Effects of Watermelon Supplementation on Aortic Blood Pressure and Wave Reflection in Individuals With Prehypertension: A Pilot Study

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BACKGROUND

Oral L-citrulline is efficiently converted to L-arginine, the precursor for endothelial nitric oxide (NO) synthesis. Oral L-arginine supplementation reduces brachial blood pressure (BP). We evaluated the effects of watermelon supplementation on aortic BP and arterial function in individuals with prehypertension.

METHODS

Heart rate (HR), brachial systolic BP (bSBP), brachial pulse pressure (bPP), aortic SBP (aSBP), aortic PP (aPP), augmentation index (AIx), AIx adjusted for HR of 75 beats/min (AIx@75), amplitude of the first (P1) and second (P2) systolic peaks, reflection time (Tr), and carotid–femoral pulse wave velocity (PWV) were evaluated in the supine position in nine subjects (four men/five women, age 54 ± 3 years) with prehypertension (134/77 ± 5/3 mm Hg). Subjects were randomly assigned to 6 weeks of watermelon supplementation (L-citrulline/L-arginine, 2.7 g/1.3 g/day) or placebo followed by a 4-week washout period and then crossover.

RESULTS

There was a significant treatment effect (change in the value of watermelon minus placebo from baseline to 6 weeks) on bPP (−8 ± 3 mm Hg, $P < 0.05$), aSBP (−7 ± 2 mm Hg, $P < 0.05$), aPP (−6 ± 2 mm Hg, $P < 0.01$), AIx (−6 ± 3%, $P < 0.05$), AIx@75 (−4 ± 2%, $P < 0.05$), and P2 (−2 ± 1 mm Hg, $P < 0.05$). There was no significant treatment effect ($P > 0.05$) on bSBP, brachial diastolic BP (DBP), aortic DBP, Tr, P1, HR, and carotid–femoral PWV.

CONCLUSIONS

This pilot study shows that watermelon supplementation improves aortic hemodynamics through a decrease in the amplitude of the reflected wave in individuals with prehypertension.

Keywords: *aortic hemodynamics; blood pressure; hypertension; L-citrulline; prehypertension; watermelon*

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L-arginine is the substrate for endothelial nitric oxide (NO) production, a main regulator of arterial blood pressure (BP) via a potent vasodilatory effect.[1] L-arginine can be synthesized from L-citrulline via the citrulline-NO cycle resulting in increased endothelial NO production.[2] Oral L-citrulline (6 g/day) provides greater circulating L-arginine levels than a similar dose of L-arginine due to an efficient conversion of L-citrulline to L-arginine.[3,4] Similarly, L-citrulline from watermelon is efficiently converted to L-arginine.[5]

Oral L-arginine supplementation has been shown to decrease brachial BP via improved endothelial NO production in adults with prehypertension and hypertension.[6–8] However, aortic BP and pulse wave reflection (augmentation index, AIx) appear to be better markers of cardiovascular risk[9–11] and therapeutic targets[12,13] than brachial BP. Although oral L-arginine (7 g) administration acutely decreases aortic AIx and stiffness (pulse wave velocity, PWV),[14] the impact of a single dose on vascular function may not be sustained for >2 h.[15] We have shown that 4 weeks of L-citrulline supplementation attenuates the acute increase in aortic BP induced by cold exposure in young men.[16] There is evidence that oral L-citrulline and watermelon supplementation can reduce peripheral BP and improve endothelium-dependent vasodilation in hypertensive and diabetic rats.[17,18] Thus, we hypothesize that watermelon supplementation, rich in natural L-citrulline,[19] will reduce BP and improve arterial function in adults with high BP. Therefore, the aim of the study was to examine the effects of watermelon supplementation on aortic BP, wave reflection, and PWV in middle-aged individuals with prehypertension.

METHODS

Subjects. Nine participants (4 men and 5 women) aged (54 ± 3 years) volunteered for this study. Prehypertension was diagnosed based on three BP measurements obtained using an Omron automated sphygmomanometer after participants were seated for at least 10 min on three separate days. Subjects had no apparent cardiovascular or metabolic diseases assessed by medical history. Exclusion criteria included regular consumption

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of L-citrulline/L-arginine rich foods or supplements, smoking, BP ≥140/90 mm Hg, and chronic diseases. Women (four postmenopausal and one premenopausal) were not using exogenous ovarian hormones. The Florida State University Human Subjects committee approved the experimental procedures, and written informed consent was obtained from all subjects. Subjects were asked to maintain their diet and exercise habits during the study period. Dietary habits were assessed by a food frequency questionnaire, whereas physical activity was recorded and reported every week.

Study design. We used a randomized, double-blind, two-period, crossover design (**Figure 1**). On the first visit, subjects received familiarization with the tests after the initial screening process. Cardiovascular tests were performed in the morning in a quiet temperature-controlled room (22–24 °C) after an overnight fast and avoiding caffeinated drinks, alcohol, and intense exercise for at least 24 h before testing. After electrocardiogram, BP, and tonometry instrumentation, participants rested for at least 20 min before data collection. Brachial BP, aortic BP, and vascular measures were collected in the supine position. The tests were conducted at the same time of the day (7–9 h) for each subject to reduce possible diurnal variations in vascular parameters at baseline and at the end of each treatment.

After baseline measurements, subjects were randomly (1:1) assigned to receive watermelon supplementation (L-citrulline/L-arginine: 1.35 g/0.65 g two times per day) or placebo for 6 weeks separated by a 4-week washout period. Watermelon powder was provided by Milne Fruit Products (Prosser, WA), consisting of sieved and freeze-dried watermelon solids. The placebo consisted of sucrose, glucose, and fructose at 2:2:1 to match the sugar composition of the watermelon powder. Both were prepared as isovolumetric powder drinks immediately before use. These doses of oral L-citrulline/L-arginine has shown to be efficacious to increase plasma levels of L-arginine and to reduce brachial systolic BP (bSBP) in individuals with hypertension.[3,5,6,8] The last dose of watermelon and placebo in all subjects was ingested ~24 h before the cardiovascular measurements. Compliance was assessed by powder's bag counts at each visit.

Anthropometrics. Height was measured using a stadiometer to the nearest 0.5 cm, and body weight was measured using a Seca scale (Sunbeam Products, Boca Raton, FL) to the nearest 0.1 kg. Body mass index was calculated as kg/m^2.

Heart rate. Heart rate (HR) was obtained from continuous electrocardiogram using a bipolar lead sampled by a data acquisition system (Biopac, Santa Barbara, CA).

PWV. After 20 min of supine rest, brachial BP and aortic PWV were measured using an automatic device (VP-2000; Omron Healthcare, Vernon Hills, IL). Carotid and femoral arterial waveforms were recorded simultaneously by two tonometers, and the transient time was calculated automatically by relating the feet of the waveforms to the R-wave of the electrocardiogram.

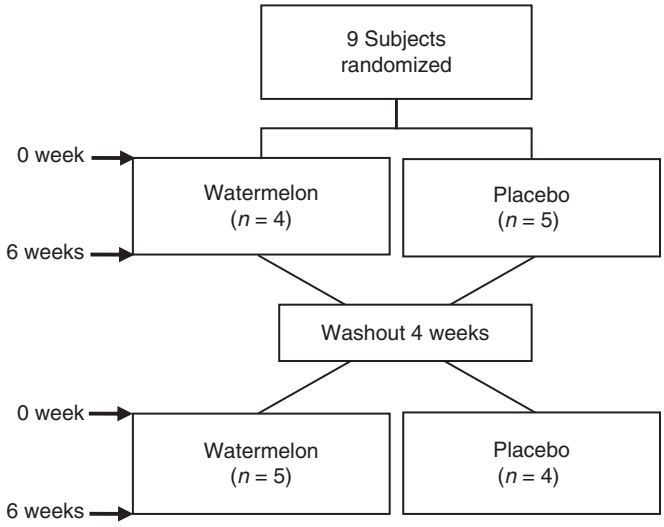

Figure 1 | Study design.

The distance from the carotid and femoral artery was measured with a nonelastic tape measure as a straight line. PWV was calculated as the distance between carotid and femoral sites divided by the transit time.[20] Two measurements were collected at each time point and averaged.

Pulse wave analysis. bSBP and brachial diastolic BP (bDBP) were used to calibrate radial waveforms, which were obtained from a 10-s epoch using a high-fidelity tonometer (SPT-301B; Millar Instruments, Houston, TX). Pulse pressure (PP) was the difference between SBP and DBP. Aortic BP waveforms were derived using a validated generalized transfer function (SphygmoCor; AtCor Medical, Sydney, Australia).[21,22] The aortic BP wave is composed of a forward wave, caused by stroke volume ejection, and a reflected wave that returns to the aorta from peripheral sites.[23] Augmentation pressure was defined as the difference between the second (P2) and first (P1) systolic peaks. The AIx was defined as the augmentation pressure expressed as a percentage of the aortic PP (aPP). AIx normalized for a HR of 75 beats/min (AIx@75) was also calculated. Transit time of the reflected wave (Tr) indicates the round-trip travel of the forward wave to the peripheral reflecting sites and back to the aorta.[23] AIx and Tr have been used as markers of wave reflection and aortic stiffness, respectively.[24] The average of two measurements of brachial BP and high-quality (operator index ≥80%) aortic hemodynamics was used in the analysis. In our laboratory, the intraclass correlation coefficients for resting aortic SBP (aSBP), aPP, AIx, and Tr calculated on two separate days are 0.97, 0.97, 0.95, and 0.97, respectively.

Statistical analysis. Unpaired *t*-test was used to detect possible difference in parameters between treatments at baseline. The effect of treatment was assessed using paired *t*-tests to compare the difference between the active and placebo treatment (watermelon minus placebo) at baseline and 6 weeks. *A priori* sample size calculation was based on previous work using oral L-arginine,[25] which showed that the mean ± s.d. of bSBP was

Table 1 | Hemodynamic parameters before and after the treatments

	Placebo		Watermelon		ΔWatermelon–placebo		
Variables	Baseline	6 Weeks	Baseline	6 Weeks	Baseline	6 Weeks	*P* value
bSBP (mm Hg)	137 ± 6	138 ± 7	134 ± 5	129 ± 4	−2.9 ± 6.6	−9.4 ± 7.0	0.10
bDBP (mm Hg)	82 ± 3	79 ± 3	77 ± 2	77 ± 2	−5.1 ± 2.6	−2.7 ± 3.0	0.34
bPP (mm Hg)	54 ± 4	58 ± 5	57 ± 3	52 ± 3	2.2 ± 5.2	−5.7 ± 5.5	0.01
aSBP (mm Hg)	127 ± 5	130 ± 5	126 ± 5	121 ± 4	−1.7 ± 2.8	−8.8 ± 3.3	0.01
aDBP (mm Hg)	81 ± 2	81 ± 3	79 ± 3	79 ± 2	−1.4 ± 1.7	−1.7 ± 1.7	0.85
aPP (mm Hg)	47 ± 3	49 ± 3	47 ± 3	43 ± 2	−0.3 ± 1.2	−6.2 ± 2.4	<0.01
AIx (%)	22.1 ± 4.0	25.4 ± 4.4	22.3 ± 4.1	19.7 ± 3.9	0.3 ± 5.4	−5.8 ± 4.14	0.03
AIx@75 (%)	17.9 ± 3.3	20.2 ± 3.6	17.1 ± 3.5	15.6 ± 3.7	−0.8 ± 3.4	−4.6 ± 4.2	0.02
Tr (ms)	145 ± 5	147 ± 6	140 ± 5	146 ± 6	−4.5 ± 2.5	−0.8 ± 3.4	0.23
P1 (mm Hg)	111 ± 3	113 ± 5	110 ± 3	107 ± 2	−1.3 ± 2.8	−6.6 ± 2.7	0.07
P2 (mm Hg)	123 ± 3	123 ± 4	124 ± 4	122 ± 4	0.3 ± 1.1	−1.6 ± 1.3	0.03
Heart rate (bpm)	65 ± 2	63 ± 3	62 ± 2	63 ± 2	−3.1 ± 1.8	0.2 ± 1.7	0.23
cfPWV (m/s)	11.8 ± 1.1	11.3 ± 0.7	11.7 ± 1.1	11.1 ± 1.0	−0.6 ± 1.4	−0.6 ± 1.0	0.59

All values are mean ± s.e.m.
Δ, watermelon minus placebo value; aDBP, aortic diastolic blood pressure; AIx, augmentation index; AIx@75, AIx adjusted for 75 beats/min; aPP, aortic pulse pressure; aSBP, aortic systolic blood pressure; bDBP, brachial diastolic blood pressure; bpm, beats/min; bPP, brachial pulse pressure; bSBP, brachial systolic blood pressure; cfPWV, carotid–femoral pulse wave velocity; P1, first systolic peak; P2, second systolic peak; Tr, reflection time.

134 ± 3 mm Hg. Based on these data, we estimated that eight subjects would enable 80% power to detect a decrease of 6% in SBP. Data are shown as means ± s.e.m. Statistical significance was defined *a priori* as $P < 0.05$. Statistical analyses were performed using SPSS version 16.0 (SPSS, Chicago, IL).

RESULTS

Watermelon supplementation was well tolerated by all subjects, and no adverse effects were reported. The compliance to both treatments was 97.1%. Height, weight, body mass index, and waist circumference were 1.70 ± 0.03 m, 82.2 ± 4.2 kg, 28.4 ± 0.9 kg/m^2, and 93.5 ± 3.0 cm, respectively. There were no differences in subject characteristics at baseline and after 6 weeks of both treatments.

Hemodynamics and arterial function

Baseline and post-treatment cardiovascular parameters are shown in **Table 1**. There were no significant differences between the treatment phases in baseline values. There were significant changes in brachial PP (bPP) (−8 ± 3 mm Hg, $P < 0.05$), aSBP (−7 ± 2 mm Hg, $P < 0.05$), aPP (−6 ± 2 mm Hg, $P < 0.01$), aortic AIx (−6 ± 3%, $P < 0.05$), aortic AIx@75 (−4 ± 2%, $P < 0.05$), and P2 (−2 ± 1 mm Hg, $P < 0.05$), suggesting treatment effects of watermelon supplementation. There was no significant effect ($P > 0.05$) of watermelon supplementation on bSBP, bDBP, aortic DBP, Tr, P1, HR, and carotid–femoral PWV.

DISCUSSION

This pilot study indicates that 6 weeks of watermelon supplementation containing natural L-citrulline and L-arginine reduced bPP, aSBP, aPP, and aortic wave reflection in middle-aged individuals with prehypertension. To the best of our knowledge, this is the first study demonstrating beneficial effects of L-citrulline/L-arginine from watermelon supplementation in arterial function in humans.

Previous studies have observed reduction in brachial BP after oral L-arginine supplementation in adults with high BP and concurrent chronic diseases. Oral L-arginine decreased bSBP (20 mm Hg) but not bDBP after 4 weeks of supplementation (6 g/day) in medicated patients with stage 2 and 3 hypertension.[6] This high reduction in SBP can be attributed to the additional influence of various antihypertensive drugs. In individuals with prehypertension to stage 2 hypertension taking atenolol, 6 months of oral L-arginine (1.6 g/day) decreased bSBP (5 mm Hg).[8] Moreover, ingestion of 10 g/day of L-arginine-enriched diet or L-arginine supplementation for 1 week reduced bSBP (6.2 mm Hg) in healthy individuals with prehypertension.[7] Consistent with these findings, we observed a reduction in bPP, which was most likely due to a decrease (5 mm Hg) in SBP.

Compared to brachial BP, aSBP and aPP have a greater influence on left ventricle afterload and on the progression of cardiovascular diseases.[10,13,26] Moreover, recent data indicate that aPP is a better predictor of adverse cardiovascular events than bPP.[10,11,27] Consistent with the present study, we previously demonstrated no influence of oral L-citrulline on DBP.[16] As PP is affected more by SBP than by DBP, the decrease in aPP can be mainly attributed to the reduction in aSBP. Because vasodilating drugs that decrease both aortic and bPP are more effective in reducing cardiovascular morbidity and mortality,[10,13,26] L-citrulline/L-arginine from watermelon supplementation may deserve to be considered as an adjunct therapy to reduce the complications of hypertension.

Watermelon supplementation decreased wave reflection (AIx and amplitude of the reflected wave) in the present study. Although aortic AIx can decrease by increased HR and decreased aortic PWV and Tr,[9,14,28] these parameters did not change in our study. Alternatively, the amplitude of the incident (P1) and reflected (P2) waves are important determinants of AIx.[9,12,23] In the present study, watermelon supplementation significantly decreased P2, but had no significant effect on P1, which is mainly determined by stroke volume and aortic PWV.[9,23] Because watermelon did not alter HR, Tr, and aortic PWV, the decrease in AIx was more likely influenced by the decrease in P2. Reduction of vascular tone in the microcirculation by vasodilating substances causes a reduction in the amplitude of the reflected wave, resulting in reduced aSBP, aPP, and consequently in AIx.[12,29] Our data are in agreement with recent results showing that despite a decrease in aSBP, aPP, and AIx, the calcium channel blocker lercanidipine does not affect aortic PWV in hypertensives.[30] These results can be explained by a significant vasodilating effect in peripheral arteries but not in the aorta.[12,29] Although it was previously reported that a single administration of oral L-arginine may acutely decrease aortic AIx and PWV,[14] the drop in PWV might have been influenced by the acute effect and/or the high dose (7 g) of L-arginine. Additionally, the vascular effects of a single dose of oral L-arginine may not persist for >2 h.[15] In the present study, BP and wave reflection were measured several hours after the last dose of the amino acids; therefore, our study has demonstrated a sustained vascular effect of watermelon supplementation.

Endothelial dysfunction in small muscular arteries results in increased aPP and AIx.[31] As increased L-arginine availability contributes to decrease brachial/aortic BP and AIx,[6,8,14] we evaluated the vascular effect of two NO precursors, L-citrulline and L-arginine from watermelon supplementation. Increased L-arginine availability after watermelon supplementation has been shown to improve serum levels of NO metabolites and aortic endothelial-mediated vasodilation in obese/diabetic rats.[17] Thus, it is possible that a similar mechanism may account for the vascular effect of watermelon supplementation in humans.

Potential limitations of this study include a small sample size and the lack of measurements of circulating L-arginine and endothelial function. Although it could be argued that our study was underpowered to detect changes in aortic PWV, the low dose of the amino acids and short duration of the intervention are the most likely explanations. To avoid the acute reduction in AIx and aortic PWV induced by the vasodilating effect of the amino acids and vasoactive substances observed in previous studies,[14,29] we evaluated arterial function 24 h after the last dose of watermelon supplementation. Further studies are warranted to confirm these findings in a larger population.

In conclusion, we found that 6 weeks of watermelon supplementation improved aortic hemodynamics in middle-aged adults with prehypertension. Our findings suggest that watermelon supplementation may decrease AIx by reducing the amplitude of the reflected wave.

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