Benefit of Nitroglycerin on Arterial Stiffness is directly due to Effects on Peripheral Arteries.

Alfredo L. Pauca MD*, Neal D. Kon MD†, Michael F. O'Rourke MD, DSc‡

From the Departments of Anesthesiology* and Cardiothoracic Surgery†, Wake Forest University School of Medicine, Winston-Salem, North Carolina and the Department of Medicine‡, University of New South Wales, St. Vincent's Hospital and Clinic, VCCRI, Sydney, Australia

Address correspondence to M. O'Rourke at Suite 810, St. Vincent's Clinic, 438 Victoria Street, Darlinghurst, NSW 2010 Australia
Ph: 61 2 8382 6874 FAX: 61 2 8382 6877 Email: M.ORourke@unsw.edu.au
Structured abstract word count: 232 words
Condensed abstract word count: 91 words
Manuscript word count: 2075
Objective was to determine in what way the vasodilator nitroglycerin (NTG) alters arterial stiffness and improves left ventricular (LV) afterload.

Background
Controversy exists regarding the effects of vasodilator drugs on stiffness of proximal (predominantly elastic) and peripheral (predominantly muscular) arteries, with recent noninvasive studies favouring the former, and downplaying effects of wave reflection from peripheral arteries.

Methods
Ascending aortic pressure waves were measured with fluid-filled catheters of high fidelity in 50 patients undergoing cardiac surgery, prior to cardiopulmonary bypass, both before and after IVI infusion of NTG. In all 50 patients, wave reflection was identifiable as a secondary boost to late systolic pressure, permitting the pressure wave to be separated into a primary component, attributable to LV ejection and properties of the proximal aorta, and a secondary component attributable to reflection of the primary wave from the peripheral vasculature.

Results
NTG infusion caused no change in amplitude of the primary wave (0.0, SD 1.4mmHg, NS), but substantial reduction (14.6, SD9.8mmHg, P<0.0001) in amplitude of the secondary reflected wave. Fall in mean pressure was attributable to a mix of arteriolar and venous dilation, with relative contributions unable to be separated.

Conclusion
Favourable effects of NTG on arterial stiffness can be attributed to effects on peripheral muscular arteries, causing reduction in wave reflection. Results conform with previous invasive studies on vasodilator agents, and their known effects on calibre and compliance of muscular arteries.

KEY WORDS: arterial stiffness, nitroglycerin, wave reflection
CONDENSED ABSTRACT

Effects of the vasodilator nitroglycerin (NTG) on arterial properties was studied from analysis of ascending aortic pressure waveforms in 50 patients at cardiac surgery. All patients showed a primary wave attributable to LV ejection and proximal aortic properties, and a distinct secondary wave attributable to wave reflections from peripheral muscular arteries. IVI infusion of NTG caused marked reduction in amplitude of the secondary wave (14.6 SD 9.8mmHg, P < 0.0001) but no change (0.0, SD 1.4mmHg, NS) in the primary wave. NTG appears to have marked effect on peripheral muscular arteries.
INTRODUCTION

Increased death and disability rates from cardiovascular disease in older persons is associated with, and attributable to, increased systolic and pulse pressure, causing greater load on the heart and greater tension in arterial walls.[1][2][3][4][5] The prime cause of increased systolic and pulse pressure is increased stiffness of the aorta and central elastic arteries.[6][7] Such awareness has led to efforts to develop drugs which may have specific effects on arterial stiffness, and thus the potential to lower pulsatile pressure while maintaining mean pressure and normal perfusion of vital organs. [8]

While beneficial effects on pulse pressure and arterial stiffness have been reported for different drugs there is no consensus on how these drugs act,[ 9][10][11][12][13][14][15][16] or on how their effects should be measured.[17] Recent major publications have focussed on compliance of the whole arterial tree for the AGE crosslinked breaker AT711 [18] and on ascending aortic characteristic impedance for omapatrilat and other drugs.[19][20] However, other recent and earlier studies had focussed on the ability of nitrates,[21] [6][14][16][22][23] calcium channel blockers and ACEIs to reduce wave reflection through increase in calibre and distensibility of peripheral small arteries. Such studies were performed during cardiac catheterisation or noninvasively,[9][10][11][12][13][14][15][22] with generation of central from peripheral waveforms using generalised transfer functions.[21][24][25] Validity and relevance of these have been questioned.[19][20] The present study was undertaken to examine the effects of intravenously infused nitroglycerin on the amplitude of the reflected pressure wave, and on central aortic pulse pressure, recorded directly in a large group of patients with cardiovascular disease, prior to open heart surgery.

METHODS

Similar equipment and methods were used as in previous studies including anesthetic agents and the matched fluid-filled pressure systems.[26][27] After the study was approved by the Institution's clinical research practices committee, written consent was obtained from 50 consecutive patients who were to undergo cardiac surgery. Patients were studied before being placed on cardiopulmonary bypass. Radial artery pressure was routinely established before induction of anaesthesia through a 5.1cm 20 gauge Teflon catheter. Recordings for this study were taken 60-90 minutes after anaesthesia had been established, and after preparations for aortic cannulation had been completed. Ascending aortic pressure was recorded at the site prepared for bypass cannulation, through a catheter identical to that used at the radial artery (RA). Both catheters were attached to individual high pressure tubes 91.4cm long. These had been attached to matched Transpac ® IV transducers (Abbott Critical Care Systems, Abbott Laboratories, North Chicago, Illinois). Frequency response and damping coefficient were obtained by the flush method at the beginning and end of the recording period in each patient, and confirmed to have natural frequency greater than 20hz and damping coefficient ≥ 0.2.[27] All transducers were calibrated statically with a mercury manometer and maintained at the same level. Matching was confirmed as previously described.[28] After control recordings of aortic and radial pressure had been obtained, nitroglycerin (NTG) was infused at an average dose of 6mcg/kg/min for 10-30 seconds, up to 16mcg/kg/min for 5-10 seconds, aiming at lowering systolic radial artery pressure to 100mmHg. Further recordings of aortic and radial pressures were taken at the peak of the nitroglycerin effect. Recordings were obtained simultaneously during a period of 2-5 minutes. Once the study was completed, the catheter was removed and the surgeon proceeded with the aortic cannulation. Data were recorded by a Siemens medical systems recorder with linear frequency response up to 500hz. Mean arterial pressure was obtained by electronic integration. Simultaneous recordings of aortic and radial pressure waves were analysed off line.
Paired aortic pressure waves over 10 second periods were compared before and after NTG infusion. Waveform types were assigned the labels of type A, B or C by visual inspection according to Murgo et al depending on the amplitude of systolic pressure augmentation to pulse pressure. [29]

There were 42 males and 8 females in the patient group, with ages ranging from 41 to 87 years. All but one (mitral valve disease) had coronary artery disease (CAD) and were to undergo coronary artery bypass or valve repair surgery. All but three were on treatment for hypertension. Details for the 50 patients are presented in table 1.

**Statistics**

We used paired two tailed T test to evaluate the effect of treatment on the aortic primary wave (amplitude from wave foot to first systolic wave shoulder, [29] primary component), aortic augmentation (amplitude from shoulder to wave peak, second component, [29]) and delay of the wave foot between aortic and radial pulse. All data were expressed as mean ± SD.

**RESULTS**

A. Baseline

Figure 1 shows typical radial and aortic pressure waves as recorded simultaneously before nitrate infusion. In 46 patients, the amplitude of the radial pressure wave was clearly greater than the aortic, while the foot of the radial wave was delayed in relation to the foot of the aortic pressure wave in all 50 patients. Two localised distinct peaks, a first (P1) and second peak (P2), were seen in 45 aortic pressure waves, but in only 21/50 of the radial pressure waves.

The aortic pressure wave showed P1, or the first component, as a shoulder on the ascending part of the wave, with P2, or the second component, forming the apex of the wave. In contrast, in the RA, the first component or P1 usually comprised the peak of the wave, with P2, when apparent, a late systolic shoulder on the falling limb of the wave before the incisura. According to the classification of Murgo et al 48 aortic control pulse waves were type A in which (P2-P1) ÷ (P2-P0) was > 0.12, and only 2 were type B in which (P2-P1) ÷ (P2-P0) ranged between 0.00-0.12. [29] None were type C in which (P2-P1) ÷ (P2-P0) was less than zero.

B) Treatment

Nitroglycerin infusion led to fall in arterial pressure, but did not change the relationships between aortic and radial systolic, diastolic and mean pressure from those under control conditions [table 2]. While the mean and diastolic pressure differences between the two sites were small, those for systolic, pulse pressure and end-systolic pressure were large [table 2] as under control conditions, and as previously described. [26][27].

Nitroglycerin markedly changed the shape of the aortic and radial pressure waveforms. In the aortic pressure tracing, the main change was a decreased P2-P1 [fig 2] while in the radial, the second shoulder, (P2), present in only 21 patients, disappeared in 18, and location of the incisura became blurred.

The effect on aortic augmentation (P2-P1), primary wave (P1-P0), and PP with NTG was clear in all observations [table 3]. P1-P0 did not change (28.7 ± 8.9 to 28.7 ± 9.0, fig 3, left), whereas P2-P1 was reduced to almost one third (23.0 ± 11.5 to 8.4 ± 7.5, P< 0.0001, fig 3, right).
Nitroglycerin infusion was associated with delay in the foot of the radial compared to the aortic pulse wave [table 3], indicating decrease in aortic to radial pulse wave velocity. However there was no perceptible increase in time from aortic wave foot to the aortic systolic shoulder (89 SD11msec before and 87 SD12msec after NTG). This has been taken as a measure of aortic pulse wave velocity [30], and suggests no significant change in aortic stiffness, despite nitrate therapy and fall in aortic pressure. The foot of the reflected wave could not be identified with the same precision as the foot of the initial wave so that this interpretation needs be taken with great caution. Heart rate increased from 67 to 69/min, with small changes in cycle length (889 ± 194 to 864 ± 193 msec) and ejection period (312 ± 45 to 295 ± 44msec, p < 0.01 for both) and no change in diastolic period 579 ± 162 to 569 ± 161msec).

Discussion

Results presented here are for a large series of patients studied at surgery prior to cardiopulmonary bypass, and receiving nitroglycerin by intravenous infusion. Findings are in line with those previously published for smaller series of patients studied by ourselves and others at cardiac catheterisation, and receiving sublingual or intravenous nitrate.[9][12][14][16][31] The predominant effect of nitrate was a substantial (63%) reduction in aortic pressure augmentation (a measure of wave reflection from peripheral vessels), with no apparent effect on the primary aortic pressure wave (a measure of ascending aortic characteristic impedance) [6][11][12][14][15][16]. In the present study, aortic flow was not measured during nitroglycerin infusion. For aortic characteristic impedance to have decreased with nitroglycerin, there would have had to be a corresponding increase in stroke volume, and there was no suggestion that this occurred, or was likely to occur. Previous invasive studies which measured aortic flow and characteristic impedance or apparent phase velocity showed no or minimal change with nitrate, while all showed reduction in wave reflection.[9][10][11][12][14][15][31] The 20% reduction in aorta-radial delay did signify decrease in pulse wave velocity in the upper limb, but this was associated with a similar (20%) reduction in mean arterial pressure (and may be a largely passive effect).[31]. Results presented here for nitrates are also in line with those published for noninvasive, acute and chronic studies in conscious subjects and in patients with arterial hypertension which also showed predominant effect in reduction of wave reflection as the explanation for reduction in calculated aortic systolic and pulse pressure. [6][16][21][24] Such studies also show that the effect on wave reflection (explicable by arterial dilation) can be achieved at far smaller doses than required for venous and arterial dilation with consequent reduction in mean and diastolic pressure.[24] In this study a relatively high dose of nitroglycerin was administered, sufficient to cause venous and arteriolar dilation, as well as arterial.[24]

Data discussed above, and that presented here can be explained and have been explained on the basis of dilation of peripheral muscular arteries. Such dilation in muscular arteries has been confirmed and has been shown associated with improved distensibility and/or compliance of these arteries.[16][23][32][33] Such widespread change in peripheral muscular arteries of the trunk and lower limbs readily explains decrease in wave reflection from the more peripheral arteries with such wave reflection being "trapped" in peripheral vessels and so unable to return to the heart and boost systolic and pulse pressure.[6][14][34]

These data provide an incentive and a challenge. The incentive is for pharmaceutical companies to develop new drugs which have a similar effect to nitroglycerin, and which can reduce aortic pulse pressure and systolic pressure with minimal effect on mean and diastolic pressure but which do not have the other problems of nitrates - including poor GIT absorption and tolerance.[24] The challenge is to those who through exclusive consideration of Windkessel models, concentrate on change in large artery stiffness and thus overlook or dismiss wave reflection in reduction of aortic systolic pressure and left ventricular load.
Despite the reality of wave travel and reflection, so apparent in the data presented here, many investigators still use a Windkessel model of the arterial system [35] (in which wave reflection cannot exist) to explain disease and drug effects on arterial stiffness. Input impedance is the long acknowledged full description of hydraulic left ventricular load presented to the left ventricle by the vascular tree. [6][29][36][37]. This can be interpreted to show peripheral resistance (a measure of predominantly of arteriolar properties), characteristic impedance (a measure of proximal aortic stiffness) and wave reflection (to which all arterial properties contribute).

This study describes the effects of nitrates on arterial stiffness and left ventricular load. Other vasodilator drugs appear to have similar, but usually less potent effects on wave reflection and left ventricular load.[13][16][22][38]. For these, effects on wave reflection appear to be dominant, and explicable on the basis of drug action on peripheral muscular rather than on central elastic arteries.[6][8][16][38]. Indeed, it is difficult to conceive how any vasodilator drug could have any effect on the disorganised and degenerate proximal aorta in older persons with isolated systolic hypertension.[39][40]. In this study as in others [14,41] there was no evidence of any effect on aortic characteristic impedance with nitroglycerine. The present study takes a new look at an old drug, and shows substantial benefit which is attributable to change in properties of muscular conduit arteries. Benefits of nitrate can exceed those of many newer drugs in the management of diseases such as angina, heart failure, and even hypertension [21]. Such benefits can be explained in large part from analysis of the pulse waveform as practised by the father of cardiology, and the founder of Heart, Sir James Mackenzie [42].

DISCLOSURE
Michael O'Rourke is a Director of Atcor Medical, manufacturer of systems for pulse waveform analysis.

Financial support provided by the Department of Anesthiology, Wake Forest University School of Medicine, Winston-Salem, NC, USA and St. Vincent's Clinic Foundation, St. Vincent's Clinic, Sydney, Australia.

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its licensees, to permit this article (if accepted) to be published in Heart and any other BMJPG products and to exploit all subsidiary rights, as set out in our licence (http://heart.bmjjournals.com/misc/ifora/licenceform.shtml)”
Figure Legends

Figure 1: Typical radial (above) and aortic (below) pressure waves recorded simultaneously in a 68-year-old patient. Features of the waves: P₀ = wave foot; P₁ = first peak or shoulder during early systole; P₂ = second peak or shoulder on late systole; I = incisura. From these features, PP (the pulse pressure), P₁-P₀ (amplitude of the first systolic wave), P₂-P₁ (augmentation), and ESP (pressure at end of systole-at the incisura) can be measured.

Figure 2: Superimposed AA pressure waves in a 62-year-old patient before and during NTG infusion, to show the typical effect of NTG: decreased augmentation (P₂-P₁) without a change in the amplitude of the initial wave (P₁-P₀). In this patient, there was little change in heart rate before and during NTG so that a second beat also appeared to align. C = control; T = treatment with NTG.

Figure 3: Left panel: Amplitude of P₁-P₀ in the AA before (left margin) and after NTG infusion (right margin) (N=50). Mean values are denoted by filled circles and bold lines. Right panel: Amplitude of the augmented systolic pressure wave (P₂-P₁) in the AA before (left margin) and after infusion of NTG (right margin) (N=50).
REFERENCES


Table 1. Descriptive Statistics for the Fifty Patients Studied

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>64.6 ± 11.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81.0 ± 14.7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172 ± 8.4</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>50 ± 13</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>32 ± 4.9</td>
</tr>
<tr>
<td>Core temperature (°C)</td>
<td>35.8 ± 0.7</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>38.5 ± 1.4</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>246.4 ± 94.5</td>
</tr>
<tr>
<td>History of hypertension (n)</td>
<td>47</td>
</tr>
<tr>
<td>For coronary artery bypass graft surgery (n)</td>
<td>49</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>4.3 ± 1.4</td>
</tr>
</tbody>
</table>
Table 2. Differences in Aortic and Radial Pressure Values on Insertion of the Radial Artery Cannula ["Initial, Left"] under Baseline Conditions (center) and after Nitroglycerin (right)

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>Baseline</th>
<th>Treatment with NTG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Radial</td>
<td>Aortic</td>
<td>Difference</td>
</tr>
<tr>
<td>SAP</td>
<td>153±19</td>
<td>127.7±15.0</td>
<td>114.5±16.2</td>
</tr>
<tr>
<td>DAP</td>
<td>76±12</td>
<td>61.2±8.8</td>
<td>62.3±9.0</td>
</tr>
<tr>
<td>MAP</td>
<td>101±12</td>
<td>83.8±9.8</td>
<td>84.8±10.0</td>
</tr>
<tr>
<td>PP</td>
<td>78±19</td>
<td>66.9±13.8</td>
<td>52.1±15.0</td>
</tr>
<tr>
<td>ESP</td>
<td>78.7±11.3</td>
<td>90.5±11.6</td>
<td>-11.8±4.5</td>
</tr>
</tbody>
</table>

All units are mmHg. Radial-aortic DAP and MAP differences were significant due to higher aortic than radial values in more than 50% of all readings.

Table 3. Aortic Baseline-treatment Differences ± Standard Deviation

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Treatment</th>
<th>Difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>52.1±14.9</td>
<td>37.2±11.7</td>
<td>14.9±8.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Augmentation (P2-P1) (mmHg)</td>
<td>23±11.5</td>
<td>8.4±7.5</td>
<td>14.6±9.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P1-P0 (mmHg)</td>
<td>28.7±8.9</td>
<td>28.7±9.0</td>
<td>0.0±1.4</td>
<td>NS</td>
</tr>
<tr>
<td>A-R delay (msec)</td>
<td>69.8±13.5</td>
<td>86.2±14.7</td>
<td>-16.4±8.4</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

NTG treatment reduced PP and augmentation, and increased aorto-radial (A-R) wave foot delay. It did not affect the height of the primary wave (P1-P0).
Benefit of nitroglycerin on arterial stiffness is directly due to effects on peripheral arteries

Alfredo L Pauca, Neal D Kon and Michael F O'Rourke

Heart published online March 10, 2005