Hemodynamic Effects of Nitroglycerin in Acute Myocardial Infarction

Decrease in Ventricular Preload at the Expense of Cardiac Output

By David O. Williams, M.D., Ezra A. Amsterdam, M.D., and Dean T. Mason, M.D.

SUMMARY

Nitroglycerin (NTG) has recently been suggested to decrease myocardial ischemia and enhance cardiac pump function during acute myocardial infarction (AMI). To evaluate the sublingual agent in this condition, the hemodynamic effects of 0.4 mg NTG administered to 16 supine patients during the first 72 hours of AMI were determined serially 5, 10 to 15, and 20 to 30 minutes post-NTG. Data were evaluated for the entire group, as well as for six patients with normal pulmonary artery wedge pressure (PAW) (< 12 mm Hg; mean 7) who formed group I and for ten patients with elevated PAW (> 12 mm Hg; mean 19) who comprised group II. In the 16 patients, NTG resulted in significant decreases in PAW (14 to 7 mm Hg; P < .01), mean systemic arterial pressure (MAP) (95 to 82 mm Hg; P < .01), cardiac index (CI) (1.79 to 1.46 L/min/m²; P < .02), stroke index (SI) (24 to 18 cc/m²; P < .01) and stroke work index (SWI) (27 to 20 gm·m/m²; P < .01). These alterations were significant in both subgroups, with the decline in PAW greater (P < .02) in group II (19 to 9 mm Hg) than in group I (7 to 4 mm Hg). The decrease in SWI related to the fall in PAW was significantly greater (P < .05) in group I (2.03 gm·m²/m²) compared to group II (0.82), thereby indicating greater impairment of ventricular function in the group II patients. Heart rate (HR) increased slightly in the 16 patients (77 to 82 beats/min; P < .05) and in group I (71 to 80 beats/min, P < .05), while there was no change in group II. There was no significant change in total peripheral vascular resistance (TPVR) for the entire group or in the two subgroups. This study demonstrates that, regardless of initial left ventricular filling pressure, sublingual NTG given in the acute phase of AMI results in rapid fall in PAW, concomitant with decreases in systemic blood pressure, cardiac output and SWI, without changes in TPVR and with little or no effect on heart rate. Since TPVR was unaltered, the decline in MAP was due to fall in cardiac output. Thus, the principal action of sublingual NTG in AMI appears to be systemic venodilation with consequent reduction of ventricular preload. This effect is translated into decline of pump output even in patients with high initial filling pressures. Although NTG may rapidly relieve pulmonary congestion and lower myocardial oxygen consumption, use of the agent sublingually is limited in AMI because these salutary effects are accompanied by potentially deleterious fall in cardiac output and systemic blood pressure.

Additional Indexing Words:

Coronary artery disease
LV unloading
Congestive heart failure
Myocardial oxygen consumption
LV preload
Vasodilator therapy
LV afterload
Ventricular function

The remarkable efficacy of nitroglycerin in angina pectoris has been recognized for many years. Because of the decline in systemic arterial pressure which may result with the drug, however, there has also been a strong traditional admonition against its use in patients with myocardial infarction.1,2 Recent recognition of the significance of the imbalance between myocardial oxygen demand and supply as the determinant of myocardial ischemia has aroused interest in therapeutic interventions which may favorably affect this imbalance and preserve viable heart muscle in acute myocardial infarction.3-4 Other agents, which reduce ventricular afterload or the impedance to left ventricular ejection, also have the potential of improving left ventricular function during acute myocardial infarction while diminishing myocardial oxygen demand.5-9 With these considerations, we investigated the hemodynamic effects of nitroglycerin (NTG) administered sublingually to patients in the acute phase of myocardial infarction with special focus on those with abnormal cardiac performance.
Materials and Method

Sixteen randomly selected patients with acute myocardial infarction underwent hemodynamic evaluation within 72 hours of the onset of symptoms. There were 13 males and 3 females ranging in age from 47 to 86 years with a mean age of 63 years. Diagnosis of myocardial infarction was based on a combination of clinical presentation, pathologic Q waves and characteristic serum enzyme abnormalities. Eight patients had transmural anterior wall infarctions and two had anterior subendocardial infarctions. The six remaining patients had inferior wall transmural myocardial infarctions. At the time of the study no patients had received digitalis compounds, diuretic agents, sympathomimetics or beta adrenergic blocking agents. Informed consent was obtained from all patients prior to their evaluation.

Under local anesthesia a 20 gauge Longdwell polyethylene catheter was inserted into either the right brachial or right radial artery and a Swan-Ganz balloon tipped flow-directed catheter was advanced to the pulmonary artery from either the left antecubital vein or right femoral vein. Pressures were obtained utilizing a Statham P23Db strain gauge with zero reference point at mid thorax. Control and post-NTG cardiac outputs were determined in duplicate using the indicator-dilution technique by the injection of indocyanine green dye into the pulmonary artery with sampling from the systemic arterial site utilizing a constant-speed Harvard withdrawal pump and Gilford densitometer. All data were recorded on a Hewlett Packard multichannel recorder.

Following a 15 min equilibration period, control values of heart rate, phasic and mean pulmonary artery pressures, mean pulmonary artery wedge pressure (PAW), phasic and mean (MAP) systemic arterial pressures, and cardiac output (CO) were obtained. Then 0.4 mg NTG was administered sublingually, and values of the above parameters were again obtained 5, 10 to 15, and 20 to 30 min later. In addition, stroke index (SI), stroke work index (SWI) (SI × [MAP-PAW] × 0.0136 gmm/m²) and total peripheral vascular resistance (MAP/CO × 80 dynes-sec-cm⁻³) were calculated.

Results

Within 5 to 10 min following administration of nitroglycerin, pulmonary artery wedge pressure was reduced from 14 ± 2 (SEM) to 7 ± 1 mm Hg (P < .01) in the 16 patients. Comparison of group I patients with normal PAW to those with elevated PAW (group II) is shown in table 1 and figure 1. In group I, pulmonary artery wedge pressure promptly declined from 7 ± 1 to 4 ± 1 mm Hg (P < .05) within 5 to 10 minutes (fig. 1A). In group II, a rapid fall in PAW also occurred, from 19 ± 1 to 9 ± 2 mm Hg (P < .001) (fig. 1B). This absolute decrement was considerably greater (P < .02) than in group I, although percent change was similar in the two groups.

Mean systemic arterial pressure fell from 95 ± 4 to 82 ± 4 (P < .01) in the 16 patients. Significant declines in mean systemic arterial pressure occurred in both groups (table 1). Within 5 to 10 min, group I mean pressure fell from 100 ± 4 to 89 ± 5 mm Hg (P < .02), and group II from 92 ± 6 to 78 ± 6 mm Hg (P < .02); there was no significant difference in this response between the two groups.

A small but significant rise (P < .05) in heart rate was seen in the 16 patients from 77 ± 3 to 82 ± 4 beats/min. In group I patients, heart rate rose from 71 ± 4 to 80 ± 4 beats/min (table 1). In group II patients, however, there was no significant change in heart rate (table 1) despite the substantial decline in systemic artery pressure.

Cardiac index declined from 1.79 ± 0.10 to 1.46 ± 0.10 (P < .02) in the 16 patients. The effects of NTG on cardiac index in the two subgroups are given in table 1 and figure 2. In group I patients, the low cardiac index of 1.83 ± 0.10 declined to 1.60 ± 0.10 L/min/m² (−11%; P < .05) by the 20–30 minute post-NTG period (fig. 2A). In contrast, in the group II patients there was a prompt decline within the 5–10 minute period from a low cardiac index of 1.77 ± 0.14

Figure 1

*Effects of sublingual nitroglycerin on left ventricular filling pressure, measured as mean pulmonary artery wedge pressure (PAW), in group I (A) and group II (B) patients.*

Figure 2

*Effects of sublingual nitroglycerin on cardiac index in group I (A) and group II (B) patients.*

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Table 1

**Hemodynamic Response of Patients to Sublingual Nitroglycerin**

<table>
<thead>
<tr>
<th></th>
<th>Group I – PAW ≤ 12 mm Hg (N = 8)</th>
<th>Group II – PAW &gt; 12 mm Hg (N = 10)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>5-10</td>
<td>10-15</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>71 ± 4</td>
<td>80 ± 4</td>
<td>77 ± 4</td>
</tr>
<tr>
<td>PAW (mm Hg)</td>
<td>7 ± 1†</td>
<td>4 ± 1</td>
<td>5 ± 1</td>
</tr>
<tr>
<td>Systemic arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Systolic</td>
<td>150 ± 8</td>
<td>128 ± 10</td>
<td>143 ± 13</td>
</tr>
<tr>
<td>Diastolic</td>
<td>78 ± 3</td>
<td>76 ± 5</td>
<td>75 ± 4</td>
</tr>
<tr>
<td>Mean</td>
<td>100 ± 4</td>
<td>89 ± 5</td>
<td>96 ± 5</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>1.83 ± .10</td>
<td>1.75 ± .22</td>
<td>1.66 ± .05</td>
</tr>
<tr>
<td>Stroke index (cc/m²)</td>
<td>26 ± 3</td>
<td>23 ± 3</td>
<td>21 ± 1</td>
</tr>
<tr>
<td>Peripheral vascular resistance (dynes-sec-cm⁻¹)</td>
<td>2600 ± 236</td>
<td>2600 ± 377</td>
<td>2643 ± 187</td>
</tr>
<tr>
<td>Stroke work index (gm · m/m²)</td>
<td>32.7 ± 3.4†</td>
<td>23.0 ± 3.3</td>
<td>25.9 ± 2.2</td>
</tr>
</tbody>
</table>

Abbreviations: PAW = pulmonary artery wedge pressure; NS = not significant.
*Significance of maximal or minimal post-NTG value compared to control value.
†Significant difference (P < .05) between control values of group I and II.
to 1.31 ± 0.10 L/min/m² (−25%; P < .02) (fig. 2B). The greatest absolute reduction in cardiac index which occurred in the 30 minutes after NTG was not significantly different between the two subgroups, this comparison being made between the decline at 20–30 minutes from pre-NTG in group I and the decline at 5–10 minutes from pre-NTG in group II.

Control mean peripheral vascular resistance was elevated in both subgroups of patients (2600 ± 236 and 2311 ± 283 dynes-sec-cm⁻², respectively) (table 1). There were no significant alterations following NTG for the entire group of patients or in either of the two subgroups (table 1).

Stroke work index of 32.7 ± 3.4 decreased to 23.0 ± 3.3 gm·m/m² (P < .05) following NTG in group I (table 1 and fig. 3A). There was also a fall in stroke work index from 22.6 ± 2.8 to 15.1 ± 2.4 gm·m/m² (P < .01) in group II (table 1 and fig. 3B). The absolute decrease in SWI was the same in the two groups. In addition, figure 3 demonstrates the relation between stroke work index and pulmonary artery wedge pressure before and after NTG in the two groups of patients. The decrease in SWI relative to the fall in PAW was significantly greater (P < .05) in group I (2.03 ± 0.90 gm·m/m²/mm Hg) compared to the group II patients (0.82 ± 0.25 gm·m/m²/mm Hg).

Discussion

This study demonstrates that sublingual nitroglycerin given during the acute phase of myocardial infarction results in a rapid decline in pulmonary artery wedge pressure which was most marked in those patients whose left ventricular filling pressures were elevated (fig. 1). Mean arterial pressure fell substantially in all patients while there was little or no change in heart rate (table 1). Since the total peripheral vascular resistance was not changed (table 1), the decline in blood pressure was due to reduction of cardiac output in all of our patients (fig. 2).

The hemodynamic alterations induced by nitroglycerin observed herein in myocardial infarction are consistent with the effects of the agent in normal individuals. Following the administration of NTG to normal subjects, Hoeschen and co-workers described a mild decrease in systemic arterial pressure and stroke volume, without an alteration of cardiac output since heart rate increased substantially. Further, in normal volunteer subjects who received sublingual 0.6 mg NTG, Brachfeld et al. reported a decline in pulmonary capillary wedge pressure and pulmonary arterial pressures, in addition to the minimal fall in brachial arterial pressure and rise in heart rate, while cardiac output and peripheral vascular resistance were unchanged. Although regional forearm vascular resistance is reduced by NTG in normal subjects, total peripheral vascular resistance is not significantly changed by the drug in normal volunteer individuals. Importantly, sublingual nitroglycerin directly relaxes the smooth muscle in the systemic capacitance bed, and this decrease in venous tone which reduces return of blood to the heart is the predominant action of sublingual NTG on the peripheral circulation. In agreement with the principal peripheral vascular action of sublingual NTG being that of systemic venodilation are the findings that external and internal ventricular dimensions are reduced by the agent. This decrease in cardiac size occurs in both end-systolic and end-diastolic dimensions with the decrease in end-diastolic size being more predominant. Thus in normal subjects sublingual NTG reduced systemic blood pressure and stroke volume and usually cardiac output because of its major action of reducing ventricular preload.

The hemodynamic effects of NTG in acute coronary disease in this study are also in agreement with the reports of the changes induced by the nitrate in patients with chronic coronary heart disease and angina pectoris. Hoeschen and co-workers observed decreases in systemic arterial pressure and stroke volume with increase in heart rate and no significant change in cardiac output following 0.6 mg sublingual nitroglycerin as in the normal subjects in their investigation. Similarly, Gorlin and colleagues found reductions in left ventricular filling pressure and pulmonary and systemic arterial pressures while heart rate and peripheral vascular resistance were not significantly altered by NTG in chronic coronary dis-
Consistent with our findings in acute coronary disease (figs. 1 and 2), these workers noted a greater fall in pulmonary capillary wedge pressure than in their normal subjects; they also noted that cardiac output tended to decline. These hemodynamic actions of NTG in chronic coronary disease have been further supported by the studies of other investigators. Christensson et al. observed declines in blood pressure, stroke volume and cardiac output without changes in total peripheral vascular resistance; Park reported decreases in left ventricular filling pressure and brachial artery pressure, and declines in stroke volume, cardiac output and stroke work without change in total systemic resistance, and associates likewise noted decreases in stroke volume and cardiac output following 0.6 mg NTG in clinical coronary disease; and Najmi and co-workers reported that 0.4 mg sublingual NTG in patients with coronary insufficiency reduced stroke and cardiac indices, increased heart rate, and lowered pulmonary and brachial arterial pressures without significant alteration in systemic vascular resistance. Finally, recent echocardiographic studies in our laboratories have shown reductions in internal left ventricular end-diastolic and end-systolic volumes, ejection fraction, stroke volume and cardiac output while total systemic arterial resistance was unchanged after sublingual nitroglycerin in patients with chronic coronary disease. Thus, it is evident that the principal action of sublingual nitroglycerin is the relaxation of the systemic venous bed which causes decreases of ventricular preload and cardiac output in coronary patients with angina, including those with chronic abnormalities of ventricular performance of elevated left ventricular filling pressure and lowered cardiac output before the nitrate, as well as in coronary patients and normal subjects with normal cardiac function at rest.

In contrast to the above observations, which indicate that sublingual nitroglycerin is primarily an agent for reducing cardiac preload, is the recent report of Gold et al. which noted improvement in reduced cardiac output and decline in total peripheral vascular resistance following 0.3 mg sublingual nitroglycerin in patients with acute myocardial infarction. These salutary hemodynamic effects occurred simultaneously with considerable decline in pulmonary artery wedge pressure, while systemic arterial pressure fell minimally and heart rate was unchanged. In addition, cardiac output was reported to rise and systemic resistance to fall in a small number of patients with chronic ischemic ventricular dysfunction. These workers attributed the beneficial effects of NTG on disturbed cardiac performance in acute and chronic coronary disease to nitrate-induced dilation in the systemic arterial and venous beds, and possibly to reduced myocardial ischemia by ventricular unloading and/or improved coronary blood flow to segmental areas of ischemic heart muscle.

The present clinical investigation of the hemodynamic effects of nitroglycerin administered during the acute phase of myocardial infarction does not support the use of the sublingual nitrate as an agent to increase cardiac output and enhance pump performance in this condition. Rather, we observed that NTG further diminished the lowered cardiac output in acute myocardial infarction (fig. 2). Furthermore, this fall in cardiac output occurred more rapidly in our patients with elevated left ventricular filling pressures (group II). Our results indicate that sublingual nitroglycerin acts principally as a ventricular preload reducing agent in acute coronary pump dysfunction with attendant reduction of cardiac output (fig. 2), similar to its primary action of decreasing venous return to the heart in chronic coronary heart disease and in subjects with normal ventricles.

Further, we did not observe a decline in total peripheral vascular resistance in any of our patients (table 1) and thereby the impedance or afterload to ventricular ejection was not diminished regardless of the level of left ventricular filling pressure in acute myocardial infarction. The impairment of sympathetic vasoconstriction in acute myocardial infarction supports the apparent absence of NTG-induced dilation of the total systemic resistance bed, since the attenuated reflex activity in this condition would not mask direct arteriolar dilation. In addition, the lack of total systemic arteriolar dilation with sublingual nitroglycerin in acute coronary heart disease is consistent with previous observations in chronic coronary disease and in normal subjects. Thus, also concerning the impedance to left ventricular ejection, it is important to emphasize that we observed no special, selective benefit on pump output in acute coronary heart failure, in contradistinction to the results of Gold et al.

In considering the effect of NTG on myocardial oxygen consumption in acute myocardial infarction, the decrease in left ventricular filling pressure (fig. 1) and mean systemic arterial pressure with little increase or no change in pulse rate (table 1) suggest that myocardial oxygen requirements were reduced in our patients. On the other hand, the decrease in cardiac index (fig. 2) and fall in coronary perfusion pressure may attenuate the beneficial effect of the agent of lowering myocardial oxygen demand by decreasing coronary blood flow.

Left ventricular dysfunction was clearly evident in our group II patients who manifested elevated end-diastolic pressures with reduced cardiac output prior.
to the nitrate (figs. 1 and 2). In addition, it is pointed out that our group I patients probably had substantially abnormal ventricular performance, despite their normal pulmonary artery wedge pressure (fig. 1), since their cardiac output was reduced (fig. 2) suggesting a relative degree of hypovolemia. It is likely that correction of reduced intravascular volume in the group I patients would have resulted in abnormally elevated left ventricular filling pressure. It is probable that group II patients had greater disturbance of ventricular function, since their decrement in pulmonary artery wedge pressure with NTG was greater than group I patients (fig. 1), while the extent of decline in cardiac output with the agent was similar in the two groups (fig. 2). Thus, the group II patients appeared to have flatter and more depressed ventricular function curves as evidenced by the generally smaller fall in stroke work index relative to ventricular filling pressure reduction compared to the group I patients (fig. 3). The finding of major importance in this study, that impaired ventricular pump function in acute myocardial infarction is not improved by sublingual NTG, is supported by the hemodynamic observations with the agent in both groups, since the two groups of patients demonstrated abnormal variables of ventricular performance prior to the drug.

The observations in this study are helpful in comparing the differential effects of the peripheral vasodilator drugs with regard to their relative relaxant properties on the systemic arterial and venous beds. Thus, sublingual nitroglycerin is principally a venodilator agent causing reduction of ventricular preload while, in contrast, inhaled amyl nitrite or intravenous nitroglycerin has a rapid and profound systemic arteriolar dilator action which thereby primarily lowers the impedance or afterload to ventricular ejection. Interestingly, intravenous nitroprusside produces an effect intermediate between sublingual nitroglycerin and inhaled amyl nitrite; thus nitroprusside has relatively equal dilator actions on the peripheral resistance and capacitance beds, thereby reducing both ventricular afterload and preload.

In conclusion, this report does not support the use of sublingual nitroglycerin in acute myocardial infarction as an agent to improve pump function. Although the agent might rapidly relieve pulmonary vascular congestion, the degree of decrease in left ventricular filling pressure is unpredictable and results in decline of cardiac output. Use of this agent for the relief of ischemic pain associated with acute myocardial infarction might be successful in some patients because of the nitrate's reduction of myocardial oxygen needs; but again the unfavorable hemodynamic consequences of sublingual NTG must be recognized.

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