

Aminoguanidine Prevents Fructose-Induced Arterial Stiffening in Wistar Rats: Aortic Impedance Analysis

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Fructose has been reported as a potent agent in forming advanced glycation end products (AGEs) and, thus, may play a significant role in the pathogenesis of diabetic complications. Herein, we determined the effects of aminoguanidine (AG), an inhibitor of AGEs, on the mechanical properties of the arterial system in fructose-fed (FF) rats, using aortic impedance analysis. Rats at 2 months were given 10% fructose in drinking water for 2 weeks and compared with untreated age-matched controls. Meanwhile, FF rats were treated for 2 weeks with AG (daily peritoneal injections of 50 mg kg⁻¹) and compared with the untreated FF group. Neither fructose nor AG affects body weight, blood glucose level, and basal heart rate. In comparison with controls, FF rats showed a decrease in cardiac output in the absence of any significant changes in mean aortic pressure, having increased total peripheral resistance (R_p), at 51.1 ± 2.9 versus 66.2 ± 1.9 mm Hg sec ml⁻¹ ($P < 0.05$). Fructose also contributed to an increase in aortic characteristic impedance (Z_c), from 1.528 ± 0.094 to 1.933 ± 0.084 mm Hg sec ml⁻¹ ($P < 0.05$) and a decrease in wave transit time (τ), from 22.6 ± 0.6 to 19.2 ± 0.7 msec ($P < 0.05$). The elevated Z_c and the reduced τ suggest that fructose may cause a detriment to the aortic distensibility in animals. After exposure to AG, FF rats exhibited a significant improvement in physical properties of the resistance vessels, as evidenced by the reduction of 21.3% in R_p . Meanwhile, AG retarded the fructose-induced decline in aortic distensibility, as reflected in the decrease of 16.0% in Z_c ($P < 0.05$) and the increase of 18.1% in τ ($P < 0.05$). By contrast, AG exerted no effects on the mechanical properties of Windkessel vessels, as well as resistance vessels, in normal diet controls. We conclude that AG may prevent the fructose-derived changes in arterial stiffening, possibly through inhibition of the fructose-

derived advanced glycation end product formation in Wistar rats. *Exp Biol Med* 229:1038–1045, 2004

Key words: advanced glycation end products; aminoguanidine; aortic input impedance; fructose; pulse wave reflection

Reducing monosaccharides, such as glucose or fructose, can nonenzymatically react with amino groups of proteins, forming a reversible adduct that over time rearranges to produce irreversible pigmented and fluorescent advanced glycation end products (AGEs) (1, 2). Excessive accumulation of those products *in vivo* is thought to be closely associated with either aging or the development of diabetic complications (3, 4). The formation of AGEs on long-lived connective tissue and matrix components may account for some of the complications of diabetes, such as cataract formation (5), stiffening of collagen (6), vascular narrowing (7), and arterial stiffening (3). As a glycation agent, fructose should receive more attention since it is more potent in forming AGEs than glucose (8) and accumulates in organs where the sorbitol pathway is active (9). The increased fructose supply may help in the formation of covalent cross-links between proteins, which could contribute to the development of certain physical changes of the vasculature. However, information is lacking as to whether the fructose loading has the potential to worsen the pulsatile nature of blood flows in arteries. Hence, the primary purpose of the present study was to determine the effect of fructose on the mechanical properties of the rat arterial system, using the aortic input impedance analysis.

Therapeutic interventions for reducing AGE formation should target AGE formation by reducing cross-link formation (10, 11). Previous studies have shown that aminoguanidine (AG) has a potent inhibitory effect on AGE formation and the development of diabetic complications in experimental diabetic rats (12–14). An *in vitro* study demonstrated that the effect of AG on the prevention of fructose-induced AGE formation may be associated in part to the trapping of the carbonyl compound derived from

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fructose autooxidation or protein-fructose adduct oxidation (15). Therefore, the secondary purpose of this study was to examine the role of AG in the prevention of arterial stiffening in animals fed with fructose. The results indicated that AG prevents the fructose-induced changes in arterial stiffening and wave reflection phenomenon possibly through inhibition of the fructose-derived AGE formation.

Methods

Animals and Catheterization. Experiments were performed in male Wistar rats that were born and maintained in the barrier facilities at the Animal Center of Medical College, National Taiwan University. The rats at age 2 months were randomly divided into four groups ($n = 7$ in each group) as follows: (i) normal diet controls (NC); (ii)

fructose-fed (FF) rats; (iii) NC treated with AG; (iv) FF rats treated with AG. The fructose-treated rats were given a 10% fructose solution, which is equivalent to a diet containing 48%–57% (by calories) fructose (16), for 2 weeks and compared with the untreated age-matched controls. Meanwhile, the FF rats were treated for 2 weeks with AG (Sigma Chemical Co., St. Louis, MO) (daily peritoneal injections of 50 mg kg^{-1}) and compared with the untreated FF group. All animals were allowed free access to Rodent Diet 5001 (PMI Lab, St. Louis, MO) and water and housed two to three per cage in a 2:12-hr light:dark cycle animal room. Periodic checks of the cages and body weights ensured that the food was administered properly. The water consumption of the animals was checked each week. Control rats drank $18.3 \pm 0.4 \text{ ml day}^{-1}$ (mean $\pm$ SE), and treated rats drank $20.2 \pm 0.4 \text{ ml day}^{-1}$. These values were not significantly different

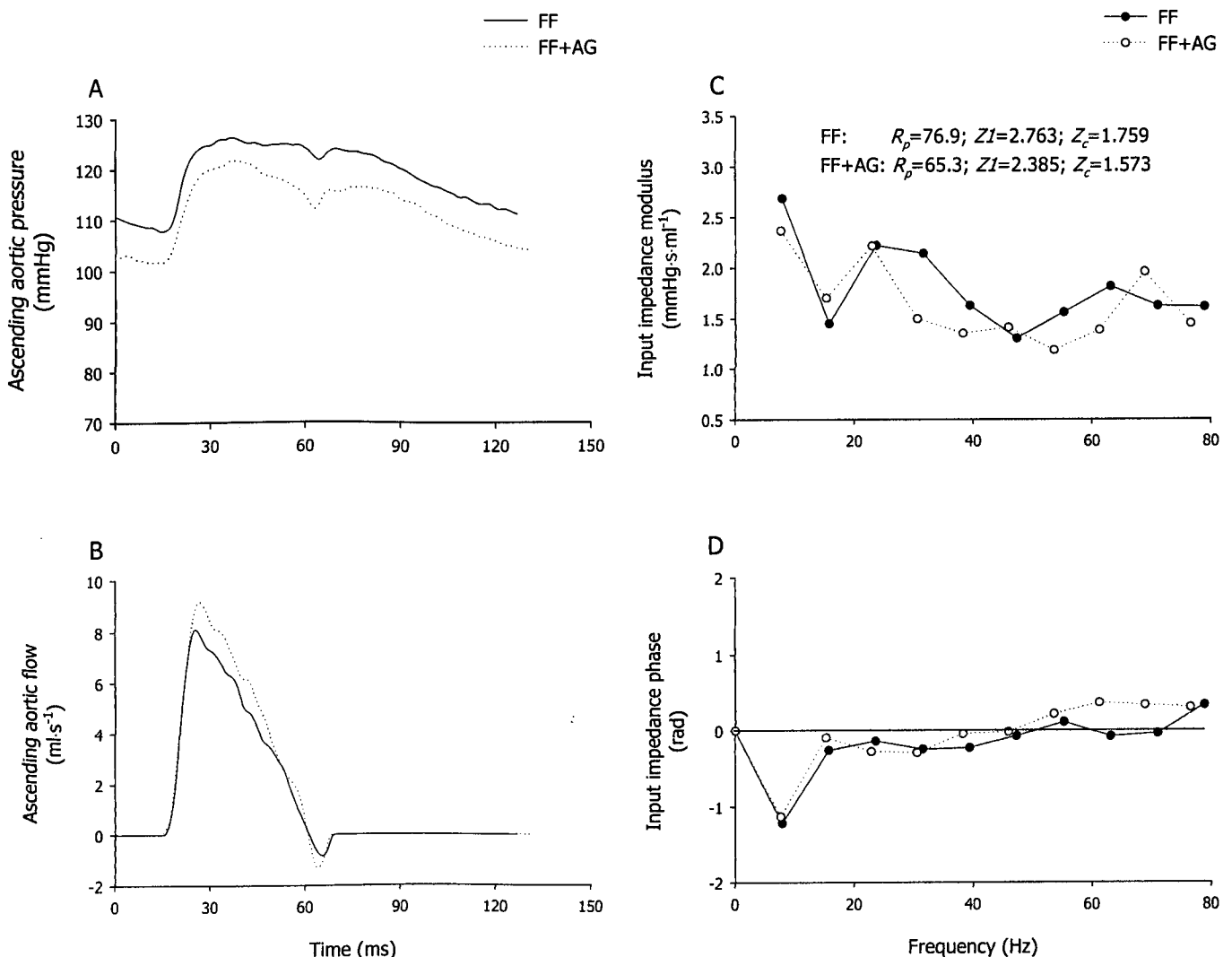


Figure 1. Left, ensemble averaged pressure and flow signals from a FF rat treated with AG (dashed lines) compared with those of an untreated FF animal (solid lines). Right, aortic input impedance spectra derived from the ascending aortic pressure and flow waveforms shown in the left panel. FF, fructose-fed rats; AG, aminoguanidine; R_p , total peripheral resistance; Z_1 , first modulus of input impedance; Z_c , aortic characteristic impedance.

and were constant throughout treatment. The animal experiments were conducted according to the *Guide for the Care and Use of Laboratory Animals*, and were approved by the Animal Care and Use Committee of the National Taiwan University.

General surgical procedures and measurement of the hemodynamic variables in anesthetized rats have been described (17). In brief, rats were anesthetized with sodium pentobarbital (35 mg kg^{-1} , ip), placed on a heating pad, intubated, and ventilated with a rodent respirator (Model 131; New England Medical Instruments, Medway, MA). The femoral vein was cannulated for the administration of supplemental pentobarbital (30 mg kg^{-1} every 2 hrs). The chest was opened through the second intercostal space of the right side. An electromagnetic flow probe (model 100 series, internal circumference 8 mm; Carolina Medical Electronics, King, NC) was positioned around the ascending aorta to measure the pulsatile aortic flow. A high-fidelity pressure catheter (model SPC 320, size 2F; Millar Instruments, Houston, TX) was used to measure the pulsatile aortic pressure via isolated carotid artery of the right side. The electrocardiogram (ECG) of lead II was recorded with a Gould ECG/Biotach amplifier (Gould Electronics, Cleveland, OH). The selective pressure and flow signals of 5–10 beats were averaged in the time domain, using the peak R wave of ECG as a fiducial point. Timing between the pressure and flow signals, because of spatial distance between the flow probe and proximal aortic pressure transducer, was corrected by a time-domain approach, in which the foot of the pressure waveform was realigned with that of the flow (18). The resulting pressure and flow signals were subjected to further vascular impedance analysis.

Aortic Input Impedance Spectra. The aortic input impedance (Z_i) could be obtained from the ratio of ascending aortic pressure harmonics to the corresponding flow harmonics (Fig. 1), using a standard Fourier series expansion technique (17, 19, 20). Total peripheral resistance of the systemic circulation (R_p) was calculated as mean aortic pressure divided by mean aortic flow. The aortic characteristic impedance (Z_c) was computed by averaging high-frequency moduli of the aortic input impedance data points (4th–10th harmonics) (14, 21). Taking Z_c into consideration, we calculated the systemic arterial compliance C at mean aortic pressure P_m by expanding the two-element (22) into the three-element Windkessel model, which accounts for a nonlinear exponential pressure-volume relationship:

$$C(P_m) = \frac{SVb}{K + Z_c SV/A_d} \times \frac{e^{bP_m}}{e^{bP_i} - e^{bP_d}}$$

SV is the stroke volume; K is the ratio of total area under the aortic pressure curve to the diastolic area (A_d); b is the coefficient in the pressure-volume relation ($-0.0131 \pm$

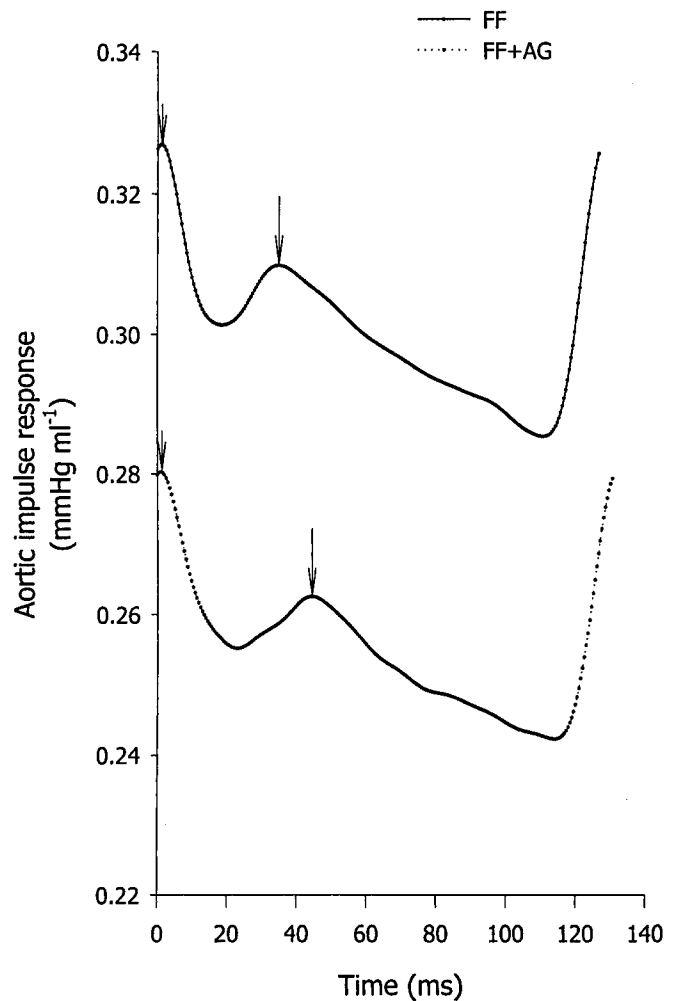


Figure 2. Impulse response function curve derived from the filtered aortic input impedance spectra shown in Figure 1. The long arrow shows the discrete reflection peak from the body circulation, and the short arrow demonstrates the initial peak as a reference. One-half of the time difference between the appearance of the reflected peak (long arrow) and the initial peak (short arrow) approximates the wave transit time in the lower body circulation. FF, fructose-fed rats; AG, aminoguanidine.

0.009 in aortic arch); P_i is the pressure at the time of incisura; and P_d is the end-diastolic pressure.

The wave transit time (τ) can be computed by the impulse response of the filtered Z_i (Fig. 2). This was accomplished by the inverse transformation of Z_i after multiplication of the first 12 harmonics by a Dolph-Chebyshev weighting function with the order 24 (23). Meanwhile, the time-domain reflection factor (R_f) can be derived as the amplitude ratio of backward-to-forward peak pressure wave by the method Westerhof *et al.* (24) proposed. Therefore, both the wave transit time and the wave reflection factor may characterize the wave reflection phenomenon in the vasculature.

Statistics. Results are expressed as means $\pm$ SE. A two-way analysis of variance (ANOVA) was used to

Table 1. Effects of Fructose and AG on Body Weight, Left Ventricular Weight, Glucose Level, and Aortic Pressure Profile in Wistar Rats^a

Variable	NC (n = 7)	NC+AG (n = 7)	FF (n = 7)	FF+AG (n = 7)
BW (g)	327.4 ± 8.0	319.3 ± 4.8	308.6 ± 5.8	314.3 ± 6.7
LVW (g)	0.612 ± 0.010	0.611 ± 0.021	0.586 ± 0.013	0.624 ± 0.011
LVW/BW (%)	0.187 ± 0.003	0.191 ± 0.004	0.190 ± 0.002	0.199 ± 0.002
Glucose (ml dl ⁻¹)	102.0 ± 2.9	112.0 ± 3.3	106.1 ± 2.9	109.0 ± 4.8
P _s (mm Hg)	115.7 ± 3.6	120.7 ± 4.1	126.9 ± 2.7	124.0 ± 3.0
P _d (mm Hg)	92.1 ± 4.4	98.6 ± 3.7	103.8 ± 2.7	96.4 ± 2.5
P _m (mm Hg)	105.2 ± 3.9	110.6 ± 4.0	116.4 ± 2.7	111.1 ± 2.4
Z ₁ (mm Hg sec ml ⁻¹)	2.289 ± 0.098	2.311 ± 0.078	2.826 ± 0.060*	2.344 ± 0.065**

^a All values are expressed as means ± SE. BW, body weight; LVW, left ventricular weight; P_s, systolic aortic pressure; P_d, diastolic aortic pressure; P_m, mean aortic pressure; Z₁, first modulus of input impedance.

* Statistical difference ($P < 0.05$) from the control group (NC).

** Statistical difference ($P < 0.05$) from the fructose-fed group (FF). AG, aminoguanidine.

determine the effects of fructose and AG on the physical properties of the rat arterial system. Simple-effect analysis was used when significant interaction between fructose and AG occurred. Differences among means within levels of a factor were determined by Tukey's honestly significant difference (HSD) method. Significant differences were assumed at the level of $P < 0.05$.

Results

Table 1 shows the effects of fructose and AG on body weight (BW), left ventricular (LV) weight, blood glucose level, and aortic pressure profile. Neither fructose nor AG produced a significant difference in BW, LVW, and LVW/BW, nor was there a fructose-AG interaction for those variables. Blood glucose level did not change significantly

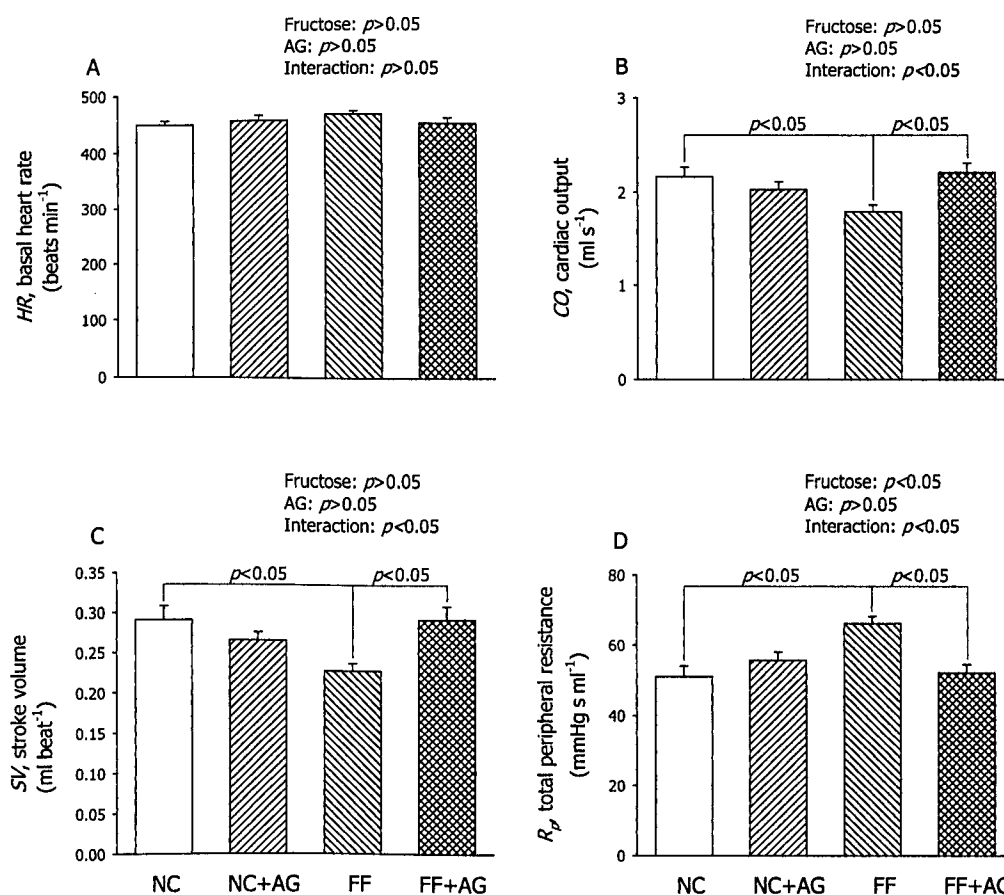


Figure 3. Effects of fructose and AG on basal heart rate (HR in A), cardiac output (CO in B), stroke volume (SV in C), and total peripheral resistance (R_p in D). Without affecting HR, the fructose loading had decreased CO and SV and increased R_p in Wistar rats. After exposure to AG, the FF rats exhibited an increase in CO and a decline in R_p. By contrast, AG exerted no effects on the mechanical properties of the resistance arterioles in the age-matched controls. NC, normotensive controls; FF, fructose-fed rats; AG, aminoguanidine.

in animals fed with fructose, nor did they change in response to AG treatment. No interaction between the effects of fructose and AG in their effects on aortic pressure profile was detected in rats. Although there was a trend toward increasing systolic, diastolic, and mean aortic pressures in the FF rats, no significant changes were detected.

Figure 1 depicts the aortic input impedance spectra from a FF rat treated with AG (dashed lines) compared with those of an untreated FF animals (solid lines). After exposure to AG, the FF rat showed a decline in maximal rate of change in aortic pressure during systole and had a larger fluctuation of the diastolic portion of the pressure. Aminoguanidine prevented the fructose-derived abnormalities in the impedance spectrum, such as an increase in modulus at zero harmonic (R_p), an increase in modulus at fundamental harmonic (Z_1), and an increase in averaging high-frequency moduli of the aortic characteristic impedance (Z_c). Figure 2 describes the impulse response function curve derived from the filtered aortic input impedance

spectra shown in Figure 1. After exposure to AG, the FF rat showed an increase in time difference between the appearance of the reflected peak and the initial peak, suggesting that the abnormality in timing of the pulse wave reflection could be retarded in the FF rat.

Figure 3 shows the effects of fructose and AG on the basic hemodynamic data, including basal heart rate (HR), cardiac output (CO), stroke volume (SV), and total peripheral resistance (R_p). Neither fructose nor AG affected HR, nor was there a fructose-AG interaction for this variable (Fig. 3A). However, a significant interaction between the effects of fructose and AG in their effects on CO (Fig. 3B), SV (Fig. 3C), and R_p (Fig. 3D) was detected. CO and SV were decreased markedly in the FF rats as compared with the age-matched controls. A decrease in CO in the absence of any significant change in P_m (Table 1) caused a rise in R_p in the FF rats, from 51.1 ± 2.9 to 66.2 ± 1.9 mm Hg sec ml^{-1} ($P < 0.05$). After exposure to AG, the FF rats exhibited an increase in CO but showed no significant alterations in P_m . Thus, the fructose-derived physical

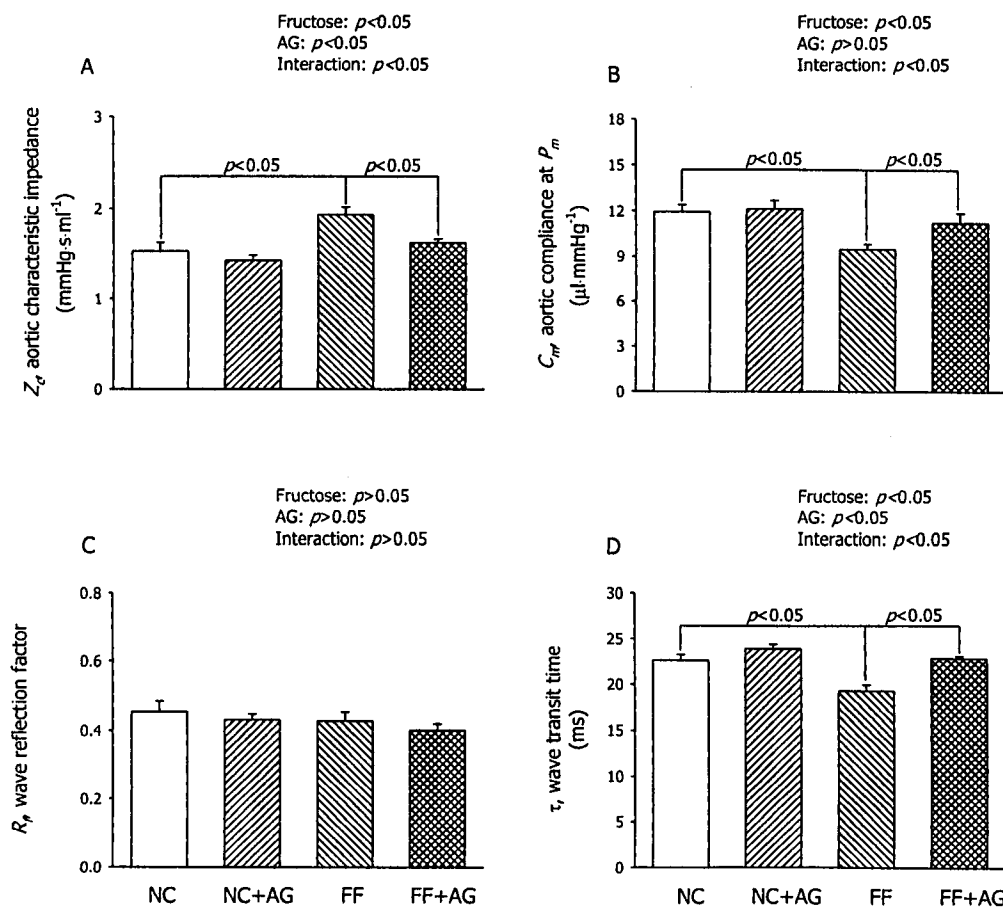


Figure 4. Effects of fructose and AG on aortic characteristic impedance (Z_c in A), systemic arterial compliance at mean aortic pressure (C_m in B), wave reflection factor (R_r in C), and wave transit time (τ in D). The fructose loading contributed to an increase in Z_c , a decrease in C_m , and a decline in τ in Wistar rats. The fructose-derived alterations in Windkessel vessels were retarded by administration of AG to rats. By contrast, AG exerted no effects on the pulsatile nature of blood flows in arteries in the age-matched controls. NC, normotensive controls; FF, fructose-fed rats; AG, aminoguanidine.

changes in resistance vessels were prevented by AG, as evidenced by the reduction of 21.3% in R_p . By contrast, AG exerted no effects on those basic hemodynamic data in normal diet controls.

Figure 4 shows the effects of fructose and AG on the pulsatile nature of blood flows in arteries in terms of aortic characteristic impedance (Z_c), aortic compliance (C_m), wave transit time (τ), and wave reflection factor (R_f). There was a significant interaction between the effects of fructose and AG in their effects on Z_c (Fig. 4A), C_m (Fig. 4B), and τ (Fig. 4D). Fructose contributed to an increase in Z_c , from 1.528 ± 0.094 to 1.933 ± 0.084 mm Hg sec ml⁻¹ ($P < 0.05$) and a decrease in C_m , from 11.94 ± 0.046 to 9.67 ± 0.33 μ l mm Hg⁻¹ ($P < 0.05$). The fructose-derived mechanical alterations in Windkessel vessels were retarded by administration of AG to rats, as reflected in the reduction of 16.0% in Z_c ($P < 0.05$) and the increase of 16.2% in C_m ($P < 0.05$). The fructose loading also caused an increase in the first modulus of impedance (Z_1), and the fructose-induced changes in Z_1 were prevented by AG (Table 1). Meanwhile, wave transit time of the FF rats (19.2 ± 0.7 ms) was significantly lower ($P < 0.05$) than that of the age-matched controls (22.6 ± 0.6 ms). Early return of the reflected wave from the peripheral circulation in the FF rats was prevented by treatment with AG, as evidenced by the increase of 18.1% in τ . By contrast, neither fructose nor AG affected R_f , nor was there a fructose-AG interaction for this variable (Fig. 4C). The oscillatory components of the ventricular afterload, including Z_c , C_m , τ , and R_f , were not modified by administration of AG to the age-matched controls.

Discussion

Fructose is a potent agent in forming AGEs and, thus, may play a significant role in the pathogenesis of diabetic complications. Aminoguanidine, a nucleophilic hydrazine compound, is a potent inhibitor of AGE formation and cross-links on proteins such as collagens. Herein, we determined whether AG treatment produces effects on the fructose-derived changes in the mechanical properties of the rat arterial system.

The fructose loading has been reported to enhance the development of hypertension in normal rats when fed with a high-fructose diet (16, 25). Herein, no significant alterations in aortic pressure profile were found in the FF animals (Table 1). By contrast, a decline in cardiac output occurred in the absence of any significant changes in mean aortic pressure, causing a rise of 29.5% in total peripheral resistance (R_p) in the FF rats (Fig. 3D). It has been shown that an increase in AGE formation and accumulation occurs in both bovine serum albumin (15) and human serum albumin (8), which were incubated with fructose. Advanced glycation end products are reported to induce free-radical production and deplete nitric oxide (NO) concentration, leading to a state of oxidative stress (26). The ability of

AGEs to quench NO is supposed to diminish the vasodilatory capacity of the peripheral muscular arteries in the FF rats. Therefore, an increase in AGEs accumulation in the FF animals may be one of several factors responsible for the increased vascular smooth muscle tone. The fructose-derived physical changes in resistance vessels were prevented by administration of AG to rats for 2 weeks, as reflected in the reduction of 21.3% in R_p . In addition to being an inhibitor of AGE formation, AG has been reported to inhibit nitric oxide synthase (NOS), especially the inducible NOS (27). The inhibition of NO production by AG could result in an increase in arterial blood pressure (28), as well as aortic characteristic impedance (21). However, such hypertensive effects of AG were not observed in this report when AG was administered to rats for 2 weeks (Table 1 and Fig. 4A). Thus, the prevention of fructose-induced vasodilatory dysfunction may result from inhibition of the AGE formation by AG to reserve NO production in the resistance vessels.

As for the pulsatile components of the arterial load, the aortic characteristic impedance increased (Z_c in Fig. 4A) and the wave transit time decreased (τ in Fig. 4D) in the FF rats as compared with the age-matched controls. Being relatively independent to body shape, the fructose-derived change in τ could be due to the change in pulse wave velocity; the shorter the wave transit time, the higher the pulse wave velocity and the stiffer the blood vessel wall (19). Both the augmented Z_c and the shortened τ suggest that a decline in aortic distensibility may occur in animals fed with fructose. It has been shown that accumulation of AGEs is associated with changes in the biomechanical properties of collagen characterized by increasing stiffness of the elastic arteries (12, 29–32). Thus, an increase in AGEs accumulation in the Windkessel vessels may be responsible for the increased aortic stiffness in the FF rats. The fructose-induced fall in aortic distensibility was prevented by administration of AG to rats for 2 weeks, as manifested by the reduction of 16.0% in Z_c and the increase of 18.1% in τ . Such prevention of the fructose-derived aortic stiffness by AG may result from inhibition of the AGE-induced chemical cross-links in the wall of the elastic reservoir. These results were similar to those reported by Takagi *et al.* (15), who found that AG prevents the fructose-derived AGE formation possibly through the trapping of the carbonyl group. No measurements on the aortic wall histological structure were made in this report; the inferences that AG exerts its effects by inhibition of the collagen AGEs accumulation are indirect.

Herein, we ascribed the changes in Z_c to stiffening of the blood vessel wall in the absence of direct histological evidence of aortic wall glycation. As is widely agreed, the aortic characteristic impedance of arterial segments depends primarily on mechanical and geometric properties of the blood vessel walls (19). These properties are known to be sensitive to mean pressure due to nonuniformity of the

elastic properties of arteries. However, Alexander *et al.* reported that the aortic characteristic impedance was not significantly influenced by mean arterial pressure (33). Although there was a trend toward increasing mean aortic pressure in the FF rats, Z_c is capable of describing the fructose-derived abnormalities in elastical properties of the vasculature.

Animal studies using a three-element Windkessel model suggest that an increase in the low-frequency harmonic of impedance may indicate a decrease in systemic arterial compliance (34). If we used the amplitude of Z_1 as an index of the low-frequency portion of the impedance spectrum, it was obvious that the moduli of the lower harmonics increase in the rats fed with fructose (Table 1). The change of lower harmonics in the FF rats supported the likelihood that the fructose loading diminished the systemic arterial compliance in Wistar rats. The connection between Z_1 and the systemic arterial compliance was evidenced by the fact that C_m was significantly reduced in the rats treated with fructose. The fructose-derived abnormality in systemic arterial compliance was prevented by the administration of AG to rats, as manifested by the reduction in Z_1 and by the increase in C_m .

Changes in timing or magnitude of the pulse wave reflection or both do impair the loading condition for the left ventricle when coupled to its arterial system (35). Without affecting the wave reflection factor (R_f in Fig. 4C), the fructose loading contributed to a reduction in wave transit time (τ in Fig. 4D) in Wistar rats. That suggests that the fructose loading may augment systolic load of the left ventricle because of the early return of the pulse wave reflection from the peripheral circulation. The enhanced systolic load of the left ventricle could cause an increase in oxygen consumption for the heart. After exposure to AG, this early return of the pulse wave reflection was prevented in the FF rats, as evidenced by the increase of 18.1% in τ . The increased τ in the absence of any significant changes in R_f suggests that AG may retard the fructose-derived increase in systolic load of the left ventricle.

Some limitations of the current study deserve consideration. Because the aortic input impedance cannot be measured in conscious animals, it is difficult to evaluate the effects of pentobarbital anesthesia on rats fed with fructose and on rats treated with AG. In this report, the results pertained only to measurements made in the open-chest rat with anesthesia. This setting induced a fall in blood pressure and may introduce reflex effects not found in the closed-chest setting. Just how much anesthesia and thoracotomy affect the pulsatile hemodynamics in rats was uncertain. However, studies with other animal models suggest that the effects are small relative to the biological and experimental variability between animals (36).

Taken together, the fructose loading produces a detriment to the physical properties of the resistance vessels and the Windkessel vessels in male Wistar rats. No hypertensive effects of AG were observed in this report when AG was

administered to animals. With unchanged aortic pressure profile, both the decreased aortic characteristic impedance and the increased wave transit time suggest that AG may prevent the fructose-derived fall in aortic distensibility. Meanwhile, the increased wave transit time in the absence of any significant changes in wave reflection factor indicate that AG can retard the fructose-induced augmentation in systolic loading condition for the left ventricle coupled to the arterial system. In conclusion, AG may impart significant protection against the fructose-derived changes in mechanical properties of the resistance vessels and the Windkessel vessels possibly through inhibition of the fructose-induced AGE formation in Wistar rats.

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