The Cardiovascular Effects of Morphine Sulfate with Oxygen and with Nitrous Oxide in Man

K. C. Wong, M.D., Ph.D.,* Wayne E. Martin, M.D.,† Thomas F. Hornbein, M.D.,‡ Felix G. Freund, M.D.,† Joel Everett, M.D.§

The cardiovascular effects of morphine, 2 mg/kg, administered intravenously at the rate of 10 mg/min with oxygen and with nitrous oxide-oxygen, were studied in ten healthy unmedicated male volunteers. Respiration was mechanically controlled to maintain a constant, normal Paco2. Morphine-oxygen increased cardiac index, heart rate, forearm blood flow, peak inspiratory blood glucose, and central venous pressure; decreased total peripheral resistance; and caused insignificant changes in stroke volume index, mean arterial pressure, forearm venous compliance, blood lactate and pyruvate, base excess, and oxygen consumption. The pre-ejection period, which provides an estimation of the period of isovolemic cardiac contraction, was prolonged. Addition of 70 per cent nitrous oxide to morphine-oxygen 60 minutes after administration of morphine increased total peripheral resistance, central venous pressure, and peak inspiratory pressure; decreased base excess, cardiac index, and heart rate; and did not significantly change the other variables. Morphine did not produce amnesia or unconsciousness in these subjects until nitrous oxide was added. The concentration of morphine in plasma was 8.0 ± 0.8 μg/100 ml 5 minutes after administration. (Key words: Morphine sulfate; Nitrous oxide; Naloxone; Cardiovascular effects; Metabolic effects; Plasma level of morphine.)

* Assistant Professor, Departments of Anesthesiology and Pharmacology.
† Professor, Departments of Anesthesiology and Physiology and Biophysics Research Career Development Awardee, 2 K03 HE 09167-06.
‡ Anesthesiology Research Fellow.
§ Anesthesiology Research Fellow.

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Reprint requests should be addressed to Dr. Wong.

Morphine in large intravenous doses (e.g., 1–3 mg/kg body weight) is being advocated for use in high-risk patients, particularly those undergoing cardiac surgery. This recommendation results from two observations: 1) in some patients—but not all—morphine alone is sufficient to permit surgery, thus allowing administration of high oxygen concentrations; 2) morphine does not seem to depress the cardiovascular system.1,2 In pentobarbital-anesthetized dogs, Vasko et al. found an enhancement of cardiac performance by morphine, 1–2 mg/kg.2 Clinical observations of more than 1,000 patients showed that blood pressure was generally well maintained, as was cardiac output on the occasions when measurements were made.2

We have studied the cardiovascular effects of morphine, 2 mg/kg, in human volunteers with controlled ventilation at a constant Pco2. Because morphine is often used with other agents, we have also measured the effect of N2O on the cardiovascular response to morphine. Studies were performed in healthy volunteers for convenience and safety, as well as to provide baseline information for a normal adult surgical population.

Methods and Materials

Ten normal, unmedicated male volunteers (21–28 years old) were studied after an overnight fast. A complete history, physical examination, routine laboratory analyses, and informed consent were obtained. We took particular care to exclude users of psychotropic drugs from this study.

With the subject supine, catheters were placed in the radial artery and in the superior vena cava or right atrium for measurement of arterial and central venous pressures. Cardiac output was determined by the dye-dilution method of Graeschi and Ward.4 The electro-
CARDIOVASCULAR EFFECTS OF MORPHINE

543

cardiogram was continuously monitored, and heart sounds were recorded from the precordium by a Sanborn 48A10 heart-sound microphone. The carotid pulse was measured with a Hewlett-Packard 21050B contact sensor microphone. Heart rate, heart rhythm, and the pre-ejection period were determined from these measurements. Cardiac index, stroke volume index, and total peripheral resistance were calculated in the usual manner.

A mercury-in-silastic strain gauge was placed around the right forearm and blood pressure cuff around the upper arm for determination of forearm blood flow and forearm venous compliance by venous-occlusion piethysmography. The occluding cuff pressure was raised suddenly to 40 torr for determination of flow, and then lowered by 10-torr increments for measurements of venous compliance. The latter was estimated from the change in forearm volume (ml/100 ml forearm mass) for the change in cuff pressure between 10 and 20 torr. Blood gases and base excess were measured using appropriate electrodes and corrected for temperature. Base excess in cico was calculated from the Severinghaus slide rule. Hemoglobin concentration and oxygen saturation were measured with an Instrumentation Laboratory Model 182 oximeter. Oxygen consumption was calculated from the Fick equation, assuming central venous blood to be a reasonable estimate of true mixed venous blood. Blood glucose, lactate and pyruvate levels were determined by standard enzymatic methods, and plasma morphine levels by a modification of the method of Takemori. Rectal temperatures were monitored, and ranged from 36.3 to 37.5 C.

Following instrumentation, each subject was permitted to relax and to breathe spontaneously until end-tidal $P_{CO_2}$ sampled from the anesthetic mask and measured by an infrared analyzer, was stable. With this value and its associated $P_{CO_2}$ as reference, controlled positive-pressure ventilation was implemented, using an Ohio 300 D/O ventilator through a conventional anesthetic circle without soda lime. The subject breathed 100 per cent oxygen by mask; $P_{CO_2}$ was controlled by altering the rate of gas inflow to the circle system. In order to enhance subject acceptance of the ventilator, we provided tidal volumes (10–15 ml/kg) somewhat larger than normal and maintained end-tidal $P_{CO_2}$ 1–3 torr below the value obtained during spontaneous breathing.

After 15–20 minutes of IPPV with oxygen, when constancy of the end-tidal $P_{CO_2}$ and relative quiescence of the abdominal electromyogram indicated a reasonably stable and relaxed state, control values were obtained. Morphine sulfate, 2 mg/kg, iv, was then given at a rate of 10 mg/min. With the subject breathing 100 per cent oxygen, all variables were measured 5, 15, 30, and 60 minutes following completion of morphine injection. The inspired gas was then changed to 70 per cent nitrous oxide–30 per cent oxygen. Because of increased muscle rigidity, endotracheal intubation was generally performed following injection of succinylcholine and thorough spraying of the larynx and trachea with 4 per cent lidocaine. Measurements were made 30 and 60 minutes after introduction of nitrous oxide.

At the completion of the study, nitrous oxide was withdrawn and the effect of morphine reversed with divided doses of naloxone, iv (average total dose 0.04 mg/kg). After observation overnight in the Clinical Research Center, the volunteer was discharged and followed for 3–7 days as an outpatient. Except for nausea and occasional vomiting following naloxone administration, no complication was noted.

Statistical analyses were performed using Student's t test for paired data.

Results

Administration of 2 mg/kg of morphine sulfate with oxygen did not produce unconsciousness. Although some subjects dozed, all were easily awakened and could respond appropriately to questions. None of the subjects had amnesia for this period. The extent of analgesia was not evaluated. When 70 per cent nitrous oxide–30 per cent oxygen was administered, the subjects lost consciousness with little excitement and exhibited marked muscle rigidity. They became responsive promptly when nitrous oxide was discontinued. Breathing, except upon verbal command, did not resume until the morphine was antagonized with naloxone.

Average values and statistical comparisons are shown in table 1 and illustrated for some variables in figures 1–4.
With the ventilator set to deliver a constant tidal volume, the peak inspiratory pressure increased following administration of morphine. The addition of nitrous oxide resulted in a further increase, at times associated with complete airway obstruction. Succinylcholine transiently reduced peak inspiratory pressure to near-normal levels.

Morphine did not significantly alter mean arterial pressure, primarily because the decrease in systemic vascular resistance was accompanied by a 25 per cent increase in cardiac index. This change in cardiac index resulted mainly from an increased heart rate, although stroke volume index also increased transiently (table 1, fig. 1). The decrease in systemic

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**Fig. 1.** The effects of morphine sulfate (2 mg/kg) with 100 per cent O₂ and with 70 per cent N₂O-30 per cent O₂ on cardiac index, stroke volume index, and heart rate. *P < 0.05 from control. † P < 0.05 from 60 minutes after morphine sulfate.

**Fig. 2.** The effects of morphine sulfate (2 mg/kg) with 100 per cent O₂ and with 70 per cent N₂O-30 per cent O₂ on total peripheral resistance and mean arterial pressure. *P < 0.05 from control. † P < 0.05 from 60 minutes after morphine sulfate.
CARDIOVASCULAR EFFECTS OF MORPHINE

Fig. 3. The effects of morphine sulfate (3 mg/kg) with 100 per cent O2 and with 70 per cent N2O-30 per cent O2 on central venous pressure and pre-ejection period. * P < 0.05 from control. † P < 0.05 from 60 minutes after morphine sulfate.

Fig. 4. The effects of morphine sulfate (2 mg/kg) with 100 per cent O2 and with 70 per cent N2O-30 per cent O2 on plasma glucose and base excess. * P < 0.05 from control. † P < 0.05 from 60 minutes after morphine sulfate.

Vascular resistance (fig. 2) paralleled the progressive increase in forearm blood flow (table 1), which was almost four times the control value 60 minutes after administration of morphine. Forearm venous compliance (table 1) did not increase after morphine, but there was an increase in central venous pressure. The pre-ejection period was prolonged.

The addition of N2O did not change arterial pressure. However, systemic vascular resistance rose 30 per cent (fig. 2) and there was an equivalent decline in cardiac index. The decrease in output resulted from depression of both stroke volume and heart rate (fig. 1). There was slight shortening of the pre-ejection period relative to that observed during the last measurement with morphine-oxygen (fig. 3). Finally, N2O caused a further rise in central venous pressure, a slight decrease in forearm venous compliance, a transient additional increase in blood glucose, a declining base excess (fig. 4), and increases in blood lactate and pyruvate concentrations (table 1).
Discussion

Although morphine is one of the oldest drugs known to man,\textsuperscript{10-12} it has only recently been used in large doses as an "anesthetic."\textsuperscript{1, 2} The stated advantages of this large-dose morphine technique are that it permits the use of high concentrations of oxygen and that it does not produce hypotension in most patients. One potential disadvantage, prolonged ventilatory depression, can be utilized to facilitate mechanical ventilation in the postoperative period.

The cardiovascular effects of morphine that we observed in healthy volunteers are similar to those reported by Lowenstein et al.\textsuperscript{2} and Hasbrook\textsuperscript{1} in cardiac surgical patients. The minimal disturbance of mean arterial pressure associated with morphine-oxygen administration supports these previous clinical observations,\textsuperscript{1, 2} as well as those of Conahan et al.\textsuperscript{22} These last workers found that morphine depressed arterial pressure less than halothane, but that severe hypotension occurred with similar frequency upon administration of either agent. Morphine caused an increase in cardiac index roughly proportional to the decrease in systemic vascular resistance. This decrease in resistance is a consistent finding in animals\textsuperscript{16, 11, 13} and man,\textsuperscript{15, 11, 14} and could contribute to the postural hypotension observed following usual analgesic doses of morphine,\textsuperscript{15} also explaining the hypotension sometimes seen following administration of morphine to hypovolemic patients.

Possible mechanisms for vasodilatation with morphine are decreased alpha-adrenergic activity, beta-adrenergic stimulation,\textsuperscript{1, 3} and histamine release.\textsuperscript{21, 16} Morphine is known to release histamine and catecholamines in dogs and in man.\textsuperscript{13} Our subjects manifested uniform flushing of the face, neck, chest, and extremities during or immediately following morphine administration, and the majority complained of itching. These responses are compatible with histamine release. There is evidence that both epinephrine\textsuperscript{17, 18} and histamine\textsuperscript{17} cause forearm arteriolar dilatation and forearm venous constriction. The increases in central venous pressure and forearm blood flow, and the decreases in total peripheral resistance and forearm venous compliance observed in this study, could result from a differential action on arteries and veins.

Catecholamine release may also account for the cardiovascular stability observed with morphine.\textsuperscript{1, 2} The increased cardiac output accompanying the decline in systemic vascular resistance is mainly a consequence of increased heart rate, but an increased stroke volume also contributed. Both changes can be explained by increased beta-adrenergic activity. The prolongation of the pre-ejection period, suggesting myocardial depression, is both physiologically small\textsuperscript{2} and statistically nonsignificant until 60 minutes after administration of morphine.

An increase in the effective filling pressure of the heart will also result in increased cardiac output. Unfortunately, because of increased muscle rigidity with morphine-oxygen,\textsuperscript{9} we do not know whether the rise in central venous pressure, also reported by Lowenstein et al.,\textsuperscript{2} actually reflects an increase in filling pressure.

Although large doses of morphine have been used as the sole "anesthetic" agent for critically ill patients, morphine alone did not produce loss of consciousness in these volunteers, and supplementation would undoubtedly have been needed to permit surgery. Because nitrous oxide is most commonly used with morphine whenever oxygenation is not a critical factor, we felt it important to ascertain whether the cardiovascular advantages of morphine were preserved upon addition of nitrous oxide. The changes we observed with morphine-nitrous oxide are best explained by alpha-adrenergic stimulation. Systemic vascular resistance increased; cardiac index fell, presumably due to reflex bradycardia; and mean arterial pressure remained constant. However, Stoelting and Gibbs\textsuperscript{19} recently reported decreases in cardiac index and mean arterial pressure in patients with valvular heart disease or coronary-artery disease receiving nitrous oxide-oxygen after 1 mg/kg morphine, iv. The difference between the MAP's observed might have resulted from differences in morphine dosage, time of measurement, and subject population. Other evidence for an adrenergic effect may be found in the rise in central venous pressure and a transient elevation of blood glucose concentration. Whether the associated increases in lactate and pyruvate resulted from nitrous oxide administration or the continuation of a
| Table 1. Summary of the Experimental Data (All Values Represent Mean ± SE) |
|---|---|---|---|---|---|---|---|---|---|---|
| | Without Morphine, Subject Ventilated with 100 Per Cent O2 | Minutes after Morphine, 2 mg/kg, iv, Subject Ventilated with 100 Per Cent Oxygen | Minutes after Replacement of 100 Per Cent O2 by 30 Per Cent N2O, and 30 Per Cent O2 |
| | Number of Subjects | Control | 5 Min | 15 Min | 30 Min | 60 Min | 30 Min | 60 Min |
| | | | | | | | | |
| **PO2 (mm Hg)** | 10 | 473 ± 7.8 | 488 ± 8.8 | 471 ± 19.9 | 487 ± 9.9 | 486 ± 10.2 | 143 ± 0.2 | 140 ± 0.9 |
| | 10 | 391 ± 1.05 | 421 ± 1.21 | 418 ± 0.99 | 416 ± 0.98 | 420 ± 1.77 | 39.8 ± 2.07 | 31.0 ± 1.31 |
| | 10 | 7.42 ± 0.011 | 7.40 ± 0.013 | 7.40 ± 0.011 | 7.40 ± 0.009 | 7.40 ± 0.018 | 7.38 ± 0.019 | 7.38 ± 0.016 |
| **pCO2 (mm Hg)** | 10 | 9.1 ± 1.13 | 9.1 ± 0.01 | 9.1 ± 0.009 | 9.8 ± 0.01 | 10.5 ± 0.09 | 10.5 ± 0.09 | 11.2 ± 0.02 |
| | 10 | 0.60 ± 0.16 | 0.60 ± 0.01 | 0.60 ± 0.009 | 0.60 ± 0.009 | 0.60 ± 0.009 | 0.60 ± 0.009 | 0.60 ± 0.009 |
| **Glucose (mg/100 ml)** | 10 | 91 ± 5.2* | 91 ± 5.4* | 94 ± 5.5* | 93 ± 4.3* | 93 ± 4.3* | 93 ± 4.3* | 93 ± 4.3* |
| | 10 | 4.2 ± 0.61 | 4.2 ± 0.61 | 4.2 ± 0.61 | 4.2 ± 0.61 | 4.2 ± 0.61 | 4.2 ± 0.61 | 4.2 ± 0.61 |
| **Plasma morphine (mg/100 ml)** | 7 | 8.58 ± 0.83 | 8.58 ± 0.83 | 8.58 ± 0.83 | 8.58 ± 0.83 | 8.58 ± 0.83 | 8.58 ± 0.83 | 8.58 ± 0.83 |
| **Oxygen consumption (ml/min)** | 10 | 275 ± 10.6 | 177 ± 17.1 | 206 ± 18.8 | 214 ± 30.5 | 193 ± 23.3 | 190 ± 8.3 | 200 ± 10.3 |
| **Peak inspiratory pressure (cm H2O)** | 9 | 10.0 ± 1.19 | 10.0 ± 1.19 | 10.0 ± 1.19 | 10.0 ± 1.19 | 10.0 ± 1.19 | 10.0 ± 1.19 | 10.0 ± 1.19 |
| **Cardiac index (1/min/m2)** | 10 | 3.08 ± 0.30* | 3.08 ± 0.30* | 3.08 ± 0.30* | 3.08 ± 0.30* | 3.08 ± 0.30* | 3.08 ± 0.30* | 3.08 ± 0.30* |
| **Stroke volume index (ml/m2)** | 10 | 48.3 ± 3.6 | 51.3 ± 3.3 | 53.8 ± 3.7 | 53.8 ± 3.7 | 53.8 ± 3.7 | 53.8 ± 3.7 | 53.8 ± 3.7 |
| **Heart rate (beats/min)** | 10 | 62 ± 3 | 70 ± 3* | 67 ± 3 | 67 ± 3 | 67 ± 3 | 67 ± 3 | 67 ± 3 |
| **Mean arterial pressure (mm Hg)** | 10 | 89 ± 2.3 | 84 ± 3.6 | 86 ± 2.9 | 86 ± 2.9 | 86 ± 2.9 | 86 ± 2.9 | 86 ± 2.9 |
| **Central venous pressure (mm Hg)** | 10 | 5.0 ± 1.1 | 7.2 ± 1.5* | 6.5 ± 1.1* | 6.0 ± 1.3* | 7.9 ± 1.5* | 10.5 ± 1.6* | 10.6 ± 1.5* |
| **Pro-ejection period (msec)** | 10 | 4.5 ± 2.0 | 4.4 ± 5.4 | 11.1 ± 5.7 | 9.4 ± 0.1 | 10.4 ± 5.0* | 12.3 ± 3.0* | 12.3 ± 4.5* |
| **Total peripheral resistance (dyne cm/sec−2)** | 10 | 1,292 ± 105 | 1,086 ± 134 | 1,025 ± 101* | 1,158 ± 132 | 1,195 ± 138 | 1,556 ± 117* | 1,471 ± 100* |
| **Forearm venous compliance (ml/100 ml/10 mm Hg)** | 10 | 0.52 ± 0.09 | 0.47 ± 0.15 | 0.44 ± 0.09 | 0.46 ± 0.09 | 0.45 ± 0.09 | 0.37 ± 0.08 | 0.45 ± 0.08 |
| **Forearm blood flow (ml/100 ml/min)** | 10 | 2.66 ± 0.35 | 7.25 ± 2.28 | 7.64 ± 2.78 | 7.68 ± 2.60 | 10.30 ± 3.21* | 0.70 ± 2.57* | 10.07 ± 3.35* |

* P < 0.05 from control.
† P < 0.05 from 60 minutes after morphine sulfate.
previously-existing trend is not clear, although the significant decrease in base excess after one hour of nitrous oxide is compatible with an enhanced catecholamine response.\(^5\) Sympathetic stimulation, predominantly alpha-adrenergic, by nitrous oxide has been observed in man when this agent was used with halothane,\(^2^1,2^2\) fluroxene,\(^2^3\) or ether.\(^2^4\) We have observed that anesthetic concentrations of \(\text{N}_2\text{O}\) (1.55 atm) also produce evidence of increased sympathetic activity.

Plasma morphine levels in this study agree well with those obtained by Takemori \(^s\) and Kuperberge \(\text{et al.}\)\(^2^5\) using similar quantitative techniques, but are smaller than those found using immunoassay techniques.\(^2^6\)

Although endotracheal intubation and surgical stimulation can considerably alter cardiovascular responses to morphine, our findings in healthy volunteers are similar to effects observed during cardiac surgery. Doses of morphine many times those used for analgesia produce little cardiovascular depression. However, changes in posture and hypovolemia can, by decreasing venous return, lead to hypotension after administration of morphine.\(^1^1\) Direct myocardial depression is not entirely ruled out, and may play a more important role in the compromised heart. Hypotension with morphine or halothane in patients undergoing cardiac surgery may be explicable on these bases. The use of \(\text{N}_2\text{O}\) with morphine is associated with cardiac depression and peripheral vasoconstriction, a combination which may not be optimal for the severely ill cardiac patient. The likelihood that other agents commonly used with morphine—thiopental, diazepam, and halothane—may attenuate some of the apparent circulatory benefits of morphine has not yet been adequately evaluated.

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Metabolism

PLASMA IONIZED CALCIUM CONCENTRATIONS Blood samples were obtained from 53 infants less than 72 hours of age admitted to the newborn nursery or the infant intensive care unit. Analyses included total calcium, pH, P CO2, total serum protein, serum proteins by electrophoresis, serum inorganic phosphorus, and ionic calcium using a flow-through calcium-specific electrode. The hypocalcemic infants were defined as having plasma total calcium of 7.5 mg/100 ml or less. Thirteen of the 53 infants studied were hypocalcemic by this criterion. There was a high incidence of perinatal morbidity in both full-term and premature infants, indicating that the results are not representative of the normal infant population. The mean plasma total calcium for the control group was 8.6 ± 0.8 mg/100 ml, in contrast to the hypocalcemic group, whose mean was 6.9 ± 0.8 mg/100 ml. The ionic calcium values for the hypocalcemic group were 3.5 ± 0.6 mg/100 ml, vs. 4.1 ± 0.6 mg/100 ml (P < 0.05). There was a linear correlation between the total calcium and ionized calcium levels in the entire series, but no significant correlation when each group was analyzed separately. The serum albumin levels of the hypocalcemic infants (2.8 ± 0.4 mg/100 ml) were significantly lower than those in the control group (3.1 ± 0.3 mg/100 ml) (P < 0.05). There was no difference in either group in serum inorganic phosphorus, total globulins, capillary pH, or P CO2. No increased binding of calcium to serum proteins secondary to alkalemia was demonstrated. There was no significant correlation between the values for ionized calcium derived from the McLean-Hastings nomogram (using the total serum protein and the total plasma calcium) and the concentrations of the ionized moiety determined by the ion-specific electrode. Hence, the authors state that this nomogram should not be used as an indicator of the concentration of serum ionized calcium in sick newborn infants. (Brown, D. M., and others: Serum Ionized Calcium in Newborn Infants, Pediatrics 49:841–846, 1972.) EDITOR'S COMMENT: Measurements of ionized calcium levels in critically ill patients (neonates, children or adults) are making it increasingly evident that the predicted relationship between total and ionized fractions does not hold as found in the otherwise well individual. It would appear that the trend is toward a lower ionized calcium concentration than predicted from the total calcium, protein and inorganic phosphorus levels. The importance of this change to hemodynamic function requires clarification.