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Vasoactive Drugs Influence Aortic Augmentation Index Independently of Pulse-Wave Velocity in Healthy Men

R.P. Kelly, S.C. Millasseau, J.M. Ritter, P.J. Chowienczyk

Abstract—Aortic augmentation index, a measure of central systolic blood pressure augmentation arising mainly from pressure-wave reflection, increases with vascular aging. The augmentation index is influenced by aortic pulse-wave velocity (related to aortic stiffness) and by the site and extent of wave reflection. To clarify the relative influence of pulse-wave velocity and wave reflection on the augmentation index, we studied the association between augmentation index, pulse-wave velocity, and age and examined the effects of vasoactive drugs to determine whether altering vascular tone has differential effects on pulse-wave velocity and the augmentation index. We made simultaneous measurements of the augmentation index and carotid-to-femoral pulse-wave velocity in 50 asymptomatic men aged 19 to 74 years at baseline and, in a subset, during the administration of nitroglycerin, angiotensin II, and saline vehicle. The aortic augmentation index was obtained by radial tonometry (Sphygmocor device, PWV Medical) with the use of an inbuilt radial to aortic transfer function. In multiple regression analysis, the aortic augmentation index was independently correlated only with age ($R=0.58$, $P<0.0001$). Nitroglycerin (3 to 300 $\mu\text{g}/\text{min}$ IV) reduced the aortic augmentation index from $4.8\pm 2.3\%$ to $-11.9\pm 5.3\%$ ($n=10$, $P<0.002$). Angiotensin II (75 to 300 ng/min IV) increased the aortic augmentation index from $9.3\pm 2.4\%$ to $18.3\pm 2.9\%$ ($n=12$, $P<0.001$). These drugs had small effects on aortic pulse-wave velocity, producing mean changes from baseline of <1 m/s (each $P<0.05$). In healthy men, vasoactive drugs may change aortic augmentation index independently from aortic pulse-wave velocity. (*Hypertension*. 2001;37:1429-1433.)

Key Words: antihypertensive agents ■ aorta ■ arteries ■ hemodynamics ■ pulse

Systolic blood pressure is augmented by the reflection of pressure from the periphery of the circulation to the aortic root.¹ The aortic augmentation index (AIx) is defined as the increment in pressure from the first systolic shoulder (inflection point) to the peak pressure of the aortic pressure waveform expressed as a percentage of the peak pressure.² This index has been used to measure the additional load imposed on the left ventricle as a result of wave reflection and correlates with left ventricular mass.^{3,4} AIx depends, at least in part, on aortic and large-artery pulse-wave velocity (PWV). A higher PWV results in earlier arrival of reflected waves and, hence, increased augmentation during early systole.^{1,5} PWV is inversely related to arterial distensibility.⁶ Therefore, AIx has been proposed as an index of “arterial stiffness”^{7,8} and has been used as a measure of this.^{9–12} However, in addition to PWV, AIx may depend on the pattern of ventricular ejection and on arterial properties determining the amount and site of wave reflection.¹ These latter factors may be influenced by the vascular tone of the small muscular arteries/arterioles rather than by the elastic properties of the aorta. To clarify the relationship between AIx and PWV, we made simultaneous measurements of AIx and carotid-to-femoral PWV (PWV_{cf}) in 50 men of varying age with a large

range of values of PWV_{cf}. To determine whether altering vascular smooth muscle tone could influence AIx independently of any effect on PWV_{cf}, we then examined the effects of systemic administration of the arterial vasodilator nitroglycerin (NTG) and the vasoconstrictor angiotensin II (Ang II) on AIx and PWV_{cf} in healthy men.

Methods

Subjects

Study 1

Fifty asymptomatic men age 19 to 74 years were recruited from the local community in response to an advertisement for cardiovascular screening. Men with a previous history of cardiovascular disease or diabetes and those taking vasoactive drugs were excluded. All men were screened by physical examination and routine biochemistry. None had evidence of cardiovascular disease other than hypertension at the time of screening. Subject characteristics are shown in the Table.

Studies 2 and 3

Studies 2 and 3 were performed in a subset of 12 of the men in study 1 age 23 to 45 years. All were normotensive (office blood pressure $<140/90$ mm Hg), and none had a serum total cholesterol >6.0 mmol/L. All subjects gave written informed consent for the

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Characteristics of Men (n=50) Participating in Study 1

Characteristic	
Age, y	43±12.2
Height, m	1.77±0.07
Weight, kg	81±12.6
BMI, kg/m ²	26±4.0
Total cholesterol, mmol/L	5.0±0.96
Systolic blood pressure, mm Hg	124±21.9
Diastolic blood pressure, mm Hg	72±12.2
AIx, %	11.2±10.7
PWV _{cf} , m/s	9.3±1.9

Values are mean±SD. BMI indicates body mass index.

study, which was approved by St Thomas' Hospital Research Ethics Committee.

Experimental Protocol

Study 1

Subjects (n=50) were studied in a quiet temperature-controlled laboratory (26±1°C) after 20 minutes of lying supine. AIx was determined by applanation tonometry of the left radial artery by using a Millar piezo-resistive pressure transducer (Millar SPT 301, Millar Instruments) coupled to a Sphygmocor device (PWV Medical). AIx was calculated from the aortic pressure waveform obtained by applying a transfer function to the radial pressure waveform.¹³ The reproducibility of this method has been found to be acceptable, with the standard deviation of the difference between repeated measurements being 4% to 5%.¹⁴ PWV_{cf} was determined by sequential acquisition of pressure waveforms from the carotid and the femoral arteries by use of the same tonometer. The timing of these waveforms was compared with that of the R wave on a simultaneously recorded ECG. PWV was determined by calculation of the difference in carotid to femoral path length divided by the difference in R wave to waveform foot times. The difference in carotid to femoral path length was estimated from the distance from the sternal notch to the femoral pulse (at the point of application of the tonometer) measured in a direct line. This method of measurement results in a systematic overestimation of path length and, hence, PWV_{cf} by ≈10% but reduces interobserver variability. In some studies, carotid to radial PWV (PWV_{cr}) was determined by sequential acquisition of pressure waveforms from the carotid and the radial arteries. The distance from the sternal notch to radial artery was used to calculate PWV_{cr}. The within-subject coefficient of variability of PWV_{cf} measurements (estimated by the method of Quan and Shih,¹⁵ from 3 measurements separated by 1 week on each of 8 healthy volunteers) was 5.3%. Blood pressure was measured in the right brachial artery by use of an automated oscillometric method (Dinamap model 1846 SX, Critikon).

Study 2

Subjects (n=10) attended on 3 days according to a single-blind, randomized, 3-phase, placebo-controlled, crossover study design. The within-subject coefficient of variability for PWV_{cf} was used to estimate the number of subjects that would give 90% power to detect a change in PWV_{cf} of <0.5 m/s. A venous cannula for the infusion of drug/saline placebo was inserted; subjects were then allowed to rest for 30 minutes. Blood pressure, AIx, and PWV_{cf} were then measured during the infusion of saline for 15 minutes and then at the end of 3 cumulative 15-minute intravenous infusions of the study drug. On the 3 separate days, these infusions were of NTG (3, 30, and 300 µg/min, David Bull Laboratories), Ang II (75, 150, and 300 ng/min, Clinalfa), or 0.9% saline placebo.

Study 3

A further study was performed in 6 subjects (4 of whom participated in study 2) to assess the effects of Ang II on PWV_{cf}. Subjects

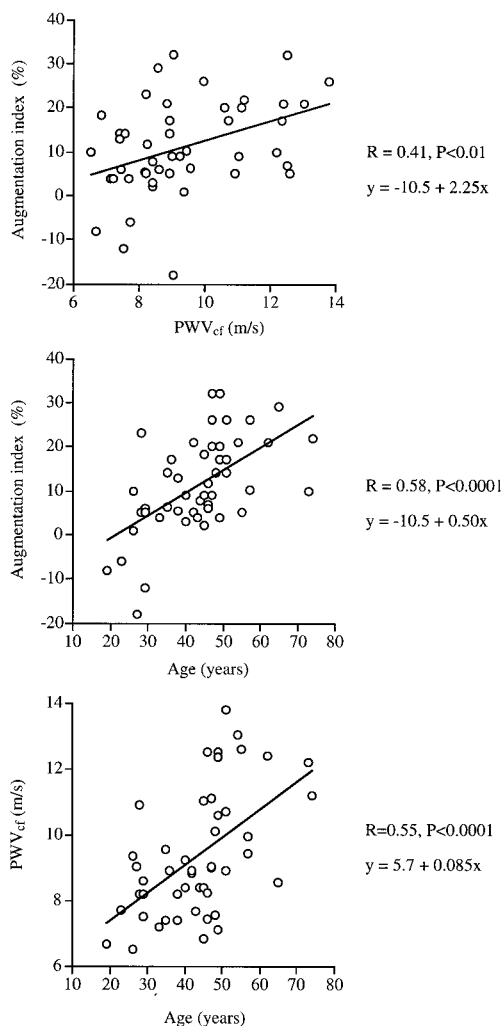


Figure 1. Relationships between AIx, PWV_{cf}, and age in 50 healthy men (univariate regression). AIx is not independently correlated with PWV_{cf} if age is taken into account in multiple regression analysis.

received Ang II and saline placebo on 2 separate occasions according to a protocol that was otherwise identical to that in study 2. PWV_{cf} was measured in addition to measurements of PWV_{cf} and AIx.

Statistical Analysis

Subject characteristics (Table) are expressed as mean±SD. Results are expressed as mean±SE. Univariate and multiple stepwise regression analyses were used to examine associations between AIx and the following variables: age, height, body mass index, heart rate, systolic blood pressure, diastolic blood pressure, serum total cholesterol, and PWV_{cf}. ANOVA for repeated measures was used to test for differences in hemodynamic variables. For analysis of the effects of Ang II on PWV_{cf} and AIx, data from studies 2 and 3 were combined with mean values used for subjects who participated in both studies. A value of $P<0.05$ was taken as statistically significant.

Results

Study 1

Mean values of AIx and PWV_{cf} are tabulated with subject characteristics in the Table. By univariate analysis, AIx was significantly correlated with age ($R=0.58$, $P<0.0001$; Figure 1), diastolic blood pressure ($R=0.46$, $P<0.001$), height

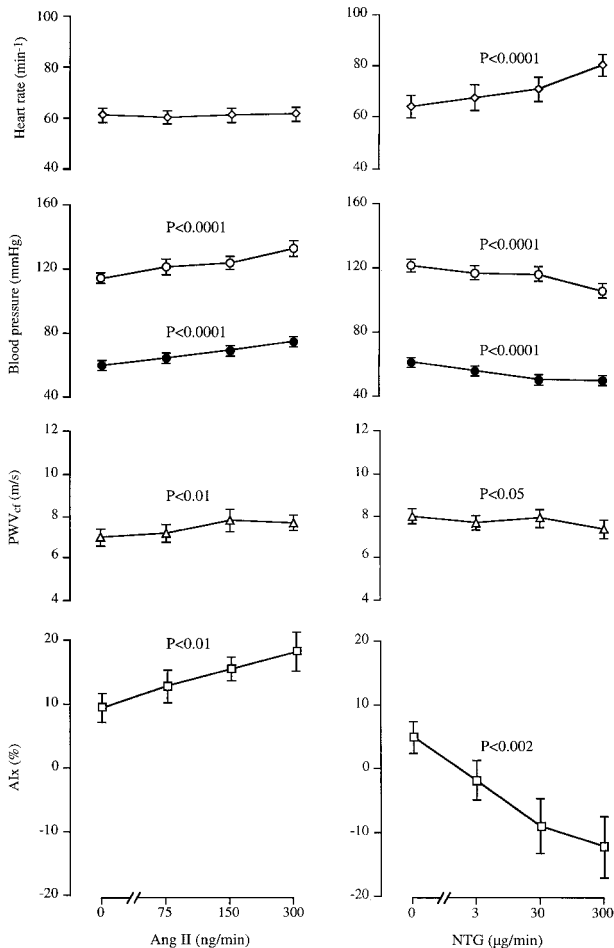


Figure 2. Heart rate, systolic blood pressure (○), diastolic blood pressure (●), PWV_{cf}, and AIx during systemic administration of nitroglycerin (NTG, n=10) and angiotensin II (Ang II, n=12) in healthy men. P values refer to ANOVA for repeated measurements over the full dose range.

($R=0.43$, $P<0.01$), PWV_{cf} ($R=0.41$, $P<0.01$), total cholesterol ($R=0.34$, $P<0.01$), and systolic blood pressure ($R=0.31$, $P<0.05$) but not with body mass index or resting heart rate. PWV_{cf} was also strongly correlated with age ($R=0.55$, $P<0.0001$; Figure 1), and the correlation between AIx and PWV_{cf} was not significant ($P=0.41$) when age was incorporated into a multiple regression model. Stepwise multiple regression analysis demonstrated age to be the only independent predictor of AIx.

Study 2

During the infusion of saline placebo, there was no significant change in heart rate or blood pressure. NTG decreased both systolic and diastolic blood pressures from $121\pm 4/61\pm 1$ mm Hg at baseline to $105\pm 4/49\pm 1$ mm Hg during infusion of the highest dose and increased the heart rate from 64 ± 4 to 80 ± 4 bpm (each $P<0.0001$, Figure 2). Ang II increased systolic and diastolic blood pressures from $114\pm 4/59\pm 2$ mm Hg to $132\pm 5/75\pm 2$ mm Hg (each $P<0.0001$) without affecting the heart rate ($P=0.50$, Figure 2).

There were no significant changes in AIx and PWV_{cf} during saline infusion. Effects of NTG and Ang II on AIx and

PWV_{cf} are shown in Figure 2. NTG produced a dose-dependent decrease in AIx from $4.8\pm 2.3\%$ at baseline to $-11.9\pm 5.3\%$ at the highest dose ($P<0.002$). Ang II produced a dose-dependent increase in AIx from $9.3\pm 2.4\%$ to $18.3\pm 2.9\%$ ($P<0.001$). NTG and Ang II produced small but significant changes in PWV_{cf} ($P<0.05$). The change in PWV from baseline during the highest dose of NTG was -0.74 m/s (95% CI -1.4 to -0.1 m/s), and that for Ang II was 0.70 m/s (95% CI 0.3 to 1.0 m/s). The highest dose of Ang II caused an increase of 2.0 ± 0.4 m/s in PWV_{cf} ($n=6$, $P<0.01$).

Discussion

AIx is a measure of left ventricular afterload correlating with left ventricular mass.^{3,4} Although AIx may be influenced by characteristics of left ventricular function, such as contractility and ejection duration, it is thought to be primarily determined by the intensity and timing of reflected pressure waves.¹ The latter is determined mainly by PWV_{cf}, and an increase in PWV_{cf} will result in a greater proportion of reflected waves arriving in early systole and, hence, in an increase in AIx.¹ PWV_{cf} is inversely related to aortic distensibility and compliance (or directly related to "aortic stiffness") by the Bramwell-Hill equation.⁶ In contrast, the intensity of wave reflection will depend on the serial distribution of vascular diameter and elasticity of the small muscular arteries/arterioles at the major sites of pressure wave reflection.¹ Therefore, alterations in vascular smooth muscle tone affecting mainly the small muscular arteries but not the elastic aorta might influence reflected wave intensity and, hence, AIx independently of PWV_{cf}. The relative contribution of PWV_{cf} and reflected wave intensity to AIx is unknown.

In the present study, in addition to the well-recognized associations between AIx and age¹⁶ and between PWV_{cf} and age,¹⁷⁻¹⁹ we observed the expected correlation between AIx and PWV_{cf}. However, the correlation between AIx and PWV_{cf} was not independent of age, and age was the only independent predictor of AIx in multiple stepwise regression. The results of such an analysis must be treated with some caution because of the strong interrelationship of the variables involved (Figure 1). Furthermore, there is inevitably some error in estimating the path length used to calculate PWV_{cf} from surface markings, although in the present study, the between-subject variation in height (coefficient of variation) was only 20% that of PWV_{cf}. The lack of an independent correlation between AIx and PWV_{cf} does not mean that PWV_{cf} does not influence AIx. However, it does suggest that aging is associated with a factor other than increased PWV_{cf}, which contributes to the increase in AIx and points to the possible importance of reflected wave intensity as a determinant of AIx independent of PWV_{cf}.

To examine the possibility that AIx may be changed independently of PWV_{cf}, we investigated the effects of the vasodilator NTG and vasoconstrictor Ang II, reasoning that these would act predominantly to alter the tone of the small muscular arteries/arterioles but would have little effect on the elastic aorta. The major finding is that NTG and Ang II are capable of producing large changes in AIx, comparable to age-related changes seen over a range of >40 years in

subjects at rest (Figure 1). By contrast, both NTG and Ang II produced little effect on PWV_{cf} , with mean changes from baseline (<1.0 m/s) being much less than age-related changes in PWV_{cf} . The predominantly elastic nature of the aorta may minimize the effects of acute changes in vascular tone and blood pressure on PWV_{cf} . Furthermore, an alteration in shear forces may result in adaptive changes mediated by endothelium-derived or other factors that also minimize the effects of acute changes in vascular tone on PWV_{cf} . In muscular arteries, such as the conduit arteries of the upper limb, Ang II would be expected to have a proportionately greater effect, and indeed, in the present study, Ang II had a greater effect on PWV_{cf} . The findings with respect to NTG are also consistent with those of other investigators,^{20–23} who demonstrated that the favorable effects of NTG on left ventricular load are mainly due to the dilatation of small arteries. The lack of a large effect of NTG and Ang II despite substantial changes in arterial blood pressure supports the hypothesis that the association of an increased aortic PWV with hypertension occurs mainly as a result of structural alterations²⁴ rather than as a result of raised blood pressure alone. It is also consistent with the finding that decreased aortic arterial compliance in hypertension cannot be attributed entirely to elevated blood pressure.²⁵

Although we cannot exclude the possibility that the effects of Ang II and NTG on AIX were secondary to altered characteristics of ventricular function, such as contractility or ejection duration, we believe that this is unlikely. The effect of Ang II on AIX was independent of heart rate. We have previously shown that in healthy volunteers, NTG produces an increase in cardiac output (presumably as a result of reflex sympathetic activation in response to peripheral vasodilation).²⁶ Thus, the contrasting effects of NTG and Ang II on AIX are unlikely to be explained by altered ventricular ejection time or contractility alone. Rather, the predominant effects of NTG and Ang II on AIX are likely to be due to an alteration in vascular tone of small arteries around the major site of pressure-wave reflection and, hence, a change in the intensity of pressure-wave reflections. Taken together, the results of the present study suggest that in healthy men, vascular tone has an important influence on AIX independent of any effect on PWV_{cf} . They do not preclude a greater influence of aortic stiffness on AIX in subjects with renal failure, multiple risk factors, or established vascular disease. These subjects may have a greatly increased PWV_{cf} ,^{27–29} which may then become a more important determinant of AIX.

It is important to note a number of limitations of the present study. The drug studies were performed in a single-blind fashion because of the difficulty in blinding the investigators in the presence of large hemodynamic changes. A relatively small number of subjects were involved. However, all measurements were automated, and confidence limits for PWV were such as to exclude changes of pathophysiological importance. AIX was determined by using a radial to aortic transfer function.¹³ The use of such a transfer function will inevitably result in some error in estimating the true AIX. Although previous work^{13,30} suggests that such an error will be small in comparison with the large changes seen in the

present study, it cannot be directly quantified without performing invasive studies. Even if such an error were substantial, the results of the present study are of practical importance because the Sphygmocor device is now in widespread use and is now being used in large multicenter trials.

In conclusion, in healthy men, AIX as determined by the Sphygmocor device is influenced by vasoactive drugs independently of effects on PWV_{cf} . PWV_{cf} and AIX cannot be regarded as interchangeable indices of “vascular stiffness.” Together, they may provide information on large-artery stiffness and small-artery tone/structure, which influence wave reflection.

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