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Effect of Morphine on Isolated Human Atrial Muscle

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The effects of 5, 10, 20, and 30 mg/100 ml morphine on the force of contraction of isolated human atrial muscle were studied. The tissue was suspended in Krebs-Ringer bicarbonate solution containing 20 mM glucose at 37 C and stimulated with supramaximal voltage at a rate of 70 pulses/min. Morphine, 5 and 10 mg/100 ml, which represents a much higher concentration than would be achieved in plasma following a usual anesthetizing dose of 2 mg/kg, had no effect on force of contraction over a 30-minute period. Twenty and 30 mg/100 ml morphine depressed force of contraction 21 and 70 per cent, respectively. Simulated morphine diluent, containing chlorbutanol and sodium bisulfite alone, had negligible effects on the force of contraction. Pyruvate, 15 mM, had a marked positive inotropic effect in control preparations. The response to pyruvate remained unimpaired in the presence of 5 and 10 mg/100 ml morphine, whereas it was markedly inhibited in the presence of 20 and 30 mg/100 ml morphine. In the 30 mg/100 ml morphine series there was complete recovery of pyruvate response after washout. It is concluded that clinical doses of morphine do not cause myocardial depression. As previously demonstrated with pentobarbital, morphine in excessive doses may exert a negative inotropic effect by interfering with energy production or utilization at a step subsequent to glycolytic formation of pyruvate. (Key words: Morphine, heart; Heart, morphine; Metabolism, heart.)

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THE ADVENT of morphine "anesthesia"[1] in recent years has created a new wave of interest in the pharmacologic properties of morphine in the cardiovascular system. Studies conducted in intact animals[2,3] and in man[4,5] indicate that morphine has no deleterious effect on myocardial function. Large doses of morphine have been shown to cause a direct cardiac depressant effect in isolated perfused hearts[6] and contracting myocardial strips.[7] To our knowledge, the direct effects of morphine on the force of contraction of isolated human cardiac tissue have not been studied. The purpose of the present study has been to investigate the inotropic effects of different doses of morphine on isolated human atrial muscle and to establish the possible mechanism of depression.

Materials and Methods

Details of the experimental procedure have been described.[8] Pieces of right atrial appendage were obtained from patients undergoing cardiac surgery on cardiopulmonary bypass. Ten- to 15-mm long muscle bundles were suspended in Krebs-Ringer bicarbonate solution containing 20 mM glucose at 37 C. The muscles were stimulated with supramaximal voltage at a rate of 70 pulses/min and allowed to contract isometrically by maintaining a constant resting tension of 750 mg. A stabilization period of 60 minutes was allowed. Only those preparations which showed good stability during this period were used in the study. The force of contraction at the end of the stabilization period was expressed as 100 per cent.

Commercially available morphine sulfate solution of Eli Lilly and Company was used for this study. This solution contains, besides morphine, preservatives, chlorbutanol and sodium bisulfite, 0.5 and 0.1 per cent, respectively.

Four series consisting of four experiments each, using 5, 10, 20, and 30 mg/100 ml morphine, and a control series were conducted. The responses of control and morphine-treated atrial muscles to pyruvate (15 mM) were determined.

In another series of four experiments the effect of simulated diluent alone on the force of contraction was studied. The amount of diluent was comparable to that present in the 30 mg/100 ml morphine series.

Addition of pyruvate (15 mM) or morphine solution had no effect on the *p*H of the bathing solution.

Results

Control

In the control series of four experiments, following the one-hour stabilization period the force of contraction had declined 11 ± 15 per cent over a 30-minute period (fig. 1).

Effect of Morphine on Force of Contraction

The effects of 5, 10, 20, and 30 mg/100 ml morphine 30 minutes after its addition to the solution bathing the muscle are shown in figures 1 and 2. Morphine, 5 and 10 mg/100 ml, decreased force of contraction only 2 ± 11 and 9 ± 4 per cent, respectively, thus showing that 5 and 10 mg/100 ml morphine have no effect on force of contraction. Morphine, 20 mg/100 ml, decreased force of contraction 21 ± 8 per cent, whereas with 30 mg/100 ml the decrease in force of contraction was very marked (70 ± 8 per cent) and statistically significant ($P < .001$).

Effect of Morphine Diluent on Force of Contraction

In a series of four experiments, simulated morphine diluent alone, equivalent to the amount present in the 30 mg/100 ml morphine series, had no effect on force of contraction (+ 4 ± 7 per cent).

Effect of Pyruvate on Control

Pyruvate, 15 mM, was added to the control series 30 minutes after the stabilization period (fig. 2). As reported previously,[8] pyruvate elicited a marked increase in force of contraction (from 89 ± 15 to 225 ± 6 per cent at 20 minutes).

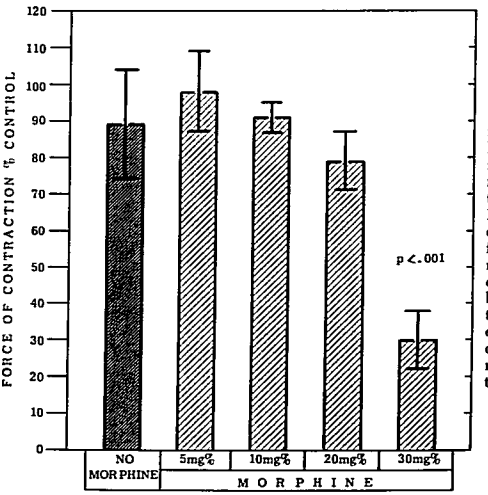

FIG. 1. Force of contraction of isolated human atrial muscle following a 30-minute exposure to morphine. Morphine was added following 60 minutes of equilibration of the muscle in modified Krebs-Ringer bicarbonate medium containing 20 mM glucose. The force of contraction after the 60-minute equilibration period was expressed as 100 per cent. Dark bar represents preparations allowed to beat 30 minutes beyond the equilibration period in the absence of morphine. Vertical lines represent ± 1 SE. *P* represents statistical significance.

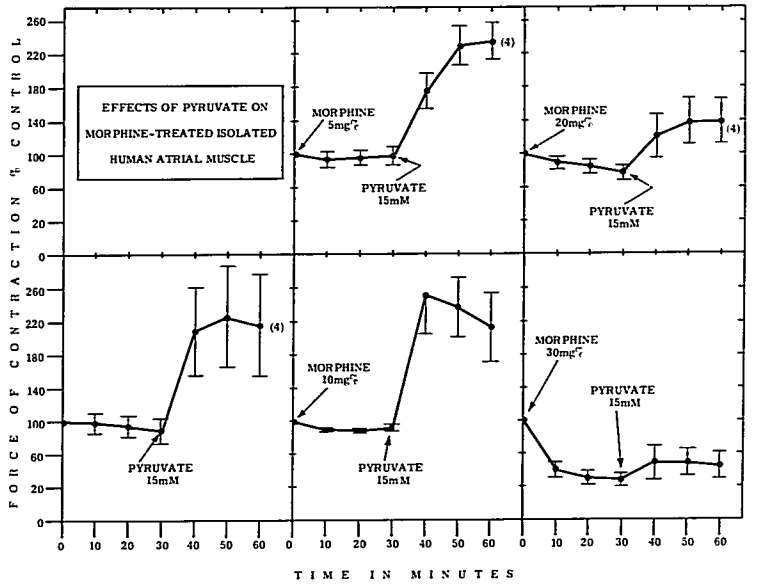

FIG. 2. Effects of pyruvate on forces of contraction of control preparations and those treated with 5, 10, 20, and 30 mg/100 ml morphine. Morphine was added at 0 time and pyruvate at 30 minutes. Vertical lines represent ± 1 SE.

EFFECT OF PYRUVATE ON MORPHINE-TREATED PREPARATIONS

The effect of 15 mM pyruvate on morphine-treated preparations is shown in figure 2. Pyruvate was added 30 minutes after morphine treatment. The response to pyruvate plateaued about 20 minutes after its addition.

The responses to pyruvate in the 5 and 10 mg/100 ml morphine series were similar to the control response (230 and 238 per cent at 20 minutes, respectively, *vs.* 225 per cent control).

In the 20 mg/100 ml series the response to pyruvate was attenuated compared with control (from 79 ± 8 to 139 ± 27 per cent). The change in force of contraction in the 30 mg/100 ml morphine series after addition of pyruvate was almost negligible (from 30 ± 8 to 50 ± 17 per cent). These results indicate that with doses of morphine that depress the myocardium, the response to pyruvate is also inhibited.

RECOVERY OF PYRUVATE RESPONSE AFTER WASH

In the 30 mg/100 ml morphine series the response to pyruvate was also studied after washout (three times with medium) of morphine. Thirty minutes after washout, *i.e.*, at 90 minutes, 15 mM pyruvate increased the force of contraction from 42 to 161 per cent within 20 minutes (fig. 3). Thus, there was almost complete recovery of the response to pyruvate after washout. These results indicate that high doses of morphine do not cause irreversible myocardial damage.

Discussion

Most studies on the hemodynamic effects of large doses of morphine in animals[2-9] and

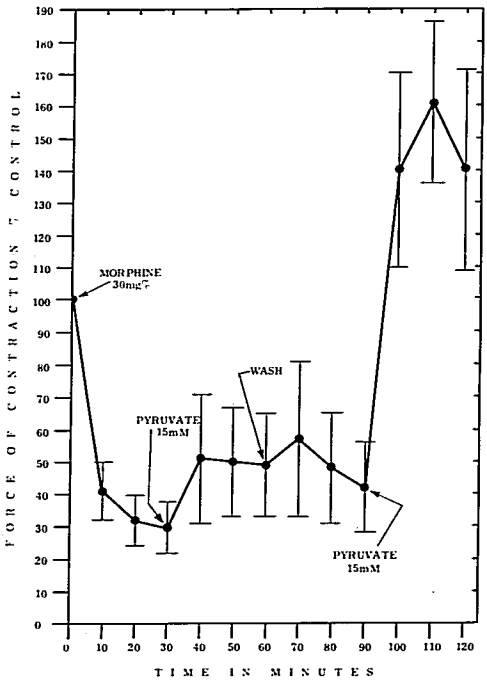

FIG. 3. Effects of pyruvate on forces of contraction of isolated human atrial muscle depressed by 30 mg/100 ml morphine and following washout of morphine. Morphine, 30 mg/100 ml was added at 0 time; pyruvate was added at 30 minutes. Wash represents return of the muscles to the normal Krebs-Ringer medium. Pyruvate was again added 30 minutes after wash.

in man[10] indicate that morphine decreases systemic vascular resistance and increases cardiac output. The effects of morphine on myocardial contractility in man and intact animals have been variously described as mild depressant, no effect, or increased contractility. Wong *et al.*[10] reported a prolonged pre-ejection period (PEP) after morphine administration in healthy individuals and concluded that morphine has a mild myocardial depressant effect. Pur-Shariari *et al.*[11] measured maximal rate of pressure rise in the left ventricle as a function of left ventricular end-diastolic pressure after morphine in dogs and concluded that morphine had no apparent effect on contractility. Vasko *et al.*[2,3] studied the effects of morphine in dogs on cardiopulmonary bypass and clearly demonstrated improved ventricular performance after morphine administration. *Beta*-adrenergic blockade or adrenalectomy abolished the positive inotropic effect of morphine. They therefore attributed improved myocardial function after morphine administration to sympathoadrenal discharge. Hasbrouck[5] reported increased plasma catecholamine levels in man after morphine administration.

In a study of isolated perfused hearts, Sullivan and Wong[6] noted a depressant effect of morphine with high doses. Strauer[12] studied the effect of morphine on isolated cat papillary muscle. He reported that morphine concentrations as high as 1 mg/100 ml had a myocardial stimulant effect, whereas concentrations exceeding 10 mg/100 ml produced depression. Our results indicate that morphine in concentrations of 5 and 10 mg/100 ml has no effect on the force of contraction of isolated human atrial muscle. These concentrations are much higher than would be achieved in the plasma following a usual anesthetizing dose of 2 mg/kg.[10] Thus, it is

concluded that clinical doses of morphine utilized to produce anesthesia do not have a myocardial depressant effect.

Dowdy *et al.*[13] studied the effects of the preservatives, chlorbutanol and sodium bisulfite, on isolated perfused rabbit hearts in conjunction with *d*-tubocurarine. An analysis of their data indicated that chlorbutanol, 9.81 mg/100 ml, and sodium bisulfite, 1.96 mg/100 ml, decreased force of contraction 12.3 ± 1.4 and 2.7 ± 1 per cent, respectively. With higher concentrations the depressant effect was much more pronounced. The results of our present study show that excessive concentrations of morphine solution depress the force of contraction (70 per cent with 30 mg/100 ml). However, a comparable concentration of the simulated diluent alone, 10 mg/100 ml chlorbutanol and 2 mg/100 ml sodium bisulfite, had negligible effect on force of contraction (+4 ± 7 per cent). The discrepancy between the results of Dowdy and our results could be related to species differences (rabbit *vs.* man) and the preparations (perfused heart *vs.* atrial muscle). We therefore conclude that the depression caused by higher concentrations of morphine solution in our study was primarily due to morphine.

On the basis of substrate studies in halothane- and methoxyflurane-depressed rat atrial preparations and a halothane-depressed human atrial preparation, Ko and Paradise[14-15-16] suggested that these anesthetics manifest their depressant effect at least partly via a block in glycolysis. In a previous study[8] we reported the effects of pyruvate on methoxyflurane- and pentobarbital-depressed human atrial muscle. Pyruvate, 15 mM, elicited a marked positive inotropic effect in control atria. The response to pyruvate remained unimpaired in the presence of methoxyflurane, whereas pentobarbital markedly inhibited it. It was concluded that these results were consistent with a block in glycolysis by methoxyflurane, whereas pentobarbital interfered with energy production or utilization below pyruvate. The response to pyruvate of morphine-depressed preparations was markedly inhibited. This would indicate that excessive concentrations of morphine manifest their depressant effect similar to pentobarbital and, unlike halothane and methoxyflurane, by interfering with energy production or utilization below pyruvate or with pyruvate transport.

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