

## Comparison of Anesthesia with Diazepam and Ketamine vs. Morphine in Patients Undergoing Heart-valve Replacement

P. R. Dhadphale, M.B., F.F.A.R.C.S.I.,\* A. P. F. Jackson, M.B., F.F.A.R.C.S.,\* S. Alseri, M.D.†

Because of its analgesic and amnesic effects, ketamine has potential advantages as a primary agent for patients undergoing open-heart surgery. However, the undesirable positive inotropic and chronotropic effects associated with ketamine have deterred its use. Diazepam pretreatment appears to block these unwanted effects. Sixteen randomly selected patients were given a combination of diazepam, 0.4 mg/kg, followed by ketamine, 2 mg/kg, and nitrous oxide, 50 per cent. The authors compared the circulatory responses to induction, intubation, and operation with those obtained in a matched group of patients who received morphine, 3 mg/kg, and nitrous oxide, 50 per cent. All patients underwent mitral- or aortic-valve replacement. Circulatory responses were not significantly different between the two groups. In both groups, heart rate, mean arterial blood pressure, and rate-pressure product increased significantly with intubation of the trachea, incision of the skin, and sternotomy. The incidences of hypertension, hypotension, and arrhythmias, and the need for inotropic drugs were not significantly different between the two groups. No intraoperative awareness occurred in either group. It is concluded that diazepam-ketamine anesthesia is a satisfactory alternative to morphine anesthesia for patients undergoing heart-valve replacement. (Key words: Analgesics, narcotic: morphine. Anesthesia, cardiovascular. Anesthetics, intravenous: ketamine. Heart: cardiac output; myocardial function. Hypnotics: diazepam.)

DESPITE some reports of the use of ketamine for open-heart surgery,<sup>1-5</sup> it has not gained wide acceptance. The most important reason for this is the marked inotropic and chronotropic effects that attend the administration of ketamine.<sup>6</sup> These effects are generally agreed to be undesirable in patients with either ischemic<sup>7</sup> or valvular<sup>8</sup> heart disease. On the other hand, ketamine does have profound analgesic and amnesic properties<sup>9-10</sup> that could be of value in patients who at times may not be able to tolerate even nitrous oxide, 50 per cent.

Zsigmond *et al.*<sup>11</sup> and we<sup>12</sup> have shown that the cardiostimulant effects of ketamine did not occur in a group of patients undergoing open-heart operations when they were given pretreatment with intravenously administered diazepam. We therefore have undertaken a controlled prospective study of the circulatory responses during induction and maintenance of

anesthesia in two matched groups of patients undergoing heart-valve replacement. One group received diazepam-ketamine-nitrous oxide and the other, morphine-nitrous oxide anesthesia.

### Methods

Thirty-two patients scheduled for elective mitral- or aortic-valve replacement were randomly assigned to one of two anesthetic techniques. All patients were evaluated preoperatively and premedicated with morphine, 5-10 mg, and scopolamine, 0.2-0.4 mg intramuscularly an hour prior to being brought to the operating room. Digitalis and diuretics had been discontinued 48 hours prior to operation. On arrival in the operating room, radial-artery and peripheral venous catheters were inserted percutaneously during local anesthesia. A 7-Fr triple-lumen, flow-directed thermodilution balloon catheter was also inserted percutaneously via the right internal jugular vein. Electrocardiogram and systematic arterial, pulmonary arterial and central venous pressures were continuously monitored with a Hewlett-Packard® four-channel display recorder. Cardiac output values were obtained by thermodilution‡ using an Electronics for Medicine® cardiac output computer with an OMP® Series 3700 CO<sub>2</sub>-powered injector.

Patients assigned to the diazepam-ketamine technique (Group I) were managed as follows: during breathing of room air, baseline circulatory data and arterial blood values were obtained. After oxygenation for 3 min, diazepam, 0.4 mg/kg, was given intravenously at a rate of 10 mg/min. Three minutes after completion of the administration of diazepam, ketamine, 2 mg/kg, was administered intravenously as a bolus injection. Three minutes thereafter the patients were given succinylcholine, 1.5 mg/kg, to facilitate tracheal intubation. Anesthesia was maintained with nitrous oxide, 50 per cent, pancuronium, 0.1 mg/kg, and a continuous infusion of ketamine at the rate of 1 mg/kg/hr using a constant-infusion pump. The ketamine infusion was discontinued at the time of sternal closure. Anesthetic management of the patients in Group II was identical except that anesthesia was induced with morphine at a rate of 5 mg/min until the patients had received 3 mg/kg.

\* Instructor.

† Resident.

Received from the Department of Anesthesiology, The University of Michigan School of Medicine, 1045 East Ann Street, Ann Arbor, Michigan 48109. Accepted for publication January 8, 1979. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, October 1977.

Address reprint requests to Dr. P. J. Cohen, Chairman, Department of Anesthesiology.

‡ Values not within 10 per cent of each other were rejected.

Any decrease in systolic blood pressure to less than 80 torr was treated with head-down tilt and intravenous fluid therapy. When these measures were not effective, phenylephrine, 0.25–0.5 mg, was given intravenously. Systolic blood pressure values 20 per cent above the highest preoperative value were treated with sodium nitroprusside, 0.02 per cent. In the immediate post-cardiopulmonary-bypass period a blood pressure of less than 85 torr that persisted for more than 2 min was treated with either an isoproterenol infusion or a combination of norepinephrine and phentolamine.

Circulatory and blood-gas data were obtained at eight intervals during anesthesia and operation. The circulatory variables included heart rate; mean arterial, central venous, pulmonary arterial and pulmonary capillary wedge pressures; and cardiac output. All patients were seen postoperatively and questioned specifically about possible awareness or unpleasant dreams during operation and emergence from anesthesia.

To determine the significance of the difference between overall group responses, an analysis of variance was carried out for each of the variables studied. Changes within treatment groups were tested for significance using the Student *t* test for paired data; those that occurred to and including endotracheal intubation (Event 5) were compared with the room-air control (Event 1) values, whereas those changes that occurred at incision of the skin (Event 7) and thereafter were compared with the values recorded immediately prior to incision of the skin (Event 6).  $P < 0.05$  was considered significant.

## Results

The two anesthetic-treatment groups were well matched for age, sex, and preoperative risk factors (table 1), and there was no significant difference in circulatory indices between them at any of the study times (figs. 1 and 2).

Heart rate, mean arterial blood pressure, and rate-pressure product all increased significantly in response to endotracheal intubation, incision of the skin, and sternotomy in both groups. Partial pressure of carbon dioxide in arterial blood ( $Pa_{CO_2}$ ) increased in both groups throughout induction of anesthesia, but returned to control values following endotracheal intubation. The maximum increase in  $Pa_{CO_2}$  in patients who received morphine anesthesia was significantly greater than that in patients who received diazepam and ketamine (fig. 1). Cardiac index did not change after endotracheal intubation, but increased significantly in both treatment groups after cardiopulmonary bypass.

TABLE 1. Characteristics of the Study Populations

	Diazepam-Ketamine (Group I) (n = 16)	Morphine (Group II) (n = 16)
Age, years (mean and range)	49 (33–79)	52 (29–72)
Sex distribution		
Male	11	13
Female	5	3
Type of operation		
Aortic-valve replacement	7	6
Mitral-valve replacement	9	10
Preoperative N.Y.H.A.* classification		
2	1	1
3	11	10
4	4	5
Preoperative atrial fibrillation	7	7
Left ventricular end-diastolic pressure (torr) from preoperative catheteriza- tion data (mean and range)	15.2 (7–40)	15.3 (7–30)

\* NYHA = New York Heart Association.

Hypertension necessitating administration of sodium nitroprusside occurred in 13 patients in Group I and ten patients in Group II, while hypotension necessitating pressor treatment was seen only in one patient in Group II during induction. Two deaths occurred, both in Group I. These were associated with intraoperative technical surgical problems. The patients died 20 min and six hours, respectively, after termination of cardiopulmonary bypass. Anesthetic contributory factors were not discernible in either case. No patient reported awareness of unpleasant dreams during operation or emergence from anesthesia.

## Discussion

The absence of differences in hemodynamic variables between the anesthetic treatment groups suggests that the diazepam-ketamine technique confers no special advantage or disadvantage compared with high-dose morphine. Undesirable hemodynamic responses to the stresses of endotracheal intubation, incision of the skin, and sternotomy were present in both groups. However, no other anesthetic technique is considered ideal in this respect, either.

Many of our patients had pulmonary hypertension preoperatively. Takahashi *et al.*<sup>13</sup> showed that ketamine increased pulmonary arterial pressure in dogs, and concluded that the drug was contraindicated for use in patients who had pulmonary hypertension. This effect was also seen in the results of Tweed and

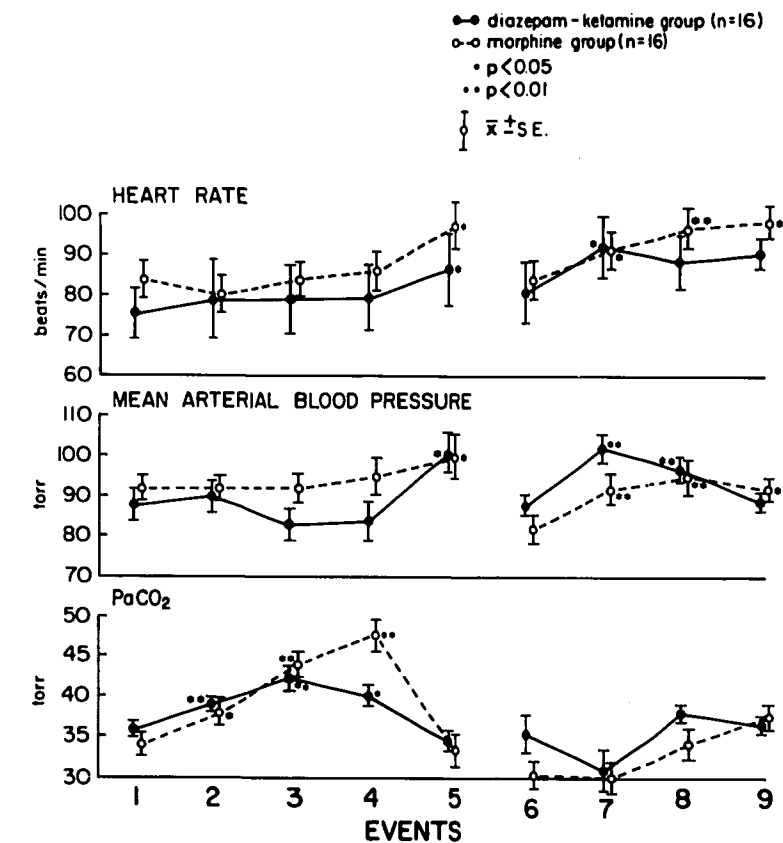


FIG. 1. Changes in heart rate, mean arterial blood pressure and  $PaCO_2$  observed during anesthesia for open-heart surgery in 16 patients given diazepam, ketamine and nitrous oxide anesthesia, compared with data from a matched group of 16 patients given morphine and nitrous oxide anesthesia.

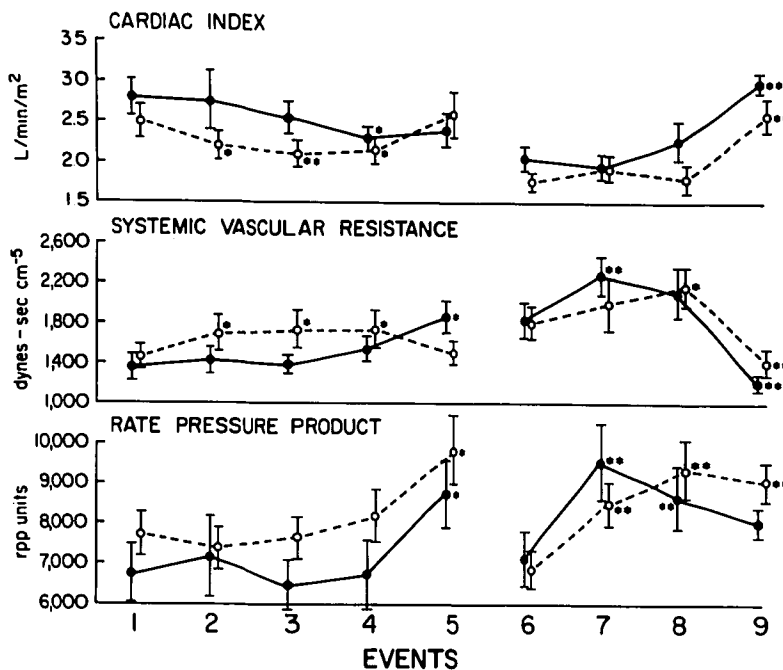


FIG. 2. Changes in cardiac index, systemic vascular resistance, and rate pressure product observed during anesthesia for open-heart surgery in 16 patients given diazepam, ketamine and nitrous oxide anesthesia, compared with data from a matched group of 16 patients given morphine and nitrous oxide anesthesia.

- |   |  |
|---|--|
| 1 Room Air (Control)                              | 6 Prior To Skin Incision                         |
| 2 After 3 Mins Preoxygenation                     | 7 2 Minutes After Skin Incision                  |
| 3 After 0.4 mg/kg diazepam or 0.75 mg/kg morphine | 8 2 Minutes After Sternotomy                     |
| 4 After 1.5 mg/kg ketamine or 1.5 mg/kg morphine  | 9 30 Minutes After End Of Cardiopulmonary Bypass |
| 5 After Intubation                                |  |

Minuck.<sup>6</sup> In our patients, mean pulmonary arterial pressure decreased slightly from  $38.8 \pm 3.45$  to  $33.8 \pm 3.86$  torr ( $\bar{x} + SE$ ) after ketamine. We agree with Gassner *et al.*,<sup>14</sup> who proposed that alterations in pulmonary hemodynamics are related to changes in cardiac index rather than to changes in pulmonary vasomotor tone.

The greater increase in  $P_{aCO_2}$  during induction seen in patients receiving morphine (Group II) was caused by the occurrence of hypoventilation due to chest-wall rigidity in 25 per cent of patients in that group. This problem, together with the unreliability of the hypnotic action of morphine and the longer duration of induction, were from a practical viewpoint important disadvantages when morphine was compared with the diazepam-ketamine technique.

Awareness during open-heart operations with morphine anesthesia is well recognized.<sup>15</sup> Our experience suggests that the continuous infusion of ketamine at the dose rate of 1 mg/kg/hour consistently produces amnesia during operation, particularly in the period immediately after cardiopulmonary bypass, when it is often necessary to withhold nitrous oxide for brief periods. Therefore, despite the similarity of behaviors of the circulatory variables in the two treatment groups, the diazepam-ketamine technique provides practical advantages that might justify its consideration as an alternative approach in this field of anesthesia.

The authors thank Dr. H. Sloan, Professor and Chairman, and Drs. M. Kirsh and D. M. Behrendt, of the Section of Cardiothoracic Surgery, for their cooperation during the study. They also thank P. Ward of the Statistical Research Laboratory, University of Michigan, for assistance in the statistical procedures, and Dr. P. J. Cohen, Chairman, Department of Anesthesiology, for advice in preparation of the manuscript.

## References

1. Corssen G, Allarde R, Brosch E, et al: Ketamine as the sole anesthetic in open-heart surgery: A preliminary report. *Anesth Analg (Cleve)* 49:1025-1031, 1970
2. Vaughan RW, Stephen CR: Ketamine for corrective cardiac surgery in children. *South Med J* 66:1226-1230, 1973
3. Szappanyos G, Gemperle M, Rifat K: Ketamine Meeting. *Proc R Soc Med* 64:1156-1159, 1971
4. Lippman M, Cleveland RJ: Emergency closed mitral commissurotomy using ketamine anesthesia: Report of a case. *ANESTHESIOLOGY* 35:543-544, 1971
5. Dillon JB: Ketamine Meeting. *Proc R Soc Med* 64:1153-1156, 1971
6. Tweed WA, Minuck M, Mymin D: Circulatory responses to ketamine anesthesia. *ANESTHESIOLOGY* 35:613-619, 1972
7. Braunwald E: Control of myocardial oxygen consumption: Physiologic and clinical considerations. *Am J Cardiol* 27:416-421, 1971
8. Arani DT, Carleton RA: The deleterious role of tachycardia in mitral stenosis. *Circulation* 36:511-515, 1967
9. Bovill JG, Dundee JW: Alterations in response to somatic pain associated with anesthesia: Ketamine. *Br J Anaesth* 43:496-500, 1971
10. Corssen G, Domino EF: Dissociative anesthesia: Further pharmacologic studies and first clinical experience with the phencyclidine derivative CI-581. *Anesth Analg (Cleve)* 45:29-39, 1966
11. Zsigmond EK, Kothary SP, Martinez OA, et al: Diazepam for prevention of the rise in plasma catecholamines caused by ketamine. *Clin Pharmacol Ther* 15:223-224, 1974
12. Jackson APF, Dhadphale PR, Callaghan ML: Hemodynamic studies during induction of anesthesia for open heart surgery using diazepam and ketamine. *Br J Anaesth* 50:375-378, 1978
13. Takahashi K, Shima T, Koga Y, et al: The effect of ketamine hydrochloride on the pulmonary hemodynamics in dogs. *Jpn J Anesthesiol* 20:842-846, 1971
14. Gassner S, Cohen M, Aygan M, et al: The effects of ketamine on pulmonary artery pressure: An experimental and clinical study. *Anaesthesia* 29:141-146, 1974
15. Lowenstein E: Morphine "Anesthesia"—a perspective. *ANESTHESIOLOGY* 35:563-565, 1971