Nitric oxide synthase inhibition increases aortic stiffness measured by pulse wave velocity in rats

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Received 5 December 2000; accepted 26 March 2001

Abstract

Objective: The present study was to examine whether endogenous nitric oxide (NO) plays a role in the regulation of vascular stiffness. Methods: Pulse wave velocity (PWV) was determined as the time delay between the foot of pressure waves recorded simultaneously at the aortic arch and abdominal aorta (just above the bifurcation) in anesthetized Sprague–Dawley rats. A decrease in vascular compliance results in an increase in PWV. Results: A bolus injection of a NO synthase inhibitor, l-NAME (30 mg/kg), significantly increased PWV, accompanied by an increase in blood pressure. Since changes in blood pressure are known to affect PWV, phenylephrine (PE) was administered to mimic the blood pressure changes induced by l-NAME, thus compensating for the pressure-dependent component of the PWV changes. At each given level of mean arterial pressure (MAP), PWV was significantly higher with l-NAME than with PE treatment, suggesting that acute withdrawal of endogenous NO reduces aortic compliance independent of changes in MAP. In rats chronically treated with l-NAME (0.5 g/l in drinking water) for 3 weeks, PWV was even higher than those acutely treated with l-NAME (at MAP = 150 mmHg). This additional increase in vascular stiffness may be due to the remodeling of the vascular wall as a result of chronic NOS inhibition and hypertension. Conclusion: These data demonstrate that NO modulates vascular compliance independent of blood pressure changes and that an intact endogenous NO system is required to maintain normal vascular compliance. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Arteries; Blood pressure; Endothelial function; Nitric oxide

1. Introduction

Windkessel function, or elastic behavior of the arterial system, is physiologically important because it converts the pulsatile cardiac ejection into a nearly continuous flow. This improves sub-endocardial perfusion during diastole and maintains a sustained perfusion to the peripheral organs. It also results in a reduction in systolic pressure and a slight increase of diastolic pressure, thus lowering cardiac afterload [1]. When the arterial system becomes stiffer or less elastic in cardiovascular diseases (i.e. atherosclerosis, diabetes and hypertension), vascular compliance or windkessel function is reduced. This impairs tissue perfusion and increases cardiac afterload, leading to cardiac hypertrophy [2–5]. In a recent Framingham and SHEP study, increased vascular stiffness was believed to be the cause of an increase in systolic and pulse pressures, which were positively correlated to increased stroke and all-cause mortality [6]. Many clinicians are now using vascular stiffness (compliance, elasticity or distensibility) as an index for cardiovascular disease. The stiffer vessel is less elastic, distensible or compliant. Vascular stiffness can be estimated by measuring the pulse wave velocity (PWV) [7,8]. The stiffer the vessel, the faster the pressure pulse moves along a vessel. Thus, PWV has been used as a surrogate marker for vascular diseases [9,10], including atherosclerosis [11].

The endothelium has many physiologically important roles. Substances released from the vascular endothelium, such as nitric oxide (NO), modulate vascular tone, attenuate smooth muscle proliferation, and inhibit platelet function [12–14]. Dysfunction of the endothelium is
associated with and/or contributes to the progression of cardiovascular diseases such as atherosclerosis [15], hypertension [16], and heart failure [17]. It has been reported recently that endothelial dysfunction is also associated with an increase in vascular stiffness [18]. However it is not clear whether endothelial dysfunction can increase vascular stiffness independent of changes in blood pressure or changes in the morphology of the vasculature. This is clinically important, since Glasser et al. summarized in a review that therapies which directly target vascular compliance may be more beneficial in reducing cardiovascular risk factors than agents which just lower blood pressure [2]. Thus, we hypothesized that the absence of NO, a major consequence of endothelial dysfunction, may directly contribute to the increase of vascular stiffness.

In the present study, we attempted to determine if endothelial dysfunction, induced acutely or chronically by pharmacologically inhibiting NO production with Nω-nitro-L-arginine methyl ester (L-NAME), could affect aortic stiffness in rats. PWV was measured to estimate the aortic stiffness. Since L-NAME treatment increases blood pressure which has been known to affect PWV, phenylephrine (PE) and isoprenaline (ISO) were used to standardize blood pressure levels among different treatments, thereby removing the pressure component that contributes to PWV changes after L-NAME treatment.

2. Methods

Experiments were performed in male Crl:CD(SD)-hrBR rats weighing 300–400 g (Charles River Laboratories, Hollister, CA). Animals were kept in a room at controlled temperature (24°C) and lighting (14:10-h light–dark cycle) with free access to food and tap water. All experimental procedures were approved by the Animal Care and Use Committee and were conducted in accordance with National Institutes of Health Guidelines for the care and use of animals.

2.1. Experimental procedures

2.1.1. Surgical preparation

Animals were anesthetized with an intraperitoneal injection of pentobarbital sodium (70 mg/kg, Butler, Union City, CA) and placed on a heated water pad at 37°C to maintain body temperature. The right jugular vein and the left femoral vein were catheterized with polyethylene tubings (PE50, VWR, San Francisco, CA) for the administration of different pharmacological agents. For measurement of PWV, two 1.4 Fr. Millar Mikro-tip pressure transducers (Millar, Houston, TX) were implanted, one in the aortic arch via the left carotid artery, and one in the abdominal aorta just proximal to the iliac bifurcation via the left femoral artery.

2.1.2. Experimental procedures

Measurements of aortic PWV were conducted similarly to what has been described in our previous publication [8], as well as by other investigators [7,19]. Briefly, pulse pressure waves from the two Millar transducers were simultaneously imported to a Gould amplifier (Gould, Valley View, OH) and displayed on a data acquisition system (PowerLab, 16/s, ADInstruments, Australia) at a sampling rate of 1000 Hz. The sampling rate and frequency response of the Millar transducers are capable of providing high fidelity pressure wave forms and high resolution measurements. After the experiment was completed, the animal was euthanized with pentobarbital sodium (200 mg/kg) and the full length of the aorta was exposed. A damp silk thread was placed along the contour of the aorta and marked at the tips of the two pressure transducers. The thread was then removed and laid straight for measurement of the distance between the two marks. This is the pulse wave propagation distance, and was used to calculate PWV (see below).

Phenylephrine (PE, 10–30 μg/kg/min, Sigma, St. Louis, MO) was infused intravenously via a catheter in the jugular vein. After blood pressure reached plateau during PE infusion, isoprenaline (ISO, 10 μg/kg, Sigma, St. Louis, MO) was injected via a catheter in the femoral vein to decrease blood pressure to the baseline. Infusion of PE was then stopped. When blood pressure was returned to the baseline, Nω-nitro-L-arginine methyl ester (L-NAME, 30 mg/kg, Sigma, St. Louis, MO), a non-specific nitric oxide synthase (NOS) inhibitor, was injected intravenously to block NO production. After a period of 30 min when blood pressure was increased and reached a plateau, an intravenous bolus injection of ISO (10 μg/kg) was given to decrease blood pressure. Since PWV is known to be significantly affected by changes in blood pressure and L-NAME increases blood pressure, with the manipulation of blood pressure by PE and ISO, PWV was able to be compared between PE and L-NAME treatments at the same multiple given levels of MAP ranging from 110 to 190 mmHg in 10 mmHg increments. This method eliminated the effect of pressure changes on PWV and thus, differentiate the effects of acute NO withdrawal from the blood pressure component on modulation of PWV. Chronic treatment of L-NAME was administered via the drinking water (0.5 g/l) for 3 weeks, and PWV was then measured. An intravenous bolus injection of ISO (10 μg/kg) was also used to decrease blood pressure to the same level (150 mmHg) for comparison of PWV across groups.

2.2. Measurement of pulse wave velocity

As illustrated in Fig. 1, PWV was calculated by dividing the propagation distance (L) by propagation time (t) in units of meters per second. The propagation time was determined using three different techniques as described below:
from person to person; and (2) lack of automation, since it is based on personal judgment rather than formulas. Although other investigators also tried to use formula-based methods to estimate foot to foot measurements in animals, these methods have been shown less reliable than foot to foot method [19]. Instead of trying to estimate the foot, DPC method identifies diastolic phase center by averaging the times at which the pulse wave crosses 1 mmHg above the minimum diastolic pressure on the down-slope and up-slope of the pressure signal (Fig. 2). The propagation time was then determined by subtracting the time difference between the diastolic phase centers of the proximal and distal waves. A total of five to nine cycles were averaged as one propagation time. Like the foot to foot method, the DPC method still utilizes the diastolic phase of the cycle, because it has been shown to be less affected by distortion than other parts of the cardiac cycle [20]. This method for determining PWV has proven to be both efficient and reliable, as it is highly correlated to the traditional manual foot to foot method (Fig. 3b), as well as to the average cycle method (Fig. 3c).

2.3. Calculations and statistics

2.3.1. Hemodynamic parameters

Mean arterial pressure (MAP), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and pulse pressure (PP) were determined from measurements made by the proximal pressure transducer located in the aortic arch and were calculated by using Chart software (PowerLab, ADInstruments, Castle Hill, New South Wales, Australia).

2.3.2. \( \beta \) index

While MAP was normalized between groups for measuring PWV, differences in DAP were still seen in the present study. It has been known that PWV is most

![Diagram of arterial blood pressure waves](image)

**Fig. 1.** Representation of the proximal (aortic arch) and distal (abdominal aorta) pressure wave forms. PWV is calculated by dividing the propagation distance \( L \) by the propagation time \( t \). Propagation time is the difference in time between the beginning of the upstroke of the two pulsatile wave forms.

2.2.1. **Manual foot to foot**

As described in details by Wang et al. [8], the propagation time for the pulse wave moving from the aortic arch to the abdominal aorta was measured manually by the time delay between the upstrokes (foot) of each pressure wave front (Fig. 1). At least ten normal consecutive cardiac cycles were individually measured and averaged as one PWV point. If an abnormal waveform fell within the ten cycles measured, it was rejected and the next viable waveform was measured. Although the manual foot to foot method is considered a reliable method for determining PWV [19] and has been widely used by other investigators [8,19], it is a very labor intensive method. Thus, the following two additional techniques were developed for analyzing propagation time.

2.2.2. **Averaged cycle foot to foot**

Raw data obtained from both the proximal and distal pressure transducers were imported into Excel (Microsoft, Seattle, WA) and the waveforms of five to nine cardiac cycles from each transducer were overlapped using a formula based on average heart rate of these cycles. Instead of analyzing PWV from several cardiac cycles individually and averaging the results, a single foot to foot propagation time was measured from the averaged cycle. This method proved to be very efficient. It is also very reliable because the same data points measured by using this method were highly correlated to those by the manual foot to foot method (Fig. 3a).

2.2.3. **Diastolic phase center (DPC)**

The DPC method was developed to overcome two drawbacks of the foot to foot measurements: (1) personal judgment in determining the foot of the wave can differ from person to person; and (2) lack of automation, since it is based on personal judgment rather than formulas. Although other investigators also tried to use formula-based methods to estimate foot to foot measurements in animals, these methods have been shown less reliable than foot to foot method [19]. Instead of trying to estimate the foot, DPC method identifies diastolic phase center by averaging the times at which the pulse wave crosses 1 mmHg above the minimum diastolic pressure on the down-slope and up-slope of the pressure signal (Fig. 2). The propagation time was then determined by subtracting the time difference between the diastolic phase centers of the proximal and distal waves. A total of five to nine cycles were averaged as one propagation time. Like the foot to foot method, the DPC method still utilizes the diastolic phase of the cycle, because it has been shown to be less affected by distortion than other parts of the cardiac cycle [20]. This method for determining PWV has proven to be both efficient and reliable, as it is highly correlated to the traditional manual foot to foot method (Fig. 3b), as well as to the average cycle method (Fig. 3c).

![Diagram of diastolic phase center (DPC)](image)

**Fig. 2.** Diastolic phase center (DPC) calculation for determining propagation time for PWV calculation, using the diastolic portion of a wave form from the proximal and distal transducers. The center of the diastolic phase is determined at 1 mmHg above minimum diastolic pressure. Propagation time is determined by subtracting the proximal wave form DPC from the distal wave form DPC.
Fig. 4. Relationship between pulse wave velocity and mean arterial blood pressure in rats infused with phenylephrine. MAP ranging from 110 to 190 mmHg in 10 mmHg increments. The data from each individual animal were plotted in Fig. 4. As blood pressure gradually increased during PE infusion, PWV also increased in a highly correlated manner. Once blood pressure reached plateau during PE infusion, ISO was given as a bolus to normalize blood pressure. When blood pressure reached baseline levels after bolus ISO during PE infusion, PWV was also reduced to its original baseline level (Fig. 5).

Fig. 3. Correlation of pulse wave velocity (m/s) measured by 3 different methods in the same 19 samples. (A) Foot to foot of averaged cycles method vs. the normal foot to foot method. (B) Diastolic phase center (DPC) method vs. normal foot to foot method. (C) Foot to foot of averaged cycles vs. the DPC method.

sensitive to the changes in DAP [11,21]. Therefore, $\beta$ index was calculated for normalizing DAP. $\beta$ index is calculated with the following formula: $2.11^{*}\text{PWV}^{2}/\text{dias-tolic pressure}$.

2.3.3. Statistics
Results are presented as mean±standard error for the number of animals (n) indicated. Single comparisons of the mean values were performed by a Student’s t-test. Multiple comparisons of the mean values were performed by a two-way ANOVA followed, if significance was indicated, by a subsequent Student–Newman–Keuls test for repeated comparisons. Differences were considered statistically significant when the $P$-value was <0.05. The statistical analysis was processed with Statview software (SAS Institute Inc., Cary, NC).

3. Results
3.1. Effect of blood pressure on PWV

Intravenous infusion of PE resulted in a gradual increase in blood pressure. PWV was obtained at given levels of MAP measured (Fig. 6B).

Acute treatment with l-NAME increased both blood pressure and PWV (Fig. 6A). In order to isolate the impact of blood pressure on PWV, in a separate group of rats, blood pressure was increased by PE infusion (peak MAP=172.6±4.2 mmHg) to the level close to that induced by l-NAME (peak MAP=163.4±3.1 mmHg). At every given level of MAP measured, PWV was higher with l-NAME than with PE treatment. No differences in MAP were observed since measurements were taken at determined levels of MAP for each individual animal. However, DAP was significantly higher, SAP significantly lower, and consequently, pulse pressure significantly lower with l-NAME than with PE treatment (Table 1). To normalize the influence of diastolic pressure on PWV, $\beta$ index was calculated which again showed significantly higher with l-NAME compared to PE treatment at every given level of MAP measured (Fig. 6B).

3.2. Acute inhibition of nitric oxide production increases PWV and $\beta$ index

Chronic treatment with l-NAME for 3 weeks resulted in sustained hypertension and increased PWV. In order to normalize blood pressure for comparison of PWV among all groups at the same pressure, ISO was given. PWV was then measured when MAP was at 150 mmHg in all groups.
Fig. 5. Pulse wave velocity and mean arterial blood pressure in rats. Baseline: before any treatment; PE: when mean arterial blood pressure reached plateau during the infusion of phenylephrine; PE+ISO: isoproterenol was given to decrease blood pressure when blood pressure reached plateau during PE infusion. The data in the PE+ISO group was taken when mean arterial blood pressure was equal to basal level in each individual animal. *, P<0.05, vs. baseline or PE+ISO.

As shown in Fig. 7, PWV was significantly higher when rats were acutely treated with L-NAME than with PE. Chronic L-NAME treatment significantly increased PWV by an additional 8% above the acute L-NAME group.

4. Discussion

The main findings of this study are that acute inhibition of nitric oxide synthase by L-NAME increased aortic stiffness (measured by PWV) independent of the concomitant increase in blood pressure, indicating that NO plays a role in modulating aortic compliance. Chronic treatment of L-NAME for 3 weeks further increased PWV. This component of the increase in aortic stiffness is probably due, at least in part, to an abnormal remodeling in the vascular wall resulting from the long-term absence of NO, as well as chronic hypertension.

As we and other authors [20–23] have demonstrated, changes in blood pressure also affect compliance of the aortic conduit vessel. Since both acute and chronic treatment of L-NAME increased blood pressure, the concomitant increase in PWV observed in both groups must be attributed, at least in part, to the increase in blood pressure. Therefore, PE was used to increase and ISO to decrease blood pressure so that MAP could be normalized across the different treatment groups. PWV was then compared at the same blood pressure level for all groups. The present results revealed that PWV was significantly higher at each given pressure level when the rats were acutely treated with L-NAME compared to those with PE. This additional increase in PWV by L-NAME over PE treatment, therefore, was blood pressure independent, and thus, could be attributed to the acute withdraw of NO. In support of this view, the present result further demonstrated that the pressure component contributing to the increase in PWV induced by PE could be completely offset when blood pressure was reduced to the baseline level by ISO.

The influence of blood pressure on aortic compliance could be via the following mechanism. There are three major elements (elastin, collagen and smooth muscle) in the vascular wall contributing in different proportions to the vascular compliance depending on transmural pressures that alter forces exerted on the various elements. Elastin has a very low elastic modulus (5×10⁶ dynes/cm³) giving the aorta its distensibility. Collagen has a very high elastic modulus (900×10⁶ dynes/cm³) giving the vessel wall strength during high transmural pressure. These two elements affect vascular compliance by their ratio in the vessel wall, which is different along the aortic tree. There
Table 1
Systolic (SAP), diastolic (DAP) and pulse (PP) arterial blood pressure at discrete mean arterial blood pressure (MAP) levels when pulse wave velocity was measured for Fig. 6 in anesthetized rats acutely treated with phenylephrine (PE) or L-NAME*

<table>
<thead>
<tr>
<th>MAP (mmHg)</th>
<th>PE</th>
<th>t-NAME</th>
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<tr>
<td>140±0.2</td>
<td>140</td>
<td></td>
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<tr>
<td>150±0.1</td>
<td>150</td>
<td></td>
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<tr>
<td>160±0.2</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td>170±0.2</td>
<td>170</td>
<td></td>
</tr>
<tr>
<td>180±0.1</td>
<td>180</td>
<td></td>
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<tr>
<td>180±0.3</td>
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<tr>
<th>SAP (P&lt;0.01) (mmHg)</th>
<th>PE</th>
<th>t-NAME</th>
</tr>
</thead>
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<tr>
<td>140</td>
<td>154±0.6</td>
<td>150</td>
</tr>
<tr>
<td>150</td>
<td>168±0.8</td>
<td>161</td>
</tr>
<tr>
<td>160</td>
<td>182±1.1</td>
<td>174±1.6</td>
</tr>
<tr>
<td>170</td>
<td>196±1.4</td>
<td>189±2.0</td>
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<tr>
<td>180</td>
<td>209±3.0</td>
<td>208±2.1</td>
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<th>DAP (P&lt;0.01) (mmHg)</th>
<th>PE</th>
<th>t-NAME</th>
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<td>125±0.6</td>
<td>131</td>
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<tr>
<td>150</td>
<td>134±0.5</td>
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<tr>
<td>160</td>
<td>142±0.5</td>
<td>148±1.0</td>
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<tr>
<td>170</td>
<td>149±0.8</td>
<td>155±1.1</td>
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<tr>
<td>180</td>
<td>158±1.6</td>
<td>159±1.2</td>
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<th>PP (P&lt;0.01) (mmHg)</th>
<th>PE</th>
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<tbody>
<tr>
<td>140</td>
<td>29±1.2</td>
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</tr>
<tr>
<td>180</td>
<td>50±4.6</td>
<td>49±3.2</td>
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* Some points in t-NAME group have only two samples, therefore no S.E. was calculated. PE group has 29 samples and t-NAME group has 17 samples. P<0.01 between two groups.

is more elastin in the aortic arch and more collagen in the distal conductance arteries [20]. Transmsural pressure across the vessel determines the distribution of the stress placed on elastin and collagen. At lower transmural pressure, much of the stress placed on the vessel wall is absorbed by the compliant elastin. At higher transmural pressure, the vessel wall expands, recruiting more non-compliant collagen. The increased stress on collagen makes the vessel less compliant or stiffer [20,22].

The role of the smooth muscle in vascular compliance is controversial. The smooth muscle has a low elastic modulus (1–8×10⁶ dynes/cm²) and only makes up about one third of the elasticity of the aortic wall. Therefore, activation of the aortic smooth muscle has been considered negligible in affecting vascular stiffness. However, investigators using different methods for measuring vessel elastic modulus have indicated that the smooth muscle is capable of contributing significantly to vascular compliance. The most useful method for measuring the functional contribution of smooth muscle to the elastic modulus is isometric analysis [20,22]. Using this method, it has been shown that activation of the smooth muscle with PE reduces vascular compliance. On the other hand, dilating vessels with calcium channel antagonists and nitrovasodilators increases compliance more than diuretics do even though they lower blood pressure similarly [1,2,22,24–26]. This suggests that decreasing vascular tone of the conductance vessel can increase vascular compliance independent of blood pressure [20,27]. Thus, while elastin and collagen passively contribute to elasticity or stiffness of the vessel, the smooth muscle appears to actively modulate vascular compliance.

Endothelial dysfunction and vascular stiffness have both been implicated in several vascular diseases that reduce cardiac function. Both tend to increase systolic pressure, pulse pressure and reduce subendocardial perfusion. Studies have shown that endothelial dysfunction is found early in atherosclerosis and may be a precursor to increased vascular stiffness by consequential constriction of the smooth muscle in the vascular wall. Experimental evidence supports that smooth muscle contribution to the elastic modulus is more important than its inherent physical properties suggests. Therefore, changes in vascular tone due to endothelial dysfunction may be an important factor independent of blood pressure leading to vascular stiffness and cardiovascular disease. The endothelium modulates vascular tone through substances such as NO [28,29]. Dysfunction of the endothelium in cardiovascular diseases can disrupt the signal transduction pathways, reducing the endothelium’s ability to modulate vascular tone and perhaps even vascular compliance [30,31]. Indeed, Ramsey et al., observed that in chronic heart failure patients with endothelial dysfunction, the endothelium NO mediated increase in conduit artery distensibility is impaired, while endothelium NO independent increase in distensibility is retained [17]. Thus, endothelium dysfunction is related to the reduction in vascular compliance. The present study tested the hypothesis that NO functionally
modulates vascular compliance. Indeed, our results demonstrated that treatment with L-NAME for 30 min significantly increased PWV, which was greater than that induced by PE. The mechanisms to account for this are still unclear, but higher smooth muscle tone in L-NAME than PE treatment may be a possible explanation. Although PWV was compared at the same given MAP levels between PE and L-NAME treatment in the present study, since L-NAME has been shown to reduce cardiac output in rats [32], peripheral vascular resistance (vascular tone) must be higher with L-NAME than with PE treatment. The fact that at each given mean blood pressure level, systolic pressure was lower (indicating a lower cardiac output) and diastolic pressure higher (indicating a higher peripheral vascular resistance or tone) after L-NAME compared to PE, suggests that L-NAME may increase vascular tone more than PE does even though MAP is the same. Thus, it supports the view that NO modulates vascular compliance via modulation of vascular tone. However, L-NAME has also been shown having non-specific effects, such as inhibiting the muscarinic receptor antagonist [33]. But it is unlikely such non-specific effects could be a major contribution to the increase in PWV, because the muscarinic influence on basal vascular tone is minimal.

In a separate group of rats, L-NAME was administered chronically via drinking water for 3 weeks. PWV in these rats was even higher than that in rats treated with L-NAME acutely when MAP was adjusted to 150 mmHg in both acute and chronic L-NAME treatment groups. This additional increase in PWV is probably the result of abnormal vascular remodeling. In support of this, it has been reported that chronic treatment with L-NAME caused vascular lesions, such as perivascular fibrosis, medial thickening and increase in intima/media or wall/lumen ratios in the mesenteric microvascular beds, arterioles, coronary arteries, and aorta [34–39]. Such remodeling of the vasculature could occur as early as 3–4 weeks following L-NAME treatment [38]. In addition, chronic hypertension could also cause structural changes in the vascular wall [20].

In summary, the present study demonstrated that there are four different components contributing to vascular stiffness as illustrated in Fig. 8. These include: (1) a basal component at normal blood pressure level; (2) a pressure component increases PWV when blood pressure is elevated to 150 mmHg by pharmacological agents; (3) increased vascular smooth muscle tone due to acute inhibition of NO contributes to an increase in PWV that is independent of blood pressure; and (4) vascular remodeling, presumably resulting from chronic inhibition of NO production, further increases aortic stiffness.

Acknowledgements

The authors would like to thank Drs Gabor Rubanyi and Valdeci da Cunha for reviewing the manuscript and contributing valuable comments.

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