Effects of Nitroglycerin on Left Ventricular Wall Motion in Coronary Artery Disease

By James T. Dove, M.D., Pravin M. Shah, M.D., and Bernard F. Schreiner, M.D.

SUMMARY

The effects of sublingual nitroglycerin (GTN) on left ventricular wall motion (LVWM) were examined by angiographic assessment in eight patients with anginal chest pain. Five of seven patients having occlusive coronary artery disease showed segmental abnormalities in LVWM characterized by regional hypokinesis or akinesis at rest. These abnormalities were accentuated by tachycardia induced by atrial pacing and were associated with the development of anginal chest pain. Two patients with one vessel coronary artery disease had normal LVWM at rest, but developed abnormalities during the stress of tachypacing. Administration of GTN reversed the LVWM abnormalities in all patients despite continued tachypacing. One patient with atypical chest pain but normal coronary arteries had normal LVWM at rest, following tachypacing, and after GTN. It is concluded that angiographic evaluation of LVWM provides a useful measure of segmental myocardial ischemia in patients with suspected coronary artery disease, and permits objective assessment of effects of antianginal drugs in reversing myocardial ischemia.

Additional Indexing Words:
Myocardial ischemia Nitroglycerin Atrial pacing Reversible segmental abnormalities
Left ventricular wall motion

Since its description in 1967 atrial "tachypacing" has become an extremely useful technique for evaluation of the myocardial performance in patients with coronary artery disease. The hemodynamics, electrophysiologic, and metabolic abnormalities precipitated by pacing-induced ischemia have been described in many reports. Some studies have demonstrated that nitroglycerin improves these parameters of ventricular function despite the continuation of the pacing stress. Experience in our laboratory has demonstrated variable hemodynamic responses to pacing stress in coronary artery disease, the so-called "pacing function curves" remaining normal in about a third of the patients. The hemodynamic parameters, therefore, do not provide a consistent end point in the evaluation of pharmacologic agents. Angiographic evaluation of left ventricular wall motion has revealed focal asynergy more consistently following the pacing "ischemic" stress, even in presence of a normal hemodynamic response. The present study, therefore, was designed to evaluate angiographically the effect of nitroglycerin on left ventricular wall motion during acute myocardial ischemia induced by atrial pacing.

Materials and Methods

Eight patients with suspected coronary artery disease (CAD) were studied. The protocol and purposes of the investigation were explained to each patient and an informed consent was obtained. The patients were not preselected on any specific criteria other than their willingness and ability to comply with the study protocol. Long-acting nitrites and propranolol were discontinued at least 24 hours prior to the study. Using standard catheterization techniques a flow-directed balloon tip catheter was passed via the right antecubital vein and positioned in the pulmonary artery and another electrode catheter in the coronary sinus in order to obtain consistent atrial pacing.

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catheter was passed into the left atrium by the transseptal technique and subsequently advanced to the left ventricle. A cannula in the left brachial artery was used for recording of arterial pressures as well as a sampling site for indicator dilution curves. Pulmonary artery (PA), left ventricular (LV), and systemic arterial (SA) pressures were recorded simultaneously. High amplifier gain and rapid paper speed were used in order to facilitate measurement of the left ventricular end diastolic pressure (LVEDP). Cardiac outputs were determined using indocyanine green as the indicator. Injections were made into the pulmonary artery with sampling from the brachial artery.

Procedures

Pressures and cardiac outputs were first obtained in the control state. Atrial pacing ("tachypacing") was then initiated at a rate which was approximately 10-15 beats/minute above the patient's resting rate. Subsequent pacing rates were increased at approximately 20 beats per minute up to a maximum of 150 beats/min or to the development of chest pain. Pressures and cardiac output were recorded 3 to 5 min after the initiation of each new pacing level. Pressures were also recorded during a brief interruption of each pacing. The LVEDP recorded during the interruption of pacing is the average value of eight consecutive beats beginning with the third beat after the interruption. After completion of this part of the study, pacing was discontinued, and followed by a 15 min recovery period. Atrial pacing was then re instituted at the initial pacing rate (IPR) and a cineangiogram was performed in the right anterior oblique position (RAO) with injection into the left atrium (LA). The electrocardiogram was recorded during the injection to confirm the presence of pacemaker capture and to record any arrhythmias which occurred during the angiogram. Fifteen minutes after the first angiogram, the pacing rate was increased to that level at which the patient developed chest pain or to a maximal rate of 150 beats/minute. When the patient developed chest pain (usually 3-5 min of pacing), a second LA angiogram was done in the RAO position. The pacing was slowed to the IPR just prior to the injection. Pacing was then discontinued for a 20 min recovery period during which time angina was spontaneously relieved. Measurements of pressures and cardiac outputs were repeated at IPR and the patient was again paced at the rapid pace rate until the development of angina (3-5 min). Repeat measurements of pressure and flow were made before giving 0.3 mg of nitroglycerin (GTN) sublingually, as well as two minutes after the administration of GTN. A third LA angiogram was then performed in the same manner as previously described. All angiograms were done at the same heart rate. i.e., IPR, so that the cycle lengths were nearly identical.

A total of approximately 120 cc of radiographic dye (Renografin 76, Squibb) was used for the LV angiograms. This amount, which did not exceed 2 ml/kg in any patient, was given over a 45-60 min period. During the time of the entire study, the patients received 500-700 ml of dextrose solution for flushing the catheters. The time and use of intravenous fluids, in the presence of good renal function, should prevent any significant change in serum osmolality.

Selective coronary angiograms were done on each patient 24-48 hours after the study.

Data Analysis

Intracardiac pressures, cardiac index (CI), and left ventricular stroke work index (LVSWI) were evaluated for each patient. Cineangiograms were interpreted independently by three observers for qualitative abnormalities of wall motion. Comparison of the control, "tachypace," and postnitroglycerin cineangiograms was facilitated by tracing the end diastolic and end systolic ventricular outlines.

Results

The patients included in this study are divided on the basis of their response to nitroglycerin. Patients 1-6 had an improvement in left ventricular wall motion following nitroglycerin. Patient 7 had a questionable response, and patient 8 had atypical chest pain but normal wall motion and normal coronary arteries.

The hemodynamic data for all patients are summarized in table 1. Data are tabulated for the pre-pace control, rapid pace, and rapid pace post nitroglycerin (pace-T) periods.

The control LVEDP was elevated at rest in three patients (RP, DF, JR). During "tachypacing" two of these patients (RP, JR) had decrease in the end diastolic pressure; however, patient DF had an increase in the LVEDP which was further accentuated during the brief interruption of pacing. In one patient (JE) a normal resting LVEDP became elevated with "tachypacing." Following GTN the LVEDP decreased or remained within the normal range in the seven patients on whom the data were available. The most dramatic reductions in LVEDP were seen during the pace interrupt recordings where the end diastolic pressures were more easily determined.

During "tachypacing" the systemic arterial pressure increased in six patients. Following nitroglycerin seven patients had significant reduction in mean systolic arterial pressure. The low resting CI in four patients (DF, LH, MA, BC) showed little change during atrial pacing. Following nitroglycerin the CI fell in all seven patients in whom it was measured. The LVSWI was reduced by rapid pacing with a further reduction following GTN in all patients.

During "tachypacing" all patients developed chest pain similar to that which they had complained of prior to hospitalization. Each patient in the past had taken GTN for this type of chest discomfort. Sublingual GTN (0.3 mg) resulted in a
Table 1

Hemodynamic Data

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age, Sex</th>
<th>State</th>
<th>HR (L/min/M²)</th>
<th>SA (mm Hg)</th>
<th>SA (mm Hg)</th>
<th>PA (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>LVEDP-I (mm Hg)</th>
<th>LVSWI (gm-m/beat/M²)</th>
<th>Chest Pain</th>
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<tr>
<td>JE</td>
<td>38 M</td>
<td>Control</td>
<td>92</td>
<td>3.9</td>
<td>140/95</td>
<td>115</td>
<td>16</td>
<td>9</td>
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<tr>
<td></td>
<td></td>
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<td>150</td>
<td>3.0</td>
<td>135/105</td>
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<td>15</td>
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<td>8</td>
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<td>RP</td>
<td>42 M</td>
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<td>115</td>
<td>14</td>
<td>15</td>
<td>—</td>
<td>58</td>
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<td></td>
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<td>Pace</td>
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<td>2.8</td>
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<td>130</td>
<td>20</td>
<td>12</td>
<td>12</td>
<td>33</td>
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<td>120</td>
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<td>6</td>
<td>8</td>
<td>27</td>
</tr>
<tr>
<td>DF</td>
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<td>Control</td>
<td>70</td>
<td>2.3</td>
<td>162/95</td>
<td>115</td>
<td>17</td>
<td>15</td>
<td>—</td>
<td>46</td>
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<td>2.6</td>
<td>195/125</td>
<td>145</td>
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<td>22</td>
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<td>35</td>
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<td>—</td>
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<td>130</td>
<td>20</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>LH</td>
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<td>63</td>
<td>2.5</td>
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<td>105</td>
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<td>95</td>
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<td>6</td>
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<td>17</td>
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<td>BC</td>
<td>58 F</td>
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<td>61</td>
<td>2.0</td>
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<td>14</td>
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<td>85</td>
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<td>7</td>
<td>6</td>
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<tr>
<td>JR</td>
<td>53 M</td>
<td>Control</td>
<td>80</td>
<td>3.7</td>
<td>150/85</td>
<td>110</td>
<td>18</td>
<td>17</td>
<td>—</td>
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<td>7</td>
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<td>HW</td>
<td>49 M</td>
<td>Control</td>
<td>75</td>
<td>2.8</td>
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<td>105</td>
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<td>24</td>
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Abbreviations: HR = heart rate; CI = cardiac index; SA = systemic artery pressure (SA = mean); PA = mean pulmonary artery pressures; LVEDP = left ventricular enddiastolic pressure; LVEDP-I = LVEDP during transient interruption of pacing; LVSWI = left ventricular stroke work index; State: Control = baseline resting state; Pace = peak pacing rate; Pace-T = peak pacing rate after nitroglycerin.

The disappearance of pain in five patients and a diminution of pain in three patients within 1–3 min. The angiographic data are summarized in table 2 and the ventricular outlines are depicted in figure 1. Five patients had severe coronary artery disease with two or three vessel involvement in four. One patient (MA) had a 60% stenosis of his LAD and

<table>
<thead>
<tr>
<th>Patient</th>
<th>Control</th>
<th>Tachypacing</th>
<th>Tachypacing post nitroglycerin</th>
<th>Coronary artery % occlusion</th>
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</thead>
<tbody>
<tr>
<td>JE</td>
<td>Antero-apical hypokinesis</td>
<td>Anterior hypokinesis</td>
<td>Antero-apical hypokinesis</td>
<td>90 75 75</td>
</tr>
<tr>
<td>RP</td>
<td>Normal</td>
<td>Apical hypokinesis</td>
<td>Normal</td>
<td>90 0 0</td>
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<tr>
<td>DF</td>
<td>Infero-apical-posterior basal hypokinesis</td>
<td>Increased infero-apical hypokinesis, posterior basal akinesis</td>
<td>Return to control with improved contraction of inferior wall</td>
<td>90 100 90</td>
</tr>
<tr>
<td>LH</td>
<td>Mild apical hypokinesis</td>
<td>Increased apical hypokinesis</td>
<td>Improved over control</td>
<td>75 0 100</td>
</tr>
<tr>
<td>MA</td>
<td>Normal</td>
<td>Anterior hypokinesis</td>
<td>Normal</td>
<td>60 0 0</td>
</tr>
<tr>
<td>BC</td>
<td>Antero-apical hypokinesis</td>
<td>Increased antero-apical</td>
<td>Normal</td>
<td>60 0 0</td>
</tr>
<tr>
<td>JR</td>
<td>Anterior hypokinesis</td>
<td>Apex moves upward</td>
<td>Similar to control</td>
<td>100 50 50</td>
</tr>
<tr>
<td>HW</td>
<td>Normal</td>
<td>Questionable change</td>
<td>Normal</td>
<td>0 0 0</td>
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Abbreviations: LAO = left anterior descending; LCX = left circumflex; RCA = right coronary artery; Control = angiographic studies at initial pacing rate; Tachypacing = at peak pacing rate.

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GTN AND LV WALL MOTION IN CAD

one patient (BC) had an abnormally small left anterior descending artery (LAD) without any discrete lesion. Patient HW had completely normal coronary arteries.

Five patients (JE, DF, LH, BC, JR) had abnormal LV wall motion on the control angigram. In four of these patients there was a definite increase in the same segmental abnormalities during "tachypacing." In one patient (JR) the changes in wall motion were difficult to evaluate due to an inadvertent alteration in position of the patient between the angiograms. This resulted in obvious distortion in ventricular outline. Three patients (RP, MA, HW) had normal control angiograms, two of whom had coronary artery disease and did develop abnormal wall motion with "tachypacing." In general the segmental abnormalities corresponded to the location of the coronary artery disease. Following nitroglycerin there was definite improvement in LVWMM in six patients. The post nitroglycerin angiogram became normal in two patients (RP, MA) in whom the abnormalities were noted only with "tachypacing." These two patients had single vessel disease. In three patients (DF, LH, BC) the post nitroglycerin cineangio- gram demonstrated strikingly better contraction pattern than that in the control study, while patient JE showed some improvement in the apical akinetic area induced by "tachypacing." Changes in end diastolic and end systolic volumes were not quantitated. However it is clear from figure 1 that both volumes were reduced uniformly following administration of nitroglycerin.

Discussion

In 1967 Sowton described the technique of atrial pacing as means of evaluating ventricular performance in patients with coronary artery disease. Since that time many studies have reported on the hemodynamic, electrocardiographic, and metabolic changes associated with "tachypacing" induced myocardial ischemia. However, many patients with severe coronary artery disease do not show hemodynamic or metabolic abnormalities with "tachypacing" despite the development of chest pain and ST segment depression. In the present study only two patients developed an elevation of the LVEDP with "tachypacing" and only one patient had a further increase in LVEDP during the interruption of pacing. Comparison of the LVEDP with the LVSWI resulted in abnormal "pacing function curves" in these two patients.

Several reports have shown that nitroglycerin effectively relieves the symptomatic complaints and improves the hemodynamic and electrocardiographic abnormalities associated with tachypacing induced myocardial ischemia. Chiong et al. studied these responses in greater detail and demonstrated that there was a reduction in the ST segment depression, CI, SA, LVEDP and mean lactate production and potassium loss following GTN despite the continuation of the pacing stress. In the present study GTN also improved chest pain and significantly lowered the CI, SA, and LVEDP. The latter was most evident in the pace interrupt data. None of the patients had an elevated LVEDP following GTN.

Segmental abnormalities of wall motion are frequently produced or accentuated during the myocardial ischemia that develops with "tachypacing". Often these abnormalities occur without any associated hemodynamic deterioration. Segmental dysfunction, therefore, is a more sensitive indicator of severe coronary artery disease and in general corresponds to the location of the coronary lesions. In the present series, two patients with
single vessel disease (LAD) had normal control angiograms but developed hypokinesis of the anterior wall with “tachypacing.” Four of five patients with abnormal initial angiograms had an accentuation of their pre-existing wall motion abnormalities. Following GTN left ventricular wall motion was improved in six patients although the degree of improvement did not directly correlate with the magnitude of the hemodynamic changes. The post nitroglycerin angiogram returned to the normal control pattern in the two patients who had normal wall motion prior to “tachypacing.” In three patients, there was improvement in left ventricular wall motion demonstrated in the post nitroglycerin angiogram compared with the control angiogram. This suggests that an element of myocardial ischemia was present at the time of the control study. Two patients with mild abnormality of the LAD coronary artery developed hypokinesis of left ventricular anterior wall with tachypacing in the absence of severe discrete coronary lesions. This may be due to an underestimation or failure of the coronary arteriograms to identify severe degrees of stenosis in these cases. Vlodaver\textsuperscript{15} has recently reported that antemortem coronary arteriograms failed to demonstrate 33% of the lesions found on postmortem examination. Other studies\textsuperscript{16, 17} have also indicated that coronary arteriograms tend to demonstrate less extensive disease than is anatomically present. The fact that both of these patients had an excellent response to nitroglycerin may be explained on the basis of this discrepancy.

The mechanism of action of nitroglycerin has been extensively studied\textsuperscript{18-27} but there is still doubt as to the relative importance of its peripheral and central effects. Mason and Braunwald\textsuperscript{21} demonstrated that GTN reduced systemic arterial pressure, lowered vascular resistance, and decreased venous tone. This resulted in a diminished venous return and presumably in smaller LV volume. Also, Williams et al.\textsuperscript{22} has reported a 6% decrease in left ventricular systolic and diastolic separation of epicardial clips following GTN. This change was interpreted as reflective of concomitant change in ventricular volumes. This reduction in preload and afterload results in a decreased myocardial oxygen requirement.\textsuperscript{22, 28} Angiographic studies,\textsuperscript{18, 19} on the other hand, have demonstrated that GTN dilates the major coronary arteries. This, however, is not necessarily reflected by a net increase in coronary blood flow since the latter is dependent on resistance changes in the smaller vessels. The results of coronary flow measurements after administration of GTN have been conflicting\textsuperscript{23, 25} although most studies have not shown an increase in net flow following GTN. A redistribution of flow through collateral channels to ischemic areas may be an important mechanism.\textsuperscript{20} Recently two separate studies\textsuperscript{26, 27} have shown an increased perfusion of ischemic areas following GTN. Thus the action of nitroglycerin may be twofold, causing a reduction in oxygen requirements and a redistribution of coronary blood flow.

Selective coronary arteriograms outline the anatomy of the coronary vessels but do not assess the functional significance of the lesions that are demonstrated. Atrial “tachypacing,” therefore, is important in evaluating ventricular performance and identifying areas of segmental myocardial ischemia. The effects of nitroglycerin on these wall motion abnormalities and on ventricular function as a whole provide additional information concerning reversibility of the abnormally contracting ischemic myocardium. With this information the need for surgical bypass and the success of these procedures can be more objectively evaluated. Furthermore, this type of investigation may be useful in objective assessment of the effects of any new antianginal drugs on the ischemic myocardium.

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