Anesthesiology
81:1454–1460, 1994

Epidural Anesthesia Modifies the Cardiovascular Response to Marked Hypercapnia in Dogs

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Background: **There is little information on the cardiovascular response to marked hypercapnia during epidural anesthesia (EA). Our objective was to assess the potential modifying effects of various levels of EA on this response.**

Methods: **We randomly assigned 48 mongrel dogs anesthetized with halothane (0.5%) to one of four groups: control (n = 12), receiving general anesthesia alone; lumbar (n = 12), also receiving lumbar EA; thoracic (n = 12), also receiving thoracic EA; and thoracolumbar (n = 12), also receiving thoracolumbar EA. During marked hypercapnia (mean arterial CO_2 tension > 90 mmHg for 15 min), we measured hemodynamic parameters and plasma catecholamine concentrations in each group.**

Results: **In the control condition, marked hypercapnia increased cardiac output, reduced systemic vascular resistance, modestly increased mean arterial blood pressure. Lumbar EA abolished the increase in cardiac output, and thoracic and thoracolumbar EA caused CO_2 to depress the cardiac output and the mean arterial blood pressure during marked hypercapnia. The physiologic increase in circulating catecholamines during marked hypercapnia was abolished only in the thoracolumbar EA group.**

Conclusions: **We conclude that sympathetic blockade by EA modifies the cardiovascular response to marked hypercapnia in dogs. Although modest hypoventilation is often effective in treating hypotension during general anesthesia, the current results suggest that hypoventilation may be detrimental during the combination of EA and general anesthesia. (Key words: Anesthetic techniques: epidural anesthesia. Carbon dioxide: hypercapnia. Sympathetic nervous system, catecholamines: epinephrine; norepinephrine.)**

THE cardiovascular responses to hypercapnia result from the direct effects of CO_2 on the myocardium and the peripheral vasculature, and its indirect effects on the sympathetic nervous system.[1] Hypercapnia decreases contractility in isolated heart muscle preparations,[2] produces peripheral vasodilation, and increases catecholamine release.[3] The latter effect is due to the respiratory acidosis during hypercapnia. The net result is hyperdynamic circulation with increases in cardiac output and arterial blood pressure which may counteract the cardiovascular depression of anesthetic agents.[4] Thus, modest hypoventilation is often effective in treating hypotension during general anesthesia. Little information, however, is available on how sympathetic blockade produced by epidural anesthesia (EA) or spinal anesthesia modifies the response to hypercapnia.

Caplan *et al.* reported 14 cases of sudden, unexpected intraoperative cardiac arrest in healthy young patients during spinal anesthesia.[5] In addition to spinal anesthesia, 12 of those patients had received at least one sedative or opioid by the intravenous route. These agents reduce ventilation, particularly in the absence of noxious stimulation such as successful spinal anesthesia.[6] Although immediately after cardiac arrest, the patients lungs were hyperventilation, the mean arterial CO_2 tension (Pa_{CO_2}) was 48 mmHg during cardiopulmonary resuscitation; thus the Pa_{CO_2} would have been expected to be much greater during the impending arrest. The sympathetic blockade produced by EA prevents the physiologic increase in circulating epinephrine and norepinephrine during hypovolemia[7,8] and hypoxia.[9] Thus, we hypothesized that EA prevents the increase in circulating catecholamines and causes cardiovascular depression during hypercapnia. To study this hypothesis, we compared the hemodynamic effects and plasma concentrations of catecholamines in markedly hypercapnic dogs that were administered EA.

Materials and Methods

With the approval of our institutional Animal Care Committee, we conducted this study in 48 healthy adult mongrel dogs of both sexes (weight: 8–13 kg).

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Received from the Department of Anesthesiology and Intensive Care Medicine, Kanazawa University School of Medicine. Accepted for publication July 19, 1994. Supported by the Yonezawa Research Foundation. Presented in part at the 10th World Congress of Anaesthesiologists, the Hague, Netherlands, June 1992.

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The animals were anesthetized with ketamine, 10 mg/kg intramuscularly, and paralyzed with pancuronium bromide. The trachea was intubated and the lungs were mechanically ventilated to maintain a Pa_{CO_2} of approximately 40 mmHg. A lead II electrocardiogram was used to record the heart rate (HR). Pulmonary arterial temperature was maintained between 37.5 and 38.5°C by a heating lamp. Ringer's lactate solution was infused at a constant rate of 10 $ml \cdot kg^{-1} \cdot h^{-1}$. Anesthesia was maintained with 1.5% halothane in O_2 during surgical procedures, which included (1) insertion of a catheter into the right femoral artery to monitor the mean arterial blood pressure (MAP) and to sample blood; (2) insertion of a pulmonary arterial thermodilution catheter (7-French, Baxter Edwards Critical-Care, Irvine, CA) *via* the right femoral vein; and (3) insertion of an epidural catheter, as described below. The two pressure catheters were connected to a polygraphic recorder (Nihon Kohden, Tokyo, Japan) using transducers.

Epidural Anesthesia

The dogs were randomly allocated to one of four groups according to the anesthetic technique: control group (n = 12) receiving halothane anesthesia alone; thoracic group (n = 12), receiving halothane and thoracic EA; lumbar group (n = 12), receiving halothane and lumbar EA; and thoracolumbar group (n = 12), receiving halothane and thoracolumbar EA. An epidural catheter was introduced through a 16-G Tuohy needle into the thoracic epidural space (usually between T8 and T9 in the control and thoracic groups) or into the lumbar epidural space (usually between L6 and L7 in the lumbar and thoracolumbar groups). The epidural space was identified by the loss-of-resistance technique. The catheter was introduced about 2 cm into the epidural space in a cephalad direction and sutured in place. Correct placement of the catheter and spread of contrast material in the epidural space were verified radiographically using either 0.25 ml/kg (thoracic and lumbar groups) or 0.5 ml/kg (thoracolumbar group) of iopamidol, which is nonionic.

Experimental Protocols

After the surgical procedure, the inspired concentration of halothane was decreased to 0.5%, and the animals rested for more than 30 min to allow blood gases and hemodynamic parameters to stabilize. Baseline readings were then taken of HR, MAP, central venous and pulmonary artery wedge pressures, and cardiac output. Cardiac output was measured by the thermodilution technique; each estimate was the mean of three determinations. Cardiac index (CI), stroke index, and systemic vascular resistance index (SVRI) were calculated using standard formulas. The dog's body surface area was calculated[10] as $0.112 \times (\text{body weight})^{2/3}$.

Arterial blood gases and acid–base status were measured with ABL-3 (Radiometer, Copenhagen, Denmark). The gas analyzer was automatically calibrated using two different mixtures of known gases. In addition, assays of plasma concentrations of epinephrine and norepinephrine were performed using high-performance liquid chromatography.[11] Blood samples were collected into chilled tubes, placed immediately in crushed ice, and stored at −40°C until assayed. Intra- and interassay variations were less than 10% for each catecholamine.

After baseline measurements, either 0.25 ml/kg of normal saline (control group) or of 1% mepivacaine (thoracic and lumbar groups) or 0.5 ml/kg of 1% mepivacaine (thoracolumbar group) was injected *via* the epidural catheter over 2 min. Measurements and blood samples were again taken 20 min after the epidural injection.

Hypercapnic Challenge

Hypercapnia was induced by bypassing the CO_2 absorber (soda lime) in the anesthesia circuit system (FO-10, Acoma, Tokyo, Japan), and changing the inspired gas from 100% O_2 to the experimental gases that consisted of a hypercapnic gas mixture (15% CO_2/85% O_2) given for 15 min at a rate of 2 l/min. Hemodynamic measurements and blood samples were taken 5 and 15 min after the initiation of hypercapnic challenge.

Statistical Analysis

Data are expressed as mean ± SD. Between-group differences and within-group changes over time were analyzed using Super ANOVA (Abacus Concepts, Berkeley, CA), a two-way analysis of variance with repeated measures. The level of statistical significance was defined as $P < 0.05$. When the analysis of variance detected a significant between-group difference or within-group change, *post hoc* testing was performed using Bonferroni's method or the least-squares means contrast method, respectively.[12]

Results

There were no significant between-group differences with respect to body weight among the control, lumbar,

thoracic, and thoracolumbar groups (11.2 ± 1.7, 10.8 ± 1.4, 11.4 ± 1.5, and 10.4 ± 1.3 kg, respectively). Radiographic findings indicated that the contrast medium spread from the T9.6 ± 1.8 to S2.4 ± 1.1, from the C5.7 ± 1.4 to L2.4 ± 1.7, and from the C6.9 ± 2.2 to S3.2 ± 1.3 segments, in the lumbar, thoracic, and thoracolumbar groups, respectively.

Blood Gas Analysis

Five min after the start of hypercapnic challenge, mean Pa_{CO_2} increased to 93 to 97 mmHg (table 1). There were no significant differences in *p*H or arterial O_2 tension among the groups at any point during the experimental period.

Hemodynamics

There were no significant differences in baseline hemodynamic variables among the groups (table 2). After epidural injection, only the HR in thoracic and thoracolumbar groups, among the measured parameters of hemodynamics, remained significantly less than in the control group. During hypercapnic challenge, a significantly lower MAP was observed in all three groups receiving EA as compared with the controls. The thoracic and the thoracolumbar groups, but not the lumbar group, demonstrated significantly lower values of HR, CI, and stroke index than the controls. Hypercapnia increased the pulmonary artery wedge and central venous pressures in the lumbar and thoracic groups, but not in the thoracolumbar group. Hypercapnia decreased the SVRI in the lumbar, but not in the thoracic, group. Thus, the hemodynamic response to hypercapnia differed among the three groups receiving EA.

Plasma Concentrations of Catecholamines

There were no significant differences in baseline plasma concentrations of epinephrine and norepinephrine among the groups (table 3). Before the hypercapnic challenge, plasma concentrations of both catecholamines were significantly lower in all groups receiving EA compared with controls. After CO_2 challenge, these concentrations increased progressively in the control, lumbar, and thoracic groups, but not in the thoracolumbar group. Thus, neither lumbar EA nor thoracic EA prevented an increase in plasma catecholamine concentration after 15 min of hypercapnia, in contrast to thoracolumbar EA.

Discussion

In the control condition, marked hypercapnia (mean $Pa_{CO_2} > 90$ mmHg for 15 min) produced an increased CI with a reduced SVRI and a modest increase in MAP. The principal consequence of EA was to modify the cardiac component of cardiovascular effects of hypercapnia. Lumbar EA abolished the usual increase in CI, and in both the thoracic and thoracolumbar EA groups hypercapnia was associated with decreased CI as well as MAP. These cardiac changes were the most impressive and important effects observed to our knowledge. Such observations have not been reported previously.

In humans as in animals, hypercapnia induces both direct and indirect cardiovascular effects. It directly depresses myocardial contractility, dilates the peripheral arterioles, and stimulates the sympathetic nervous system at several levels.[4] Thus, the cardiovascular response to hypercapnia results from a direct effect of CO_2 as well as an indirect effect on the sympathetic nervous system. These responses are reported to be modified during the administration of an anesthetic agent at a concentration which produces anesthesia equal to or greater than that of halothane, enflurane, or isoflurane.[13,14,15] Many reports have described the response during general anesthesia, but few data are available on responses during EA. Sundberg *et al.* observed that in elderly patients, thoracic EA did not modify the responses to mild hypercapnia,[16] but thoracolumbar EA did.[17] However ethical considerations limited the changes in Pa_{CO_2} to only a small increment (less than 5 mmHg). Thus, the effects of EA on cardiovascular responses have not been fully investigated.

In the current study, acute hypercapnia induced a similar grade of respiratory acidosis in all groups of animals; hyperdynamic circulation with increases in MAP and CI was seen only in controls. The hemodynamic responses to EA during normocapnia and halothane anesthesia were minimal except for HR, whereas more marked responses to EA were observed during hypercapnia. Acute respiratory acidosis produces hyperdynamic circulation with increases in cardiac output and arterial blood pressure.[4,18] This effect is induced by the stimulation of the sympathetic nervous system, resulting in a release of catecholamines from sympathetic nerve endings and from the adrenal medulla, which is innervated from segment T4 to L2 in dogs.[19,20] Therefore, the differences in MAP and CI between the animals receiving EA and the controls can be attributed to the preexisting sympathetic blockade by EA. Our findings confirmed that in the case of marked hypercapnia, as with hypotension,[7,8] the sympathetic blockade of these segments prevented the increase of circulating catecholamines due to sympathetic hyper-

Table 1. Blood Gas Analyses in Control (C), Thoracic (T), Lumbar (L), and Thoracolumbar (TL) Groups

			Time after the Start of CO_2 Challenge	
	Baseline	Post-EA	5 min	15 min
pH_a (units)				
C	7.31 ± 0.02	7.32 ± 0.03	7.03 ± 0.03*	6.96 ± 0.04*
L	7.32 ± 0.04	7.33 ± 0.04	7.02 ± 0.04*	6.95 ± 0.03*
T	7.31 ± 0.05	7.35 ± 0.06	7.03 ± 0.03*	6.97 ± 0.03*
TL	7.34 ± 0.06	7.35 ± 0.06	7.02 ± 0.04*	6.96 ± 0.05*
Pa_{CO_2} (mmHg)				
C	38 ± 1	39 ± 2	97 ± 5*	115 ± 9*
L	39 ± 3	38 ± 3	93 ± 6*	110 ± 8*
T	40 ± 2	38 ± 3	96 ± 8*	110 ± 6*
TL	40 ± 3	38 ± 2	95 ± 5*	112 ± 6*
Pa_{O_2} (mmHg)				
C	581 ± 43	548 ± 53	516 ± 41*	495 ± 48*
L	577 ± 34	572 ± 41	490 ± 41*	477 ± 31*
T	587 ± 27	588 ± 36	523 ± 47*	503 ± 38*
TL	584 ± 45	584 ± 45	493 ± 37*	507 ± 37*
HCO_3^- (mEq/L)				
C	19 ± 2	20 ± 2	24 ± 3*	25 ± 2*
L	19 ± 1	19 ± 1	22 ± 2*	23 ± 3*
T	20 ± 2	20 ± 2	24 ± 3*	24 ± 2*
TL	20 ± 2	20 ± 2	23 ± 3*	24 ± 2*

Values are mean ± SD.

Post-EA = 20 min after epidural injection and just before CO_2 challenge. There was no significant between-group difference.

* $P < 0.05$ *versus* post-EA values (within-group).

activity. By withdrawing the inotropic support of the sympathoadrenal system, EA may have unmasked the direct actions of CO_2 on the myocardium and peripheral vasculature.

The hemodynamic response to hypercapnia differed according to the level and extent of sympathetic blockade. The primary cause of the abolition of the usual increase in CI during lumbar EA appeared to involve the myocardium rather than the peripheral vasculature, because the increase in central venous pressure and reduction in SVRI were similar to those in the control condition. The β_2-adrenergic effect of epinephrine could have led to the reduction in SVRI in the two conditions. In addition to ventricular function, venous factors appeared to be the major contributors to severe hypotension with about a 50% reduction in CI during thoracolumbar EA, because minimal changes in pulmonary artery wedge pressure, central venous pressure, and SVRI were observed at the 5th min of hypercapnia. Withdrawal of adrenergic stimulation could increase venous compliance and account for the lack of the usual increase in venous return.

Direct assessment of the extent of the sympathetic blockade is difficult in animal studies. We assumed that sympathetic blockade corresponded to the spread of radiographic contrast material in the epidural space. This assumption is supported by the following rationales: (1) previous studies in awake and trained dogs report that 0.3 to 0.6 ml/kg of local anesthetic was required to provide adequate sensory blockade of the thoracic dermatome in dogs[9,21]; and (2) in contrast to the lumbar group, the finding that the HR had remained significantly lower after epidural injection, and that the normal reflex tachycardia associated with hypotension had been absent in both the thoracic and thoracolumbar groups suggested a sympathetic blockade of the upper fourth or fifth thoracic segments.[21] In addition, we inferred that our results were related to sympathetic blockade rather than to an increase in the plasma mepivacaine concentration. Liu *et al.* reported that, in anesthetized dogs, minimal change were seen in stroke volume, MAP, systemic vascular resistance after the intravenous administration of 3 mg/kg of mepivacaine.[22] The peak concentration of plasma mepivacaine would have been expected to be much lower in the current study than in that of Liu *et al.* We observed differing hemodynamic responses in the lumbar and thoracic groups after epidural injection of the same dose of me-

Table 2. Hemodynamics in Control (C), Lumbar (L), Thoracic (T), and Thoracolumbar (TL) Groups

			Time after Start of CO_2 Challenge	
	Baseline	Post-EA	5 min	15 min
HR (beats/min)				
C	138 ± 13	137 ± 14	133 ± 13	138 ± 20
L	141 ± 13	132 ± 15	127 ± 13	126 ± 16
T	140 ± 21†	110 ± 17*	104 ± 14*	101 ± 13*
TL	143 ± 11†	114 ± 11*	105 ± 14*	97 ± 12*†
MAP (mmHg)				
C	94 ± 13	92 ± 10	94 ± 12	105 ± 12†
L	94 ± 11	86 ± 13	78 ± 12*	83 ± 11*
T	99 ± 13	86 ± 12	66 ± 15*†	67 ± 17*†
TL	98 ± 9	81 ± 10	47 ± 7*†	43 ± 8*†
PAWP (mmHg)				
C	6 ± 2	7 ± 1	11 ± 3†	13 ± 3†
L	7 ± 2	7 ± 2	9 ± 2†	10 ± 2†
T	7 ± 3	7 ± 3	10 ± 3†	11 ± 3†
TL	8 ± 3	7 ± 2	8 ± 3*	9 ± 3*
CVP (mmHg)				
C	4 ± 1	4 ± 1	6 ± 2†	7 ± 2†
L	5 ± 2	4 ± 2	6 ± 1†	7 ± 1†
T	4 ± 1	4 ± 1	6 ± 2†	7 ± 2†
TL	5 ± 1	5 ± 2	5 ± 2	6 ± 2
CI ($L \cdot min^{-1} \cdot min^{-2}$)				
C	3.6 ± 0.5	3.6 ± 0.6	4.7 ± 0.9†	4.8 ± 1.0†
L	3.7 ± 0.5	3.5 ± 0.5	3.7 ± 0.6	3.9 ± 0.7
T	3.9 ± 0.6†	3.2 ± 0.5	2.4 ± 0.8*†	2.7 ± 0.9*†
TL	3.6 ± 0.5†	2.8 ± 0.4	1.7 ± 0.4*†	1.5 ± 0.5*†
SI ($ml \cdot m^{-2}$)				
C	27 ± 4	26 ± 5	35 ± 8†	35 ± 8†
L	26 ± 4	26 ± 4	29 ± 5	31 ± 6
T	28 ± 5	29 ± 4	23 ± 6*†	24 ± 6*†
TL	25 ± 4	25 ± 3	16 ± 4*†	17 ± 4*†
SVRI (10^3 dyne $\cdot s \cdot cm^{-5} \cdot m^2$)				
C	2.0 ± 0.5	2.0 ± 0.4	1.6 ± 0.4†	1.7 ∓ 0.4†
L	2.0 ± 0.3	1.9 ± 0.2	1.6 ± 0.4†	1.6 ± 0.2†
T	2.0 ± 0.4	2.1 ± 0.5	2.0 ± 0.6	1.8 ± 0.5
TL	2.2 ± 0.4	2.2 ± 0.5	2.1 ± 0.7	1.7 ± 0.3†

Values are mean ± SD.

Post-EA = 20 min after epidural injection and just before CO_2 challenge; HR = heart rate; MAP = mean arterial pressure; PAWP = pulmonary artery wedge pressure; CVP = central venous pressure; CI = cardiac index; SI = stroke index; SVRI = systemic vascular resistance index.

* $P < 0.05$ *versus* control group.

† $P < 0.05$ *versus* post-EA values (within-group).

pivacaine. These findings suggest that our observations were related mainly to the influence of sympathetic blockade, and that any direct effect of mepivacaine on the cardiovascular system was minimal.

Halothane given at a concentration of 1% or greater produces myocardial depression, interferes with carotid chemoreceptor control of the circulation,[23] and reduces the hemodynamic response to hypercapnia.[14] The background anesthesia which consisted of 0.5% halothane and pancuronium may have influenced our results. However, the effects of such light anesthesia on reflex control of the circulation seemed to be minor, because the hypercapnic challenge increased the CI, stroke index, and the plasma concentrations of epinephrine and norepinephrine in the control group. Furthermore, the combination of EA and light general anesthesia is increasingly used today.[24,25] Thus our results have clinical relevance, even if background anesthesia had some mitigating influence on our findings.

Table 3. Plasma Catecholamine Concentrations in Control (C), Lumbar (L), Thoracic (T), and Thoracolumbar (TL) Groups

			Time after Start of CO_2 Challenge	
	Baseline	Post-EA	5 min	15 min
Epinephrine (ng/ml)				
C	0.67 ± 0.31	0.61 ± 0.27	0.90 ± 0.48	1.24 ± 0.56†
L	0.67 ± 0.21	0.34 ± 0.19*	0.65 ± 0.4	1.13 ± 0.68†
T	0.58 ± 0.24†	0.26 ± 0.16*	0.48 ± 0.29*	0.78 ± 0.4†
TL	0.54 ± 0.19†	0.04 ± 0.02*	0.09 ± 0.07*	0.15 ± 0.11*
Norepinephrine (ng/ml)				
C	0.18 ± 0.08	0.20 ± 0.09	0.71 ± 0.25†	1.10 ± 0.41†
L	0.22 ± 0.07	0.13 ± 0.07*	0.39 ± 0.17*†	0.74 ± 0.39†
T	0.20 ± 0.08	0.10 ± 0.07*	0.31 ± 0.14*	0.51 ± 0.24*†
TL	0.20 ± 0.07†	0.03 ± 0.01*	0.05 ± 0.02*	0.07 ± 0.03*

Values are mean ± SD.

Post-EA = 20 min after epidural injection and just before CO_2 challenge.

* $P < 0.05$ *versus* control group.

† $P < 0.05$ *versus* post-EA values (within-group).

We conclude that preexisting sympathetic blockade by EA modifies the cardiovascular response to marked hypercapnia in dogs. Furthermore, thoracolumbar EA, which blocks increases in circulating catecholamines in the presence of hypercapnia, may produce marked cardiovascular depression. Although modest hypoventilation is often effective in treating hypotension during general anesthesia, the current results suggest that hypoventilation may be detrimental during the combined administration of epidural and general anesthesia.

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