

## The Effects of Morphine on the Isolated Heart during Normothermia and Hypothermia

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The effects of morphine were studied in 100 isolated rabbit hearts, using a modified Langendorff preparation. Morphine significantly depressed peak left ventricular  $dP/dt$  and heart rate in a concentration of  $10^{-6}$  g/ml at 32 C. Hearts cooled to 22 C were less depressed, and hearts perfused at 37 C were more depressed, by morphine. Pretreatment of the rabbits with reserpine (5 mg/kg) did not alter the heart's response to morphine. Increased calcium in the perfusate resulted in less depression of peak  $dP/dt$  by morphine, while decreased calcium resulted in more depression. Calcium concentration did not alter the action of morphine on heart rate. (Key words: Morphine; Isolated heart; Peak left ventricular  $dP/dt$ ; Heart rate; Hypothermia; Calcium; Reserpine.)

MORPHINE in high doses is popular for anesthesia of patients undergoing cardiac surgery. Blood pressure is usually well maintained in patients and volunteers receiving 1–2 mg/kg.<sup>1–3</sup> However, the pre-ejection period, representing the time for isovolumic contraction,<sup>4</sup> is prolonged after 2 mg/kg, suggesting myocardial depression.<sup>3</sup> To study this possibility further, the isolated heart has been employed. This permits identification of direct cardiac effects of morphine and obviates the modifying influences of catecholamine release,<sup>5, 6</sup> reflex compensatory mechanisms,<sup>7, 8</sup> histamine release,<sup>9, 10</sup> and respiration.<sup>11</sup>

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The isolated heart also allows study of modification of the action of morphine on the heart by factors such as temperature and calcium ion and local norepinephrine release. These factors are of clinical relevance. They also help to elucidate possible mechanisms of morphine action, and point the way for further study.

### Methods

The hearts of 100 6–10-week-old New Zealand rabbits, weighing 1.7–2.5 kg, were excised after cervical fracture. Approximately a minute was needed to isolate the heart and re-establish coronary-artery perfusion via the aorta in a modified Langendorff preparation. A constant column of perfusate of 56 cm  $H_2O$  over the aortic valve was maintained with the use of a run-off arm. The perfusate, Chenoweth solution,<sup>12</sup> contained NaCl 119.8 mM, KCl 5.63 mM,  $CaCl_2$  2.16 mM,  $MgCl_2$  2.10 mM, dextrose 10 mM, and  $NaHCO_3$  25.0 mM.  $CaCl_2$  concentrations of 4.32, 1.08, and .54 mM were each used in seven experiments. The solution was equilibrated at room temperature with 95 per cent  $O_2$  and 5 per cent  $CO_2$ .  $P_{O_2}$ ,  $P_{CO_2}$ , and pH of the solution were measured intermittently. Perfusion solution was not recycled following administration of morphine.

The cardiac electrogram was monitored with platinum electrodes in the right atrial appendage and the left ventricular wall 1 cm from the apex. The same electrodes were used to pace the heart with a stimulus of 2-msec duration and a 1.5–2× threshold potential (10–15 v).

Left ventricular pressure was recorded continuously with a model MS 5 Microdot, high-frequency transducer from a catheter inserted through the left atrial appendage and the mitral valve into the left ventricle. Aortic perfusion pressure was monitored with a Statham P23AC transducer. The left ventricular  $dP/dt$  was derived electrically. All variables were displayed on a Tektronix RM 565 oscilloscope

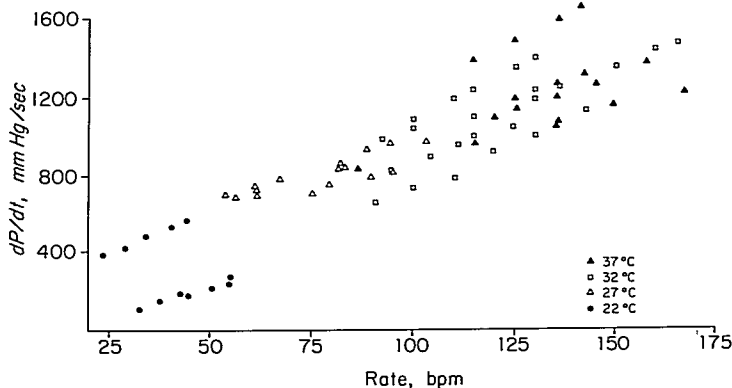


FIG. 1. The effects of increasing heart rate by pacing on peak left ventricular  $dp/dt$  at 22, 27, 32 and 37 C. Slopes =  $3.4 \pm 0.9$  SD.

and continually recorded on a Grass model 7 polygraph.

Myocardial temperature was regulated by adjusting the perfusate temperature with a Lauda K-2/R thermoregulator. Temperature was monitored with a thermoprobe inserted through the pulmonary valve into the right ventricle. Morphine sulfate solutions were prepared just before administration by adding powdered or serially diluted morphine sulfate to the control solution previously equilibrated with oxygen and carbon dioxide. Hearts were perfused with the morphine solution for 10 minutes and then returned to the control solution. Rabbits receiving reserpine were pretreated with 5 mg/kg, ip, 24 hours prior to sacrifice. The effects of temperature change on hearts beating at a constant rate were determined by pacing a heart at a rate slightly above its spontaneous rate and then slowly lowering the temperature 5 degrees while continuing to pace at the same rate. Statistical significance was calculated using Student's *t* test for paired or unpaired data. Differences with a probability of 0.05 or less were considered significant.

### Results

#### EFFECT OF RATE CHANGE WITHOUT MORPHINE

An increase in rate resulted in an increase in peak  $dp/dt$ . For a given heart there was a

linear relation between rate and peak  $dp/dt$  at a constant temperature (correlation coefficients greater than 0.97). The amounts of increase in peak  $dp/dt$  for an increase in rate of 10 beats/min ranged from 46 to 106 mm Hg/sec in different hearts, with a mean of 68 mm Hg/sec. The ranges were approximately the same at 22, 27, 32, and 37 C (fig. 1).

#### EFFECTS OF TEMPERATURE CHANGE WITHOUT MORPHINE

Cooling from 37 to 22 C in 5-degree decrements depressed spontaneous heart rate and peak  $dp/dt$ , with no significant effect on left ventricular pressure (fig. 2). Less depression of peak  $dp/dt$  was seen with cooling in hearts paced at a constant rate. Hearts could not be paced at the same rate while cooling from 27 to 22 C because of prolongation of systole with insufficient time for diastole.

#### EFFECTS OF MORPHINE

Morphine's actions on the isolated heart at 32 C are summarized in table 1. Although not statistically significant,  $dp/dt$ 's of 11 of 28 hearts were depressed at  $10^{-6}$  to  $10^{-8}$  g/ml morphine sulfate. Peak  $dp/dt$  and heart rate were significantly depressed at  $10^{-5}$  g/ml morphine (fig. 3). Pretreatment with reserpine in five animals resulted in no change in degree of morphine depression observed.

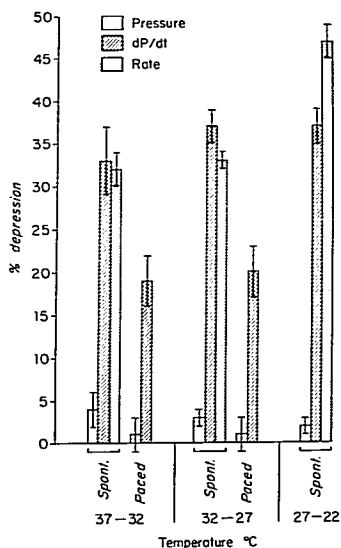


FIG. 2. The effects of cooling from 37 to 22 C in 5-degree decrements on left ventricular pressure, peak dP/dt, and heart rate in spontaneously beating and paced hearts. Means  $\pm$  SE. Pressure changes were not significantly different from control ( $P < 0.05$ ).

After morphine, peak dP/dt returned to within 3 per cent of the control value following a washout period, except after the  $10^{-4}$  g/ml

dose, when dP/dt averaged 91 per cent of control, and after  $10^{-3}$  g/ml, when dP/dt averaged 82 per cent of control.

#### EFFECTS OF TEMPERATURE ON RESPONSE TO MORPHINE

Morphine,  $10^{-4}$  g/ml, produced significantly more depression of peak dP/dt and spontaneous heart rate when given to a heart at 37 C than when given to a heart at 22 C (fig. 4). Since significant depression was just detectable at a concentration of morphine of  $10^{-5}$  g/ml, we elected to study modifying factors at higher concentrations of morphine so that significant change might be more accurately observed.

Since heart rate is a factor in determining peak dP/dt, at each temperature six hearts were paced to maintain a constant rate slightly above their spontaneous rate and then treated with  $10^{-4}$  g/ml morphine. No significant difference between degrees of depression of peak dP/dt in paced and spontaneously beating hearts was demonstrated (fig. 4B).

#### EFFECTS OF CALCIUM ON RESPONSE TO MORPHINE

Morphine,  $10^{-4}$  g/ml, produced significantly more depression of peak dP/dt when given to a heart perfused with 0.54 mM calcium than when given to a heart perfused with 2.16 mM calcium. Significantly less depression of peak dP/dt occurred with morphine when the perfusate contained 4.32 mM calcium. The depression of rate with morphine was not affected by change in calcium concentration (fig. 5).

TABLE 1. Incidences of Depression and Stimulation of Peak Left Ventricular dP/dt, Pressure, and Heart Rate after Morphine Sulfate in Spontaneously Beating Isolated Hearts at 32 C\*

Morphine sulfate, g/ml	dP/dt			Pressure			Rate			Total
	†	0	↓	†	0	↓	†	0	↓	
$10^{-9}$	0	8	0	0	8	0	0	6	2	8
$10^{-8}$	1	7	2	1	9	0	1	8	1	10
$10^{-7}$	0	5	4	0	8	1	0	7	2	9
$10^{-6}$	1	3	5	0	8	1	0	4	5	9
$10^{-5}$	0	1	9	0	8	2	0	5	5	10
$10^{-4}$	0	1	15	0	8	8	0	3	13	16
$10^{-3}$	0	0	8	0	0	8	0	0	8	8

\* Values changed less than 5 per cent were considered unchanged.

## PERFUSION

The perfusion solutions in this study had pH's of 7.28-7.40;  $P_{CO_2}$ 's of 36-54 torr, and  $P_{O_2}$ 's of 472-640 torr with or without the addition of morphine sulfate. Measured concentrations of sodium ion ranged from 144.5 to 150 mEq/l. Potassium ion concentrations ranged from 5.2 to 5.7 mEq/l.

Deterioration of peak dP/dt over 20 minutes in hearts at 32, 27, or 22 C was 3 per cent or less. At 37 C deterioration was as much as 8 per cent over 20 minutes. For this reason most studies were done at 32 C. Stable preparations usually lasted four hours.

## Discussion

## RESPONSE TO RATE CHANGES

An increase in rate resulted in an increase in peak dP/dt. Our findings are compatible with those in two earlier experiments in cardiac tissue preparations which showed increased pressure and tension with increased rate<sup>13,14</sup> over the rate range we employed. It was possible to increase the heart rate only over a narrow range, after which there was insufficient time for diastole or marked depression occurred when rate was further increased.

## RESPONSE TO TEMPERATURE CHANGE

Our findings of decreased peak dP/dt with decrease in temperature have been consistently found in ejecting hearts.<sup>15</sup> We have further shown that the decrease in peak dP/dt is partially due to a decrease in rate which can be prevented by pacing the heart at a constant rate.

The decrease in dP/dt with temperature which is independent of rate is yet to be explained. Slowed chemical reactions and increased mechanical resistance may play a part. However, in cardiac tissue preparations in which tension is allowed to increase, dP/dt increases with cooling.<sup>16</sup>

## RESPONSE TO MORPHINE

The degree of depression of rate by morphine which we found is similar to that found by Kennedy and West in a study of the effects of morphine on the SA node.<sup>17</sup>

Earlier studies<sup>18-23</sup> of isolated hearts showed depression of tension only by 10-20 times the

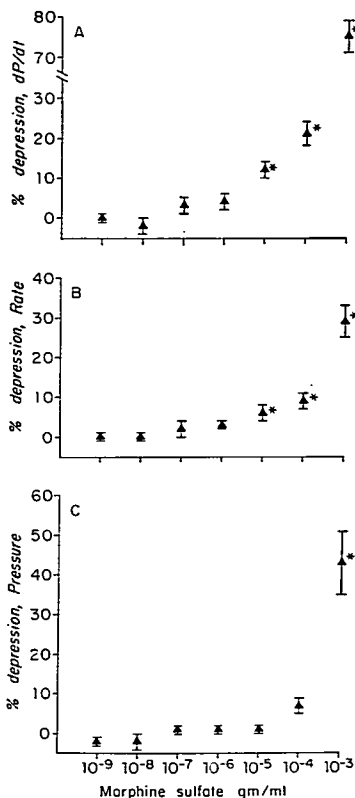


FIG. 3. The effects of morphine on peak left ventricular dP/dt, heart rate, and left ventricular pressure at 32 C. Means  $\pm$  SE. Asterisks indicate values significantly depressed from control ( $P < 0.05$ ).

concentration of morphine which significantly depressed dP/dt in our study. The greater sensitivity to morphine reported here is probably the result of the use of peak dP/dt rather than peak tension as a measure of myocardial function. Rushmer has demonstrated that peak dP/dt is a more sensitive index of contractility in man than tension.<sup>24</sup>

However, our results still suggest that the myocardial depressant action of morphine is not important clinically. The depressant effect on peak  $dP/dt$  even at  $10^{-4}$  g/ml was less than 20 per cent in our hearts. About half the depression occurs in the first two minutes of exposure. Reported plasma levels in man vary widely, being as high as  $1.4 \times 10^{-6}$  g/ml after a 10-mg bolus (Ellison N, Behar MC, University of Pennsylvania) and  $3.0 \times 10^{-6}$  g/ml during a slow infusion of 2 mg/kg morphine (Way WL, Fourcade HE, Larson CP, et al, University of California, San Francisco). But redistribution is rapid, and 5 minutes after infusion of 2 mg/kg, plasma levels are less than  $10^{-7}$  g/ml.<sup>3</sup> In addition, a portion of plasma morphine may be biologically inactive due to protein binding. It is worth pointing out that while not statistically significant, 11 of 28 hearts were depressed at  $10^{-6}$  to  $10^{-5}$  g/ml morphine sulfate, and rabbit hearts are more resistant to morphine than those of other species.<sup>19, 21</sup> Indiscriminate use of excessive amounts of morphine will undoubtedly produce significant cardiac depression.

The mechanism of depression of the heart by morphine is not known. Kakunaga<sup>22</sup> has shown in mice that intraperitoneal or intracasternal calcium injections antagonize the analgesic effect of morphine. It is interesting to speculate that morphine may interfere with calcium transport both in the heart and in the central nervous system. Indeed, Mulé<sup>26</sup> has shown that calcium ion is transported across a methanol-water-chloroform interface in the presence of phosphatidylcholine or phosphatidic acid and that this transport is inhibited 56 per cent and 13 per cent, respectively, by  $3.5 \times 10^{-4}$  g/ml morphine. The specificity of this inhibition is not known, but it does suggest that morphine in high concentrations may in some way compete for sites which bind calcium ion.

Our studies of the effect of morphine in hearts perfused with various concentrations of calcium tend to support this hypothesis. Depression of peak  $dP/dt$  was inhibited by a high calcium concentration and potentiated by a low calcium concentration in the perfusate. However, depression of rate by morphine did not

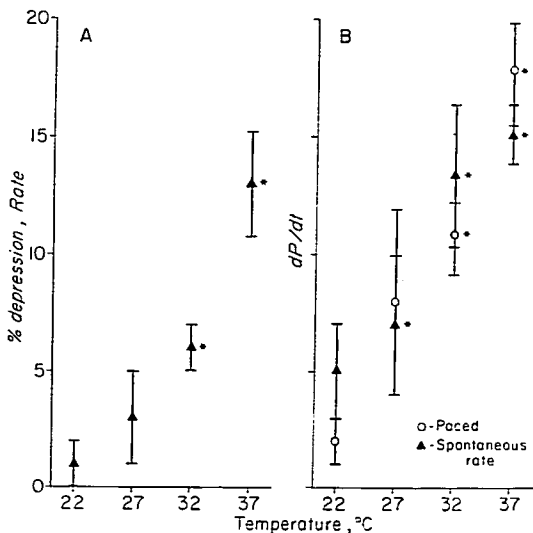


FIG. 4. Effects of morphine,  $10^{-4}$  g/ml, on: A. spontaneous rate, and B. left ventricular peak  $dP/dt$ , at 22, 27, 32 and 37 C. Means  $\pm$  SE. Asterisks indicate values significantly depressed from control ( $P \leq 0.05$ ).

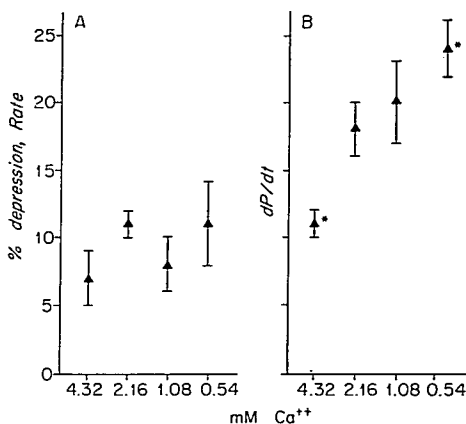


Fig. 5. Effects of morphine,  $10^{-4}$  g/ml, on: A, spontaneous rate, and B, left ventricular peak  $dP/dt$ , at decreasing calcium concentrations. Means  $\pm$  SE. All values are significantly different from control. Asterisks indicate values significantly different from values with 2.16 m $\text{M}$   $\text{CaCl}_2$  ( $P < 0.05$ ).

appear to be affected by changing calcium concentrations. Cooling the heart protects it from the depressant effects of morphine. While no mechanism is directly implicated, it is reasonable to speculate that differences in the cellular distribution and biochemical reaction of calcium at the contractile site during hypothermia may play an important role. Studies of the location of morphine in the cell and of calcium uptake during morphine administration might clarify some of these points.

Morphine is known to release adrenal catecholamines in rats, rabbits, dogs, and cats.<sup>5, 27</sup> In addition, cardiac depletion of norepinephrine has been shown in rats following chronic morphine administration,<sup>28</sup> which suggests that morphine may release norepinephrine in the heart. However, in this study hearts from reserpinized rabbits with presumed cardiac catecholamine stores of less than 10 per cent of normal<sup>29</sup> had the same response to morphine as nonreserpinized hearts. Therefore, we conclude that the depressant action of morphine on the isolated heart is not mediated through myocardial catecholamine release.

#### THE PREPARATION

The major criticism of our preparation is the marginal oxygenation of the hearts known to exist in Langendorff preparations. It is pos-

sible that the increased depression of the isolated heart by morphine at higher temperatures is due to the poorer oxygenation which exists at these temperatures.

Factors other than contractility known to affect peak  $dP/dt$  are afterload, preload, conduct pathway, and heart rate.<sup>30</sup> An attempt was made to minimize these factors. Afterload was stabilized with a constant column of fluid. Preload was near zero as the left atrium drained freely. Heart rate was controlled by electrical pacing when necessary. No increase in left ventricular pressure (LVP) was observed here because of the fixed afterload facing the heart when the aortic valve opened. Maximum LVP in this study was limited by the height of the run-off arm. Peak  $dP/dt$  occurred toward the end of the isovolemic contraction.

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