Electrophysiologic Effects of Nitroglycerin during Experimental Coronary Occlusion

By Rafael Levites, M.D., Monty M. Bodenheimer, M.D., and Richard H. Helfant, M.D.

SUMMARY

Previous studies have shown that nitroglycerin (TNG) exerts beneficial electrophysiological effects in the setting of acute myocardial ischemia. To investigate the basis for these actions, the effects of TNG during coronary occlusion were studied in 19 anesthetized mongrel dogs. Refractory periods (obtained by extrastimulus method) and conduction times measured from local electrograms were determined in potentially ischemic and nonischemic areas prior to and after varying periods of occlusion of the left anterior descending coronary artery and following administration of TNG (300-400 μg intravenous bolus followed by an infusion titrated to reduce systolic blood pressure by 20 mm Hg). Following 15 minutes of occlusion, refractory periods in the ischemic zones shortened to 83% of control (P < 0.001) resulting in a difference between refractory periods in the nonischemic and ischemic zones of 17.7%. After TNG administration this difference was decreased to 10.0% (P < 0.001). However, with periods of occlusion of 60-90 min TNG did not significantly affect the difference of refractory periods. TNG had no significant effects on conduction times in nonischemic or ischemic areas.

In six dogs, the effects of coronary occlusion and TNG on ventricular automaticity were examined by induction of complete heart block. The idioventricular rate and ventricular escape intervals after cessation of ventricular overdrive were used as indices of automaticity. Control idioventricular rates (62.5 ± 3.7 beats/min) remained unchanged following both coronary occlusion (62.0 ± 3.9) and TNG administration (60.7 ± 3.2). Similarly, mean control escape intervals (1.84 ± 0.2 sec) did not change after occlusion (1.78 ± 0.3 sec) or TNG administration (1.86 ± 0.2 sec). In conclusion, these observations suggest that 1) TNG enhances the electrical stability of the acutely ischemic myocardium by decreasing the difference of refractory periods between nonischemic and ischemic areas in the immediate period following occlusion, 2) since TNG has no significant effects on ventricular automaticity, its beneficial effects might be limited in suppression of arrhythmias of re-entrant origin.

This investigation was therefore undertaken to examine the electrophysiological effects of TNG during experimental coronary occlusion.

Methods

Experiments were performed on 19 mongrel dogs weighing 20–25 kg, anesthetized with intravenous sodium pentobarbital (30 mg/kg) and ventilated with room air using a Harvard respirator and a cuffed endotracheal tube. After performing a midline thoracotomy, the heart was supported in a pericardial cradle. Heart rates were kept constant throughout all interventions by right atrial pacing after destroying the sinus node by injecting 0.2 ml of formaldehyde. A polyethylene tube was introduced through an external jugular vein for intravenous infusion and drug administration. Central aortic pressure was obtained using an aortic catheter introduced through a carotid artery using a P23Db transducer. Fine teflon-coated stainless steel bipolar plunge electrodes (0.003 inch diameter) were inserted into the left ventricular myocardium, two in each potentially ischemic and nonischemic zone using techniques previously described. The electrodes comprising each pair were placed one mm apart. In each zone, the pair of sensing electrodes was placed at a distance of 5–8 mm from the pair of stimulating electrodes. Bipolar electrograms (frequency response 40–500 Hz), standard ECG leads, and aortic pressure were simultaneously recorded using an Electronics for Medicine DR-8 oscilloscopic recorder at paper speeds of 50–100 mm/sec.
Refractory periods of ventricular myocardium were determined using the extrastimulus method by scanning the R-R interval. premature stimuli were of 2 msec duration and two times diastolic threshold and were delivered after every eight atrially paced beats. The refractory period was defined as the longest R-to-stimulus interval that did not result in a propagated response (fig. 1). Because in some experiments there were minor differences between refractory periods in the nonischemic and potentially ischemic zones during control measurements, absolute as well as relative changes in refractory periods were determined and compared using the formula:

\[
\% \Delta \text{RP} = \frac{\text{RP}^2 - \text{RP}^1 \times 100}{\text{RP}^1}
\]

Figure 1

Measurement of refractory periods. The test stimulus delivered to the ischemic zone was started late in the cardiac cycle and moved progressively earlier. Panels A and B) Coupling intervals of 200 and 195 msec resulted in a propagated response as seen in the electrogram recorded from the sensing electrodes located in the ischemic zone (reference area). Panel C) The refractory period of the ischemic zone was reached at a coupling interval of 190 msec. Note the absence of a propagated response in the ischemic zone sensing electrodes (reference area).

where RP = refractory period and superscripts 1 and 2 refer respectively to measurements during control conditions and after interventions.

Intramyocardial conduction times were determined by measuring the interval from the onset of the local electrogram in a distant area to the local electrograms in potentially ischemic and nonischemic zones.

In six dogs, complete heart block was produced by injecting 0.2–0.4 mL of formaldehyde in the area of the bundle of His. The rate of the idioventricular pacemaker and the effects of sudden termination of 30 sec of rapid ventricular pacing (120 beats/min) on the time needed for a ventricular escape to occur were determined before, 15 minutes after coronary ligation, and following TNG administration and utilized as indices of ventricular automaticity.

Data were obtained during control conditions and 15 minutes after left anterior descending coronary occlusion. At that point, TNG was administered as a 300–400 μg bolus followed by an infusion of 100–200 μg/min titrated to reduce systolic blood pressure by 20 mm Hg. Three to five minutes after a stable reduction in blood pressure was achieved, measurements were again obtained. TNG was then discontinued. In four experiments, methoxamine was administered after the TNG had been obtained in a dose which maintained aortic pressure at control levels. After 60–90 min of coronary occlusion, TNG was again administered in similar manner and data again obtained. In any single study, a minimum interval of 45 minutes between two TNG interventions was allowed, at which time the blood pressure changes produced by TNG had returned to control values.

Coronary occlusion per se did not induce significant changes in systemic arterial pressure in any of the experiments.

Each dog served as its own control and statistical significance was determined using Student’s t-test for paired values.

Results

Refractory Periods

15 Minute Occlusions (13 Dogs)

Control refractory periods in nonischemic and potentially ischemic zones were similar (table 1).

Table 1

<table>
<thead>
<tr>
<th>Duration of occlusion</th>
<th>Control N</th>
<th>Postocclusion N</th>
<th>Post TNG N</th>
</tr>
</thead>
<tbody>
<tr>
<td>15'</td>
<td>118.7</td>
<td>120.0</td>
<td>98.7*</td>
</tr>
<tr>
<td>60–90'</td>
<td>125.7</td>
<td>126.4</td>
<td>92.1*</td>
</tr>
<tr>
<td>15'</td>
<td>4.9</td>
<td>2.8</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Values are given in msec as mean ± standard error of the mean.

Cycle length was 430 msec in all experiments for determination of refractory periods as well as conduction times.

* = P < 0.001 as compared to control.

** = P < 0.001 as compared to postocclusion.

Abbreviations: N = nonischemic zone; I = ischemic zone; TNG = nitroglycerin.
Following coronary occlusion, refractory periods in the nonischemic zones remained essentially unchanged (100.7 ± 0.8% of control) while in the ischemic zones they shortened by 17.0 ± 2.3% (to 83% of control) \( (P < 0.001) \), resulting in a difference of refractory periods between the two zones of 17.7% (fig. 2). Following TNG administration, refractory periods in nonischemic zones were unaffected \( (100.0 ± 1.05\% \, \text{of control}) \) while in ischemic zones they prolonged to 90.0 ± 2.3% of control, thus decreasing the difference from 17.7% to 10.0% \( (P < 0.001) \) (fig. 2). Observations from a typical experiment are shown in figure 3.

The effect of TNG on ventricular refractoriness was not affected in the four experiments in which blood pressure was controlled at preocclusion levels with methoxamine (fig. 4).

60–90 Minute Occlusions (Ten Dogs)

Control nonischemic and potentially ischemic zones had similar refractory periods (table 1). With 60–90 minutes of coronary occlusion, refractory periods in the nonischemic area were unchanged \( (98.4 ± 1.3\% \, \text{of control}) \) whereas in the ischemic zone they decreased by 27.0 ± 3.6% to 73% of control \( (P < 0.001) \), causing a difference of refractory periods of 25.4% (fig. 5). After TNG administration, refractory periods in nonischemic zones were unchanged while in the ischemic zones small and inconsistent changes were seen, resulting in no over-all effect in the differences of refractory periods (fig. 5).

Intra-myocardial Conduction

Control conduction times to nonischemic \( (14.0 ± 3.2 \, \text{msec}) \) and potentially ischemic areas \( (14.8 ± 2.5 \, \text{msec}) \) were similar. Following 15 minutes of coronary occlusion, conduction times to the nonischemic zones were unchanged \( (14.8 ± 3.3 \, \text{msec}) \) while in the ischemic zone they prolonged to 23.2 ± 2.4 msec \( (P < 0.01) \). Following TNG administration, neither conduction times in nonischemic nor times in ischemic areas changed significantly \( (14.6 ± 2.5 \, \text{and} \, 22.2 ± 3.1 \, \text{msec}, \, \text{respectively}) \).

Ventricular Automaticity

After inducing complete heart block, the mean control rate of the idioventricular pacemaker was 62.5 ± 3.7 beats/min. The ventricular rates remained essentially unchanged following coronary occlusion \( (62.0 ± 3.9 \, \text{beats/min}) \). TNG administration resulted in no essential change in rate from control or occlusion \( (60.7 ± 3.2 \, \text{beats/min}) \).

The mean control escape intervals after cessation of ventricular overdrive were 1.84 ± 0.2 sec and did not change significantly after occlusion \( (1.78 ± 0.3 \, \text{sec}) \). TNG administration did not change the ventricular
ELECTROPHYSIOLOGIC EFFECTS OF TNG

Refractory periods after 15 minutes of coronary occlusion and following TNG and methoxamine. Coronary occlusion resulted in a difference of refractory periods of 19.7% which was decreased to 10.4% after TNG administration. When methoxamine was given during the TNG effect the difference of refractory periods was changed to 8.3% but that difference was insignificant as compared to the difference after TNG.

escape interval (1.86 ± 0.2 sec). The results from a typical experiment are shown in figure 6.

Discussion

The present study confirms the marked shortening of the ischemic zone refractory periods that follows coronary occlusion.12,13,16 This leads to an inhomogeneous ventricular refractoriness. Ventricular arrhythmias are generally believed to be due to re-entry or enhanced automaticity. The conditions which are known to predispose to re-entry are unidirectional conduction delay or block with subsequent recovery of excitability at the time of impulse arrival. In addition, Wiggers,17 Han18 and others9,12 have postulated that increased dispersion of refractoriness during coronary occlusion can cause fractionation of wavefronts and lead to re-entrant arrhythmias. The present study indicates that, following coronary occlusion, differences in refractory periods of the ischemic and non-ischemic zones occur. This would create a situation in which a relative unidirectional conduction abnormality could occur resulting in re-entry. Thus, to the degree that differences in refractory periods are responsible for re-entrant arrhythmias, the finding that nitroglycerin reduces this difference may, in part, explain its antiarrhythmic action during acute myocardial ischemia. However, the fact that TNG had no effect on ventricular automaticity (fig. 6) suggests that its beneficial antiarrhythmic effects might be limited to suppression of arrhythmias of re-entrant origin. It should be pointed out that the lack of effect of TNG on ventricular automaticity demonstrated in this experiment, at a time when enhanced automaticity does not play a role in the generation of spontaneous arrhythmias,19 may not be applicable to the enhanced ventricular automaticity that occurs later during acute myocardial infarction.8

The mechanisms whereby TNG exerts its electrophysiological effects are speculative. TNG induced changes only in ischemic zone refractory periods and had no effects on nonischemic areas. This finding is consistent with the observation of an increase in the fibrillation threshold only in the presence of ischemia6 and suggests that TNG-induced changes relate to the ischemia per se and were not due to a nonspecific membrane-stabilizing effect. It is thus possible that TNG decreased the difference between refractory periods by favorably altering the balance between myocardial oxygen supply and demand in the ischemic zone. The decrease in arterial pressure caused by TNG decreases myocardial oxygen consumption20 and therefore favorably affects this balance. However, when the systemic pressure was kept at control levels with methoxamine, the effects of TNG on ischemic zone refractory periods were also observed (fig. 4). Another secondary mechanism whereby the oxygen supply-to-demand ratio may be favorably altered by TNG relates to an increase in coronary blood flow to the affected left ventricular zone.21 This effect of TNG has been controversial.22

The enhancement of the electrical stability of acutely ischemic myocardium was only seen when TNG was administered after 15 minutes of coronary occlusion. On the other hand, no effects on ventricular refractoriness were apparent after the administration of TNG following occlusion for 60–90 minutes (fig. 5). These data are consistent with our previous observations that the improvement of the functional and electrical abnormalities following institution of reperfusion is progressively attenuated with the lapse of time.13,23,24

The extrapolation of these data to the clinical setting of myocardial infarction should be made with
caution. The beneficial electrophysiological effects of TNG in acute ischemia suggests that it may be of value at the very outset of acute myocardial infarction. This may, therefore, have clinical relevance to the problem of sudden death. Since the beneficial effects of TNG on the central ischemic zone were seen after only 15 minutes of occlusion, at a time when this area is still viable, it is conceivable that the responsiveness of the ischemic border zones could persist for longer periods of time. This could account for the clinical effectiveness of TNG in the coronary care unit setting.

Acknowledgments

We thank Miss Janice Phillips and Mr. Joseph Lewandowskie for their technical assistance and Miss Jeanne Harrison and Ms. Marcy Moore for their help in preparing the manuscript.

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Circulation, Volume 52, December 1975
Electrophysiologic effects of nitroglycerin during experimental coronary occlusion.
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Circulation. 1975;52:1050-1055
doi: 10.1161/01.CIR.52.6.1050
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

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the World Wide Web at:
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