

Cardiovascular Responses to the Induction of Mild Hypothermia in the Presence of Epidural Anesthesia

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Background: **The combining of epidural anesthesia with general anesthesia impairs central and peripheral thermoregulatory control and therefore is often accompanied by unintended intraoperative hypothermia. However, little is known about the cardiovascular response to hypothermia during combined epidural and general anesthesia. The authors assessed the effects of hypothermia during such combined anesthesia.**

Methods: **The authors randomly assigned 30 mongrel dogs anesthetized with isoflurane (1.0%) to three groups of 10: control, receiving general anesthesia alone; thoracic injection, additionally receiving thoracic epidural anesthesia; and lumbar injection, additionally receiving thoracolumbar epidural anesthesia. Core temperature was lowered from 38.5°C to approximately 34°C (mild hypothermia) using a femoral arteriovenous shunt in an external cool water bath. During hypothermia, the authors measured heart rate, cardiac output, and plasma catecholamine concentrations in each group. Ejection fraction was also measured using echocardiography.**

Results: **Compared with measurements during baseline conditions (general anesthesia alone with no epidural injection and no hypothermia) in the control, thoracic, and lumbar injection groups, the injections followed by hypothermia produced 17, 32, and 41% decreases in heart rate; 22, 32, and 47% reductions in cardiac output; 66, 85, and 92% decreases in the epinephrine concentrations; and 27, 44, and 85% decreases in the norepinephrine concentrations. In contrast, ejection fraction did not change in any group.**

Conclusion: **Mild hypothermia during combined epidural anesthesia and general anesthesia markedly reduced cardiac output in dogs, mainly by decreasing heart rate.**

INTRAOPERATIVE hypothermia is a common problem in anesthetic practice. The degree of hypothermia depends on many factors, such as patient age, ambient operating room temperature, type of surgery, and anesthetic technique.[1–4] Combination of epidural anesthesia with general anesthesia impairs central and peripheral thermoregulatory control and therefore often is accompanied by unintended intraoperative hypothermia.[5] Many reports have described cardiovascular responses to hypothermia during general anesthesia,[6,7] but little information is available concerning responses during combined epidural and general anesthesia. Hypothermia has adverse physiologic effects, including decreases in heart rate and cardiac output. In addition, thoracolumbar epidural anesthesia has been shown to attenuate the catecholamine response after perioperative hypothermia.[8] We therefore hypothesized that hypothermia would produce rather large decreases in heart rate and cardiac output during epidural and general anesthesia. To test this hypothesis, we evaluated hemodynamic changes and plasma concentrations of catecholamines in mildly hypothermic dogs in which epidural anesthesia was administered together with general anesthesia.

Materials and Methods

After approval from the institutional Animal Care and Use Committee of Kanazawa University School of Medicine, we conducted this study in 30 healthy, adult mongrel dogs of both sexes (weight: 8–15 kg). The animals were anesthetized with ketamine (10 mg/kg intramuscular) and paralyzed using succinylcholine. The trachea was intubated, and the lungs were ventilated mechanically to maintain an arterial carbon dioxide tension between 35 and 45 mmHg. A lead II electrocardiograph was used to record heart rate (HR). Pulmonary arterial temperature was maintained at approximately 38.5°C by a heating lamp. Lactated Ringer's solution was infused at a constant rate of 5 $ml \cdot kg^{-1} \cdot h^{-1}$. Anesthesia was maintained with 2.0% isoflurane in oxygen during surgical procedures, which included insertion of a catheter into the right femoral artery to monitor the mean arterial blood pressure (MAP) and to sample blood; insertion of a pulmonary arterial thermodilution catheter (7 French; Baxter Edwards Critical Care, Irvine, CA) *via* the right femoral vein; insertion of shunt catheters into the left femoral artery and vein to induce hypothermia, as described herein; and insertion of an epidural catheter, as described herein. The two pressure catheters were connected with transducers that supplied input to a polygraphic recorder (Nihon Kohden, Tokyo, Japan).

Epidural Anesthesia

The dogs were randomly allocated to three groups of 10 dogs each: a control group, receiving isoflurane anesthesia alone; a thoracic injection group, receiving isoflurane and thoracic epidural anesthesia; and a lumbar injection group, receiving isoflurane and thoracolumbar epidural anesthesia. An epidural catheter was inserted through a 16-gauge Tuohy needle either into the thoracic epidural space (usually between T8 and T9) in the control and thoracic injection groups or into the lumbar

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epidural space (usually between L6 and L7) in the lumbar injection group. The epidural space was identified by loss of resistance to the advancing needle. The catheter was inserted approximately 2 cm into the epidural space in a cephalad direction and then sutured in place. Correct placement of the catheter, permitting spread of nonionic contrast material within the epidural space, was verified radiographically using either 0.2 (thoracic injection group) or 0.5 ml/kg (lumbar injection group) iopamidol.

Experimental Design and Protocols

After the surgical procedure, animals were placed in the left lateral decubitus position and kept in this posture during the entire study period. The inspired concentration of isoflurane was decreased to 1.0%, and at least 30 min was allowed for blood gases and hemodynamic parameters to stabilize. Baseline readings then were taken of HR, cardiac output, MAP, and central venous pressure. Cardiac output was measured by thermodilution; each estimate was the mean of three determinations. Cardiac index (CI), stroke index, and systemic vascular resistance index were calculated using standard formulas. The body surface area of the dog was calculated[9] as $0.112 \times (\text{body weight})^{2/3}$.

Arterial blood gases were measured with an automated analyzer (ABL-3; Radiometer, Copenhagen, Denmark). In addition, plasma concentrations of epinephrine and norepinephrine were assayed by high-performance liquid chromatography.[10] Blood samples were collected and placed in chilled tubes, placed immediately in crushed ice, and stored at −40°C until assayed. Intra- and interassay variation was less than 10% for each catecholamine.

After baseline measurements, 0.2 ml/kg normal saline (control group), 0.2 ml/kg mepivacaine, 1% (thoracic injection group), or 0.5 ml/kg mepivacaine, 1% (lumbar injection group), was injected *via* the epidural catheter over 2 min. Measurements and blood samples were repeated 30 min after the epidural injection.

Echocardiographic Measurements and Calculations

Echocardiographic evaluations were performed according to the recommendations of The Specialty of Cardiology of the American College of Veterinary Internal Medicine.[11] The echocardiograph (SSA-250A; Toshiba, Tokyo, Japan) was equipped with a 5-MHz transducer. The transducer was placed at the left sternal border between the fifth to seventh intercostal spaces. Standard left apical four-chamber views were obtained. The area (Ad and As) and the length of the long axis (Ld and Ls) of the left ventricle were measured at end-diastole and end-systole, respectively. All measurements were obtained for at least three consecutive cardiac cycles. No cardiac cycles that followed left ventricular asymmetries or arrhythmias were analyzed. Each estimate was the mean of three determinations. End-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction were calculated according to standard formulas[12]: $EDV = 8Ad^2/3\pi Ld$; $ESV = 8As^2/3\pi Ls$; and ejection fraction = (EDV − ESV)/EDV. Cardiac pump function and preload were estimated as the ejection fraction and EDV/body surface area, respectively.[13]

Cooling Procedure

Mild hypothermia was induced using an external shunt between the femoral artery and vein. The shunt was filled with 35 ml hydroxyethyl starch. After administration of low-molecular-weight heparin (100 IU/kg intravenous), the shunt was opened. Blood was circulated, at a flow rate of 20 ml/min using a roller pump (Masterflex; Cole-Parmer, Barrington, IL), with the shunt coil immersed in a 20°C water bath, aiming for an end point pulmonary artery temperature of 34°C. In this manner, the temperature was manipulated without affecting total blood volume. After reaching 34°C, the shunt was closed. After the cardiovascular system of the animal was allowed to equilibrate for 30 min, hemodynamic measurements and blood samples were obtained.

Statistical Analysis

Data are expressed as mean ± SD. Between-group differences and within-group changes over time were analyzed using a two-way analysis of variance with repeated-measures (Super ANOVA; Abacus Concepts, Berkeley, CA). 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 the Bonferroni method or the least-squares means contrast method, respectively.[14]

Results

No significant differences were noted with respect to body weight between the control, thoracic injection, and lumbar injection groups (10.3 ± 2.1, 10.2 ± 2.0, and 10.4 ± 2.2 kg, respectively) or the total time to reach a pulmonary artery temperature of 34°C (40 ± 7, 39 ± 10, and 37 ± 7 min, respectively). Radiographic findings indicated that the contrast material extended from C6 ± 1 to T11 ± 1 and from the C6 ± 1 to S2 ± 1 segments in the thoracic injection and lumbar injection groups, respectively. Arterial carbon dioxide and oxygen tension did not differ significantly between the three groups at any point during the experimental period.

Hemodynamics

No significant differences in baseline hemodynamic variables were evident between the groups (table 1). After epidural injection, HR in the thoracic and lumbar

Table 1. Hemodynamics in Control (C), Thoracic Injection (T), and Lumbar Injection (L) Groups

	Baseline	Epidural Injection	Hypothermia
Heart rate (beats/min)			
C	137 ± 13	132 ± 16	114 ± 19
T	136 ± 12*	113 ± 8†	92 ± 7*†
L	137 ± 17*	111 ± 13†	81 ± 15*†
Cardiac index ($l \cdot min^{-1} \cdot m^{-2}$)			
C	3.7 ± 0.9	3.5 ± 0.8	2.9 ± 0.8
T	3.4 ± 0.9	2.6 ± 0.9	2.3 ± 0.6
L	3.4 ± 0.7*	2.4 ± 0.5†	1.8 ± 0.4*†
Mean arterial pressure (mmHg)			
C	110 ± 11	108 ± 13	111 ± 16
T	115 ± 18	97 ± 13	88 ± 12
L	116 ± 16*	90 ± 12†	72 ± 12*†
Stroke index (ml/m^2)			
C	28 ± 8	27 ± 7	26 ± 7
T	25 ± 8	23 ± 9	25 ± 7
L	25 ± 4	22 ± 4	23 ± 5
Ejection fraction (%)			
C	49 ± 9	51 ± 6	50 ± 6
T	46 ± 12	46 ± 14	42 ± 11
L	52 ± 8	52 ± 8	51 ± 9
EDV/BSA (ml/m^2)			
C	50 ± 11	50 ± 10	45 ± 10
T	48 ± 10	46 ± 9	43 ± 10
L	52 ± 5	46 ± 6	45 ± 7
Central venous pressure (mmHg)			
C	3.8 ± 0.9	3.7 ± 0.8	3.5 ± 0.9
T	3.4 ± 0.9	3.3 ± 0.8	3.1 ± 0.7
L	3.7 ± 1.0	3.5 ± 0.9	3.6 ± 1.0
SVRI (10^3 dyne $\cdot$ s $\cdot$ $cm^{-5} \cdot m^2$)			
C	2.4 ± 0.8	2.5 ± 0.7	3.2 ± 1.0
T	2.7 ± 0.6	3.1 ± 0.7	3.0 ± 0.7
L	2.8 ± 0.9	3.0 ± 0.9	3.1 ± 0.8

Values are mean ± SD.

* $P < 0.05$ versus epidural injection values (within-group). † $P < 0.05$ versus control group.

EDV/BSA = end-diastolic volume/body surface area; SVRI = systemic vascular resistance index.

injection groups and CI and MAP in the lumbar injection group decreased compared with the those of the control group. During hypothermia, these parameters remained significantly lower than those in the controls. Compared with measurements during baseline conditions (general anesthesia alone with no epidural injection and no hypothermia) in the control, thoracic, and lumbar injection groups, epidural injections followed by mild hypothermia produced 17, 32, and 41% decreases in HR; 22, 32, and 47% reductions in CI; and 0, 23, and 38% decreases in MAP, respectively. Thus, the response of HR, CI, and MAP to hypothermia differed markedly among the three groups. In contrast, stroke index, ejection fraction, EDV/body surface area, central venous pressure, and systemic vascular resistance index did not differ significantly among the three groups at any point during the experimental period.

Plasma Concentrations of Catecholamines

No significant differences were present in baseline plasma concentrations of epinephrine and norepinephrine among the groups (table 2). After epidural injection but before hypothermia, plasma concentrations of both catecholamines were lower in the lumbar injection group than in the other two groups. During hypothermia, although the decrease in the lumbar injection group was not significant, the epinephrine concentration decreased in all groups. In contrast, the norepinephrine concentration was unchanged by hypothermia in all groups. Thus, the effect of the combination of epidural anesthesia and hypothermia on the epinephrine concentrations were greater than corresponding effects on norepinephrine. Compared with measurements during baseline conditions in the control, thoracic, and lumbar injection groups, epidural injection followed by hypothermia produced 66, 85, and 92% decreases in the epinephrine concentrations and 27, 44, and 85% decreases in the norepinephrine concentrations.

Discussion

Unanesthetized patients do not become hypothermic even when exposed to a cool operating room environment because thermoregulatory vasoconstriction or shivering maintains core temperature.[15] In contrast,

Table 2. Plasma Catecholamine Concentrations in Control (C), Thoracic Injection (T), and Lumbar Injection (L) Groups

	Baseline	Epidural Injection	Hypothermia
Epinephrine (pg/ml)			
C	410 ± 170	510 ± 260	140 ± 90*
T	520 ± 210	330 ± 140	80 ± 50*
L	510 ± 300	110 ± 170†	40 ± 60
Norepinephrine (pg/ml)			
C	150 ± 70	160 ± 90	110 ± 90
T	160 ± 70	120 ± 70	90 ± 80
L	200 ± 90	40 ± 40†	30 ± 30

Values are mean ± SD.

* $P < 0.05$ versus epidural injection values (within-group). † $P < 0.05$ versus control group.

anesthetized patients have been shown in several studies to become hypothermic *via* impairment of such thermoregulatory control mechanisms.[16] Core temperature frequently decreases more than 1°C during the first hour of general anesthesia.[17] During epidural anesthesia alone, hypothermia is as common and nearly as severe as it is during general anesthesia.[2] Joris *et al.*[5] demonstrated that thoracic epidural anesthesia reduced the threshold for thermoregulatory vasoconstriction and directly inhibited vasoconstriction in the area of sympathetic blockade. In their study, mean esophageal temperature decreased from 36.6°C to 35.1°C at 3 h after anesthesia in patients given enflurane anesthesia alone, but decreased from 36.5°C to 33.9°C in those given a combination of thoracic epidural anesthesia with enflurane anesthesia. MAPs were similar in the two groups before surgery, but significantly lower during surgery in the patients given the combined anesthesia. Therefore, hypothermia is not only more likely during combined epidural and general anesthesia, but our findings and those of Joris *et al.* suggest that its hemodynamic consequences are more severe.[5]

In the control group, mild hypothermia (approximate core temperature: 34°C for 30 min) produced a 17% decrease in HR, a 22% reduction in CI, and no decrease in MAP. In contrast, in the lumbar injection group, mild hypothermia produced a 41% decrease in HR, a 47% reduction in CI, and a 38% decrease in MAP. Therefore, cardiovascular alterations with mild hypothermia during general anesthesia alone were minor, whereas more marked changes with mild hypothermia were observed during combined thoracolumbar epidural anesthesia and general anesthesia. Despite the profound decrease of MAP in the lumbar injection group, HR remained significantly lower than before hypothermia; the normal reflex tachycardia associated with hypotension was absent. The direct effect of hypothermia on HR, the extensive sympathetic blockade produced by thoracolumbar epidural anesthesia, or both could have exerted exaggerated negative chronotropic effects. Although hypothermia may create a favorable perioperative state in terms of reduced metabolic requirements,[18] it has adverse physiologic effects, including decreases in HR and cardiac output and a leftward shift in the hemoglobin oxygen saturation curves. These factors result in decreased oxygen delivery to tissues and an increased incidence of early postoperative myocardial ischemia.[1,2,6,19] In unanesthetized subjects within the temperature range in which the response to hypothermia is effective (to approximately 33°C), HR, cardiac output, and MAP increase along with shivering and increased sympathetic stimulation. When sympathetic stimulation is prevented by anesthesia or when core temperature decreases below this range, these parameters decrease as core temperature continues to decrease.[6,7] Miao *et al.*[20] found that using guinea pig papillary muscle, myocardial contractile depression by volatile anesthetics was greater at 30 than at 37°C. Therefore, one would surmise that, with hypothermia, negative inotropic effects of anesthesia would be greater than those observed at normothermia.

In agreement with previous reports, hypothermia produced a gradual decrease in HR, CI, and MAP, but only minimal changes were observed in cardiac pump function (estimated by stroke index and ejection fraction), preload (estimated by central venous pressure and EDV/body surface area), or afterload (estimated by systemic vascular resistance index) in any group. Tveita *et al.*[7] found that, in dogs anesthetized with pentobarbital, marked hypothermia (core temperature approximately 25°C) produced a 60% decrease in HR, a 63% reduction in cardiac output, and a 50% decrease in MAP. In their study, stroke index and systemic vascular resistance index remained unchanged during cooling, despite a gradual reduction in cardiac output. Carli *et al.*[8] observed that, in patients with mild hypothermia (< 35°C), thoracic epidural anesthesia produced a 27% decrease in systolic arterial pressure without changes in central venous pressure. Thus, neither myocardium nor peripheral vasculature seems to be the primary cause of hypotension in the studies of Carli *et al.*[8] and Tveita *et al.*[7] The current results indicate that HR was the major contributor to the decreases in CI and MAP even during combined epidural and general anesthesia.

Before induction of hypothermia, the plasma epinephrine concentration decreased more after the lumbar in-

jection than after the thoracic injection. The epinephrine concentration is mainly influenced by its release from the adrenal medulla, which is innervated from segments T4 to L2.[21] Therefore, the difference in the epinephrine concentration between the thoracic and lumbar injection groups can be attributed to different extent of sympathetic blockade.[22] During hypothermia, the epinephrine concentration decreased significantly in the control and thoracic injection groups. There was a trend, however not significant, in the decrease of the concentration in the lumbar injection group. We believe this was only because the concentration had already decreased so much with the lumbar injection alone. Conversely, the norepinephrine concentration was unchanged. Despite several previously reported clinical studies,[8,23] questions remain about the effect of general anesthesia on catecholamine response to mild hypothermia, which has been reported to be increased[8] or unchanged.[23] In contrast to previously reported results, we found a decrease in plasma epinephrine concentration. Experimental design differed importantly between the previous studies[8,23] and ours, including type of species studied (humans *versus* dogs) and unintended *versus* induced hypothermia. In addition, we obtained measurements in the absence of surgical trauma, whereas surgical trauma was a factor in previous clinical investigations performed in the intra- or postoperative period.

The main limitation of our study was that mechanisms of temperature regulation differ in dogs and humans and therefore has only limited applicability to hypothermia in humans. Many reports have described cardiovascular responses to hypothermia during general anesthesia alone, but little has been known regarding responses during combined epidural and general anesthesia. Joris *et al.*[5] observed that the threshold for thermoregulatory vasoconstriction was lower during combined epidural and general anesthesia in humans than during general anesthesia alone, but these authors did not mention the cardiovascular response. Thus, our results have clinical relevance, even though species differences must be considered in interpreting our findings.

In summary, the current study showed that mild hypothermia markedly decreased HR, CI, and MAP when epidural and general anesthesia were combined. Hypothermia is aggravated by a combination of central and peripheral thermoregulatory impairment during combined epidural and general anesthesia. The current findings therefore suggest that, to prevent hypothermia-induced cardiovascular depression, particularly close attention should be given to monitoring and management of temperature in patients given combined epidural and general anesthesia.

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