Augmentation Pressure Is Influenced by Ventricular Contractility/Relaxation Dynamics

Novel Mechanism of Reduction of Pulse Pressure by Nitrates

Henry Fok,* Antoine Guilcher,* Ye Li, Sally Brett, Ajay Shah, Brian Clapp, Phil Chowicienczyk

Abstract—Augmentation pressure (AP), the increment in aortic pressure above its first systolic shoulder, is thought to be determined mainly by pressure wave reflection but could be influenced by ventricular ejection characteristics. We sought to determine the mechanism by which AP is selectively reduced by nitroglycerin (NTG). Simultaneous measurements of aortic pressure and flow were made at the time of cardiac catheterization in 30 subjects (11 women; age, 61±13 years [mean±SD]) to perform wave intensity analysis and calculate forward and backward components of AP generated by the ventricle and arterial tree, respectively. Measurements were made at baseline and after NTG given systemically (800 μg sublingually, n=20) and locally by intracoronary infusion (1 μg/min; n=10). Systemic NTG had no significant effect on first shoulder pressure but reduced augmentation (and central pulse pressure) by 12.8±3.1 mm Hg (P<0.0001). This resulted from a reduction in forward and backward wave components of AP by 7.0±2.4 and 5.8±1.3 mm Hg, respectively (each P<0.02). NTG had no significant effect on the ratio of amplitudes of either backward/forward waves or backward/forward compression wave energies, suggesting that effects on the backward wave were largely secondary to those on the forward wave. Time to the forward expansion wave was reduced (P<0.05). Intracoronary NTG decreased AP by 8.3±3.6 mm Hg (P<0.05) with no significant effect on the backward wave. NTG reduces AP and central pulse pressure by a mechanism that is, at least in part, independent of arterial reflections and relates to ventricular contraction/relaxation dynamics with enhanced myocardial relaxation. (Hypertension. 2014;63:1050-1055.) * Online Data Supplement

Key Words: pulse wave analysis

Aortic or central pulse pressure (cPP) determines the pulsatile load on the left ventricle, coronary, and carotid arteries and is a major risk factor for adverse cardiovascular events, with at least as strong a relation to such events as peripheral pulse pressure.1-11 CPP is widely assumed to be determined by the interaction of an outgoing forward pressure wave (FPW) generated by ventricular contraction and a backward going pressure wave (BPW) generated by reflections from the periphery of the circulation.12 These components of cPP are separated by the first systolic shoulder of the aortic pulse (Figure 1). The height of this above diastolic blood pressure (P1) is attributed to the FPW and the height above P1, the augmentation pressure (AP), to the BPW. Augmentation index (AIx), the ratio of AP to cPP, is widely used as a measure of pressure wave reflection. This interpretation has, however, been criticized because of the poor relationship between the magnitude and timing of reflected waves with respect to AP.7,8 Nitroglycerin (NTG) has a particularly marked action to reduce AP and hence cPP attributed to a change in timing or amplitude of pressure wave reflections.9-11 However, an alternative explanation relates to an influence of nitrovasodilators on contraction–relaxation dynamics of the myocardium, effects observed in isolated myocytes and in vivo.12,13

The aim of the present study was to determine the mechanism by which AP is selectively reduced by NTG. We made simultaneous measurements of aortic pressure and flow and used wave intensity analysis to separate pressure waves into FPW and BPW components.14 Pressure waves were further categorized as compression or expansion (suction). A primary forward compression wave (FCW) arises from the push of the ventricle against the arterial tree and a systolic backward compression wave (BCW) from the push of the arterial tree against the ventricle. A late systolic forward expansion wave (FEW) arises from the braking effect of the ventricle in late systole.15 These measurements together with cardiac output and the impedance of the arterial tree were obtained at baseline and after systemic administration of NTG. To further distinguish between effects of NTG related to an action on the myocardium and arterial tree, we examined effects of intracoronary infusion of NTG at a dose below the threshold required to produce systemic effects.
Figure 1. Central aortic pressure and flow waveforms showing components of central pulse pressure, height above diastolic pressure of the first shoulder of the aortic pressure waveform (P1), and augmentation pressure (AP).

### Methods

Subjects (n=30; 11 women; age, 61±13 years [mean±SD]) were recruited from those attending Guy’s and St Thomas’ cardiothoracic unit for diagnostic angiography or elective percutaneous coronary angioplasty. Subjects with acute coronary syndromes, those with significant valvular disease, heart failure of severity greater than New York Heart Association grade 2 and rhythm other than sinus rhythm were excluded. Subject characteristics including medication are shown in Table 1.

### Study 1: Central Hemodynamics and Response to Systemic NTG

After routine preparations for angiography, vascular access to the right femoral or radial artery was established with a 6Fr hemostatic sheath. A 6Fr guiding catheter was advanced to the aortic root over a 0.35-in. wire using standard techniques and connected to a closed flushing system with a hemostatic valve. A straight tip Combowire (9500XT, VolcanoCorp, USA) pressure and Doppler flow velocity transducer were passed through the guiding catheter and, using fluoroscopic guidance, the tip of the wire was positioned in the proximal aortic root. The transducers had a frequency response flat to >100 Hz. The subject was heparinized systemically with unfractionated heparin to reduce the risk of thrombus formation within the catheter. The Combowire was positioned carefully to obtain optimal coaxial stable flow (maximizing the Doppler audio signal) and pressure tracings.

### Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Study 1 (n=20)</th>
<th>Study 2 (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63±11</td>
<td>57±17</td>
</tr>
<tr>
<td>Sex (men/women)</td>
<td>10/10</td>
<td>9/1</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>Aortic systolic blood pressure, mm Hg</td>
<td>136±23</td>
<td>139±39</td>
</tr>
<tr>
<td>Baseline diastolic blood pressure, mm Hg</td>
<td>73±13</td>
<td>69±8.3</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>28±8.6</td>
<td>28±3.1</td>
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<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.5±1.2</td>
<td>5.0±0.2</td>
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<tr>
<td>High-density lipoprotein, mmol/L</td>
<td>1.2±0.5</td>
<td>1.0±0.3</td>
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<td>Drug treatment</td>
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<tr>
<td>ACEI/ARB, %</td>
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<td>70</td>
</tr>
<tr>
<td>β-Blocker use, %</td>
<td>45</td>
<td>40</td>
</tr>
<tr>
<td>CCB, %</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>Nitrate, %</td>
<td>20</td>
<td>10</td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and CCB, calcium channel blocker.

Baseline measurements of aortic root pressure and Doppler flow velocity were then obtained during ≥10 cardiac cycles. NTG (800 μg) was then administered sublingually, and measurements of aortic pressure and velocity were repeated 22 minutes after NTG when hemodynamic responses were stable. All measurements were taken before the administration of ionic contrast agents for the subsequent angiogram or angioplasty.

### Study 2: Central Hemodynamic Response to Intracoronary NTG

Preparation and placement of a Combowire pressure/flow transducer in the proximal aortic root were as described for study 1. A diagnostic coronary angiogram was performed before the research study to ensure the absence of significant left main stem or critical left anterior descending coronary artery disease that could affect the distribution of NTG within the left ventricle. Baseline pressure and flow measurements were obtained from the Combowire in the aortic root as in study 1. The guiding catheter was then advanced to the left coronary ostium for NTG (Hospira Incorporation) infusion at 1 μg/min. This dose was determined by previous studies that found no significant systemic effects when NTG 1 μg/min was infused locally into the brachial artery and by dose ranging studies where intravenous NTG infusion at 3 μg/min was found to be the threshold dose above which systemic effects on aortic waveform indices (AP and AIx obtained noninvasively from carotid tonometry) were observed (n=10, unpublished data). After a 7-minute infusion of NTG, the guiding catheter was pulled back into the proximal aortic root and Combowire repositioned in the aortic root with fluoroscopic screening used to ensure position of the Combowire was similar to that at baseline (this taking ≈1 minute). Measurements of pressure and flow were then repeated as previously described. In 4 subjects after the placement of the Combowire in the proximal aortic root for continuous pressure/Doppler flow velocity measurements, a separate guiding catheter was inserted via a second vascular access in the contralateral femoral artery to simultaneously infuse NTG for 7 minutes into the left coronary ostium.

### Waveform Post Processing

Flow velocity and pressure waveforms were acquired at 1 kHz through the analog output of a ComboMap monitor and stored for postprocessing analysis in Matlab (2007b, Mathworks, USA). A minimum of a 10-s period free of ectopic beats or other artifacts was selected for ensemble averaging and subsequent analysis. The upstroke of each pressure wave was used to determine the foot of the waveform as the fiducial point. The length of each beat was adjusted to be equal to the average duration of each pulse in the 10-s period (to reduce artifacts at end diastole arising from beats of unequal duration) before ensemble averaging. The first systolic shoulder of the aortic pressure waveform was identified as the first local minimum of the first derivative of the pressure curve (and confirmed by visual inspection by an observer blinded to the results) to determine P1 and AP. Wave decomposition was performed using the equations derived by Euler in 1775, based on the conservation of mass and momentum. The aorta was considered as an elastic tube, blood as an incompressible and inviscid fluid, and the flow was assumed to be unidimensional. These equations were solved using the method of Parker and the following formulas were obtained for FPW and BPW:

\[
FPW = \frac{1}{2} \int_0^T \left( \frac{dP}{dt} + \rho c \frac{dU}{dt} \right) \, dt
\]

\[
BPW = \frac{1}{2} \int_0^T \left( \frac{dP}{dt} - \rho c \frac{dU}{dt} \right) \, dt
\]

where \( P \) and \( U \) are the pressure and the flow velocity, respectively; \( T \) the duration of a pulse, \( \rho \) the density of blood; and \( c \) is the speed of travel of waves equal to the local pulse wave velocity. Pulse wave velocity was estimated using the single point method described by Davies et al. This produces the same waveform separation as an analysis in the frequency domain. Aortic flow velocity waveforms were integrated over time and multiplied by aortic cross-sectional area.
(estimated from body surface area) to obtain a measure of stroke volume and hence cardiac output and total systemic vascular resistance.

Statistics
Unless where stated, results are expressed as mean±SE. Changes from baseline in hemodynamic measures after NTG were compared using Student paired t test or by ANOVA for repeated measures. In the case of non-normally distributed data (heart rate, pulse wave velocity, and FEW), a Wilcoxon signed-rank test was used. All tests were 2-tailed and P<0.05 was considered significant.

Results

Contributions of FPW and BPW to AP
Decomposition of the aortic pressure wave demonstrated that P1 was almost entirely attributed to the FPW, and that the BPW contributed only a minor component to P1 (mean contributions at baseline of 37.1±2.8 and 1.6±1.1 mm Hg, respectively). The FPW also provided the major contribution to AP although the BPW also provided a significant contribution (mean contributions of 15.6±2.9 and 11.0±2.8 mm Hg for the FPW and BPW, respectively; Figure 2).

Effects of Systemic NTG on Hemodynamics and Pulse Pressure Components
Systemic administration of NTG had no significant effect on P1 but reduced AP by 12.8±3.1 mm Hg (from 26.1±3.1 to 13.3±2.6 mm Hg; P<0.0001; Figure 2) and reduced central systolic blood pressure and cPP by similar amounts (from 136±5 to 127±6 mm Hg and from 63.0±4.0 to 51.3±3.9 mm Hg, respectively; each P<0.01). AIx decreased by 17.3±3.0% (from 39.5±3.6 to 22.±5.0%; P<0.0001). By contrast, NTG had no significant effect on mean arterial blood pressure, total peripheral resistance, or aortic pulse wave velocity (Table 2).

Effects of Intracoronary NTG on AP
There was no significant change in central systolic blood pressure, mean arterial pressure, P1, or heart rate after intracoronary NTG (1 μg/min for 7 minutes, data not shown). However, intracoronary injection of NTG reduced AP by 8.3±3.1 mm Hg (from 27.6±9.7 to 19.2±8.4 mm Hg; P<0.05; Figure 4) and reduced AIx by 9.3% (from 31.0±6.5 to 21.7±5.6%; P<0.05). Effects of intracoronary NTG on FPW and BPW components of AP and AIx did not reach statistical significance but there was a trend for a reduction in the FPW components of AP and AIx (P=0.17 and P=0.08, respectively) but not the BPW components of AP and AIx (P=0.50 and P=0.96). Thus, the
reduction in AP and AIx by intracoronary NTG was potentially explained by an effect on the FPW alone.

**Discussion**

AP accounts for the much of the intersubject variability in cPP, and an increase in AP is the major cause of the age-related increase in cPP. AP has, hitherto, been attributed to augmentation of the FPW (which determines P1) by the BPW, the BPW being attributed to wave reflection. However, the interpretation of AP as an index of reflection assumes that the FPW plateaus at P1 and has been criticized because of the poor relationship between the magnitude and timing of reflected waves with respect to AP. Although we observed a significant contribution of the BPW to the AP, the major contribution to AP derived from the FPW with the contribution of the FPW to AP being approximately twice that of the BPW. This suggests that AP is in large part independent of processes such as pressure wave reflection or other hemodynamic effects that may influence the BPW.

NTG is markedly effective in reducing AP, an effect that has been attributed to dilation of conduit arteries and a change in magnitude and timing of wave reflections. In the present study, systemic administration of NTG at a dose that dilates conduit arteries by between 10% and 20% reduced AP by >46%. The aortic pressure wave is determined by the interaction of ventricular contraction with the input impedance of the aorta and more distal circulation as seen at the aortic root (the point of pressure recording). Thus, a reduction in AP could, in principle, result from a change in myocardial contraction / relaxation and change in input impedance. With the relatively low dose of NTG we used, we observed no significant change in the modulus or phase of the impedance, but there was a trend to a shift to the left of the phase of the impedance in keeping with previous observations, which have been attributed to a delay in reflections. To probe the hemodynamic determinants of this effect of NTG on AP further, we performed waveform decomposition before and after NTG. The reduction in AP was only partially explained by the BPW with the reduction in the FPW component of AP contributing proportionately more than that of the BPW to the total reduction in AP. Furthermore, the ratio of the BPW to the FPW, whether measured as the ratio of the maximum amplitudes of the waves or as ratio of wave energy in FCW and BCW, did not change significantly after NTG, suggesting that most of the reduction in the BPW was secondary to that in the FPW.

Because P1 occurs at the time of peak systolic stress (ie, peak contraction in individual myocytes) in the myocardium, the reduction of the FPW component of AP but not of P1 by...
NTG implies an earlier or more pronounced relaxation of the myocardium after peak stress. The observation that the maximal wave intensity of the FCW that occurs before P1 is unaltered but FCW energy that includes components after P1 during augmentation is reduced is consistent with a reduction of the forward wave during pressure augmentation. Earlier onset of the FEW is consistent with earlier onset of relaxation of the ventricle. It is notable that sodium nitroprusside, an NO donor thought to act through the same downstream cGMP effector pathway as NTG delivered locally into the coronary circulation with negligible systemic delivery to the peripheral circulation, hastens the onset of relaxation of the ventricle\(^13\) and a similar effect is seen in isolated myocytes exposed to NO\(^5\) or to cGMP mimetics acting downstream of the NO-soluble guanylyl cyclase pathway.\(^24\)

To test the possibility that the effect of NTG to reduce the FPW component of AP relates to myocardial contraction/relaxation, we injected NTG directly into the left coronary circulation at a dose below that observed to generate systemic effects when given intravenously and \(=50\)-fold lower than that used to achieve systemic effects in the present study (assuming bioavailability of sublingual NTG to be approximate 35%).\(^25\) We observed a significant, albeit less pronounced, effect on AP. This is consistent with an influence of NTG on the FPW component of AP through a direct action on the myocardium to hasten the onset of relaxation after P1. However, delivery of NTG through the myocardial circulation to the central venous return (via the coronary sinus) may result in a relatively greater concentration in pulmonary vessels than achieved by a systemic venous infusion and, because we did not measure left ventricular end-diastolic pressure or volume, we cannot be certain that preload was not altered by intracoronary NTG. Similarly, the reduction in pulse pressure at the baroreceptors brought about by NTG could result in an increase in sympathetic activity. Thus, although our intracoronary studies indentify an action of NTG on ventricular contraction/relaxation dynamics independent of an action on the peripheral arterial tree, this could be because of direct and indirect actions on the myocardium.

Our study is subject to several other limitations. By necessity it was limited to subjects that had clinical indications for coronary angiography and a substantial proportion of these had established coronary artery disease. Thus, we cannot exclude the possibility that results in subjects without coronary disease might differ and the results of our study cannot necessarily be extrapolated to younger subjects. The interpretation of our study relies, in part, on wave separation theory. However, this theory relies on relatively few assumptions other than conservation of mass and momentum, and results obtained using differing mathematical techniques are similar.\(^18\) Furthermore, the main finding of our study that AP is influenced by ventricular dynamics is borne out by our intracoronary study independent of wave separation analysis. Accuracy of cardiac output and total peripheral resistance measurements was limited by the estimation of aortic cross-sectional area, but this would not affect the relative change before and after NTG.

**Perspectives**

Our results challenge the conventional view that effects of NTG to reduce AP and cPP are mediated mainly by a reduction in wave reflection. Instead, they identify a novel mechanism whereby AP and cPP are influenced predominantly by the FPW and hence the contractility/relaxation dynamics of the myocardium. Interestingly, Schultz et al\(^26\) have reached a similar conclusion on dominance of the FPW as responsible for change in the central pulse during exercise. Our results have implications for the age-related increase in pulse pressure, incidence of isolated systolic hypertension, and impaired ventricular-vascular coupling. Ventricular relaxation is known to decrease with age, and there is a strong correlation between ventricular relaxation and AP.\(^27\) This has been assumed to be because of the additional afterload imposed by increased AP.\(^27\) Our results raise the possibility of an opposite direction of causality: that changes in myocardial contraction/relaxation drive those in AP. Thus, increased AP, cPP, and isolated systolic hypertension could result, in part, from an age-related decline in myocardial function with a delayed onset of relaxation. This, in turn, could be because of an age-related decline in the availability of endogenous NO from endothelial or neuronal NO synthase.\(^28,29\) Further interventional studies will be required to explore this possibility.

In conclusion, AP is determined in large part by the FPW and ventricular contraction/relaxation dynamics. NTG reduces AP by a reduction in the FPW resulting from earlier onset and more pronounced ventricular relaxation. The NO pathway may present a novel target to reduce AP, systolic blood pressure, and improve ventricular-vascular coupling.
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Disclosures
King’s College London has formed a spin-out company to develop technology in central blood pressure measurement (not used in the present study). Dr Guilcher, Dr Brett, Dr Clapp, and P. Chowienczyk have an interest in this company. The other authors report no conflicts.

References


Novelty and Significance

What is New?
- Nitroglycerin reduces augmentation pressure and central pulse pressure through an effect on ventricular contraction/relaxation dynamics.

What is Relevant?
- Increased pulse pressure in hypertension may relate, in part, to decreased relaxation of the ventricle.
- Nitrovasodilators and interventions to increased endogenous nitric oxide may have beneficial effects on ventricular relaxation and pulse pressure.

Summary
Augmentation pressure is determined in large part by the forward pressure wave and ventricular contraction/relaxation dynamics. Nitroglycerin reduces augmentation pressure and pulse pressure by a reduction in the forward pressure wave resulting from earlier onset and more pronounced ventricular relaxation. Nitrovasodilators and the endogenous NO pathway may present a novel target to reduce augmentation pressure, systolic blood pressure, and improve ventricular-vascular coupling.

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Augmentation pressure is influenced by ventricular contractility/relaxation dynamics: novel mechanism of reduction of pulse pressure by nitrates

Short title: augmentation pressure and ventricular dynamics

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Table S1 Wave intensity analysis

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>NTG</th>
<th>P value</th>
</tr>
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<tr>
<td>FCW</td>
<td>0.50±0.066</td>
<td>0.48±0.063</td>
<td>0.58</td>
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<tr>
<td>FEW</td>
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<td>0.95</td>
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<tr>
<td>BCW</td>
<td>0.084±0.013</td>
<td>0.060±0.0091</td>
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<tr>
<td>BCW:FCW</td>
<td>0.19±0.026</td>
<td>0.14±0.018</td>
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<tr>
<td><strong>Wave Timing (ms)</strong></td>
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<tr>
<td>FCW</td>
<td>59.0±7.43</td>
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<tr>
<td>FEW</td>
<td>314±14.0</td>
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<tr>
<td>BCW</td>
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<td><strong>Wave Energy (J.m⁻²x10⁶)</strong></td>
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<tr>
<td>FCW</td>
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<tr>
<td>BCW</td>
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<td>0.0084±0.00094</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>BCW:FCW</td>
<td>0.25±0.021</td>
<td>0.22±0.23</td>
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</table>

FCW, forward compression wave; FEW, forward expansion wave; BCW, backward compression wave
Figure S1

Average modulus a) and phase b) of aortic input impedance at baseline and after sublingual nitroglycerin (n=20).
Figure S2

Typical wave intensity plots at baseline and after NTG.