Circulatory Effects of Morphine Sulfate Following Experimental Myocardial Infarction[1] (35652)

JOHN R. HAMILTON, BRIAN T. PAASO, STEPHEN R. CORDAY, AND DONALD C. HARRISON

Cardiology Division, Stanford University School of Medicine, Stanford, California 94305

Although morphine sulfate is commonly administered to patients with acute myocardial infarction there are few controlled studies dealing with the circulatory effects of morphine after acute myocardial infarction. In an uncontrolled study in man, Thomas *et al.* (1) studied 13 patients with acute myocardial infarction of varying severity and found that intravenously administered morphine produced varying effects on heart rate, blood pressure, pulse pressure, and cardiac output, depending on the pretreatment circulatory status of the patients. Vasko *et al.* (2) reported on the mechanism of action of morphine in the treatment of experimentally produced acute pulmonary edema, including acute pulmonary edema secondary to myocardial infarction, but did not report the circulatory effects of morphine in acute myocardial infarction without pulmonary edema. In addition, their studies were made in a right heart bypass preparation which did not allow study of the entire circulatory effects of morphine.

Accordingly our studies were designed to define the effects of morphine on the heart and circulation after acute myocardial infarction.

Methods. Twenty-one mongrel dogs ranging in weight from 12 to 30 kg were anesthetized with a mixture of alpha-chloralose and urethane, 66 and 400 mg/kg, respectively. Artificial ventilation was maintained and supplemental anesthetic was administered during the procedure as necessary.

A sternum-splitting midline thoracotomy was performed and the tidal volume of the respirator was adjusted to provide complete expansion of the lungs. Arterial blood pH and pO_2 were analyzed frequently during each procedure and the tidal volume and respiratory rate were adjusted to maintain blood pH at 7.40 $\pm$ 0.05 and arterial oxygen tension at 95 $\pm$ 10 mm Hg. Fluid filled polyethylene catheters (PE-240) were inserted into the right atrium, left atrium, left ventricle, and ascending aorta. Catheters were connected to Statham P23Db transducers and pressures recorded on a Beckman Model R direct-writing oscillograph. Mean aortic blood flow was measured with a gated sine-wave electromagnetic flowmeter (Biotronics, Silver Spring, Maryland); the flow probe was positioned around the ascending aorta immediately above the takeoff of the coronary arteries. The systemic vascular resistance was calculated by the formula: systemic vascular resistance = (mean aortic pressure — right atrial pressure)/cardiac output (liters/min). Myocardial contractility was estimated by measurement of the maximal rate of pressure rise in the left ventricle (LV dp/dt) recorded directly from the left ventricular pressure by means of an RC differentiating circuit; the frequency response of this system averaged 30 CPS. The left ventricular catheter was made of stiff polyethylene and was 50 cm in length. Electrocardiographic lead II was recorded continuously throughout each procedure.

Myocardial infarction. Myocardial infarction was produced by serially ligating branches of the circumflex artery and anterior descending artery supplying the apex of the left ventricle, as previously described from this laboratory (3). Myocardial infarction was considered to have been obtained when

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TABLE I. Hemodynamic Effects of Acute Infaction.

Parameter	No. of dogs	Preinfarction value	60-min post infarction	Mean Absolute change	Mean Percentage change
Aortic mean pressure (mm/Hg)	14	113.8 ± 4.4[a]	99.0 ± 5.2	−14.8	−12.1 ± 4.6
LV *dp/dt* (mm Hg/sec)	14	3938 ± 271	3069 ± 411	−869 ± 304	−23.2 ± 7.0
Aortic blood flow (ml/min)	14	2064 ± 202	1619 ± 197	−446 ± 110	−21.6 ± 4.9
Heart rate[b] (beats/min)	12	179.6 ± 5.0	189.8 ± 8.8	10.2 ± 8.2	6.0 ± 5.0
Stroke vol (ml/beat)	14	11.3 ± 1.2	8.7 ± 1.1	−2.6 ± 0.7	−23.0 ± 5.2
Systemic vascular resistance (relative units)	14	60.9 ± 6.0	69.4 ± 7.7	8.5 ± 5.9	18.4 ± 11.2
Left atrial pressure (mm Hg)	14	3.1 ± 0.3	9.5 ± 1.2	6.4 ± 1.1	244 ± 60

[a] All values are mean ± standard error.

[b] Two dogs paced continuously throughout experiment were excluded.

the area of the left ventricle supplied by the ligated vessels became dusky in color, ceased to contract, and moved paradoxically during the cardiac cycle. To suppress arrhythmias, lidocaine (0.45 mg/min) was infused continuously throughout each study using a Harvard infusion pump.

Extent of myocardial infarction. At the conclusion of each procedure, the extent of myocardial infarction was determined by injecting Evans blue solution into the right and left coronary arteries through the coronary ostia. The left ventricular free wall and interventricular septum were dissected from the remainder of the heart. The unstained, infarcted portion of the left ventricle and septum was separated from the stained, uninfarcted muscle, weighed and expressed as percentage weight of the total left ventricular free wall and interventricular septum.

Heart rate. Heart rate was maintained at a constant rate in 4 dogs with a bipolar pacing electrode attached to the right atrial appendage.

Morphine sulfate. After myocardial infarction had been produced, circulatory dynamics were allowed to stabilize for 60 min and then base line measurements were recorded. Morphine sulfate (0.5 mg/kg) was injected into the right atrium. Physiologic measurements were recorded continuously for 5 min after injection and again at 10, 15, and 30 min after injection.

Control dogs. Seven dogs, instrumented as described above but not subjected to myocardial infarction, were given morphine sulfate in the same dose as dogs with myocardial infarction and were monitored in an identical manner.

Results. Effects of acute myocardial infarction. The circulatory effects of myocardial infarction are shown in Table I. Aortic mean pressure, left ventricular *dp/dt*, aortic blood flow, and stroke volume were decreased significantly. Left atrial mean pressure was significantly increased. Heart rate and systemic vascular resistance rose moderately; however, these changes were not significant.

Effects of morphine sulfate. Aortic mean pressure. Immediately following the injection of morphine, the mean aortic pressure fell significantly in both control and myocardial infarction groups. By 10 min after injection, however, aortic mean pressure had returned to, or toward, normal in both groups and thereafter remained essentially unchanged

TABLE II. Percentage Change in Aortic Mean Pressure, LV *dp/dt*, and Aortic Blood Flow After Morphine in Control and Myocardial Infarction Groups.

	(min)	Control group (7)	Myocardial infarction group (14)
Aortic mean pressure	1	−29.3 ± 16.1[a]	−28.8 ± 3.6
	5	− 4.1 ± 1.5	− 7.3 ± 2.0
	10	− 2.1 ± 2.1	− 3.6 ± 1.8
	15	− 0.5 ± 2.3	+ 1.9 ± 2.8
	30	+ 3.5 ± 2.9	+ 6.5 ± 3.5
Lv *dp/dt*	1	−26.2 ± 7.3	−23.7 ± 4.6
	5	− 3.0 ± 4.9	− 8.5 ± 6.2
	10	+ 1.1 ± 5.4	− 4.6 ± 4.1
	15	+ 7.9 ± 7.6	− 1.6 ± 4.3
	30	+ 9.3 ± 5.8	+ 2.9 ± 5.8
Aortic blood flow	1	− 9.1 ± 4.0	−20.2 ± 11.2
	5	− 7.2 ± 2.6	− 6.6 ± 3.8
	10	− 5.5 ± 2.3	− 5.9 ± 4.4
	15	− 6.2 ± 2.7	− 1.8 ± 4.7
	30	− 4.4 ± 3.1	− 9.5 ± 6.7

[a] All values are mean ± standard errors.

(Table II). Typical circulatory effects produced by morphine for one animal after myocardial infarction are shown in Fig. 1.

Left ventricular dp/dt. The effects of morphine on the rate of rise of left ventricular pressure are presented in Table II. In the control group, morphine produced an initial significant depression of LV *dp/dt*, followed by a rapid return toward normal by 5 min and a moderate but not significant increase at 15 and 30 min.

In the myocardial infarction group, morphine produced a highly significant fall in LV *dp/dt* at 1 min postinjection (−23.7 ±

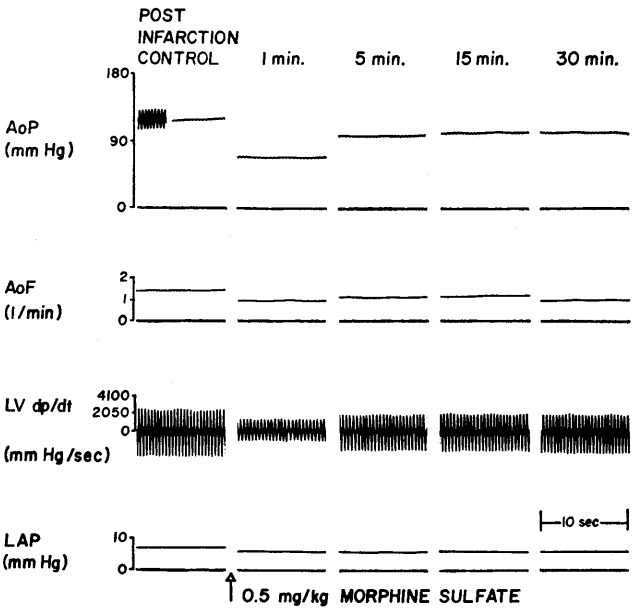

FIG. 1. Responses of aortic pressure (AoP); aortic blood flow (AoF); rate of rise of left ventricular pressure (LV *dp/dt*); and left atrial pressure (LAP) to morphine sulfate (0.5 mg/kg) in one dog after myocardial infarction.

TABLE III. Percentage Change in Systemic Vascular Resistance, Heart Rate, and Left Atrial Pressure After Morphine Sulfate.

	(min)	Control group (7)	Myocardial infarction group (14)
Systemic vascular resistance	1	—12.4 ± 6.6[a]	—20.5 ± 5.2
	5	+ 4.2 ± 4.2	+ 1.4 ± 4.9
	10	+11.3 ± 5.1	+ 3.4 ± 4.3
	15	+ 3.5 ± 5.0	+ 9.7 ± 5.3
	30	+18.9 ± 10.2	+11.8 ± 5.4
Heart rate	1	— 0.8 ± 1.3	— 6.1 ± 1.0
	5	— 0.9 ± 1.8	— 4.2 ± 1.1
	10	— 0.2 ± 2.3	— 2.4 ± 1.7
	15	+ 1.7 ± 2.6	— 1.9 ± 2.1
	30	+ 3.0 ± 1.6	— 0.3 ± 2.3
Left atrial pressure	1	—11.5 ± 5.8	—16.1 ± 4.6
	5	— 1.3 ± 7.9	—11.9 ± 4.2
	10	— 3.3 ± 7.9	— 5.1 ± 2.5
	15	— 4.1 ± 8.0	— 5.1 ± 2.6
	30	— 8.3 ± 9.7	— 9.7 ± 3.9

[a] All values are mean ± standard errors.

4.6%). This depression was more prolonged than in the control group, returning to normal at the 15-min observation (Table II).

Aortic blood flow. In both groups, morphine sulfate produced moderate decreases in aortic blood flow. In the myocardial infarction group, aortic blood flow was significantly depressed at 1, 5, and 10 min. The depression of aortic blood flow in the control group, although similar, was not significant.

Systemic vascular resistance. The effect on systemic vascular resistance (SVR) was similar in both groups. After an initial fall, SVR rapidly returned to base line levels and was elevated after 10 min. In the myocardial infarction group, the elevation of the SVR noted after 5 min and at 30 min was significant ($p<0.05$).

Heart rate. In the control group, morphine sulfate produced essentially no change in heart rate (Table III). In the myocardial infarction group, by contrast, the heart rate at the 1- and 5-min observation periods was decreased in 7 animals and unchanged in 3 (the 2 animals which were paced throughout being excluded).

Blood gases. Blood gases and pH were maintained within physiologic range during the course of the experiments except for mild depressions of pCO_2.

Size of myocardial infarction. The estimated amount of infarction in the 14 infarcted dogs was 28.3 ± 1.1% of the weight of the left ventricle.

Effect of pacing. Pacing the heart at the premorphine heart rate in 4 animals had no effect on aortic blood flow, aortic mean pressure, or LV *dp/dt*.

Left atrial pressure. Morphine sulfate had no significant effect on left atrial pressure in the control group. In the myocardial infarction group, which had a higher left atrial pressure following production of the infarction, morphine sulfate produced a rapid, persistent, and significant fall in left atrial pressure (Table III).

Discussion. In this animal model for studying experimental myocardial infarction, it is of interest that the circulatory depression resulting from the myocardial infarction was not profound at 60 min after infarction. Although the mean aortic pressure, left ventricular *dp/dt*, cardiac output, and stroke volume declined, these changes were rather small. Systemic vascular resistance and heart rate increased slightly. The only significant change was a threefold increase in left atrial mean pressure. It seems likely that circulatory adjustments to the effects of acute myocardial infarction had been called into play and were active by 60 min after the infarction. Immediately after ligation of the

coronary arteries, the circulation was unstable. Marked decreases in arterial pressure, cardiac output, and LV *dp/dt* occurred. These changes were transient, however, and have previously been reported (3).

Lidocaine was used for suppressing ectopic ventricular arrhythmias. Although lidocaine in large doses has been shown to produce circulatory depression, the dose administered in these dogs (0.45 mg/min) has been shown to produce no detectable myocardial depression following acute myocardial infarction in this same animal model in previous studies from this laboratory (3).

A comparison of the changes in the circulation produced by the administration of morphine sulfate between control animals and those animals with extensive myocardial infarction reveals several interesting points for consideration. Heart rate was essentially unchanged at 1 and 5 min after infarction and increased by only an average of 6 beats at the 30-min observation period. This contrasts with the findings of Pur-Shahriari *et al.* (4) who reported that 0.25 mg/kg of morphine sulfate in chloralose-anesthetized dogs produced an initial increase in heart rate, followed by a significant decrease in heart rate at 30 min. These investigators studied dogs weighing from 20 to 24 kg, ventilated at 225 ± 26 ml tidal volume, at a rate of 15/min. Studies from our laboratories have shown that dogs of this size ventilated at the stated volume and rate developed respiratory hypercapnia and acidosis (unpublished data). Other studies from this laboratory have shown that heart rate varies directly with pCO_2; therefore, we would suggest that the decreases in heart rate observed in these studies was due to hypercapnia, rather than to the effects of morphine (5).

Aortic pressure and left ventricular *dp/dt*, were significantly reduced at 1 min following the administration of morphine in the control animals. These changes persisted for 1 to 3 min in all animals and no significant changes were noted at the 5-min period of observation. Other parameters were not different from the base line observations.

The circulatory changes produced in the animals when morphine was administered 60 min after acute myocardial infarction are qualitatively similar to those observed in the control animals. Following the intravenous administration of morphine, aortic pressure, left ventricular *dp/dt*, aortic blood flow, systemic vascular resistance, heart rate, and left atrial pressure declined significantly. At 5 min these depressed circulatory variables had not returned to control levels. In the postinfarction animals, the left atrial pressure remained decreased significantly for 30 min after infarction. Slight, but not significant increases in systemic vascular resistance and aortic pressure were noted at 30 min after the administration of morphine in the postmyocardial infarction animals.

The major circulatory changes produced by morphine in the control animals, and those animals following acute myocardial infarction were similar, but the effects were more prolonged in the animals following acute myocardial infarction. Studies reported by Vasko and associates (6) demonstrated that 15 to 30 min after the administration of morphine, the left ventricular pressure and left ventricular *dp/dt* were elevated. They attributed these delayed positive inotropic effects to the release of catecholamines from the adrenal glands, since they could be blocked by the administration of propranolol. Whether the release of catecholamines from the adrenal is a direct effect of morphine or secondary to the transient hypotension produced by the intravenous administration of morphine is not clear. Since aortic mean pressure and aortic blood flow were both depressed following the administration of morphine in the control animals and in the animals following acute myocardial infarction, systemic vascular resistance was also reduced. These findings are in agreement with those of Henny *et al.* (7), who showed that morphine produced a marked fall in systemic vascular resistance, which returned to, or above, base line levels in 30 min. Since the LV *dp/dt* remained depressed in our animals following acute myocardial infarction throughout the period of observation, it is suggested that morphine has either a direct myocardial depressant effect, or that the inotropic effect, which has been observed by

Vasko (4) and in our control animals, is not manifest because of the decreased response to circulating catecholamines by the damaged myocardium following acute myocardial infarction.

Summary. The circulatory effects of morphine sulfate were studied in anesthetized dogs in which myocardial infarction had been produced by serial ligation of coronary arteries. In control dogs, morphine sulfate (0.5 mg/kg) produced early and transient decreases in aortic mean pressure, the rate of rise of left ventricular pressure and systemic vascular resistance, without significant changes in left atrial pressure, heart rate, or aortic blood flow. Following myocardial infarction, morphine sulfate (0.5 mg/kg), produced a similar early and transient depression of aortic mean pressure. The rate of rise of left ventricular pressure was more greatly depressed and remained depressed for a longer period of time. Systemic vascular resistance fell initially but was elevated at 15 and 30 min. Left atrial pressure was markedly decreased while heart rate and aortic blood flow were moderately depressed. It is concluded that morphine sulfate has a mild transient depressant effect on the circulation in intact animals, while in animals with myocardial infarction, morphine sulfate has a more pronounced and more persistent depressant effect on the circulation.

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