

## Cardiovascular Effects of Ketamine in Humans with Cervical or Lumbar Epidural Blockade

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To examine the effect of sympathectomy induced by epidural blockade on the cardiovascular effects of ketamine anesthesia, the authors compared the changes in arterial blood pressure (AP) and heart rate (HR) following intravenous administration of ketamine in patients who had cervical epidural anesthesia ( $n = 18$ ), lumbar epidural anesthesia ( $n = 16$ ), or light general anesthesia alone ( $n = 16$ ). Ketamine, 2 mg/kg, iv, produced statistically significant increases in both AP and HR in all patients studied. However, the per cent increases in systolic AP in the cervical group were statistically less than those in the lumbar epidural group and control groups ( $P < 0.05$ ), which did not significantly differ from each other. The changes in HR following ketamine in the cervical group were significantly less than those in the other two groups (at 3-10 min following ketamine) ( $P < 0.05$ ). These results indicate that the cardiovascular stimulatory effects of ketamine are suppressed partially by a high level of epidural anesthesia but not by a low level of epidural blockade. Since patients with cervical epidural anesthesia had an analgesic level extending between C<sub>4</sub> and Th<sub>8</sub>, the above attenuative effects of epidural blockade may be considered to be attributable to cardiac sympathectomy induced by a high level of epidural anesthesia. (Key words: Anesthetics, intravenous: ketamine. Anesthetic technique: epidural; cervical. Heart: blood pressure; heart rate. Sympathetic nervous system: sympathectomy; cardiac.)

KETAMINE ANESTHESIA produces significant increases in blood pressure and heart rate.<sup>1-4</sup> These cardiovascular effects of ketamine appear to be mediated by the sympathetic division of the autonomic nervous system via direct stimulation of central nervous system (CNS) structures.<sup>5</sup>

Blockade of the sympathetics might be expected to modify the cardiovascular effects of ketamine. Indeed, in an animal study, Traber and Wilson<sup>6</sup> showed an ablation of its cardiostimulatory action by a ganglionic blocker and high epidural anesthesia. Because they did not measure the analgesic level or extent of sympathetic denervation induced by epidural anesthesia, the

precise role of the sympathetic nervous system in the cardiostimulatory responses to ketamine can not be determined from their observations.

Epidural anesthesia produces a reversible segmental sympathetic denervation in humans.<sup>7,8</sup> A high level of sympathectomy induced by cervical epidural blockade can interrupt sympathetic efferents to the heart,<sup>7,9,10</sup> while sympathectomy induced by lumbar epidural anesthesia leaves them intact. Although thoracic or cervical epidural anesthesia does not cause any remarkable cardiovascular perturbation,<sup>11,12</sup> we speculate that such a sympathectomy could modify the cardiovascular effects of ketamine. In addition, since ketamine has direct myocardial depressant properties in the absence of autonomic control,<sup>13</sup> there may exist considerable differences in ketamine-induced cardiovascular changes between patients with cervical sympathectomy and those with lumbar sympathectomy. With these points in mind, we compared the changes in arterial blood pressure and heart rate following ketamine in patients who had either cervical epidural blockade or lumbar epidural blockade, or neither. The results elucidate some of the mechanisms of ketamine-induced cardiovascular responses in humans.

### Materials and Methods

Fifty ASA I or II patients who were scheduled to have cervical or lumbar epidural anesthesia or general anesthesia alone for their surgical procedures were selected for this study. The study protocol and consent forms were approved by the Clinical Research Committee of our hospital. Informed consent was obtained from each patient. None of the patients selected had cardiopulmonary or neurologic disorders. Premedication consisted of 100 mg hydroxyzine and 0.5 mg atropine intramuscularly 1 h prior to arrival in the operating room. An intravenous cannula was placed for infusion of lactated Ringer's solution and for drug administration.

A radial artery catheter was inserted to permit continuous recording of arterial blood pressure and electronic calculation of heart rate. Thirty-four of the patients had either cervical epidural anesthesia (cervical group,  $n = 18$ ) or lumbar epidural anesthesia (lumbar group,  $n = 16$ ), while the rest had no epidural block and served as the control (control group,  $n = 16$ ). Following sterile preparation and draping of each patient

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TABLE 1. The Mean Values of Age, Body Weight, Height, and Area of Sensory Block in the Three Groups of Patients

	Age (yr)	Body Weight (kg)	Height (cm)	Level of Sensory Block
Cervical epidural (n = 18)	42 ± 9 (19-54)	51 ± 7 (47-58)	154 ± 5 (148-164)	C3.8 ± 1.6-Th6.7 ± 2.7 (C <sub>2</sub> -Th <sub>11</sub> )
Lumbar epidural (n = 16)	39 ± 10 (25-57)	50 ± 6 (44-60)	155 ± 7 (147-166)	Th8.7 ± 1.9-S2.1 ± 2.5 (Th <sub>5</sub> -S <sub>5</sub> )
Control (n = 16)	39 ± 9 (21-54)	49 ± 5 (46-59)	152 ± 5 (146-162)	—

Values are means ± SD.

in the lateral decubitus position, a 17-gauge Tuohy needle was inserted into the epidural space using the hanging-drop technique. Next, 10 ml 2% plain mepivacaine was injected into the space over 30 s and was followed by the placement of an epidural catheter for continuous blockade. Then each patient was placed in the supine position. The level of analgesia was measured using a pin-prick method 15 min after the injection.

After establishment of either cervical or lumbar epidural anesthesia, baseline measurement of blood pressure and heart rate was done. Then ketamine, 2 mg/kg, was administered intravenously. Control patients were anesthetized with ketamine, 2 mg/kg, after control recording of blood pressure and heart rate. Blood pressure and heart rate were measured for 10 min after ketamine injection, while arterial blood gas analysis was done 5 min after ketamine administration.

None of the patients received a pressor agent to maintain arterial blood pressure following the epidural blockade.

Analysis of covariance for multiple comparisons within the values of each time including the baseline values among the three groups was performed; thereafter significant differences were performed using Student's *t* test for paired data. Results are presented as the means ± SD with a statistically significant change being considered to have occurred when *P* values were 0.05 or less.

### Results

There were no difference in age distribution, body weight, and height among the three groups of patients (table 1). The mean analgesic levels obtained by epidural anesthesia were between C<sub>4</sub>-Th<sub>7</sub> in the cervical group and between Th<sub>9</sub>-S<sub>2</sub> in the lumbar epidural group (table 1).

There was a significant difference in the baseline systolic arterial blood pressure between the cervical and control groups, and the lumbar and control groups, respectively, but not between the cervical and

lumbar epidural groups. The baseline diastolic arterial blood pressure in the cervical group was significantly less than that of the control group. The baseline heart rate in the cervical group was significantly less than those of the other two groups (table 2).

Ketamine produced significant increases in blood pressure and heart rate in all patients studied. But at 1 and 10 min after ketamine, systolic blood pressure in the cervical group did not differ from the baseline value (table 2). The per cent increases in systolic and diastolic blood pressure from the baseline values in the cervical group were significantly less than those in the lumbar epidural and control groups at any time course after the injection of ketamine. The per cent increases in heart rate in the cervical group also were significantly less than those in the lumbar epidural and control groups during 3-10 min and 5-10 min following ketamine iv, respectively. There was no difference between the lumbar epidural and control groups in changes in systolic blood pressure, but there was a significant difference in the changes in heart rate from 6 to 10 min after the administration of ketamine (fig. 1).

The values of arterial blood gas analyses 5 min after ketamine injection showed a significantly greater decrease in PaO<sub>2</sub> and a greater increase in PaCO<sub>2</sub> in the cervical epidural group than observed in the other two groups (table 3).

### Discussion

In the present study, we compared the circulatory effects of ketamine, 2 mg/kg, iv, in premedicated patients with those in patients who had either cervical sympathectomy or lumbar sympathectomy induced by epidural anesthesia. We observed less increases in blood pressure and heart rate in the patients who had cervical epidural block. Also, we found no difference in the changes in blood pressure and heart rate in the absence of epidural block or with lumbar epidural blockade. From our previous study,<sup>14</sup> the differences in circulatory changes induced by ketamine could not

be due to the systemic pharmacologic effect of mepivacaine absorbed from epidural space but rather to the neural effect of mepivacaine administered epidurally.

Initial blood pressure does not affect the degree of hypertension produced by ketamine.<sup>15</sup> Regarding heart rate, however, it is unknown whether initial heart rate may affect changes following ketamine injection. In the present study, we compared the per cent changes in blood pressure and heart rate from the baseline values as an index of the cardiostimulatory effects of ketamine among the three groups of patients. We also attempted to avoid any other factors that might affect the cardiovascular dynamics of ketamine, such as the addition of epinephrine to our local anesthetic solution or positive-pressure ventilation.<sup>16</sup> Moreover, to ensure a complete segmental blockade, we administered a high concentration of a potent local anesthetic into the epidural space.

The partial blockade of respiratory muscles induced by cervical epidural anesthesia may account for the slight but significant increases in PaCO<sub>2</sub> and decreases in PaO<sub>2</sub> following ketamine in the cervical group. These changes in PaCO<sub>2</sub> and PaO<sub>2</sub> could increase arterial blood pressure and heart rate. However, since we observed less increases in these in the cervical epidural group, we can discount the possibility of an important effect induced by the changes in PaO<sub>2</sub> and PaCO<sub>2</sub> on the results.

In goats, ketamine produced cardiovascular stimulation via excitation of the central sympathetic apparatus, since a cardiovascular stimulating action was produced by injecting very small doses into the carotid artery.<sup>5</sup> Its action is reduced or abolished by general anesthesia.<sup>17</sup> Traber and Wilson<sup>18</sup> concluded in dogs given a β-blocker that sympathetic innervation to the heart must play a small part in the cardiovascular responses to ketamine. Bovill and Dundee<sup>19</sup> also reported similar results in humans. In the present study, we found that the cardiostimulatory effects of ketamine could be attenuated by cardiac sympathectomy. One possible explanation for the discrepancy between their results and ours has been suggested by Hug<sup>20</sup>: the experimental conditions employed by Traber and Wilson<sup>18</sup> and Bovill and Dundee<sup>19</sup> including the dose of propranolol, may have been inadequate to produce complete sympathectomy.

The reasons for the attenuation we observed are speculative. The extent of the block (C<sub>4</sub>-Th<sub>7</sub>) in the cervical group should involve sympathetic efferents to the heart, carotid, and aortic baroreceptors and part of the peripheral vasculature and adrenal glands. Ketamine unlikely affects the baroreceptors,<sup>5,21</sup> and it has been reported that epidural blockade can suppress partially the baroreceptor function by interrupting sympathetic efferent fibers innervating the heart.<sup>10</sup> Thus the

TABLE 2. The Mean Values of Systolic (SAP) and Diastolic (DAP) Arterial Blood Pressure (mmHg) and Heart Rate (HR, Beats/Min) measured 20 Min after Epidural Injection for Baseline Values (B) and after Ketamine Administration in the Three Groups of Patients

	B	1	2	3	4	5	6	7	8	9	10
Cervical	132 ± 15	136* ± 15	146 ± 21	147 ± 22	149 ± 21	147 ± 23	145 ± 24	142 ± 23	140 ± 25	140 ± 25	136* ± 25
SAP Lumbar	140 ± 14	153 ± 23	169 ± 19	173 ± 21	176 ± 20	176 ± 20	175 ± 19	174 ± 17	171 ± 15	171 ± 15	169 ± 14
Control	149† ± 13	177 ± 22	186 ± 25	186 ± 24	186 ± 24	181 ± 24	181 ± 23	178 ± 22	176 ± 20	176 ± 20	174 ± 20
Cervical	71‡ ± 10	76 ± 10	84 ± 13	84 ± 13	84 ± 12	82 ± 12	81 ± 12	80 ± 12	78 ± 13	78 ± 13	76 ± 14
DAP Lumbar	75 ± 9	84 ± 12	94 ± 9	95 ± 10	95 ± 10	94 ± 10	92 ± 11	92 ± 11	89 ± 10	89 ± 10	89 ± 9
Control	79 ± 9	101 ± 11	103 ± 14	102 ± 13	100 ± 13	97 ± 14	96 ± 12	95 ± 12	94 ± 11	94 ± 11	93 ± 12
Cervical	74§ ± 10	79 ± 8	84 ± 10	84 ± 11	84 ± 12	82 ± 12	81 ± 11	80 ± 11	79 ± 12	79 ± 12	79 ± 12
HR Lumbar	83 ± 12	92 ± 17	99 ± 16	102 ± 15	103 ± 15	106 ± 14	106 ± 15	106 ± 15	106 ± 15	106 ± 15	105 ± 15
Control	84 ± 7	93 ± 10	96 ± 9	98 ± 9	99 ± 10	101 ± 11	100 ± 11	100 ± 11	99 ± 11	99 ± 11	99 ± 11

Values are means ± SD.

\* Not significantly different from baseline value in cervical group  $P < 0.01$ .

† §  $P < 0.01$  versus the other two.

‡  $P < 0.01$  versus the control group.

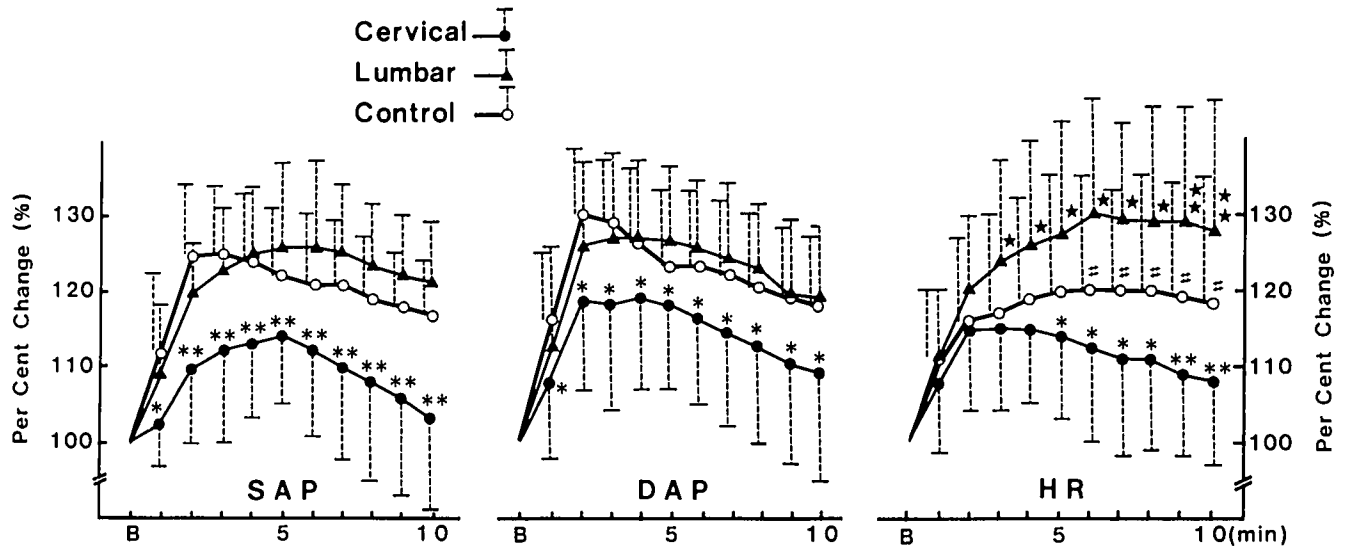


FIG. 1. The per cent changes from the baseline values (B) in systolic (SAP), diastolic (DAP) arterial blood pressure, and heart rate (HR) in the three groups of patients. Values are means  $\pm$  SD. \*  $P < 0.05$  versus the control group. \*\*  $P < 0.01$  versus the control group. #  $P < 0.05$  versus the lumbar group. ★  $P < 0.05$  versus the cervical group. ★★  $P < 0.01$  versus the cervical group.

baroreceptors do not seem to play an important role for the attenuation observed.

Ketamine causes an increase in plasma epinephrine and norepinephrine,<sup>22,23</sup> and a high level of epidural blockade could block catecholamine release from the adrenal glands,<sup>24</sup> which are innervated sympathetically by Th<sub>5</sub>–Th<sub>11</sub>. However, since lumbar sympathectomy (Th<sub>8</sub>–S<sub>2</sub>) induced by lumbar epidural blockade did not modify the increases in arterial blood pressure and heart rate after ketamine when compared with those in the absence of epidural blockade, the blockade of the peripheral vasculature and adrenal glands is unlikely to have affected the present results.

Therefore, the smaller changes in blood pressure and heart rate in the cervical epidural blockade group most likely can be attributed to the cardiac sympathectomy induced by a high level of epidural blockade. One clinical implication of these results may be that ketamine and cervical epidural anesthesia, in combination,

could be indicated for patients with ischemic heart disease undergoing superficial surgery of the thorax.

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TABLE 3. The Blood-Gas Analyses 5 Minutes after the Administration of Ketamine in the Three Groups of Patients

	PH	P <sub>i</sub> O <sub>2</sub> (mmHg)	P <sub>i</sub> CO <sub>2</sub> (mmHg)	BE (mEq/l)
Cervical epidural (n = 18)	7.4 $\pm$ 0	72 $\pm$ 14*	43 $\pm$ 4†	-2 $\pm$ 2
Lumbar epidural (n = 16)	7.4 $\pm$ 0	88 $\pm$ 9	38 $\pm$ 3	-3 $\pm$ 2
Control (n = 16)	7.4 $\pm$ 0	85 $\pm$ 12	38 $\pm$ 4	-3 $\pm$ 2

Values are means  $\pm$  SD.

†  $P < 0.01$  versus the other two.

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