Use of Sublingual Nitroglycerin in Congestive Failure following Acute Myocardial Infarction

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SUMMARY

The effect of 0.3 mg sublingual nitroglycerin (NTG) was evaluated by hemodynamic measurements and precordial S-T-segment mapping in 17 patients following acute myocardial infarction.

In all cases NTG produced a prompt reduction in mean pulmonary capillary wedge pressure (PCW) from an average of 19 ± 2 to 14 ± 1 mm Hg associated with a small fall in mean arterial pressure from a mean of 85 ± 4 to 82 ± 4 mm Hg. No significant change in heart rate occurred.

In patients without left ventricular failure (PCW 3–12 mm Hg) cardiac output (CO) fell 9%. By contrast, in patients with moderate left ventricular failure (PCW 13–22 mm Hg) CO rose 18%. In three patients with refractory left ventricular failure (PCW 25–31 mm Hg) CO rose 25%. Two of these patients were treated with repetitive NTG doses in addition to previously ineffective diuretic therapy with resolution of resistant pulmonary edema. No significant changes in the magnitude of S-T-segment elevations were noted.

NTG may have a special role in the management of acutely ill patients with myocardial infarction in whom pulmonary edema does not respond to conventional therapy.

Additional Indexing Words:
Pulmonary edema Vasodilator therapy

PULMONARY congestion following acute myocardial infarction usually responds favorably to therapy with morphine, oxygen, tourniquets, and intravenous diuretics. In some patients, however, pulmonary edema resists these interventions and may even continue into a chronic phase. Such patients may show signs of diminished peripheral perfusion with a normal blood pressure and at the time of hemodynamic measurement have an elevated peripheral vascular resistance.

Persistent pulmonary edema with an elevated peripheral vascular resistance has the elements of a vicious cycle. Increased preload and afterload increase myocardial oxygen demand, while pulmonary congestion may limit oxygen supply. The cycle may be interrupted by an agent which can lower left ventricular filling pressure while improving peripheral perfusion without increasing myocardial oxygen demand. Nitroglycerin has been shown to abruptly lower left ventricular filling pressure during acute angina pectoris with resolution of myocardial ischemia1–4 but is seldom used after acute myocardial infarction because of the possibility of severe hypotension.

The following study was performed (1) to determine whether sublingual nitroglycerin can lower left ventricular filling pressure significantly in patients with established myocardial infarction, (2) to delineate the effects on arterial pressure in these patients, and (3)
to observe electrocardiographically the effect on the extent and magnitude of myocardial injury.

Method

Hemodynamic studies were performed in 17 patients admitted to the MIRU Intensive Study Area. There were 15 males with an average age of 53 years and two females with an average age of 62 years. All had acute or remote infarctions involving the anterior wall. At the time of study, four patients had acute myocardial infarction without evidence of left ventricular failure (group I, pulmonary capillary wedge pressure [PCW] 3-12 mm Hg); 10 patients had acute myocardial infarction with evidence of left ventricular failure (group II, PCW 13-22); and three patients had intractable left ventricular failure (group III, PCW 25-31) 1 month after infarction. All patients in groups I and II were studied within 1 week of the acute infarct. In all instances the occurrence of a myocardial infarction was documented by the presence of a typical history, diagnostic electrocardiographic changes, and serum enzyme studies.

All patients had received therapy in the form of oxygen, antiarrhythmic agents, diuretics, digitalis, and anticoagulants. Diuretic and pressor agents were discontinued 3 hours prior to study and none was administered during the time of the study. Four patients in group II and one patient in group III were receiving circulatory assistance with the AVCO intravenous balloon pump.

Pulmonary artery (PA) and PCW pressures were monitored by the Swan-Ganz flow-directed catheter, and arterial pressures through an indwelling radial artery cannula. Cardiac output (CO) measurements were made at least in duplicate by the dye-dilution technic with 1-ml injections (7 mg) of indocyanine green dye into the pulmonary artery followed by 5 ml saline flush. Sampling was carried out through a Gilford densitometer from the radial artery with a Harvard constant-speed withdrawal pump (30 ml/min). Blood was reinfused into the artery after each output measurement. Dye curves were recorded directly and the output signal was passed to a Lexington analog computer. Outputs were accepted if the integration curve held constant during exponential decay for 3 points separated by 0.5-sec intervals. The computer was calibrated with a 1:1000 dilution of dye in blood, prepared with a Hamilton microcannula.

Nine patients in groups I and II underwent precordial electrocardiography using a 35-electrode blanket, recently described by Maroko et al. The sum of the S-T-segment elevations and the number of sites in which S-T-segment elevations exceeded 0.1 mv were analyzed independently by two observers.

During the 10-min control period heart rate, mean arterial pressure (MAP), PA, PCW pressure, and CO were recorded together with the precordial S-T-segment map. After completion of control measurements, 0.3 mg nitroglycerin was administered sublingually. MAP and PCW pressures were then continuously monitored and the initial measurements were repeated at peak nitroglycerin effect (5-10 min after the dose). A third set of measurements was taken at 60 min when pressures had returned to control levels.

Total peripheral resistance (TPR) in units was calculated by the formula: MAP/CI. The left ventricular stroke-work index (LVSWI) in g-m/m² was calculated by the formula: LVSWI = SI x (MAP-PCW) x 13.6/1000 where SI = stroke index in ml/m². The sum of S-T-segment elevations in 35 leads (ΣST) was used as an index of tissue injury, and the number of sites of S-T-segment elevation exceeding 0.1 mv (N-ST) was taken to reflect the extent of myocardial ischemic injury.

Student's t test for paired and unpaired data was used for all statistical calculations where applicable.

Results

At the time of study, all cases in group II had clinical evidence of left ventricular failure with rales and radiographic signs of pulmonary congestion. However, none was dyspneic and none noted subjective improvement. Two patients in group II were given nitroglycerin during persistent pain (table 1, A.I. and M.G.). Both stated that the pain diminished. The S-T-segment map in one (A.I.) showed a definite decrease in both N-ST and ΣST.

All patients in group III had clinical and X-ray evidence of pulmonary edema. All experienced improvement in their dyspnea. One, whose pulmonary edema had been present for 2 weeks on an intensive medical program, showed dramatic changes (fig. 1) with a rise in arterial pO₂ from 51 to 237 mm Hg 30 min following nitroglycerin administration (table 1, patient 17). Repetitive doses were given every 30 min and later, hourly, until pulmonary edema resolved. The effect of each dose was maximal at 5-10 min and was dissipated by 30 min. No tachyphylaxis was noted. This patient was discharged 3 weeks later on digitalis and
Table 1

**Clinical Data**

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Abbreviations: C = control before NTG; NTG = after nitroglycerin; HR = heart rate; MAP = mean arterial pressure; PCW = mean pulmonary capillary wedge pressure; CO = cardiac output; CI = cardiac index; LVSWI = left ventricular stroke work index; TPR = total peripheral resistance.

*On circulatory assistance.
†Died.
Figure 1

Hemodynamic effect of NTG on a patient with refractory pulmonary edema. Control hemodynamic measurements are shown at left. Administration of 0.3 mg NTG resulted in a prompt reduction in PCW pressure below the pulmonary edema range as shown at right. This fall in PCW pressure was accompanied by a 400 ml/min increase in CO.

80 mg of furosemide daily. No case in any group showed clinical deterioration.

One patient in group I and six in group II died following emergency surgical revascularization. Two of the three in group III died, one from arrhythmia and the other with progressive myocardial ischemia.

Hemodynamic Results

When the series was considered as a whole, there was a significant fall in the PCW (19–14 mm Hg, P < 0.01) and a small but significant fall in MAP (85–82 mm Hg, P < 0.05). There was no significant change in HR, CI, or TPR.

The average values for the entire series obscure significant differences between groups. These differences are not apparent in PCW pressure, which fell 5 mm in group I, 4 mm in group II, and 6 mm in group III (fig. 2). Similarly, MAP response was uniform, falling 3 mm in group I, 3 mm in group II, and 4 mm in group III (fig. 3). CO, however, increased significantly in patients with elevated PCW, averaging 13% in group II (P < 0.01 and 25% in group III (P < 0.05). By contrast, group I patients with normal filling pressures showed a decreased CO of 9% (fig. 4). LVSWI followed cardiac output increasing 19% (P < 0.01) in group II, 25% in group III (P < 0.05), and falling 7% in group I (fig. 5). TPR decreased by approximately 8% in both group II and III patients, but was unchanged in group I. The heart rate remained constant in all groups. Repeat measurements at 1 hour were not significantly different from control.

All nine patients who underwent precordial S-T mapping showed persistent S-T-segment elevation (1–3 days after infarction). Only one

Figure 2

Effect of NTG on mean pulmonary capillary wedge pressure. An immediate reduction in filling pressure occurred in all three groups of patients, averaging 5 mm Hg (GROUP I), 4 mm Hg (GROUP II), and 6 mm Hg (GROUP III).

Figure 3

Effect of NTG on mean arterial pressure. The response to NTG was similar in all three groups of patients. The fall in mean arterial pressure averaged 3 mm Hg (GROUP I), 3 mm Hg (GROUP II), and 4 mm Hg (GROUP III).
NITROGLYCERIN FOLLOWING ACUTE MI

Effect of NTG on cardiac output. CO increased significantly in patients with elevated PCW, averaging 13% in GROUP II and 25% in GROUP III. In patients with normal PCW, CO decreased 9%.

had persistent pain. Nitroglycerin produced no significant change in seven, and a minimal change in one (fig. 6, A). The only case that showed obvious S-T-segment improvement was the patient with persistent pain (fig. 6, B).

Discussion

Previous investigations in patients6,11 have shown that nitroglycerin lowers systemic arterial pressure and left ventricular filling pressure, and our findings in patients with myocardial infarction are in agreement with this observation. There is considerable dispute, however, concerning the effects of this drug on cardiac output which has been reported to rise, remain unchanged, or slightly decline. While these results are not entirely explained, the differences may be related to varying degrees of failure present in populations studied. Our results demonstrate that patients without failure or with lesser degrees of failure respond to nitroglycerin with either no change or a fall in cardiac output. No patient in this series whose PCW pressure fell to 5 mm Hg or less raised his cardiac output. In contrast, when failure is more advanced, peripheral vasodilatation results in a decreased afterload at a more appropriate filling pressure, and CO and LVSWI rise.

It is uncertain whether the reduction in left ventricular filling pressure is entirely secondary to the peripheral vascular action of the drug or in part due to direct or reflex effects on the myocardium and coronary circulation. Numerous studies have supported the view favoring a primary peripheral action of drug.

Figure 4

Effect of NTG on cardiac output. CO increased significantly in patients with elevated PCW, averaging 13% in GROUP II and 25% in GROUP III. In patients with normal PCW, CO decreased 9%.

Figure 5

Effect of NTG on stroke-work index. SWI increased significantly in patients with elevated PCW, averaging 19% in GROUP II and 25% in GROUP III. In patients with normal PCW, SWI decreased 7%.
significant change in heart rate occurred, suggesting no marked increase in sympathetic tone. Nevertheless, both mechanisms could have been operative. It is also possible that some of the effects here reported result from a direct action of nitroglycerin on coronary circulation. Improved collateral flow, for example, could produce directionally similar results.

It is generally believed that nitroglycerin is contraindicated in acute myocardial infarction because of the potential deleterious effects of a decrease in coronary perfusion pressure and a reflex rise in heart rate. In the present study, during continuous hemodynamic monitoring, the fall in MAP was small and consistent whether or not the initial MAP was 100 or 70 mm Hg. Heart rate did not change. Furthermore, 35-lead preordial maps showed no evidence of increased myocardial injury. Other investigators, however, have noted precipitous falls in arterial pressure following the administration of nitroglycerin to patients with coronary artery disease,16 and for this reason the drug should be administered only during continuous hemodynamic monitoring. Also, since the beneficial effect appears to correlate with the level of the left ventricular filling pressure, monitoring of PCW pressure is important.

It is recognized that this mode of therapy is only temporary, and that patients must eventually respond to more conventional measures. If these measures are ineffective, however, sublingual nitroglycerin may acutely lower left ventricular filling pressure and may afford a means of rapidly reversing the vicious cycle of pulmonary edema. Repeated doses can be used until pulmonary edema can be controlled with digitalis and diuretic therapy. Sublingual nitroglycerin may have a special role in the management of the acutely ill patient with myocardial infarction.

Acknowledgment

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NITROGLYCERIN FOLLOWING ACUTE MI

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