Improvement in Left Ventricular Wall Motion Following Nitroglycerin

By John H. McAnulty, M.D., Mark T. Hattenhauer, M.D., Josef Rösch, M.D., Frank E. Kloster, M.D., and Shahbudin H. Rahimtoola, M.B.

SUMMARY
Coronary artery disease patients frequently have left ventricular wall motion abnormalities. Though nitroglycerin is commonly used in ischemic heart disease, its effects on wall motion abnormalities is unknown. In this study we have evaluated the effects of nitroglycerin on wall motion abnormalities and on ejection fraction in 25 patients. Sixteen had coronary artery disease (>70% luminal narrowing). Six had no evidence of heart disease and three had congestive cardiomyopathies with normal coronary arteries. Left ventricular angiography was performed prior to and six minutes after administration of 0.4 mg of sublingual nitroglycerin.

Twelve of the 16 coronary artery disease patients had wall motion abnormalities, and in seven of these, segmental wall motion improved after nitroglycerin. In five, wall motion did not change. The initial heart rate, left ventricular systolic and end-diastolic pressure, and left ventricular end-diastolic volumes were not different for those whose wall motion improved versus those whose did not. The increase in the former and fall in the latter three hemodynamic parameters were significant (P < 0.01) and similar for the two groups. In those whose wall motion abnormalities improved after nitroglycerin, ejection fraction (mean ± se) increased significantly (P < 0.05), from 0.47 ± 0.025 to 0.62 ± 0.046. In those without improvement, the ejection fraction went from 0.55 ± 0.056 to 0.58 ± 0.051 (NS). Three patients with congestive cardiomyopathy showed no improvement in ventricular wall motion or ejection fraction after nitroglycerin.

Left ventricular wall motion abnormalities and ejection fraction improved in some coronary artery disease patients following nitroglycerin. The mechanism for this is unknown; however, ventriculography before and after nitroglycerin may be of potential usefulness for identifying areas of reversible wall motion abnormalities.

Additional Indexing Words:
Coronary artery disease
Left ventricular ejection fraction
Asynergy
Aortocoronary bypass surgery

Methods and Materials
Twenty-five patients, nine females and 16 males, with a mean age of 52.7 years (range 30 to 64 years) were studied. Sixteen subjects had significant coronary artery disease with greater than 70% luminal narrowing of at least one major coronary artery. Four patients had one-vessel disease, five had two-vessel disease, and seven had three-vessel disease. Nine of 25 patients had normal coronary arteries, of whom six had no evidence of heart disease by cardiac catheterization and angiography and three had congestive cardiomyopathies.

Prior to any use of contrast agent, aortic and left ventricular pressures were recorded using a Statham P23-Gb transducer at the midchest position and a Hewlett-Packard recorder. Heart rate was obtained from the electrocardiogram. Left ventricular angiography was performed in the right anterior oblique position using 40 cc of Renografin-76 (meglumine diatrizoate and Na diatrizoate). Coronary angiography followed using the Judkins technique. After the last angiogram, a waiting period of at least 30 minutes elapsed to allow time for dissipation of the effects of previously administered contrast agent or nitroglycerin. Following the waiting period, left ventricular and arterial pressure as well as heart rate were recorded. Each patient was given nitroglycerin, 0.4 mg sublingually, and four minutes later pressure and heart rate

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measurements were repeated. Six minutes after nitroglycerin, left ventricular angiography was repeated. Ventricular wall motion was evaluated by visual inspection of the superimposed traced silhouettes of end-systole and end-diastole using a fixed external reference system. To further quantitate degrees of asynergy, a long axis (aortic root midpoint to the apex) was drawn for each end-diastolic and end-systolic silhouette. This axis was divided into hemiaxes by a perpendicular line at the midpoint and perpendicular lines were drawn at the midpoints of these hemiaxes. These perpendicular lines from the long axis to the endocardial surface and from the midpoint of the long axis to the apex were called "chords." The percent of chord shortening with systole for each chord was determined in the control state and after nitroglycerin. Left ventricular volumes and ejection fractions were determined by previously described methods. All patients were premedicated with intramuscular diazepam (5 to 10 mg) and atropine (0.4 to 0.8 mg). Each gave informed consent for the study. Statistical analysis was performed on all the data in the usual manner. A P value of greater than 0.05 was considered insignificant.

Results

Abnormal Wall Motion with Coronary Artery Disease

Of the 16 coronary artery disease patients (table 1), one had dyskinesis, or paradoxical outward movement of the ventricular wall during systole, and this did not improve following nitroglycerin. Four patients had akinesis, or lack of motion of a segment of the left ventricular wall during systole, and in two of these there was no change. Seven patients had hypokinesis, and in five, nitroglycerin produced improved wall motion (fig. 1). Thus, seven patients had improvement in wall motion abnormalities with nitroglycerin. Three of these seven had electrocardiographic evidence (0.04 sec Q waves) of a myocardial infarction in the involved region. Of five patients in whom wall motion abnormalities did not improve after nitroglycerin, three had electrocardiographic evidence of a myocardial infarction in the region of wall motion abnormality (asynergy). Evaluation of collateral flow to the regions of asynergy, as judged from the coronary angiograms, revealed no correlation between it and improvement following nitroglycerin.

The patients were divided into those who improved after nitroglycerin and those who did not, as described above, on the basis of the visual inspection of superimposed traced silhouettes of end-systole and end-diastole. Once divided into groups, an attempt was made to further quantify the degree of asynergy in these patients by evaluating the extent of chord shortening as described. The chords closest to the regions of asynergy were evaluated. Figure 2 shows the percent of chord shortening in areas of wall motion abnormalities in coronary artery disease patients. In patients without improvement in wall motion after nitroglycerin, the mean percent of chord shortening increased from 8% to 11% following nitroglycerin, a change that was not statistically significant. In patients who were felt to have improved wall motion on the basis of visual inspection of superimposed car-

Table 1

<table>
<thead>
<tr>
<th>Wall Motion in Coronary Artery Disease Patients</th>
<th>Number</th>
<th>Improved with NTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyskinesis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Akinesis</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Hypokinesis</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Normal wall motion</td>
<td>4</td>
<td>0</td>
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<tr>
<td>Totals</td>
<td>16</td>
<td>7</td>
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NTG = nitroglycerin.

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diac silhouettes, the mean percent of chord shortening increased significantly ($P < 0.01$) from 7% in the control state to 16% following nitroglycerin. These data only provide quantification of the wall changes determined by visual evaluation and should not be used to prove the accuracy of separation of patients into the two groups.

Hemodynamic parameters before and after nitroglycerin were evaluated in all patients (table 2). In those coronary artery disease patients whose wall motion abnormalities improved with nitroglycerin (fig. 3), heart rate increased significantly and left ventricular systolic and end-diastolic pressures decreased significantly ($P < 0.01$). However, in coronary artery disease patients whose wall motion abnormalities did not improve with nitroglycerin (fig. 3), heart rate also increased significantly ($P < 0.01$) and left ventricular systolic pressure, end-diastolic pressure, and volume decreased significantly ($P < 0.01$) following nitroglycerin. The smaller end-diastolic volumes in patients who improved could have played a role in the favorable response to nitroglycerin. However, neither the initial values for these hemodynamic parameters, including end-diastolic volume, nor their degree of change was significantly different for the two groups.

Ejection fraction (mean ± se) in those with coronary artery disease and wall motion abnormalities (fig. 4) that did not improve after nitroglycerin increased from 0.55 ± 0.056 in the control state to 0.58 ± 0.051 after nitroglycerin (NS). Coronary artery disease patients whose wall motion abnormalities improved had an initial mean ejection fraction of 0.47 ± 0.025 and this increased to 0.62 ± 0.046 following nitroglycerin. The $P$ value for the increase was <0.01. The initial values for ejection fraction for these two groups of patients did not differ significantly. Thus, improvement of segmental wall motion after nitroglycerin was accompanied by an increase in ejection fraction.

Normal Wall Motion: With or Without Coronary Artery Disease

Ten of our patients had normal wall motion, four with coronary artery disease and six with normal coronary arteries. Their hemodynamic parameters differed from those with wall motion abnormalities and coronary artery disease only in that the initial mean end-diastolic volume was smaller ($P < 0.05$). The changes after nitroglycerin in end-diastolic volume as well as in left ventricular systolic and end-diastolic pressures, heart rate, and ejection fraction were not significantly different from those with wall motion abnormalities. In those with normal wall motion the initial ejection fraction was 0.67 ± 0.022 (normal ± 0.54)$^{17}$ and increased to 0.72 ± 0.024 after nitroglycerin, an insignificant change.

<table>
<thead>
<tr>
<th>Table 2</th>
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<tr>
<th>Changes in Hemodynamic Parameters with Nitroglycerin in the Various Groups</th>
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<tbody>
<tr>
<td>CAD patients with WMA</td>
<td>No improvement with NTG</td>
<td>Improved with NTG</td>
<td>CAD patients with WMA</td>
<td>No improvement with NTG</td>
<td>Improved with NTG</td>
<td>CAD patients with WMA</td>
<td>No improvement with NTG</td>
<td>Improved with NTG</td>
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<td></td>
<td>(t)</td>
<td>After NTG</td>
<td>(10)</td>
<td>After NTG</td>
<td>After NTG</td>
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<td>After NTG</td>
<td>After NTG</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>72.8 ± 3.2</td>
<td>72.8 ± 3.2</td>
<td>79.3 ± 5.0*</td>
<td>79.3 ± 5.0*</td>
<td>79.3 ± 5.0*</td>
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<td>LVSP (mm Hg)</td>
<td>124 ± 6.2</td>
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<td>LVdP/dt (mm Hg)</td>
<td>16.4 ± 2.7</td>
<td>16.4 ± 2.7</td>
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<tr>
<td>LVESV (cc)</td>
<td>169 ± 11.7</td>
<td>169 ± 11.7</td>
<td>169 ± 11.7</td>
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<tr>
<td>LVEF (%)</td>
<td>0.67 ± 0.025</td>
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**All values are mean ± one standard error.**

**P < 0.05**

**P < 0.01**

| Abbreviations | CAD = coronary artery disease; WMA = wall motion abnormalities; NTG = nitroglycerin; LVSP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; LVEF = ejection fraction. |

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NTG AND VENTRICULAR WALL MOTION

Hemodynamic parameters in the control state and following nitroglycerin in coronary artery disease patients whose wall motion abnormalities did not improve following nitroglycerin (left) and those whose wall motion abnormality improved (right). Abbreviations as in table 2.

Congestive Cardiomyopathies: Normal Coronary Arteries

Three patients with congestive cardiomyopathies and associated generalized wall motion abnormalities showed a heart rate increase and a fall in left ventricular systolic and end-diastolic pressures after nitroglycerin. Despite this, their wall motion abnormalities did not improve and the ejection fractions showed minimal change, 0.32 ± 0.100 to 0.31 ± 0.110.

Discussion

Nitroglycerin produced improvement in wall motion abnormalities in seven of 12 patients with coronary artery disease and asynergy, indicating that their localized ventricular disease may be reversible. In these patients, improvement in ejection fraction was greater than that found in the patients who did not show improved wall motion and in patients who initially had normal wall motion.

The maximum effects of sublingual nitroglycerin occur between three and ten minutes after administration,8,9 and in our study the drug effects should have been present at the time of the

Figure 3

Figure 4

Ejection fractions for coronary artery disease patients whose wall motion abnormalities did not improve after nitroglycerin (left) and for those whose WMA improved (right). The change in the unimproved group was not significant. Abbreviations as in table 2.
angiograms. The reductions in left ventricular systolic pressure and left ventricular end-diastolic pressure and the increases in heart rate following nitroglycerin are comparable with those found in other studies in patients not in clinical congestive heart failure. They are evidence for a significant physiological effect from the 0.4 mg of sublingual nitroglycerin.

It is not unreasonable to expect improvement of abnormal wall motion from nitroglycerin in some patients as other interventions have been shown to improve asynergy. Aortocoronary bypass surgery has resulted in angiographically demonstrated improvement in wall motion in some patients. In addition, asynergy shown to develop with anginal pain and electrocardiographic ST-segment abnormalities returned to normal with their disappearance. The observation of viable appearing muscle tissue at the time of surgery, in areas where preoperative asynergy was demonstrated angiographically, is also consistent with the hypothesis that wall motion abnormalities may improve. The potential for improvement in wall motion is supported by all of these, but as yet, there is no way to predict which patients with asynergy at the time of preoperative left ventricular angiography will have improvement with bypass surgery. The results of this study suggest that the response of ventricular wall motion to nitroglycerin may be a way of predicting which patients might gain improved ventricular function from surgical correction.

The mechanism by which nitroglycerin improved wall motion is conjectural at the present time. There are at least three ways to explain angiographically demonstrated improvement in wall motion abnormalities after nitroglycerin. First, nitroglycerin may have its effect by decreasing afterload. Secondly, the drug may have a direct or indirect inotropic effect, and thirdly, nitroglycerin may alter the balance between myocardial oxygen supply and demand.

By reducing aortic pressure, nitroglycerin might be expected to improve an area of localized wall motion abnormality. As the afterload is decreased, the ventricle, or in this case the localized segment of left ventricular wall, would have a reduced force, or load, against which it would have to shorten and the velocity of contraction would increase. On angiography, this might be visualized as improved wall motion. Left ventricular systolic pressure, however, was not significantly different between the group of patients that improved and those that did not improve following nitroglycerin and this suggests that a decrease in afterload is not the primary or only mechanism for improvement in wall motion abnormalities. In addition, the patients with congestive cardiomyopathies had no improvement in their wall motion abnormalities even though systolic pressure fell after nitroglycerin. This suggests that wall motion improvement is more than a nonspecific response to a reduction in afterload. On the other hand, in favor of the afterload effect of nitroglycerin are the two of four patients with akinesia whose wall motion improved. Presumably these were regions of nonviable myocardium and were passively pulled by areas of surrounding normal myocardium, an action which may have been facilitated when afterload was lowered with nitroglycerin. Thus, improvement in asynergy seen in our patients may have been apparent rather than real, with nitroglycerin having its effect on the myocardium surrounding the poorly moving segment rather than on the asynergistic segment.

There is some evidence that nitroglycerin may have a direct or indirect inotropic effect. An improvement in left ventricular performance after nitroglycerin is shown in this study. However, other variables (preload, afterload, coronary blood flow, and response of the autonomic nervous system) were altered or uncontrolled. Therefore, it is not possible to relate this improvement of left ventricular function to a change in the inotropic state.

A likely mechanism for improvement in wall motion abnormalities following nitroglycerin in this group of patients is an improvement in the balance between myocardial oxygen supply and demand. An increase in coronary blood flow following nitroglycerin has been demonstrated in dogs and in some normal subjects, although other studies have shown a lack of response from the drug in coronary artery disease patients. Recent work with dogs indicates that regional blood flow to ischemic areas may be increased by the effect of nitroglycerin on the collateral vessels supplying those areas. The reduction in left ventricular end-diastolic pressure and volume caused by nitroglycerin would reduce myocardial tension, and therefore, myocardial oxygen consumption. In addition, the diastolic coronary blood flow to the region might be improved because the lowered wall tension could decrease coronary vascular resistance. Both could improve the performance of the areas of ischemic myocardium. It would seem that the five coronary artery disease patients with asynergy that did not improve may have had fixed or nonreactive vasculature supplying the involved segment, or that irreversible muscle damage was present.

From this study we conclude that nitroglycerin can improve wall motion abnormalities, as judged angiographically, in some coronary artery disease patients. The ejection fraction increased significantly in our patients whose wall motion abnormalities improved after nitroglycerin. Although improvement in the balance between myocardial oxygen supply and demand seems a likely explanation, the mechanism
for improvement in wall motion with nitroglycerin is unknown. However, ventriculography before and after nitroglycerin may have potential for identifying areas of wall motion abnormalities that are reversible.

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Improvement in left ventricular wall motion following nitroglycerin.
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