Reduction of Ischemic Injury by Sublingual Nitroglycerin in Patients with Acute Myocardial Infarction

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SUMMARY The effect of sublingual nitroglycerin (NTG) on myocardial ischemic injury was evaluated in eleven patients with acute anterior myocardial infarction. Precordial 35-lead ST-segment maps were obtained in each patient immediately before and 3–10 minutes after 0.4 mg sublingual NTG. The following measurements were made from each ST map: N-ST (number of leads showing ST elevation > 1 mm), ΣST (total ST elevation in all leads), ST (average ST-segment elevation in those leads with > 1 mm elevation). Following 0.4 mg sublingual NTG evidence of myocardial ischemic injury as assessed by ST-segment mapping decreased in association with reduction of heart rate \times \text{systolic blood pressure product (10.80 \times 10^4 to 9.49 \times 10^4)}}. Group mean values diminished significantly for N-ST (18.1 to 14.4, \(P < 0.001\)), \ΣST (37.9 to 30.1, \(P < 0.005\)) and ST (1.7 to 1.4, \(P < 0.001\)). Evaluation performed by the technique of precordial ST-segment mapping suggests that sublingual nitroglycerin in a commonly employed clinical dose is associated with evidence of reduced ischemic cardiac injury in patients with acute myocardial infarction. This effect appears to be related to reduction of myocardial oxygen demand by the nitrate.

CURRENT UNDERSTANDING of the pathophysiology of myocardial infarction has resulted in recent emphasis on therapeutic manipulation of the determinants of myocardial oxygen consumption (MVO₂) in order to reduce myocardial ischemia and decrease injury. Since the complication of ST segment elevation in acute myocardial infarction in man. Comparison of a precordial mapping technique and the Frank vector system. Am J Cardiol 36: 155, 1975


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ischemic injury in myocardial infarction.\textsuperscript{1,2,18,19} On the basis of this method NTG has been reported to limit infarct size in experimental infarction\textsuperscript{20,21} and to reduce ischemic injury during myocardial infarction in man.\textsuperscript{22-24} The previous clinical studies have been performed with dosages of NTG considerably greater than that conventionally utilized.\textsuperscript{22-24} In this study we applied the technique of precordial ST-segment mapping in order to investigate the effects of a standard clinical dose of sublingual NTG on the extent of myocardial ischemic injury in patients with acute myocardial infarction.

\textbf{Methods and Materials}

The study group was comprised of eleven patients with acute myocardial infarction. There were ten males and one female ranging in age from 31 to 81 years (mean 50 years). All patients were admitted to the Cardiac Monitoring Unit within six hours of chest pain typical of myocardial infarction. Diagnosis of myocardial infarction was by classic history, subsequent electrocardiographic evolution of pathologic Q waves and characteristic serum enzyme patterns. Infarct location by electrocardiogram was anterior in five patients, anteroseptal in five and lateral (involving leads V\textsubscript{4} and V\textsubscript{5}) in one. All patients had ST-segment elevation involving multiple precordial leads of the standard 12-lead electrocardiogram. Patients with hypotension, conduction disturbance, persistent arrhythmia, symptomatic cardiac failure or pericarditis were excluded. Informed consent for evaluation was obtained in all cases. The 35-lead precordial ST blanket,\textsuperscript{2} comprised of five horizontal and seven vertical rows of electrodes, was positioned on the anterior chest with lead one of the blanket placed in the second right intercostal space adjacent to the sternum and the short dimension of the blanket parallel to the sternum. A constant blanket position was maintained. All recordings were obtained utilizing the V lead of the standard electrocardiograph and recorded on Hewlett-Packard electrocardiographic paper at a speed of 25 mm/sec. One mm electrocardiographic excursion was standardized to correspond to 0.1 mV.

Control ST maps and blood pressure by sphygmanometry were obtained immediately prior to administration of 0.4 mg NTG sublingually. The ST maps were repeated with the appearance of NTG effect, as indicated by a fall in blood pressure, within 3-10 minutes following NTG. The following data were determined in control and post-NTG ST maps: number of leads with ST elevation > 1 mm (N-ST); sum of all ST elevations in leads having > 1 mm elevation (\textit{SST}); and average ST elevation (\textit{ST}) (\textit{SST}/N-ST). ST segments were measured at a point 60 msec after the J-junction of the QRST complex. Only leads with technically adequate recordings were used for data acquisition. If a lead was not clearly recorded in either the control or post-NTG ST maps, it was not used in measurements in either map. Only a total of five leads in three patients were excluded from the data on this basis. Six beats were recorded in each lead and changes in these were averaged. A single representative beat was then used for illustration. Control and post-NTG heart rate and blood pressure were measured during the recording of the ST maps.

\textbf{Statistical calculations were performed by Student's t-test for paired data.}

\textbf{Results}

Table 1 lists the effects of NTG on heart rate (HR) and blood pressure (BP). Following NTG, systolic BP decreased significantly from a mean of 138 mm Hg to 117 mm Hg (\textit{P} < 0.001) and HR rose slightly but significantly from 79/min to 82/min (\textit{P} < 0.02). The HR \times BP product (calculated as HR \times systolic BP) decreased significantly from 10.80 \times 10\textsuperscript{4} to 9.49 \times 10\textsuperscript{4} (\textit{P} < 0.001) following NTG. The absolute decrease in HR \times BP product in the individual patients ranged from -0.62 \times 10\textsuperscript{4} to -1.92 \times 10\textsuperscript{4}.

Figure 1 illustrates representative ST maps before and after NTG in patient 6. As shown, N-ST, \textit{SST} and \textit{ST} all decreased after the nitrate. Figure 2 depicts the measured values for N-ST, \textit{SST} and \textit{ST} in the eleven patients studied with precordial mapping. Administration of NTG was associated with significant decrease in N-ST (18.1 to 14.4 \% [-20\%], \textit{P} < 0.001), \textit{SST} (37.9 to 30.1 \% [-21\%], \textit{P} < 0.005) and \textit{ST} (1.7 to 1.4 \% [-18\%], \textit{P} < 0.001). In one of the eleven patients (No. 1) \textit{SST} increased (42.2 to 51.0) and \textit{ST} rose (1.28 to 1.76). N-ST decreased slightly. The

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|c|c|}
\hline
\textbf{No.} & \textbf{HR} & \textbf{SBP} & \textbf{DBP} & \textbf{HR \times SBP \times 10\textsuperscript{4}} & \textbf{HR} & \textbf{SBP} & \textbf{DBP} & \textbf{HR \times SBP \times 10\textsuperscript{4}} \\
\hline
1 & 71 & 110 & 60 & 7.81 & 72 & 90 & 60 & 6.48 \\
2 & 130 & 120 & 80 & 15.60 & 134 & 106 & 78 & 14.20 \\
3 & 57 & 130 & 70 & 7.40 & 60 & 112 & 70 & 6.72 \\
4 & 70 & 120 & 70 & 8.40 & 72 & 108 & 68 & 7.78 \\
5 & 74 & 140 & 80 & 10.36 & 74 & 120 & 76 & 8.88 \\
6 & 83 & 115 & 69 & 9.54 & 85 & 90 & 60 & 7.65 \\
7 & 88 & 120 & 70 & 10.56 & 90 & 96 & 70 & 8.64 \\
8 & 64 & 130 & 78 & 8.32 & 68 & 110 & 76 & 7.48 \\
9 & 75 & 200 & 80 & 15.00 & 84 & 160 & 84 & 13.40 \\
10 & 70 & 160 & 90 & 11.20 & 74 & 136 & 90 & 10.06 \\
11 & 86 & 170 & 60 & 14.62 & 84 & 156 & 60 & 13.10 \\
\hline
\textbf{Mean} & 79 & 138 & 73 & 10.80 & 82* & 117* & 72 & 9.49** \\
\textbf{SEM} & \pm 6 & \pm 8 & \pm 3 & \pm 0.90 & \pm 6 & \pm 7 & \pm 3 & \pm 0.85 \\
\hline
\end{tabular}
\caption{Heart Rate and Blood Pressure Response to Nitroglycerin in Acute Myocardial Infarction}
\end{table}

*Medical Innovations, Waltham, Mass.
other ten patients all showed reduction in N-ST, $\Sigma ST$ and ST.

The ST elevation in patient 1, a unique occurrence in this study limited to this individual, was not associated with any untoward clinical effects such as pain, arrhythmias or cardiac failure.

Discussion

This study suggests that sublingual nitroglycerin can acutely reduce myocardial ischemic injury, as reflected by the technique of precordial ST mapping, in patients with acute myocardial infarction. On the basis of this method, it is suggested that both extent and intensity of ischemic...
damage were attenuated with administration of the drug. These results are consistent with those of early experimental39, 40 and clinical22-24 reports, based on precordial ST-segment mapping, supporting reduction of cardiac injury by nitroglycerin in acute myocardial infarction. However, in this study the beneficial effects of the drug were achieved with a commonly employed dosage and route of administration whereas previous clinical investigations utilized unusually high doses of nitroglycerin.22-24 Considerably in excess of those generally applied, as well as intravenous administration.22, 23

Evidence of decreased myocardial injury after NTG was associated with hemodynamic changes consistent with diminished MVO2, manifested by a decrease in HR × BP product.25 Reduction of blood pressure appears to be the principal factor in this effect on MVO2 since heart rate was unaltered. Further, on the basis of the known systemic venodilator actions of NTG on cardiac function,5, 26 it is probable that decrease in ventricular volume by the drug contributed to improvement in myocardial oxygen balance and alleviation of ischemia in our patients.

The major determinants of myocardial oxygen consumption are heart rate, intramyocardial tension, a function of blood pressure and ventricular volume, and the contractile state of the myocardium.13 Among the most significant hemodynamic actions of NTG are diminution of left ventricular volume and pressure throughout the cardiac cycle,10-12 which are effected by the peripheral vasodilating actions of the drug.8, 26 These alterations thus favor considerable reduction in MVO2. Since myocardial ischemia results from an imbalance between the requirements of the heart for oxygen and its availability, reduction of MVO2 by NTG can alleviate this abnormality by improving the balance between cardiac oxygen supply and demand. The consistent antianginal efficacy of NTG is in large measure attributed to decrease in myocardial ischemia resulting from reduction in MVO2 by the aforementioned hemodynamic actions of the drug.7-12 Similar beneficial hemodynamic alterations have been noted in acute myocardial infarction.14-17 Thus the nitrate may possess similar potential for reduction of ischemia in myocardial infarction. In addition to attenuation of myocardial ischemia by reduction of MVO2, it has been suggested that NTG improves myocardial oxygenation by increasing blood flow to areas of inadequate perfusion. Thus, favorable redistribution of myocardial blood flow by NTG has been demonstrated experimentally27 and in man the drug has produced evidence of increased blood flow to zones of myocardial ischemia.28

Despite the remarkable efficacy of NTG as an antianginal agent, it has been traditionally proscribed in acute myocardial infarction because of its hypotensive action and thus the hazard of augmenting myocardial ischemia by both reduced coronary perfusion pressure and reflex tachycardia. Although recent systematic evaluation of the hemodynamic effects of NTG in the acute phase of myocardial infarction have demonstrated the general safety of the drug14, 17 fall in cardiac output is common when left ventricular filling pressure is markedly lowered by the nitrate4 and profound hypotension may occur after its use in patients with myocardial infarction.19 Further, during NTG administration in myocardial infarction in experimental animals20, 39 and in man,24 maintenance of arterial pressure by concomitant vasopressor therapy to avert the effects of the nitrate on blood pressure and heart rate has resulted in greater reduction of myocardial ischemic injury than with NTG alone, although this has not been confirmed by other studies.20 That maintenance of blood pressure during NTG therapy may enhance the actions of the nitrate in reducing ischemic injury suggests that the effects of the drug on factors other than blood pressure may play an important role in its alleviation of myocardial ischemia. This would relate most clearly to decrease in ventricular volume and thereby intramyocardial tension by the nitrate.5, 10, 12

The significance of the increase in ST and ST in the single patient (No. 1) in whom these atypical results occurred after NTG is unclear. However, N-ST was slightly reduced, decrease in blood pressure was mild and comparable to that in the other patients, heart rate was unaltered and there was no clinical evidence of augmented myocardial ischemia such as pain, arrhythmia or cardiac failure. There is the possibility that cardiac output, which was not measured in this study, may have fallen significantly and contributed to reduction in myocardial perfusion in excess of fall in cardiac oxygen requirements.

The conclusion that NTG reduced myocardial ischemic injury in ten of our 11 patients is based on the indirect technique of precordial ST mapping. Extensive investigation suggests that ST-segment mapping is a valid and sensitive method of assessing the extent and severity of ischemic injury after experimental coronary occlusion. Direct correlation has been documented between epicardial ST elevation and ischemic damage of underlying myocardium in experimental infarction, as indicated by a fall in intramyocardial oxygen tension,29, 30 ultrastructural and histologic changes,31 tissue enzyme depletion,32 alteration of cellular membrane potential33 and onset of anerobic metabolism by the myocardium.34 Clinical application of precordial ST mapping has also revealed that it reliably reflects the onset and course of ischemic damage in myocardial infarction when compared with clinical status and serum enzyme analysis.18 Further, this technique may demonstrate infarct extension which is not revealed by conventional electrocardiography.18 In terms of the validity of the method for assessing acute changes in underlying ischemia, it has been shown both experimentally and clinically that precordial ST maps are stable in the absence of further myocardial damage, allowing their application in the evaluation of acute interventions to modify myocardial ischemia.18, 21, 36

The technique of ST-segment mapping has been foremost in experimentally demonstrating reduction of myocardial infarct size by favorable manipulation of those variables determining the balance between myocardial oxygen supply and demand. Thus, factors that improve myocardial perfusion and those that reduce oxygen demand have been associated with evidence of a decrease in ischemic cardiac damage.1-4 The technique is limited in that it can be used only for anterior myocardial infarctions and ST elevation is not a valid indicator of myocardial ischemic injury in the presence of other causes of deviation of the ST segment such as pericarditis, ventricular aneurysm, intraventricular conduc-
tion abnormalities and electrolyte alterations. The presence of these factors must be recognized for appropriate application of this method.

Acknowledgment

The authors gratefully acknowledge the technical assistance of David Janzen and Steven Rendig and the secretarial assistance of June Boris and Karen Gilmore.

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Reduction of ischemic injury by sublingual nitroglycerin in patients with acute myocardial infarction.
N A Awan, E A Amsterdam, Z Vera, A N DeMaria, R R Miller and D T Mason

Circulation. 1976;54:761-765
doi: 10.1161/01.CIR.54.5.761
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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