Left Ventricular Volume Changes After Amyl Nitrite and Nitroglycerin in Man as Measured by Ultrasound

By Gary W. Burggraf, M.D., and John O. Parker, M.D.

SUMMARY
The therapeutic effect of nitrates in myocardial ischemia is considered to be due in part to a reduction of left ventricular volume but measurement of this parameter in man has been difficult. The technique of echocardiography was used to measure changes in left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV) after administration of amyl nitrite (AN) and nitroglycerin (NG) in 20 normal subjects. Control LVEDV was 131 ± 8 ml (mean ± sem) and LVESV 30 ± 2 ml. After AN, LVEDV fell 18 ± 2% (P < 0.001) and LVESV by 57 ± 3% (P < 0.001) in 15 sec to 1 min. Heart rate (HR) rose from 68 ± 3 to 108 ± 4 beats/min at 1 min and blood pressure (BP) fell from 119/69 ± 3/2 to 99/47 ± 4/3 mm Hg. Following NG, LVEDV fell 11 ± 2% (P < 0.001) and LVESV 21 ± 3% (P < 0.001) within 2–5 min. HR rose from 65 ± 2 to 72 ± 3 beats/min and BP fell from 111/67 ± 3/2 to 102/70 ± 5/2 mm Hg at 3 min. Cardiac output increased from 6.9 ± 0.3 to 11 ± 0.9 L/min 30 sec after AN while no significant change occurred with NG. Stroke volume decreased from 101 ± 6 to 93 ± 5 ml/beat 5 min after NG while no significant change occurred after AN. This study has shown that both AN and NG produce significant decreases in LVEDV and LVESV which may contribute to their beneficial effects in myocardial ischemia.

Additional Indexing Words: Angina pectoris Myocardial oxygen consumption Echocardiography

Although the primary pharmacologic activity of the nitrates is to relax smooth muscle, their effects on the intact mammalian circulation are complex because of multiple sites of action and the secondary responses they evoke. Previous investigations concerning the mechanism of relief of myocardial ischemia by nitroglycerin have suggested two principal modes of action: redistribution of coronary blood flow and a decrease in myocardial oxygen requirements through changes in preload and afterload. It is well established that a decrease in left ventricular end-diastolic pressure occurs after administration of nitroglycerin. This implies a reduction in left ventricular end-diastolic volume assuming no change in the pressure-volume characteristics of the ventricle. Similarly a reduction in left ventricular end-diastolic pressure occurs after administration of amyl nitrite. Bousvaros, Campbell and McGregor using postero-anterior chest films demonstrated a 3.1% decrease in transverse cardiac diameter after administration of nitroglycerin to normal subjects. However, the only data relating particularly to changes in left ventricular dimensions after nitrate exposure in man is that of Williams, Glick and Braunwald where the distance between radiopaque epicardial markers implanted at the time of heart surgery was utilized.

There is now adequate documentation of the validity of the echocardiographic technique for estimation of left ventricular volume. Accordingly we have applied this method to determine left ventricular volume after administration of two nitrate drugs, amyl nitrite and nitroglycerin, to 23 normal subjects in an attempt to further elucidate their mechanism of action.

Methods
The subjects were 23 normal medical students or hospital staff, 19 males and four females, ages ranging from 21 to 27 years (average 24 years). In 17 subjects the response to both nitroglycerin and amyl nitrite was determined; in three, only the effects of nitroglycerin...
were analyzed, and in another three only the response to amyl nitrite was examined. Thus the effects of each drug were determined in 20 subjects. Because the determinations of left ventricular dimensions were made intermittently for a period of approximately 40 min it was of utmost importance that only subjects with distinct and readily obtainable left ventricular dimensions be studied. Fifteen other subjects were examined but their records were not included for analysis as they were not considered technically satisfactory. The most frequent reason for rejecting a study was obscuration of the echogram by the effects of hyperventilation induced by the nitrites. In others it was apparent on inspection of the records that the septal or posterior wall endocardial echoes were not consistently of adequate quality for determination of left ventricular dimensions.

Echocardiograms were recorded with an ultrasonoscope* and a strip chart recorder.† Blood pressure was obtained by sphygmomanometry and heart rate from an electrocardiogram recorded simultaneously with the echocardiogram. Four sets of control measurements were made, each separated by at least 30 seconds. During continuous recording of the echocardiogram and electrocardiogram the subjects inhaled vapour from one amyl nitrite ampoule held under the nose for 30 seconds while instructions were given to the subjects to not hyperventilate during exposure to amyl nitrite as this made determination of left ventricular diameters impossible. The recorder ran continuously for three minutes and intermittently at set intervals up to 10 minutes. After a

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*Ecoline-20, Smith Kline and French Instruments, Inc.
†Electronics for Medicine DR12 recorder.

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**Figure 1**

Echocardiograms before and after amyl nitrite and nitroglycerin in the same subject. Abbreviations: AN = amyl nitrite, LVEDD = left ventricular end-diastolic dimension, LVESD = left ventricular end-systolic dimension, MV = mitral valve, NG = nitroglycerin, PWE = posterior wall endocardium, SE = septal endocardium.
15 minute recovery period four control determinations were obtained and 0.5 mg of nitroglycerin was administered sublingually, similar recordings being made for 15 minutes.

The technique for obtaining left ventricular dimensions was that described by Feigenbaum. With the subject lying supine in 15° right anterior oblique, the transducer position giving the optimal mitral valve echogram was determined. The transducer was then angled slightly laterally and inferiorly to obtain clear left ventricular septal and posterior wall endocardial echoes. In this position the mitral echogram was discontinuous and the posterior leaflet was usually better visualized. Using the echoes obtained from the mitral apparatus as landmarks, a reproducible left ventricular dimension could be obtained. Left ventricular end-systolic diameter (LVESD) was measured at the point of least separation of the septal and posterior wall endocardial echoes and left ventricular end-diastolic diameter (LVESDD) at their point of maximum separation. Although LVESDD has been measured at the time of the peak of the R wave on the electrocardiogram, in most studies the correlation of echocardiographically determined left ventricular volumes with left ventriculography has been equally acceptable when LVESDD was measured as maximal separation of septal and posterior wall endocardial echoes. Each dimension was averaged for five to ten consecutive cardiac cycles to eliminate respiratory variation.

Left ventricular end-systolic volume (LVESV) and end-diastolic volume (LVEDV) were determined by the cube of their respective diameters multiplied by 1.047 as described by Popp and Harrison.

Stroke volume (SV) and cardiac output (CO) were derived as follows:

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SV = LVEDV - LVESV
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\[
CO = HR \times SV / 1000
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Where SV, LVEDV and LVESV are in ml, HR is heart rate in beats/min and CO is in L/min.

Statistical comparisons were made using the Student's paired t-test.

**Results**

Representative echocardiograms showing left ventricular dimensions during the control period, after amyl nitrite and following nitroglycerin are seen in figure 1. To assess the reproducibility of LVESDD and LVESV four control recordings were made for each of the 20 subjects prior to administration of both drugs. Therefore 80 sets of left ventricular dimensions were determined before giving each drug and each set was an average of five to ten cardiac cycles. These data prior to amyl nitrite administration are summarized in table 1. The mean control LVEDD for the group before amyl nitrite was 5.0 cm and for LVESD 3.0 cm.

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Abbreviations: LVESD = left ventricular end-diastolic dimension; LVESV = left ventricular end-systolic dimension.

*All values in cm.
The maximum variation among the four control determinations for both dimensions prior to amyl nitrite for any individual subject was 4 mm. The mean intra-individual range of variation of LVEDD for the 20 subjects was 1.5 ± 0.2 mm (mean ± SEM) and for LVESD was 2.0 ± 0.2 mm. Although there was variation in the four control values of LVESD and LVEDD for most individuals, when the group means were calculated they were identical for each of the control determinations. When the dimensions were converted to left ventricular volumes the LVEDV for the entire group before amyl nitrite was 131 ± 8 ml and for LVESV was 30 ± 2 ml. The maximum intra-individual variations for LVEDV and LVESV among the four control determinations were 28 ml and 13 ml with mean values of 11 ± 1 ml and 6 ± 0.6 ml, respectively. When the four control determinations of LVESV and LVEDV were averaged for each subject the mean variation from this value for the entire group was ±9% and ±4%, respectively. The same results were obtained when this analysis was applied to the control determinations before nitroglycerin administration.

Table 2 illustrates the individual values for LVESD and LVEDD during the control periods and at the time of maximum change after nitrite administration. Each control value represents the mean of four separate determinations. Figure 2 shows the changes in left ventricular volume after each drug expressed as the average of the maximal

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<td>0.1</td>
<td>3.4</td>
<td>5.2</td>
<td>3.2</td>
</tr>
<tr>
<td>22</td>
<td>3.2</td>
<td>5.6</td>
<td>2.4</td>
<td>5.2</td>
<td>0.8</td>
<td>0.4</td>
<td>3.5</td>
<td>5.7</td>
<td>3.3</td>
</tr>
<tr>
<td>23</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2.6</td>
<td>4.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Group mean</td>
<td>3.0</td>
<td>5.0</td>
<td>2.2</td>
<td>4.6</td>
<td>0.8</td>
<td>0.4</td>
<td>3.1</td>
<td>5.0</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Abbreviations: AN = amyl nitrite; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; NC = no change; NG = nitroglycerin.

*All values in cm.

Figure 2

Mean maximum fall in left ventricular volumes after amyl nitrite (AN) and nitroglycerin (NG) in 20 subjects. Abbreviations as in table 3.
change seen in each subject. The average fall in LVESV after amyl nitrite was 17 ± 2 ml (57 ± 3%) with a range of 6–29 ml (29–81%). LVEDV fell by 23 ± 4 ml (18 ± 2%) with a range of 3–43 ml (2–43%). These changes occurred between 15 seconds and 1 minute after the start of amyl nitrite inhalation. After nitroglycerin the maximum decrease in volume occurred between 2 and 5 minutes. LVESV fell by 7 ± 1 ml (21 ± 3%) with a range of 0–17 ml (0–47%) and LVEDV by 16 ± 1 ml (12 ± 2%) with a range of 0–45 ml (0–28%). Although three subjects showed no response to nitroglycerin, when the paired t-test was utilized comparing the control values with the volume at maximum effect, the changes in LVESV and LVEDV after both drugs were significant (P < 0.001).

Tables 3 and 4 summarize the changes that occurred in LVEDV, LVESV, heart rate, blood pressure, stroke volume and cardiac output after amyl nitrite and nitroglycerin. These data are also graphically illustrated in figures 3–5. All values in these tables represent the mean ± SEM for 20 subjects. As the data in tables 3 and 4 and figures 3–5 are plotted at specified time intervals after drug administration the changes are not as striking as in figure 2 which represents the average of the maximal response in each subject. However the volume changes were still significant as indicated by the P values in the tables. Table 3 and figure 3 demonstrate that the tachycardia and hypotension that occur with amyl nitrite exposure are paralleled by decreases in LVEDV and LVESV. However, the heart rate and blood pressure returned to control values by 2 minutes while the volumes did not completely return to control until 5 minutes. Figure 5 shows that cardiac output increased from 6.9 ± 0.5 to 11.0 ± 0.9 L/min 30 seconds after amyl nitrite and returned to normal in 2 minutes. Stroke volume showed no significant change. The tachycardia and hypotension following nitroglycerin (table 4, fig. 4) paralleled the decreases in LVEDV and LVESV but were less marked than after amyl nitrite.

### Table 3

**Response to Amyl Nitrite—20 Subjects**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Control</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>10</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDV (ml)</td>
<td>131 ± 8</td>
<td>118 ± 9</td>
<td>122 ± 9</td>
<td>127 ± 8</td>
<td>125 ± 9</td>
<td>126 ± 9</td>
<td>130 ± 9</td>
<td>133 ± 9</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>30 ± 2</td>
<td>16 ± 2</td>
<td>18 ± 2</td>
<td>25 ± 2</td>
<td>25 ± 2</td>
<td>27 ± 2</td>
<td>30 ± 3</td>
<td>30 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>68 ± 3</td>
<td>108 ± 4</td>
<td>95 ± 4</td>
<td>70 ± 4</td>
<td>70 ± 3</td>
<td>67 ± 3</td>
<td>64 ± 3</td>
<td>64 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td>119 ± 3</td>
<td>99 ± 4</td>
<td>119 ± 4</td>
<td>121 ± 3</td>
<td>118 ± 3</td>
<td>116 ± 3</td>
<td>116 ± 3</td>
<td>113 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>99 ± 6</td>
<td>101 ± 7</td>
<td>104 ± 7</td>
<td>102 ± 6</td>
<td>97 ± 6</td>
<td>99 ± 7</td>
<td>100 ± 7</td>
<td>103 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>6.9 ± 0.5</td>
<td>11 ± 0.9</td>
<td>10 ± 0.7</td>
<td>7 ± 0.5</td>
<td>6.9 ± 0.5</td>
<td>6.7 ± 0.5</td>
<td>6.5 ± 0.5</td>
<td>6.5 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: BP = brachial arterial pressure; CO = cardiac output; HR = heart rate; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; SV = stroke volume.

*All values are mean ± SEM.

†P values determined at maximum change from control.

### Table 4

**Response to Nitroglycerin—20 Subjects**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Control</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDV (ml)</td>
<td>134 ± 8</td>
<td>135 ± 8</td>
<td>129 ± 7</td>
<td>127 ± 7</td>
<td>127 ± 8</td>
<td>122 ± 8</td>
<td>127 ± 8</td>
<td>131 ± 9</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>33 ± 3</td>
<td>34 ± 3</td>
<td>32 ± 3</td>
<td>31 ± 3</td>
<td>31 ± 3</td>
<td>29 ± 3</td>
<td>31 ± 3</td>
<td>32 ± 3</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>65 ± 2</td>
<td>67 ± 3</td>
<td>71 ± 3</td>
<td>72 ± 3</td>
<td>71 ± 3</td>
<td>71 ± 3</td>
<td>67 ± 2</td>
<td>66 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td>111 ± 3</td>
<td>111 ± 3</td>
<td>104 ± 5</td>
<td>102 ± 4</td>
<td>107 ± 2</td>
<td>103 ± 5</td>
<td>108 ± 2</td>
<td>107 ± 3</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>101 ± 6</td>
<td>101 ± 6</td>
<td>97 ± 5</td>
<td>96 ± 5</td>
<td>96 ± 5</td>
<td>93 ± 5</td>
<td>97 ± 6</td>
<td>101 ± 6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>6.5 ± 0.3</td>
<td>6.6 ± 0.4</td>
<td>6.9 ± 0.4</td>
<td>6.9 ± 0.3</td>
<td>6.8 ± 0.4</td>
<td>6.5 ± 0.3</td>
<td>6.5 ± 0.3</td>
<td>6.6 ± 0.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: Same as Table 2.

*All values are mean ± SEM.

†P values determined at maximum change from control.
**LV VOLUME CHANGES AFTER NITRITES**

**RESPONSE to AMYL NITRITE** (20 Subjects)

- **LVEDV** (ml)
  - Control: 120
  - 0.5: 130
  - 1: 135
  - 2: 135
  - 3: 135
  - 4: 135
  - 5: 135
  - 10: 135

- **LVESV** (ml)
  - Control: 20
  - 0.5: 30
  - 1: 30
  - 2: 30
  - 3: 30
  - 4: 30
  - 5: 30
  - 10: 30

- **HR** (beats/min)
  - Control: 80
  - 0.5: 120
  - 1: 200
  - 2: 200
  - 3: 200
  - 4: 200
  - 5: 200
  - 10: 200

- **BP** (mm Hg)
  - Control: 120
  - 0.5: 30
  - 1: 30
  - 2: 30
  - 3: 30
  - 4: 30
  - 5: 30
  - 10: 30

**Figure 3**
*Time course of changes in LVESV, LVEDV, HR and BP after amyl nitrite. Abbreviations as in table 3.*

**EFFECTS on STROKE VOLUME and CARDIAC OUTPUT** (20 Subjects)

- **SV** (ml)
  - Control: 100
  - 0.5: 100
  - 1: 100
  - 2: 100
  - 3: 100
  - 4: 100
  - 5: 100
  - 10: 100

- **CO** (L/min)
  - Control: 7
  - 0.5: 12
  - 1: 11
  - 2: 10
  - 3: 9
  - 4: 8
  - 5: 7
  - 10: 6

**Figure 4**
*Time course of changes in LVESV, LVEDV, HR and BP after nitroglycerin. Abbreviations as in table 4.*

**Figure 5**
*Time course of changes in cardiac output and stroke volume after amyl nitrite and nitroglycerin. Abbreviations: SV = stroke volume, CO = cardiac output.*
nitrite. In contrast, however, the cardiac output did not change significantly while the stroke volume decreased from 101 ± 6 to 93 ± 5 ml/beat.

**Discussion**

This study has demonstrated a decrease in left ventricular end-systolic and end-diastolic volumes after amyl nitrate and nitroglycerin administration in normal human subjects. In 1925 Beck and Holman using chest roentgenograms showed a decrease in the transverse diameter of the cardiac silhouette of the dog following amyl nitrite. More recently decreases in left ventricular dimensions after amyl nitrite and nitroglycerin have been demonstrated in the dog using the techniques of implanted ultrasound transducers and left ventriculography. Using chest roentgenograms in humans the transverse cardiac diameter has been shown to decrease after nitroglycerin by 3-9% in the sitting position. In another study total cardiac volume as estimated from antero-posterior chest films decreased 9% when supine and 13% when standing. Williams, Glick and Braunwald were able to demonstrate decreases in left ventricular diameter in humans after nitroglycerin by following the changes in distance between radiopaque clips attached to the left ventricular epicardium. This method did not lend itself to actual measurement of left ventricular volume but did indicate a qualitative change.

The technique of echocardiography used in this study has some advantages over previous radiological studies in humans as it can isolate the left ventricular chamber and it provides an estimate of volume changes that the epicardial marker technique cannot accomplish. It also is superior to angiographic methods as it is noninvasive, can be repeated and is not associated with depression of left ventricular performance.

The decrease in left ventricular volume after nitroglycerin may be due to reduced venous return, increased heart rate, decreased afterload or increased myocardial contractility. The changes in heart rate and blood pressure in our subjects were small: 7 beats/min and 9 mm Hg systolic, respectively. In the study of Williams and coworkers similar changes occurred in left ventricular dimensions when heart rate was allowed to vary or when maintained constant by electrical pacing. Vatner et al., using implanted ultrasonic transducers in dogs, showed that when heart rate was maintained constant by pacing, sublingual nitroglycerin was followed by smaller decreases in left ventricular volume than when heart rate varied freely. However, the average increase in heart rate in their dogs after nitroglycerin was 32 beats/min which is considerably greater than the change in our normal human subjects. In patients given nitroglycerin in a study by Campion and associates the resulting decrease in left ventricular end-diastolic pressure which presumably reflects left ventricular volume, was not related to the extent of the accompanying changes in heart rate and blood pressure. Thus, although in our study heart rate and afterload were not controlled, their changes would not appear to be adequate to explain the reduction in left ventricular volume with nitroglycerin.

On the other hand the substantial changes in heart rate and blood pressure after amyl nitrite administration may explain the much greater decreases in left ventricular volume which it produced. Studies by Mason and Braunwald have demonstrated a decrease in venous tone in the human forearm after nitroglycerin lasting up to 30 minutes while amyl nitrite resulted in an abrupt increase in tone of only two minutes duration. Thus, the left ventricular volume changes after amyl nitrite may be related mainly to tachycardia and decreased afterload and not to venous pooling. The fact that left ventricular volumes returned to control values more slowly than heart rate and blood pressure, suggests that some other factor may be influencing the response. Although speculative, this factor may be an increase in myocardial contractility due to catecholamine release. The observed marked increase in cardiac output after amyl nitrate and lack of change after nitroglycerin is consistent with the proposed different effects on the venous reservoir.

One of the major determinants of myocardial oxygen consumption is the wall tension generated during ventricular systole. For a given systolic pressure the tension developed by the myocardium is directly related to the radius of the chamber and inversely to its wall thickness. The reduction in left ventricular volume demonstrated in this investigation after amyl nitrite and nitroglycerin administration would then have a salutary effect on the balance of myocardial oxygen requirements and supply. The decrease in systolic blood pressure (i.e. afterload) observed in this study would also diminish myocardial oxygen consumption. Stroke volume, a minor determinant of myocardial oxygen consumption, was also diminished by nitroglycerin. The beneficial effects of the larger reduction in left
LV VOLUME CHANGES AFTER NITRITES

ventricular volume after amyl nitrite than with nitroglycerin would be countered by the increase in oxygen requirements due to the marked tachycardia and probable increase in myocardial contractility.

Finally this study illustrates the feasibility of using echocardiography to noninvasively investigate volume relationships of the left ventricle over a prolonged period after pharmacological and physiological interventions.

References

Left Ventricular Volume Changes After Amyl Nitrite and Nitroglycerin in Man as Measured by Ultrasound

GARY W. BURGGRAF and JOHN O. PARKER

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