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Aminoguanidine prevents age-related deterioration in left ventricular–arterial coupling in Fisher 344 rats

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1 In recent studies, aminoguanidine (AG), an inhibitor of advanced glycation endproducts, has been identified as a prominent agent that can prevent the age-related aortic stiffening and cardiac hypertrophy. The aim of this study was to determine whether AG had effects on the left ventricular (LV)–arterial coupling in aged Fisher 344 rats in terms of the ventricular and arterial chamber properties.

2 Normotensive rats were treated from 18 to 24 months with AG ($1\,g\,l^{-1}$ in drinking water) and compared with a control group. LV pressure and ascending aortic flow signals were recorded to construct the ventricular and arterial end-systolic pressure–stroke volume relationships to calculate LV end-systolic elastance (E_{es}) and effective arterial volume elastance (E_a), respectively. The optimal afterload (Q_{load}) determined by the ratio of E_a to E_{es} was used to measure the efficiency of mechanical energy transferred from the left ventricle to the arterial system.

3 In comparison with the 6-month-old rats, the 24-month-old animals had decreased E_{es}, at 567.4 ± 26.7 vs $639.0 \pm 20.7\,mmHg\,ml^{-1}$, decreased E_a, at 411.5 ± 18.6 vs $577.9 \pm 15.7\,mmHg\,ml^{-1}$, and decreased Q_{load}, at 0.9428 ± 0.0024 vs 0.9962 ± 0.0014.

4 Treatment with AG for 6 months did not significantly affect E_{es}; however, when normalized to LV weight (i.e., $E_{esn} = E_{es}/\text{LV weight}$), E_{esn} showed a significant rise of 22.8%, suggesting that AG may retard the aging process on the intrinsic contractility of the left ventricle. On the other hand, the decrease in E_a in aging rats was prevented by AG, as reflected in the increase of 19.7% in this variable ($P<0.05$). The 24-month-old treated rats also exhibited a significant rise of 21.6% in E_a/E_{es}, causing an increase of 5.2% in Q_{load} ($P<0.05$).

5 We conclude that in healthy older Fisher 344 rats without diabetes, long-term treatment with AG may improve both the arterial and ventricular function and optimize the matching condition for the left ventricular–arterial coupling.

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Abbreviations: AG, aminoguanidine; AGEs, advanced glycation endproducts; BW, body weight (g); CO, cardiac output ($ml\,s^{-1}$); E_a, effective arterial volume elastance ($mmHg\,ml^{-1}$); E_{es}, left ventricular end-systolic elastance ($mmHg\,ml^{-1}$); E_{esn}, end-systolic elastance normalized to left ventricular weight ($mmHg\,kg\,ml^{-1}$); HR, basal heart rate ($beats\,min^{-1}$); LVW, left ventricular weight (mg); P_{es}, end-systolic pressure of the left ventricle (mmHg); P_{isomax}, peak isovolumic pressure of the left ventricle (mmHg); Q_{load}, optimal afterload; R_p, total peripheral resistance ($mmHg\,min\,ml^{-1}$); SV, stroke volume ($ml\,beat^{-1}$); V_{eed}, effective end-diastolic volume of the left ventricle (ml)

Introduction

Glucose and other reducing sugars react with proteins by a non-enzymatic modification process, forming a reversible adduct which, over time, rearranges to produce a class of products termed advanced glycation endproducts (AGEs) (Brownlee *et al*., 1988). The formation of AGEs on long-lived connective tissue and matrix components accounts largely for the increase in collagen crosslinking that accompanies increased arterial wall stiffness and decreased myocardial compliance during aging (Bucala & Cerami, 1992; Lakatta, 1993; Li *et al*., 1996; Cantini *et al*., 2001). An increase in aortic stiffness increases the vascular load imposed on the heart, resulting in adverse changes in left ventricular (LV) structure and function, as well as efficiency of ventricular coupling with the arterial system (Lakatta, 1993). Aminoguanidine (AG), an inhibitor of AGEs formation, has been proven effective in slowing or preventing the age-related aortic stiffening and cardiac hypertrophy in rats (Li *et al*., 1996; Corman *et al*., 1998; Chang *et al*., 2003). These results indicate that AG improves both arterial and ventricular function in older animals, and suggest that this drug may improve impaired coupling between the heart and the vasculature. To test this hypothesis, we determined the effects of chronic AG treatment on the integrated actions of cardiac performance and vascular function in aged Fisher 344 rats, using the pressure–stroke volume (SV) analysis.

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In this study, healthy older Fisher 344 rats without diabetes were treated from 18 to 24 months with AG (1 g l^{-1} in drinking water) and compared with a control group. Our data indicated that the aging process worsens not only the intrinsic contractile status of the left ventricle, but also the efficiency of mechanical energy transferred from the left ventricle to the arterial system. Administration of AG to rats for 6 months may improve both the ventricular and arterial function and optimize the matching condition for the left ventricular–arterial coupling.

Methods

Animals and catheterization

The specific pathogen-free male Fisher 344 rats at the ages of 6 ($n=7$) and 24 ($n=14$) months were used to determine the effects of aging and AG on the coupling efficiency between the heart and the vasculature. Animals were obtained from the colony maintained in the barrier facilities at the Animal Center of Medical College, National Taiwan University. All animals were allowed free access to the Purina chow and water and housed two to three per cage in a 12-h light/dark cycle animal room. Periodic checks of the cages and body weights (BWs) ensured that the food was administered properly. At the age of 24 months, rats were randomized into two groups, control ($n=7$) and experimental ($n=7$). Animals in the experimental group were treated from 18 to 24 months with AG and compared with the control group. AG hemisulfate (Sigma) was added to the drinking water (1 g l^{-1}) in the experimental group. The water consumption of the animals was checked each week. Control rats drank 17.3 ± 0.4 ml day^{-1} (mean $\pm$ s.e.), and treated rats drank 18.2 ± 0.5 ml day^{-1}. These values were not significantly different 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 (Chang *et al*., 2001). In brief, rats were anesthetized with sodium pentobarbital (35 mg kg^{-1}, i.p.), placed on a heating pad, intubated, and ventilated with a rodent respirator (Model 131, New England Medical Instruments, Medway, MA, U.S.A.). The femoral vein is cannulated for the administration of supplemental pentobarbital (30 mg kg^{-1} every 2 h). 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, U.S.A.) 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, U.S.A.) was used to measure the pulsatile LV pressure *via* the isolated right carotid artery into the left ventricle. The electrocardiogram (ECG) of lead II was recorded with a Gould ECG/Biotach amplifier (Cleveland, OH, U.S.A.). The selective LV pressure and aortic flow signals of 5–10 beats were averaged in the time domain, using the peak R wave of ECG as a fiducial point. A single-beat estimation technique was used to evaluate the ventriculoarterial coupling without altering LV loads (Takeuchi *et al*., 1991; Chang *et al*., 2001).

Coupling of the left ventricle and the arterial system

To quantitate the ventriculoarterial coupling, both the left ventricle and the arterial system are considered elastic chambers with known volume elastance E_{es} and E_a, respectively; E_{es} represents the LV end-systolic elastance and E_a represents the effective arterial elastance (Sunagawa *et al*., 1983; 1984; 1985). LV pressure and ascending aortic flow signals can be recorded to construct the ventricular and arterial end-systolic pressure–SV (P_{es}–SV) relationships to calculate E_{es} and E_a, respectively. E_{es} can be determined by the ratio of peak isovolumic pressure (P_{isomax}) to the effective LV end-diastolic volume (V_{eed}). P_{isomax} could be obtained by making use of a nonlinear least-squares approximation technique proposed by Sunagawa *et al*. (1980). On the other hand, dividing the LV P_{es} by the SV yields E_a. In the steady state, E_a is independent of E_{es}. The optimality of energy transmission from the left ventricle to the arterial system, that is, the optimal afterload (Q_{load}), can be determined from the ratio of stroke work to its theoretical maximal value and can be expressed using E_a/E_{es} as follows (Burkhoff & Sagawa, 1986; Kubota *et al*., 1992):

$$Q_{load} = \frac{4 \cdot E_a/E_{es}}{(1 + E_a/E_{es})^2} \quad (1)$$

when E_a equals E_{es}, Q_{load} becomes unity and the arterial system extracts maximal energy from a given E_{es} and V_{eed}.

Statistics

All data are expressed as means $\pm$ s.e. Analysis of variance (ANOVA) was used to determine the statistical significance, while multiple comparison were made for the effects of aging and AG on the left ventricular–arterial interaction. Significant differences were assumed at the level of $P<0.05$. If ANOVA for a hemodynamic variable reached the significant level, then Tukey's honestly significant difference (HSD) method was used to determine the groups of rats having different mean values of the variable.

Results

Table 1 shows the effects of aging and AG on BW, LV weight (LVW), basal heart rate (HR), cardiac output (CO), LV end-systolic pressure (P_{es}), and peak isovolumic pressure (P_{isomax}). Rats treated with AG did not differ in BW from untreated controls; however, the significant age-related increase in LVW was not observed in the corresponding AG-treated group. HR was decreased with age ($P<0.05$); however, this decrease was not significantly modified by treatment with AG. *CO*, P_{es}, as well as P_{isomax} did not change significantly as animals aged, nor did they change in response to AG treatment. Administration of AG to rats for 6 months showed no alteration in blood glucose level between the 24-month-old controls (105.1 ± 6.0 mg dl^{-1}) and the 24-month-old treated rats (103.4 ± 5.3 mg dl^{-1}).

Figure 1 demonstrates the effects of aging and AG on the chamber properties of the left ventricle and the arterial system, which were derived from the pressure–SV plane. The increased SV (Figure 1a) as well as the decreased P_{es} with age were responsible for a significant fall in E_a (Figure 1b) from

Table 1 Hemodynamics and left ventricular performance in 6-, 24-, and 24-month-old rats treated with aminoguanidine

	BW	*LVW*	*HR*	*CO*	P_{es}	P_{isomax}
Age (months)						
6 ($n=7$)	340.7±10.5	595.8±10.7	401.3±12.3	1.412±0.075	118.2±4.2	244.6±7.4
24 ($n=7$)	435.5±12.1	735.6±13.6	330.8±9.9	1.388±0.080	103.9±3.9	260.1±10.8
24+AG ($n=7$)	392.0±11.8	601.7±10.6	345.2±10.5	1.356±0.078	112.7±3.3	231.4±10.2
P-value						
6 vs 24	<0.05	<0.05	<0.01	NS	NS	NS
24 vs 24+AG	NS	<0.05	NS	NS	NS	NS

All values are expressed as means±s.e. BW, body weight (g); LVW, weight of the left ventricle (mg); HR, heart rate (beats min^{-1}); CO, cardiac output (ml s^{-1}); P_{es}, LV end-systolic pressure (mmHg); P_{isomax}, peak isovolumic pressure (mmHg); NS, not significant ($P>0.05$).

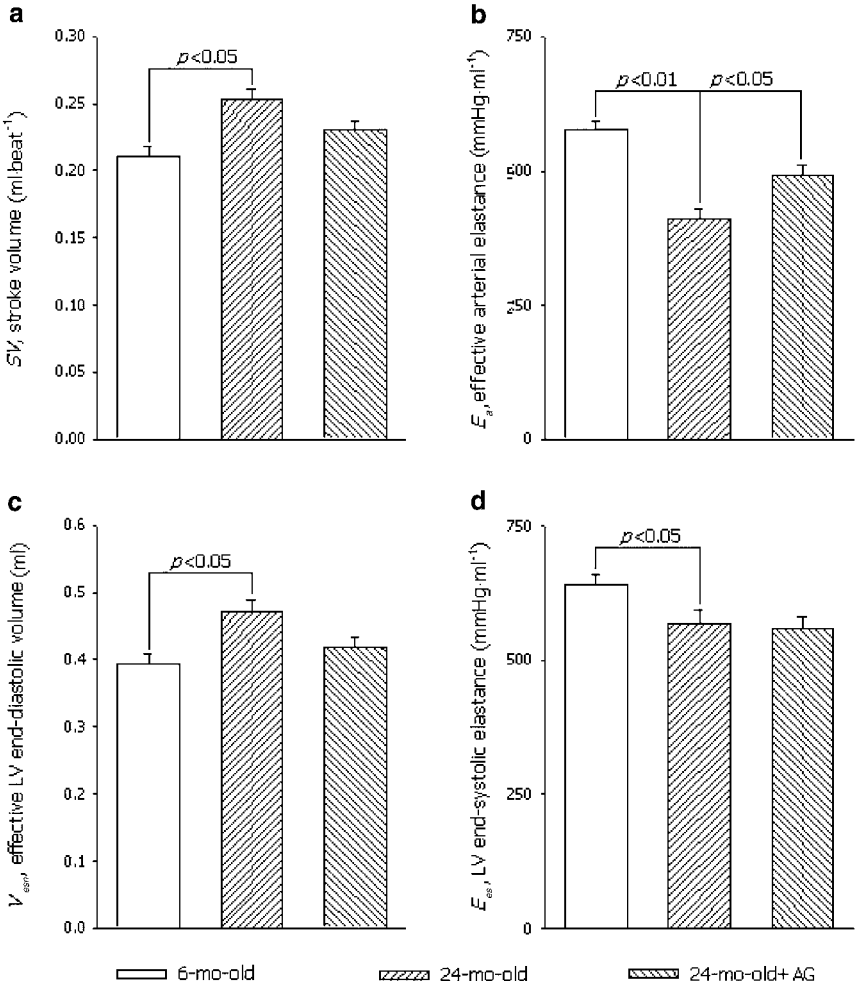

Figure 1 Effects of aging and AG on the chamber properties of the left ventricle and the arterial system. E_{es} (d) and E_a (b) described the elastic chamber properties of the left ventricle and the arterial system, respectively.

577.9±15.7 mmHg ml^{-1} in the 6-month-old rats to 411.5±18.6 mmHg ml^{-1} in the 24-month-old rats ($P<0.01$). The decline in E_a in aging rats was prevented by treatment with AG for 6 months, as reflected in the increase of 19.7% in this variable ($P<0.05$). As for the chamber properties of the left ventricle, aging exerted no effect on P_{isomax}, but showed an increase of 19.4% in V_{eed} (Figure 1c), causing a significant fall in E_{es} (Figure 1d) from 639.0±20.7 mmHg ml^{-1} in the 6-month-old rats to 567.4±26.7 mmHg ml^{-1} in the 24-month-old rats ($P<0.05$). After AG treatment, no significant change in E_{es} was observed in older animals compared with the aged untreated controls. By contrast, when normalized to LV weight (i.e., $E_{esn}=E_{es}$/LV weight), E_{esn} showed a significant rise of 22.8% in the 24-month-old treated rats (Figure 2).

In comparison with the 6-month-old rats, the 24-month-old rats had decreased E_a/E_{es}, at 0.7431±0.0202 vs 0.9103±0.0194 ($P<0.05$), and diminished Q_{load}, at 0.9428±0.0024 vs 0.9962±0.0014 ($P<0.05$). On the other hand, AG administration to

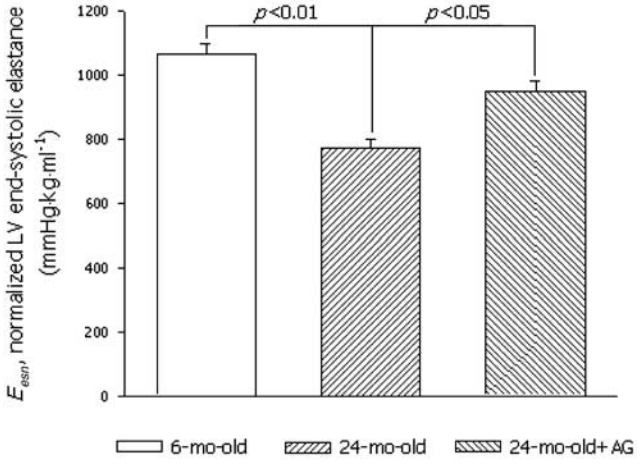

Figure 2 Effects of aging and AG on the contractile status of the left ventricle. E_{esn} was used as an indicator for the assessment of the contractile status of the left ventricle.

rats for 6 months produced a significant rise of 21.6% in E_a/E_{es}, causing an increase of 5.2% in Q_{load} ($P<0.05$).

Discussion

Long-lived proteins (e.g., vascular and myocardial collagen) undergo continual cross-linking during aging because of the formation of AGEs (Bucala & Cerami, 1992). AG, a nucleophilic hydrazine compound, is a potent inhibitor of AGEs formation and glucose-derived cross-links on proteins such as collagens (Brownlee *et al*., 1986). In this study, we determined whether AG treatment produces effects on the coupling efficiency between the heart and the vasculature in aged Fisher 344 rats.

Effects of aging and AG on the systolic mechanical behavior of the left ventricle

As mentioned earlier, the LV E_{es} could be determined by the ratio of P_{isomax} to V_{eed}. As no alteration was noted in P_{isomax} as a function of age, the increased V_{eed} became the predominant factor responsible for the diminished E_{es} in rats with advancing age. In this report, we measured LV intrinsic contractility in terms of E_{es} because of its independence of preload, afterload, and heart rate in a given constant contractile state of the ventricle (Suga *et al*., 1973; Sagawa 1978; 1981). Since a change in LV mass with age may affect the elastic behavior of the ventricular pump, E_{es} was normalized to LV weight (i.e., $E_{esn} = E_{esn}$/LV weight) for studying the contractile status of the left ventricle. We compared E_{esn} between the two groups at the age of 6 and 24 months and found it to be still significantly lower for senescent animals (Figure 2). The reduced contractility of the heart with advancing age was in accordance with many other reports in the literature (Lakatta, 1993; Klebanov, *et al*., 1997; Chang *et al*., 2000). After exposure to drug, neither P_{isomax} nor V_{eed} was affected by the action of AG. Thus, rats treated with AG for 6 months had no alteration in LV E_{es} compared with the aged untreated controls. To account for the difference in LV mass by AG (Table 1), we compared E_{esn} between the 24-month-old controls and the 24-month-old treated rats. AG, as reflected in the significant rise of 22.8% in E_{esn} (Figure 2), prevented the reduction in myocardial contractility that occurred in rats between 6 and 24 months of age. Our data were similar to those obtained by ALT-711, an AGEs cross-link breaker, which improves LV function in nondiabetic aged dogs (Wolfenbuttel *et al*., 1998; Asif *et al*., 2000).

Effects of aging and AG on the chamber property of the arterial system

As mentioned earlier, E_a could be determined by the ratio of P_{es} to SV. Although there was a trend toward decreasing P_{es} by aging process, no significant difference was observed between rats at the age of 6 and 24 months. Obviously, a significant increase in SV was the predominant factor responsible for the diminished E_a in animals with increasing age. If a small difference between LV P_{es} and mean aortic pressure is ignored, then one can calculate total peripheral resistance of the systemic circulation (R_p) using the ratio of LV P_{es} to the mean aortic flow (Sunagawa *et al*., 1984). In comparison with the 6-month-old rats, the 24-month-old animals had decreased R_p, at 1.248 ± 0.078 vs 1.397 ± 0.102 mmHg min ml^{-1}, but this did not reach statistical significance. Since the product of R_p and HR can reasonably approximate E_a (Sunagawa *et al*., 1984), the diminished HR mainly accounted for the decreased E_a in rats with age. After AG treatment, the decline in E_a in aging rats was prevented by the action of AG, as reflected in the increase of 19.7% in this variable ($P<0.05$). Thus, administration of AG to rats for 6 months may prevent the age-related alteration in the elastic chamber properties of the vasculature.

It should be noted that E_a represents, not the physical elastance or compliance of the arterial system, but an 'effective' arterial elastance. E_a changes more with changes in physical arterial resistance than with changes in physical arterial compliance (Sunagawa *et al*., 1985). In this study, the prevention of age-related fall in E_a by AG does not mean that AG may cause an elevation in physical arterial stiffening in older animals. By contrast, AG has been reported to retard the age-related decline in aortic distensibility, as evidenced by the decreased aortic characteristic impedance and the increased wave transit time (Corman *et al*., 1998; Chang *et al*., 2003). This is why AG has been supposed to prevent the age-related cardiac hypertrophy *via* the drug-induced decline in systolic loading condition of the left ventricle. Our results were similar to those by Kass *et al*. (2001) in that ALT-711 treatment improves total arterial compliance in aged humans in terms of pulse pressure.

Effects of aging and AG on the matching condition for the ventricular–arterial coupling

Equilibrium SV could be determined as the intersection between the ventricular and arterial P_{es}–SV relationships. It has been shown that SV is directly proportional to V_{eed} and is inversely related to E_a/E_{es} (Burkhoff & Sagawa, 1986). In the intact, anesthetized, thoractomized rat with age, the systolic mechanical behavior of the ventricular pump was abnormal, as evidenced by the decreased E_{esn}. Ventricular dilatation developed in aged Fisher 344 rats, as defined by an increase in V_{eed}. The ratio of E_a to E_{es} decreased

significantly as animals aged. Thus, the equilibrium SV in aging rats would be augmented due to increased V_{eed} and decreased E_a/E_{es}. Despite lower HR and depressed cardiac contractility, rats with advancing age are able to enhance SV, maintaining blood flow and LV P_{es} as seen in younger animals.

The optimal afterload, Q_{load}, has been used as a measure for the optimality of energy transmission from the left ventricle to the arterial system (Sunagawa *et al*., 1985). Since the aging process worsened the mean value of E_a/E_{es} to a lower level, the 24-month-old rats exhibited lower Q_{load} than did the 6-month-old rats. This suggests that the efficiency of mechanical energy transferred from the left ventricle to the vasculature may be diminished in aging rats. Despite a marked decline of 18.4% in E_a/E_{es}, rats with advancing age showed only a fall of 5.4% in Q_{load} ($P<0.05$). It is likely that performance of the cardiovascular system would be more essential than efficiency for the tissue perfusion of body organs. To improve the matching condition for the left ventricular–arterial coupling, administration of AG to rats from 18 to 24 months is expected to diminish the discrepancy between E_a and E_{es}. As mentioned earlier, AG slowed the age-related decline in E_a without changing E_{es} in older animals. Thus, AG produced a significant rise of 21.6% in E_a/E_{es}, preventing the age-related decline in optimal afterload. Our data were similar to those obtained by ALT-711, which prevents the age-related decline in both arterial and ventricular function, optimizing the ventricular–arterial coupling in rhesus monkeys (Vaitkevicius *et al*., 2001).

Limitations

It should be noted that the anti-aging effects of AG might be linked to decreased protein glycation; however, there may also be a benefit from inhibition of inducible nitric oxide synthase that is activated during repeated infections (McCann *et al*., 1998). No measurements on the aortic and ventricular wall histological structures were made in this report; we cannot reach any direct conclusions that AG exerts its effects only by inhibition of collagen AGEs accumulation in aged heart and vasculature.

In summary, we determined the effects of long-term treatment with AG on the matching condition for the left ventricular–arterial coupling in aged Fisher 344 rats. No hypertensive effects of AG were detected in this report when AG was administered to rats from 18 to 24 months. Our data reveal that the aging process diminishes the LV end-systolic elastance and the effective arterial volume elastance, as well as the ratio of E_a to E_{es}. Thus, the aging process worsens not only the contractile status of the left ventricle, but also the coupling efficiency between the heart and the vasculature. Treatment with AG for 6 months improves both the ventricular and arterial function and optimizes the ventricular–arterial coupling with special reference to the energy transmission from the left ventricle to the vasculature in older animals.

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