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A Prospective Random Comparison of Halothane and Morphine for Open-heart Anesthesia:

One Year's Experience

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In 128 consecutive operations, a prospective, randomized comparison of morphine and halothane as primary agents for cardiac valvular repair and/or replacement was made. During induction, average systolic and mean blood pressures were lower (9 torr and 6 torr, respectively) with halothane than with morphine. However, the incidences of serious hypotension with the two agents were similar. Six of 61 patients with halothane and seven of 67 patients with morphine reached systolic blood pressures of 70 torr or less before incision. Intraoperative hypertension was more frequent and more severe with morphine, necessitating frequent use of supplementary chlorpromazine. Cardiac output data suggest that the higher average blood pressure seen with morphine was related to increased peripheral vascular resistance rather than increased cardiac output. There appeared to be hemodynamic differences between the agents, but neither mortality rates nor durations of hospital stay or postoperative stay in the intensive care unit demonstrated a clear-cut advantage of either morphine or halothane for anesthesia during cardiac-valve operations. (Key words: Halothane; Morphine; Open-heart anesthesia.)

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NARCOTICS were first recommended as general anesthetics for cardiac surgery by Bailey and co-workers in 1958.[1] In 1969, Lowenstein *et al.*[2] reported that "Morphine stands in striking contrast to other anesthetic agents, which uniformly have a cardiac-depressant effect." Hasbrouck [3] subsequently has stated that "The use of morphine as the sole anesthetic agent . . . is the technique of choice in the desperately ill patient who requires intracardiac operation for survival."

Despite the substantial enthusiasm for narcotic anesthesia, no previous study has utilized a *prospective randomized design* to compare morphine directly with another anesthetic agent in a large number of patients under clinical conditions. In an effort to determine whether there is indeed a clinically important difference between morphine and halothane anesthesia for cardiac-valve repair or replacement, we undertook such a comparison of these two agents.

Methods

PATIENT POPULATION

With two exceptions,¶ every patient requiring open-heart operation for acquired valvular disease at the Hospital of the University of Pennsylvania during one calendar year was included. On the day before operation each patient was randomly assigned halothane or morphine as the primary anesthetic. One hundred twenty-eight anesthetics were administered to 126 patients, ranging in age from 14 to 67 years (mean = 49.7). Surgical procedures and ASA physical status of the patients

¶ These exceptions were an emergency patient whose anesthetic was administered by a physician not familiar with the randomization technique and a moribund emergency patient who received no anesthetic drug.

are shown in table 1. The group of patients who received halothane was comparable to the morphine group in age, weight, distribution of lesions, physical status, and preoperative heart rate and blood pressure. One hundred twenty-five anesthetics were administered by first- or second-year residents with staff supervision. The remaining three were done by either staff anesthesiologists or third-year residents.

TABLE 1. Distribution of Patients by Operation and Physical Status

	Halothane	Morphine	Total
Aortic-valve replacement	20	25	45
Mitral-valve replacement	15	25	40
Mitral comissurotomy (open)	13	7	20
Multiple valve replacement and/or repair	13	9	22
TOTAL	61	67*	128
ASA physical status			
I	0	0	0
II	3	6	9
III	27	19*	46
IV	29	40	69
V	2	2	4

* One patient to whom morphine was assigned sustained a myocardial infarction prior to bypass and had no valve repair or replacement.

ANESTHETIC TECHNIQUE AND MEASUREMENTS

Each patient was visited preoperatively by his anesthesiologist and informed consent obtained. ASA physical status was assigned at this time. Maximum premedication was morphine (1 mg/10 kg) and scopolamine (0.04 to 0.08 mg/10 kg), with less or no premedication for extremely ill patients. Induction of anesthesia was not begun until direct arterial pressure, central venous pressure, and ECG monitoring had been established. These measurements, along with the EEG, were displayed on the oscilloscope screen of an Electronics for Medicine IR-4C unit, and photographically recorded. Mean arterial blood pressure was determined electronically and displayed by a meter on the same unit.

Induction of anesthesia was accomplished with 75 per cent nitrous oxide in oxygen (fresh-gas flow of 8 l/min) supplementing the primary anesthetic agent (halothane or morphine). Nitrous oxide concentration was reduced to 50 per cent within three minutes of the start of administration. Morphine was administered at a maximum rate of 10 mg iv every two minutes until consciousness was lost or until a maximum total morphine dose of 2 mg/kg was reached. Mean total dose was 1.53 mg/kg (SE = 0.0659 mg/kg). Halothane was vaporized in a Dräger "Vapor" vaporized. Inspired halothane concentration was increased slowly until a satisfactory depth of anesthesia was achieved. The maximum inspired halothane concentration was 1.0 per cent. If hypotension occurred, anesthetic administration was temporarily discontinued. If the central venous pressure (CVP) was decreasing, the table was tilted head down and plasma protein fraction, 5 per cent, or whole blood administered. Hypotension associated with increasing CVP was treated with calcium chloride (initial dose 250 mg) or isoproterenol (initial dose 2–4 μg).

Moderate *hypertension* (*e.g.*, systolic blood pressure 0–20 per cent higher than the highest preoperative value) in an otherwise-adequately-anesthetized patient was not treated. Chlorpromazine (initial dose 1.0 mg) was given intravenously to treat hypertension beyond this range. Succinylcholine was used to facilitate tracheal intubation. *d*-Tubocurarine was used as needed for muscle relaxation during the operation. Total paralysis was neither sought nor achieved. We attempted to maintain the lightest plane of anesthesia compatible with patient comfort and satisfactory operating conditions, and were intermittently able to communicate with many patients, who responded to questions by head nodding or hand and eye signals. Postoperatively, a few recalled some intraoperative communication, but none recalled any discomfort.

Arterial P_{O_2}, P_{CO_2}, and *p*H were analyzed repeatedly during anesthesia. Ventilation and inspired O_2 concentration were adjusted to maintain Pa_{CO_2} between 33 and 38 torr and Pa_{O_2} at or above 90 torr. During bypass, oxygen and CO_2 were supplied to the oxygenator to maintain the arterial blood gases in the same range. Anesthesia was maintained with the primary agent during bypass. The Mayo-Gibbon and Sarnes-Travenol pump oxygenators were used. The Mayo-Gibbon unit was employed when prolonged bypass was anticipated.

In the post-bypass period, anesthetic agents were administered only if the patient evidenced discomfort. When anesthesia was necessary, N_2O was gradually increased to a maximum of 50 per cent (usual concentration 30 per cent) if a satisfactory Pa_{O_2} could be maintained. In the few cases in which still further anesthesia was needed, the primary agent was again administered in minimal amounts. Ventilation was assisted or controlled in every patient at least until the morning following operation.

Analysis of Data

The ranges of heart rate and systolic blood pressure of each patient were recorded during the preoperative hospital stay, and provided control data for comparison with pulse rates and blood pressures recorded in the operating room.

We evaluated heart rate and systolic blood pressure *decreases* (below the *lowest* preoperative value) in the period between start of anesthesia and start of operation, believing that, unmodified by surgical stimulation, this period would best reflect anesthetic-induced depression. Heart rate and systolic blood pressure *increases* (above the *highest* preoperative value) in the period between incision and initiation of cardiopulmonary bypass were recorded as an index of degree of anesthetic control of cardiovascular response to surgical stimulation. Both lowest and highest mean arterial blood pressures during cardiopulmonary bypass were recorded. We excluded 10-minute periods at the beginning and the end of bypass to eliminate measurements made under unrepresentative, partial-bypass conditions. Both highest and lowest systolic blood pressures occurring between the end of cardiopulmonary bypass and the end of the operation were recorded. Cardiac output was measured by the indocyanine green dye-dilution technique in 25 patients. Student's t test was used to detect statistical significance of differences between means. Chi-square testing was applied when incidence rates were compared.

Results

Mean Decreases in Blood Pressure and Heart Rate during Induction

The mean lowest and highest preoperative systolic blood pressures and heart rates are shown in table 2. There was no apparent difference between control values for the two groups. Table 2 also lists mean lowest systolic blood pressures, lowest mean blood pressures, and lowest heart rates between start of anesthesia and incision. Systolic blood pressure and mean blood pressure were significantly lower with halothane than with morphine. Only halothane caused a significant ($P < 0.01$) decrease of systolic blood pressure from the lowest preoperative value. The mean lowest heart rate noted during induction with either agent was significantly ($P < 0.01$) lower than the mean lowest rate recorded preoperatively. Comparison of heart rates *between* the two groups revealed no significant difference.

Clinically Significant Decreases in Blood Pressure and Serious Complications during Induction

Figure 1 depicts the ranges of systolic blood pressure depression measured during the induction-to-incision periods with the two agents. Negative values represent systolic blood pressures lower than the lowest value recorded preoperatively. Although the mean depression of systolic blood pressure was greater with halothane than with morphine, there were approximately equal incidences of clinically important systolic blood pressure depression with the two agents. The lowest systolic pressure observed in the halothane group was 40 torr, with six patients having systolic pressures of 70 torr or less. The lowest systolic pressure in the morphine group was 50 torr, with seven patients having systolic pressures of 70 torr or less. One of the morphine patients whose systolic pressure reached 70 torr before incision sustained a myocardial infarction. Shortly thereafter, ventricular fibrillation occurred and was successfully treated. The operation was terminated and the patient returned for valve replacement the following year. Results for this patient are reported for the period between start of anesthesia and incision only.

Cardiac Output and Peripheral Resistance Comparisons

Table 3 summarizes the results of determinations of cardiac output, mean arterial blood pressure, and total peripheral resistance. Logistical problems limited these measurements to the pre-bypass period and to only 25 of the

TABLE 2. Effects of Anesthesia on Blood Pressure and Heart Rate

	Halothane			Morphine			Significance of Difference
	Number of Patients	Mean	SE	Number of Patients	Mean	SE	
Preoperative							
Systolic blood pressure (torr)							
Lowest		102.2	2.03		101.4	1.69	*N.S.*
Highest	61	139.6	3.38	67	138.4	3.61	*N.S.*
Heart rate (beats/min)							
Lowest		77.7	2.17		79.7	2.00	*N.S.*
Highest	61	91.9	2.25	67	90.4	2.36	*N.S.*
Start of anesthesia to incision							
Lowest systolic blood pressure		91.6	2.33		100.5	2.67	$P < 0.01$
Lowest mean arterial blood pressure	61	66.9	1.63	67	73.2	1.75	$P < 0.01$
Lowest heart rate		68.0	2.39		67.5	1.93	*N.S.*
Incision to bypass							
Highest systolic blood pressure		128.8	3.06		152.2	3.84	$P < 0.01$
Highest mean arterial blood pressure	61	90.4	2.40	66	103.3	2.00	$P < 0.01$
Highest heart rate		97.4	2.82		98.8	2.45	*N.S.*
During bypass							
Lowest mean perfusion pressure		52.8	1.75		57.1	1.60	*N.S.*
Highest mean perfusion pressure	61	81.6	2.24	66	93.5	1.98	$P < 0.01$
After bypass							
Systolic blood pressure							
Lowest		84.7	2.09		92.2	2.45	$P < 0.05$
Highest	59	131.5	2.98	62	141.4	2.57	$P < 0.02$
Mean arterial blood pressure							
Lowest		68.1	1.60		70.9	1.79	*N.S.*
Highest	59	95.9	1.83	62	100.0	2.33	*N.S.*
Highest heart rate		106.4	2.73		111.1	2.80	*N.S.*

126 patients, and these 25 patients were selected for reasons of convenience rather than by the strictly randomized methods used in the remainder of the study. Because the variation was large and the group small, differences between halothane and morphine approach, but do not achieve, statistical significance. Nevertheless, these data suggest that the lower mean arterial blood pressure produced by halothane was actually accompanied by a *higher* mean cardiac index. The higher mean arterial blood pressure in the morphine group was associated with greater total peripheral resistance.

MEAN INCREASES IN BLOOD PRESSURE AND HEART RATE FROM INCISION TO BYPASS

Mean values for highest systolic blood pressure, highest mean blood pressure, and highest heart rate between incision and the start of cardiopulmonary bypass are shown in table 2. The range of systolic blood pressure elevations is shown in figure 2. Systolic blood pressure and mean blood pressure were significantly

TABLE 3. Comparison of Anesthetic Effects on Cardiac Index

	Halothane (n = 9)		Morphine (n = 16)	
	Mean	SE	Mean	SE
Best cardiac index, induction to bypass ($l/m^2/min$)	2.08	0.35	1.75	0.22
Mean arterial blood pressure at time of best cardiac index (torr)	76.8	4.6	91.4	4.9
Total peripheral resistance associated with best cardiac index (dyne sec cm^{-5})	2,210	402	2,832	282

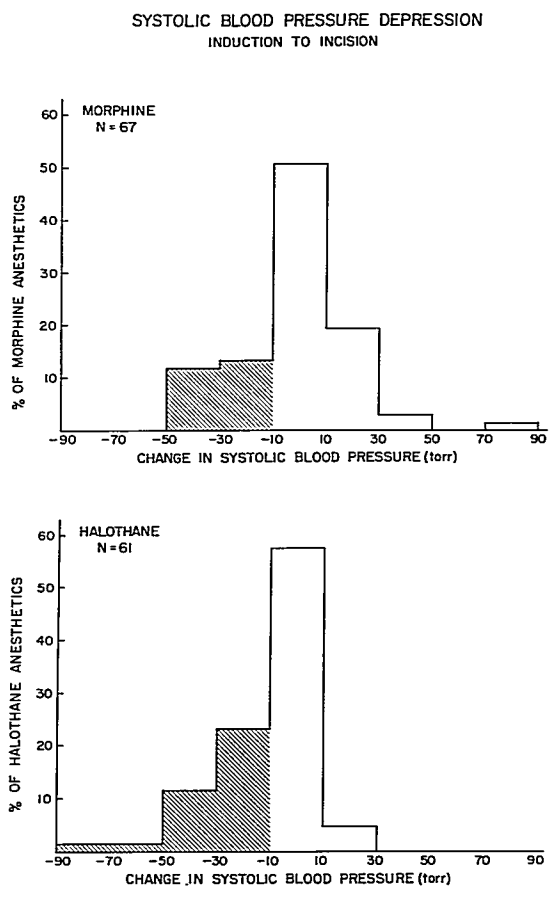

FIG. 1. Systolic blood pressure *depression*—start of anesthesia to incision. The shaded area represents systolic blood pressure depression of more than 10 torr below the lowest preoperative systolic blood pressure.

greater with morphine than with halothane. The mean of highest systolic blood pressure recorded during surgical stimulation was above the mean of preoperative maximum systolic blood pressure with morphine only. There was no apparent difference between the groups in greatest heart rate, and only in the morphine group was this value significantly greater ($P < 0.02$) than the highest preoperative heart rate.

PERFUSION PRESSURE DURING AND FOLLOWING BYPASS

The highest and lowest perfusion pressures during cardiopulmonary bypass are shown in table 2. The only significant difference be-

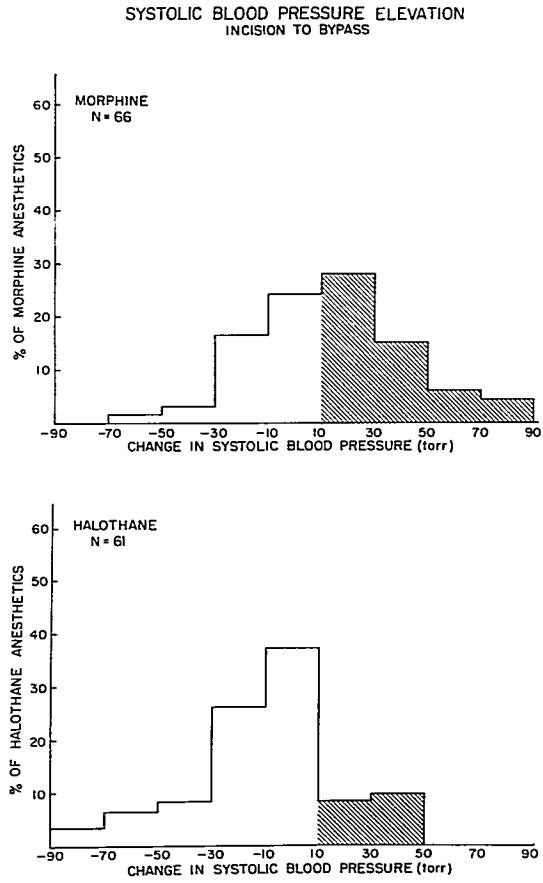

FIG. 2. Systolic blood pressure *elevation*—incision to start of cardiopulmonary bypass. The shaded area represents systolic blood pressure elevation of more than 10 torr above the highest preoperative systolic blood pressure.

tween the groups was the higher maximum perfusion pressure with morphine. Table 2 also shows the comparison between blood pressures and heart rates in the post-bypass period. Differences between the groups in both lowest and highest systolic blood pressures were significant, but mean blood pressure differences were not. The highest heart rates in the post-bypass period were similar in the two groups.

NEED FOR SUPPLEMENTARY INOTROPIC DRUGS AND/OR CHLORPROMAZINE

Table 4 summarizes the use of inotropic agents and chlorpromazine. In any given period, inotropic agents were needed with ap-

TABLE 4. Supplementary Medication

	Start of Anesthesia to Incision		Incision to Bypass		During Bypass*		After Bypass	
	Halothane	Morphine	Halothane	Morphine	Halothane	Morphine	Halothane	Morphine
Total number of patients	61	67	61	66	61	66	59†	62†
Isoproternol								
Number of patients	1	3	3	3	2	4	7	9
Mean dose (μg)	35.0	2.7	40.7	134.7	4.5	14.6	107.3	84.0
Median dose (μg)		2.0	20.0	2.0	4.5	13.3	100.0	7.0
Calcium chloride								
Number of patients	1	0	6	1	6	6	21	18
Mean dose (mg)	250	—	633	500	850	458	814	888
Median dose (mg)			750		625	500	1000	1000
Chlorpromazine								
Number of patients	0	6	0	28	4	32	1	13
Mean dose (mg)	—	5.0	—	5.0	2.0	4.5	15.0	5.5
Median dose (mg)		5.0		4.0	2.0	3.0		5.0

* Inotropic agents administered "during bypass" were given under partial-bypass conditions at the end of perfusion.

† Six patients (4 morphine, 2 halothane) could not sustain life without extracorporeal circulatory support.

proximately equal frequency in the two groups. There was a striking difference between groups in the need for chlorpromazine. It was used in six morphine patients prior to the start of operation and in 28 morphine patients between incision and bypass. No halothane patient needed the drug in either of these periods. During cardiopulmonary bypass, 32 morphine patients received chlorpromazine to reduce perfusion pressure. Only four halothane patients needed the drug in the same period. Between the end of bypass and the end of the operation, 13 patients in the morphine group needed chlorpromazine, while only one patient in the halothane group did. No patient who received chlorpromazine developed clinically significant hypotension in response to the drug.

Intraoperative and Postoperative Morbidity and Mortality

There were nine operating room deaths, eight from cardiac failure (3 halothane, 5 morphine) and one from uncontrollable bleeding (morphine). Only two of these nine patients were undergoing their first cardiac operations. Mean durations of postoperative stay in the intensive care unit were 6.9 days (SE = 0.7) for the halothane group and 7.9 days (SE = 0.8) for the morphine group. These figures did not differ significantly, and the median stay was 5 days for each group. Mean durations of postoperative hospitalization were 20.0 days (SE = 1.1) for the halothane group and 21.9 days (SE = 1.3) for the morphine group (no significant difference). The median stays were 17 and 18 days, respectively. Overall mortality rates did not differ significantly (13.1 per cent for halothane and 15.1 per cent for morphine).

A more precise measurement of degree of postoperative ventilatory impairment would be one based on objective criteria for discontinuing mechanical ventilation. The development of such criteria was begun during the course of this study, and a separate study based upon them has revealed no difference between durations of postoperative mechanical ventilation with the two anesthetics.[4]

Discussion

The results observed during administration of halothane were those that would have been expected: decreases in blood pressure, with serious hypotension during induction occurring

in a few of the patients. It is with this as a background that the effects of morphine anesthesia must be considered.

Morphine produced higher average systolic and mean blood pressures. This might be considered an advantage, except in those cases where the blood pressure increases were extreme. Intraoperative hypertension was more likely with morphine, and its potential hazards, bleeding and increased myocardial work, can be significant problems in cardiac patients.

The initial decrease in peripheral vascular resistance in response to a large dose of morphine has been demonstrated by Henney *et al.*[5] Peripheral vascular resistance then gradually increased over their 30-minute study period until it reached or exceeded control levels. Their findings are compatible with the hypotension seen during morphine induction in the current study, as well as with the higher total peripheral resistance found in the morphine group in which cardiac output and total peripheral resistance were measured. The gradually increasing peripheral vascular resistance would also explain the need for chlorpromazine to control intraoperative hypertension in almost half of the morphine patients.

This study has not provided a definite answer to the critical clinical question of patient safety. Morphine, on the average, produced less hypotension, but serious hypotension was possible, and occurred with similar frequencies with the two agents. Operative and overall mortality rates and stays in the intensive care unit and in the hospital were similar with the two agents. We have found no data which justify the conclusion that morphine (or halothane) is superior for cardiac anesthesia. We believe that skill and care in administration remain more critical than the choice of anesthetic agent.

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Drugs and Their Actions

PROSTAGLANDINS AND LABOR The effects of oxytocin and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) for elective induction of labor in 100 uncomplicated pregnancies in multiparas were compared. Maternal vital signs, frequency and intensity of uterine contractions, and fetal heart tones were monitored throughout labor; the majority of patients were subjected to electronic fetal monitoring. There was no significant difference between the success rates of induction with the two drugs, nor between the induction–delivery times. Uterine hypertonicity occurred more frequently with $PGF_{2\alpha}$. One patient developed a severe generalized rash while receiving prostaglandin. The authors concluded that $PGF_{2\alpha}$ is as safe and efficacious as oxytocin for induction of labor in multiparas at term. However, the authors do point to the need for a larger study. The incidence of uterine hypertonicity observed with $PGF_{2\alpha}$ was high (seven times in 50 patients), and may have resulted from the relatively large doses of the drug administered. (*Vakhariya, V. R., and Sherman, A. I.: Prostaglandin $F_{2\alpha}$ for Induction of Labor, Am. J. Obstet. Gynecol. 113: 212–222, 1972.*)