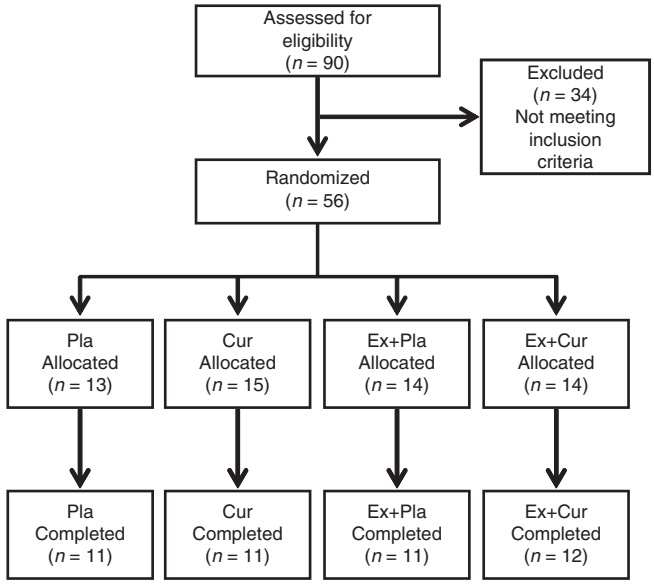

Figure 1 | A flow diagram as per the consolidated standards of reporting trials statement. Cur, curcumin; Ex+Cur, exercise training+curcumin; Ex+Pla, exercise training+placebo; Pla, placebo.

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.[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_2peak) were measured before and after 8 weeks of each intervention. Subjects abstained from caffeine and fasted for at least 12 h before the experiment. Furthermore, subjects were studied 24 h 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) (Choletest; 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 oscillometry-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) (AP_{75} and AIx_{75}, 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 VO_2peak, 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, AP_{75}, AIx, AIx_{75} after eliminating influences of the expected confounding factors (e.g., changes in brachial BP, body mass, or blood cholesterols). 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). VO_2peak 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/m^2	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
VO_2peak, 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; DBP, 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; VO_2peak, peak oxygen uptake.
*$P < 0.05$ vs. before intervention; **$P < 0.05$ vs. Pla group.

group-differences in baseline variables. Aortic SBP and diastolic BP significantly decreased in Ex+Cur group but not in the other groups. Aortic pulse pressure did not change with the intervention in all groups. There were no significant changes in aortic AP and AIx throughout the intervention, whereas the HR-corrected values (e.g., aortic AP_{75} and AIx_{75}) were significantly decreased in Ex+Cur group but not in the other groups. Carotid AIx did not change significantly in each group. Radial AIx decreased in Ex+Cur group, albeit not significant. Consequently, radial AIx was significantly lower in Ex+Cur group compared with Pla and Ex+Pla groups after the intervention.

As shown in **Figure 2**, the magnitudes of reduction in AP_{75} and AIx_{75} were significantly greater in Ex+Cur group compared with those in Pla and Ex+Pla groups, respectively. These differences remained significant when the influences of the expected confounding factors (i.e., changes in brachial mean arterial pressure, body mass, or blood cholesterols) were statistically excluded. Aortic PWV did not change significantly with the intervention in all groups.

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.*[22] 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

Table 2 | Estimated aortic blood pressure, central and peripheral arterial augmentation index, and aortic pulse wave velocity before and after the intervention

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_{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_{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_{75}, AIx normalized by HR at 75 bpm; AP, augmented pressure; AP_{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.

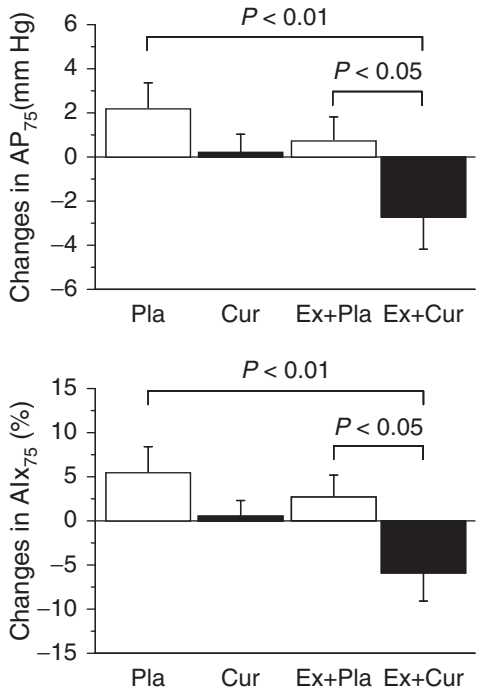

Figure 2 | Changes in aortic augmented pressure (AP_{75}) and augmentation index (AIx_{75}) normalized for heart rate at 75 bpm. Data are mean ± s.e.m. bpm, beats per minute; Cur, curcumin; Ex+Cur, exercise training+curcumin; Ex+Pla, exercise training+placebo; Pla, placebo.

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_{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.[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

of debate (i.e., existence of individual difference).[27,28] 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., $\alpha > 0.80$). 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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1. Nichols W, O'Rourke MF. *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical principles*, 5th edn. Arnold: London, 2005.
2. Roman MJ, Devereux RB, Kizer JR, Lee ET, Galloway JM, Ali T, Umans JG, Howard BV. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. *Hypertension* 2007; 50:197–203.
3. Brown DW, Giles WH, Croft JB. Left ventricular hypertrophy as a predictor of coronary heart disease mortality and the effect of hypertension. *Am Heart J* 2000; 140:848–856.
4. Roman MJ, Devereux RB, Kizer JR, Okin PM, Lee ET, Wang W, Umans JG, Calhoun D, Howard BV. High central pulse pressure is independently associated with adverse cardiovascular outcome the strong heart study. *J Am Coll Cardiol* 2009; 54:1730–1734.
5. Safar ME, Blacher J, Pannier B, Guerin AP, Marchais SJ, Guyonvarc'h PM, London GM. Central pulse pressure and mortality in end-stage renal disease. *Hypertension* 2002; 39:735–738.
6. Safar ME, Levy BI, Struijker-Boudier H. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. *Circulation* 2003; 107:2864–2869.
7. Hayward CS, Kelly RP. Gender-related differences in the central arterial pressure waveform. *J Am Coll Cardiol* 1997; 30:1863–1871.
8. McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). *J Am Coll Cardiol* 2005; 46:1753–1760.
9. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation* 2007; 116:1081–1093.
10. Whelton PK, He J, Appel LJ, Cutler JA, Havas S, Kotchen TA, Roccella EJ, Stout R, Vallbona C, Winston MC, Karimbakas J. Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program. *JAMA* 2002; 288:1882–1888.
11. Yoshizawa M, Maeda S, Miyaki A, Misono M, Choi Y, Shimojo N, Ajisaka R, Tanaka H. Additive beneficial effects of lactotripeptides and aerobic exercise on arterial compliance in postmenopausal women. *Am J Physiol Heart Circ Physiol* 2009; 297:H1899–H1903.
12. Yoshizawa M, Maeda S, Miyaki A, Misono M, Choi Y, Shimojo N, Ajisaka R, Tanaka H. Additive beneficial effects of lactotripeptides intake with regular exercise on endothelium-dependent dilatation in postmenopausal women. *Am J Hypertens* 2010; 23:368–372.
13. Anand P, Sundaram C, Jhurani S, Kunnumakkara AB, Aggarwal BB. Curcumin and cancer: an "old-age" disease with an "age-old" solution. *Cancer Lett* 2008; 267:133–164.
14. Hatcher H, Planalp R, Cho J, Torti FM, Torti SV. Curcumin: from ancient medicine to current clinical trials. *Cell Mol Life Sci* 2008; 65:1631–1652.
15. Sasaki H, Sunagawa Y, Takahashi K, Imaizumi A, Fukuda H, Hashimoto T, Wada H, Katanasaka Y, Kakeya H, Fujita M, Hasegawa K, Morimoto T. Innovative preparation of curcumin for improved oral bioavailability. *Biol Pharm Bull* 2011; 34:660–665.
16. Sugawara J, Otsuki T, Tanabe T, Hayashi K, Maeda S, Matsuda M. Physical activity duration, intensity, and arterial stiffening in postmenopausal women. *Am J Hypertens* 2006; 19:1032–1036.
17. Miyaki A, Maeda S, Otsuki T, Ajisaka R. Plasma pentraxin 3 concentration increases in endurance-trained men. *Med Sci Sports Exerc* 2011; 43:12–17.
18. Sugawara J, Hayashi K, Tanaka H. Distal shift of arterial pressure wave reflection sites with aging. *Hypertension* 2010; 56:920–925.
19. Karamanoglu M, O'Rourke MF, Avolio AP, Kelly RP. An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. *Eur Heart J* 1993; 14:160–167.
20. Kelly R, Hayward C, Avolio A, O'Rourke M. Noninvasive determination of age-related changes in the human arterial pulse. *Circulation* 1989; 80:1652–1659.
21. Sugawara J, Hayashi K, Yokoi T, Cortez-Cooper MY, DeVan AE, Anton MA, Tanaka H. Brachial-ankle pulse wave velocity: an index of central arterial stiffness? *J Hum Hypertens* 2005; 19:401–406.
22. Tanaka H, DeSouza CA, Seals DR. Absence of age-related increase in central arterial stiffness in physically active women. *Arterioscler Thromb Vasc Biol* 1998; 18:127–132.
23. Baksi AJ, Treibel TA, Davies JE, Hadjiloizou N, Foale RA, Parker KH, Francis DP, Mayet J, Hughes AD. A meta-analysis of the mechanism of blood pressure change with aging. *J Am Coll Cardiol* 2009; 54:2087–2092.
24. Davies JE, Baksi J, Francis DP, Hadjiloizou N, Whinnett ZI, Manisty CH, Aguado-Sierra J, Foale RA, Malik IS, Tyberg JV, Parker KH, Mayet J, Hughes AD. The arterial reservoir pressure increases with aging and is the major determinant of the aortic augmentation index. *Am J Physiol Heart Circ Physiol* 2010; 298:H580–H586.
25. Sharman JE, Davies JE, Jenkins C, Marwick TH. Augmentation index, left ventricular contractility, and wave reflection. *Hypertension* 2009; 54:1099–1105.
26. Tyberg JV, Davies JE, Wang Z, Whitelaw WA, Flewitt JA, Shrive NG, Francis DP, Hughes AD, Parker KH, Wang JJ. Wave intensity analysis and the development of the reservoir-wave approach. *Med Biol Eng Comput* 2009; 47:221–232.
27. Hope SA, Meredith IT, Cameron JD. Arterial transfer functions and the reconstruction of central aortic waveforms: myths, controversies and misconceptions. *J Hypertens* 2008; 26:4–7.
28. Segers P, Mahieu D, Kips J, Van Bortel LM. The use of a generalized transfer function: different processing, different results! *J Hypertens* 2007; 25:1783–1787.