Effects of Morphine on Coronary and Left Ventricular Dynamics in Conscious Dogs

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ABSTRACT We studied the effects of i.v. 2 mg/kg morphine sulfate (MS) on coronary blood flow and resistance, left ventricular (LV) diameter and pressure (P), rate of change of pressure (dP/dt), and dP/dt/P in conscious dogs. An initial transient reduction in coronary vascular resistance, associated with increases in heart rate, dP/dt, dP/dt/P, and reductions in LV end-diastolic and end-systolic size were observed. This was followed by a prolonged increase in mean coronary vascular resistance, lasting from 5 to 30 min, while heart rate, arterial pressure, and LV end-diastolic diameter returned to control levels and dP/dt/P remained slightly but significantly above control. At 10 min, late diastolic coronary flow had fallen from 44±3 ml/min to a minimum level of 25±3 ml/min, while late diastolic coronary resistance had risen from 1.68±0.10 to 3.04±0.28 mm Hg/ml/min. Morphine also induced substantial coronary vasoconstriction when heart rate was held constant. Neither the MS-induced coronary vasoconstriction nor the positive inotropic response was abolished by bilateral adrenalectomy. The positive inotropic response of MS was reversed after beta blockade, but not the coronary vasoconstriction. Alpha receptor blockade abolished the late coronary vasoconstrictor effects of morphine, and only dilatation occurred. In anesthetized dogs MS failed to produce late coronary vasoconstriction. Coronary vasoconstriction was not observed in conscious dogs after a respiratory-depressant dose of morphine, 10 mg/kg i.v. Smaller doses of MS, 0.25 mg/kg every 15 min, produced significant coronary vasoconstriction after a total dose of 0.75 mg/kg in the conscious dogs. The effects of morphine may differ in the normal dog and man and may vary depending upon the presence or absence of coronary artery disease. However, in the normal conscious dog, MS elicits a mild beta adrenergic increase in contractility and an important coronary vasoconstrictor effect, which is mediated through alpha adrenergic receptors.

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INTRODUCTION

The clinical utility of opiates has been established for centuries. The most common opium alkaloid, morphine sulfate (MS),[1] constitutes one of the most important therapeutic agents available for treatment of the pain and pulmonary edema that occur during the course of acute myocardial infarction. Moreover, it is commonly administered as a preanesthetic, or as the sole anesthetic for cardiovascular surgical procedures (1, 2), and as an analgesic and narcotic in a wide variety of conditions. In addition, morphine and other opiates are commonly involved in drug addiction. Despite its prevalent use, the effects of morphine on the heart and coronary vessels are poorly understood. Morphine is thought to have little effect on systemic hemodynamics (1, 3, 4), although both a transient decrease (5), or no change (1, 3, 4) in systemic vascular resistance as well as reduced (6–8) and enhanced (9) myocardial contractility have been observed. Despite its frequent use in patients with myocardial ischemia, little is known about the effects of morphine on the coronary vascular bed. Earlier studies concluded that it had little effect (8) or that it dilated the coronary bed (3, 10–13). However, only one of these studies was conducted in the intact animal (3), and none measured coronary blood flow continuously or took into account changes in cardiac

[1] *Abbreviations used in this paper:* dP/dt, rate of change of pressure; LV, left ventricular; MS, morphine sulfate.

function that could exert a secondary effect on the coronary circulation.

The goal of the present study was to clarify the effects of morphine on the normal coronary circulation and left ventricle of the conscious dog. It was deemed important to assess the effects of morphine in the healthy, conscious animal, since other cardioactive pharmacologic agents, e.g., norepinephrine (14), dopamine (15), and cardiac glycosides (16, 17), have been shown to exert differing effects on the heart and coronary circulation in the presence and absence of general anesthesia. Since the effects of a pharmacologic agent on the coronary circulation cannot be assessed without appreciation of factors influencing myocardial metabolic demand, the effects of MS on instantaneous and continuous measurements of coronary blood flow and resistance were examined in combination with simultaneous measurements of heart rate, arterial pressure, left ventricular (LV) pressures (P), and dimensions and indices of myocardial contractility.

The mechanism of action of the drug was analyzed by comparing its effects (*a*) in large and small doses; (*b*) in spontaneous rhythm and with heart rate constant; (*c*) in the presence and absence of alpha and beta adrenergic receptor blockades; (*d*) in the conscious and anesthetized states; and (*e*) before and after bilateral adrenalectomy.

METHODS

15 mongrel dogs, weighing between 22 and 35 kg, were anesthetized with 30 mg/kg pentobarbital Na. Through a thoracotomy in the fifth left intercostal space, miniature pressure gauges[2] were implanted within the left ventricle through a stab wound in the apex, ultrasonic diameter transducers were implanted on opposing endocardial surfaces of the left ventricle, Doppler ultrasonic or electromagnetic flow transducers were placed around the left circumflex coronary artery, stimulator electrodes were sutured to the left atrium, and heparin-filled Tygon catheters were chronically implanted in the thoracic aorta. Three of these dogs underwent bilateral adrenalectomy at a later date, performed under pentobarbital Na anesthesia, 30 mg/kg, through bilateral flank incisions. The animals after adrenalectomy were maintained on 1 mg desoxycorticosterone acetate and 10 mg cortisone acetate daily.

The miniature LV pressure gauges were calibrated before and after implantation against a mercury manometer and in vivo against a catheter passed retrograde into the left ventricle and a calibrated Statham P23 Db strain gauge manometer.[3] In six dogs a catheter had been implanted in the left atrium for simultaneous zero reference. At autopsy the position of the LV pressure gauges and diameter transducers within the left ventricle were confirmed. Arterial pressure was measured with a Statham P23 Db strain gauge manometer.[3] Left circumflex coronary blood flow was measured with a Doppler ultrasonic flowmeter in 14 dogs. This system has been previously described in detail (18, 19). It has a reliable electrical zero (18, 19), and in these experiments electrical zero blood flow, corresponding to zero Doppler shift, was determined repeatedly and confirmed terminally. The linearity of the flowmeter in the flow range encountered in these experiments has been demonstrated previously and was confirmed by calibrations in these experiments. The relationship between velocity, as measured by the Doppler flowmeter, and volume flow is linear as long as the cross-sectional area of the blood vessels within the transducer remains constant (19). At autopsy, it was observed that the vessels were firmly adherent to the flow transducer through a fibrous scar, which minimized change in the cross-sectional area of the vessel within the flow transducer. In the dog in which an electromagnetic flowmeter (Statham SP2200)[3] was used to measure coronary blood flow, zero flow was obtained by inflation of an hydraulic occluder distal to the flow transducer. An ultrasonic transit time dimension gauge was used to measure LV diameter (20). It operates on the principle of measuring the transit time of ultrasonic impulses traveling through blood at the velocity of 1.5×10^5 cm/s between the 3-MHz piezoelectric crystals positioned on the LV endocardium at opposing sites. The diameter gauge was calibrated by substituting signals of known time duration from a calibrated pulse generator. A voltage proportional to transit time was recorded and calibrated in terms of crystal separation. In this fashion a measure of internal diameter of the left ventricle could be continuously recorded. At a constant temperature the drift of the instrument is less than 0.15 mm/h, and its frequency response is flat to 60 Hz. An Instrumentation Laboratory (Model 113) blood gas analyzer[4] was used to determine arterial blood P_{O_2}, P_{CO_2}, and pH. In eight dogs arterial samples were taken during the control period and at 10, 15, and 30 min after the administration of morphine.

The experiments were conducted 2 wk–2 mo after the operation, when the dogs had recovered from the operation and were again vigorous and healthy. While the unsedated dogs were resting quietly on the experimental table, control records of LV diameter and pressure, the rate of change of pressure (dP/dt), phasic and mean arterial pressure, and phasic and mean coronary flows were obtained. These variables were continuously recorded before, during, and for 30 min after the administration of morphine, since all hemodynamic variables had essentially returned to control levels by 45 min after morphine. 15 mg/ml MS[5,6] was diluted to a total volume of 12 ml in sterile normal saline so that each 12 ml would deliver 2 mg/kg to each dog in which this dose was studied. The vehicle for one preparation of MS[5] included chlorobutanol and sodium bisulfite, while the other[6] included formaldehyde sulfoxylate, sodium phosphate, phenol, and sulfuric acid. In 15 dogs, through an indwelling venous catheter, 2 mg/kg morphine was infused over 2½ min with a constant rate infusion pump.[7] This dose consistently resulted in reproducible hemodynamic effects without evidence of vomiting, respiratory depression, or loss of consciousness. In three dogs the 2 mg/kg dose was repeated on three separate days.

12 of the dogs were also studied with heart rate controlled by an electronic stimulator.[8] This experimental pro-

[2] Konigsberg P22, Konigsberg Instruments, Inc., Pasadena, Calif.

[3] Statham Instruments, Inc., Oxnard, Calif.

[4] Instrumentation Laboratory, Inc., Lexington, Mass.

[5] Eli Lilly and Company, Indianapolis, Ind.

[6] Elkins-Sinn, Inc., Cherry Hill, N. J.

[7] Harvard Apparatus Co., Inc., Millis, Mass.

[8] Medtronic, Inc., Minneapolis, Minn.

TABLE I

Effects of 2 mg/kg MS in Conscious Dogs in Spontaneous Rhythm

	Control	2½ min	5 min	10 min	15 min	30 min
Heart rate, *beats/min*	77±3 (SEM)	147±14‡	103±10*	80±5	82±4	79±4
Mean arterial pressure, *mm Hg*	91±3	97±6	75±5*	88±5	87±4	89±3
Late diastolic arterial pressure, *mm Hg*	73±2	78±5	69±6	76±4	75±4	74±4
Coronary flow, *ml/min*	39±2	105±11‡	39±5	26±2‡	28±3‡	34±3*
Late diastolic coronary flow, *ml/min*	44±3	115±12‡	31±2‡	25±3‡	28±3‡	36±3‡
Coronary resistance, *mm Hg/ml/min*	2.29±0.11	0.97±0.06‡	2.38±0.53	3.57±0.31‡	3.33±0.39*	2.62±0.23*
Late diastolic coronary resistance, *mm Hg/ml/min*	1.68±0.10	0.70±0.03‡	2.26±0.42*	3.04±0.28‡	2.75±0.36‡	2.08±0.23*
LV systolic pressure, *mm Hg*	120±2	130±8	115±12	122±10	126±9	128±8
End-diastolic pressure, *mm Hg*	9±1	4±1‡	4±1‡	6±1*	7±1	8±1
End-diastolic diameter, *mm*	38.3±1.6	35.6±1.8‡	34.3+2.0‡	36.6±1.9	37.3±1.8	38.4±2.0
End-systolic diameter, *mm*	29.6±1.7	26.2±2.2‡	27.4±2.1‡	28.3±2.0	29.1±1.8	29.6±1.9
dP/dt, *mm Hg/s*	3,070±130	6,140±950‡	2,840±250	3,080±130	3,390±190*	3,540±190*
dP/dt/P, s^{-1}	66±3	115±19*	61±7	65±5	73±5*	75±4‡

* Significantly different from control, $P < 0.05$.

‡ Significantly different from control, $P < 0.01$.

cedure was repeated on separate days (at least 3 days apart) in (*a*) normal, conscious dogs; (*b*) after beta adrenergic blockade with 1 mg/kg propranolol i.v. and with heart rate maintained constant (six dogs); (*c*) after combined alpha adrenergic blockade with 1 mg/kg phentolamine and 4–6 mg/kg phenoxybenzamine i.v. and beta receptor blockade with 0.5 mg/kg propranolol with heart rate maintained constant (six dogs); (*d*) after general anesthesia with 30 mg/kg pentobarbital Na with respiration controlled with a constant volume respirator[7] (six dogs); and (*e*) in three conscious dogs after recovery from bilateral adrenalectomy. The experiments with blockades and anesthesia were randomized.

In all experiments in the conscious state, the dogs spontaneously breathed room air. Propranolol was administered 10 min before morphine. Phentolamine was administered 5 min before morphine. Phenoxybenzamine was administered 30 min before morphine. The adequacy of beta adrenergic blockade was tested with 5 μg isoproterenol i.v., and the adequacy of alpha adrenergic blockade was tested with 10 μg norepinephrine i.v. before and after completion of the experiment. The effects of both morphine vehicles were tested on separate days and found not to be significant.

The effects of smaller doses of morphine were studied in six dogs with heart rate maintained constant. After control records were obtained, MS was administered in an i.v. bolus, at a dose of 0.25 mg/kg every 15 min for 1 h until a total dose of 1 mg/kg had been administered. In three dogs the effects of a larger dose, 10 mg/kg infused i.v. over 5 min were examined.

Data were recorded on a multichannel tape recorder and played back on a direct writing oscillograph. Electronic resistor-capacitor filters having a 2-s time constant were used to derive mean arterial blood pressure and mean left circumflex coronary blood flow. Mean and late diastolic coronary resistances were calculated as the quotients of mean and late diastolic arterial pressures and coronary blood flows, respectively. Continuous records of dP/dt and dD/dt, i.e. velocity, were derived from LV pressure and diameter signals, with electronic differentiators having frequency responses of 60 and 30 Hz, respectively. A triangular wave signal with known slope (rate of change) was substituted for the pressure signal to calibrate the dP/dt channel directly.

The effects of morphine on peak and isolength velocity (dD/dt) and on peak LV dP/dt and the quotient of dP/dt and developed pressure (LV isovolumic minus end-diastolic pressure), i.e., (dP/dt)/P, were assessed. The same level of pressure that occurred during isometric contraction, before and after morphine, was used for this calculation, and dP/dt and P were determined at that level of pressure. These techniques for evaluating the myocardial contractile state have been described in detail previously (14, 15, 17, 21).

The responses to morphine were analyzed statistically with standard errors of the mean and paired *t* tests (22).

RESULTS

Infusion of 2 mg/kg MS produced a biphasic response. Initially a transient excitement response, reaching a peak at 2½ min, was observed. By 5 min the animals were tranquil and remained so for the duration of the experiments (30 min). While data were collected continuously, effects at 2½, 5, 10, 15, and 30 min after infusion were compared to the control levels recorded before morphine administration. When 0.25 mg/kg MS

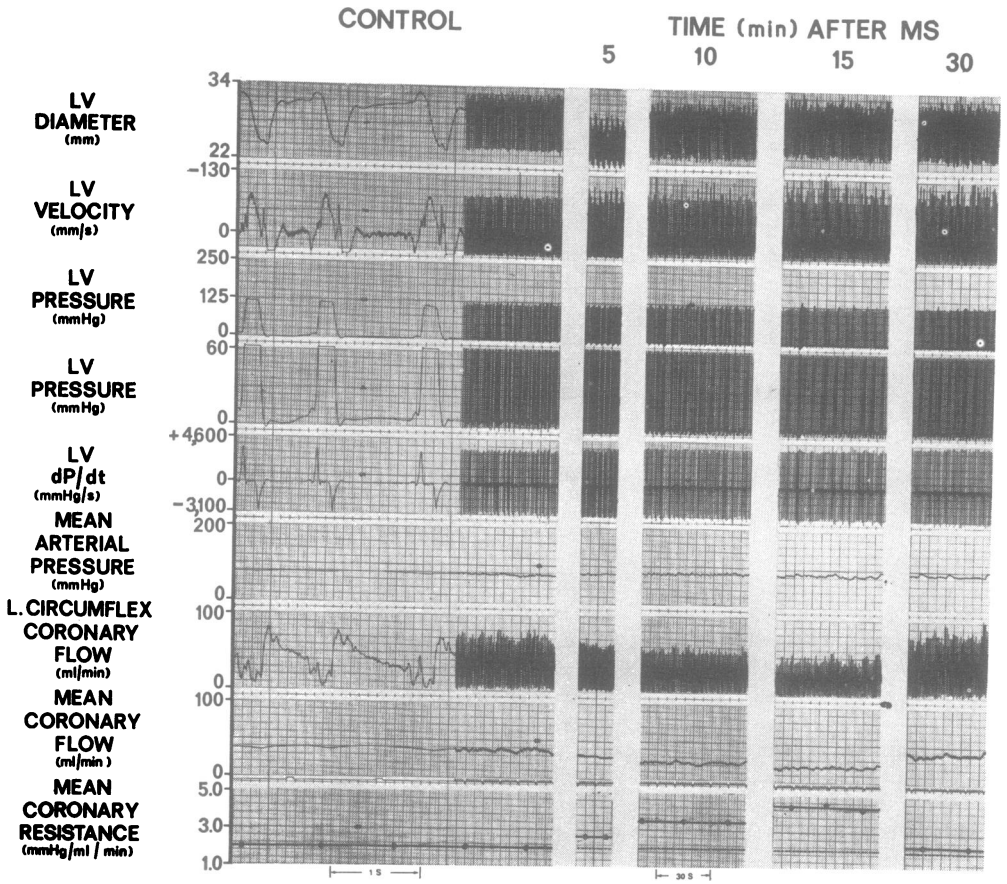

FIGURE 1 Typical responses at 5, 10, 15, and 30 min after 2 mg/kg i.v. morphine, compared with control in a normal conscious dog in spontaneous rhythm. The phasic measurements of LV diameter, velocity, pressure, end-diastolic pressure, dP/dt, mean arterial pressure, phasic and mean left circumflex coronary flow, and calculated mean coronary resistance are shown. Note the early reduction in cardiac size (5 min), the moderate later increases in dP/dt, and the sustained rise in coronary resistance (5–30 min).

was administered i.v. every 15 min, data points were compared to control at 15-min intervals, just before the next dose of morphine. While values for both mean and late diastolic coronary resistances are shown in Table I, the effects of the drug on late diastolic coronary flow and resistance are presented in detail.

Effects of 2 mg/kg MS in normal conscious dogs in spontaneous rhythm

Systemic effects. Heart rate rose initially, returned to control by 10 min, and remained at this level for the remainder of the experiment (Table I). Mean but not late diastolic arterial pressure fell significantly only at 5 min. All other values during the experiment were not significantly different from the control values of 91±3 (mean) and 73±2 mm Hg (late diastolic pressure), respectively (Table I).

Left ventricle. Peak LV pressure did not change, while LV end-diastolic pressure fell initially, up to 10 min, and returned to values not significantly different from control at 15–30 min. LV end-diastolic and end-systolic diameter decreased significantly below control only at 2½–5 min after morphine (Fig. 1). Peak dP/dt and dP/dt/P were significantly elevated at 2½ min and then again between 15 and 30 min (Table I). Peak and isolength velocity rose from values of 79±3 and 76±3 to 86±4 and 82±3 mm/s, respectively, at 30 min ($P < 0.05$).

Coronary dynamics. The early response (2½ min) to morphine involved substantial coronary vasodilation (Table I). However, from 5 to 30 min the vasodilation was replaced by a sustained reduction in coronary flow and significant coronary vasoconstriction (Fig. 1) ($P < 0.01$).

Blood gases. There was no significant change in P_{O_2}, P_{CO_2}, or pH of arterial blood gases between the control period and 15 min after morphine infusion. Arterial P_{O_2} was 79±4 mm Hg at control and 77±4 mm

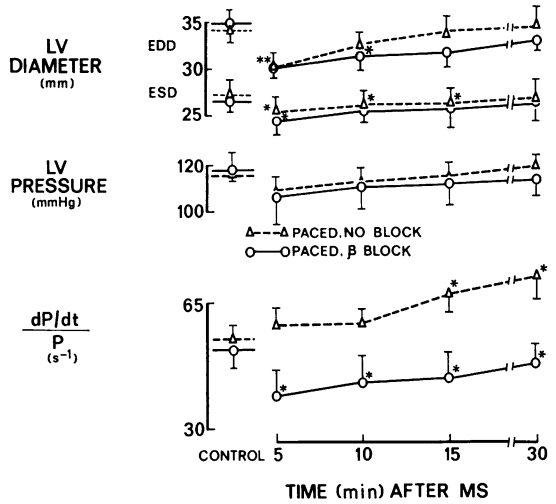

FIGURE 2 Average ±SEM values for the sustained LV effects of morphine, 2 mg/kg, i.v. In conscious dogs with heart rate constant without autonomic blockade (12 dogs) (triangles) morphine induced a significant rise in dP/dt/P at 15 and 30 min. In contrast, with heart rate constant after beta adrenergic blockade (6 dogs) (circles) the increases in dP/dt/P were abolished and actually a negative inotropic response was observed. $*P < 0.05$ change from control.

Hg at 15 min, while arterial P_{CO_2} and pH remained at control levels of 32±2 mm Hg and 7.42±0.01, respectively.

Effects of 2 mg/kg MS in normal conscious dogs with heart rate held constant

Systemic effects. Heart rate was maintained constant at 118±6 beats/min during the control period and again between 5 and 30 min after morphine, but not before 5 min after morphine, because spontaneous rates were too high. Mean and late diastolic arterial pressures did not change significantly from control after morphine.

Left ventricle. Morphine did not affect peak LV pressure and significantly reduced end-diastolic pressure at 5 and 10 min. As was observed in spontaneous rhythm, LV end-diastolic diameter was significantly decreased ($P < 0.05$) at 5 min, but not from 10 to 30 min. Peak dP/dt was significantly elevated from 15 to 30 min. dP/dt/P also rose ($P < 0.01$) at 15 min and remained elevated at 30 min (Fig. 2). Peak and isolength velocity rose at 30 min ($P < 0.05$) from controls of 75±3 and 73±3 to 82±4 and 79±3 mm/s.

Coronary dynamics. As in the dogs with spontaneous rhythm, late diastolic coronary flow was significantly lower 5–30 min after morphine; at 10 min it had fallen from a control level of 57±6 to 31±5 ml/min ($P < 0.01$). Late diastolic coronary resistance was increased significantly above control from 5 to 30 min (Fig. 3); at 10 min it had risen from 1.41±0.15 to 2.79±0.30 mm Hg/ml/min ($P < 0.01$). Thus, the major effects of morphine, i.e., a reduction in coronary flow and an increase in coronary resistance from 5 to 30 min and the later increases in contractility (from 15 to 30 min), occurred with heart rate constant as well as in spontaneous rhythm.

Effects of 2 mg/kg MS in normal conscious dogs after beta adrenergic blockade with heart rate constant

Systemic effects. When heart rate was maintained constant at 120±3 beats/min, mean and late diastolic arterial pressures did not change significantly from control after morphine.

Left ventricle. Peak LV pressure did not change significantly from control throughout the experiment. LV end-diastolic and end-systolic diameters fell significantly after morphine, as had occurred in the unblocked dogs (Fig. 2); LV end-diastolic diameter was significantly reduced at 5 and 10 min after morphine. A correspondingly significant decrease in LV end-diastolic pressure occurred as well. Beta adrenergic blockade abolished the morphine-induced increases in dP/dt and dP/dt/P. Actually a negative inotropic effect was observed, as reflected by reductions in dP/dt/P, which fell from 52±4 to 38±5 s^{-1} ($P < 0.01$) at 5 min and remained depressed significantly through 30 min (Fig. 2). At 30 min, peak and isolength velocities had fallen

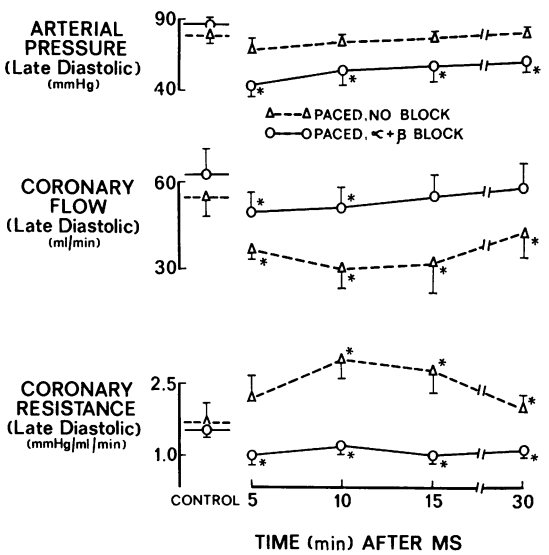

FIGURE 3 Average ±SEM values from the sustained coronary dynamic effects of morphine, 2 mg/kg, i.v. In conscious dogs with heart rate constant and without autonomic blockade (12 dogs) prolonged coronary vasoconstriction was observed. In contrast, in conscious dogs after combined beta and alpha adrenergic blockade (6 dogs) and with heart rate constant, prolonged coronary dilatation occurred. $*P < 0.05$ change from control.

($P < 0.01$) from 65±4 and 60±4 to 52±4 and 49±3 mm/s, respectively.

Coronary dynamics. The reductions in mean and late diastolic coronary flows and the increases in mean and late diastolic coronary resistances induced by morphine at 10–30 min were not significantly different after beta receptor blockade as compared to responses in the absence of blockade.

Thus, beta receptor blockade reversed the positive inotropic response to morphine, but not the prolonged period of coronary vasoconstriction.

Effects of 2 mg/kg MS in the normal conscious dogs after alpha and beta adrenergic blockades with heart rate constant

Systemic effects. With heart rate maintained constant at 116±5 beats/min, mean arterial pressure fell after morphine from 104±4 to 51±7 mm Hg at 5 min ($P < 0.01$) and remained below control for the duration of the experiment. Similarly, late diastolic arterial pressure decreased and remained depressed ($P < 0.01$).

Left ventricle. Peak LV pressure fell at 5 min and remained depressed. Both LV end-diastolic and end-systolic diameters were persistently below control ($P < 0.05$) from 5 to 30 min after morphine. Peak dP/dt and dP/dt/P remained essentially at control levels of 2,250± 100 mm Hg/s and 45±2 s^{-1}, respectively, throughout the experiment. Peak and isolength velocities remained at control levels of 68±4 and 65±4 mm/s as well.

Coronary dynamics. The morphine-induced coronary vasoconstriction was abolished by the addition of alpha adrenergic blockade. Late diastolic coronary flow fell from 62±8 to 49±7 ml/min ($P < 0.01$) at 5 min and remained significantly depressed at 10 min, but not at 15–30 min. At no point did late diastolic coronary resistance rise above control; in fact, it decreased from 1.57±0.16 to 0.91±0.16 mm Hg/ml/min ($P < 0.05$) at 5 min and remained depressed for the remainder of the experiment (Fig. 3). Mean coronary flow and resistance followed a similar pattern.

Thus, with heart rate constant and with sufficient beta adrenergic blockade to prevent the augmentation of contractility, the addition of alpha adrenergic blockade reversed the coronary vasoconstrictor response to one of sustained coronary vasodilation.

Effects of 2 mg/kg MS in conscious dogs after adrenalectomy

The effects of morphine were qualitatively similar before and after recovery from bilateral adrenalectomy (Table II). In all three dogs, peak dP/dt and dP/dt/P were moderately increased (Table II). As in the dogs before adrenalectomy, morphine induced a marked increase in mean and late diastolic coronary resistances from 10 to 30 min after morphine infusion (Table II).

Effects of 2 mg/kg MS in normal anesthetized dogs

Systemic effects. The response to morphine after pentobarbital was quite similar to the response after beta and alpha adrenergic blockades. Mean arterial pressure fell significantly ($P < 0.01$) from 5 to 30 min after morphine, from 87±4 mm Hg to 49±9 mm Hg at 5 min, and remained depressed throughout the 30-min observation period. Heart rate increased from 123±4 beats/min to 162±22 at 2½ min and remained elevated for 10 min.

Left ventricle. Peak LV pressure fell ($P < 0.05$) at 5 min and remained depressed for 30 min. Both LV end-diastolic and end-systolic diameters remained below control levels from 5 to 30 min after morphine ($P < 0.01$) at all points. Contractility, as reflected in dP/dt/P, did not change significantly from control.

Coronary dynamics. Late diastolic coronary flow did not change significantly after the morphine infusion, and late diastolic coronary resistance fell from 1.53± 0.14 to 0.77±0.03 ($P < 0.01$) at 5 min and remained below control at 10 min, but returned to control at 15–30 min (Fig. 4).

Thus, the response to the same dose of morphine was different in the dogs after general anesthesia, in that the fall in arterial pressure and the rise in heart rate were greater and more sustained, and coronary resistance did not increase.

Effects of 0.25 mg/kg MS every 15 min in the normal conscious dog

With heart rate constant, small doses of morphine had no significant effect on mean arterial pressure, peak dP/dt, dP/dt/P, LV dimensions, or late diastolic arterial pressure. However, at 45 min after a total dose of 0.75 mg/kg of morphine had been administered, a significant reduction in late diastolic coronary flow, from 49±4 ml/min to 43±4 ml/min ($P < 0.01$) was observed. Coronary flow remained significantly depressed at 60 min. Similarly, with the same dose, late diastolic coronary resistance increased from a control level of 1.76±0.15 mm Hg/ml/min to 2.12±0.20 mm Hg/ml/min at both 45 and 60 min ($P < 0.01$) (Fig. 5).

Thus, a significant reduction in coronary flow and rise in coronary resistance occurred with a much smaller dose of morphine as well.

Effects of 10 mg/kg morphine in the normal conscious dog

In three dogs a relatively large dose of morphine (10 mg/kg, i.v.) was given, which exerted a mild respira-

TABLE II

Effects of 2 mg/kg MS after Adrenalectomy

	Dog	Control	2½ min	5 min	10 min	15 min	30 min
Heart rate, *beats/min*							
Spontaneous rhythm	1	82	144	90	100	74	68
	2	75	210	120	75	68	66
	3	85	165	105	72	72	68
Paced	1	120		120	120	120	120
	2	120		120	120	120	120
	3	128		128	128	128	128
Aortic pressure, *mm Hg* (mean/late diastolic)							
Spontaneous rhythm	1	116/100	136/118	124/104	140/128	120/98	120/100
	2	106/80	120/90	92/76	92/72	96/75	100/78
	3	124/96	140/120	100/80	115/88	115/86	115/88
Paced	1	124/106		128/107	142/132	126/105	126/105
	2	124/100		90/76	104/84	108/90	115/92
	3	135/118		110/90	126/100	124/104	126/106
Coronary flow, *ml/min* (mean/late diastolic)							
Spontaneous rhythm	1	41/41	59/67	41/48	37/30	37/33	37/33
	2	48/45	126/138	45/40	36/32	33/24	39/25
	3	33/33	74/93	28/30	19/19	19/19	24/24
Paced	1	48/56		46/44	44/44	41/41	41/41
	2	68/68		48/42	42/32	39/36	45/42
	3	44/56		31/30	26/26	26/26	33/33
Coronary resistance, *mm Hg/ml/min*, (mean/late diastolic)							
Spontaneous rhythm	1	2.83/2.44	2.31/1.76	3.02/2.74	3.78/4.27	3.24/2.97	3.24/3.03
	2	2.21/1.78	0.95/0.65	2.04/1.90	2.56/2.25	2.91/3.13	2.56/3.12
	3	3.76/2.91	1.89/1.29	3.57/2.67	6.05/4.63	6.05/4.53	4.79/3.67
Paced	1	2.58/1.89		2.78/2.36	3.23/3.00	3.07/2.56	3.07/2.56
	2	1.82/1.47		1.88/1.81	2.48/2.63	2.77/2.50	2.56/2.19
	3	3.07/2.11		3.55/3.00	4.85/3.80	4.77/4.00	3.82/3.21
LV pressure, *mm Hg*							
Spontaneous rhythm	1	136	156	135	152	144	144
	2	130	155	120	124	124	124
	3	145	165	124	132	132	142
Paced	1	138		144	155	152	152
	2	145		124	128	132	132
	3	152		129	145	145	145
(dP/dt)/(dP/dt/P), *mm Hg* s^{-1}/s^{-1} Spontaneous rhythm	1	3,590/67	5,130/98	3,760/72	3,760/72	3,930/76	3,760/75
	2	4,200/84	8,400/150	4,500/96	4,650/90	4,500/87	4,500/85
	3	4,050/84	7,200/130	4,725/91	4,500/87	4,500/93	4,280/93
Paced	1	3,590/69		3,930/76	4,190/76	4,280/79	4,820/79
	2	4,500/88		5,100/96	4,650/90	4,500/94	4,500/88
	3	4,450/80		4,725/91	5,400/103	5,400/103	5,400/103

tory depressant effect for the first 15 min. In contrast to the results with 2 mg/kg morphine, where arterial P_{O_2} and P_{CO_2} remained constant, with a dose of 10 mg/kg arterial P_{O_2} fell from an average of 80 to 63 mm Hg, while P_{CO_2} rose from an average of 31 to 39 mm Hg. In these three animals heart rate rose at 15 min to an average of 92 from a control of 77 beats/min, while late diastolic arterial pressure, coronary flow, and coronary resistance were not changed significantly from control; late diastolic coronary resistance averaged 1.75 during control and 1.72 mm Hg/ml/min at 15 min after morphine.

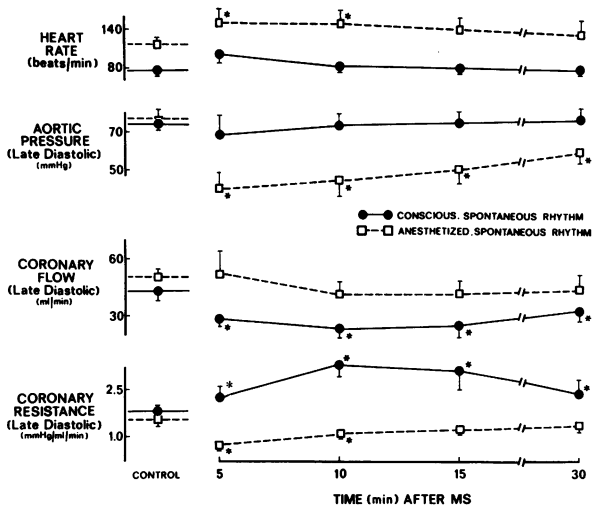

FIGURE 4 Comparison of the effect of 2 mg/kg morphine i.v. in dogs in spontaneous rhythm studied in the conscious state (15 dogs) (circles) and after general anesthesia (6 dogs) (squares). The sustained rise in coronary resistance observed in conscious dogs did not occur after general anesthesia. $*P < 0.05$ from control.

DISCUSSION

While MS is considered to exert a salutary action in the alleviation of acute pulmonary edema through central nervous system depression and peripheral venous pooling (5, 23, 24), it is thought to exert little effect on the normal circulation, as reflected by alterations in heart rate, arterial pressure, cardiac output, and systemic vascular resistance (1, 3, 4). Except for a transient increase in heart rate and fall in arterial pressure produced by a relatively large dose of i.v. morphine sulfate, 2 mg/kg, no significant sustained effect on heart rate or arterial pressure was observed in the present study as well. In contrast to the trivial effects on pressure and heart rate, an important coronary vasoconstrictor action was observed. This vasoconstrictor response was not altered by habituation, since similar responses were observed in three animals studied on three separate occasions. Earlier studies conducted in isolated perfused hearts suggested that morphine had little effect on the coronary bed (8) or resulted in dilatation (10–13). In contrast, the results of the present study, conducted in intact, unanesthetized animals with all control mechanisms intact, indicate that i.v. morphine elicits an important coronary vasoconstrictor action. When a respiratory depressant dose of morphine was administered to anesthetized or conscious dogs, it reduced P_{O_2} and increased P_{CO_2}, but failed to constrict the coronary vessels. Thus, the vasoconstrictor action of the drug observed in the conscious dog was most likely offset by the tendency of hypoxia and CO_2 retention to dilate coronary vessels. 2 mg/kg morphine was shown to dilate coronary vessels in conscious primates (3). The primates exhibited a similar degree of respiratory depression, resulting in mild hypoxia and CO_2 retention, as in the conscious dogs with the 10 mg/kg dose of morphine. This could account in part for the coronary dilatation observed in the primates (3). In addition, the extent to which inotropic influences affected coronary dynamics in that study is unknown (3). However, until similar experiments can be conducted in both dogs and primates, a difference due to species or methodology cannot be excluded.

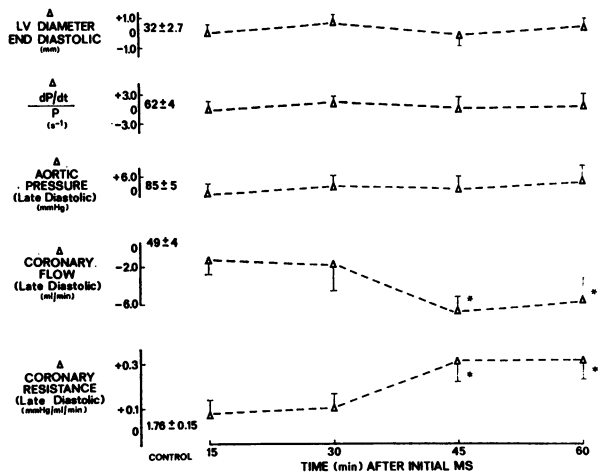

FIGURE 5 The average ±SEM changes from control are shown for LV end-diastolic diameter, dP/dt/P, late diastolic arterial pressure, coronary flow, and resistance after small doses of morphine, i.e., 0.25 mg/kg every 15 min (6 dogs). At 45 and 60 min significant reductions in coronary flow and increases in coronary resistance were observed, while other parameters remained constant.

Mechanisms of morphine-induced coronary vasoconstriction. The morphine-induced coronary vasoconstriction observed in the conscious dog could have been caused by several mechanisms. Vascular resistance in the coronary bed is regulated to a great extent by changes in myocardial oxygen consumption (25). Accordingly, if myocardial metabolic demands fell, then a secondary rise in coronary resistance would be expected. Alternatively, morphine might act directly on coronary vessels to cause vasoconstriction. Finally, morphine might elicit vasoconstriction neurogenically, through central or peripheral activation of the sympathetic nervous system.

The first possibility, involving a reduction in myocardial metabolic demand, was considered unlikely, since morphine produced coronary vasoconstriction at a constant heart rate when LV pressures and dimensions were not significantly different from control and myocardial contractility was actually elevated slightly. The increase in the intropic state by increasing myocardial oxygen demand should have acted to dilate the coronary vessels, indicating that the coronary vasoconstriction observed in this study may have actually been underestimated.

The second possibility, i.e., a direct vasoconstrictor action, was considered unlikely, on the one hand because morphine is known to dilate peripheral vessels when injected intra-arterially (26, 27), and on the other because the bulk of evidence indicating that morphine dilates the coronary vessels is based on studies in which morphine is administered directly either to isolated perfused hearts or isolated coronary rings (10–13). More importantly, morphine failed to constrict the coronary vessels after alpha adrenergic blockade, and in fact caused vasodilatation under these circumstances. This finding argues against the possibility of a direct action unless it is postulated that morphine activates alpha adrenergic receptors in the coronary vessels directly. It is more likely that morphine's vasoconstrictor effects are due to activation of alpha adrenergic receptors through stimulation of the sympathetic nervous system. Coronary vasoconstriction mediated by alpha adrenergic activation has been observed previously in our laboratory, when either dopamine or norepinephrine was administered intravenously to conscious dogs (14, 15).

The sympathetically induced coronary vasoconstriction observed in the conscious animals could have been due to central or peripheral activation of the sympathetic nervous system or to the release of adrenal catecholamines. The latter effect is known to occur after morphine (28). However, since bilateral adrenalectomy did not prevent this vasoconstriction, release of adrenal catecholamines could not have been solely responsible.

Pilot experiments, not presented in the present study, demonstrated that morphine dilated the coronary bed after alpha adrenergic blockade alone. Since beta adrenergic-mediated increases in contractility also occurred, it was not clear whether this coronary dilatation was due to a direct effect of morphine on coronary vessels or secondarily to the positive inotropic response. Therefore, it was decided to conduct the alpha adrenergic blockade experiments in the presence of partial beta adrenergic blockade as well. However, a dose of propranolol resulting in a relatively complete beta blockade was not selected, since under these circumstances morphine elicited a negative inotropic response, which would tend to reduce myocardial oxygen requirements and thereby cause coronary constriction. Accordingly, the responses to morphine after alpha blockade were examined in the presence of an incomplete blocking dose of propranolol, 0.5 mg/kg, where changes in contractility would not complicate the interpretation of the results of these experiments. In these experiments, conducted at a constant heart rate, without a significant change in myocardial contractility, and at a reduced pressure and cardiac size, morphine elicited substantial coronary vasodilation (Fig. 3). This vasodilation may have been due to several possible mechanisms: (*a*) a direct effect of morphine on coronary vessels (*b*) an autoregulatory mechanism in response to the fall in arterial pressure; or (*c*) release of histamine by morphine (29).

Histamine release may have played a role in the early transient coronary vasodilation observed at 2½ min in the experiments without autonomic blockade. However, the strong positive inotropic and chronotropic responses that also occurred, which would have acted to increase myocardial oxygen consumption (25), could have been responsible for the transient early coronary vasodilation. Two other mechanisms responsible for the early transient coronary vasodilation must be considered. First, the time course of this response is similar to the central sympatholytic action of morphine observed by Lowenstein, Whiting, Bittar, Sanden, and Powell (26). Finally, morphine has also been shown to possess a ganglionic blocking effect (30). These last four mechanisms may have all played a role in the early coronary vasodilator response observed at 2½ min, but since all of the mechanisms result in coronary vasodilation, they are unlikely explanations for the more prolonged coronary vasoconstriction observed from 5 to 30 min after morphine.

Effects of morphine on cardiac contractility. How morphine affects the myocardial contractile state remains controversial. Studies in papillary muscle preparations indicate that morphine exerts a direct negative inotropic effect, while the present investigation in the intact animal indicates a positive inotropic action, mediated through beta adrenergic receptors. This finding should not be interpreted to indicate that morphine does not cause direct depression of contractility, as reported from studies in isolated cardiac muscle preparations (6–8), since after the beta adrenergic effects were prevented by propranolol, morphine did elicit a slight negative inotropic effects (Fig. 2). Thus, it appears that morphine induces a complex reaction, the beta adrenergic effects slightly overshadowing any direct negative inotropic action of the drug. A previous study by Vasko, Henney, Brawley, Oldham, and Morrow, also found a positive inotropic effect with morphine and attributed it solely to release of adrenal catecholamines (9). While the latter may contribute to the positive inotropic response to morphine, it is not the sole mechanism, since morphine also increased contractility after adrenalectomy in the present study. Thus, as with the alpha adrenergic coronary vasoconstrictor effects of morphine, the beta adrenergically-mediated increases in contractility were at least in part mediated by sympathetic nerve activation. The increases in dP/dt/P and velocity of myocardial fiber shortening that occurred after morphine in the present study most likely represented a positive inotropic response, since these responses could be abolished with propranolol on the one hand, and since the increases in dP/dt/P and velocity occurred

when preload and afterload, which could influence these measurements, had already returned to control levels, on the other.

Effects of morphine on cardiac size. The beneficial effects of morphine in the therapy of acute pulmonary edema are attributed to its sedative action and to a reduction in venous return due to peripheral venous pooling (5, 23, 24). A reduction in venous return due to venous pooling would tend to reduce cardiac preload, i.e., end-diastolic size. This effect was observed in the present study only early after morphine administration. The reduction in cardiac size was also partially due to a slight reduction in afterload and to the accompanying tachycardia, which also reduces diastolic filling time (31).

In conclusion, morphine induces a transient reduction in cardiac size and a more prolonged beta adrenergically mediated increase in myocardial contractility. In the face of this moderate increase in contractility, morphine elicits substantial and prolonged coronary vasoconstriction with doses that do not cause respiratory depression, hypoxia, or CO_2 retention. It is difficult to extrapolate from the results of this study, conducted in conscious dogs with normal coronary vessels, to a different situation in man with diseased coronary arteries, where morphine has been consistently observed to produce a salutary effect. The effects of morphine could be different in the ischemic heart, where coronary vessels are dilated due to the intense local hypoxia caused by impaired coronary perfusion, or where the central sympatholytic (26) and ganglionic blocking (30) effects of the drug may assume greater importance.

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