Nitroglycerin and premature ventricular complexes in myocardial infarction¹

Suzanne B. Knoebel, Susan Rasmussen, R. Joe Noble, and Michael J. Mihalick²

From the Krannert Institute of Cardiology; the Department of Medicine, Indiana University School of Medicine; the Veterans Administration Hospital, Indianapolis, Indiana; and the Hendricks County Hospital, Danville, Indiana, U.S.A.

Because of clinical observations suggesting that nitroglycerin may suppress premature ventricular complexes during acute ischaemia, a study was undertaken to assess the effect of nitroglycerin on the incidence of premature ventricular complexes in patients with acute myocardial infarction.

Forty patients with acute myocardial infarction were studied. Twenty-six patients received 0.4 mg nitroglycerin sublingually every 4 hours for the first 24 hours after admission to the coronary care unit. The total premature ventricular complex count for the 26 patients for 15 minutes before nitroglycerin was 592, and 276 for the 15 minutes after the drug ($P < 0.005$). In the remaining 14 patients on the same nitroglycerin schedule, a single electrocardiographic lead was continuously recorded on tape. During the first hour after nitroglycerin, the premature ventricular complex count decreased by 58 per cent, and the second and third hours showed a decrease from control count of 71 and 65 per cent respectively. By the end of 4 hours the ectopic count was back to control level.

The data indicate that nitroglycerin may decrease the number of premature ventricular complexes for up to 3 hours in patients with acute myocardial infarction. The mechanism of action of nitroglycerin is not elucidated by this study, but the observation may be of value in further studies of specific antiarrhythmic therapy and prevention of arrhythmias in patients with coronary artery disease.

An important consideration in patients with coronary artery disease, in whom the combination of premature ventricular complexes and a lowered fibrillation threshold may have lethal potential, is the need to develop reliable drugs for the treatment and prevention of ventricular arrhythmias. Numerous clinical observations provide a heuristic model for investigations into the effects of anti-ischaemic interventions on ventricular premature complexes. For example, the occurrence of premature ventricular complexes or ventricular tachycardia during episodes of variant angina with ST segment elevation, and diminution of the ectopy with alleviation of pain and disappearance of electrocardiographic changes has been documented (Prinzmetal *et al.*, 1960). In addition, it has been clinically observed

that an increase in ventricular ectopic beats may occur during periods of probable imbalance in the supply/demand ratio for myocardial oxygenation, as with anaemia, hypoxia (Rothschild and Kissin, 1933), or heart failure (Katz and Pick, 1956); treatment of these conditions may result in decreased ectopy. The occurrence of ventricular ectopic complexes coincidentally with the onset of exertional angina and the decrease in ectopy when angina diminishes (Scherf and Schott, 1953; Porter, 1948; Mathieu, 1927) are further evidence for a reciprocal relation between ischaemia and frequency of premature ventricular complexes. A beneficial effect of nitroglycerin on ventricular fibrillation threshold and spontaneous ventricular fibrillation during acute ischaemia in the experimental animal has been reported (Kent *et al.*, 1974; Borer *et al.*, 1974).

Subjects and methods

Forty patients with acute myocardial infarction, confirmed by typical electrocardiographic abnormalities, a clinical history compatible with myocardial infarction,

Received 7 April 1975.

¹Supported in part by the Herman C. Krannert Fund, by grants from the National Heart and Lung Institute of the National Institutes of Health, U.S. Public Health Service, and by the Indiana Heart Association.

²Research initiated during Dr. Mihalick's tenure as a U.S.P.H.S. Trainee in Cardiology.

TABLE 2 Hourly premature ventricular complex count rate in 14 patients with acute myocardial infarction given 0.4 mg nitroglycerin sublingually every 4 hours

	Control	After nitroglycerin			
		1 hour	2 hours	3 hours	4 hours
Total premature ventricular complexes per hr for group	438	182	126	154	406
Premature ventricular complexes per patient per hr	31.3	13	9	11	29

totalled 438 during the control period of one hour just before administration of nitroglycerin. During the hour after nitroglycerin, the occurrence of premature ventricular contractions decreased by 58 per cent to 182 premature ventricular contractions per hour ($P < 0.001$). For the second and third hours the counts were 126 and 154, respectively, and for the fourth hour the count was 406, not significantly different from control (Table 2). As in the previous group, there was a significant increase in heart rate after nitroglycerin from 79 to 84 beats/min ($P < 0.001$). However, this increase occurred during the first 5 minutes after nitroglycerin. The continuous monitoring of heart rate showed that there was no significant increase in heart rate when analysed per hour. This group also showed a significant ($P < 0.001$) decrease in systolic and diastolic blood pressure with nitroglycerin (12 mmHg (1.6 kPa) systolic and 4 mmHg (0.5 kPa) diastolic). As blood pressure was not continuously monitored, the duration of this effect could not be evaluated.

Discussion

The data indicate that nitroglycerin administered sublingually decreases the number of premature ventricular complexes in patients with acute myocardial infarction, and suggest that the effect may last up to 3 hours. While this is longer than is usually believed to be the therapeutic duration of sublingual nitroglycerin, this is a controversial area (Goldstein and Epstein, 1973). In addition, from our data, it is not possible to be certain exactly when recurrence of premature ventricular complexes began. The fact that the count was somewhat greater at 3 hours than at 2 hours might suggest that recurrence of ectopy began some time after 2 hours. Thus, our results are compatible with a shorter duration of nitroglycerin effect. Larger numbers of patients monitored continuously would be required to allow statistical analysis of duration of the suppressive effect of nitroglycerin.

While this study did not provide definite evidence for the mechanism of reduction of premature ventricular complexes, alleviation of ischaemia might be

inferred from what is thought to be the action of nitroglycerin. In addition, nitroglycerin has been shown to decrease the extent of ischaemic area experimentally (Hirshfeld *et al.*, 1974). Whether nitroglycerin effects primarily a reduction in myocardial oxygen demand (Bernstein *et al.*, 1966; Mason, Zelis, and Amsterdam, 1971), increase in myocardial blood flow (Knoebel *et al.*, 1973), redistribution of myocardial blood flow to the advantage of an ischaemic area (Fam and McGregor, 1964, 1968; Becker, Fortuin, and Pitt, 1971; Winbury, Howe, and Weis, 1971), or whether the actions of the drug are entirely peripheral (Ganz and Marcus, 1972; Mason and Braunwald, 1965), there is consensus that the supply/demand ratio for myocardial oxygenation is favourably altered (Knoebel *et al.*, 1973; Becker *et al.*, 1971; Honig, Tenney, and Gabel, 1960; Smith *et al.*, 1973). It is possible, for example, that nitroglycerin, by altering left ventricular filling pressure (Gold, Leinbach, and Sanders, 1972), may cause reduction in myocardial oxygen requirement as well as improvement in sub-endocardial flow (Knoebel *et al.*, 1973; Becker *et al.*, 1971; Smith *et al.*, 1973). Similar reasoning has been used to explain facilitation of defibrillation in acute ischaemia by mechanical reduction in left ventricular volume by left ventricular drainage (Kuhn *et al.*, 1972) and a decrease in premature ventricular complexes with a decreased venous return achieved by the use of lower extremity tourniquets (Knoebel and Rasmussen, 1974). Other combinations of potential nitroglycerin effects, such as decreased afterload, collateral vessel dilatation, decrease in extravascular compressive forces, etc. could be similarly invoked to explain a salutary effect on myocardial oxygen demand and supply (Becker and Pitt, 1971) and thus ischaemic area dimension. Electrophysiologically, such a reduction in ischaemic area mass might decrease the potential for sustained re-entrant activity (Han, 1969; Han, Goel, and Hanson, 1970), thought to be the mechanism for premature ventricular complexes, short bursts of ventricular tachycardia, and fibrillation (Wellens, Lie, and Durrer, 1974; Han

et al., 1974). Heterogeneity of conduction and excitability (Han and Moe, 1964; Hope *et al.*, 1974), an underlying electrophysiological condition for re-entrant activity, is accentuated by ischaemia (Han, 1969; Friedman, Stewart, and Wit, 1973).

Despite the effectiveness of nitroglycerin in decreasing premature ventricular complexes in acute infarction as shown in this study, the drug cannot as yet be recommended as a primary antiarrhythmic agent in this condition. While in this series of patients no deleterious side effects were encountered, excessive hypotension has been reported to result (Russek, Urbach, and Zohman, 1955). While adverse effects could be prevented by intravenous administration of the drug, with haemodynamic monitoring, including observation of left ventricular filling pressure, there are other effective intravenous drugs which may be easier to use (Killip and Kimball, 1967; Pitt, Lipp, and Anderson, 1971). The importance of these acute observations may, rather, lie in the possible implications to be drawn concerning chronic ventricular arrhythmia therapy and prophylaxis (Koch-Weser, 1971). It seems appropriate that an independent study be undertaken to assess the effects of nitroglycerin in the ambulatory patient with coronary artery disease. It must be recognized, however, that a changing state of myocardial perfusion produced by nitroglycerin, and thus changing relations between the electrophysiological properties of normal and ischaemic zones (Hope *et al.*, 1974) could potentially be more hazardous than a stable condition (Warren, 1974; Battle *et al.*, 1974; Cox, Daniel, and Boineau, 1973).

References

- Battle, W. E., Naimi, S., Avitall, B., Brilla, A. H., Banas, J. S., Jr., Bete, J. M., and Levine, H. J. (1974). Distinctive time course of ventricular vulnerability to fibrillation during and after release of coronary ligation. *American Journal of Cardiology*, **34**, 42.
- Becker, L. C., Fortuin, N. J., and Pitt, B. (1971). Effect of ischemia and antianginal drugs on the distribution of radioactive microspheres in the canine left ventricle. *Circulation Research*, **28**, 263.
- Becker, L. C., and Pitt, B. (1971). Regional myocardial blood flow, ischemia and antianginal drugs. *Annals of Clinical Research*, **3**, 353.
- Bernstein, L., Friesinger, G. C., Lichtlen, P. R., and Ross, R. S. (1966). The effect of nitroglycerin on the systemic and coronary circulation in man and dogs. Myocardial blood flow measured with Xenon¹³³. *Circulation*, **33**, 107.
- Borer, J. S., Kent, K. M., Goldstein, R. E., and Epstein, S. E. (1974). Nitroglycerin-induced reduction in the incidence of spontaneous ventricular fibrillation during coronary occlusion in dogs. *American Journal of Cardiology*, **33**, 517.
- Cox, J. L., Daniel, T. M., and Boineau, J. P. (1973). The electrophysiologic time-course of acute myocardial ischemia and the effects of early coronary artery reperfusion. *Circulation*, **48**, 971.
- Fam, W. M., and McGregor, M. (1964). Effect of coronary vasodilator drugs on retrograde flow in areas of chronic myocardial ischemia. *Circulation Research*, **15**, 355.
- Fam, W. M., and McGregor, M. (1968). Effect of nitroglycerin and dipyridamole on regional coronary resistance. *Circulation Research*, **22**, 649.
- Friedman, P. L., Stewart, J. R., and Wit, A. L. (1973). Spontaneous and induced cardiac arrhythmias in subendocardial Purkinje fibers surviving extensive myocardial infarction in dogs. *Circulation Research*, **33**, 612.
- Ganz, W., and Marcus, H. S. (1972). Failure of intracoronary nitroglycerin to alleviate pacing-induced angina. *Circulation*, **46**, 880.
- Gold, H. K., Leinbach, R. C., and Sanders, C. A. (1972). Use of sublingual nitroglycerin in congestive failure following acute myocardial infarction. *Circulation*, **46**, 839.
- Goldstein, R. E., and Epstein, S. E. (1973). Nitrates in the prophylactic treatment of angina pectoris. *Circulation*, **48**, 917.
- Han, J. (1969). Mechanisms of ventricular arrhythmias associated with myocardial infarction. *American Journal of Cardiology*, **24**, 800.
- Han, J., Goel, B. G., and Hanson, C. S. (1970). Reentrant beats induced in the ventricle during coronary occlusion. *American Heart Journal*, **80**, 778.
- Han, J., Goel, B. G., Yoon, M. S., and Rogers, R. (1974). Effect of procainamide and lidocaine on ventricular automaticity and reentry during acute coronary occlusion. *American Journal of Cardiology*, **34**, 171.
- Han, J., and Moe, G. K. (1964). Nonuniform recovery of excitability in ventricular muscle. *Circulation Research*, **14**, 44.
- Hirshfeld, J. W., Jr., Borer, J. S., Goldstein, R. E., Barrett, M. J., and Epstein, S. E. (1974). Reduction in severity and extent of myocardial infarction when nitroglycerin and methoxamine are administered during coronary occlusion. *Circulation*, **49**, 291.
- Honig, C. R., Tenney, S. M., and Gabel, P. V. (1960). The mechanism of cardiovascular action of nitroglycerine. An example of integrated response during the unsteady state. *American Journal of Medicine*, **29**, 910.
- Hope, R. R., Williams, D. O., El-Sherif, N., Lazzara, R., and Scherlag, B. J. (1974). The efficacy of antiarrhythmic agents during acute myocardial ischemia and the role of heart rate. *Circulation*, **50**, 507.
- Katz, L. N., and Pick, A. (1956). *Clinical Electrocardiography*, p. 164. Lea and Febiger, Philadelphia.
- Kent, K. M., Smith, E. R., Redwood, D. R., and Epstein, S. E. (1974). Beneficial electrophysiologic effects of nitroglycerin during acute myocardial infarction. *American Journal of Cardiology*, **33**, 513.
- Killip, T., and Kimball, J. T. (1967). Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. *American Journal of Cardiology*, **20**, 457.
- Knoebel, S. B., McHenry, P. L., Bonner, A. J., and Phillips, J. F. (1973). Myocardial blood flow in coronary artery disease. Effect of right atrial pacing and nitroglycerin. *Circulation*, **47**, 690.
- Knoebel, S. B., and Rasmussen, S. (1974). Myocardial blood flow: newer clinical considerations. *Heart and Lung*, **3**, 78.
- Knoebel, S. B., Rasmussen, S., Lovelace, D. E., and Anderson, G. J. (1975). Nonparoxysmal junctional tachycardia in acute myocardial infarction: computer assisted detection. *American Journal of Cardiology*, **35**, 824.
- Koch-Weser, J. (1971). Antiarrhythmic prophylaxis in acute myocardial infarction. *New England Journal of Medicine*, **285**, 1024.

- Kuhn, L. A., Lajam, F., Sakurai, H., Castro-Blanco, J., Unger, A., Novick, S., Marano, A. J., and Litwak, R. S. (1972). Successful defibrillation with the use of left ventricular drainage after prolonged refractory ventricular fibrillation in experimental acute myocardial infarction. *American Journal of Cardiology*, 30, 248.
- Mason, D. T., and Braunwald, E. (1965). The effects of nitroglycerin and amyl nitrite on the arteriolar and venous tone in the human forearm. *Circulation*, 32, 755.
- Mason, D. T., Zelis, R., and Amsterdam, E. A. (1971). Actions of the nitrites on the peripheral circulation and myocardial oxygen consumption. Significance in the relief of angina pectoris. *Chest*, 59, 296.
- Mathieu, L. (1927). Un cas d'angor d'effort s'accompagnant de bigéminisme. *Revue Médicale de l'Est (Nancy)*, 55, 100.
- Pitt, A., Lipp, H., and Anderson, S. T. (1971). Lignocaine given prophylactically to patients with acute myocardial infarction. *Lancet*, 1, 612.
- Porter, W. B. (1948). The probably grave significance of premature beats occurring in angina pectoris and induced by effort. *American Journal of the Medical Sciences*, 216, 509.
- Prinzmetal, M., Ekmekci, A., Kennamer, R., Kwoczynski, J. K., Shubin, H., and Toyoshima, H. (1960). Variant form of angina pectoris. *Journal of the American Medical Association*, 174, 1794.
- Rothschild, M. A., and Kissin, M. (1933). Production of the anginal syndrome by induced general anoxemia. *American Heart Journal*, 8, 729.
- Russek, H. I., Urbach, K. F., and Zohman, B. L. (1955). Paradoxical action of glyceryl trinitrate (nitroglycerin) in coronary patients. *Journal of the American Medical Association*, 158, 1017.
- Scherf, D., and Schott, A. (1953). *Extrasystoles and Allied Arrhythmias*, p. 424. William Heinemann Medical Books, London.
- Smith, E. R., Redwood, D. R., McCarron, W. E., and Epstein, S. E. (1973). Coronary artery occlusion in the conscious dog. *Circulation*, 47, 51.
- Warren, J. V. (1974). Di si dolce morte. *Circulation*, 50, 415.
- Wellens, H. J. J., Lie, K. I., and Durrer, D. (1974). Further observations on ventricular tachycardia as studied by electrical stimulation of the heart. *Circulation*, 49, 647.
- Winbury, M. M., Howe, B. B., and Weiss, H. R. (1971). Effect of nitroglycerin and dipyridamole on epicardial and endocardial oxygen tension - further evidence for redistribution of myocardial blood flow. *Journal of Pharmacology and Experimental Therapeutics*, 176, 184.
- Requests for reprints to Professor Suzanne B. Knoebel, Indiana University School of Medicine, 1100 West Michigan Street, Indianapolis, Indiana 46202, U.S.A.