Systemic, but not pulmonary, hemodynamics are depressed during combined high thoraco-cervical epidural and general anesthesia in dogs

[L'hémodynamique générale, mais non pulmonaire, est déprimée pendant l'anesthésie combinée péri-durale haute thoraco-cervicale et générale chez les chiens]

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Purpose: An epidural block is frequently combined with general anesthesia. Both systemic and pulmonary hemodynamics may be affected by high epidural anesthesia and the combined general anesthetic. These effects were investigated in a canine model.

Methods: Systemic and pulmonary hemodynamics during a combined high thoraco-cervical epidural and general anesthesia were studied in dogs; the animals were anesthetized with propofol, 10 mg·kg⁻¹·hr⁻¹, or 2% sevoflurane, and then 1% mepivacaine, 5 mL, was injected epidurally between T1 and T2. Cardiac output (CO), pulmonary capillary wedge pressure (PCWP), pulmonary arterial pressure (PAP), mean arterial pressure (MAP), central venous pressure (CVP), electrocardiogram, and arterial and mixed venous gases were monitored for over 90 min after epidural mepivacaine. The interval between sevoflurane and propofol studies was two hours.

Results: Baseline measurement of MAP with sevoflurane anesthesia was significantly lower ($P < 0.05-0.01$) at every time point than with propofol anesthesia. After epidural mepivacaine (C1-T7/8 blockade), MAP ($P < 0.05-0.01$), CO ($P < 0.05-0.01$), and heart rate ($P < 0.05-0.01$) decreased significantly during both propofol and sevoflurane anesthesia. In the sevoflurane group, stroke volume decreased significantly ($P < 0.05-0.01$) but recovered; however, MAP ($P < 0.01$) and CO ($P < 0.05$) did not recover 90 min after the injection. Mean CVP and systemic vascular resistance were not altered. There were no changes in mean PAP, mean PCWP, and pulmonary vascular resistance.

Conclusion: A combined high thoracic/general anesthesia depressed systemic hemodynamics, whereas the pulmonary circulation was not affected. The extent of the depression varied with the general anesthetics used, sevoflurane and propofol.

Objectif : Un bloc péri-dural est souvent combiné à l'anesthésie générale. L'hémodynamique générale et pulmonaire peut subir les effets de l'anesthésie péri-durale haute et générale combinée. Ces effets ont été vérifiés chez un modèle canin.

Méthode : L'hémodynamique générale et pulmonaire a été étudiée chez des chiens pendant une anesthésie péri-durale haute thoraco-cervicale et générale combinée ; les animaux ont été anesthésiés avec 10 mg·kg⁻¹·hr⁻¹ de propofol ou du sévoflurane à 2 %, suivi de mépivacaïne à 1 % donnée par injection péri-durale entre T1 et T2. Le débit cardiaque (DC), la pression capillaire pulmonaire bloquée (PCPB), la tension artérielle pulmonaire (TAP), la tension artérielle moyenne (TAM), la pression veineuse centrale (PVC), l'électrocardiogramme et la gazométrie artérielle et du sang veineux mêlé ont été surveillés pendant 90 min après l'administration péri-durale de mépivacaïne. Les données sur le sévoflurane et le propofol ont été prises à deux heures d'intervalle.

Résultats : Pour tous les temps de mesure, la TAM de base avec le sévoflurane a été significativement plus basse ($P < 0,05-0,01$) qu'avec le propofol. Après la mépivacaïne péri-durale (bloc C1-T7/8), la TAM ($P < 0,05-0,01$), le DC ($P < 0,05-0,01$) et la fréquence cardiaque ($P < 0,05-0,01$) ont baissé significativement pendant l'anesthésie au propofol ou au sévoflurane. Dans le groupe sévoflurane, le volume d'éjection a diminué de façon significative ($P < 0,05-0,01$) mais s'est rétabli ; cependant, la TAM ($P < 0,01$) et le DC ($P < 0,05$) ne sont pas rétablis 90 min après l'injection. La PVC moyenne et la résistance vasculaire générale n'ont pas été touchées. Il n'y a pas eu de modification de la TAP, de la PCPB moyenne ou de la résistance vasculaire pulmonaire.

Conclusion : Une anesthésie thoracique haute et générale combinée déprime l'hémodynamique générale, mais la circulation pulmonaire n'est pas affectée. L'étendue de la dépression varie selon l'anesthésique utilisé, le sévoflurane ou le propofol.

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Accepted for publication November 29, 2002.

Revision accepted February 12, 2003.

A combination of epidural and general anesthesia is now widely used. Combined anesthesia has been suggested to attenuate the stress response during surgery compared with general anesthesia alone,¹ to decrease postoperative pain and facilitate early extubation in aortic surgery,² to stabilize hemodynamics perioperatively and reduce postoperative morbidity in abdominal aortic surgery,³ and to decrease intraoperative blood loss in hip arthroplasty.⁴ In addition, the epidural catheter is available for both preemptive analgesia⁵⁻⁷ and post-surgical analgesia.⁸

Epidural anesthesia produces not only a nociceptive but also a sympathetic blockade. The cervico-thoracic viscera (C1–T5) and upper limbs (C4–T2) are innervated by the upper spinal cord, while the abdominal viscera (T5–L2) and lower limbs (L2–S3) receive sympathetic supply from the lower spinal cord.⁹ Vascular beds included in the former may be smaller than those in the latter. Thus, hemodynamic changes may differ between spinal blockade of upper and lower segments.

During lower-segment spinal and epidural anesthesia, hypotension is produced mainly by increasing the capacity of vascular beds (a decrease in systemic vascular resistance (SVR) due to sympathetic blockade),¹⁰ as well as the subsequent decreasing preload. However, the heart is innervated via the cardiac nerve originating in the upper spinal segments (T1–T4).⁹ High-segment spinal and epidural anesthesia (C1–T6) may result in decreased cardiac function predominantly rather than a decrease in SVR. In addition, the lungs and bronchi are innervated via the thoracic spinal segments (T1–T6),⁹ and pulmonary hemodynamics may be influenced by high-segment epidural anesthesia.

Volatile anesthetics such as sevoflurane or *iv* anesthetics such as propofol are used for general anesthesia, and their hemodynamic effects vary. At a clinical dosage, sevoflurane depresses hemodynamics,¹¹⁻¹³ whereas hemodynamic depression of propofol is mild.^{13,14} Therefore, hemodynamics during combined anesthesia may vary when different anesthetics are administered. Thus, systemic and pulmonary hemodynamics during combined high thoraco-cervical epidural and general anesthesia were studied in dogs anesthetized with sevoflurane or propofol. The results may give some suggestion for anesthetic management of patients with pulmonary disorders, such as pulmonary hypertension (PH) and chronic obstructive pulmonary diseases (COPD).

Methods

We obtained approval from the Institutional Committee for Animal Investigation. Twenty-five

female Beagles were randomly assigned to four groups: 13 dogs were anesthetized with propofol in combination with epidural anesthesia (PE group, $n = 7$) or a placebo (PC group, $n = 6$); 12 dogs were anesthetized with sevoflurane in combination with epidural anesthesia (SE group, $n = 6$) or a placebo (SC group, $n = 6$). The dogs used were similar in body weight and length, 9.0–10.0 kg and 0.49–0.52 m (from the protrusion to the hip), to standardize the amount of local anesthetic injected into the epidural space.

Anesthesia was induced with thiopental sodium, 300 mg *iv*, the trachea intubated, and the lungs ventilated mechanically with air or air-oxygen at a final concentration of 21% oxygen. General anesthesia was maintained with propofol infused at a rate of 10 mg·kg⁻¹·hr⁻¹ (Infusion Pump 201, ATOM, Tokyo, Japan) or with sevoflurane (Sevotec 3, Datex-Ohmeda, Helsinki, Finland) at an end-tidal concentration of 2% (ULT-1, Capnomac Ultima, Datex-Ohmeda, Helsinki, Finland). Ventilation was set at an end-tidal CO₂ (ETCO₂) of 35–40 mmHg. Throughout the experiment, the animal was placed in the right lateral position, and rectal temperature was maintained between 36.5°C and 37.5°C using a warming blanket. All settings were maintained constant throughout the experiment.

The right saphenous vein was cannulated for the infusion of lactated Ringer's solution (5 mL·kg⁻¹·hr⁻¹), and vecuronium bromide at a rate of 0.1 mg·kg⁻¹·hr⁻¹. A Swan-Ganz catheter (93A-124-5F, Baxter, Deerfield, USA) was inserted into the pulmonary artery via the left femoral vein to monitor mean pulmonary arterial pressure (PAP), mean pulmonary capillary wedge pressure (PCWP), and to measure cardiac output (CO; average of triplicate measurements) by thermodilution (OT-53S, Fukuda Denshi, Tokyo, Japan). A catheter was inserted into the left femoral artery to measure mean arterial pressure (MAP). A catheter was introduced near the right atrium via the right femoral vein to measure mean central venous pressure (CVP). Each catheter was connected to a pressure transducer (Uniflow, Baxter, Deerfield, USA). Waveforms of the electrocardiogram, MAP, PAP, PCWP, and CVP were monitored on an electrical display (Polygraph System, Nihon Kohden, Tokyo, Japan). Mixed venous and arterial blood was sampled to analyze blood gases (Stat Profile 5, Nova Biochemical, Waltham, USA). Stroke volume, SVR and pulmonary vascular resistance (PVR) were obtained by calculation.

The third thoracic spinal process was removed surgically. A Teflon catheter (0.8-mm diameter, without a side orifice) was inserted into the epidural space, and the catheter tip was placed at the T1 spinal level. The

area surrounding the catheter was firmly closed with bone wax. Five millilitres of 1% mepivacaine, or 5 mL of saline, were injected epidurally through the catheter.

The hydrostatic baseline for measurements of MAP, PAP, and CVP was set at the midline of the thorax. Arterial and mixed-venous blood samples were harvested in heparinized syringes. Each variable was recorded before (zero) and ten, 20, 30, 45, 60 and 90 min after the epidural block. Blood was analyzed immediately after sampling. No other drugs were used during the experiment. The interval between sevoflurane and propofol studies was two hours.

After the experiments, 5 mL of 0.004% indigo-carmin solution were injected into the epidural space. The animals were killed by exsanguination and laminectomy was performed. Spinal spread of the dye was recorded.

Statistics

We determined sample size as follows: to achieve 80% power to detect a difference of 40 mmHg in MAP and a difference of 0.5 L·min⁻¹ in CO between epidural mepivacaine and saline groups with $\alpha = 0.05$ (two-tailed), four animals per group were shown to be necessary. Thus six or seven animals were included in each group. Data were analyzed using a two-way repeated-measures analysis of variance (ANOVA) in combination with Dunnett's test. A $P < 0.05$ was considered significant. Values are expressed as means $\pm$ standard deviation (SD).

Results

Spread of dye in the epidural space

The dye spread from C1 to T7 or T8 spinal segments in all animals. The region from T7 or T8 to T12 was coloured in part.

Systemic hemodynamics

Baseline MAP in the SE and SC groups were significantly lower than in the PE and PC groups, respectively, at every time point (10–90 min; Figure 1). In the SE and PE groups, MAP decreased significantly after epidural mepivacaine: in the PE group MAP recovered after 90 min, whereas recovery was not observed in the SE group (Figure 1). Heart rate (HR) decreased after epidural mepivacaine (10–60 min) in the PE and SE groups (Figure 1).

In the PE and SE groups, CO was significantly reduced compared with baseline. The reduction in CO in the PE group recovered after 90 min, whereas recovery was not observed in the SE group. Meanwhile, stroke volume in the SE group decreased significantly 20, 30, and 45 min after epidural mepi-

FIGURE 1 Mean arterial pressure (MAP), pulmonary artery pressure (PAP) and heart rate (HR) with combined high thoracic-cervical epidural and general anesthesia. • = propofol in combination with epidural anesthesia and sevoflurane in combination with epidural anesthesia (PE and SE groups); ° = placebo combination and sevoflurane combination (PC and SC groups). Values are mean $\pm$ SD. * $P < 0.05$ and ** $P < 0.01$ compared with the values before epidural injection (0 min). † $P < 0.05$ and †† $P < 0.01$ compared with the respective control groups. ‡ $P < 0.05$ and ‡‡ $P < 0.01$ for comparison between the PC and SC, as well as PE and SE groups.

vacaine, whereas no significant decrease in stroke volume was observed in the PE group (Figure 2).

No significant changes in CVP or SVR were noted in the PE and SE groups (Figure 3). Also, there were no significant changes in any systemic hemodynamic variables of the PC and SC groups after epidural saline (Figures 1 to 3).

Pulmonary hemodynamics

The baseline PAP did not vary significantly among the four groups (Figure 1). In addition, no changes in PAP, PCWP, or PVR were observed in the four groups after epidural anesthesia (Figures 1 and 4).

Blood gas analyses

There were no significant differences in baseline values of arterial and mixed-venous pH, PO₂, and PCO₂

FIGURE 2 Cardiac output (CO) and stroke volume. Symbols are the same as in Figure 1. Values are mean $\pm$ SD.

FIGURE 3 Mean central venous pressure (CVP) and systemic vascular resistance (SVR). Symbols are the same as in Figure 1. Values are mean $\pm$ SD.

among the four groups (Tables I and II, available as additional material on the Journal's web site at www.cja-jca.org). Values of arterial blood gases in the four groups did not change significantly throughout the study (Table I). Mixed-venous PO_2 decreased significantly in both the PE and SE groups, although values for both control groups were unchanged. Mixed-venous pH and PCO_2 in the four groups did not change significantly after the epidural block (Table II).

Discussion

The present study shows that systemic, but not pulmonary, hemodynamics are depressed during combined high thoraco-cervical epidural and general

FIGURE 4 Pulmonary capillary wedge pressure (PCWP), and pulmonary vascular resistance (PVC). Symbols are the same as in Figure 1. Values are mean $\pm$ SD.

anesthesia. Interestingly, CO decreased but CVP and SVR did not change after upper spinal blockade. This suggests that the hypotension seen in this study is attributable to a decrease in CO, which may have been induced by blockade of the cardiac plexus. During lower spinal blockade by lumbar epidural and spinal anesthesia, previous studies have found a decrease in SVR (or total peripheral resistance).¹⁰ Thus, the underlying mechanisms for the observed hemodynamic changes between upper and lower spinal blockade are different.

Based on the observed spread of dye, our animals had a complete blockade from the C1 to the T7/8 spinal segments (C1-T7/8 blockade), whereas the lower spinal cord (T8/9-S5) was unblocked. The epidural dye used in this study, indiocarmine, has the same gravity and viscosity as local anesthetics.¹⁵ Consequently, spread in the epidural space is expected to be similar.

Taniguchi *et al.*¹⁶ demonstrated that when an epidural anesthesia is limited to certain segments, the unblocked segments can augment sympathetic activity in a compensatory manner. Magnúsdóttir *et al.*¹¹ have shown that high thoracic epidural anesthesia does not inhibit sympathetic nerve activity in the lower extremities. Low thoraco-lumbosacral sympathetic blockade causes visceral and lower limb vasodilatation with a large vascular capacity and the subsequent reduction of venous return, which may evoke tachycardia. However, HR did not increase in this study. Contrarily, cardiac plexus blockade in this study resulted in bradycardia. Therefore, the lower spinal segments may have maintained a near normal sympathetic tone, including vasomotor constriction of splanchnic organs and leg muscles with a large vascular capacity.

In this study, the epidural catheter was placed at the T1 level, which is very high compared to levels used in clinical practice for abdominal or lower limb surgery. Lower thoraco-lumbosacral epidural anesthesia may not cause cardiac plexus blockade but may block the splanchnic nerves and lumbosacral plexus, decreasing SVR and venous return. When a large amount of local anesthetic is injected, the anesthetic may easily extend to the T1 level. In such circumstances, thoraco-lumbosacral blockade may be induced simultaneously. Thus, the fall in MAP may be more profound.

In this study, the depth of propofol and sevoflurane anesthesia may not have been equivalent, but typical canine dosages were used for both drugs. However, hemodynamic depression with sevoflurane at a clinical dosage is important,¹²⁻¹⁴ whereas hemodynamic depression with propofol at a clinical dosage is mild.^{14,17} This may explain, in part, why the decrease in MAP was more profound in the SE group than the PE group, the recovery of MAP and CO was delayed, and stroke volume was reduced in the SE group.

Comparing between these and previous results,⁹ changes in MAP, CO, HR, and stroke volume with high thoracic epidural anesthesia alone appear to be smaller than changes when combined anesthesia with sevoflurane is used, and close to combined anesthesia with propofol. Thus, hemodynamic depression secondary to epidural anesthesia is augmented by general anesthesia and relates to the depressive potency of the general anesthetic.

There were no notable changes in pulmonary hemodynamic variables despite a decrease in CO. This result may be attributed to differences between systemic and pulmonary circulations such as capillary structure^{18,19} and sympathetic innervation or catecholamine receptor distribution.²⁰ Furthermore, the pulmonary plexus innervating the lung is controlled predominantly by the vagus nerve and the innervation associated with bronchial smooth muscle.²¹ Therefore, the lung may be neurologically independent of thoracic epidural blockade.

Whatever the explanation, combined anesthesia appears to have minimal effects on pulmonary function and arterial blood gases remained unchanged at all time points in all groups. A significant decrease in mixed-venous PO₂ in the PE and SE groups was noted. This may have resulted from a decrease in oxygen supply to the tissues secondary to the decrease in CO. In addition, redistribution of blood from the abdomen and lower limbs to the neck, upper limbs, and chest might be another explanation for this observation.

In conclusion, a combined high thoracic/general anesthesia depressed systemic hemodynamics, whereas

the pulmonary circulation was not affected. The extent of the depression varied with the general anesthetics used, sevoflurane and propofol. The present results provide insights into the mechanisms involved and may help improve the management of combined epidural/general anesthesia for patients with pulmonary disorders, including PH or COPD.

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