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# Effects of morphine on cardiovascular responses to acute myocardial ischaemia in rats

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**1** The effects of acute coronary artery ligation on cardiac rhythm and haemodynamics were studied in rats receiving either acute or chronic morphine-treatment.

**2** In chronic opiate-treated animals, increasing concentrations of morphine sulphate were administered in drinking water over a 3 week period, and the development of morphine tolerance and dependence was verified by decreased analgesic responses to morphine in the tail-immersion test and the occurrence of naloxone-precipitated withdrawal syndromes, respectively.

**3** Acute coronary artery ligation induced a decrease in blood pressure, a slight increase in heart rate, and ventricular tachycardia or fibrillation in anaesthetized rats.

**4** The changes in blood pressure and heart rate following acute coronary artery ligation were not significantly altered by acute or chronic morphine administration.

**5** The incidence and the time of onset of ventricular tachycardia or fibrillation were found to be significantly reduced and prolonged, respectively, in chronically morphine-treated rats, but were not significantly affected by acute morphine administration in naïve animals.

**6** These findings suggest that chronic morphine treatment lessens the occurrence of early ventricular arrhythmias caused by acute myocardial ischaemia in rats. The mechanism of this effect is unclear.

## Introduction

Ventricular arrhythmias appear to be an important cause of death from acute myocardial infarction. Various experimental findings and clinical evidence, such as raised plasma catecholamine concentrations, have indicated that their production may be attributed to an increase in sympathetic nervous activity during acute myocardial ischaemia (Ceremuzynski *et al.*, 1969; Jewitt et al., 1969; Staszewska-Barczak, 1971; Mueller & Ayres, 1978). β-Adrenoceptor blockade has also been shown to protect the experimental animals against ventricular arrhythmias caused by acute coronary artery ligation (Fitzgerald, 1982).

Administration of exogenous opiates such as morphine or of endogenous opioids has been found to influence the cardiovascular system by enhancing the parasympathetic and inhibiting the sympathetic outflow through a direct action on the central nervous system (Holaday, 1983). In the isolated atria [Leu] enkephalin was found to antagonize the chronotropic effects of noradrenaline (Ruth & Eiden, 1984). Recent evidence has also shown that chronic morphine treatment results in decreased cardiovascular responses to stimulation of peripheral sympathetic nerves in rats (Leung *et al.*, 1986). Therefore, it is possible that the occurrence of ventricular arrhythmias during acute myocardial ischaemia may be modified by acute or chronic morphine administration.

The present study examines the influence of acute or chronic morphine treatment on the changes in cardiac rhythms and haemodynamics induced by acute coronary artery ligation in rats.

## Methods

### *Animals*

Male Sprague-Dawley rats were housed in groups of 4 per cage and allowed free access to tap water and a standard laboratory diet of Purina rat chow (Ralston Purina, U.S.A.). The animals were kept in an air-conditioned room where temperature was maintained at 23 ± 1°C and relative humidity at 60–70%, and were exposed to a 12h day-night cycle.

*Coronary artery ligation*

The technique of acute coronary artery ligation in anaesthetized rats described by Clark *et al.* (1980) was used. It was performed in animals receiving acute or chronic morphine treatment, as well as their controls.

The rats were anaesthetized with pentobarbitone sodium (Abbott) 60 mg kg$^{-1}$ intraperitoneally. The trachea was cannulated to allow artificial ventilation. Arterial blood pressure was recorded by a Statham P231D pressure transducer connected to the right common carotid artery. The electrocardiogram (ECG) was monitored via standard limb lead II by the use of an Universal coupler (Narco Bio-systems); the heart rate from the ECG waveform was triggered by a biotachometer coupler (Narco Bio-systems). The parameters were displayed on a physiograph (Narco Bio-systems).

The rats were subjected to left thoracotomy at the fifth intercostal space. The fourth and fifth ribs were sectioned approximately 2 mm from the left margin of the sternum. Immediately after opening the chest, the animals were artificially ventilated (82 strokes min$^{-1}$, 1 ml 100 g$^{-1}$) using a respirator (Palmer, U.K.). The pericardium was then opened, and the heart exteriorised by gentle pressure on the right chest wall. A 6/0 braided silk suture attached to a 10 mm micro-point reverse cutting needle (Mersilk W 812, Ethicon) was placed under the main left coronary artery about 2 mm distal to the aortic root. The heart was then replaced in the chest cavity. After allowing a period of 10 min for equilibrium, the ligature was tied. In animals receiving acute treatment, morphine or saline was injected intraperitoneally at this time, and the coronary artery ligated 15 min later. This procedure usually produced transient sinus arrhythmias and a few ventricular extrasystoles lasting no longer than 2 min. Animals in which this procedure produced persistent arrhythmias were discarded. The rats were observed for 30 min following coronary artery ligation. The occurrence and the time of onset of persistent (> 5s) ventricular tachycardia (VT) (defined as continuous run of ventricular extrasystoles) and ventricular fibrillation (VF) were recorded. Completeness of coronary artery ligation was verified at the end of the experiment by visualization of the coronary artery distribution following intravenous injection of 1 ml 1% methylene blue in saline.

*Morphine treatment*

In the acute morphine treatment studies, rats weighing 400–500 g were used. They were given morphine sulphate (Macfarlan Smith, Middlesex) 4 or 8 mg kg$^{-1}$ (expressed as the salt), injected intraperitoneally 15 min before coronary artery ligation. Equivalent volumes (1 ml kg$^{-1}$) of 0.9% w/v NaCl solution (saline) were administered by the same route and at the same time to those animals acting as controls.

In the chronic morphine treatment studies, the opiate was administered in the drinking water (Badawy *et al.*, 1982; Ho *et al.*, 1985). The rats, weighing 280–300 g at the start of the experiment, were provided *ad libitum* with morphine sulphate dissolved in drinking tap-water for 3 weeks. The drug was given in increasing concentrations (48 h apart) of 0.1, 0.2, 0.3 and finally 0.4 mg ml$^{-1}$ (expressed as the salt). The animals continued to receive the final concentration of morphine sulphate until the end of the 3 week chronic treatment period. Control animals received tap-water without morphine sulphate. The body weight was measured in all rats. Daily fluid and food intakes were

**Table 1** Effects of coronary artery ligation on blood pressure and heart rate in rats receiving acute and chronic morphine-treatment.

| | | *Before coronary artery ligation* | | *Maximal changes after coronary artery ligation* | |
|---|---|---|---|---|---|
| *Treatment* | *Number of rats* | *BP* (mmHg) | *HR* (min$^{-1}$) | *Decreases in BP* (%) | *Increases in HR* (%) |
| *Acute (i.p.)* | | | | | |
| Saline 1 mg kg$^{-1}$ | 10 | 88.5 ± 8.8 | 484.0 ± 15.5 | 31.70 ± 5.70 | 4.12 ± 0.86 |
| Morphine | | | | | |
| 4 mg kg$^{-1}$ | 8 | 94.4 ± 7.5 | 461.3 ± 9.2 | 37.00 ± 8.60 | 5.20 ± 1.00 |
| 8 mg kg$^{-1}$ | 10 | 100.2 ± 5.3 | 447.5 ± 13.0 | 36.25 ± 6.20 | 5.04 ± 1.40 |
| *Chronic (drinking)* | | | | | |
| Tap-water | 12 | 88.0 ± 4.8 | 487.6 ± 13.0 | 30.40 ± 5.30 | 4.32 ± 1.00 |
| Morphine | 16 | 92.9 ± 5.6 | 484.5 ± 10.9 | 31.60 ± 4.18 | 5.50 ± 1.50 |

BP = mean blood pressure; HR = heart rate.
The values are the mean ± s.e.mean.

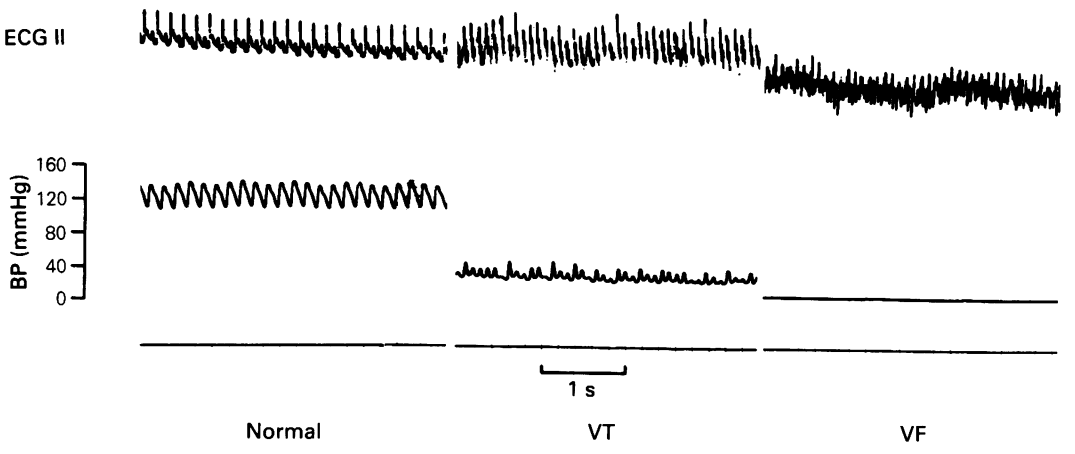


**Figure 1** Ventricular arrhythmias and blood pressure changes induced by left coronary artery ligation in anaesthetized rats. ECG = electrocardiogram; BP = blood pressure; VT = ventricular tachycardia; VF = ventricular fibrillation.

estimated for each animal by taking the average consumption of the 4 rats in each cage. Evidence for the development of opiate tolerance and dependence was examined in separate groups of animals receiving the same chronic treatment. Tolerance to the analgesic action of morphine was examined on day 17 by using the tail-immersion test as previously described (Dai *et al.*, 1984; Ho *et al.*, 1985). Opiate dependence was evaluated by observing the naloxone-precipitated withdrawal syndrome at the end of the 3 week chronic treatment period. The severity of the withdrawal syndrome was expressed by the number of behavioural signs observed for 20 min, faecal weight at 20 min and body weight loss at 4 h following intraperitoneal injection of naloxone HCl (Endo) 1 mg $kg^{-1}$ (expressed as the salt) (Collier *et al.*, 1974; Dai *et al.*, 1984; Ho *et al.*, 1985). For comparison, similar observations were made in a group of naïve rats injected with the same dose of naloxone and in separate groups of naïve and chronic morphine-treated animals injected with equivalent volumes (1 ml $kg^{-1}$) of saline.

*Statistical analysis*

The reaction time measured with the tail-immersion test, parameters of naloxone-precipitated withdrawal syndrome, the times of onset of ventricular arrhythmias, mean blood pressure, and heart rate were expressed as means ± s.e.mean and were analysed by Student's *t* test. The incidence of occurrence of ventricular tachycardia (VT) or ventricular fibrillation (VF) following coronary artery ligation was analysed by the Chi square-test.

## Results

*Acute morphine treatment*

In the saline-treated controls, acute coronary artery ligation produced a reduction in arterial blood pressure and a slight increase in heart rate (Table 1). These changes peaked within 1 min following ligation. Thereafter, both blood pressure and heart rate remained stable until the onset of VT or VF. Marked ventricular ectopic activities began to appear at about 3 min, and persistent VT or VF occurred by 5–6 min after coronary artery ligation (Figure 1). Intraperitoneal injection of morphine sulphate 4 or 8 mg $kg^{-1}$ did not cause noticeable haemodynamic changes. The blood pressure and heart rate, as well as the changes induced by acute coronary artery ligation, of the acutely morphine-treated rats were not significantly different from those of the saline controls (Table 1). They also exhibited the same incidence and time of onset of VT or VF resulting from acute myocardial ischaemia (Table 2).

*Chronic morphine treatment*

Both control and morphine-treated rats showed a steady increase in body weight as well as food and fluid intake during the 3 week treatment period. No statistically significant differences in these parameters were seen between the two groups. The average daily intake of morphine sulphate 0.4 mg $ml^{-1}$ solution (from day 7 onwards) was 47.3 ml per rat; the estimated daily intake of morphine sulphate by the test group during

**Table 2** Effects of acute and chronic morphine-treatment on the incidence and time of onset of ventricular tachycardia (VT) and ventricular fibrillation (VF) occurring in anaesthetized rats subjected to main left coronary artery ligation.

| | | VT or VF | |
|---|---|---|---|
| *Treatment* | *Number of rats* | *Incidence (%)* | *Onset time (min)* |
| *Acute (i.p.)* | | | |
| Saline (1 ml kg$^{-1}$) | 16 | 100 | 6.16 ± 0.40 |
| Morphine | | | |
| 4 mg kg$^{-1}$ | 8 | 100 | 6.81 ± 0.83 |
| 8 mg kg$^{-1}$ | 10 | 100 | 5.38 ± 0.27 |
| *Chronic (drinking)* | | | |
| Tap-water | 10 | 100 | 5.97 ± 0.54 |
| Morphine | 16 | 37.5* | 9.25 ± 0.09* |

The values of onset are the mean ± s.e.mean.
*$P < 0.01$ when compared with tap-water controls.

this period was, therefore, about 47.9 mg kg$^{-1}$.

The tail-immersion test on day 17 showed that intraperitoneal injection of acute morphine sulphate 8 or 16 mg kg$^{-1}$ significantly prolonged the reaction time in both control ($P < 0.001$ for both doses) and chronically morphine-treated control ($P < 0.05$ and $P < 0.001$ for 8 and 16 mg kg$^{-1}$, respectively) (Figure 2). However, the reaction time of the latter group was significantly less than that of the former group, indicating the development of tolerance to the analgesic effects of the opiate.

Table 3 shows the naloxone-precipitated withdrawal effects in chronically morphine-treated rats. When compared with the controls injected with naloxone, or with the chronically morphine-treated animals injected with saline, this group of rats showed significantly greater values for withdrawal signs, faecal excretion and body weight loss ($P < 0.001$ for all three parameters), indicating the development of opiate dependence.

When these rats were anaesthetized at the end of the 3 week treatment period, the blood pressure and heart rate of the 2 treatment groups were essentially similar (Table 1). Like the naïve rats acutely injected with saline or morphine, the tap-water drinking control animals exhibited a marked decrease in blood pressure and a slight rise in heart rate following acute coronary artery ligation. These changes reached their peak by 1 min after ligation and, thereafter, became relatively stable until the onset of VT or VF. All control animals developed VT or VF at about 5–6 min after ligation. In chronically morphine-treated rats, the responses of blood pressure and heart rate to acute coronary artery ligation were not qualitatively or quantitatively dif-

**Table 3** Naloxone-precipitated withdrawal effects in rats chronically treated with morphine for 21 days

| *Treatment (i.p.)* | *Dose* | *Number of rats* | *Number of withdrawal signs* | *Faecal wt. at 20 min after injection (g)* | *Body wt. loss at 4 h after injection (%)* |
|---|---|---|---|---|---|
| *Control* | | | | | |
| Saline | 1 ml kg$^{-1}$ | 12 | 0.58 ± 0.19 | 1.16 ± 0.27 | 2.31 ± 0.20 |
| Naloxone | 1 mg kg$^{-1}$ | 12 | 0.66 ± 0.22 | 0.87 ± 0.16 | 2.42 ± 0.20 |
| *Chronic-morphine* | | | | | |
| Saline | 1 ml kg$^{-1}$ | 12 | 0.42 ± 0.15 | 1.24 ± 0.26 | 2.43 ± 0.20 |
| Naloxone | 1 mg kg$^{-1}$ | 12 | 4.75 ± 0.35*,† | 6.59 ± 0.45*,† | 5.60 ± 0.30*,† |

The values are the mean ± s.e.mean.
*$P < 0.001$ when compared with the corresponding values in naloxone-injected controls.
†$P < 0.001$ when compared with the corresponding values in chronic morphine-treated rats injected with saline.

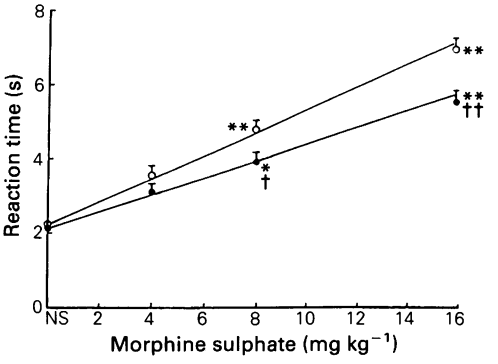


**Figure 2** Effects of morphine on the reaction time of rats in the tail-immersion test. The values are the mean with vertical lines indicating s.e.mean NS = normal saline; (○) control; (●) morphine-treated rats. $n = 12$ for each group. $^{*}P < 0.05$, $^{**}P < 0.001$ when compared with the saline control of the same group. $\dagger P < 0.05$, $\dagger\dagger P < 0.001$ when compared with the corresponding control values.

ferent from those in the control group (Table 1). However, the incidence and the time of onset of VT or VF resulting from acute myocardial ischaemia were significantly lower and prolonged, respectively, in chronically morphine-treated animals when compared with the control group (Table 2).

## Discussion

Ligation of the left coronary artery in rats has been accepted as a relatively simple and useful model for producing experimental cardiac dysrhythmias (Clark *et al.*, 1980). When the left coronary artery is occluded, ventricular arrhythmias arise within a few minutes. It is during this period that ventricular tachycardia or fibrillation is most likely to occur (Dai, 1986). If the animals survive, there occurs later on an arrhythmia-free period which is followed by further pronounced ventricular ectopic activity some hours later. It is the early life-threatening ventricular arrhythmia that is the subject of the present study. Therefore, the current investigation observed the rats for only 30 min after coronary artery ligation.

Administration of morphine in drinking water has been recommended as a better means of inducing morphine tolerance and dependence than other methods (Fuentes *et al.*, 1978), but consumption of significant amounts of morphine solution by the animals is often not attained probably due to its bitter taste. Badawy *et al.* (1982) have found that opiate tolerance and dependence could be successfully induced in rats by administering increasing concentrations of morphine in drinking water for 3 weeks. This regimen was adopted in the present study. The reduced responses to acutely administered morphine in the tail-immersion test and the elicitation of the naloxone-precipitated withdrawal syndrome confirmed that the rats were opiate-tolerant and -dependent when they were subjected to coronary artery ligation after drinking morphine solution for 3 weeks. Numerous studies have shown that chronic morphine administration, besides producing tolerance and physical dependence, can also induce certain physiological changes which are not seen after acute morphine treatment. These include altered sensitivity to catecholamines, acetylcholine, 5-hydroxytryptamine, arachidonic acid and dopamine (Schulz & Goldstein, 1973; Kromer & Steigemann, 1982; Rae *et al.*, 1983; Dai *et al.*, 1985; Martin & Takemori, 1986). It was found in the present study that the incidence and the time of onset of ventricular arrhythmias induced by acute coronary ligation were significantly lower and prolonged, respectively, in chronically morphine-treated rats. These findings indicate that some physiological changes, related to the occurrence of ventricular arrhythmias, may have been induced by chronic morphine treatment.

The mechanism of the effects of chronic morphine-treatment is unclear. It has been demonstrated that there is early activation of cardiac efferent sympathetic nerves during experimental myocardial ischaemia (Brown & Malliani, 1971; Bosnjak *et al.*, 1979). Increased regional sympathetic activity in the ischaemic myocardium has been considered as an important cause for the development of serious ventricular arrhythmias in acute myocardial ischaemia (Corr & Gillis, 1978; Hjalmarson, 1980). It was recently found by Leung *et al.* (1986) that chronic morphine administration in the rat led to a decrease in cardiovascular responses to sympathetic nerve stimulation. Therefore, it is possible that the reduced and delayed occurrence of ventricular arrhythmias in chronically morphine-treated animals, as observed in the current study, may be secondary to the decreased responses to sympathetic overactivity during the early stage of acute myocardial ischaemia. However, evidence has shown that the release of other endogenous substances such as catecholamines (Riemersma, 1982), prostaglandins and thromboxanes (Coker, 1982), cyclic AMP (Podzuweit, 1982), endorphins (Fagbemi *et al.*, 1982) and histamine (Dai, 1986) may also be involved in the genesis of ventricular arrhythmias caused by myocardial infarction. Therefore, further studies are required before a firm conclusion can be drawn.

It has been suggested that increased sympathetic activity during acute myocardial ischaemia may contribute to the genesis of ventricular arrhythmia (Corr & Gillis, 1978; Hjalmarson, 1980) and that the opiates

may reduce sympathetic outflow from the central nervous system (Holaday, 1983). Based on the protective effects of naloxone, Fagbemi *et al.* (1982) have also postulated that activation of opiate receptors by endorphins released during the early stages of myocardial ischaemia may have detrimental effects of cardiac rhythm. Therefore, it is conceivable that acute morphine administration may retard or aggravate the occurrence of ventricular arrhythmias following acute coronary artery ligation. However, these possibilities can be excluded by the findings of the current investigation. Intraperitoneal injection of morphine sulphate 4 or 8 mg $kg^{-1}$ 15 min before coronary artery ligation failed to alter the incidence or the time of onset of VT or VF. Cohen *et al.* (1982) have shown that doses of naloxone which are sufficient to reverse the action of administered exogenous opioids may not be enough to block the activity of endogenous opioids. This suggests that the exogenous opiates may not be quantitatively equivalent to the endogenous opioids. Therefore, the present results cannot exclude the potential involvement of endogenous opioids in the production of ventricular arrhythmias during acute myocardial ischaemia. The effects of large dose of morphine sulphate, 16 mg $kg^{-1}$, were examined in a preliminary study. However, it was found that these animals exhibited very intense decreases in blood pressure and heart rate following coronary artery ligation, and finally died of cardiac arrest within a few minutes. The reasons for the high mortality rate are not clear.

The present investigation shows that, in acute saline-treated and chronic tap-water drinking control rats, acute coronary artery ligation causes a marked decrease in arterial blood pressure which is associated with relatively small changes in heart rate. This is in agreement with earlier findings (Dai, 1986). It also reveals that the alterations in blood pressure and heart rate induced by acute coronary artery occlusion are not significantly affected by acute or chronic morphine administration. However, the mechanisms causing haemodynamic changes during acute myocardial ischaemia remain unclear. Whatever the mechanism may be, the present results suggest that it is not influenced by either acute or chronic morphine treatment.

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