THE EFFECTS OF MORPHINE AND HALOTHANE ANAESTHESIA ON URINE NOREPINEPHRINE DURING AND AFTER CORONARY ARTERY SURGERY

THODORE H. STANLEY, JESUS ISERN-AMARAL, AND GEORGE D. LATHROP

ANAESTHETIC DOSES of intravenous morphine (0.5–3.0 mg/kg) administered with oxygen have been shown to produce a minimum of cardiovascular depression in man.[1,2] Experiments in animals have suggested that one reason for this might be that morphine stimulates endogenous catecholamine release.[3–5] Although work in dogs has indicated that morphine has a positive cardiac inotropic effect which is catecholamine dependent,[3] the effects of anaesthetic doses of morphine on human blood or urine catecholamine levels have not been investigated adequately. This study was conducted to determine and compare the effects of anaesthetic doses of morphine and halothane on urine norepinephrine concentrations and excretion rates during and after coronary artery bypass operations in man.

METHODS

Twenty-eight patients with coronary artery disease and scheduled to undergo aortocoronary grafting with saphenous vein were randomly assigned preoperatively to two groups of fourteen each. Group I was given morphine intravenously and inhaled 100 per cent oxygen until consciousness was lost while group II received halothane (0.1–1.5 per cent) in oxygen. All patients were premedicated with atropine (0.05 mg/10 kg), morphine (1 mg/10 kg) and pentobarbitone (1 mg/kg) 90 minutes before the scheduled time of operation. A bladder catheter was inserted at the time premedication was given and urine was collected from then until anaesthesia was begun (first study period). Urine was also collected during the period from the beginning of anaesthesia until the incision was made (second study period), from the time of the incision until the start of cardiopulmonary bypass (third study period), during bypass (fourth study period), from the end of bypass until the end of the operation (fifth study period) and during the first two postoperative hours (sixth study period). Urine specimens were collected in amber coloured glass containers with sufficient 0.1 N hydrochloric acid added to maintain the pH between 2 and 3. Each specimen was frozen until time of analysis. Collected urine was analyzed for norepinephrine* by the automated fluorometric method of Viktora, Baukal and Wolff.[6]

Presented at the 1974 Meeting of the American Society of Anesthesiologists in Washington, D.C. in October 1974.

From the Department of Anesthesiology, The University of Utah College of Medicine, 50 North Medical Drive, Salt Lake City, Utah 84132 and the Epidemiology Division, Brooks Air Force Base, San Antonio, Texas 78235.

*Urine epinephrine was not measured because the reagents necessary for the analysis were not available.

Preoperative preparation and intraoperative fluid administration schedules have been described previously.[7] All patients received oxygen to breathe while morphine sulfate was injected intravenously at a rate of 5–15 mg/min or while halothane was added slowly to the inspired mixture. Respirations were first assisted and then controlled in order to keep arterial P_{CO_2} between 30–40 torr. Arterial blood samples for blood gas analysis were obtained every 15 minutes. When the patient became unresponsive, succinylcholine (1.5 mg/kg) was given intravenously and the trachea intubated. Controlled ventilation was continued. When succinylcholine paralysis had disappered the patient was given d-tubocurarine (0.5 mg/kg) over a period of 20 minutes and the operation was started. If additional anaesthesia was considered necessary during the operation, patients in Group I received 10 mg supplements of morphine and those in Group II a higher concentration of halothane. During cardiopulmonary bypass 0–0.5 per cent halothane was passed through the oxygenator in patients receiving halothane while those getting morphine received no other medication.

Intraoperative, bypass and postoperative blood administration schedules also have been described previously.[7] The extracorporeal system (Bentley oxygenator; Sarns roller pump) was primed with 20–25 ml/kg of lactated Ringer's solution. Mixed venous blood samples were obtained at the venous inflow to the oxygenator every 15 minutes and analyzed on a Radiometer acid-base analyzer for P_{O_2}, P_{CO_2} and pH. Bypass flows were maintained between 40 and 70 ml/kg/min in order to keep mixed venous oxygen tension between 38–42 torr. Mean blood pressure and extracorporeal flow rate were recorded every 15 minutes during bypass. Intraoperative oesophageal temperature was monitored by means of a Yellow Springs temperature probe. Patients were cooled to 32° C during bypass and rewarmed to 37° C at its conclusion. Temperature corrections of blood gas analyses obtained during periods of hypothermia were made using standard nomograms. At the conclusion of bypass calcium chloride (200–600 mg) was given routinely. No other inotropic agents were needed during the other operative periods. Postoperatively all patients were given 100 per cent oxygen to breathe and ventilation was controlled for at least two hours. During this period inotropic and analgesic drugs were not required.

Results

Mean preoperative data of the two groups was similar and is given in Table I. Patients in Group I received an average of 3.5 mg/kg of morphine. Both groups had similar arterial blood pressures before and after bypass and in the recovery room; however, during bypass mean arterial pressures were significantly higher in Group I than in Group II (Table II). Extracorporeal flow rates, times of bypass and total operative times were similar for the two groups.

Mean urine volumes and urine norepinephrine contents, concentrations and excretion rates are given in Table III. Patients receiving morphine had urine outputs that were not significantly different from those getting halothane during all periods. Urine norepinephrine contents, concentrations and excretion rates of the two groups were also similar during the first three study periods. However, during bypass patients receiving morphine excreted twice the amount of nore-

TABLE I

PRE-OPERATIVE DATA (means ± SD)

	Anaesthetic	Number of Patients	Age (years)	Weight (kg)	Cardiac Output (l/min)
Group I	Morphine	14	55 ±6.6	68 ±14	4.5 ±1.4
Group II	Halothane	14	53 ±7.2	71 ±11	4.6 ±0.9

TABLE II

INTRAOPERATIVE DATA (means ± SD)

				Bypass	
	Anaesthetic	Length of Procedure (hr)	Time (min)	Mean Arterial Pressure (mm Hg)	Flow (ml/kg)
Group I	Morphine	6.2 ±1.1	111 ±29	80* ±11	57 ±6
Group II	Halothane	6.0 ±1.2	113 ±26	54 ±14	55 ±7

*$P < 0.001$, when compared to Group II.

pinephrine excreted by those getting halothane. Urine norepinephrine contents, concentrations and excretion rates were also significantly higher in morphine recipients after bypass and postoperatively. Halothane patients did not have urine norepinephrine concentrations or excretion rates that were significantly different from preoperative values during any of the operative study periods but did have significantly higher ($P < 0.05$) postoperative values. In patients anaesthetized with morphine, urine norepinephrine concentrations were not significantly increased over preoperative values until bypass; however, subsequent specimens showed markedly elevated norepinephrine concentrations. Urine norepinephrine excretion rates of Group I became significantly elevated when compared to preoperative values, after bypass and postoperatively (Table III).

DISCUSSION

The results of this study demonstrate that anaesthetic doses of morphine are not initially associated with increased urine norepinephrine concentrations in patients undergoing coronary artery grafting procedures but concentrations increase some hours later. Since urinary norepinephrine excretion has been shown to parallel norepinephrine blood levels[8] our findings suggest that plasma norepinephrine concentrations are also increased during this time.*

Increased plasma catecholamine levels during morphine anaesthesia may be an explanation of the remarkable cardiovascular stability observed with this technique in critically ill patients. A number of authors have demonstrated that 1 to 3

*Plasma norepinephrine values were not determined because 15 ml of plasma or 30–40 ml of blood are necessary for each determination in our laboratory. This would have necessitated 180–240 ml of blood to be taken from each patient, which we felt was an undue risk.

TABLE III

URINARY NOREPINEPHRINE CONTENTS, CONCENTRATIONS AND EXCRETION RATES DURING AND AFTER MORPHINE AND HALOTHANE ANAESTHESIA (means ± SD)

		Preoperative	Pre-Incision	Pre-Bypass	Bypass	Post-Bypass	Postoperative
Study Period		I	II	III	IV	V	VI
Time	Morphine	90	61 ± 13	99 ± 21	111 ± 29	98 ± 38	120
	Halothane	90	60 ± 11	95 ± 26	113 ± 26	90 ± 41	120
Urine Output (ml)	Morphine	115 ± 41	141 ± 51	199 ± 44	134 ± 27	135 ± 39	140 ± 60
	Halothane	112 ± 45	147 ± 37	187 ± 57	102 ± 33	123 ± 44	136 ± 41
Urine Norepinephrine Concentration (μg/l)	Morphine	26 ± 15	21 ± 11	21 ± 15	35 ± 11†	43 ± 11*	54 ± 16*
	Halothane	24 ± 13	19 ± 9	19 ± 8	23 ± 12§	22 ± 8‡	38 ± 11†‡
Urine Norepinephrine Content (μg)	Morphine	3.0 ± 0.4	3.0 ± 0.8	4.0 ± 1.1	4.6 ± 1.0†	5.9 ± 1.3*	7.3 ± 2.0*
	Halothane	2.7 ± 0.7	2.8 ± 0.9	3.5 ± 0.9	2.3 ± 0.7‡	2.7 ± 1.0‡	5.2 ± 0.9†‡
Urine Norepinephrine Excretion rate (μg/hr)	Morphine	2.0 ± 0.6	3.0 ± 0.4	2.4 ± 0.8	2.5 ± 0.5	3.6 ± 0.7†	3.7 ± 0.9†
	Halothane	1.8 ± 0.6	2.8 ± 0.7	2.2 ± 0.5	1.2 ± 0.4§	1.8 ± 0.3§	2.6 ± 0.3†§

*P < 0.025, Students t-test for paired data when compared to preoperative (study period I) values.
†P < 0.05, Students t-test for paired data when compared to preoperative (study period I) values.
‡P < 0.025, Students t-test for paired data when compared to morphine values during the same study period.
§P < 0.05, Students t-test for paired data when compared to morphine values during the same study period.

mg/kg of morphine plus oxygen has little effect on cardiovascular dynamics in man.[1,2,7] Lowenstein, Hallowell, Levine, Daggett, Austen and Laver[1] have found that these doses of morphine uniformly increase cardiac output in patients with severe aortic valve disease who need valve replacement. In spite of its apparent advantages, the morphine and oxygen technique has been criticized for being associated with a high incidence of severe hypertension.[9,10] Significant elevations in blood pressure not associated with pre-existing hypertensive disease or apparent light anaesthesia have been especially common in patients with coronary artery disease both intraoperatively and in the recovery room.[10] Arens, Brenbow, Ohnsner and Theard[10] have reported that 36 per cent of their 200 patients undergoing aortocoronary artery bypass operations under morphine anaesthesia had a rise in systolic arterial blood pressure above 200 mm Hg or an increase of 60 mm Hg over pre-morphine levels at some time during the intraoperative or postoperative periods. They suggested that the clinical picture (marked increases in systolic and diastolic blood pressure and peripheral vascular resistance) was consistent with intense arterial vasoconstriction secondary to increased plasma levels of norepinephrine. Our findings appear to corroborate their impressions. While none of our morphine recipients had markedly elevated blood pressure before or after bypass or postoperatively, Group I did have significantly greater bypass pressures than Group II in spite of similar extracorporeal flow rates. Urine norepinephrine concentrations during and after bypass and postoperatively were also markedly greater in the former group. Norepinephrine excretion rates of Group I patients were approximately double those of Group II during and after bypass. Giesecke, Jenkins, Crout and Collett[11] have observed similar intraoperative and postoperative elevations in urine epinephrine levels in patients anaesthetized with fentanyl, droperidol and nitrous oxide. The latter anaesthetic combination is also associated with relatively stable cardiovascular dynamics and for this reason is popular for patients undergoing open-heart operations.[12] It is interesting that severe hypertension during open-heart operations is not unusual with fentanyl-droperidol-nitrous oxide anaesthesia, especially when only small amounts of droperidol are employed, this being the amnesic and alpha adrenergic blocking component of the combination.[12]

Although our data do not indicate a mechanism for the rise in urine norepinephrine levels after morphine, at least three possible explanations may be advanced: (1) morphine may directly or indirectly by a central nervous mechanism stimulate adrenal medullary and/or peripheral nerve release of norepinephrine; (2) norepinephrine may be released in response to pain or inadequate anaesthesia; (3) norepinephrine release may be a normal response to the abnormal circulatory dynamics of extracorporeal circulation. Elmes and Jefferson[13] showed that morphine and pentobarbitone anaesthesia result in a 2.69 per cent per hour loss of adrenal gland adrenaline in cats. Stitzel and Campos[4] found similar reductions in adrenal medullary catecholamine content after morphine in the rabbit. The latter workers also observed a significant increase in cardiac catecholamine content in these animals after morphine. Vasko, Henney, Oldham and Brawley[3] found that 1 mg/kg of morphine resulted in a significant increase in myocardial contractility in dogs. Since this could be abolished by adrenalectomy or by beta

adrenergic blockade, they suggested that morphine stimulates adrenal medullary catecholamine release. Although there have been no well controlled studies on the effects of morphine on plasma epinephrine or norepinephrine levels in man, Hasbrouk[14] has presented some data indicating that plasma levels of both amines may be elevated with morphine anaesthesia in patients during open-heart operations.

Why urine norepinephrine concentrations and excretion rates were not elevated in our patients until late in the procedure is not clear. However, one reason could be that morphine itself *did not* increase plasma norepinephrine concentrations. It is possible that as morphine blood levels became lower towards the end of the operation less analgesia was produced. Pain is a well known cause of increased levels of circulating catecholamines.[15] Unfortunately correlation of urine norepinephrine concentrations with plasma morphine levels cannot be made as measurements of the latter were not obtained. Emotional anxiety, as might occur from awareness during the surgical procedure, is another possible cause of increased levels of norepinephrine.[15] Awareness during morphine anaesthesia, especially in patients with coronary artery disease and relatively normal cardiac output is not uncommon.[9] Lack of amnesia should have been even more likely during this study because supplements such as scopolamine, diazepam or nitrous oxide, which are frequently used in combination with morphine were not employed. While careful discussion with all patients postoperatively revealed that only one morphine recipient recalled any aspect of the operative procedure, it is possible others were aware intraoperatively but repressed the memory later.

Increased plasma and urine norepinephrine and epinephrine levels have been reported during and after cardiopulmonary bypass in patients anaesthetized with a variety of agents.[8,16,17] However, halothane is one agent that apparently prevents elevations in plasma catecholamine concentration during and after extracorporeal circulation.[8] Anton, Gravenstein and Wheat [8] found that plasma catecholamines were not raised from pre-bypass levels in patients anaesthetized with halothane, until the postoperative period. Our findings in patients anaesthetized with halothane are similar. From these findings and the fact that extracorporeal circulation is associated with increased plasma catecholamines during anaesthesia with most agents, it could be interpreted that the elevated urine norepinephrine concentrations observed in Group I patients are a normal response to cardiopulmonary bypass rather than a specific reaction to morphine. On the other hand, urine epinephrine, which was not measured in this study, may have been elevated in the morphine recipients even before bypass. Giesecke, *et al.*[11] have shown that fentanyl-droperidol-nitrous oxide anaesthesia results in an immediate increase in urine epinephrine excretion but does not appreciably change urine norepinephrine excretion until the postoperative period in patients undergoing general surgical procedures. If the catecholamine response to morphine is similar to that of fentanyl-droperidol-nitrous oxide, then elevations in urine norepinephrine concentration, which did not become manifest until bypass in this study, may represent a slower release of norepinephrine than of epinephrine after morphine administration. Urine epinephrine concentrations could have been elevated at the beginning of the operation or even during induction. Additional studies measur-

ing urine or plasma epinephrine and norepinephrine levels in patients anaesthetized with morphine and not undergoing cardiopulmonary bypass will have to be done before the latter questions can be resolved.

Summary

Urine concentrations and excretion rates of norepinephrine were measured in 28 patients anaesthetized with halothane or morphine before, during and for two hours after aortocoronary artery grafting procedures. All patients were paralyzed with d-tubocurarine, intubated and respiration was controlled. Urine was obtained for 90 minutes before induction, during induction, before, during and after bypass and postoperatively. In patients anaesthetized with halothane, urinary norepinephrine concentrations and excretion rates were not significantly different from preoperative values until the postoperative period. Patients anaesthetized with morphine did not have urine norepinephrine concentrations different from preoperative values until bypass, when they became significantly increased. All subsequent urine norepinephrine concentrations and excretion rates were significantly elevated when compared to preoperative values. These findings do not indicate a mechanism but they do demonstrate that morphine anaesthesia is associated with increased urinary and probably also increased plasma levels of norepinephrine during and after cardiopulmonary bypass in patients undergoing coronary artery operations.

Résumé

Nous avons mesuré la concentration urinaire et la vitesse d'excrétion de la norépinéphrine chez 28 patients anesthésiés à l'halothane ou à la morphine avant, pendant et après pontages aorto-coronariens. Tous les patients furent curarisés par la d-tubocurarine, intubés et la respiration contrôlée. L'urine fut prélavée durant 90 minutes avant l'induction, au cours de l'induction, avant, pendant et après la C.E.C., puis au cours des deux premières heures post-opératoires. Chez les patients anesthésiés à l'halothane, la concentration urinaire et la vitesse d'excrétion de la norépinéphrine ne furent pas différentes, de façon significative, des valeurs pré-opératoires, sauf durant la période post-opératoire. Les patients anesthésiés à la morphine n'ont pas eu de concentrations urinaires en norépinéphrine différentes des valeurs pré-opératoires jusqu'à la C.E.C. alors qu'elles devinrent plus élevées. Toutes les valeurs subséquentes de concentration urinaire et de vitesse d'excrétion de norépinéphrine furent augmentées de façon significative, comparativement aux valeurs pré-opératoires. Ces résultats n'indiquent pas par quel mécanisme, mais démontrent que l'anesthésie à la morphine s'accompagne d'une augmentation de la norépinéphrine dans les urines, et probablement aussi dans le plasma, durant et après la circulation extra-corporelle chez les patients opérés pour pontage aortocoronarien.

2. WONG, K.C., MARTIN, W.E., HORNBEIN, T.F., FREUND, F.G., & EVERETT, J. The cardiovascular effects of morphine sulfate with oxygen and with nitrous oxide in man. Anesthesiology *38*: 542–549 (1973).
3. VASKO, J.S., HENNEY, R.P., OLDHAM, H.N., BRAWLEY, R.K., & MORROW, A.G. Effects of morphine on ventricular function and myocardial contractile force. Am. J. Physiol. *210*: 329–334 (1966).
4. STITZEL, R.E., CAMPOS, H.A., & SHIDEMAN, F.E. Effect of hemicholinium on the catecholamine depleting actions of reserpine, morphine and insulin in rabbitt tissues. J. Pharmacol. Exp. Ther. *149*: 193–198 (1962).
5. TANZ, R.D. & GUNTHEROTH, W.G. Response of mammalian cardiac muscle to certain sympathomimetics in presence of morphine. Pro. Soc. Exp. Biol. Med. *122*: 754–758 (1966).
6. VIKTORA, J.K., BAUKAL, A., & WOLFF, F.W. New automated fluorometric methods for estimation of small amounts of adrenaline and nonadrenaline. Anal. Biochem. *23*: 513–528 (1968).
7. STANLEY, T.H. & ISERN-AMARAL, J.H. Periodic analysis of mixed venous oxygen tension to monitor the adequacy of perfusion during and after cardiopulmonary bypass. Can. Anaesth. Soc. J. *21*: 454–460 (1974).
8. ANTON, A.H., GRAVENSTEIN, J.S., & WHEAT, M.W. Extracorporeal circulation and endogenous epinephrine and norepinephrine in plasma, atrium and urine in man. Anesthesiology 25: 262–269 (1964).
9. LOWENSTEIN, E. Morphine "anesthesia" – a perspective. Anesthesiology *35*: 563–565 (1971).
10. ARENS, J.F., BENBOW, B.P., OHNSNER, J.L., & THEARD, R. Morphine anesthesia for aorto-coronary bypass procedures. Anesth. and Analg. *51*: 901–907 (1972).
11. GIESECKE, A.H., JENKINS, M.T., CROUT, J.R., & COLLETT, J.M. Urinary epinephrine and norepinephrine during Innovar-nitrous oxide anesthesia in man. Anesthesiology *28*: 701–704 (1967).
12. CORSSEN, G., CHODOFF, P., DOMINO, E.F., & KAHN, D.R. Neurolept analgesia and anesthesia for open-heart surgery. J. Thorac. Cardiov. Surg. *59*: 901–920 (1965).
13. ELMES, P.C. & JEFFERSON, A.A. The effect of anaesthesia on the adrenaline content of the suprarenal glands. J. Physiol. *101*: 355–361 (1942).
14. HASBROUCK, J.D. Morphine anesthesia for open-heart surgery. Ann. Thorac. Surg. *10*: 364–369 (1971).
15. VON EULER, U.S. Quantitation of stress by catecholamine analysis. Clin. Pharmacol. Ther. *5*: 398–404 (1964).
16. REPLOGLE, R., LEVY, M., DEWALL, R.A., & LILLEHEI, R.C. Catecholamine and serotonin response to cardiopulmonary bypass. J. Thorac. Cardiov. Surg. *44*: 638–648 (1962).
17. BELISLE, C.A., WOODS, E.F., NUNN, D.B., PARKER, E.F., LEE, W.H., & RICHARDSON, J.A. The role of epinephrine and norepinephrine in rebound cardiovascular phenomena in azygos flow studies and cardiopulmonary bypass in dogs. J. Thorac. Cardiov. Surg. 39: 815–820 (1960).