Anesthesiology
55:236–243, 1981

Morphine Effects on Cardiac Output and Regional Blood Flow Distribution in Conscious Dogs

Lawrence L. Priano, M.D., Ph.D., and Stephen F. Vatner, M.D.†*

This study documents the changes in selected regional hemodynamics occurring in response to large doses of intravenous morphine. It was performed in normal conscious dogs. Their cardiovascular systems was unaltered by the presence of other drugs or recent surgery. The animals had been surgically prepared previously by implantation of chronic indwelling electromagnetic and Doppler ultrasonic flow probes on the aorta and the cranial mesenteric, renal and iliac arteries and placement of aortic catheters. Morphine, 1 mg/kg, produced mesenteric vascular dilation (30 per cent maximum decrease in resistance), renal vascular dilation (11 per cent maximum decrease in resistance) and nonsignificant changes in iliac vascular resistance. Morphine, 3 mg/kg, resulted in a similar amount of renal dilation (maximum 12 per cent decrease in resistance) but constricted the mesenteric vasculature (maximum 120 per cent increase in resistance) and the iliac vasculature (68 per cent maximum increase in resistance). These changes were observed despite the lack of sustained major changes in cardiac output, blood pressure, total peripheral resistance, or heart rate. It is therefore concluded that morphine has only minimal effects on systemic hemodynamics, but has significant effects when the alterations it produces in regional hemodynamics are considered. Such alterations may be physiologically significant when perfusion to these individual organs is a concern. The minimal systemic effects of high dose morphine is a phenomenon, for the most part, common to both dogs and humans. Whether similar regional hemodynamic changes as these occur in humans cannot be determined at this time since continuous flow monitoring techniques have, as yet, not been applied to humans. (Key words: Analgesics: morphine. Arteries: mesenteric; renal; iliac. Heart: cardiac output. Kidney; blood flow. Measurement techniques: regional blood flow, conscious dogs.)

* Associate Professor, Department of Anesthesiology, University of Texas Medical Branch, Galveston, Texas. At the time this work was performed, Dr. Priano was supported by a PHS-NIH National Research Service Award #1-F32-HL05530-01.

† Associate Professor, Department of Medicine, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Massachusetts, 02115; Established Investigator, American Heart Association.

Received from the Department of Anesthesiology, University of Texas Medical Branch, Galveston, Texas 77550, the Department of Medicine, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Massachusetts 02115, and the New England Regional Primate Research Center, Southboro, Massachusetts 01772. Accepted for publication January 22, 1981. A preliminary report of this work was presented at the annual meeting of the American Society of Anesthesiology, San Francisco, California, October 1979.

Address reprint requests to Dr. Lawrence L. Priano: Associate Professor of Anesthesiology, University of Texas Medical Branch, Department of Anesthesiology, Galveston, Texas 77550.

TRADITIONALLY the mainstay of surgical anesthesia has been primarily potent inhalational agents. In the 1940s the use of parenterally administered narcotic agents, whose principle action was that of providing analgesia, was instituted to supplement anesthesia.[1–4] Morphine in high doses is currently used extensively as the analgesic component of a balanced anesthetic. Its popularity is attributed to a lack of systemic toxicity and to a lesser degree of cardiovascular depression compared to inhalational agents. Because of the latter fact, morphine is often considered to be indicated for critically ill patients.[5–9] The generalized cardiovascular responses for high-dose morphine have been characterized.[5,10–12] With the exception of several studies that looked at the coronary circulation,[13–15] little data is available concerning what alterations, if any, occur in organ blood flow and cardiac output distribution when morphine is administered in the absence of other pharmacologic agents.

The objectives of the present study were threefold: 1) to examine the alterations in cardiac output and some regional blood flows and vascular resistances that occur in response to large doses of intravenous morphine; 2) to do so utilizing techniques designed to yield instantaneous and continuous measurements of these variables; and 3) to perform the study in healthy, conscious animals in which the effects of recent surgery and anesthesia, which can modify these circulatory responses, were absent.

Methods

This study was performed on 24 conscious, unmedicated mongrel dogs. These animals were of either sex and ranged in weight from 20–30 kg. They were free of heart worms, intestinal parasites and pneumonia and were healthy in appearance.

Surgery for implanting instrumentation was performed under intravenous sodium pentobarbital anesthesia, 30 mg/kg. Two groups of animals were initially instrumented; one for evaluation of systemic and one for evaluation of regional hemodynamics. In the regional hemodynamics group, ten animals received a midline laparotomy. Electromagnetic flow probes, (Zepeda Instruments, Seattle, Washington) 5–6 mm in diameter, were implanted around the

0003-3022/81/0900/0236 $00.90

cranial mesenteric and right iliac arteries. A hydraulic cuff occluder was placed around each of these arteries distal to the flow probe for flow zeroing purposes. A 6-mm Doppler ultrasonic flow probe was placed around the left renal artery. A small heparin-filled Tygon® catheter was positioned in the aorta via a lumbar artery. In the systemic hemodynamics group, seven animals received a thoracotomy through the left fifth intercostal space. Electromagnetic flow probes, 20–26 mm in diameter, were positioned around the ascending aorta. A small heparin-filled Tygon® catheter was placed in the thoracic aorta. In both groups of animals, the instrumentation wires and catheters were run subcutaneously and exteriorized at an interscapular site. The animals were then allowed to recover.

Aortic pressure was measured via the previously implanted Tygon® catheters with a Statham® P23 Db strain gauge manometer (Statham Instruments, Inc., Oxnard, California). Arterial blood gases were measured with a PHM-71 MK-2 acid-base analyzer (Radiometer, Copenhagen, Denmark). Cardiac output, mesenteric arterial blood flow, and iliac arterial blood flow were measured with electromagnetic flowmeters (Benton Instruments, Cupertino, California). Zero flow was determined in the mesenteric and iliac beds by inflation of the hydraulic occluders. Zero flow in the aorta was assumed during the diastolic phase of the cardiac cycle. Renal arterial blood flow was measured with a Doppler ultrasonic flowmeter.[16,17] This system had an accurate electronic zero and its calibration for volume flow has been previously described.[18]

Experiments were performed after the animals had regained their presurgical vigor and sufficient time had elapsed for adequate tissue growth around the flow probes, usually 14–21 days. Aortic pressure, cardiac output, and heart rate in the systemic group, or aortic pressure, mesenteric, renal and iliac blood flows and heart rate in the regional group, were recorded continuously on an eight-channel direct-writing oscillograph (Gould-Brush®, Cleveland, Ohio). Electronic resistance-capacitance filters with 2- to 8-s time constants were used to obtain mean values for aortic pressure, cardiac output, and mesenteric, renal, and iliac blood flows. In the systemic group, total peripheral resistance was calculated in resistance units by dividing mean arterial pressure by cardiac output, *i.e.*, torr/l·min^{-1}. In the regional group, mesenteric vascular resistance, iliac vascular resistance and renal vascular resistance were calculated in resistance units by dividing mean arterial pressure by the respective mean blood flow, *i.e.*, torr/ml·min^{-1}.

With the animals resting quietly on their right side, a peripheral iv was established. Control or baseline measurements of all cardiovascular data were then recorded for a sufficient period of time to assure a steady state had been reached. Morphine sulfate (Knoll Pharmaceutical Co., Whippany, New Jersey), diluted with normal saline to a total volume of 10 ml, was then infused intravenously over a 5-min period. All variables were continuously recorded for an additional 25 min for a total recording period of 30 min from the beginning of the drug infusion. Changes from the control values were noted at 2.5 and 5 min (midpoint and end of drug infusion, respectively) as well as at 10, 15, 20, and 30 min. The changes at each of these time points were compared statistically with the baseline values by use of a Student's paired t test. Thus, each animal served as its own control. Statistically significant changes were indicated by a p value of < 0.05. Two morphine dosages were administered: 1 mg/kg and 3 mg/kg. Both dosages were administered randomly to each animal in the systemic and regional hemodynamics groups. Twenty-four hour intervals were allowed after an animal received 1 mg/kg and 48-h intervals after receiving 3 mg/kg of morphine before the other dose was studied. For various technical reasons, it was very difficult to keep all of the instrumentation working perfectly in all animals during the course of the study. Thus, while the systemic and regional hemodynamic groups initially had ten and seven animals, respectively, the data points in the figures may represent a lesser number of animals. This will be pointed out in the Results section, where applicable.

Because arterial blood gases changed during the high-dose morphine infusion it was felt necessary to instrument a third group of animals. These experiments were designed to see if the noted regional hemodynamic alterations were perhaps due to changes in Pa_{CO_2} and/or Pa_{O_2} rather than morphine itself. Since the observed changes had been smaller in the renal circulation than in the mesenteric and iliac areas, and since this vascular bed was considered to be the most vital of the three studied, we elected to examine this phenomenon only in the renal bed. Seven additional animals were instrumented with a Doppler ultrasonic flow probe on the renal artery and an aortic catheter. These animals, while lying on their right side awake and breathing room air spontaneously through a standard canine anesthesia mask, had baseline cardiovascular and arterial blood gas data recorded. The anesthesia mask was then connected to an Ayres T piece with a Jackson-Reese modification into which was flowing a mixture of nitrogen 12 l/min, carbon dioxide 1 l/min (6.6 per cent) and oxygen 2 l/min

TABLE 1. Effects of 1 mg/kg (n = 6) and 3 mg/kg (n = 7) of Morphine on Systemic Hemodynamics in Conscious Dogs

	1 mg/kg Morphine						
	Control*	2.5 Min	5 Min	10 Min	15 Min	20 Min	30 Min
HR	83 ± 7	36 ± 13†	10 ± 5	−1 ± 5	−4 ± 7	−8 ± 6	−9 ± 5
MBP	96 ± 4	18 ± 5†	−2 ± 1	−5 ± 2	−2 ± 8	−8 ± 3†	−8 ± 2†
CO	2.96 ± 0.21	20 ± 6†	6 ± 2	1 ± 4	−2 ± 5	−3 ± 5	−13 ± 3†
TPR	33 ± 2	−1 ± 3	−7 ± 2†	−6 ± 2†	0 ± 7	−4 ± 4	7 ± 4
	3 mg/kg Morphine						
	Control	2.5 Min	5 Min	10 Min	15 Min	20 Min	30 Min
HR	72 ± 5	34 ± 8†	31 ± 13†	4 ± 6	10 ± 9	0 ± 5	−6 ± 3
MBP	98 ± 4	5 ± 7	−5 ± 7	10 ± 6	11 ± 6	10 ± 6	8 ± 5
CO	2.75 ± 0.29	21 ± 4†	9 ± 8	−8 ± 5	−4 ± 5	−4 ± 5	−8 ± 3
TPR	38 ± 4	−13 ± 6	−12 ± 5	22 ± 10	17 ± 9	17 ± 11	19 ± 11
		← Infusion →					

HR = heart rate (beats/min), MBP = mean arterial blood pressure (torr), CO = cardiac output (l/min), and TPR = total peripheral resistance (torr/l·min^{-1}).

* Actual mean control values ± SEM for these variables are indicated under the control column. The mean per cent change ± SEM from those controls are noted for 30 min.

† Statistically significant changes ($P < 0.05$) from the control values.

(13 per cent). They continued to breathe this mixture for 15 min during which time serial arterial blood gases were taken and continuous renal hemodynamics recorded. The animals were then returned to room air and data were again recorded 5 min later. This regime reproduced Pa_{CO_2} and Pa_{O_2} changes in a spontaneously breathing conscious animal, similar to those noted in animals receiving the higher dose of morphine. Again, changes were compared to the baseline values with Student's *t* test for paired data.

Results

In table 1 and figures 1 and 2, changes discussed will be referred to as early (2.5–5 min), middle (5–15 min) and late (15–30 min) with reference to the observation period.

Systemic Hemodynamics (Table 1)

Morphine, 1 mg/kg (n = 6). Morphine produced an early 36 ± 13 per cent increase ($P < 0.05$) in heart rate (HR). HR then decreased to values not significantly different from the control value of 83 ± 7 beats/min. Mean aortic pressure (MBP) was increased 18 ± 5 per cent early ($P < 0.02$), and was decreased 8 ± 3 per cent late ($P < 0.05$), from a control level of 96 ± 4 torr. Cardiac output (CO) increased 20 ± 6 per cent early ($P < 0.05$) and was decreased by 13 ± 3 per cent late ($P < 0.01$), from a control value of 2960 ± 210 ml/min. Total peripheral resistance (TPR) decreased slightly 7 ± 2 per cent midperiod ($P < 0.05$) from a control value of 33 ± 2 torr/l·min^{-1} but was otherwise unchanged. There was one less animal in this dosage group than in the high dose systemic group because of the development of an electronic problem with the aortic flow probe.

Morphine, 3 mg/kg, (n = 7). This dose of morphine increased HR 31–34 per cent early ($P < 0.01$) from a control value of 72 ± 5 beats/min. HR then returned to near control levels and was unchanged thereafter. MBP did not change significantly. CO increased 21 ± 4 per cent ($P < 0.001$) but then returned to levels not significantly different from the control value of 2750 ± 290 ml/min. TPR was not significantly altered.

Regional Hemodynamics

Morphine, 1 mg/kg (n = 9), (fig. 1). In the mesenteric bed (n = 7), this dose of morphine increased mesenteric arterial blood flow (MA) 26–55 per cent ($P < 0.05$) from a control value of 348 ± 97ml/min and decreased mesenteric vascular resistance (MR) 22–30 per cent ($P < 0.01$) from a control of 0.46 ± 0.13 torr/ml·min^{-1}, most of the observation period.

In the kidney (n = 9), morphine increased renal artery blood flow (KA) 13 ± 5 per cent early ($P < 0.05$), from a control value of 155 ± 17 ml/min. Renal vascular resistance (KR) decreased 11 ± 5 per cent ($P < 0.05$) from a control of 0.74 ± 0.10 torr/ml·min^{-1} middle-late period.

Morphine increased iliac artery blood flow (IA) (n = 7) 59 ± 15 per cent early ($P < 0.01$) from a control value of 223 ± 17 ml/min, but thereafter this flow returned to near control levels and was not significantly altered. Iliac resistance (IR) was unchanged.

Morphine, 3 mg/kg (n = 10), (fig. 2). In the mesenteric bed (n = 9), this dose of morphine decreased MA 29–44 per cent ($P < 0.01$), for most of the period of

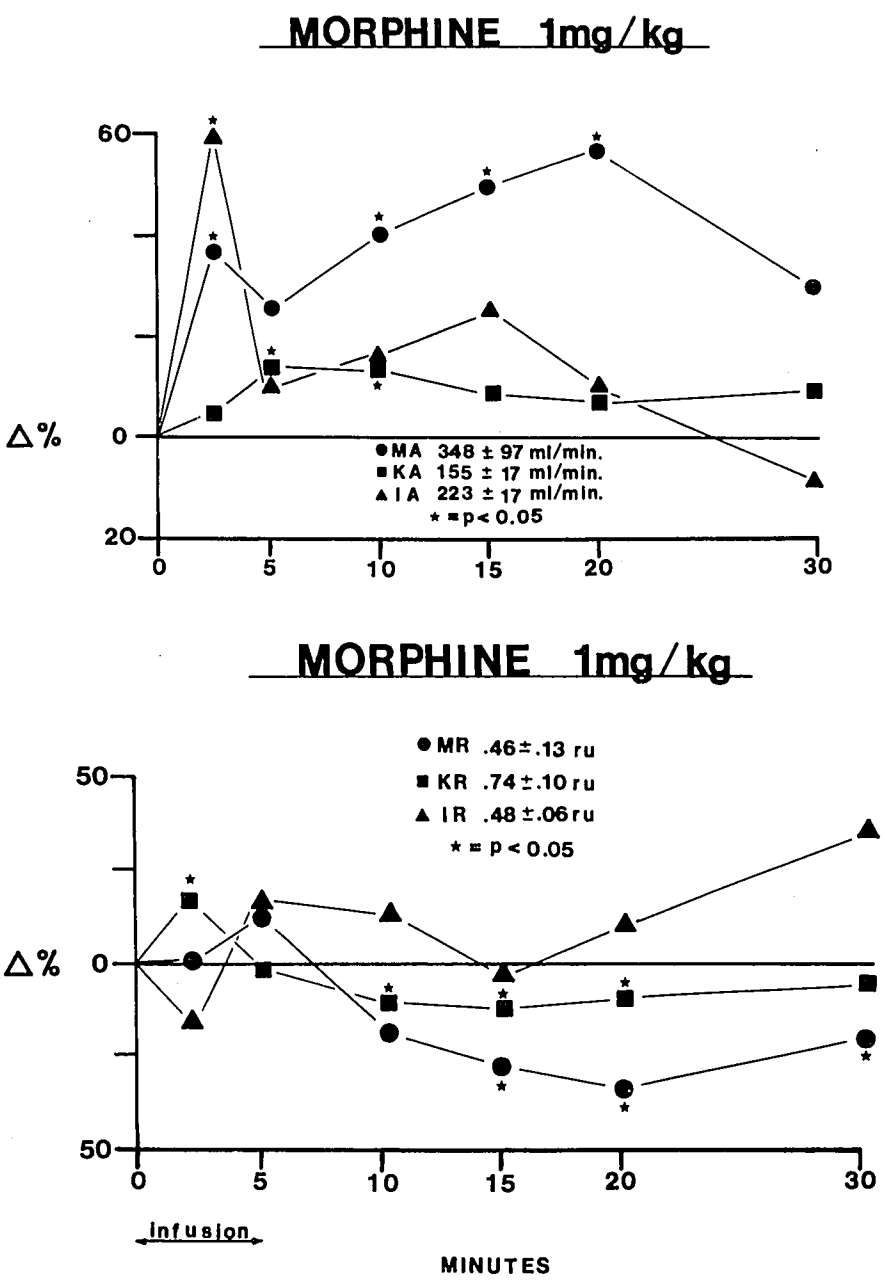

FIG. 1. Depicted are the changes in mesenteric artery (MA), renal artery (KA), and iliac artery (IA) blood flows and the corresponding mesenteric (MR), renal (KR) and iliac (IR) vascular resistances noted during a 30-min observation period in conscious dogs in response to a 5-min iv infusion of 1 mg/kg of morphine. Variations are depicted on the ordinate as mean per cent change from the conscious control value. The actual control flow and resistance values ± SEM are shown in the inset. Asterisks indicate statistically significant changes from control at the $P < 0.05$ level.

observation, from a control value of 352 ± 40 ml/min. MR was correspondingly increased throughout, the highest value being 120 ± 31 per cent ($P < 0.01$) above the control level of 0.32 ± 0.04 torr/ml·min^{-1}.

In the kidney (n = 10), KA increased 21–34 per cent ($P < 0.05$) throughout the recording period, from a control level of 163 ± 15 ml/min. However, KR was significantly decreased only late in the period, by 12 ± 4 per cent ($P < 0.02$), from a control value of 0.67 ± 0.08 torr/ml·min^{-1}.

Morphine produced a 25 ± 6 per cent decrease ($P < 0.01$) in IA (n = 10) and a 57–68 per cent increase ($P < 0.05$) in IR from their respective control values of 231 ± 27 ml/min and 0.50 ± 0.06 torr/ml·min^{-1}.

Arterial blood-gas changes were studied during the 30-min observation period only in the two systemic hemodynamic groups. They showed that 1 mg/kg of morphine caused no significant changes in Pa_{O_2} or Pa_{CO_2}. Morphine, in the 3 mg/kg dose, produced a 5–7 torr increase ($P < 0.02$) in Pa_{CO_2} from a control level of 32 ± 2 torr and a 12 ± 16 torr decrease ($P < 0.05$) in Pa_{O_2} from a control value of 86 ± 3 torr. These changes generally occurred early by the end of the morphine infusion and lasted the duration of the observation period.

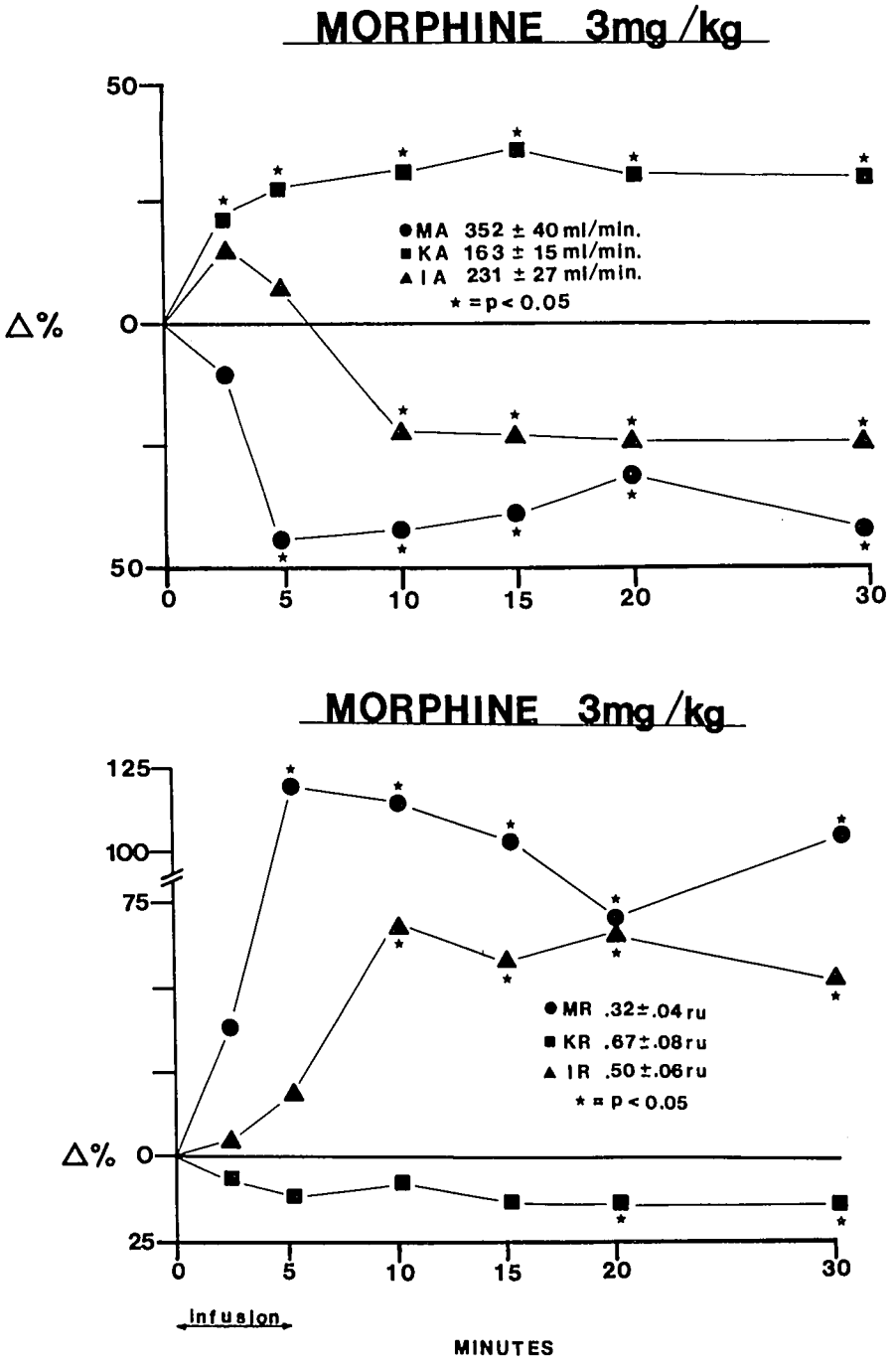

FIG. 2. Depicted are the changes in mesenteric artery (MA), renal artery (KA), and iliac artery (IA) blood flows and the corresponding mesenteric (MR), renal (KR), and iliac (IR) vascular resistances noted during a 30-min observation period in conscious dogs in response to a 5-min iv infusion of 3 mg/kg of morphine. Variations are depicted on the ordinate as mean per cent change from the conscious control value. The actual control flow and resistance values ± SEM are shown in the inset. Asterisks indicate statistically significant changes from control at the $P < 0.05$ level.

HYPERCARBIA/HYPOXIA-RENAL HEMODYNAMICS (TABLE 2)

Administration of a gas mixture containing elevated carbon dioxide (6.6 per cent) and lowered oxygen (13 per cent) concentrations (n = 7) resulted in Pa_{CO_2} and Pa_{O_2} levels comparable to those seen upon administration of high-dose morphine. Both KA and KR increased slightly but these changes were not statistically significantly different from their control values. In the case of KA they do not approximate to the 21–34 per cent increase that occurred with 3 mg/kg of morphine and in the case of KR the changes actually are in the opposite direction of those seen with morphine.

Discussion

These studies have confirmed that large intravenous doses of morphine have only small or transient systemic effects on the normal canine cardiovascular

TABLE 2. Effects of Hypercarbia/Hypoxia on Renal Hemodynamics in Conscious Dogs (n = 7)

	Control*	2.5 Min	5 Min	10 Min	15 Min	20 Min
Pa_{CO_2}	33 ± 1	42 ± 2†	44 ± 2†	42 ± 1†	44 ± 2†	34 ± 1
Pa_{O_2}	98 ± 1	71 ± 2†	71 ± 2†	72 ± 4†	73 ± 1†	95 ± 2
MBP	101 ± 4	9 ± 4†	10 ± 2†	9 ± 3†	6 ± 3	0 ± 2
KA	105 ± 11	4 ± 6	9 ± 8	6 ± 7	5 ± 5	−3 ± 3
KR	1.0 ± 0.07	7 ± 7	4 ± 7	5 ± 6	2 ± 5	3 ± 3
		← Hypercarbia/Hypoxia →				

Pa_{CO_2} = arterial partial pressure carbon dioxide (torr), Pa_{O_2} = arterial partial pressure oxygen (torr), MBP = mean arterial blood pressure (torr), KA = renal artery blood flow (ml/min), and KR = renal vascular resistance (torr/ml·min^{-1}).

* Actual mean control values ± SEM for these variables are indicated under the control column and were taken with the animals breathing room air. The mean actual values ± SEM for Pa_{CO_2} and Pa_{O_2} and the mean per cent change ± SEM from control for MBP, KA, and KR are noted during a 15-min period of breathing a high-CO_2 low-O_2 mixture and also 5 min after returning to breathing room air (20 min).

† Statistically significant changes ($P < 0.05$) from the control value.

system. This would agree, with a few exceptions, with data reported in conscious humans.[5,10,11] These exceptions are the transient elevations in HR and MBP seen at the 2.5- to 5-min periods. These changes may be contrary to traditional thinking about systemic morphine changes in humans,[19] namely, bradycardia and hypotension. This was probably related to a brief central nervous system excitation as the drug was initially being administered to these unsedated animals. Also, it was administered at a somewhat faster rate than is employed clinically. However, during the mid-late portion of the observation period, HR, CO, and MBP were changed minimally from their respective control values; systemic effects were similar to those in normal humans.[5] Our animals were normovolemic, conscious and in a recumbent lateral position. With similar conditions in humans, it is unusual to see significant hypotension with morphine.

This study has also documented important regional circulatory changes. Morphine, 1 mg/kg, dilates the mesenteric bed while a 3 mg/kg dose constricts this bed. Likewise, small intravenous doses of morphine in humans seem to dilate the splanchnic vasculature.[20] A constricting effect of high-dose morphine, occurring on the venous outflow side, has been noted in the splanchnic circulation in anesthetized dogs.[21,22] Similarly, in the iliac bed there is a variable effect with dose. The smaller dose does not change IA significantly but the large dose reduces IA and increases IR considerably. These dual effects of morphine are interesting. Smaller doses of morphine may produce a central sympathetic withdrawal action as has been proposed in human studies involving forearm blood flow[23–25] as well as in helical strip preparations with canine cutaneous arteries.[26] It also may be that direct local dilatory actions contribute. This latter effect has been shown in anesthetized dogs with an acutely denervated skeletal muscle preparation.[27] A mixed local and centrally mediated action for morphine has recently been proposed for human peripheral vasculature.[28] With the larger dose of morphine, central nervous system actions of the drug may predominate in terms of regional vascular effects. Morphine has been shown to increase catecholamine levels in dogs via an adrenal medullary release mechanism,[29–31] as well as by a lesser important mechanism of catecholamine release from sympathetic nerve endings.[32,33] The fact that the increase in perfusion pressure of an isolated rabbit artery preparation perfused with plasma from a conscious dog given high-dose morphine is attenuated by phentolamine,[30] confirms this. Our results also agree with Lowenstein's results in dogs anesthetized with chloralose-urethane.[27] In his study, flows were controlled with a perfusion device and intravenous morphine increased limb resistance, indicating vasoconstriction. A decrease in skeletal muscle flow with high-dose morphine has likewise been noted utilizing radioactive microsphere techniques on conscious monkeys.[15]

The present study demonstrated increased blood flow and decreased vascular resistance in the renal bed with both dosages of morphine. The flow changes appeared to be dose-related. These results can be contrasted with existing data for morphine and other anesthetics. It is generally held that inhalational anesthetics reduce renal blood flow.[34,35] Studies on halothane, utilizing similar techniques to those utilized in this investigation, showed it reduced renal resistance but either did not change or slightly decreased renal blood flow.[36] One other study on the effects of morphine on renal blood flow demonstrated a slight decrease in flow utilizing a radioactive microsphere technique in conscious monkeys.[15] The discrepancy between this latter study and our results with morphine may be explained by the fact that the microsphere technique only measures flow at a single point

in time. Thus, important changes may have been missed. Also to be considered is a species difference between monkeys and dogs. It is interesting in the present study that the renal bed dilated while the other beds constricted. This may be related to differences in either the density or sensitivity of adrenergic receptors in the kidney. Previous work in conscious dogs examined regional vascular responses to acute blood loss, a situation that produces reflex adrenergic activation. Under such conditions, the iliac and mesenteric beds constricted early whereas the renal bed dilated slightly and did not constrict until the blood loss has progressed to a severe level.[37]

A major question in the present study that required answering, was whether the observed regional hemodynamic alterations could have been due to changes in blood gases induced by 3 mg/kg of morphine rather than to the morphine itself. It is very difficult to control ventilation in a conscious animal. To do so, it is necessary to introduce additional surgery and/or pharmacologic agents. Both of these violate one of the basic objectives of this study: to examine changes in an intact, conscious animal preparation. By simply allowing the animals to breathe a controlled gas mixture that would simulate blood-gas changes seen with morphine, the surgical and pharmacological purity of the preparation was maintained. The results clearly demonstrated that changes in Pa_{CO_2} and Pa_{O_2} did not affect renal hemodynamics in the manner that high-dose morphine did. This is strong evidence that the observed changes with morphine were due to the drug *per se* and not blood-gas alterations. This is not totally surprising. The kidney is an organ whose blood flow is not thought to be metabolically dependent as is the case with CO_2 and O_2 in the brain and heart. While it cannot be ruled out that our regional flows with morphine were influenced indirectly by altered ventilatory patterns, this also is unlikely. Ventilatory patterns were definitely changed upon administration of the elevated CO_2 and lowered O_2 mixture. However, renal parameters only changed minimally. A separation of direct morphine effects and indirect blood-gas effects is also supported by systemic data from conscious dogs breathing carbon dioxide.[38] There, HR and MBP changes were not similar to those seen in the present study with morphine. The fact that renal parameters did not change with altered blood gases in this study does not definitely prove that changes seen in the mesenteric and iliac beds could not have been so influenced. But in view of the convincing renal data, we feel this is an unlikely possibility.

In conclusion, implantation of chronically indwelling flow probes in humans is not feasible. Thus, this study utilized a well-established conscious animal model.[14,36,37,39] Such a model offered several advantages: 1) hemodynamic changes can be continuously monitored; 2) the specific effects of an intervention, in this case, effects of high-dose intravenous morphine on regional circulations, can be examined; and 3) these can be accomplished without the confounding interactions of other drugs and acute surgical manipulations, both of which have been present in previous human and animal studies.[21,22,27,39–43] It has been found that systemic hemodynamics in the dog remain reasonably stable with high-dose intravenous morphine, as they do in clinical situations. However, significant changes occur in regional hemodynamics. These are manifested as mesenteric and renal dilation with minimal effects in the iliac bed with 1 mg/kg of morphine. Three mg/kg of morphine results in mesenteric and iliac constriction and again renal dilation. Mechanisms of these changes can only be speculated upon at this time. Both direct end organ effects as well as indirectly mediated changes via reflex neural control mechanisms are probably involved. Good data in this area are lacking and work is currently underway to elucidate the mechanism of these individual organ hemodynamic changes.

The authors thank Pat Quinn, Tina Marrone, and Lisa Monaco for their help with the technical preparation and care of the animals and Arnold Sherman, Marc Beckerman and Rich Thomas for their help with the electronics and instrumentation portion of this study.

References

1. Brotman M, Cullen SC: Supplementation with demerol during nitrous oxide anesthesia. ANESTHESIOLOGY 10: 696–705, 1949
2. Neff W, Mayer EC, Perales M: Nitrous oxide and oxygen anesthesia with curare relaxation. California Med 66:67–69, 1947
3. Papper EM, Rovenstein EA: The management of pain in the elderly. Geriatrics 1:420–426, 1946
4. Rovenstein EA: Geriatric anesthesia. Geriatrics 1:46–53, 1946
5. Lowenstein E, Hallowell T, Levine FH, et al: Cardiovascular response to large doses of intravenous morphine in man. N Engl J Med 281:1389–1391, 1969
6. Hasbrouck JD: Morphine anesthesia for open heart surgery. Ann Thorac Sug 10:364–369, 1970
7. Conahan TJ, Ominsky AJ, Wolman H: A prospective random comparison of halothane and morphine for open-heart anesthesia. ANESTHESIOLOGY 38:528–535, 1973
8. Stoelting RK, Gibbs TS: Hemodynamic effects of morphine-nitrous oxide in valvular heart disease and coronary artery disease. ANESTHESIOLOGY 38:45–52, 1973
9. Arens JF, Benbow BT, Ochsner JL, et al: Morphine anesthesia for aortocoronary bypass procedures. Anesth Analg (Cleve) 51:901–909, 1972
10. Wong KC, Martin WE, Hornbein TF, et al: The cardiovascular effects of morphine sulfate with oxygen and with nitrous oxide in man. ANESTHESIOLOGY 38:542–549, 1973

11. Ryan TJ, Brand E, Ramaswamy K: Effects of morphine on ventricular function in man. Clin Res 14:260, 1966
12. Drew JH, Dripps RD, Comroe JH: Effects of morphine on circulation of man and the circulatory and respiratory responses to tilting. ANESTHESIOLOGY 7:44–61, 1966
13. Leaman DM, Nellis SH, Zelis R, et al: Effects of morphine sulfate on human coronary blood flow. Am J Cardiol 41: 324–326, 1978
14. Vatner SF, Marsh JD, Swain JA: Effects of morphine on coronary and left ventricular dynamics in conscious dogs. J Clin Invest 55:207–217, 1975
15. Miller RL, Forsyth RT, Melmon KL: Morphine-induced redistribution of cardiac output in the unanesthetized monkey. Pharmacology 7:138–148, 1972
16. Franklin DL, Schlegel WA, Rushmer RF: Blood flow measured by Doppler frequency shift of back-scattered ultrasound. Science 134:564–565, 1961
17. Franklin DE, Watson NW, Pierson KE, et al: Technique for radiotelemetry of blood-flow velocity from unrestrained animals. Am J Med Electron 5:24–28, 1966
18. Vatner SF, Franklin D, Van Citters RL: Simultaneous comparison and calibration of the Doppler and electromagnetic flowmeters. J Appl Physiol 29:907–910, 1970
19. Eckenhoff JE, Oech SR: The effects of narcotics and antagonists upon respiration and circulation in man—a review. Clin Pharmacol Ther 1:483–524, 1960
20. Leaman DM, Leverson L, Zelis R, et al: Effect of morphine on splanchnic blood flow. Br Heart J 40:569–571, 1978
21. Green JF, Jackman AP, Parsons G: Effects of morphine on the mechanical properties of the systemic circulation in the dog. Circ Res 42:474–478, 1978
22. Green JF, Jackman AP, Krohn KA: Mechanism of morphine-induced shifts in blood volume between extracorporeal reservoir and systemic circulation of the dog under conditions of constant blood flow and vena caval pressures. Circ Res 42:479–486, 1978
23. Flaim SF, Zelis R, Eisele JH: Differential effects of morphine on the cutaneous circulation. Clin Pharmacol Ther 23: 542–546, 1978
24. Zelis R, Mansour EJ, Capone RJ, et al: The cardiovascular effects of morphine—the peripheral capacitance and resistance vessels in human subjects. J Clin Invest 54:1247–1258, 1974
25. Zelis R, Flaim SF, Eisele JH: Effects of morphine on reflex arteriolar constriction induced in man by hypercapnia. Clin Pharmacol Ther 22:172–178, 1977
26. Flaim SF, Vismara LA, Zelis R: The effects of morphine on isolated cutaneous vascular smooth muscle. Res Commun Chem Pathol Pharmacol 16:191–194, 1977
27. Lowenstein E, Whiting RB, Bittar DA, et al: Local and neurally mediated effects of morphine on skeletal muscle vascular resistance. J Pharmacol Exp Ther 180:359–367, 1972
28. Hsu HO, Hickey RF, Forbes AR: Morphine decreases peripheral vascular resistance and increases capacitance in man. ANESTHESIOLOGY 50:98–102, 1979
29. Kayaalp SO, Kaymakcalan S: Studies on the morphine-induced release of catecholamines from the adrenal glands in the dog. Arch Int Pharmacodyn Ther 172:139–147, 1968
30. Fennessey MR, Ortiz A: Studies on the morphine-induced release of catecholamines from the adrenal glands in the dog. Eur J Pharmacol 3:177–185, 1968
31. Bodo RC, Cotui FW, Benaglia AE: Studies on the mechanism of morphine hyperglycemia; role of adrenal glands. J Pharmacol 61:48–57, 1937
32. Bodo RC, Cotui FW, Benaglia AE: Studies on the mechanism of morphine hyperglycemia; role of sympathetic nervous system with special reference to sympathetic supply to the liver. J Pharmacol 62:88–105, 1938
33. Klingman GE, Maynert EW: Tolerance to morphine. III. Effects on catecholamines in the heart, intestine and spleen. J Pharmacol Exp Ther 135:300–305, 1962
34. Smith NT, Smith P: Circulatory effects of modern inhalation anesthetic agents, Handbook Experimental Pharmacology, Volume 30. Edited by Chenoweth MB. Berlin, Springer-Verlag, 1972, pp 149–241
35. Deutsch S, Goldberg M, Stephen GW, et al: Effects of halothane anesthesia on renal function in normal man. ANESTHESIOLOGY 27:793–804, 1965
36. Vatner SF, Smith NT: Effects of halothane on left ventricular function and distribution of regional blood flow in dogs and primates. Circ Res 34:155–167, 1974
37. Vatner SF: Effects of hemorrhage on regional blood flow distribution in dogs and primates. J Clin Invest 54:225–235, 1974
38. Horwitz LD, Bishop VS, Stone HL: Effects of hypercapnia on the cardiovascular system of conscious dogs. J Appl Physiol 25:346–348, 1968
39. Manders MT, Vatner SF: Effects of sodium pentobarbital anesthesia on left ventricular function and distribution of cardiac output in dogs with particular reference to the mechanism for tachycardia. Circ Res 39:512–517, 1976
40. Patschke D, Eberlein W, Oser G, et al: Hämodynamik, koronarduchblutung und myokardialer sauerstoff verbrauch unter honen morphin, pethidin, fentanyl und piritromiddosen. Anaesthesist 26:239–248, 1977
41. Glover FL, Webb GE, Bevis V, et al: Effects of morphine and halothane anesthesia on coronary blood flow. Ann Thorac Surg 22:429–435, 1976
42. Priano LL, Traber DL, Wilson RD: Barbiturate anesthesia: an abnormal physiologic situation. J Pharmacol Exp Ther 165:126–135, 1969
43. Stoelting RK: Influence of barbiturate anesthesic induction on circulatory responses to morphine. Anesth Analg (Cleve) 56:615–617, 1977