



## Brief report

## Fuzhuan tea reverses arterial stiffening after modest weight gain in mice



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## ABSTRACT

**Objectives:** The aim of this study was to examine the effects of a Western diet (WD) and supplementation with Fuzhuan tea on large artery stiffness, as determined by aortic pulse wave velocity (aPWV).

**Methods:** Mice were subjected to a standard diet (SD;  $n = 12$ ) or WD ( $n = 10$ ) for 7 mo, and were then separated to receive nonsupplemented drinking water (SD-W and WD-W) or water supplemented with Fuzhuan tea (SD-T and WD-T) (200 mg/kg daily); mice were then maintained on their respective diets for an additional 2 mo.

**Results:** After the initial 7-mo feeding period, WD elicited a modest and significantly greater increase in body weight than did SD ( $39.6 \pm 0.71$  versus  $34.5 \pm 1.16$  g;  $P < 0.01$ ). PWV was significantly elevated in WD but not in SD ( $459.3 \pm 4.8$  versus  $422.4 \pm 6.4$  cm/s;  $P < 0.001$ ). Following an additional 2 mo, PWV continued to increase in WD-W, but returned to control levels in WD-T (WD-W:  $519.8 \pm 12.8$ ; WD-T:  $426.5 \pm 18.6$ ; SD-W:  $429.7 \pm 8.6$ ; SD-T:  $429.1 \pm 6.1$  cm/s;  $P < 0.001$ , WD-W versus all groups). The increase in PWV in WD-W was accompanied by an increase in aortic collagen (WD-W:  $38.8 \pm 4.6$  versus SD-W:  $17.5 \pm 5.1$  percent cross-sectional area;  $P < 0.05$ ).

**Conclusion:** The results of the present study suggest that the increase in arterial stiffness after modest, diet-induced weight gain can be reversed by supplementation with Fuzhuan tea.

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## Introduction

Cardiovascular disease (CVD) remains the leading cause of death in Western societies [1]. Large artery stiffening has emerged as an early prognostic indicator for CVD [2]. Pulse wave velocity (PWV), the gold standard for measuring large artery stiffness, can be determined noninvasively in both humans and animals [3]. PWV is an independent predictor of cardiovascular events and mortality in numerous populations, and data from the Framingham Heart Study suggest that PWV improves risk prediction when added to traditional risk factors [2].

Numerous studies have demonstrated that PWV is increased in obese compared with nonobese individuals, and may represent an important link between obesity and cardiovascular events [4,5]. However, much less is known regarding how small

increases in body weight, independent of obesity status, affect PWV. In experimental animals, the issue is more nebulous because of a lack of threshold values for overweight and obesity. However, most high-fat diets commonly used to induce metabolic and cardiovascular derangements in small experimental animals cause massive weight gain (>50% of body weight) after only a few months, which limits the relevance to human weight gain [6–8]. In light of these issues, the primary aim of the present study was to examine if modest weight gain (~20% greater body weight increase compared with control) in mice, induced over an extended period of several months to more closely mirror human weight gain, increases PWV.

No specific pharmaceutical treatments exist for lowering PWV, and thus lifestyle modifications and nutraceuticals remain important treatment strategies. Fuzhuan tea is a post-fermented brick-style tea that is chemically distinct from green tea, and is characterized by a unique fermentation by the fungus *Eurotium cristatum* [9,10]. Recent data indicate that Fuzhuan tea mitigates weight gain and metabolic derangements after a high-fat diet in

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experimental animals [11], although no studies have examined its effects on cardiovascular function. Therefore, the secondary aim of the present study was to examine whether Fuzhuan tea could reverse the hypothesized increase in PWV after modest weight gain in mice.

## Methods

### Animals and experimental design

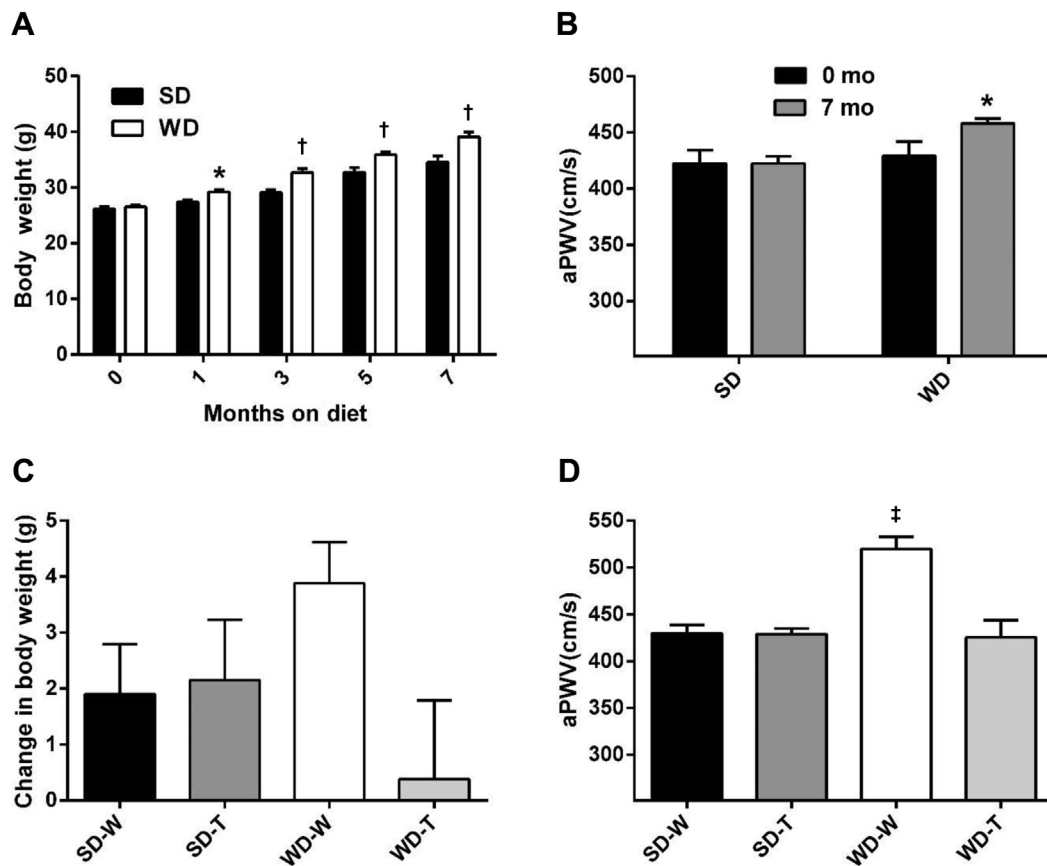
Male C57 BL/6J mice were obtained from the Jackson Laboratory (Bar Harbor, ME, USA) and acclimated for 2 wk with ad libitum access to standard diet (SD; Teklad 2018, Harlan Laboratories, Madison, WI, USA) consisting of 18% fat, 58% carbohydrate, and 24% protein calories and nonsupplemented drinking water. Mice were individually housed in a temperature- and humidity-controlled environment on a 12 h–12 h light/dark cycle. All animal procedures were reviewed and approved by the Colorado State University Institutional Animal Care and Use Committee. Once acclimated, mice were randomly assigned to a standard diet (SD;  $n = 12$ ) or Western diet (WD;  $n = 10$ ) (Teklad TD.96132 Adjusted Fat Diet) consisting of 40.6% fat (41% saturated, 17% trans), 40.7% carbohydrate (17% sucrose), and 18.7% protein calories for 7 mo. The diet was chosen because it has been shown to induce modest ( $\sim 20\%$  greater than SD) increases in body weight over extended periods of time (5–7 mo) [12]. Body weight and food intake were recorded weekly. Blood glucose was determined via glucometer after fasting mice for 4 h (Abbott, Chicago, IL, USA). After 7 mo, mice in both dietary groups were separated so that they either continued to receive nonsupplemented drinking water (SD-W and WD-W) or drinking water supplemented with Fuzhuan tea (SD-T and WD-T) powder extract (Naturalin Bio-resources, Hunan, China). The concentration of tea was adjusted each week based on the weekly ad libitum fluid intake and average animal weight to maintain a target daily tea dose of 200 mg/kg, as described previously [13].

### In vivo aortic pulse wave velocity

Mice were anesthetized using 2% isoflurane, placed supine on a heating board with legs secured to electrocardiographic (ECG) electrodes, and maintained at a target heart rate of  $\sim 450$  bpm by adjusting isoflurane concentration. Doppler probes (20 MHz) (Mouse Doppler data acquisition system; Indus Instruments) were placed on the transverse aortic arch and abdominal aorta and the distance between the probes was determined with precision calipers. Pre-ejection time, the time between the R-wave of the ECG and the foot of the Doppler signal, was determined for each site. Aortic PWV (aPWV) was calculated by dividing the distance (cm) between the probes by the difference in pre-ejection times (seconds) of the thoracic and abdominal regions.

### Animal termination and vascular endothelial function

Mice were fasted for 4 h before sacrifice via cardiac puncture. Blood was collected via cardiac puncture and stored at  $-80^{\circ}\text{C}$  for subsequent analyses. Circulating triacylglycerol and total cholesterol levels were determined via commercial assays following manufacturer's instructions (Cayman Chemical, Ann Arbor, MI, USA). Visceral white adipose tissue (mesenteric fat) was dissected and weighed. Vascular function was determined as previously described [14]. Briefly, carotid arteries were excised and placed in pressure myograph chambers (DMT Inc., Atlanta, GA, USA) containing warm physiologic saline solution (PSS: 0.288 g  $\text{NaH}_2\text{PO}_4$ , 1.802 g glucose, 0.44 g sodium pyruvate, 20 g bovine serum albumin, 21.48 g NaCl, 0.875 g KCl, 0.7195 g  $\text{MgSO}_4 \cdot 7 \text{H}_2\text{O}$ , 13.9 g MOPS sodium salt, and 0.185 g EDTA per liter solution at pH 7.4), cannulated onto steel micropipettes and secured with suture. Arteries were equilibrated for 45 min at  $37^{\circ}\text{C}$  and an intraluminal pressure of 50 mm Hg. Arteries were constricted with increasing doses of phenylephrine ( $10^{-9}$  to  $10^{-5}$  M) followed immediately by a dose–response with endothelium-dependent dilator carbachol ( $10^{-9}$  to  $10^{-4}$  M). After a washout period, a dose–response to endothelium-independent dilator sodium nitroprusside ( $10^{-10}$  to  $10^{-4}$  M) was obtained. Percent dilation was



**Fig. 1.** Effects of diet-induced weight gain and Fuzhuan tea supplementation on arterial stiffness. Western diet (WD) feeding for 7 mo significantly increased body weight (A) and pulse wave velocity (B) compared with standard diet (SD) ( $n = 10$ –12). Two months of daily treatment with water supplemented with Fuzhuan tea (200 mg/kg) trended to attenuate body weight gain with WD (C) and significantly reduced pulse wave velocity in WD-fed mice (D) ( $n = 5$ –6). aPWV, aortic pulse wave velocity. \* $P < 0.05$  versus SD; † $P < 0.01$  versus SD; ‡ $P < 0.001$  versus all.

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