The Effects of the Beta-blocker Atenolol and Nitroglycerin on Left Ventricular Function and Geometry in Man

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SUMMARY

Left ventricular (LV) systolic and diastolic function was studied in 12 subjects with and 12 without coronary artery disease (CAD). Six in each group received the β-blocking agent atenolol, 5 mg i.v., and six received nitroglycerin (NTG), 0.8 mg sublingually. LV cineangiograms were performed in the 40° right anterior oblique projection before and after the drug. Global systolic function was measured as ejection fraction and mean normalized systolic ejection rate. Regional function was determined as mean shortening velocity and percentage shortening of basal, middle and apical transverse diameters. Diastolic function was quantitated throughout diastole in terms of logarithmic pressure-volume (log P-V) and logarithmic midwall circumferential stress-midwall circumference (log σ-C) relations. Changes in slope k and α of the log P-V and log σ-C curves, respectively, were regarded as changes in passive elastic stiffness. LV geometry was analyzed in terms of 1) eccentricity, 2) minor/major axis ratios, 3) shape index and 4) the linear relation between minor/major axis ratio and diastolic volume, with slope q and intercept r. Results varied with the quantity measured and the presence or absence of CAD, but atenolol tended to reduce and NTG to increase parameters of both global and regional systolic function. Velocity indices appeared to be more sensitive than nonvelocity indices in detecting alterations induced by both drugs. With respect to diastolic function, results also varied with the parameter measured and the presence or absence of CAD, but atenolol tended to reduce and NTG to increase passive elastic stiffness of the myocardium. Log σ-C relations detected NTG-induced changes when log P-V relations did not. None of the geometric parameters reflected a consistent drug-induced alteration in geometry except r. The data suggest that geometrical influences in drugs may mask alterations in LV diastolic properties and that analysis of log σ-C relations may be more appropriate than log P-V relations for detection of these drug-induced changes.

BOTH β BLOCKERS and nitroglycerin (NTG) are widely used in the treatment of patients with coronary artery disease. The systemic hemodynamic effects of these agents are well established, but their actions on systolic and diastolic left ventricular (LV) function are controversial. We have observed the effects of β blockade and NTG administration on ventricular function in normal subjects and coronary patients. Since part of the controversy surrounding responses to β blockade may be related to the use of nonselective drugs, we chose to study atenolol, a predominantly cardioselective agent.1

Patients and Methods

Twenty-four male patients underwent diagnostic cardiac catheterization for evaluation of suspected or known coronary artery disease. All had chest pain, either typical or atypical for angina pectoris.

Of these, 12 subjects (mean age 45.7 years, range 30–57 years) had normal coronary arteriograms and LV angiograms. The other 12 patients (mean age 47.2 years, range 33–59 years) had significant angiographic coronary lesions, defined as ≥ 50% obstruction. Five patients had three-vessel disease, four two-vessel disease and three single-vessel disease.

All 24 patients had sinus rhythm and none had mitral regurgitation as assessed by LV angiography, although one patient without coronary disease had mild mitral valve prolapse. Two patients with coronary disease had suffered a prior myocardial infarction, one inferior and the other anterior. One patient was in clinical heart failure, and none was taking digitalis or β-blocking agents at the time of study.

Catheterization was performed 1 hour after oral premedication with 10 mg diazepam. After routine right-heart catheterization, a micromanometer catheter (PC-481, Millar Instruments, Houston, Texas) was advanced into the left ventricle via a brachial arteriography. A second catheter was introduced retrogradely from the femoral artery to the ascending aorta. Mid-chest level was used as reference zero for pressure measurements. To correct for any baseline drift of the micromanometer, the pressure signal was superimposed on that obtained by the conventional system.

As a part of the catheterization protocol, half of both the normal and the coronary artery disease groups received a β blocker, atenolol, 5 mg intravenously, and the other half NTG 0.8 mg sublingually. All patients gave informed consent. Before and after drug administration a LV cineangiogram was obtained in the 40° right anterior oblique (RAO) projection at 80 frames/sec by injecting 35–40 ml of contrast material through the lumen of the LV catheter. In all patients a second angiogram was per-
formed 15 minutes later. NTG was given 5 minutes before the second angiogram. Atenolol was infused over 5 minutes, starting 5 minutes after the first angiogram. High-fidelity LV pressure was sampled synchronously with frame exposure via the tip-manometer and was displayed on the corresponding cine frame as a digital number. LV pressure and its first derivative (dP/dt) were also recorded on a strip chart at a paper speed of 250 mm/sec, along with aortic pressure, the ECG and a cine frame marker. Before moving the patient and x-ray equipment, the LV catheter was filmed during lateral displacement of the table by exactly 4 cm. The subsequently measured lateral displacement of the catheter tip on the film was compared with this 4-cm distance to derive a correction factor for x-ray magnification. After the second ventriculogram, selective coronary arteriograms were performed in multiple projections using the Sones technique.

To evaluate global and regional systolic function, projected end-diastolic and end-systolic silhouettes were traced by hand. Volumes were calculated using a modified area-length method,6 where the long axis was always defined from the apex to the aortic-mitral valve junction. End-diastolic and end-systolic volumes were normalized for body surface area.4.5 Volumes were not corrected by a regression equation. Extrasystoles and the first postextrasystolic beat were excluded from analysis. Heart rate (HR), end-diastolic pressure (EDP) and maximum dP/dt were taken from the same beat as that from which volume was obtained. Ejection fraction (EF) was determined as: (end-diastolic volume – end-systolic volume) • 100/ end-diastolic volume.6 Mean normalized systolic ejection rate (MNSER) was derived as: (end-diastolic volume – end-systolic volume)/(end-diastolic volume • ejection time).7 8 Ejection time was measured from the high-speed aortic pressure curve.

Regional systolic function was evaluated in terms of shortening velocity and percentage shortening of basal (B), middle (M) and apical (A) transverse diameters. Diameters were directly measured at 25, 50 and 75% increments of the long axes (aortic-mitral valve junction to apex) at both end-diastole and end-systole.9 10 Mean velocity (V) of segmental shortening was derived as: (end-diastolic diameter – end-systolic diameter)/(end-diastolic diameter • ejection time).11 12 Ejection time was measured as described above. Percentage shortening was calculated as: end-diastolic diameter – end-systolic diameter) • 100/end-diastolic diameter.

To evaluate diastolic function, angiographic films were projected to a video camera and silhouettes were outlined on a video screen with a light pen. Volumes were calculated every 25 msec by a computer system (Grafomed, Philips Corporation, Eindhoven, the Netherlands) using a multiple-slice technique (50 perpendicular slices with long axis defined as above) and applying Simpson’s rule.13

From the diastolic volumes and simultaneous highfidelity pressures, pressure-volume relations were determined from the lowest diastolic pressure value to the peak of the a wave. The natural logarithm of pressure was used in linear regression analysis of pressure and volume from which a slope k and an extrapolated intercept b were derived.14-16 Changes in k were regarded as changes in volume stiffness.

Wall thickness was outlined on the last diastolic frame. From this and simultaneous volume, the computer calculated LV mass, 17 and, assuming constant mass, back-calculated wall thickness for each diastolic volume point. From computer-derived ventricular major and minor semiaxes for each volume point, wall thickness and simultaneous pressure and midwall circumferential stress was calculated during diastole according to the formula of Mirsky.18 The natural logarithm of stress was used in linear regression analysis of stress and midwall circumference from which an extrapolated intercept β and slope α were derived. Changes in α were regarded as changes in muscle stiffness.

For the geometrical analysis, on each end-diastolic and end-systolic silhouette the major axis (L) and the minor axes (D) in the basal, middle and apical segment were defined as above. LV geometry was determined at both end-diastole and end-systole in terms of:

1. Eccentricity (e):19

\[ e = \sqrt{a^2 - b^2}/a, \]

where a = L/2 and b = DM/2. Theoretically, this quantity can vary from 1 to 0, with 0 indicating a circle.

2. D/L ratios, including DA/L, DM/L and DS/L. This quantity varies from 0 to 1, with larger values denoting a more circular geometry.

3. Shape index (SI):20

\[ SI = (4 \pi \text{ area})/\text{perimeter}^2. \]

This quantity also varies from 0 to 1, with 1 representing a circle. The areas were planimetered by hand, and perimeter measurements were made with a map measurer.

Changes in LV geometry throughout diastole were evaluated by plotting instantaneous (i) DM/L ratio vs instantaneous diastolic volume. Linear regression analysis of this relation reveals:

\[ (DM/L)_i = q \cdot Vol + r \]

where q is the rate of change of DM/L ratio coincident with changing volume (Vol) and indicates the dynamic behavior of LV shape in diastole. The constant r is the extrapolated axis ratio (DM/L) at zero volume. Although this is a nonentity in a physiological sense, it approximates an “average” diastolic LV configuration.

Observations before and after drug administration were analyzed statistically using the paired two-tailed t test. A p < 0.05 was considered significant.
Table 1. Drug Effects on Hemodynamics, Volumes and Global Systolic Function

<table>
<thead>
<tr>
<th></th>
<th>BSA (m²)</th>
<th>HR (beats/min)</th>
<th>EDP (mm Hg)</th>
<th>EDVI (ml/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects</td>
<td>C</td>
<td>1.84 ± 0.08</td>
<td>68 ± 11</td>
<td>12 ± 4</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>A</td>
<td>59 ± 10</td>
<td>16 ± 5</td>
<td>87 ± 28</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>&lt;0.02</td>
<td>&lt;0.025</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>C</td>
<td>1.82 ± 0.11</td>
<td>66 ± 8</td>
<td>16 ± 6</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>A</td>
<td>60 ± 6</td>
<td>20 ± 5</td>
<td>97 ± 21</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>&lt;0.01</td>
<td>&lt;0.02</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects</td>
<td>C</td>
<td>1.88 ± 0.12</td>
<td>60 ± 11</td>
<td>15 ± 7</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>N</td>
<td>71 ± 10</td>
<td>10 ± 4</td>
<td>75 ± 23</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>&lt;0.005</td>
<td>&lt;0.02</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>C</td>
<td>1.88 ± 0.12</td>
<td>63 ± 9</td>
<td>15 ± 5</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>N</td>
<td>71 ± 15</td>
<td>11 ± 5</td>
<td>94 ± 26</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are group means ± sd before (C) and after atenolol (A) or nitroglycerin (N).
Abbreviations: BSA = body surface area; HR = heart rate; EDP = left ventricular (LV) end-diastolic pressure; EDVI = LV end-diastolic volume index; ESVI = LV end-systolic volume index; SAP = systolic aortic pressure; DAP = diastolic aortic pressure; EF = LV ejection fraction; MNSER = mean normalized systolic ejection rate; max dP/dt = maximal LV dP/dt.

Results

Hemodynamics and Volumes

The drug effects on hemodynamics and volumes in normal subjects and coronary patients are summarized in Table 1. In both groups β blockade with atenolol produced a significant fall in HR and significant increases in EDP and volume index at end-diastole (EDVI) and end-systole (ESVI). NTG, on the contrary, produced a significant increase in HR and a significant decrease in EDP, EDVI and ESVI in both normal subjects and patients with coronary artery disease.

Peak systolic aortic pressure was unchanged in normals and in coronary patients after atenolol administration and was significantly decreased by NTG.

Table 2. Drug Effects on Regional Systolic and Diastolic Left Ventricular Function

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>Middle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>V (circ/sec)</td>
<td>S (%)</td>
</tr>
<tr>
<td>Atenolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects</td>
<td>C</td>
<td>1.15 ± 0.18</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>A</td>
<td>1.01 ± 0.25</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>C</td>
<td>1.29 ± 0.33</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>A</td>
<td>1.11 ± 0.17</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects</td>
<td>C</td>
<td>1.35 ± 0.25</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>N</td>
<td>1.51 ± 0.26</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>C</td>
<td>1.16 ± 0.27</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>N</td>
<td>1.34 ± 0.30</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are group means ± sd before (C) and after atenolol (A) or nitroglycerin (N).
Abbreviations: V = mean shortening velocity; S = percentage shortening of basal, middle and apical transverse diameters; k = slope and b = extrapolated intercept of the diastolic logarithmic pressure-volume relation; α = slope and β = extrapolated intercept of the diastolic logarithmic stress-circumference relation (see text).
Table 1. (Continued)

<table>
<thead>
<tr>
<th>ESVI (ml/m²)</th>
<th>SAP (mm Hg)</th>
<th>DAP (mm Hg)</th>
<th>EF (%)</th>
<th>MNSER (sec⁻¹)</th>
<th>max dP/dt (mm Hg/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 ± 10</td>
<td>126 ± 19</td>
<td>81 ± 7</td>
<td>63 ± 3</td>
<td>2.16 ± 0.11</td>
<td>1632 ± 232</td>
</tr>
<tr>
<td>36 ± 15</td>
<td>131 ± 21</td>
<td>82 ± 5</td>
<td>59 ± 7</td>
<td>1.90 ± 0.26</td>
<td>1402 ± 224</td>
</tr>
<tr>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>34 ± 10</td>
<td>140 ± 27</td>
<td>80 ± 10</td>
<td>63 ± 8</td>
<td>2.06 ± 0.50</td>
<td>1724 ± 248</td>
</tr>
<tr>
<td>40 ± 10</td>
<td>144 ± 23</td>
<td>80 ± 9</td>
<td>58 ± 7</td>
<td>1.73 ± 0.33</td>
<td>1463 ± 206</td>
</tr>
<tr>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.02</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>24 ± 9</td>
<td>121 ± 18</td>
<td>72 ± 10</td>
<td>71 ± 7</td>
<td>2.21 ± 0.26</td>
<td>1482 ± 349</td>
</tr>
<tr>
<td>21 ± 8</td>
<td>111 ± 13</td>
<td>73 ± 10</td>
<td>72 ± 7</td>
<td>2.47 ± 0.29</td>
<td>1630 ± 348</td>
</tr>
<tr>
<td>&lt;0.005</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>39 ± 12</td>
<td>114 ± 13</td>
<td>69 ± 8</td>
<td>62 ± 6</td>
<td>2.03 ± 0.16</td>
<td>1507 ± 342</td>
</tr>
<tr>
<td>35 ± 12</td>
<td>107 ± 15</td>
<td>70 ± 10</td>
<td>63 ± 9</td>
<td>2.19 ± 0.28</td>
<td>1609 ± 387</td>
</tr>
<tr>
<td>&lt;0.025</td>
<td>&lt;0.02</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

in both groups. Diastolic aortic pressure was not significantly changed by either drug in either group of subjects.

Global Systolic Function

The drug effects on global systolic function are summarized in Table 1. In normals β blockade with atenolol produced a significant decrease in MNSER but no significant change in EF. Maximum rate of LV pressure rise (max dP/dt) was significantly decreased by atenolol and significantly increased by NTG in normal subjects and coronary patients.

Regional Systolic Function

The drug effects on regional systolic function are shown in Table 2 and figures 1 and 2. After atenolol administration, shortening velocity decreased significantly in all segments among patients with coro-

Table 2. (Continued)

<table>
<thead>
<tr>
<th>k (dyn/cm²)</th>
<th>b (dyn/cm²)</th>
<th>α (dyn/cm²)</th>
<th>β (dyn/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apical V (circ/sec)</td>
<td>S (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.32 ± 0.22</td>
<td>37.8 ± 4.7</td>
<td>0.016 ± 0.008</td>
<td>0.540 ± 0.946</td>
</tr>
<tr>
<td>1.03 ± 0.21</td>
<td>31.7 ± 5.0</td>
<td>0.015 ± 0.007</td>
<td>0.665 ± 0.969</td>
</tr>
<tr>
<td>&lt;0.025</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>1.16 ± 0.45</td>
<td>35.0 ± 9.6</td>
<td>0.013 ± 0.006</td>
<td>0.361 ± 1.080</td>
</tr>
<tr>
<td>1.02 ± 0.36</td>
<td>32.3 ± 9.2</td>
<td>0.011 ± 0.005</td>
<td>0.803 ± 1.145</td>
</tr>
<tr>
<td>&lt;0.025</td>
<td>&lt;0.05</td>
<td>&lt;0.005</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1.27 ± 0.33</td>
<td>40.8 ± 10.6</td>
<td>0.010 ± 0.004</td>
<td>1.023 ± 0.820</td>
</tr>
<tr>
<td>1.59 ± 0.39</td>
<td>46.3 ± 11.0</td>
<td>0.013 ± 0.008</td>
<td>0.698 ± 0.958</td>
</tr>
<tr>
<td>&lt;0.01</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>1.14 ± 0.41</td>
<td>35.0 ± 12.9</td>
<td>0.011 ± 0.004</td>
<td>0.466 ± 0.714</td>
</tr>
<tr>
<td>1.20 ± 0.49</td>
<td>35.0 ± 15.7</td>
<td>0.018 ± 0.009</td>
<td>-0.835 ± 1.487</td>
</tr>
<tr>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
nary artery disease, but only in the apical segment among normal subjects. Percentage shortening decreased in the apical segment in both normal subjects and coronary patients, whereas in the basal and middle segments no significant change occurred in either group. After NTG, shortening velocity increased significantly in the basal and middle segments among coronary patients and in all segments among normal subjects. Percent shortening did not change significantly in any segment in either group.

Pressure-Volume Relations

Figure 3A shows the effects of atenolol on diastolic logarithmic pressure-volume relations in a representative normal subject. In the normal group as a whole,
β blockade produced no significant change in either b or k (table 2). In the coronary group, there was an upward displacement of the regression line with a significant increase in intercept b and decrease in slope k (table 2).

Figure 3B plots the logarithmic pressure-volume relations before and after NTG in one coronary patient. In both normal subjects and coronary patients, NTG caused a slight decrease in intercept b and an increase in slope k, but these changes were not statistically significant (table 2).

Stress-Circumference Relations

Figure 4A depicts the effects of atenolol on the diastolic logarithmic stress-circumference relationship in the same normal subject as in 3A. Among all normals neither the slope α nor the intercept b was altered significantly after β blockade (table 2). In the coronary group, atenolol shifted the curve upwards, resulting in a significant increase in β as well as a significant decrease in α. Figure 4B shows alterations in the stress-circumference relationship after NTG in the same coronary patient as in 3B. There was a significant decline in intercept β and a significant rise in slope α in both normal subjects and patients with coronary artery disease (table 2).

Left Ventricular Geometry

The results are summarized in table 3. Among normal subjects, atenolol produced no significant change in any of the end-diastolic shape parameters. Among patients with coronary artery disease, atenolol resulted in a significant change in eccentricity and in D/L ratio of the basal segment only. There was no change in shape index. Among normal subjects at end-systole, atenolol produced a significant change in D/L of the apical segment and in shape index but no significant change in eccentricity. In coronary patients there was a significant change only in D/L of the middle segment. Dynamic analysis of LV geometry throughout diastole revealed an unchanged slope q of the D₅₀/L vs volume relationship in normals as well as in coronary patients. Intercept r, however, increased in both groups, indicating a shift to a more globular diastolic configuration of the left ventricle after atenolol (table 3).

NTG was associated with no significant change in any of the geometry indices in either group at end-diastole. Among normal subjects at end-systole, NTG resulted in a significant change in eccentricity and D/L ratios of the middle and apical segments, but not in shape index. Among coronary patients at end-systole, NTG failed to produce a significant change in any geometry parameter. Figure 5 shows the effects of NTG on diastolic geometry in a representative patient. After NTG the left ventricle in both normals and coronary patients showed a less globular diastolic configuration as demonstrated by a significant decrease in intercept r of the D₅₀/L vs volume relation. Slope q did not change in either group (table 3).

Discussion

Systolic Function

A major limitation of all quantitative angiographic methods is accuracy in defining the LV silhouette. In the present study the drawings represent the consensus of two experienced observers, and any errors should be consistent. The significance of any error is further limited by the fact that only within-patient com-
comparisons were made. Another limitation of this study is that all the angiographic indices of global LV function are relative rather than absolute, since they are influenced by factors such as preload and afterload;\textsuperscript{8, 21, 22} nevertheless, all have been shown to be clinically useful.\textsuperscript{7, 8, 23}

There is no general agreement as to the best method of defining regional LV function. Methods have varied with respect to 1) systems for relating end-diastolic and end-systolic silhouettes in space, 2) definition of axes or segments, and 3) quantities measured. The method we chose uses an internal reference system,
namely the long axis, and corrects for movement or tilting of the heart in space. In most patients with coronary heart disease, single-plane methods tend to underestimate EF, but might overestimate this quantity because abnormalities of regional contraction are missed. In normal subjects single-plane methods tend to overestimate EF. Since in this study only the RAO projection was used, some indices of both global and regional function may be slightly in error. But only within-patient comparisons were made, and the observed directional changes should be valid.

**Global Systolic Function**

Global systolic LV function was assessed in terms of EF and MNSER. Mean velocity of circumferential fiber shortening was not evaluated because it is considered an index of regional, rather than global, myocardial function in the presence of coronary artery disease. In our normal subjects, atenolol significantly reduced MNSER but did not alter EF. Other investigators have noted a decrease in EF in response to propranolol in some normals and no change in others. In our patients with coronary artery disease, atenolol significantly reduced both MNSER and EF. Data concerning the effects of β blockade in LV function in coronary patients are conflicting.

Some of the effects of β blockade on global LV function may be related to uncontrolled effects on HR, preload and afterload. By lowering HR and secondarily increasing ejection time, β blockers could cause a decrease in velocity indices. Such a significant change in HR was observed in the present study. Ejection indices of LV function may be decreased by increases in afterload, independent of any effect on contractile state. However, we noted no increase in peak systolic or diastolic aortic pressure after atenolol. Ejection phase indices may be increased by increases in preload, independent of any contractile effect, and such an increase in EDVI occurred in the present study. Despite this, the net effect of atenolol in both normal subjects and patients with coronary artery disease was to depress the inherent contractile state, as reflected by a decrease in MNSER and LV max dP/dt.

In our normal subjects and coronary patients, NTG caused a significant increase in MNSER but no change in EF. There are no previous reports on the effects of NTG on MNSER. There are several reports on the effects of NTG on EF, some showing an increase, others showing no change or a decrease. Some authors have noted an increase in EF after NTG in coronary patients only when reversible wall motion abnormalities were present.

There are several mechanisms which could account for the different effects of NTG on LV function. Liedtke et al. have shown that NTG reduces preload by diminishing LV end-diastolic volume; our data confirm these findings. This could reduce global indices of LV function independent of any effect on the inherent contractile state of the myocardium. NTG may reduce afterload by its effect on aortic pressure and systemic vascular resistance, and hence may increase global indices of function independent of any effect on contractile state. In our study, there was a significant lowering of peak systolic pressure. It has been suggested that NTG has a negative inotropic effect, either direct or indirect through an adrenergic blocking action. In contrast, the studies of Vatner et al. support a reflex positive inotropic action of intravenous NTG through its effect on HR and an action which can be abolished by β blockade, with HR held constant. Our patients showed a significant increase in HR and a slight but significant rise in LV max dP/dt after NTG. The consequences of uncontrolled preload, afterload and HR may account for some of the varied results in human subjects. In any case, our data suggest that the net effect of NTG in both normal subjects and patients with coronary artery disease is to enhance velocity indices of global systolic LV function. Of course, in coronary patients with more extensive regional contraction abnormalities the net effect of NTG might be different.

**Regional Systolic Function**

Our study indicates that both atenolol and NTG affect regions of the left ventricle in a nonuniform manner and that these drugs alter velocity and non-velocity indices unequally. In normal subjects the apical segment was affected by atenolol (both shortening velocity and percentage shortening decreased), but the basal and middle segments were unaffected. After NTG in normals, all three segments were affected, but only shortening velocity increased. In coronary patients, in the apical segment both velocity and non-velocity parameters were decreased by atenolol, but neither was affected by NTG. In the basal and middle segments of coronary patients, only the velocity index was changed by both atenolol and NTG. Previous studies in man have shown variable and apparently conflicting effects of β blockers and NTG on regional systolic function. This apparent conflict in results is attributable in part to major differences in methods and patient selection. The differences in methods involve reference systems for superimposing end-diastolic and end-systolic silhouettes, ways of defining long and short axes and analysis of axes vs hemiaxes. The differences in patient selection involve definition of normal groups, extent of coronary artery disease, presence or absence of previous myocardial infarction, extent of infarction and presence or absence of reversible ischemia.

The relationship between global and regional systolic LV function is complex, and it is difficult to account for drug-induced changes in global function solely on the basis of changes in regional function. In the present study, regional changes in percent diameter shortening were not always accompanied by comparable changes in EF. However, changes in regional velocity indices in at least one segment were always associated with comparable changes in MNSER. In considering global and regional function
TABLE 3. Drug Effects on Left Ventricular Configuration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Eccentricity</th>
<th>Shape Index</th>
<th>Dv/L</th>
<th>ED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ED</td>
<td>ES</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects</td>
<td>C</td>
<td>0.832 ± 0.337</td>
<td>0.893 ± 0.207</td>
<td>0.853 ± 0.032</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>A</td>
<td>0.818 ± 0.360</td>
<td>0.880 ± 0.239</td>
<td>0.863 ± 0.038</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>C</td>
<td>0.825 ± 0.345</td>
<td>0.890 ± 0.456</td>
<td>0.870 ± 0.038</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>A</td>
<td>0.817 ± 0.314</td>
<td>0.882 ± 0.382</td>
<td>0.863 ± 0.043</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.05</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects</td>
<td>C</td>
<td>0.837 ± 0.339</td>
<td>0.915 ± 0.259</td>
<td>0.800 ± 0.043</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>N</td>
<td>0.847 ± 0.403</td>
<td>0.922 ± 0.293</td>
<td>0.768 ± 0.044</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>C</td>
<td>0.843 ± 0.207</td>
<td>0.908 ± 0.147</td>
<td>0.813 ± 0.039</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>N</td>
<td>0.850 ± 0.310</td>
<td>0.912 ± 0.194</td>
<td>0.800 ± 0.052</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are group means ± sd before (C) and after atenolol (A) or nitroglycerin (N).

Abbreviations: Dv/L, Dm/L, Dq/L = ratios of basal, middle and apical diameters, respectively, to long axis; q = slope and r = intercept of linear plot of minor/major axis ratio vs volume throughout diastole; ED = end-diastole, ES = end-systole.

in general, it appears that velocity indices are more sensitive than nonvelocity indices in detecting alterations induced by both atenolol and NTG, as might be anticipated from other studies.5

Diastolic Function

Evaluation of the passive elastic properties of the left ventricle demands accurate and simultaneous determination of multiple pressure and volume values.61 In the present study LV pressure was measured with a high-fidelity tipmanometer system. LV volume was determined using single-plane RAO methods which have been shown to have acceptable accuracy.52 The volume measurements were not corrected by a regression equation; this was not considered important, because only within-patient comparisons were made.

The reproducibility between paired angiograms is also important. The data suggest that two triculograms performed within 15–30 minutes agree closely with each other.53-54 Various models for determining wall stress have been proposed. In the present investigation we used a

![Figure 5. Effects of nitroglycerin on the relation between minor/major axis ratio (ordinate) and diastolic volume (abscissa) in a representative patient with coronary artery disease.](image-url)
thin-walled model to calculate circumferential stress at the equator of the ventricle, where fiber orientation is predominantly circumferential. Stress values from similar thin-walled models agree closely with those using more complex thick-wall theory. We determined wall thickness in the present study from RAO cineangiograms. Such determinations have been shown to correlate well with frontal plane measurements in the absence of right ventricular hypertrophy.

Four of the 12 normal subjects (one in the atenolol and three in the nitroglycerin-treated group) had an EDP during control angiography ≥ 16 mm Hg. In all four, EDP before ventriculography was ≤ 15 mm Hg. Although we tried to perform ventriculograms in held mid-inspiration, these four may have done an inadvertent Valsalva maneuver, which could account for the mean values in EDP given in table 1. There apparently was no significant decrease in volume, as observed by others during the Valsalva; table 1 shows that EDVI in the two normal subgroups before drugs was similar. For this reason, we doubt that the Valsalva had a major role in elevating EDP. Theoretically, volume loading due to the injected contrast material might also have increased EDP in these patients. However, there is no significant effect on volume in the early phase of angiography. It has also been shown that EDP may rise during contrast injection without an increase in volume.

Pressure-Volume Relations

The curvilinear diastolic pressure-volume relationship of the left ventricle can be represented as a straight line by plotting the natural logarithm of pressure against volume. This line has a slope k and an extrapolated intercept b. The slope k is a reflection of the passive elastic stiffness of the myocardium. Intercept b has been postulated as an indicator of tension development or failure of relaxation. This concept is open to question because the pressure-volume relation at zero volume is based on extrapolation. Also, the intercept is greatly influenced by absolute pressure values. Any small error in diastolic pressure measurement will be exaggerated by logarithmic transformation, and will markedly affect the extrapolation. Therefore, we regarded intercept b as having poor reproducibility and chose not to draw any conclusions from observed changes in this quantity.

The values of k among normal subjects closely agree with those reported in four patients with mitral stenosis by Gaasch. Coltart observed among two normals and six patients with coronary artery disease that propranolol generally produced an increase in slope and decrease in intercept. These observations were made during constant HR; four of the coronary patients had advanced disease with enlarged end-diastolic volumes and reduced EFs. Patients who had a downward shift of their pressure-volume curve also showed impaired myocardial function in response to β-adrenergic blockade. We found no effect on k by atenolol among normals, but among coronary patients we noted effects exactly opposite to those observed by Coltart; that is, k decreased. In contrast to Coltart's patients, our coronary patients had a normal EDVI and four had normal EFs in the control state. Furthermore, atenolol, used in the present study, has been shown to be a cardioselective agent, in contrast to propranolol. These factors may explain the differing results in these two studies. In any case, our data are consistent with a reduction of passive elastic volume stiffness by atenolol.

Other studies noted a downward shift of the pressure-volume relations after NTG, but did not comment on changes in slope. In our observations...
after NTG, k increased in some patients, but among both the normal and coronary artery disease groups as a whole there was no significant change.

**Stress-Circumference Relations**

Changes in passive volume stiffness derived from pressure-volume data may not indicate alterations of the passive elastic properties of the myocardium itself, so-called muscle stiffness. Analysis of muscle stiffness requires determination of the stress-strain relationships of the muscle fibers. However, there are problems with this approach. Calculation of Lagrangian strain requires the definition of a reference or "resting" length that is easily obtainable in experiments on excised muscles but remains questionable in in vivo investigations. If one makes certain assumptions, it can be shown that the logarithmic stress-circumference relationship is linear and that changes in the slope of this relationship closely approximate those of the muscle stiffness constant (see Appendix). Also, midwall circumference at the ventricular equator can be easily measured from ventriculograms. For these practical reasons, we chose to analyze muscle stiffness using stress-circumference relations instead of the theoretically more appropriate stress-strain relations.

The diastolic logarithmic stress-circumference plot had a slope \( \alpha \) and an extrapolated intercept \( \beta \). Changes in slope \( \alpha \) were assumed to reflect alterations in passive elastic stiffness of the myocardium (Appendix). Since there are problems in reproducibility of intercept \( \beta \) similar to those previously discussed with respect to intercept \( b \), and since the intercept is influenced by changes in the slope (Appendix), we chose to draw no conclusions from changes in this parameter. Values for \( \alpha \) among all normal subjects combined fell within a relatively narrow range. After atenolol administration, normals showed no significant change in \( \alpha \), whereas in coronary patients there was a decrease in passive elastic stiffness. In contrast to atenolol, NTG resulted in a significant increase in passive elastic stiffness in both study groups.

**Relation Between Geometry and Diastolic Function**

Apparent differences between volume stiffness and muscle stiffness have been attributed to the influence on pressure-volume relations of wall mass and geometry. In our study, involving only within-patient comparisons, wall mass should not have been a factor. The influence of geometry was examined in terms of several parameters, since there is no uniformity as to the best method for defining geometry of the left ventricle.

LV geometry has most often been analyzed in terms of the ratio between the major and equatorial minor axes. This assumes a simple ellipsoidal model that may not be appropriate, especially for diseased ventricles. This simple ratio will only reflect geometric changes related to the long and short axes.

In an attempt to define regional geometric changes, Liedtke et al. analyzed in dogs the ratio between the major axis and basal and apical minor axes. We used a similar method, except that the ratio is minor-to-major axis (D/L) and the long axis is defined differently.

Eccentricity reflects chamber curvature but, like the D/L ratio, assumes an ellipsoidal reference figure. It will only reflect regional abnormalities related to the semimajor and equatorial semiminor axes.

Shape index has the advantage of assuming no idealized chamber shape and avoids definition of a long axis, which can be a problem in some diseased ventricles. This quantity should be affected by regional abnormalities at any point on the perimeter.

Systematic comparison of these indices in the same patients gave nonuniformity of results. There was less influence by the drugs at end-diastole than in end-systole. NTG induced no significant change in any parameter in any group at end-diastole, and atenolol induced nonuniform changes only in coronary patients. At end-systole, both atenolol and NTG resulted in nonuniform changes in the measured parameters in both groups. Regional drug-induced geometric changes, as reflected by alterations in segmental D/L ratios, were not accompanied by directionally opposite changes in other segments. Liedtke et al., analyzing basal and apical length-to-width ratios in dogs, noted a less rounded configuration in both segments at both end-diastole and end-systole after NTG. Helfant et al. concluded qualitatively that propranolol induced an elongation in the shape of the left ventricle during both systole and diastole, but in quantitatively analyzing end-diastolic L/D ratios in 10 patients (six normal, four with coronary artery disease), found no significant change after propranolol.

All the above analyses in both the present and previous studies were concerned with geometric changes only at end-diastole and end-systole. Such an approach might overlook changes occurring during the diastolic phase. To examine this possibility, D/L ratio was plotted against volume throughout diastole. The results in terms of \( r \) indicate consistent geometric changes in response to both drugs, atenolol producing a more globular and NTG a less globular configuration. In the case of atenolol, the results of volume stiffness and muscle stiffness analysis were identical, both \( k \) and \( \alpha \) changing in coronary patients and neither changing in normals, despite a consistent change in geometry. In the case of NTG, pressure-volume analysis failed to reflect altered stress-circumference relations in both normals and coronary patients. These data suggest that geometrical influences of drugs may mask alterations in diastolic properties of the left ventricle, and that analysis of stress-strain or stress-circumference relations may be more appropriate than analysis of pressure-volume relations for detection of these drug-induced changes.

This study has demonstrated that both atenolol and NTG can profoundly affect both systolic and diastolic LV function. However, we have assumed a purely elastic left ventricle, and thus have ignored various diastolic properties both intrinsic (completeness of
ventricular relaxation, viscous properties, diastolic suction, etc.) and extrinsic (pericardial properties, overload of the right ventricle, etc.) to the ventricular chamber. Previous studies have not found changes in muscle stiffness in response to drugs and have attributed drug-induced changes in volume stiffness to these factors. Our data conflict with this view and suggest that acute interventions with atenolol and NTG can result in alterations in measured muscle stiffness. We still do not know to what degree drug-induced changes in LV systolic performance might be caused by alterations in diastolic function.

References

40. Khemka M, Prakash R, Aronow WS, Kern JC, Cassidy J,
Vatner, Greenberg, Gillis, Williams, Hammermeister, Vine, Brooker

Angiology 26: 276, 1975


Dumesnil JG, Rirman EL, Davis GD, Gau GT, Rutherford BD, Frye RL: Regional left ventricular wall dynamics before and after sublingual administration of nitroglycerin. Am J Cardiol 36: 419, 1975


Sandler H, Alderman E: Determination of left ventricular size and shape. Circ Res 34: 1, 1974

Appendix

The stress-strain relationship is generally defined as:

$$\sigma = (a/k) \exp[(k/e) - 1]$$  \hspace{1cm} (1)

where $\sigma$ = muscle stress (force per unit area), $e$ = muscle strain (relative change of muscle length) due to stretching, and $a$ and $k$ are constants of elasticity. Differentiation of equation (1) gives the tangent modulus:

$$E = d \sigma/de = a \exp(e)$$  \hspace{1cm} (2)

Substituting $\sigma = (a/k)$ from equation (1) for a $\exp(k/e)$ results in:

$$E = k \sigma + a$$  \hspace{1cm} (3)

where $k$ (the slope of this linear relationship) is the myocardial stiffness constant.$^m$

The stress-strain relationship for the intact ventricle at the equator according to the Lagrangian definition of strain is given by the expression:

$$\sigma = (a/k) \exp\left[(k/C_e) (C-C_0)\right] - (a/k)$$  \hspace{1cm} (4)

where $\sigma$ and $C$ are instantaneous midwall stress and instantaneous midwall circumference at the equator, respectively, $a$ and $k$ are elasticity constants as in (1), and $C_0$ is midwall circumference at an unstretched state of zero stress (that cannot be readily obtained in vivo). Since the constant $a$ has been shown to be negligible except at very low stress values, equation (4) simplifies to:

$$\sigma = (a/k) \exp[(k/C_e) (C-C_0)]$$  \hspace{1cm} (5)

and can be transformed logarithmically to:

$$\ln \sigma = \ln (a/k) + (k/C_e) (C-C_0)$$  \hspace{1cm} (6)
Combining all constants results in:

\[ \ln \sigma = \beta + \alpha C \]  

(7)

where

\[ \beta = \ln \left( \frac{a}{k} \right) - k, \]  

(8)

and

\[ \alpha = \frac{k}{C_0}, \]  

(9)

If one assumes that muscle length at zero stress does not vary considerably over a short time in a given muscle,\(^9\) then \(C_0\) would be constant in a first-order approximation and any change of \(\alpha\) due to an intervention should reflect an alteration in the elastic stiffness constant \(k\) that is identical to \(k\) in equation (3). Further, equation (8) demonstrates that intercept \(\beta\) of the logarithmic stress-circumference relation (equation 7) will be influenced by any change in \(k\) and thereby \(\alpha\).

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**Characteristics of Ventricular Function in Single Ventricle**

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TOHRU MORI, M.D., SUSUMU NAKANO, M.D., SHINTARO BEPPU, M.D.,
AND TAKAHIRO KOZUKA, M.D.

**SUMMARY** Functional characteristics of the single ventricle were studied by means of biplane angiocardiography in 34 patients. Group 1 consisted of 14 patients with normal or increased pulmonary vascular marking on chest film and no pulmonary stenosis. Group 2 included 20 patients with severe angiographic pulmonary stenosis and decreased pulmonary vascular marking. Ventricular volume parameters were calculated according to Simpson's rule and were compared with normal values. The sum of the normal left and right ventricular volumes was assumed to be 100%.

In group 1, ventricular end-diastolic volumes averaged 143 ± 11% and were significantly \((p < 0.001)\) larger than end-diastolic volumes in group 2 (81 ± 4%). The presence or absence of severe pulmonary stenosis affecting pulmonary blood flow was a main factor regulating the ventricular chamber size in single ventricle. In both groups, the ejection fraction of a single ventricle was significantly lower than that of a normal left or right ventricle. Ventricular size and function in patients with a single ventricle should be carefully assessed before ventricular septation surgery.

THE ANATOMY OF SINGLE VENTRICLE has been well described,\(^1\) \(^2\) but its functional characteristics have not been reported. Correction of this complicated cardiac anomaly by septation surgery, in which the single ventricle is divided into two chambers, has become a challenge for cardiac surgeons.\(^3\)\(^-\)\(^12\) Therefore, it is important to know the volume and function of the single ventricle before surgical intervention.

We studied the functional characteristics of the single ventricle by analyzing biplane ventricular angiograms in 34 patients with a diagnosis of single ventricle confirmed angiographically or at autopsy.

**Methods**

**Patient Population**

Biplane, large-film angiograms (6 frames/sec) of 34 patients, 20 males and 14 females, ranging in age from 4 months to 12 years, were analyzed. The availability of angiograms of good quality was the sole criterion for patient selection. All patients were diagnosed as having a single ventricle by the definition reported previously.\(^1\)\(^-\)\(^13\) A single ventricle is one ventricle that receives both the tricuspid and mitral valves, or a common atrioventricular (AV) valve. This definition excludes tricuspid and mitral atresia. The angiographic morphology of the single ventricle was classified into three types (I, II and III). Details of this angiographic classification were also previously reported.\(^12\) In brief, type I is identical to the anatomic type A of Van Praagh et al.,\(^1\) type II is comparable to type C, and type III is equivalent to Van Praagh's types B and D.

There were seven, 13 and 14 patients with types I, II and III single ventricle, respectively. Three patients with type I, eight with type II and nine with type III had severe valvular and subvalvular pulmonary stenosis (PS) or pulmonary atresia. In one patient with type I single ventricle, the ventriculotriangular relationship was normal; four other type I patients had a transposition of the great arteries (TGA), and two had a double outlet right ventricle (DORV). Three patients with a type I single ventricle had two AV valves and four patients had a common AV valve. Of

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