The effect of nitroglycerin on forearm arterial distensibility

Harold Smulyan, M.D., Sakti Mookherjee, M.D., and Robert A. Warner, M.D.

ABSTRACT Nitroglycerin acts, in part, to reduce arterial impedance, and thus left ventricular work. The reduction in arterial impedance is largely attributable to a fall in systemic vascular resistance, but may also be due to an increased distensibility of the arterial tree. In this study, volume distensibility of forearm arteries was calculated from measurements of pulse-wave velocity before and during intravenous nitroglycerin infusion. Since a fall in blood pressure itself increases arterial distensibility, the induced blood pressure change was controlled as a variable by repeating the measurements with the subject’s forearm in a plastic cylinder and repeating the measurements at a variety of altered cylinder pressures. At every studied pressure, nitroglycerin infusion increased forearm arterial distensibility, demonstrating another way in which nitroglycerin reduces left ventricular afterload. Since the pulsatile portion of cardiac work is approximately 10% of total work, the magnitude of this nitroglycerin effect on cardiac function is probably small. 

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THE SALUTARY EFFECTS of nitroglycerin in patients with angina pectoris are due to the widespread action of the drug as a smooth muscle vasodilator. This vasodilation operates in the systemic veins to induce pooling, in the arterioles to reduce coronary and systemic vascular resistance, and in the epicardial coronary arteries where both normal segments and those affected by atherosclerosis are dilated. We reasoned that nitroglycerin might also increase the distensibility of peripheral muscular arteries. If this were true, such an action would reduce the oscillatory component of arterial impedance and translate into reduced left ventricular afterload and left ventricular work. This action would be yet another way in which nitroglycerin reduces myocardial oxygen need and relieves the symptoms of angina pectoris.

Since nitroglycerin lowers the blood pressure, and a lowered blood pressure itself is known to increase arterial distensibility, a problem arises in demonstrating an effect on arterial distensibility by nitroglycerin independent of its hypotensive effect. In the present study, we calculated arterial distensibility from measurements of pulse-wave velocity and controlled for changes in blood pressure by repeating the pulse-wave velocity measurements at a variety of transmural arterial pressures before and during administration of nitroglycerin.

Methods

Twenty male patients, 40 to 78 years old (mean 58.5 years), were studied. Each patient had significant coronary atherosclerosis, as evidenced by at least a 50% narrowing of a major epicardial artery at coronary arteriography (14 patients) or electrocardiographically proven myocardial infarction (six patients). All patients had symptomatically stable angina pectoris and were receiving individually determined doses of a variety of β-adrenergic–blocking drugs, but none was receiving calcium channel–blocking agents. Ten patients underwent pulse-wave velocity studies before and during intravenous infusions of nitroglycerin, and the remaining 10 control patients were studied before and during intravenous infusion of saline.

In each patient all nitrate therapy was discontinued at least 12 hr before the beginning of the study. In the experimental group, nitroglycerin was administered intravenously with a calibrated Harvard infusion pump. The infusate was prepared with a nitroglycerin concentration of 140 μg/ml and the infusion was started at a rate of 50 μg/min. Cuff blood pressures were measured in the left arm with an Arteriosonde device every 2 min and the infusion rate was increased every 6 min until the systolic arterial pressure had fallen at least 10 mm Hg. This rate of infusion was then maintained throughout the remainder of the study. The average time to reach the effective infusion rate was 22.5 ± 6.5 min. Mean infusion rate was 89.5 μg/min, with a range of 50 to 200 μg/min. The 10 control patients received a similar intravenous volume of normal saline for 20 min in place of nitroglycerin.

Initially, the blood pressure was measured in both arms by the standard cuff method to exclude previously undetected arterial obstruction in either arm. Pixie strain gauges, imbedded in plastic (Endevco Corporation, San Juan Capistrano, CA), were placed over the right brachial and right radial artery of each
patient and held in place with soft clastic bands. Each gauge was one arm of a Wheatstone Bridge, the balanced bridge outputs were amplified (model VR6, Electronics for Medicine), and the radial dilation waves of both models were displayed on an oscilloscope. The gauge positions were then adjusted until undistorted pulse waves were observed. These pulses were then recorded on ultraviolet sensitive paper (Honeywell Viscorder, model 1508) at a speed of 250 mm/sec. The moment of pulse arrival was arbitrarily chosen as a point on the upstroke of the brachial and radial pulse that was 10% of the maximum pulse amplitude. The time interval between these two points was measured with the use of the inscribed time lines as a reference (figure 1). This interval was measured on 8 beats and the mean of these values was designated the pulse transmission time. With the use of the distance between the strain gauges, the pulse-wave velocity between the two arterial loci was calculated. The pulse-wave velocity (PWV) was then converted to volume distensibility (VD) with a modification of the Bramwell-Hill equation:\[ VD = (3.57/PWV)^2 \]

The frequency response of the Pixie strain gauges has been studied previously and an average 5% loss of signal amplitude at frequencies up to 20 cycles/sec has been found. These gauges have also been found to be linear from zero force to gauge fracture.\[ ^2 \]

With the gauges in place, the supinated arm of each subject, with elbow and wrist extended, was placed in a large plastic cylinder. The cylinder was closed at the distal end and bound proximally to the upper arm with a soft rubber sleeve. The sleeve was encircled with a blood pressure cuff and the cuff was inflated, during pulse-wave recordings, to pressures just higher than those within the cylinder. This arrangement produced only slight compression by the inflated cuff on the upper arm, but minimized air leak from within the cylinder. The cylinder pressures were varied in 10 mm Hg increments from 0 to +50 mm Hg. Satisfactory records could not be reliably obtained at cylinder pressures higher than 50 mm Hg because of pulse distortion that probably resulted from intermittent arterial collapse. Since nitroglycerin lowered the arterial blood pressure, one set of pulse-wave velocity measurements was made during drug infusion in each patient at a negative cylinder pressure of 10 mm Hg. This served to raise the transmural pressure and to match the transmural pressure before administration of nitroglycerin. Cylinder pressures, both positive and negative, were varied with an industrial vacuum cleaner and an adjustable leak and monitored with a mercury U tube. In previous studies using this technique, a full range of negative cylinder pressures was also employed.\[ ^3 \] Pressures more negative than minus 10 mm Hg were not used in this study to shorten study duration and minimize the discomfort of the patient resulting from maintaining a constant arm position within the cylinder for long periods of time. Since the relationship between volume distensibility and transmural arterial pressures is curvilinear (see below), the differences between volume distensibility before and during infusion of nitroglycerin should be small at negative cylinder (high transmural) pressures.

Altered cylinder pressures were maintained for 30 to 60 sec before pulse waves were recorded and ambient pressures were reestablished for several minutes between runs. At the conclusion of each study, the gauges were removed and a strip of adherent paper tape was placed over the forearm running between the two gauge positions. The location of the skin indentations from the metal gauge extension was marked on the tape and the tape was removed. This strip was then placed on a flat surface and the distance between the marks was measured.

Blood pressure was measured with the Arteriosonde device in the opposite arm during the recording of arterial pulses at each cylinder pressure. The transmural arterial pressure was calculated for each run by adding or subtracting the cylinder pressure from the mean arterial pressure (mean arterial pressure = diastolic pressure + pulse pressure/3). Plots were then constructed for pulse-wave velocity and calculated volume distensibility vs transmural pressure for each patient before and during infusion. The relationship between transmural pressure and volume distensibility was curvilinear (figure 2), but that between trans-

![FIGURE 1](image1)

**FIGURE 1.** Technique for pulse-wave velocity measurement. The brachial and radial artery pulses are exact tracings from the original record. Pulse arrival time is a point on the upstroke that is 10% of the pulse amplitude. The pulse transmission time is the interval between brachial and radial arrival times. Paper speed is calibrated, but time lines are omitted from the reproduction. See text for details.

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![FIGURE 2](image2)

**FIGURE 2.** Plot of calculated volume distensibility vs transmural arterial pressure in a single patient before saline infusion.
mural pressure vs log volume distensibility over the range of transmural pressures in this study was linear (figures 3 and 4). Linear regression was calculated for each plot with the method of least squares, thus permitting the calculation of pulse-wave velocity, log volume distensibility, and volume distensibility at any given pressure for each patient. The entire technic for measuring pulse-wave velocity has been described in greater detail previously.\(^2\)\(^3\)

The pulse-wave velocity has been shown to predict satisfactorily the arterial distensibility measured by independent direct methods.\(^4\)\(^-\)\(^7\) However, calculated volume distensibility cannot distinguish between the active or static properties of arterial wall behavior. Use of the cylinder to provide variations in transmural arterial pressure requires the assumption that cylinder pressures are transmitted faithfully to the arterial wall. Previous studies testing this assumption have shown that the transmission of increased or decreased air pressure is satisfactory.\(^8\)\(^-\)\(^9\) Since each patient served as his own control, individual differences in blood viscosity from patient to patient should have had little effect on the results. Velocity of blood flow adds to the pulse-wave velocity, but flow velocity is small when compared with the velocity of pressure pulse travel.

Data were analyzed by use of the paired t test, and Student’s t test for group data.

The study was approved by the human experimentation committee of the medical center, and each patient gave informed consent.

Results

The control and experimental groups were similar with regard to age, blood pressure, heart rate, and the prevalence of diabetes and myocardial infarction. Fourteen coronary arteriograms, seven in each group, were reviewed and the average number of coronary arteries significantly affected by atherosclerosis were also similar in both groups. No significant differences were found between the two groups in any of the baseline volume distensibility measurements or calculated values.

The relationship of transmural pressure to volume distensibility over the range of transmural pressures used in this study was curvilinear. This is illustrated by the results from a single patient in figure 2. When log volume distensibility was plotted against transmural pressure, however, the relationship became linear (figure 3), and could be represented by a regression line by the method of least squares. The equation for such a linear relationship could then be applied to calculate the volume distensibility for any selected transmural pressure within the experimental range.

Figure 4 illustrates the similarity and reproducibility of the log volume distensibility vs transmural pressure relationships for the same patient before and during control infusion of saline. For the entire control group, there was no significant change in volume distensibility at any transmural pressure from 40 through 100 mm Hg during the infusion of saline. The slopes of the

![Graph](http://circ.ahajournals.org/doi/abs/10.1161/01.CIR.6.9.1266)

**Figure 3.** Plot of calculated log volume distensibility vs transmural arterial pressure in a single patient before saline infusion.

**Figure 4.** Plot of calculated log volume distensibility vs transmural arterial pressure in a single patient before and after saline infusion.
regression lines relating these two variables were also unchanged.

The infusion of saline also produced no significant change in heart rate or systolic, diastolic, or mean blood pressure (figure 5). Figure 5 also illustrates that nitroglycerin infusion significantly reduced systolic and mean blood pressure but had no effect on diastolic blood pressure or heart rate. Tables 1A and 1B display the volume distensibility and pulse-wave velocity data from the control and nitroglycerin groups for representative transmural pressures of 40, 60, and 90 mm Hg. At these illustrative transmural pressures, nitroglycerin significantly increased volume distensibility when patients served as their own controls or when the response to nitroglycerin was compared with that to saline. The effect of nitroglycerin on volume distensibility over the full range of transmural pressures can be seen in figure 6, and the effects of nitroglycerin on the log volume distensibility vs transmural pressure relationship are illustrated in figure 7. The slope of the regression line before and after nitroglycerin was not significantly different.

### TABLE 1A
**Effect of nitroglycerin vs saline on pulse-wave velocity**

<table>
<thead>
<tr>
<th>TMP (mm Hg)</th>
<th>PWV (m/sec)</th>
<th>p value (paired t test)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Saline</td>
</tr>
<tr>
<td>40</td>
<td>4.19 ± 0.41</td>
<td>4.14 ± 0.33</td>
</tr>
<tr>
<td>60</td>
<td>6.57 ± 0.53</td>
<td>6.34 ± 0.40</td>
</tr>
<tr>
<td>90</td>
<td>10.14 ± 0.73</td>
<td>9.64 ± 0.55</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>Nitroglycerin</td>
</tr>
<tr>
<td>40</td>
<td>4.06 ± 0.53</td>
<td>2.74 ± 0.24</td>
</tr>
<tr>
<td>60</td>
<td>6.35 ± 0.42</td>
<td>4.97 ± 0.33</td>
</tr>
<tr>
<td>90</td>
<td>9.81 ± 0.52</td>
<td>8.32 ± 0.54</td>
</tr>
</tbody>
</table>

Values are mean ± SE.

PWV = pulse-wave velocity; TMP = transmural pressure.

### Discussion

The difficulty in understanding the mechanism of nitroglycerin action in patients with angina pectoris arises from the multiplicity of demonstrated pharmacologic effects and the lack of information regarding the precise role played by each. Nitroglycerin produces both its peripheral vascular and secondary cardiac effects by relaxing smooth muscle through the activation of guanylate cyclase and the resultant increase in the levels of cyclic guanosine monophosphate. This relaxation operates in the smooth muscle of arterioles, venules, and systemic veins and in the epicardial coronary arteries. The mid-sized systemic arteries are muscular in nature and thus susceptible to nitroglycerin action, but there has been little study of the effects of nitroglycerin on arterial distensibility. Si-
mon et al., using a pulsed Doppler technique with a double transducer probe, have shown an increase in the diameter of the brachial artery during the infusion of nitroglycerin. These authors also used the diastolic portion of the brachial arterial pressure curve and the systemic vascular resistance, calculated from blood pressure and cardiac output measurements, to demonstrate an increase in arterial compliance. Although in agreement with the results of the present study, some of the increased arterial compliance demonstrated by Simon et al. could have been due to the fall in blood pressure itself. In that study, nitroglycerin was administered in a lower dose, which reduced the systolic but not the mean or diastolic pressure. In the present investigation, both systolic and mean blood pressures were lowered, with no significant change in heart rate. This probably was due to the concomitant use of β-adrenergic-blocking agents in our patients. Nitroglycerin, however, increased forearm arterial distensibility at every studied transmural pressure.

Arterial stiffness may be characterized by two quantities — volume distensibility and the modulus of elasticity (Young’s modulus). Volume distensibility measures the percentage change in volume of an arterial segment resulting from a unit change in distending pressure and is therefore independent of arterial diameter. The elastic modulus, on the other hand, is a measure of the stress-strain relationship for the blood vessel wall and quantifies its behavior when it is de-

formed. Elastic modulus depends both on volume distensibility and vessel geometry — specifically, the ratio of wall thickness to diameter. However, these measurements are difficult to obtain in vivo. Since volume distensibility can be calculated from the noninvasive measurements of pulse-wave velocity without explicit knowledge of arterial geometry, volume distensibility has been frequently used to assess arterial stiffness in noninvasive studies in vivo.

In the present study, the infusion of nitroglycerin reduced the mean arterial blood pressure from 90 to 85 mm Hg. Without nitroglycerin, this reduction in blood pressure alone would induce an increase in volume distensibility of 15%. The same reduction in blood pressure induced by nitroglycerin increased volume distensibility by 69%. It is well understood that distensible arteries present less opposition to left ventricular ejection than do stiff ones. However, the changes in volume distensibility demonstrated here are difficult to relate quantitatively to the reduction in left ventricular work.

Total left ventricular work can be divided into two major parts. The first is that portion of cardiac effort that drives the blood steadily through the peripheral resistance and is usually calculated as the product of mean blood pressure and mean flow. The second is the ventricular work that drives no blood, but is spent in making the system pulsatile. Under basal conditions this pulsatile component is approximately 10% of the total ventricular work and is determined largely by the distensibility of the arterial tree. Measurement of arterial impedance offers a means for assessing that portion of the total opposition to left ventricular ejection that is due to the stiffness of the arterial tree. Total arterial impedance is frequency dependent. At zero frequency, the impedance is due to “steady flow” and is equal to the systemic vascular resistance. Correspondingly smaller is the input impedance from pulsations, which represents the opposition to left ventricular ejection at higher frequencies. This input impedance is determined by several factors, including reflected waves, pulse-wave velocity, and arterial distensibility. Averaging the higher frequency impedances yields the “characteristic impedance,” which is determined largely by arterial distensibility. Pulse-wave velocity is directly related to characteristic arterial impedance when the latter is expressed in terms of linear flow velocity (dyne·sec·cm⁻³) rather than in terms of the more familiar volume flow (dyne·sec·cm⁻³). Although our measurements of pulse-wave velocity can be used to calculate characteristic impedance of the forearm arteries, the aortic input im-

**FIGURE 7.** Plot of calculated log volume distensibility vs transmural arterial pressure before and during nitroglycerin infusion for the entire group.
pedance and systemic vascular resistance were not measured.

Calculation of characteristic impedances of the brachial artery from our pulse-wave velocity data showed that a reduction in mean blood pressure from 90 to 85 mm Hg without nitroglycerin would reduce characteristic impedance by 5.8%, while the same reduction due to nitroglycerin lowered characteristic impedance by 21%. Larger doses of nitroglycerin might, of course, have a larger effect. Since the influence of the characteristic impedance of the brachial artery on the aortic input impedance is unknown in these patients and since the portion of the arterial tree that behaves like the forearm arteries is also unknown, any further attempt to quantify the reduction in left ventricular work by this mechanism would be largely speculative.

The only other agent that is similar to nitroglycerin whose effects on arterial stiffness have been studied is nitroprusside, and these results have been conflicting. Pepine et al. 17 reported a reduction in characteristic aortic impedance during the infusion of nitroprusside in patients with cardiomyopathy and congestive heart failure. This reduction was sustained in three patients even when their blood pressures were restored to baseline levels by phenylephrine. These results could not be confirmed in the aorta by Yin et al.,18 who did, however, find a reduction of characteristic impedance in the pulmonary artery. In patients with angina pectoris but no heart failure, Gundel et al. 19 also reported no significant change in aortic input impedance during the infusion of nitroprusside. There are obvious differences between these studies and the present one. Nitroglycerin and nitroprusside may differ in their effects on arterial smooth muscle. Measurements of aortic input impedance may be more sensitive to changes in the proximal aortic wall, where there is less smooth muscle, than to changes in the more muscular peripheral arteries. Finally, there have been no studies of effects of nitroglycerin on aortic input impedance or of nitroprusside on the distensibility of peripheral arteries.

The reduced arterial stiffness demonstrated in this study resulted from brief infusions of nitroglycerin and may not be applicable to longer acting forms of nitrate therapy. However brief, any increase in arterial distensibility should reduce the pulsatile component of arterial impedance and thus reduce left ventricular work. Such an effect could conceivably occur with or even without a concomitant reduction in systemic vascular resistance. It remains uncertain, however, whether the changes in arterial distensibility are of sufficient magnitude to play a significant role in the relief of angina pectoris or in improvement in patients with congestive heart failure.

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References
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