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# Nitroglycerin and premature ventricular complexes in myocardial infarction[1]

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*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).

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## Subjects and methods

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

and characteristic curves of enzyme activity, form the study group. All patients were admitted to a coronary care unit and examined by one of the investigators at the time of admission and at least twice daily during the study period. The clinical data including the presence or absence of signs of heart failure, site of infarction, and laboratory values were recorded on data code sheets. A clinical estimate of the time intervening between the onset of infarction and admission to the coronary care unit was made in all cases. Heart failure was considered to be present if a diastolic filling sound and râles, persistent after coughing, were present. Patients were excluded from the study group if clinical shock or a systolic blood pressure of 100 mmHg (13.3 kPa) or less were present.

Twenty-six of the patients were studied with the following protocol. Every patient was given 0.4 mg nitroglycerin sublingually every 4 hours for 24 hours after admission to the coronary care unit. Premature ventricular complexes were recorded continuously for 15 minutes before and for 15 minutes after administration of nitroglycerin. Thus, during any 24-hour period, premature ventricular contractions were counted for a total of 3 hours. The counts for six 15-minute periods were averaged for each patient, before and after nitroglycerin. Blood pressure was taken 5 minutes before and 5 minutes after nitroglycerin.

An additional 14 patients received 0.4 mg nitroglycerin sublingually every 4 hours for the first 24 hours while in the coronary care unit. These patients, however, had continuous magnetic tape recording of a single lead electrocardiogram for the entire 24-hour period, the purpose being to estimate the duration of nitroglycerin effect. The 24-hour recordings were data reduced by a previously described computer technique (Knoebel *et al.*, 1975). With this system, data reduction is implemented on a Honeywell Model 316 digital computer. R wave detection is accomplished by a modification of the derivative technique and is based on three criteria: maximum negative secant, threshold value, and a secant difference test. Rhythm monitoring is accomplished using a normalized histogram displaying the percentage of RR intervals having a given duration versus the duration of the intervals. The R wave detection algorithm has been previously verified by concomitant visual count (Knoebel *et al.*, 1975).

The statistical significance for blood pressure, heart rate, and premature ventricular complex changes was calculated as the difference between means of paired data.

## Results

The clinical and electrocardiographic data for the 26 patients with short-term monitoring, i.e. 15 minutes after nitroglycerin, are shown in Table 1. The patients showed a decrease in premature ventricular contractions for the 15 minutes after the drug was given to 276, a 53 per cent decrease ($P < 0.005$), only 2 patients in the group showing no significant change. Nitroglycerin administration resulted in an increase in average heart rate for the group from 79 beats/min to 83 beats/min ($P < 0.001$) and an average decrease, 5 minutes after nitroglycerin, in systolic and diastolic pressures of 12 mmHg and 7 mmHg (1.6 and 0.9 kPa), respectively ($P < 0.005$).

The 14 patients studied by continuous electrocardiographic monitoring were in all respects comparable to the other group studied except for a higher incidence of inferior infarction in this group, 71 per cent as against 38 per cent for the short-term group. Premature ventricular complexes

TABLE 1 *Clinical and electrocardiographic data for 26 patients with acute myocardial infarction who received 0.4 mg nitroglycerin sublingually every 4 hours for 24 hours*

| | | |
|---|---|---|
| Male | | 12 |
| Female | | 14 |
| Average age (yr) | | 63 |
| Average time from onset of pain to CCU admission (hr) | | 6.3 |
| Site of infarction: inferior | | 10 |
| anterior and anteroseptal | | 16 |
| Deaths in CCU | | 3* |
| Heart failure | | 17 |
| | *Before nitroglycerin* | *After nitroglycerin* |
| Average heart rate (beats/min) | 79 | 83‡ |
| Average premature ventricular complexes per 15 minutes† | 592 | 276§ |
| Average blood pressure (mmHg) | 130/76 | 118/69§ |

* All patients with anterior infarction; all deaths were associated with refractory heart failure

† Average of six 15 minute counts in each of the 26 patients.

Significance of change: ‡ $P < 0.001$; § $P < 0.005$

*Conversion from Traditional units to SI units :* 1 mm Hg ≈ 0.133 kPa.

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

| | | *After nitroglycerin* | | | |
|---|---|---|---|---|---|
| | *Control* | *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 subendocardial 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 salutory 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).

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