Studies on the feasibility and safety of thoracic epidural anesthesia in dogs

（犬における胸部硬膜外麻酔の応用性および安全性に関する研究）

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General introduction

Anatomical considerations

The term “epidural anesthesia” refers to a form of regional anesthesia involving injection of drugs through a needle or a catheter placed into the epidural space. The injection of a local anesthetic with or without an opioid can exert both a loss of sensation (anesthesia) and a loss of pain (analgesia), by blocking the transmission of signals through nerves in or near the spinal cord.

The epidural space is a potential space that lies between the dura matter and the periosteum lining inside of the vertebral canal (Fig. 0-1). It extends from the foramen magnum to the sacral hiatus. There is no epidural space in the cranial cavity, since dura matter doubles as periosteum in this space. The arachnoid exits inside of the dura mater, and is attached to the dura matter by many trabeculae, giving a spider-like appearance. The space between arachnoid and pia mater is the subarachnoid space, which is filled with cerebrospinal fluid (CSF). CSF constitutes the content of all intracranial ventricles, cisterns, and sulci (singular sulcus), and serves four primary purposes: neutral buoyancy, physical protection, chemical stability, and prevention of brain ischemia. The spinal cord is in intimate contact with the pia mater. In most adult dogs, spinal cord commonly ends at 6th lumbar vertebra, and subarachnoid space ends approximately at 7th lumbar vertebra. Hence the

probability of direct spinal cord trauma caused by epidural puncture at lumbosacral space is low. In cats, the spinal cord usually terminates more caudally, at the level of the sacrum (Kurt 2002). The lumbosacral epidural anesthesia is frequently used for the surgical procedures caudal to the umbilicus such as lower urinary system, pelvic or perineal surgeries.

Spinal nerves originate from dorsal and ventral roots. These two roots merge within the foramina and form a spinal nerve except in the lumbar and coccygeal regions where these two roots merge within the vertebral canal. Epidural space contains semisolid epidural fat and internal vertebral venous plexus, which is particularly along the floor of the canal. Agent administered epidurally is likely to distribute along the epidural venous plexus (Lee et al. 2004) and deposited mainly in epidural fat, CSF and blood vessels. Those epidurally injected drugs may exert their systemic effects by being absorbed from epidural venous plexus (Torske and Dyson 2000). The onset and the duration of epidural anesthesia are affected by the disposition and the absorption of local anesthetics in and from the structures described above (Higuchi et al. 2004; Lee et al. 2004). Changes of the relative volume of these contents with respect to the epidural space may cause the variable extent of epidural blockade, even the drug is administered at a dose on the basis of

the ideal body weight of the patient. In obese patients, since there is an increased fat in the epidural space, a more cranial movement of drugs may occur. This extensive cranial spread of drugs can also be observed in pregnant patients. Expected for the cause of decreased relative volume of the epidural space, it may also be resulted from the increased systemic absorption caused by the engorgement of the epidural blood vessels during pregnancy. Moreover, in pregnant patients, hormonal changes such as progesterone may increase the sensitivity of neural tissue to the drugs (Datta et al. 1986). Therefore, in these patients, epidural injectate volume is supposed to be reestimated and reduced to some degree (Oliver WH 2000; Torske and Dyson 2000).

The history of epidural anesthesia and analgesia

It is generally stated that the first documented use of epidural anesthesia was performed in dogs by Coring using cocaine in 1885. In 1899, Bier described the first use of the epidural anesthesia in human followed by the Sciard and Cattalin's report in which they performed epidural analgesia via the caudal approach in animals and humans in 1901 (O'Connor 1993). The technique was not applied widely to human subjects until the beginning of the 20th century, and before that era, the approach to the epidural space was almost limited in the lumbar part of segments. In 1921 the Spanish surgeon Pagés published the article called "*Anestesia Metamérica*" (i.e.

metameric anesthesia or epidural anesthesia). In this study he described the technique he had developed. He injected the local anesthetic through the lumbar space between 4th and 5th vertebrae, leaving the spinal canal untouched. He applied this anesthesia technique in 43 patients, described the details of each step, and suggested the adequate doses of local anesthetics as well. However, after his premature death in 1923, his work had been forgotten, and no reference was made to his method. In 1931 the Italian surgeon Dogliotti resurrected and popularized this epidural approach, and the lumbar epidural technique had been used world widely. Two years later, he performed abdominal surgery with lumbar epidural anesthesia by a single bolus injection of a local anesthetic. Besides, according to the study of clinical cases and human cadavers, Dogliotti advocated the epidural injection site and the amount of drugs could be selected to provide a segmental blockade to the target segments without an extensive anesthesia or an undesirable motor paralysis. He proposed this technique as “epidural segmental anesthesia” (Dogliotti et al. 1933). In his study, he explained the various epidural injections sites and their corresponding surgeries in detail; epidural injection site at 3rd and 4th lumbar level for surgeries involving the lower limbs, the pelvis and its organs, the groin and the pubic region; at 12th thoracic to 1st or 2nd lumbar level for surgeries in the lower abdominal region; at 8th to 12th

thoracic or 1st lumbar level for surgeries in the upper abdominal region, at 4th to 10th thoracic level for surgeries of the thorax and the upper limbs with the total injection volume less than 40 mL; and at 4th to 5th cervical vertebral level for surgeries involving the head and neck. Moreover, Dogliotti first described the “loss of resistance” (LOR) technique to confirm the correct placement of the needle in the epidural space. In the same year, Gutierrez reported another technique for the same purpose, named as “hanging drop” method based on the negative pressure inside of the epidural space (Aldrete et al. 2005).

The technique of continuous epidural anesthesia developed contemporaneously. In 1931, the Romanian obstetrician, Aburel injected chinocaine through a silk ureteral catheter to block the lumboaortic plexus of laboring women. He deserves recognition not only for using a lumbosacral approach, but also for suggesting a method for obtaining a continuous peridural (epidural) block. In the United States, Hingson and Edwards devised a method for continuous caudal epidural anesthesia and used it in 33 laboring patients in 1942. A spinal needle was inserted within the canal, and the hub of the needle was attached to a rigid rubber tube connecting with a continuous spinal apparatus. Two years later, Hingson and Southworth published a second paper described the same technique using a silk ureteral catheter advanced

“to but not into the peridural (epidural) space”. In 1945 Tuohy introduced Huber point needle which made it quite easy to indwell the catheter into the epidural space. In 1949 the Cuban Curbelo and the American Flowers described the plastic epidural catheter for continuous epidural anesthesia during surgery and obstetrics. After that, epidural techniquew or instruments used for epidural anesthesia have been improved and used widely to provide the adequate effect of anesthesia and/or analgesia during and after operation or in the pain clinic.

On the other hand, general anesthesia served as the main approach to surgical pain control in western medicine for more than 150 years. Despite the introduction and wide use of amide local anesthetics beginning in 1943, general anesthesia had continued to be the sole agent for performing many painful procedures. The concomitant administration of both regional anesthesia and general anesthesia was recommended by the American surgeon Crile in 1913 for the first time. Several surgeons during that era observed that the general anesthetics such as ether, chloroform, and nitrous oxide did not block the stress response to the surgical stimulation satisfactorily. The additive properties of general and epidural anesthetic techniques are brought together in combined anesthesia to maximize the analgesia, while minimize the side effects of the individual techniques. General anesthetics can

be given in lower concentration, accordingly recovery characteristics are superior. Clinical studies indicate that the use of epidural anesthesia combined with general anesthesia not only provides better analgesic effect perioperatively, but also is associated with fewer cases of postoperative respiratory failure. Adequate intensity of epidural anesthesia can block the stress responses to the surgical stimulation, which improves the outcome of surgeries (Yeager et al. 1987; Handley et al. 1997; Rigg et al. 2002; Delis et al. 2004; Kaufman et al. 2005; Sinha & Unnikrishnan 2005; Li et al. 2008).

Medicines used for epidural administration

Common used drugs for epidural anesthesia and analgesia are local anesthetics and opioids. Various local anesthetics and opioids or their combinations are used for epidural administration. The selection of drugs to be administered epidurally depends on the degree and desired duration of anesthesia and the dermatomes to be blocked. The use of other classes of drugs, such as nonsteroidal anti-inflammatory drugs (Wetmore & Glowaski 2000), alpha-2 adrenoreceptor agonists (Jones 2001), ketamine (Martin et al. 1997) and neostigmine (Chia et al. 2006) are also considered.

Local anesthetics (LAs)

Coca is a plant native to western South America, which is best known world

widely because of its alkaloids, cocaine, a powerful stimulant. Traditional medical uses of coca are foremost to overcome fatigue, hunger, and thirst. Before stronger anesthetics had been available, it had been used to alleviate the pain of headache, rheumatism, wounds and sores, broken bones, childbirth, and trephining operations on the skull. The first agent used as a local anesthetic was cocaine. Cocaine was isolated from coca leaves by the German Niemann in the 1860s, and then in 1868, the Peruvian army surgeon Maiz reported its effects on the experimental animal. Since the first use of cocaine as a local anesthetic in 1884, a less toxic and less addictive substitute has been searched and several synthetic local anesthetics were developed and put into clinical use. Procaine, which has less toxicity, side effects and addiction compared with cocaine, was first synthesized in 1905 by the German chemist Einhorn. In 1943, the first amino amide-type local anesthetic, lidocaine was synthesized under the name Xylocaine by the Swedish chemist Löfgren. After that, mepivacaine in 1956, bupivacaine in 1957 and prilocaine in 1959 were synthesized in succession.

However, the introduction of bupivacaine on the market in 1965 paralleled the progressive and cumulative reports of central nervous system (CNS) and cardiovascular (CV) toxicity, leading to the restriction of its use. Ropivacaine was

developed after bupivacaine and introduced into the market in 1996 as the hydrochloride of the pure *S*-(-) enantiomer. Ropivacaine was found to have less cardiotoxicity than bupivacaine in animal models. More recently, levobupivacaine, the *S*-enantiomer of bupivacaine, has been introduced. Compared to bupivacaine, it is associated with less vasodilation and a longer duration of action. Similar to ropivacaine, levobupivacaine is also less toxic than bupivacaine, which is attributed to a low affinity for brain and myocardial tissue as compared with bupivacaine (Thomas & Schug 1999). The precise mode of action of local anesthetics is unknown. Perhaps best accepted is the idea that local anesthesia results when local anesthetics bind to sodium-selective ionic channels in nerves, inhibiting the sodium permeability that underlies action potential and depolarization of the cell membrane. Other mechanisms of action by which local anesthetics produce epidural or spinal analgesia may include the binding to neural calcium channels, as well as the binding to sodium and potassium channels within the dorsal and ventral horns, which causes hyperpolarization of cell membranes. Alterations in membrane calcium ion may be responsible for deformation or expansion of the cell membrane and thus the transmission or conduction of nerve impulses. Local anesthetics may inhibit substance P binding and its evoked increases in intracellular calcium ion and

potentiate γ-aminobutyric acid (GABA)-mediated chloride currents by inhibiting GABA uptake. Spinal anesthesia may also be mediated via complex interactions in a neural synapses and disruption of electrical information coding (Skarda & Tranquilli 2007 a).

Analgesia without loss of motor function is frequently desirable and can be achieved with appropriate use of local anesthetics. Small nerve fibers tend to be more susceptible to the action of local anesthetics than large nerve fibers. Myelinated fibers also tend to be blocked more readily than unmyelinated fibers of the same diameter. In general, autonomic fibers (small unmyelinated C fibers and myelinated B fibers) and pain fibers (small unmyelinated C fibers and myelinated Aδ fibers) are blocked before other sensory and motor fibers (large myelinated Aγ, Aβ and Aα fibers). In myelinated nerves, it is generally agreed that the spread of local anesthetics in a high enough concentration to block three consecutive nodes of Ranvier is the minimum requirement for inhibiting electric transmission through an axon. Compared with that, sensory fibers are more sensitive to blockade by local anesthetics because they have longer action potentials and discharge at higher frequencies than other types of fibers (i.e. frequency-dependent blockade). Moreover, some local anesthetics such as bupivacaine and ropivacaine block sensory selectively

rather than motor function.

Opioids

The first published report on opioids for intrathecal injection belongs to the Romanian surgeon Racoviceanu-Pitesti, who presented his experience at Paris in 1901. It was almost a century before the opioids were used for epidural analgesia. Behar and his colleagues published the first report on the epidural use of morphine for the treatment of pain in *The Lancet* in 1979. Opioid receptors are present in the spinal cord in high concentrations in laminae I and II of the dorsal horn. When an opioid is administered epidurally, it binds to opioid receptors easily and provides analgesic effect with lower doses than that by systemic administration (Yaksh 1981; Wetmore & Glowaski 2000). The potency of the different opioids, when they are administrated intrathecally, is not directly related to systemic potency but related to lipid solubility. Highly lipid-solubility opioids such as fentanyl, sufentanil, when administered epidurally or intrathecally, are rapidly absorbed and exert their effects by systemic uptake and redistribution to the brain. Plasma concentrations are at the same level whether these drugs are infused intravenously or intrathecally. Opioids of intermediate lipid solubility such as morphine will effectively reach the dorsal horn and produce spinal-mediated analgesia. Epidural administration of hydrophilic

opioids is expected to cause analgesia of slow onset and prolonged duration at lower than systemic doses. Systemic absorption occurs, but the low dose of hydrophilic opioids does not usually result in systemic effects.

Advantages and disadvantages of epidural anesthesia

Pain is an awareness of acute or chronic discomfort occurring in various degrees of severity resulting from injury or diseases. It not only arises unpleasant sensory associated with tissue damage, impedes the return of normal pulmonary function, modifies certain aspects of the stress response to injury, and alters hemodynamic values and cardiovascular function, but also accompanies by fear, anxiety, panic and other unpleased emotion experience. The stress response of the pain may increase cardiac output, myocardial work and oxygen consumption. Evoked vasoconstriction, especially of the splanchnic vascular beds, can lead to gastrointestinal ischemia and hypoxia with intestinal paralysis and release of myocardial toxins. Renal failure may ensue as a result of intense vasoconstriction and the release of arginine vasopressin and aldosterone. In many patients with severe traumatic or postsurgical pain, these neuroendocrine responses are of sufficient magnitude to initiate and maintain shock. Attenuation of the stress response through adequate pain relief and supportive therapy should improve patient outcome and promote wound healing. Blockade of

afferent and efferent neural pathways by local anesthetics seems to be the most effective analgesic modality in lessening the physiologic response to pain and injury (Lewis et al. 1994). A deep level of general anesthesia may attenuate the pain noxious stimulus aroused by surgery. However, it is hardly for common general anesthetics used alone at clinical dose to provide adequate analgesic effect as needed (Zbinden et al. 1994). Additive use of local anesthetics in general anesthesia is recommended for improving pain management after surgery (Kaufman et al. 2005).

Large-scale meta-analyses have clearly demonstrated the advantages of thoracic epidural anesthesia with regard to the postoperative pain control and morbidity and mortality impairment. The reducing of cardiac morbidity and mortality is related to the blockade of cardiac sympathetic fibers, improvements in regional blood flow and a reduction of the major determinants of cardiac oxygen consumption, which lessen the severity of the ischemic injury. Moreover, thoracic epidural anesthesia has been reported to be beneficial to gastrointestinal and pulmonary function and may have a positive effect on the immunologic and coagulation system (Waurick & Van Aken 2005; Clemente & Carli 2008).

There are many merits associated with the use of epidural administration. Meanwhile, in the other hand, complications associated with the use of epidural

blockade have been documented in previous studies (Tanaka et al. 1993; Horlocker 2000; Horlocker & Wedel 2000). Technique-related complications such as epidural abscess, epidural hematoma and headache have been reported in human; however the incidence of serious neurological sequelae after epidural anesthesia is low, and the epidural technique could be improved by practicing well. Neurological complications accompanied with epidural anesthesia include Horner's syndrome, Shiff sherrington-like reflexes and signs associated with local anesthetic toxicity, such as muscle twitch coma and convulsions (Biousse et al. 1998; Skarda and Tranquilli 2007 b; Bosmans et al. 2009). In addition, during neuraxial blockade, a decrease of spinal sympathetic outflow may induce a concomitant hypotension. Hypotension could be prevented by preloading with a crystalloid solution, and occasionally treatment may also be necessary with a crystalloid and/or a vasopressor drug, or other drugs.

Epidural techniques and drug delivery methods

Multiple methods of delivery of epidural administration are acceptable, including a single dose injection, intermittent injection, continuous infusion, as well as patient-controlled injection (patient-controlled epidural analgesia; PCEA). Continuous epidural infusions can offer a safety advantage over bolus or intermittent

epidural injections because abrupt concentration changes of the analgesic agent can be avoided (Shafer & Donnelly 1991). The incidence of side effects appeared to be reduced with the use of continuous infusion techniques (Mulroy 1996). Compared with needle technique, a greater analgesic effect may be obtained when drugs were delivered through an epidural indwelling catheter (Omote et al. 1992). It has been known that the technique of PCEA is associated with a lower dose requirement (Mulroy 1996). Moreover, when PCEA is used to maintain epidural analgesia following initial continuous epidural infusion, except for providing effective analgesia with less anesthetist workload and reducing local anesthetic consumption, it can also prevent the occurrence of hyperalgesia (Missant et al. 2005). Additional advantages of continuous epidural anesthesia provided by catheter are the ability to tailor the anesthesia duration depending on the operation time and to maintain a route for analgesia during surgery and postoperatively (Skarda & Tranquilli 2007 b).

Epidural site is determined by the dermatomes corresponding to the area of desired anesthesia or analgesia. In human, thoracic vertebrae, from C7 to L1, are divided into three segments: high-thoracic (C7 to T2), mid-thoracic (T2 to T6), and low-thoracic (T6 to L1). It reflects the different fields of surgery for which these epidural sites are typically used such as cardiac, thoracic and abdominal surgery,

respectively. In the clinical setting, thoracic epidural anesthesia provides optimal analgesia during and after thoracic and major abdominal surgery and decreases postoperative morbidity and mortality mainly by blocking sympathetic nerve fibers. Lumbar epidural anesthesia is frequently used for pain relief in obstetrics. While in dogs, epidural anesthesia is almost limited in lumbosacral region, which is described for surgical courses caudal to the umbilicus.

Epidural anesthesia and analgesia in veterinary medicine

In the small animal clinical setting, epidural anesthesia and analgesia is usually carried out in caudal lumbar and lumbosacral regions, which is the most frequently used neuraxial blockade for surgical procedures caudal to the umbilicus (Skarda & Tranquilli 2007 b). This technique is recommended for cesarean section because, unlike other anesthetic techniques, it is related to a higher respiratory rate and less depressant effect on neurological reflexes of the puppies (Luna et al. 2004). On the other hand, although thoracic epidural administration is expected to provide potent analgesic effect for thoracic surgery in dogs as well as humans, reports are limited in experimental animals (Hotvedt et al. 1983; Hotvedt et al. 1984a; Hotvedt et al. 1984b; Lundberg et al. 1991). Thoracic epidural technique is not routinely used because of its potential technical difficulties associated with anatomical structures. However, it

has been documented that procedures of myelography or epidurography can be performed from a thoracic vertebrae tap (Shores 1993), suggesting that epidural needle puncture and catheterization is possible to be preformed at thoracic vertebral level.

In dogs, epidural anesthesia is usually applied under general anesthesia because needle puncture or placement of the catheter into epidural space is actually impossible in conscious animals. Isoflurane and propofol are two commonly used representatives in inhalation and injectable general anesthesia, and their cardiovascular effects have been well studied. Although the combination of general anesthesia and lumbosacral epidural anesthesia has already been used in dogs for surgeries caudal to the umbilicus, few studies were reported about the cardiovascular effects of combining use of these general anesthetics and thoracic epidural anesthesia in dogs.

Purpose of this study

The purpose of this study was to investigate the technique feasibility and cardiovascular safety of thoracic epidural anesthesia in dogs.

In chapter 1, the technical safety and difficulty of epidural needle puncture and catheterization were studied at thoracic and lumbar vertebral levels. Time required

for the process of epidural catheterization, macro- and microscopical examinations and subjective technical difficulty evaluation were recorded and compared. In chapter 2, by means of computered tomography (CT) epidurography, the spreading pattern of a single dose of contrast medium injected through a thoracic and a lumbar epidural catheter was studied. Besides, the distribution of contrast medium administered through a thoracic epidural catheter with a single dose and a continuous infusion were also compared.

In chapter 3, cardiovascular effects of thoracic and lumbar epidural anesthesia after epidural injection of a single dose of 2% lidocaine under isoflurane and propofol anesthesia were studied respectively. Finally, in chapter 4, cardiovascular effects of continuous thoracic epidural infusion with 2% lidocaine at three incremental rates, as well as serum concentration of lidocaine were compared.

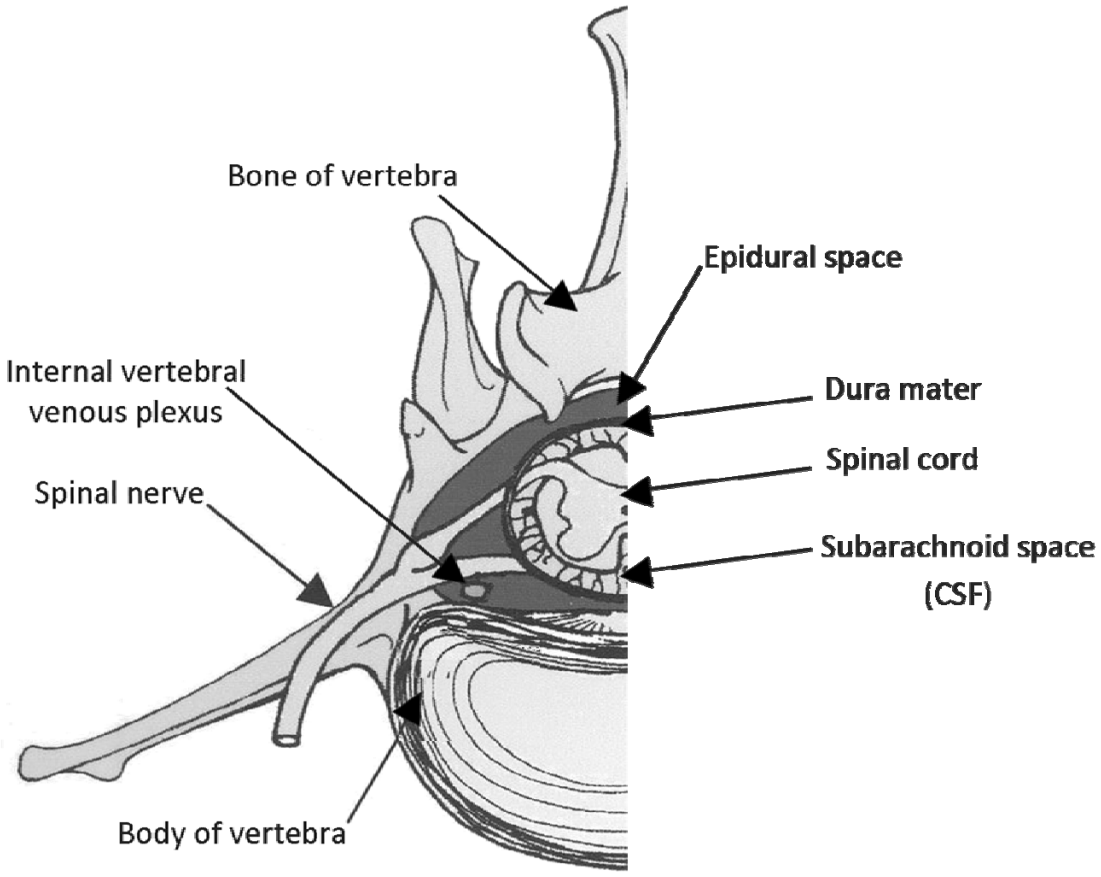

Fig. 0-1 Canine spine diagram (Quoted with permission from Dr. Iseri T. PhD dissertation, The University of Tokyo, 2007).

Chapter 1

The technical difficulty and safety of thoracic and lumbar epidural catheterization in dogs

Introduction

Epidural anesthesia and analgesia have been widely used in human medicine. Drugs can be delivered either directly through the epidural needle or following the placement of an epidural catheter. Epidural catheterization provides the opportunity for repeated or constant delivery of analgesics to the spinal cord, allowing surgeons to tailor the anesthesia duration to the length of operation and maintain a route for analgesia during and after surgery. Epidural administration can be selected at various vertebral levels to match the site of surgery. Thoracic epidural anesthesia is well known for providing optimal perioperative anesthesia and analgesia in cardiac, thoracic, and upper abdominal surgery and decrease postoperative morbidity and mortality (Hasenbos et al. 1987; Rodgers et al. 2000; Muehling et al. 2009).

In contrary, caudal lumbar or lumbosacral epidural anesthesia and analgesia is the most frequently used neuraxial blockade for surgical procedures caudal to the umbilicus in dogs (Skarda & Tranquilli 2007 b). Although experimental studies on thoracic epidural analgesia have been reported in dogs (Hotvedt et al. 1983; Hotvedt et al. 1984a; Hotvedt et al. 1984b; Lundberg et al. 1991), the epidural catheter was placed into the epidural space through a surgical approach. Thoracic epidural technique is not used routinely in the clinical setting because of anatomical concerns

and the consequent technical difficulties. However, procedures involving myelography or epiudrography can be performed with a thoracic vertebrae tap (Shores 1993), suggesting that epidural needle puncture and catheterization is also possible to be preformed at thoracic vertebral level.

Limited information is known on the technical difficulty and safety of thoracic epidural needle puncture and catheter placement in dogs. Therefore in this chapter, by using healthy dogs, the technical difficulty and safety of thoracic epidural catheterization was studied by comparing with lumbar catheterization.

Materials and methods

This study was approved by the Ethics Committee of Animal Use and Care Committee of the Graduate School of Agricultural and Life Sciences, the University of Tokyo.

Animals

Thirteen healthy male beagles with a mean age of 48.3 months (37 to 82 months) and a mean body weight of 13.0 kg (11.2 to 15.5 kg) were used in this study. Each dog was used for one experiment. Dogs were housed in individual cages maintained at a constant temperature and humidity. Food was withheld for at least 12 hr before each anesthesia.

Experimental procedures

Dogs were not premedicated. A 22G IV catheter was placed into the cephalic vein for intravenous injection before anesthesia. General anesthesia was induced with isoflurane (Escain; Mylan Inc., Osaka) by mask. After endotracheal intubation, aesthesia was maintained with isoflurane diluted in 100% O_2, and its end-tidal concentration was adjusted around 1.3 to 1.5 MAC until euthanasia. The intermittent positive pressure ventilation (KV-1a; Kimura Medical Instrument Co. Ltd., Tokyo) was adjusted to maintain normocapnia. The end-tidal concentrations of isoflurane

and CO_2, arterial oxygen saturation, respiratory rate, and lead II EAG were measured with a multifunction monitor (BP-508; Colin Medical Technology Corp., Aichi)

Epidural catheterization

Dogs were randomly assigned to one of two treatment groups: group TEA and group LEA depending on the epidural catheterization site. Each group consisted of six dogs; one dog was not catheterized and used as a general anesthesia and anatomical control. Except the control dog, other twelve dogs were positioned in sternal recumbency with hind limbs pulled forward symmetrically, and hair was clipped and the skin surface around the needle puncture site was sterilized according to a surgical preparation procedure. An 18G Tuohy needle and a 20G radiotransparent flexible catheter (Hakko Co. Ltd., Nagano) were used for epidural catheterization. All procedures of epidural needle puncture and indwelling catheter insertion were performed without any auxiliary equipment. The skin puncture site was determined by palpating the iliac wings, the dorsal spinous process of L7 or the bone body of 13th rib, and counting the dorsal spinous processes of lumbar segments cranially or caudally up to the intended site. In group TEA, the needle skin puncture site was at L1/L2 interspace. The puncture site was on the right or left side approximately 0.5 to 1 cm lateral to the spinous process, slightly posterior to the

intended intervertebral space. The needle was inserted into the epidural space via the paramedian approach. After penetrating the subcutaneous tissue, the needle was advanced anteroventrally with its bevel facing cephalad until a distinct popping sensation was felt as the needle point penetrated the interarcuate ligament. Correct placement of the needle in the epidural space was confirmed by "loss of resistance (LOR)" technique with saline. If there was no LOR, needle was redirected or a second puncture was performed. Each new skin puncture was recorded as another attempt, regardless of whether it was at the intended vertebral level or at an adjacent vertebral level (cranial or caudal to the intended level). Simply redirecting the needle without a new skin puncture was not counted as an additional attempt. The correct placement of needle in the epidural space was indicated by a positive LOR response. Then an epidural catheter was introduced through the needle and advanced 10 cm into the epidural space. After needle withdrawal, the catheter was aspirated using a syringe to confirm no blood or cerebrospinal fluid. The catheter was then secured to the skin with a butterfly tape and suture. In group LEA, the needle was placed on the midline and caudal to the spinous process of L7 and inserted into the epidural space through the L7/S1 interspace via the midline approach. Other manipulations such as needle insertion, epidural space confirmation, catheter placement were identical to

those in group TEA.

A volume of saline (0.2 mL/kg) was injected through the catheter manually within 2 min in both groups. The time taken from needle puncture to epidural space confirmation and the time from needle skin puncture to epidural catheter placement and saline injection were recorded. The depth of needle inserted (from skin puncture site to the needle tip) was also recorded by checking the mark on the needle. The overall procedure was evaluated subjectively according to a composite subjective evaluation scale (Table 1-1).

After epidural injection of saline, all dogs were euthanized with an intravenous injection of thiopental sodium (70 mg/kg, Ravonal®; Mitsubishi Tanabe Pharma Corporation, Osaka) along with isoflurane anesthesia to ensure deep anesthesia, which was confirmed by the absence of corneal reflexes and muscle tone; then followed by intravenous injection of potassium chloride (300 mg/kg, KCl drip injection 15%; Maruishi Pharmaceutical Co. Ltd., Osaka). Death was confirmed by lack of palpable pulse and of audible heartbeats, as assessed by auscultation.

Catheter position and tip location were confirmed by epidurography under X-ray with iohexol (Omnipaque 300; Daiichi Seiyaku Co. Ltd., Tokyo). The number of spinal bodies contacted by the catheter was recorded by using a modified method

based on a previous report (Lee et al. 2007); a complete segment contacted by the catheter was counted as 1 vertebral body unit (VBU), and part of a segment was counted as 0.5 VBU. The control dog was also euthanized and subjected to radiography.

After radiography, the catheter within the epidural space and the spinal cord were exposed and inspected macroscopically by excising vertebral arches. The side position of the catheter tip with respect to the spinal cord, technique-related tissue injuries, including tissue bleeding, dural puncture and canalization were recorded. In addition, spinal cord tissue samples at: (1) the tip of the catheter, (2) the needle puncture site, and (3) the middle portion between (1) and (2) were collected. Tissue samples were fixed in 10% neutral formalin solution, mounted into paraffin sections, and stained with hematoxylin and eosin (H&E) for microscopic evaluation.

Statistical analysis

Time-related data and needle insertion depth were compared between two groups by unpaired *t* test. The subjective evaluation and epidural catheter position were analyzed by Mann-Whitney *U* test. Time-related results were expressed as mean ± SD. Others were expressed as median (min-max) unless otherwise stated. A significant level of $p < 0.05$ was used for all statistical tests.

Results

Epidural catheterization was successfully performed at the first attempt in 3 and 5 dogs in group TEA and LEA, respectively. In the remaining dogs (three dogs in group TEA and one dog in group LEA), successful puncture and catheterization were performed at the second attempt. There was no significant difference either in the time from needle skin puncture until epidural space confirmation ($p = 0.445$) or the time from needle skin puncture until epidural catheter insertion and saline injection ($p = 0.907$) between two groups (Table 1-2).

The length of needle inserted from the skin surface to the epidural space was longer in group TEA than LEA ($p = 0.039$). Actual needle puncture site in group TEA was at L1/L2 interspace in 5 dogs and at L2/L3 interpace in one dog (Fig. 1-1); in group LEA, it was at L6/L7 interpace in 3 dogs and at L7/S1 interspace in the other 3 dogs. The median number of vertebral segments contacted by epidural catheter was 3 in each group. There was no difference between two groups in catheter tip location side with respective to the spinal cord ($p = 0.240$) (Table 1-3).

Subcutaneous bleeding around the needle puncture site was detected in 3 dogs in group TEA but in no dog in group LEA. There were no macroscopic injuries (bleeding, dural puncture and canalization) to the spinal cord tissue in the control dog

and in any of the catheter-treated dogs. No significant histopathological changes were observed in either the control dog or the catheter-treated dogs.

Results of subjective evaluation are shown in Table 1-4. The score of the overall technical difficulty was slightly but significantly higher in group TEA than group LEA ($p = 0.009$).

Discussion

In dogs, epidural anesthesia is commonly provided in lumbosacral space for surgical procedures involving regions caudal to the umbilicus (Skarda & Tranquilli 2007 b). Epidural injection of local anesthetics at more cranial segments is expected to provide preferred analgesic effect for surgeries in more cranial regions, such as thoracotomy or upper abdominal surgery. However, needle puncture and catheterization in thoracic region is thought to be technically difficult and clinically risky because of anatomical structures. Unobvious landmarks and the relatively narrow intervertebral spaces at thoracic segments may result in difficulties in identifying the epidural puncture site and threading the catheter. To avoid such problems, in group TEA, the catheterization was performed via the lumbar approach, in which the catheter was inserted into the epidural space through a needle placed at cranial lumbar level and advanced into the thoracic level.

The puncture site was identified by palpating the iliac crest and spinous processes, whereas, the actual epidural puncture site in either group TEA or group LEA was not always consistent with the prediction. In clinical studies, body weight or body habitus is of a high variability among individuals, which may possibly affect the quality of landmarks, consequently affect the result of the correct placement of the

needle in the epidural space at the first chosen site (Sprung et al. 1999; de Filho et al. 2002). However, since standard experimental dogs were used in this study, and their body weights varied within a narrow range, unintended epidural sites in both two groups were unlikely related to the body weight. It has been known that even though bony landmarks are most often used to determine levels, they do not always provide definitive methods to determine a given vertebral interspace accurately (Lirk et al. 2004). The actual puncture sites were located within one interpsace of the predicted level in both two groups, and they were still clinically acceptable. The accuracy of epidural puncture at the predicted site is supposed to be enhanced after more practice.

In this study, the paramedian approach was used for epidural catheterization in group TEA. Anatomically, the intervertebral space in thoracolumbar region is relatively narrow compared with that in lumbosacral region. The difficulty of catheterization may be encountered when using midline approach in thoracolumbar region. Therefore the paramedian approach was thought to be more feasible to be used for catheterization in group TEA.

Although statistically not significant, the apparent difference in the time needed to identify the epidural space was caused by two dogs in group TEA in which

identification of the epidural space was time-consuming and took more than 2 minutes, due to several redirections of the epidural needle. It may be attributed to the lack of obvious landmarks in thoracolumbar region, resulting in difficulty in determining the predicted intervertebral space. However, the total time from needle puncture until catheter placement and saline injection was comparable between two groups, indicating that less time was consumed for the catheter threading in group TEA. This finding was consistent with a previous report in which the epidural catheter placement via the paramedian approach was faster compared with the midline approach (Leeda et al. 2005). One possibility was thought to be the steeper angle of entry of the paramedian epidural needle into the epidural space, facilitating catheter insertion (Blomberg et al. 1989; Leeda et al. 2005). In group TEA, because the needle was inserted into the epidural space via the paramedian approach, the long axis of the needle was more parallel to the longitudinal axis of the spinal cord. In contrary, in group LEA, needle punctured according to the traditional method that needle penetrated into the skin and epidural space perpendicularly via the midline approach. It is speculated that less resistance may be encountered during introducing the catheter into the epidural space through the needle in group TEA than group LEA.

In the present study, regardless of epidural sites, catheter tip was located on the right side with respect to the spinal cord in more cases. The exact reason is unclear, maybe it just occurred occasionally. In humans, it has already known that epidural catheters do not follow a straight and predictable course in the epidural space during catheter insertion (Hsin et al. 2001; Lim et al. 2002). Presumably, any incidental factor during needle puncture and catheter insertion, or even the type of needle and catheter used may affect the final catheter tip location in the epidural space.

According to the evaluation criteria used in this study, except a mild subcutaneous bleeding was observed in 3 dogs receiving thoracic epidural catheterization, neither macroscopic or microscopic injuries of selected spinal cord segments were detected in both two groups. In humans, it has known that multiple attempts are associated with complications such as trauma to neural structures (Auroy et al. 1997; Horlocker et al. 1997; Puolakka et al. 2000) and spinal hematoma (Wulf 1996). It is reasonable to presume that this subcutaneous bleeding may also be caused by multiple puncture attempts, however, it seems inappropriate. In fact, in three affected dogs, expect one dog received the second epidural puncture, other two dogs was punctured only once. Redirecting needle subcutaneously, as well as multiple puncture attempts may both contribute to this mild trauma. Nevertheless

under clinical circumstances, the mild subcutaneous bleeding is unlikely to influence anesthesia and surgery considerably in patients with normal coagulation function.

Data of subjective evaluation showed the score of technical difficulty was slightly but statistically higher in group TEA than group LEA. Lack of obvious landmarks and the relatively narrow intervertebral spaces in the thoracolumbar region may be the potential causations for the higher subjective difficulty score in group TEA.

In conclusion, in the present chapter, the technical difficulty and safety of epidural catheterization was compared between thoracic and lumbar vertebral levels. Time-related results were comparable between two treatments, and no obvious technique-related injuries of the spinal cord were observed. Although the overall technical difficulty score was statistically higher in group TEA, the difference was slight. Hence the thoracic epidural catheterization is supposed to be used as feasibly and safely as lumbar epidural catheterization in medium or large dogs.

Table 1-1 A composite subjective evaluation scale.

Item	Criteria	Score
Determination of skin puncture site	The landmark is obvious and the puncture site can be determined easily	1
	The landmark can be palpated and the puncture site can be determined	2
	The landmark is unclear, and the puncture site can not be determined by palpating landmarks	3
Needle puncture attempt	Needle can be inserted into the epidural space at the first attempt without needle redirection	1
	Needle can be inserted into the epidural space within two attempts after needle redirection	2
	Needle cannot be inserted into the epidural space after three attempts	3
Resistance of catheterization	Mild resistance, catheter can be inserted easily	1
	Moderate resistance, catheter can be inserted	2
	Catheter cannot be inserted	3

Table 1-2 Time (sec) consumed from needle skin puncture until epidural space confirmation, and until epidural catheter insertion and saline injection. Values were shown as mean ± SD.

Time consumed from needle skin puncture	Group TEA (n=6)	Group LEA (n=6)
until epidural space confirmation	90 ± 44	74 ± 19
until epidural catheter insertion and saline injection	226 ± 63	229 ± 26

There were no significant differences between two groups.

Table 1-3 Epidural catheter position and tip location in the epidural space in group TEA and LEA.

Item	Group TEA (n=6)	Group LEA (n=6)
Needle insertion depth (cm; median, min-max)	4* (3-5)	3 (2-4)
Actual puncture site (number of dogs)	L1/L2 (5) L2/L3 (1)	L6/L7 (3) L7/S1 (3)
Catheter tip location (number of dogs)	T11 (2) T11/T12 (1) T12 (1) T12/T13 (2)	L3/L4 (2) L4 (2) L5 (2)
Number of vertebral segments contacted by epidural catheter (median, max-min)	3 (2-3.5)	3 (1.5-3.5)
Catheter tip location side (number of dogs)	R:M:L= 5:1:0	R:M:L= 4:0:2

R: right side to the spinal cord; M: dorsal lateral to the spinal cord; L: left side to the spinal cord.
* Statistically different between two groups (p = 0.039).

Table 1-4 Subjective evaluation of the overall technical difficulty in group TEA and group LEA. Data shown as median (min-max).

	Group TEA	Group LEA
Subjective evaluation (median, min-max)	5* (4-6)	3 (3-5)

* Statistically different between two groups (p = 0.009).

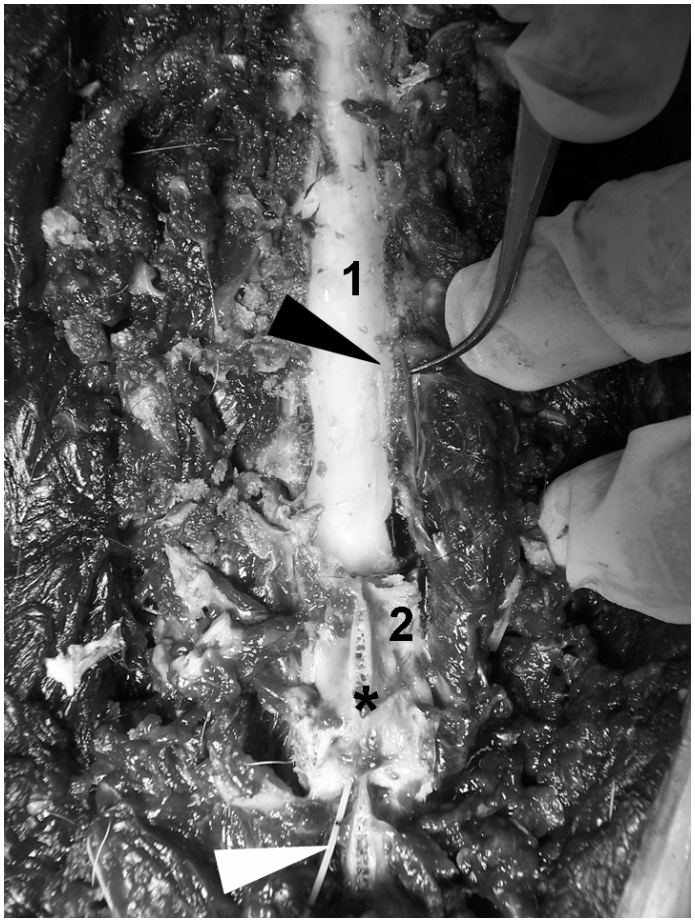

Fig. 1-1 Photograph of spinal cord (vertebral arch was partly removed). The epidural catheter was inserted into the epidural space from the L1/L2 interspace.
Black arrow: the catheter tip; white arrow: catheter located in the subcutaneous tissue; asterisk (*): stubbed spinous process of L1.
1: spinal cord; 2: the vertebral body of L1.

Chapter 2

Distribution of contrast medium epidurally administrated at low thoracic and lumbar vertebral segments in dogs

Introduction

The results obtained in chapter 1 suggest that epidural needle puncture and catheterization in thoracolumbar region is feasible to be performed in medium or large dogs and unlikely to induce injuries to the spinal cord.

Anesthetic and analgesic effects induced by epidural injection of local anesthetics are various depending on the injection site, such as thoracic and lumbar segments. In humans, patterns of distribution of sensory blockade have been studied in different epidural injection sites. Typical spreads in cranial and caudal directions after a loading dose of local anesthetics (10 to 20 mL) at C7-T2, T6-L1 and L2-L5 levels are C7-T1 to T6-T11, C6-T1 to T11-L4 and T8-10 to S5, respectively (Visser et al. 2008). Besides, the epidural distribution of drugs and the consequent neural blockade may be also various depending on different delivery methods such as bolus injection directly through the epidural needle, intermitted or continuous administration through an epidural catheter (Husain et al. 1997; Okutomi et al. 2001). The spreading pattern of drugs after epidural administration has also been reported in animals (Kim et al. 1998; Iseri et al. 2010; Kim et al. 2010), however, few published studies motioned the spreading pattern of drugs continuously infused at the thoracic vertebral level.

Epidurography has been used to evaluate the distribution pattern of drugs injected into the epidural space in both human and animal studies (Stevens et al. 1989; Kim et al. 1998; Yokoyama et al. 2004). It has been reported that this technique was helpful in predicting the exact dermatomal distribution of analgesia blockade (Yokoyama et al. 2004). Furthermore, computed tomography (CT) epidurography in known for providing better insight into the morphology of the epidural space compared with radiography, and it also allows for tomographical imaging of the spinal cord (Iseri et al. 2010). Hence the detection of contrast medium with the use of CT epidurography is thought to be more accurate.

Therefore, the aim of this chapter was to study, with the use of CT epidurography, the distribution of contrast medium administered through an epidural indwelling catheter in a dog epidural model. As epidural anesthesia is usually applied under general anesthesia because needle puncture or placement of the catheter into epidural space is actually impossible in conscious dogs, the experiments in this chapter were conducted under general anesthesia. Two experiments were involved in this chapter. In experiment 1, the spreading pattern of contrast medium after bolus injection of contrast medium at thoracic and lumbar vertebral segments in dogs under isoflurane anesthesia was studied. In experiment 2, the distribution of contrast medium after

thoracic epidural administration with a single bolus injection and a continuous infusion was evaluated and compared in dogs under isoflurane and propofol anesthesia, respectively.

Materials and methods

This study was approved by the Animal Care Committee of the Graduate School of Agricultural and Life Sciences at the University of Tokyo.

Animals

Six healthy female beagles with a mean age of 22.2 months (range, 17 to 42 months) and mean body weight of 11.8 kg (range, 11.0 to 13.6 kg) were used in both experiment 1 and experiment 2. Dogs were housed in individual cages in which temperature and humidity were kept constant. Food was withheld for at least 12 hr before each experiment, but water was available ad libitum. Each dog was used repeatedly with a washout period of at least 7 days.

Experimental procedures

Dogs were not premedicated. In experiment 1, general anesthesia was induced and maintained with isoflurane (Isoflu; Dainippon Pharmaceutical Co. Ltd., Osaka). After endotracheal intubation, the end-tidal concentration of isoflurane vaporized in pure oxygen was maintained at 1.8% (approximately equivalent to 1.4 MAC). The end-tidal concentration of CO_2 was kept between 35 and 40 mmHg by intermittent positive pressure ventilation (KV-1a; Kimura Medical Instrument Co. Ltd., Tokyo). The end-tidal concentration of isoflurane and CO_2, arterial oxygen saturation,

respiratory rate, and lead II ECG were measured with a multifunction monitor (BP-508; Colin Medical Technology Corp., Aichi). In experiment 2, dogs were anesthetized with isoflurane (group ISO) and propofol (group PRO), respectively. In group ISO, dogs were treated by isoflurane with the same procedure as in experiment 1. In group PRO, anesthesia was induced and maintained with propofol (1% propofol injection, Maruishi Pharmaceutical Co. Ltd., Osaka) at an infusion rate of 30 mg/kg/hr. Other manipulations were the same as in experiment 1.

Epidural catheterization

After being anesthetized, dogs were positioned in sternal recumbency with hind limbs pulled forward symmetrically. Hair was clipped and the skin surface around the needle puncture site was sterilized according to a surgical preparation procedure. An epidural catheterization set (Hakko Co. Ltd., Nagano) was used. In experiment 1, dogs were randomly allocated to one of two treatment groups: TEA and LEA. In group TEA, an 18G Tuohy needle supplied with the catheterization set punctured the skin at the thoracolumbar level (T12 to L1); in group LEA, the needled punctured the skin at the lumbosacral level (L6 to S1). In experiment 2, the epidural needle puncture was performed only at thoracic vertebral level (T12 to L1) with the same type of Tuohy needle as used in experiment 1. Two treatment groups, Bolus and CRI,

were divided depending on different epidural administration regimens. Correct needle placement in the epidural space was identified by the “loss of resistance” (LOR) technique with saline. If there was a positive LOR response, a 20G radioparent flexible catheter supplied with the catheterization set was introduced through the needle and advanced 10 cm into the epidural space. After confirming the absence of blood and cerebrospinal fluid by aspiration with a syringe connected to the catheter, the remainder of the catheter was secured onto the skin. The dogs were turned to the supine position and prepared for CT scanning.

CT epidurography

Before epidural injection of contrast medium, control images were obtained using a 4-slice helical CT unit with a slice thickness of 8 mm and a pitch of 0.875 at 120 kV and 150 mA (Asteion S4; Toshiba Medical Systems Corporation, Tokyo). In experiment 1, a single dose of 0.2 mL/kg of iohexol (140 mg I/mL Omnipaque; Daiichi Sankyo Co. Ltd., Tokyo) was epidurally injected through the catheter attached to a syringe pump (TOP syringe pump TOP-5500; TOP Corporation, Tokyo) at a rate of 0.01 mL/sec (Iseri et al. 2010). CT epidurographic images were obtained at 5, 10, 15, 20, and 30 min after the bolus injection under the same CT conditions. In experiment 2, after obtaining control imagines, a dose of 0.2 mL/kg of iohexol was

injected in bolus through the epidural catheter attached to a syringe pump at a rate of 0.01 mL/sec in both Bolus and CRI groups. Then the contrast medium was continuously infused at a rate of 0.2 mL/kg/hr for 30 minutes in group CRI, but no more administration in group Bolus. CT epidurographic images were obtained at 5, 10, 15, 20, and 30 min after the initial bolus injection of contrast medium under the same CT conditions.

In both experiment 1 and 2, the longitudinal distribution of contrast medium was evaluated according to a modified method described previously (Lee et al. 2007), and expressed as the total number of vertebral segments reached by the contrast medium cranial to the lumbosacral space. A complete vertebral segment contacted by the contract medium was counted as 1 vertebral body unit (VBU), and part of a segment was counted as 0.5 VBU. The maximal CT values of the epidural space at C7/T1, T4/T5, T13/L1 and L4/L5 interspaces were evaluated at 5, 10, 15, 20, and 30 min after the initial bolus injection of contrast medium.

Statistical analysis

In both experiment 1 and 2, the total number of vertebral segments reached by the contrast medium was expressed as the median (min-max). The maximal CT value was expressed as mean ± SD. Wilcoxon's rank-sum test was used to analyze the

number of spreading segments and paired Student's *t* test was used to the evaluate CT value. Differences were considered to be significant at $p < 0.05$.

Results

Experiment 1

The epidural catheter was successfully inserted into the epidural space in all dogs. The catheter tip was located at the T7 to T10 level in group TEA and at the L2 to L4 level in group LEA. No adverse events due to needle puncture, epidural catheterization, or contrast medium injection were observed in either group.

The distribution of contrast medium

Contrast medium was found within the epidural space after injection in all dogs. The median number of vertebral segments reached by the contrast medium was 17.0, 18.0, 18.75, 20.0, and 20.25 in group TEA and 18.5, 19.75, 20.0, 20.5, and 21.5 in group LEA at 5, 10, 15, 20, and 30 min after epidural injection, respectively. A time-related increasing trend in the number of spreading segments was found during the initial 20 min after contrast medium injection in both groups. However, no difference in the total spread of contrast medium was found between two groups (Table 2-1-1). The contrast medium spread in both the cranial and caudal directions comparably from the catheter tip in group TEA, whereas it spread more cranially than caudally in group LEA ($p < 0.05$) (Fig. 2-1-1).

The maximal CT value

With the exception of C7/T1, there was a time-related decreasing trend in the maximal CT value at other selected vertebral levels in both two groups, but significant differences were only observed at T4/T5 level in group TEA and T13/L1 level in both two groups, at which CT values were significantly decreased at 20 and 30 min compared with those at 5 and 10 min. The maximal CT values were significantly higher at C7/T1 and T4/T5 levels in group TEA, whereas they were significantly higher at T13/L1 and L4/L5 levels in group LEA (Fig. 2-1-2).

Experiment 2

The epidural catheter was successfully inserted into the epidural space in all dogs. Catheter tip was placed at T6 to T9 vertebral segments. No adverse events due to needle puncture, epidural catheterization, or contrast medium injection were observed in any group. Moderate or occasionally severe muscle tremors were observed in 3 specific dogs in both PRO-Bolus and PRO-CRI groups, which were not observed under isoflurane anesthesia. All data in group ISO-Bolus were used the results of group TEA in experiment 1.

The distribution of contrast medium

Contrast medium was found within the epidural space by CT epidurography after administration in all dogs. Under isoflurane anesthesia, the median number of vertebral segments reached by contrast medium was 17.0, 18.0, 18.75, 20.0, and 20.25 in group ISO-Bolus and 16.0, 17.0, 17.5, 17.75 and 18.5 in group ISO-CRI at 5, 10, 15, 20, and 30 min after the initial single dose of epidural contrast medium, respectively. Under propofol anesthesia, it was 16.5, 18.0, 18.5, 18.5, 19.25 in group PRO-Bolus and 17.5, 19.0, 19.5, 20.25 and 20.75 in group PRO-CRI at the same measurement time points. Under either isoflurane or propofol anesthesia, the number of spreading segments increased generally in a time-related manner, particularly

within the initial 20 min after epidural bolus injection of contrast medium. However, no differences were found between epidural bolus injection and continuous epidural infusion. In addition, no differences in the total number of segments were found between isoflurane and propofol anesthesia (Table 2-2-1).

The maximal CT value

In ISO-Bolus group, at T4/T5 level, the maximal CT values decreased significantly at 20 and 30 min after epidural injection compared with 5 min, and the value at 30 min was also significantly lower than that at 10 min. At T13/L1 level, the maximal CT values decreased significantly at 30 min after epidural injection compared with 5 min. Under isoflurane anesthesia, the maximal CT values were significantly higher at the C7/T1 and T4/T5 levels than those at the T13/L1 and L4/L5 levels in both ISO-Bolus and ISO-CRI groups. In group ISO-CRI, CT values were relatively high at the C7/T1 and T4/T5 but relatively low at the T13/L1 and L4/L5 levels compared with those in group ISO-Bolus, although differences were not significant. Under propofol anesthesia, the maximal CT values in both Bolus and CRI groups changed similarly with those under isoflurane anesthesia. There were no differences in the maximal CT values between isoflurane and propofol anesthesia (Fig. 2-2-1).

Discussion

In experiment 1, the contrast medium was bolus injected with a single dose of 2 mL/kg in both TEA and LEA groups, because this bolus injection volume of 2% lidocaine was reported to generally achieve good anesthesia for abdominal and orthopedic surgeries caudal to the diaphragm in dogs (Skarda & Tranquilli 2007 b).

The total spreading segments were similar between TEA and LEA groups. Moreover, because there was an extensive cranial spread in group LEA, the cranial vertebral level reached by the contrast medium was comparable between two groups. A similar result was also shown in a previous study in which a comparable total spread but a greater cranial extent of contrast medium was observed when contrast medium was injected via the catheter placed at the T12 level than at the T7 level in rabbits (Kim et al. 1998). Three possible reasons might contribute to this result. First, the catheter tip was placed approximately at the mid portion of the thoracic and lumbar vertebral levels in group TEA and group LEA, respectively. Compared with group TEA, there was less space for the contrast medium to spread caudally than cranially from the tip of the catheter in group LEA. In addition, the lumbosacral enlargement and cauda equina located in the caudal lumbar and sacral regions may have also prevented its caudal spread in group LEA. Another possibility is the

presence of various pressure gradients within the epidural space. Previous studies reported the possibility of lower pressure in the middle portion of the thoracic vertebral level might facilitate drug distribution from both low and high thoracic epidural injection sites to the mid thoracic level (Visser et al. 1998; Yokoyama et al. 2004; Lee et al. 2007). It may be speculated that the potential difference in the epidural pressure between these two epidural sites, which was relatively lower at the T7 to T10 level but relatively higher at the L2 to L4 level, may have caused the greater cranial distribution in group LEA. Moreover, the cranial epidurographic distribution was generally limited to the C5 and C6 levels in both groups (Fig. 2-2-2). The intervertebral foramina at the cervicothoracic vertebral level were relatively enlarged for the passage of the brachial plexus. Therefore, the contrast medium may be more easily to leak out from the epidural space at this level, resulting in the similar cranial distribution between TEA and LEA groups. On the other hand, although the contrast medium was distributed to a similar vertebral level cranially, the maximal CT values were significantly different between two groups. In group TEA, the maximal CT values were higher at the C7/T1 and T4/T5 levels, whereas in group LEA, they were higher at the T13/L1 and L4/L5 levels. High CT values indicated that a greater amount of contrast medium was distributed in the thoracic

vertebral region when it was epidurally injected from the thoracic vertebral level; meanwhile, more contrast medium was distributed in the lumbar region when it was injected from the lumbar level. This result is consistent with a previous a study indicating that spinal cord segments may receive more local anesthetic when the segment is closer to the injection site (Kamiya et al. 2009). It is implied that epidural anesthesia performed at the thoracic level may be useful for thoracic or upper abdominal surgeries because a greater amount of drug may be distributed to the target spinal cord in the related regions.

In experiment 2, the same single dose (0.2 mL/kg) was used in two Bolus groups as in experiment 1. The continuous infusion rate of 2% lidocaine (0.2 mL/kg/hr) used in two CRI groups followed the rate which has been reported in both humans and animals (Takasaki & Kajitani 1990; Iseri 2007). At this infusion rate, 2% lidocaine could decrease the consumption of sevoflurane and suppress the stress hormone responses better than 1% lidocaine (Shono et al. 2003). In an unpublished study, 2% lidocaine infused at the rate of 0.2 mL/kg/hr was known to provide a potent analgesic effect, but with less systemic accumulation (Iseri 2007).

Under isoflurane anesthesia, no significant differences in the number of vertebral segments reached by contrast medium were observed between ISO-Bolus and

ISO-CRI groups, mainly because contrast medium tended to leak out from the epidural space when it was administered continuously (Fig. 2-2-2). On the contrary, the maximal CT values were higher at C7/T1 and T4/T5 levels in group ISO-CRI than group ISO-Bolus over all measurement period. Moreover, compared with group ISO-Bolus, the CT values were well preserved after at 30 min after starting epidural infusion in group ISO-CRI. It may be speculated that the use of continuous epidural anesthesia may be more suitable for long time surgery because it could provide an effective concentration of drugs to the target segments.

Under propofol anesthesia, changes in either the epidural distribution of contrast medium or the maximal CT values were similar to those under isoflurane anesthesia. The total number of vertebral segments tended to increase time-relatedly, particularly within the initial 20 min (Table 2-2-1). Then median of spreading segments were higher in PRO-CRI group than PRO-Bolus group, although differences were not significant. Moreover, CT values were also significantly high at C7/T1 and T4/T5 levels compared with T13/L1 and L4/L5 levels in both Bolus and CRI groups under propofol anesthesia. In addition, although differences were not significant, CT values at T4/T5 level tended to decrease time-relatedly in PRO-Bolus group, whereas they were well maintained in PRO-CRI group throughout the measurement period. It is

also suggested that the ability of continuous epidural anesthesia in keeping concentration of epidural drugs, which could not be achieved by a single dose injection.

No differences was observed in either the total number of spreading segments or the maximal CT values between isoflurane and propofol anesthesia, which indicated that general anesthesia achieved by isoflurane (EtISO 1.8%) or propofol (30 mg/kg/hr) was unlikely to affect the spreading pattern of epidural drugs. However, it has to be noted that muscle tremors and myoclinic twitching, particularly in uni- or bi-forelimb(s), were observed in 3 specific dogs under propofol anesthesia, indicating an enhanced muscle tone in forelimb(s). But this phenomenon was not observed in any dog under isoflurane anesthesia. After the cessation of propofol infusion, muscle tremors disappeared gradually. Muscle tremors have been reported in both human and animals under propofol anesthesia (Robertson et al. 1992; Smedile et al. 1996; Walder et al. 2002). The exact reason was still unclear, a change of propofol cerebral concentration might be a potential causation (Walder et al. 2002).

In conclusion, results in this chapter showed that there were no differences in the total number of vertebral segments reached by contrast medium between thoracic and

lumbar epidural bolus injection, or between bolus injection and continuous infusion at the thoracic level under isoflurane and propofol anesthesia. However, thoracic epidurography could provide a relatively high concentration of contrast medium at thoracic vertebral level, and the concentration tended to be maintained during continuous thoracic epidural infusion. It may imply that the use of thoracic epidural anesthesia may be more suitable for surgery involving thoracic and upper abdominal regions, because it could provide an effective concentration of drugs at the target segments. Moreover, continuous epidural anesthesia is more suitable for long surgery and provides postoperative analgesia. In another hand, general anesthesia obtained by infusing propofol at a rate of 30 mg/kg/hr may be inadequate to provide a stable condition for surgical manipulations. Some adjuvant such as systemic opioids which is commonly used for the “balanced anesthesia” may be necessary.

Table 2-1-1 The total number of vertebral segments reached by contrast medium after epidurally injected a single dose of contrast medium at thoracic and lumbar vertebral level. The number of spreading segments was shown as median (min-max).

Group	Epidural puncture site	Epidural catheter tip location	Minutes after injecting a single dose of contrast medium				
			5	10	15	20	30
TEA	T12-T13	T7-T10	17.0 (12.5-22.5)	18.0 (14.0-24.0)	18.75* (14.0-26.0)	20.0*† (15.5-26.0)	20.25*†# (16.5-26.0)
LEA	L6-S1	L2-L4	18.5 (14.0-22.0)	19.75* (14.5-24.0)	20.0* (14.5-24.0)	20.5*† (14.5-24.5)	21.5*†# (14.5-24.5)

There were no significant differences in the number of spreading segments between two groups over all measurement time points. A time-related longitudinal extent of contrast medium was observed within each group.
C: cervical vertebra; T: thoracic vertebra; L: lumbar vertebra; S: sacral vertebra.
* Significant difference compared with 5 min, † Significant difference compared with 10 min, # Significant difference compared with 15min ($p < 0.05$).

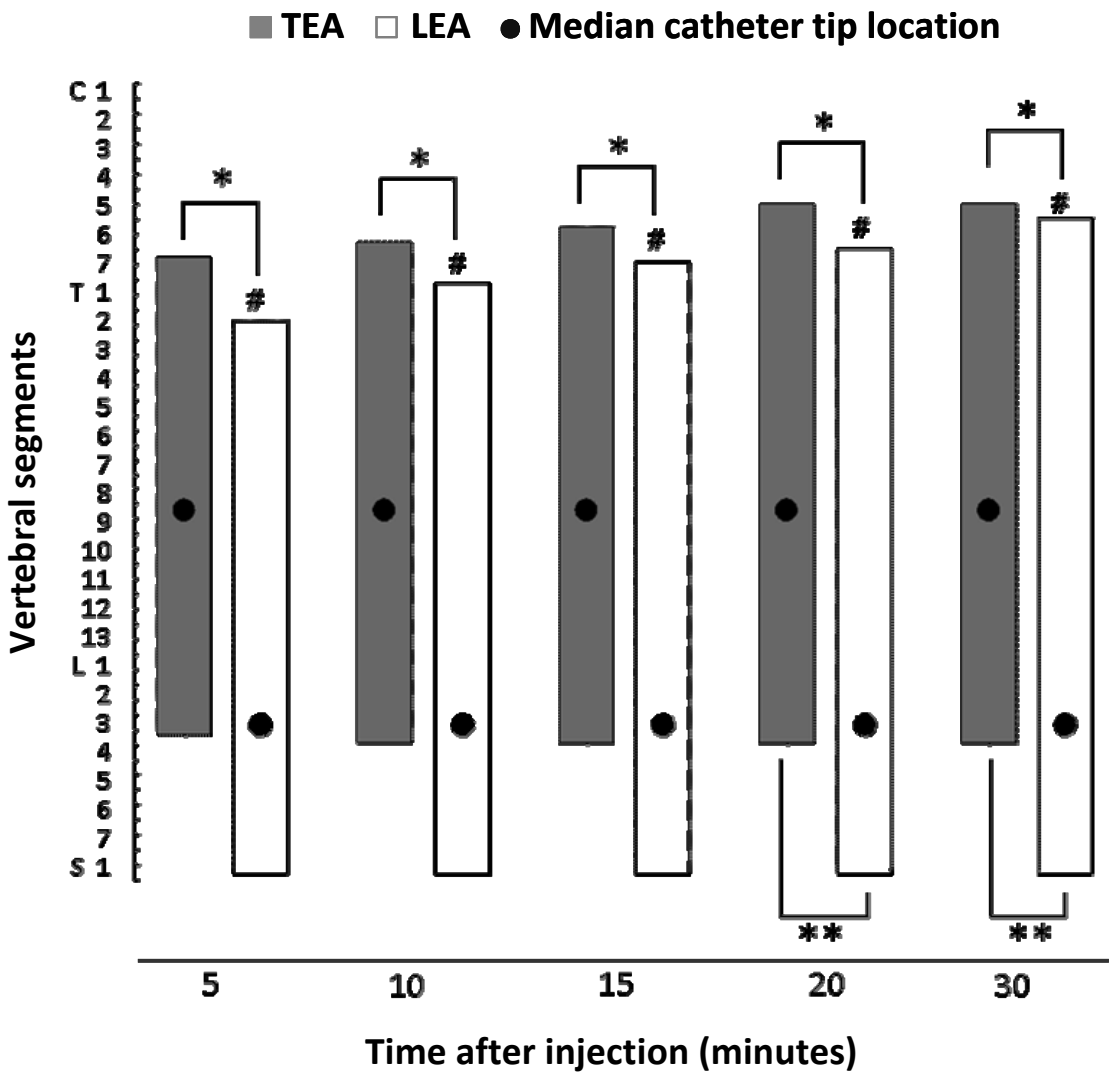

Fig. 2-1-1 Epidurographic distribution after injection of 0.2 mL/kg iohexol (140 mg I/mL) in TEA and LEA groups.
From the tip of the catheter, contrast medium equally spread in both cranial and caudal directions in group TEA, but it spread more cranially than caudally in group LEA.
C = cervical segment; T = thoracic segment; L = lumbar segment; S = sacral segment.
# Significant difference between cranial and caudal extents within each group ($p < 0.05$).
* Significant difference in cranial extent, ** Significant difference in caudal extent ($p < 0.05$).

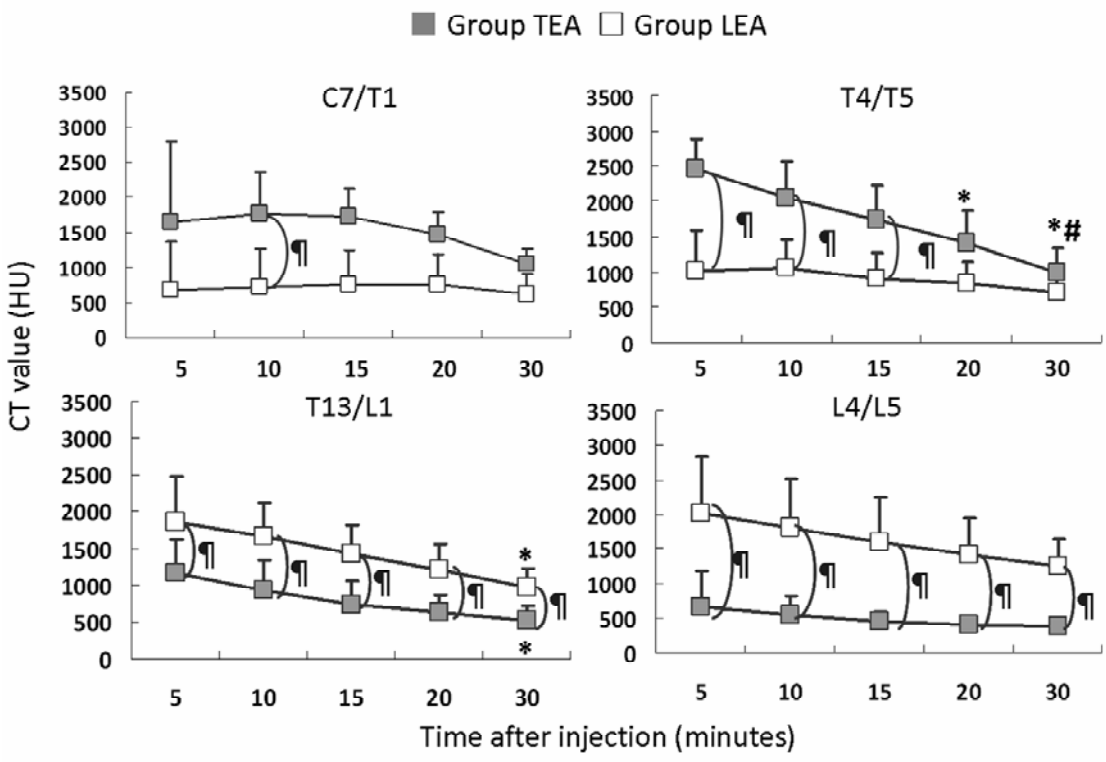

Fig.2-1-2 The maximal CT values at four selected vertebral levels over measurement time points between TEA and LEA group.

At T4/T5 level, in group TEA, the maximal CT values decreased significantly at 20 and 30 min after epidural injection compared with 5 min, and the value at 30 min was also significantly lower than that at 10 min. At T13/L1 level, the maximal CT values decreased significantly at 30 min after epidural injection compared with 5 min in both two groups. Between two groups, the maximal CT values were relatively high at C7/T1 and T4/T5 levels in group TEA, whereas they were significantly higher at the T13/L1 and L4/L5 levels in group LEA.

* Significant difference between 5 min, # Significant difference between 10 min ($p < 0.05$).

¶ Significant difference between TEA and LEA groups ($p < 0.05$).

Table 2-2-1 The total number of spreading segments after thoracic epidurography with a bolus injection and a continuous infusion of contrast medium under isoflurane and propofol anesthesia in dogs. The number of spreading segments was shown as median (min-max).

Group	Catheter insertion site	catheter tip location	Minutes after the initial dose of contrast medium injected at thoracic vertebral level				
			5	10	15	20	30
ISO-Bolus	T12-T13	T7-T10	17.0 (12.5-22.5)	18.0 (14.0-24.0)	18.75* (14.0-26.0)	20.0*† (15.5-26.0)	20.25*†# (16.5-26.0)
ISO-CRI	T11-T13	T6-T8	16.0 (13.5-19.5)	17.0* (13.0-19.5)	17.5* (13.0-20.0)	17.75*† (13.5-20.0)	18.5*† (14.0-20.5)
PRO-Bolus	T11-T13	T6-T9	16.5 (14.5-21.0)	18.0* (16.0-22.5)	18.5*† (16.5-24.0)	18.5*† (16.5-24.0)	19.25*† (16.5-24.5)
PRO-CRI	T11-T13	T6-T8	17.5 (14.5-21.5)	19.0* (15.5-22.5)	19.5* (18.0-24.0)	20.25*†# (18.5-25.0)	20.75*†# (18.5-25.0)

A time-related increasing extent of contrast medium was found in each of the four groups. Under either isoflurane or propofol anesthesia, no differences were found in the total number of vertebral segments reached by contrast medium between bolus injection and continuous infusion over all time points. No differences were found in the spreading segments between isoflurane and propofol anesthesia.
C: cervical vertebra; T: thoracic vertebra; L: lumbar vertebra; S: sacral vertebra.
* Significant difference compared with 5 min, † Significant difference compared with 10 min, # Significant difference compared with 15 min ($p < 0.05$).

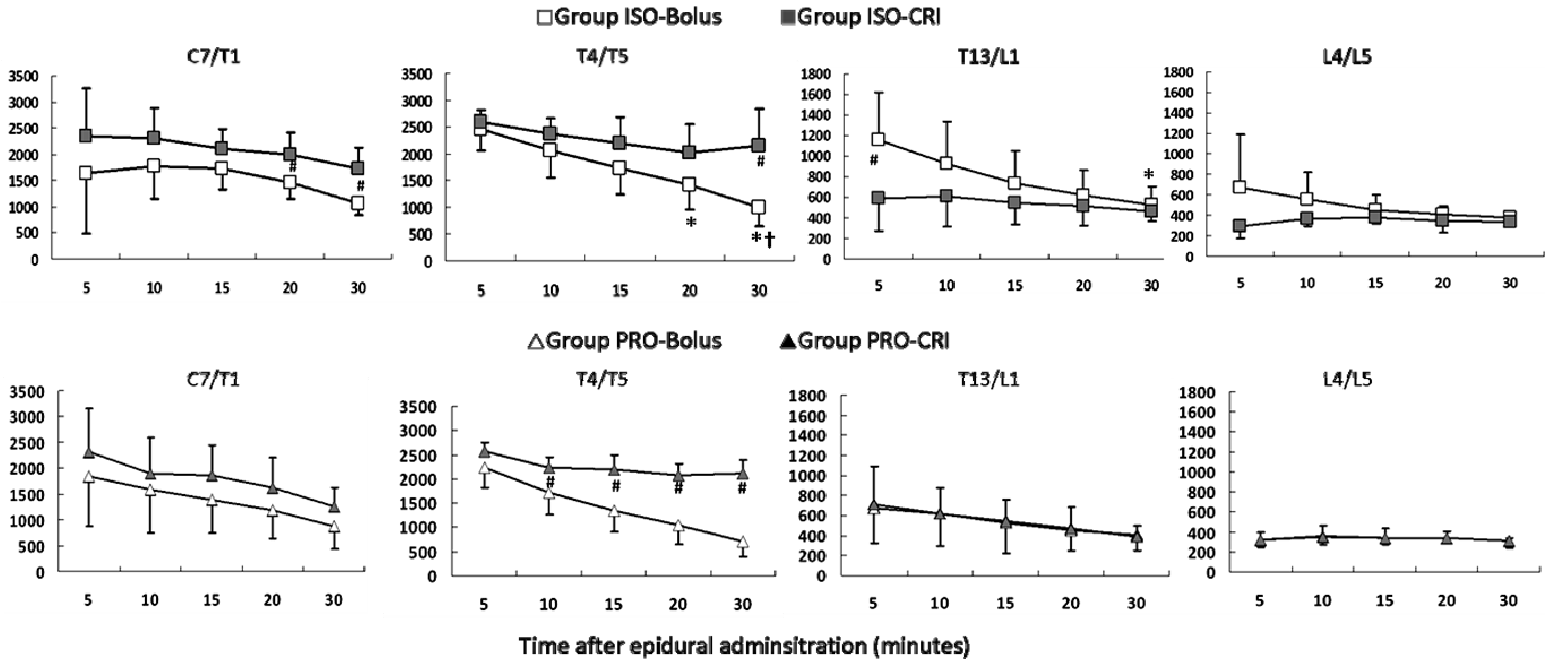

Fig. 2-2-1 The maximal CT values of the epidural space at four selected vertebral levels after thoracic epidurography with a bolus injection and a continuous infusion of contrast medium under isoflurane or propofol anesthesia.

In ISO-Bolus group, at T4/T5 and T13/L1 levels, the maximal CT values decreased significantly at 20 and 30 min after epidural injection. CT values were significantly higher at C7/T1 and T4/T5 levels than T13/L1 and L4/L5 levels in both ISO-Bolus and ISO-CRI groups. In group ISO-CRI, CT values were higher at C7/T1 and T4/T5, but relatively low at T13/L1 and L4/L5 levels compared with group ISO-Bolus. Under propofol anesthesia, the maximal CT values in both PRO-Bolus and PRO-CRI groups changed similarly to those under isoflurane anesthesia. There were no differences in the maximal CT value between isoflurane and propofol anesthesia.

* Significant difference between 5 min, † Significant difference between 10 min ($p < 0.05$).

Significant difference between Bolus and CRI groups ($p < 0.05$).

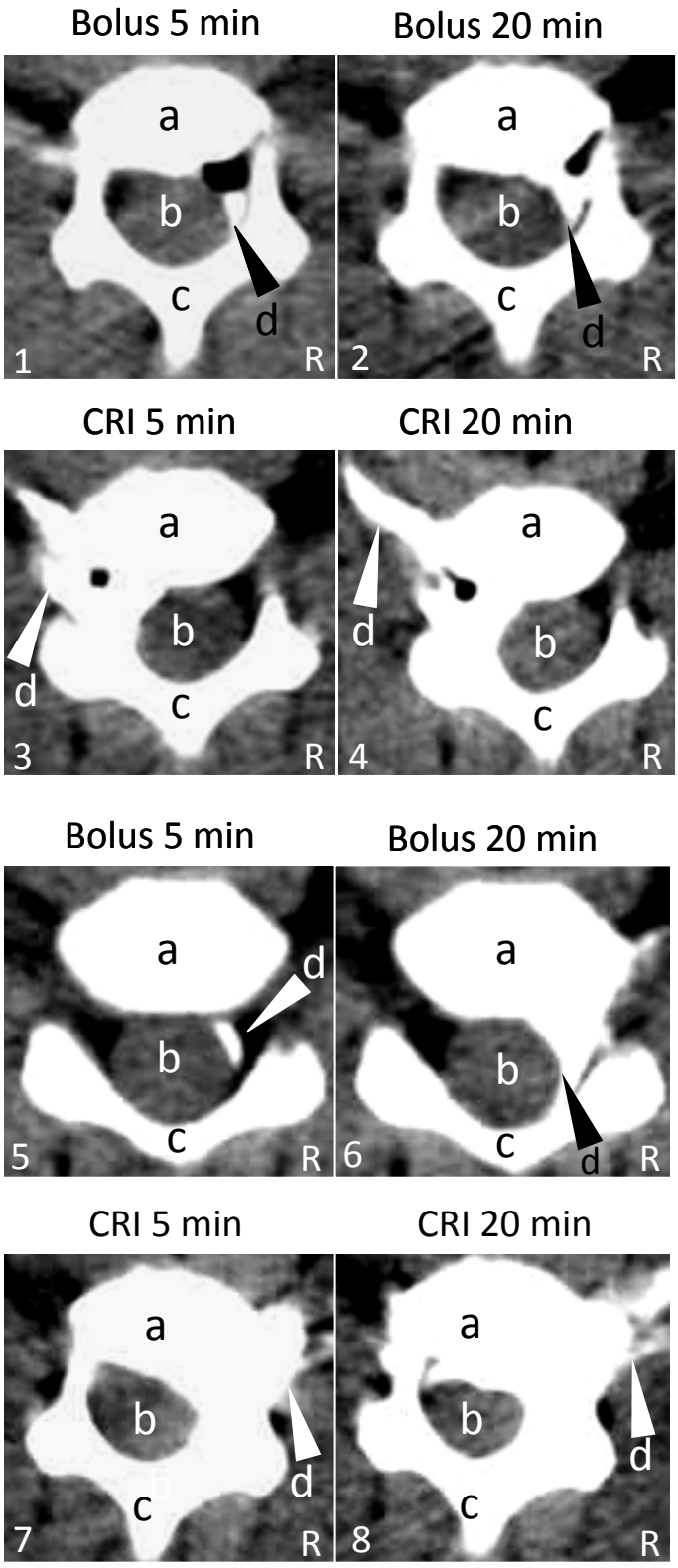

Fig. 2-2-2 Typical CT images of the extent pattern of contrast medium in the epidural space at C7/T1 vertebral level at 5 and 20 min after thoracic epidurography with a bolus injection (Bolus) and a continuous infusion (CRI).
1-4, under isoflurane anesthesia
5-8, under propofol anesthesia
a: centrum body
b: spine cord
c: vertebral arch
d: contrast medium
R: right side

Chapter 3

Cardiovascular effects of 2% lidocaine epidurally injected in bolus at low thoracic and lumbar vertebral segments combined with isoflurane or propofol anesthesia in dogs

Introduction

Results of previous chapters suggest that low thoracic epidural catheterization is feasible and safe in dogs. Epidural anesthesia induces different segmental neural blockade depending on the puncture site at which local anesthetics are injected. Thoracic epidural anesthesia is expected to be useful for surgeries involving thoracic and upper abdominal regions, while lumbar epidural anesthesia is frequently used for surgeries caudal to the umbilicus (Skarda & Tranquilli 2007 b). However, some adverse effects related to the use of epidural anesthesia have been reported. Cardiovascular effects after epidural injection of local anesthetics such as bradycardia and/or hypotension are of clinical importance particularly during surgery and anesthesia. In humans, cardiovascular effects of thoracic epidural anesthesia have been well studied but still controversial. Some studies revealed a modest but obvious decrease in heart rate, blood pressure and cardiac output, meanwhile in others, only a minor drop in blood pressure without significant change in cardiac output was observed (Peters et al. 1990; Lundberg et al. 1991; Raner et al. 1994; Licker et al. 1995; Nakayama et al. 2000; Clemente & Carli 2008). Discrepant conclusions may be partly due to the differences in study design such as premedication, general anesthetics, type of epidural injection drugs or drug dose,

volume and concentration. In veterinary medicine, few data of cardiovascular effects induced by thoracic epidural anesthesia are known. A decreased heart rate, mean arterial blood pressure, cardiac output and left ventricular function were reported in pentobarbital- or chloralose-anesthetized dogs after thoracic epidural anesthesia with bupivacaine (Hotvedt et al. 1984a, Lundberg et al. 1991). Unlike humans, epidural anesthesia is seldom used as a sole technique in dogs, because epidural needle puncture or catheter placement is difficult in conscious animals. Epidural anesthesia is commonly used as an adjunct technique in combination with general anesthesia. Therefore, the cardiovascular effects of epidural anesthesia should be evaluated under general anesthesia in dogs from the viewpoint of clinical application.

Hence, in this chapter, cardiovascular effects of thoracic and lumbar epidural anesthesia after a single dose of lidocaine combined with isoflurane or propofol general anesthesia were studied.

Materials and methods

This study was approved by the Animal Care Committee of the Graduate School of Agricultural and Life Sciences at the University of Tokyo.

Animals

Six beagles with a mean age of 21.8 months (range, 17 to 42 months) and mean body weight of 12.0 kg (range, 10.9 to 14.0 kg) were used in this study. Dogs were housed in individual cages in which temperature and humidity were kept constant. Food was withheld for at least 12 hour before each experiment, but water was available ad libitum. Each dog was used repeatedly with a washout period of at least 7 days.

Animal preparation and anesthesia protocol

Dogs were unpremedicated. They were generally anesthetized and monitored similarly as those described in chapter 2. A 22G IV catheter was placed into the cephalic vein for intravenous administration. Anesthesia was induced by either inhalation of 5% isoflurane (group ISO) or intravenous bolus injection of propofol (group PRO) with a dose of 6 to 10 mg/kg. After endotracheal intubation, anesthesia was maintained with the end-tidal concentration of isoflurane (EtISO) at 1.8% or continuous infusion of propofol at a rate of 30 mg/kg/hr for 2 hours in two groups,

respectively. The respiratory rate and the tidal volume were adjusted to maintain the end-tidal concentration of CO_2 ($EtCO_2$) between 35 and 40 mmHg by intermittent positive pressure ventilation (KV-1a; Kimura Medical Instrument Co. Ltd., Tokyo). Pure oxygen was delivered at 2 L/min and arterial oxygen saturation (SpO_2) was maintained above 98%. A 24G catheter was placed percutaneously in a dorsal pedal artery for measuring direct systolic, diastolic and mean arterial blood pressure (SAP, DAP, MAP) and collecting blood samples for blood gas measurements. Esophageal temperature was maintained within a range of 37.5 to 38.5℃ using a warm air blanket (Bair Hugger Mode 1505; Arizant Healthcare Inc; MN, USA). Lactated Ringer's solution (Lactated Ringer's Solution "Fuso", FUSO Pharmaceutical Industries, Ltd., Osaka) was used for intravenous infusion. The total infusion rate was kept at 10 mL/kg/hr throughout the experiment under either isoflurane or propofol anesthesia

Epidural catheterization

Procedures of the epidural puncture and catheterization were performed similarly as those in experiment 1 of chapter 2. Briefly, dogs were turned into sternal recumbency and were repeatedly treated with thoracic catheterization (group TEA) or lumbar catheterization (group LEA), with the epidural catheter indwelled into the

epidural space at T12 to L1 or L6 to S1 level, respectively. Catheter tip location in the epidural space was immediately confirmed by fluoroscopy after injecting a volume of iohexol (Omnipaque 300, Daiichi Seiyaku Co. Ltd., Tokyo).

Swan-Ganz catheterization and cardiovascular measurements

After epidural catheterization, dogs were placed left lateral recumbency. A 5F catheter introducer (Radifocus® introducer Ⅱ H; Terumo Corporation; Tokyo) was placed into the right jugular vein. Through the introducer, a 75-cm 5F Swan-Ganz thermodilution (TD) catheter (Swan-Ganz catheter Model 132F5; Edwards Lifesciences Inc., Tokyo) was advanced into the pulmonary artery. Correct placement of the TD catheter was confirmed by fluoroscopy and typical pressure waveforms. The thermodilution technique was used to determine cardiac output by injecting of 3 ml of 0 to 4℃ saline solution into the right atrium during end-expiration. Determinations were performed in triplicate, and their mean value was used as data.

Pulmonary arterial blood pressure (PAP), pulmonary capillary wedge pressure (PCWP) and cardiac output (CO) and central venous pressure (CVP) were measured through the Swan-Ganz catheter, and PAP, PCWP and CO were monitored using the same equipment (BSM-8301; Nihon Konden Corp., Tokyo). Other variables including HR, MAP, CVP, SpO_2, $EtCO_2$, EtISO as well as the esophageal

temperature were evaluated and monitored by a multi-function monitor (BP-508; Colin Medical Technology Corp., Aichi).

The derived cardiovascular variables were calculated by standard formulae: rate pressure product (RPP) = SAP×HR (mmHg·beat/min), cardiac output index (CI) = CO/body weight (L/min/kg), stroke volume index (SI) = CI/HR (L/beat/kg), systemic vascular resistance index (SVRI) = (MAP−CVP)/CO×79.9/body weight (mmHg·min/L/kg), pulmonary vascular resistance index (PVRI) = (PAP−PCWP)/CO×79.9/body weight (mmHg·min/L/kg), left ventricular work index (LVWI) = 0.0136×(MAP−PCWP)×SI (mmHg·L/beat/kg), right ventricular work index (RVWI) = 0.0136×(PAP−CVP)×SI (mmHg·L/beat/kg), coronary perfusion pressure (CPP) = DAP−PCWP (mmHg). All cardiovascular variables were recorded before (the baseline), immediately after epidural injection (T0), and followed by a 10-minute interval until 120 min (T120).

Arterial blood gas

Arterial blood pH, PO_2, PCO_2, $[HCO_3^-]$ and lactate level were measured using a commercial cartridge (i-STAT cartridge CG4+, i-STAT300F analyzer, Fuso Pharmaceutical Industries, Ltd. Osaka) by 0.5 mL blood sample withdrawn from the arterial indwelling catheter. Values were recorded at the baseline and 0, 10, 60 and

120 min after lidocaine epidural injection.

Propofol plasma concentration

In PRO-TEA and PRO-LEA groups, plasma concentration of propofol was measured before (the baseline) and 120 min after epidural injection (T120) using high performance liquid chromatography/fluorescence (FL-HPLC) method.

Experiment procedures

Animals were stabilized for twenty minutes after all preparation was performed, and the baseline values of all variables were measured. Then epidural anesthesia was achieved by a bolus injection of 2% lidocaine (Xylocaine® Injection 2%, AstraZeneca K.K., Osaka) at a dose of 0.2 mL/kg via a catheter over 1 min in all 4 groups. Cardiovascular variables, arterial blood gas and plasma concentration of propofol were measured at their specific time points.

Statistics analysis

Values were expressed as mean ± SD. Within each group changes over time were analyzed with one-way repeated analysis of variance (ANOVA) followed by Dunnett's (the baseline values *vs.* values at each time point) multiple comparison post-hoc test. Student's paired *t* test was used for paired data at the same time point between groups. A value of $p < 0.05$ was counted as statistically significant.

Results

Cardiovascular effects

Under isoflurane anesthesia

In both group ISO-TEA and ISO-LEA, there were no differences in all cardiovascular variables between the baseline values and values at following time points after epidural injection (Table 3-1). Results of HR, MAP, CI, SI, RPP and SVRI were shown in Fig. 3-1. Between two groups, MAP, CI, SI and RPP were relatively higher in group ISO-TEA. MAP was significantly higher in ISO-TEA than ISO-LEA group from 10 to 80 min after epidural injection. CI was significantly higher in ISO-TEA than ISO-LEA group at 30, 60, 70, 90, 110 and 120 min after epidural injection. SI was significantly higher in ISO-TEA than ISO-LEA group at the baseline and 0 30, 60, 70 and 110 min after epidural injection. RPP was significantly higher in ISO-TEA than ISO-LEA group at 20 to 60, 80 and 90 min after epidural injection. There were no differences in HR and SVRI between two groups (Fig. 3-1).

Under propofol anesthesia

The tendency of changes in cardiovascular variables under propofol anesthesia was generally similar to those under isoflurane anesthesia. HR was comparable

between groups, but the baseline values of MAP and SVRI were significantly higher in PRO-TEA and PRO-LEA groups than those in ISO-TEA and ISO-LEA groups respectively. In group PRO-TEA, except SI and LVWI decreased significantly at 10 min after epidural injection, there were no significant differences in other cardiovascular variables compared with their baseline values. In group PRO-LEA, MAP and CPP at 10 to 30 min and LVWI at 10 to 40 min decreased concordantly and significantly from the baseline values. Between PRO-TEA and PRO-LEA groups, values of MAP, CI, SI and RPP were lower in group PRO-LEA than group PRO-TEA. In group PRO-TEA, MAP were significantly higher from 10 to 40 min compared with group PRO-LEA. Values of CI and SI were higher in group PRO-TEA. Significantly higher values were found in group PRO-TEA at 0, 30 to 80 and 100 min in CI, and at the baseline, 0, 30 to 120 min in SI compared with group PRO-LEA. Values of SVRI and PVRI in group PRO-LEA were higher than those in group PRO-TEA. Significant differences were observed at the baseline, 0, from 40 to 80, 100 and 110 min in SVRI, and from 0 to 120 min except 20 and 90 min in PVRI. LVWI was higher in group PRO-TEA. Significant differences were observed from 0 to 110 min (except for 10 min). RPP changed similarly to MAP, with significantly lower values from 10 to 40 min in group PRO-LEA.CPP was more depressed in

group PRO-LEA, and significant lower values were found from 20 to 40 min compared with group PRO-TEA (Fig. 3-2, Table 3-1).

Arterial blood gas

All parameters were generally stable and changed within a clinical acceptable range throughout measurement time points. Under isoflurane anesthesia, lactate level in group ISO-LEA was higher than group ISO-TEA, with significant differences from the baseline to 60 min. Under propofol anesthesia, in group PRO-TEA, lactate decreased significantly at 60 and 120 min after epidural injection. Between group PRO-TEA and PRO-LEA, lactate level was higher in group PRO-TEA, with significant differences from the baseline to 10 min. The overall values of lactate in both TEA and LEA groups were higher under isoflurane than those under propofol anesthesia (Table 3-2).

Propofol plasma concentration

After endotracheal intubation, propofol was continuously infused at a rate of 30 mg/kg/hr for 2 hours in both PRO-TEA and PRO-LEA groups. Plasma concentration of propofol tended to decrease at 120 min compared with the baseline value in both two groups. Significant difference was found in group PRO-TEA ($p = 0.019$), but not in group PRO-LEA ($p = 0.71$). There was no difference in plasma concentration of

propofol between group PRO-TEA and PRO-LEA at each time point (Table 3-3).

Discussion

In this study, lidocaine was used for a local anesthetic injected into epidural space. Although lidocaine has some adverse effects and other new and safer local anesthetics are available, it is one of the most commonly used local anesthetics because of its effectiveness and cheapness. Therefore I used lidocaine in this study.

In ISO groups, no significant change from the baseline value was observed in any cardiovascular variable except for a temporary change. However, some significant differences were observed between group ISO-TEA and group ISO-LEA, cardiovascular variables were generally less depressed after thoracic epidural anesthesia than lumbar epidural anesthesia. Results of experiment 1 in chapter 3 showed that CT values were higher at C7/T1 and T4/T5 levels after thoracic epidural injection, but higher at T13/L1 and L4/L5 levels after lumbar epidural injection. Therefore, lidocaine may mainly distribute, with an effective concentration, in the thoracic region after thoracic epidural anesthesia, which may block the cardiac sympathetic and splanchnic nerves. While after lumbar epidural injection, lidocaine may mainly distribute in lumbar region, exerting its peripheral sympathetic blockade. Therefore more potent cardiovascular depression was predicted with thoracic epidural anesthesia than with lumbar epidural anesthesia. However, results obtained

in this study were opposite to what have been predicted.

Since systemic vascular resistance index was similar between two groups, changes in cardiac output index or stroke volume index were supposed to determine the changes of arterial blood pressure. Although the exact mechanism was unclear, the overall values of stroke volume index were higher in group ISO-TEA than group ISO-LEA, which indicated that ventricular function was less affected by thoracic epidural anesthesia. Similar results were found in healthy volunteers and in patients with heart disease. An improved ventricular perfusion after thoracic epidural anesthesia might be a potential cause (Ottesen et al. 1978; Kock et al. 1990).

The exact mechanism of action was also unknown, similar tendency in changes of cardiovascular variables was observed in PRO groups. In both PRO-TEA and PRO-LEA groups, arterial blood pressure and stroke volume index decreased after epidural injection, but arterial blood pressure was more substantially decreased in group PRO-LEA compared with the baseline value. Between two groups, cardiac output index, stroke volume index was significantly higher in group PRO-TEA than PRO-LEA, however a substantially high level of systemic vascular resistance index was observed in group PRO-LEA and maintained throughout all measurement time points, which indicated an enhanced vascular tone in dogs in group PRO-LEA.

It is hard to compare the cardiovascular effects of inhaled and injectable anesthetics, because the potential unequal anesthesia depths may contribute to the significantly higher baseline value of arterial pressure in PRO groups than in ISO groups. However, the doses used in this study, 1.73 ± 0.05% end-tidal concentration for isoflurane anesthesia and 30 mg/kg/hr for propofol anesthesia, were determined under the same standard in the pilot experiment (the minimal dose providing a smooth experiment condition, meanwhile avoiding severe cardiovascular depression). The concentration of isoflurane presents a modest anesthesia depth. The dose used for propofol anesthesia was slightly higher than the dose producing a light surgical anesthesia depth in dogs (Hall & Chambers 1987; Keegan & Greene 1993). Additionally, propofol infused at a rate of the 30 mg/kg/hr has been reported to produce comparable cardiovascular effects of isoflurane with approximately 1.9% end-tidal concentration (Cutfield et al. 1988; Puttick et al. 1992). Results indicated that differences in the baseline arterial pressures in PRO and ISO groups were mainly caused by the more potent vascular dilation effect of isoflurane as compared with propofol. It has been reported that isoflurane and propofol affect cardiovascular system by altering afterload and preload respectively by their selective vascular actions; a vasodilative effect of isoflurane and a venodilative effect of propofol

(Albertin et al. 2008).

It has to be noted that during propofol infusion, muscle tremors and myoclinic twitching were observed in 2 specific dogs. Because the motor nerves were blocked by epidural anesthesia, the intensity of muscle tremors and myoclinic twitching was impaired more or less after epidural injection. However since a possible limited cranial neural blockade after lumbar epidural injection this impairment effect of lumbar epidural anesthesia tended to be less than thoracic epidural anesthesia. Mild muscle tremors were still observed after lumbar epidural injection. Hence the enhanced muscular tone, which was more substantial in group PRO-LEA, may contribute to the high systemic vascular resistance index compared with PRO-TEA group.

The plasma concentrations of propofol tended to decrease in both two groups at 120 min compared with the baseline values, but it decreased significantly in PRO-TEA group. It has been known propofol is metabolized predominantly by the liver, so the liver perfusion may influence its blood concentration. Although liver blood flow was not measured in this study, it has been reported previously that thoracic but not lumbar epidural anesthesia increased liver blood perfusion (Kortgen et al. 2009). Therefore, after thoracic epidural lidocaine, changes in liver blood flow

may consequently affect propofol plasma concentration in PRO-TEA group.

In conclusion, cardiovascular variables were mildly affected after thoracic epidural anesthesia with a single dose of lidocaine compared with lumbar epidural anesthesia. Under propofol anesthesia combined with either thoracic or lumbar epidural anesthesia, the arterial blood pressure was well preserved. However, muscle tremors caused by the enhanced muscular tone may occur in some cases. In terms of cardiovascular effects, the use of thoracic or lumbar epidural anesthesia in combination with general anesthesia produced by isoflurane or propofol is clinically safety. However, the use of epidural anesthesia in combination with propofol infusion with a dose of 30 mg/kg/hr may be unable to provide a stable condition for surgical manipulations. Some adjuvant such as systemic opioids which is commonly used for the “balanced anesthesia” may be necessary.

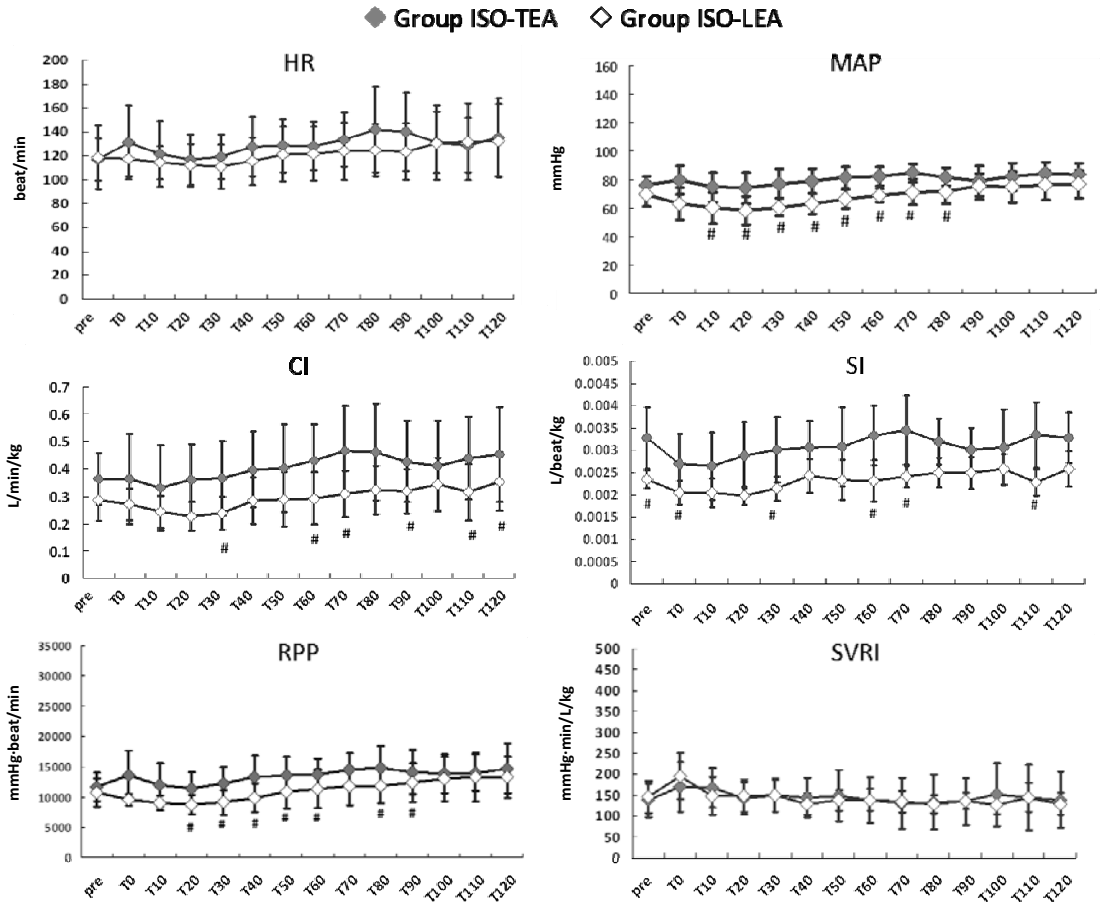

Fig. 3-1 Changes in heart rate (HR), mean arterial blood pressure (MAP), cardiac output index (CI), stroke volume index (SI), rate pressure product (RPP) and systemic vascular resistance index (SVRI) between two epidural groups under isoflurane anesthesia.

In HR, MAP, CI, SI, RPP and SVRI, no differences were found between the baseline values and values at following time points after epidural injection. Between two groups, MAP, CI, SI and RPP were relatively higher in group ISO-TEA. MAP was significantly higher in ISO-TEA than ISO-LEA group from 10 to 80 min after epidural injection. CI was significantly higher in ISO-TEA than ISO-LEA group at 30, 60, 70, 90, 110 and 120 min after epidural injection. SI was significantly higher in ISO-TEA than ISO-LEA group at the baseline and 0, 30, 60, 70 and 110 min after epidural injection. RPP was significantly higher in ISO-TEA than ISO-LEA group at 20 to 60, 80 and 90 min after epidural injection. There were no differences in HR and SVRI between two groups.

Significant difference between group ISO-TEA and group ISO-LEA ($p < 0.05$).

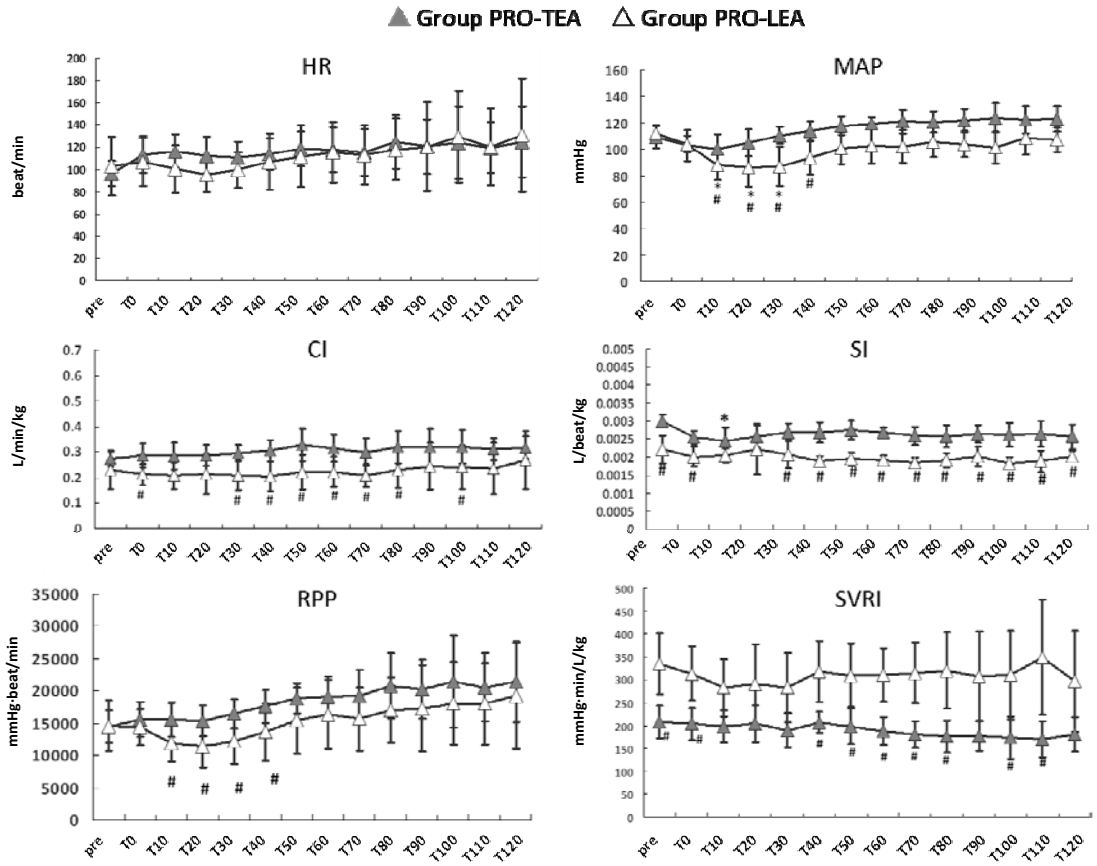

Fig. 3-2 Changes in heart rate (HR), mean arterial blood pressure (MAP), cardiac output index (CI), stroke volume index (SI), rate pressure product (RPP) and systemic vascular resistance index (SVRI) between two epidural groups under propofol anesthesia.

In group PRO-TEA, SI decreased significantly at 10 min after epidural injection. In group PRO-LEA, MAP decreased significantly from 10 to 30 min compared with the baseline values. Between two groups, MAP was significantly depressed from 10 to 40 min in group PRO-LEA compared with group PRO-TEA. RPP changed similarly to MAP, with significantly lower values from 10 to 40 min in group PRO-LEA. Values of CI and SI were lower in PRO-LEA than PRO-TEA group. Significantly lower values were found at 0, 30 to 80 and 100 min in CI, and at the baseline, 0, 30 to 120 min in SI. SVRI was higher in group PRO-LEA, and significant differences were observed at the baseline, 0, from 40 to 80, 100 and 110 min after epidural injection. No differences were found in HR between two groups.

* Significant difference between the baseline value ($p < 0.05$).

Significant difference between group PRO-TEA and group PRO-LEA ($p < 0.05$).

Table 3-1 Changes in cardiovascular variables after epidural bolus injection of 0.2 mL/kg of 2% lidocaine in four different anesthesia regimens. Data were shown as mean ± SD.

Cardiovascular variables	Groups	Baseline	Epidural injection of 2% lidocaine with a single dose of 0.2 mL/kg											
			T0	T10	T20	T30	T40	T50	T60	T70	T80	T90	T100	T110	T120
HR (beat/min)	ISO-TEA	116.7±17.9	131.2±31.1	121.7±27.3	116.7±20.9	119.0±18.9	127.7±25.0	128.5±22.3	128.2±20.1	133.5±22.6	141.7±35.7	140.0±32.6	131.2±25.5	129.0±23.1	135.3±32.5
	ISO-LEA	118.8±26.7	117.7±15.0	114.3±14.1	112.2±17.9#	111.0±18.7	115.5±20.0	121.3±22.6	121.7±22.3	123.8±23.9	124.7±21.9	123.7±23.1	130.8±31.0	131.8±32.0	132.5±30.7
	PRO-TEA	96.2±11.3	113.5±17.0	116.3±15.1	112.5±16.6	110.7±14.4	114±14.1	118.7±15.5	117.8±20.5	115.5±20.8	124.8±24.2	120.7±24.4	124.3±32.6	119.7±23.0	125±31.7
	PRO-LEA	103.3±26.3	106.8±21.6	100. 7±21.2	95.2±15.2	99.7±15.7	107.2±25.3	112.0±27.8	115.5±27.5	113.2±26.3	118.0±27.6	120.5±39.8	129.3±41.2	120.2±34.5	130.8±50.9
MAP (mmHg)	ISO-TEA	76.3±6.3	79.8±9.9	74.8±10.4	74.2±11.0	77.3±10.5	79.2±8.8	81.3±7.6	82.3±6.4	84.7±6.3	81.8±6.5	79.0±10.7	82.0±9.9	84.2±8.2	83.5±8.0
	ISO-LEA	69.8±9.6#	63.0±6.5#	60.2±7.0†#	58.5±7.5†#	60.7±9.6†#	63.0±10.6†#	66.3±11.5†#	69.2±11.8†#	71.2±11.4†#	71.5±10.8†#	75.5±11.3#	74.8±7.9#	76.2±10.1#	76.8±7.3#
	PROTEA	109.3±7.8†	119.8±17.7†	100.2±11.2†#	105.0±10.2†#	110.5±6.3†#	113.8±7.3†#	117.5±6.9†	119.3±4.6†	121.0±9.0†	120.7±8.3†	121.5±9.0†	123.7±11.1†	122.2±10.2†	123.0±9.5†
	PRO-LEA	112.0±5.7	103.8±6.3	88.0±11.5*	86.2±14.4*	87.0±14.7*	93.3±12.5	100.5±11.9	102.3±13.2	102.2±12.2	105.3±11.2	103.8±10.0	101.3±12.1	108.7±12.7	107.0±9.1
PAP (mmHg)	ISO-TEA	13.2±2.4	13.8±1.5	11.3±2.6	10.8±2.0	11.7±2.2	12.0±2.8	12.5±3.1	12.5±2.8	14.0±2.9	15.3±2.8	15.2±2.2	14.8±2.0	14.8±1.7	14.8±2.0
	ISO-LEA	13.3±2.3	15.0±2.5	12.3±1.4	12.2±1.1	12.5±1.3	12.7±1.2	13.3±1.4	13.3±1.9	13.3±1.7	14.7±1.8	14.3±1.8	15.0±1.6	15.2±2.0	15.2±1.6
	PRO-TEA	12.4±1.3	14.0±1.5	11.8±0.7	11.7±1.1	12.8±1.6	12.5±1.5	12.8±1.7	12.5±1.5	12.7±1.2	13.0±1.3†	13.3±1.4†	13.0±1.0†	12.8±1.5†	13.3±1.2
	PRO-LEA	13.2±1.7	13.21.1	12.2±1.6	11.8±2.5	12.7±1.2	12.7±1.4	13.5±1.8	13.7±1.5	13.7±1.4	14.2±2.1	14.0±2.4	14.2±2.4	14.0±1.8	14.3±2.4
PCWP (mmHg)	ISO-TEA	5.5±2.3	5.8±2.3	6.5±2.2	6.5±1.6	7.2±1.5	6.7±1.7	7.3±1.7	7.8±1.6	7.3±1.9	7.3±2.1	8.0±2.6	7.5±2.3	7.8±2.0	8.0±2.1
	ISO-LEA	5.7±2.1	6.2±3.1	5.5±1.7	5.8±2.3	5.8±1.6	5.8±1.9	5.8±2.0	6.2±2.4	6.7±2.4	7.0±2.9	6.5±2.4	7.4±3.0	8.0±3.5	8.8±1.9
	PRO-TEA	5.7±1.5	5.8±1.3	4.5±2.2†	4.8±2.1†	5.3±2.2†	5.0±1.8†	5.8±2.1	5.3±1.5†	5.7±1.8†	5.7±1.8†	5.7±1.8	5.8±2.0	6.0±1.5†	6.0±2.1
	PRO-LEA	5.7±1.9	5.7±1.2	5.5±1.4	5.5±0.8	5.7±1.1	6.0±1.4	5.5±2.1	5.8±1.3	6.2±2.5	6.7±2,7	6.7±3.1	6.3±3.5	6.8±2.7	6.5±3.4
CVP (cmH_2O)	ISO-TEA	1.2±1.1	1.2±1.3	1.8±1.6	2.0±1.2	2.2±1.2	2.0±1.2	1.7±1.4	2.2±1.2	2.3±1.5	2.0±1.7	2.3±1.5	2.3±1.9	2.3±1.9	2.0±2.0
	ISO-LEA	1.3±0.7	1.2±0.9	1.3±0.5	1.2±0.4	1.7±1.1	1.8±1.2	1.3±0.9	1.8±0.9	1.5±0.8#	1.5±0.8	1.8±0.9	1.8±1.1	1.7±0.7	1.8±0.7
	PRO-TEA	2.5±0.7#	2.5±0.5#	1.8±0.7	2.2±1.1	2.7±0.7	2.8±0.9	2.7±0.7†#	2.7±0.7#	3.2±0.7#	3.2±0.7#	3.2±0.4#	3.2±0.7#	3.2±0.7#	3.5±1.4#
	PRO-LEA	0.8±0.9	1.2±0.9	1.8±1.1	2.8±2.7	2.3±2.4	1.3±1.7	0.5±0.5	0.7±0.5	0.5±0.5	1.0±0.6	0.8±0.4	1.3±0.9	1.0±0.6	1.3±0.7
SVRI (mmHg·min/L/kg)	ISO-TEA	137.4±40.3	170.1±58.9	167.6±46.7	142.5±38.0	150.0±39.6	144.4±47.5	148.0±62.0	137.0±54.9	130.1±60.5	132.9±66.9	135.2±55.5	150.9±76.2	143.8±79.3	138.5±68.0
	ISO-LEA	145.0±38.1#	194.8±55.6#	146.7±45.2#	148.3±39.1#	148.6±39.1#	128.2±23.3#	136.8±25.5#	138.4±26.2#	133.3±25.9#	128.4±22.1#	135.8±19.0#	126.1±22.2#	144.6±34.4#	128.5±26.3#
	PRO-TEA	207.4±36.3†#	204.0±35.0†#	198.3±34.9	203.8±39.9†	189.4±37.9†	206.5±22.9#	198.2±38.2#	187.5±30.3†#	180.429.7†#	176.6±35.5†#	177.7±33.4†	174.0±46.6#	170.0±39.8#	179.9±37.8†
	PRO-LEA	334.8±67.3	313.4±59.6	283.1±63.1	290.0±87.6	283.4±75.0	317.5±66.9	310.1±69.1	311.0±58.0	315.2±66.6	320.2±83.2	307.3±97.5	310.7±97.1	349.3±126.5	296.6±110.9
PVRI (mmHg·min/L/kg)	ISO-TEA	14.3±6.0	16.4±8.1	11.1±7.5	8.3±3.7	10.8±4.8	12.2±5.5	11.1±6.6	9.7±5.2	10.6±5.4	12.3±4.6	12.0±4.4	13.1±5.7	12.0±6.9	11.0±4.6
	ISO-LEA	16.0±4.4	19.7±6.2	16.5±4.5	16.7±4.9	16.6±3.9	14.5±4.0	16.6±6.4	15.0±4.3	12.8±3.9	14.2±3.8	15.0±4.6	15.1±4.8	16.2±5.9	16.2±7.0
	PRO-TEA	16.3±5.7	15.1±5.3#	14.6±5.1#	16.7±6.3	14.2±4.3#	15.7±6.7#	15.4±6.6#	15.6±6.5#	13.9±6.7#	14.4±5.4#	15.4±4.9	15.0±6.6#	14.2±5.6#	14.7±4.9#
	PRO-LEA	23.2±7.5	22.7±3.4	21.9±4.1	23.0±11.1	23.6±6.5	23.3±6.0	25.0±6.2	24.3±5.8	23.6±6.6	23.0±6.5	21.1±6.2	24.3±8.2	23.6±8.4	20.7±4.9
CI (L/min/kg)	ISO-TEA	0.36±0.09	0.36±0.16	0.33±0.16	0.36±0.13	0.37±0.14	0.40±0.14	0.40±0.16	0.43±0.13	0.47±0.17	0.46±0.18	0.43±0.15	0.41±0.17	0.44±0.15	0.45±0.17
	ISO-LEA	0.29±0.08#	0.27±0.06#	0.24±0.06	0.23±0.05	0.24±0.06†	0.29±0.09#	0.29±0.10#	0.29±0.10†	0.31±0.09†#	0.32±0.09#	0.32±0.08†	0.35±0.10#	0.32±0.10†	0.35±0.11†
	PRO-TEA	0.27±0.03	0.29±0.05#	0.28±0.05	0.29±0.04	0.30±0.03#	0.30±0.04#	0.33±0.06#	0.32±0.05#	0.30±0.05†#	0.32±0.06#	0.32±0.07	0.32±0.07#	0.31±0.05	0.32±0.04
	PRO-LEA	0.23±0.07	0.21±0.04	0.21±0.05	0.21±0.08	0.21±0.06	0.21±0.06	0.22±0.07	0.22±0.06	0.21±0.04	0.23±0.07	0.25±0.09	0.24±0.09	0.24±0.10	0.27±0.11
SI (L/beat/kg) $\times10^{-3}$	ISO-TEA	3.28±0.69	2.70±0.66	2.64±0.76	2.89±0.74	3.01±0.73	3.07±0.60	3.09±0.88	3.33±0.67	3.44±0.79	3.20±0.52	3.01±0.49	3.07±0.86	3.34±0.74	3.28±0.57
	ISO-LEA	2.35±0.20†	2.05±0.27†	2.04±0.32	1.98±0.21	2.15±0.28†	2.43±0.38#	2.33±0.45#	2.32±0.47†	2.42±0.26†#	2.50±0.34#	2.49±0.35#	2.58±0.33#	2.28±0.29†	2.59±0.40#
	PRO-TEA	3.01±0.16#	2.54±0.19#	2.44±0.39*	2.57±0.30	2.69±0.24#	2.69±0.29#	2.75±0.27#	2.68±0.15#	2.60±0.25#	2.56±0.31#	2.65±0.25#	2.62±0.34#	2.64±0.36#	2.57±0.34#
	PRO-LEA	2.22±0.38	2.01±0.27	2.05±0.20	2.23±0.70	2.08±0.39	1.90±0.12	1.95±0.19	1.91±0.15	1.86±0.12	1.91±0.20	2.02±0.27	1.83±0.17	1.89±0.30	2.03±0.15
RPP (mmHg·beat/min)	ISO-TEA	11672.9 ±2322.6	13616.7 ±4015.2	11992.2 ±3603.9	11384.3 ±2685.0	12224.8 ±2725.2	13354.2 ±3503.6	13642.5 ±3007.0	13674.3 ±2595.3	14505.6 ±2723.5	14855.2 ±3554.6	14150.0 ±3621.3	13849.5 ±3272.3	14064.7 ±2970.9	14728.3 ±4140.0
	ISO-LEA	10712.8 ±2394.3#	9583.2 ±928.6	9063.8 ±1206.3	8781.2 ±1584.8†#	9123.7 ±2085.5†#	9868.7 ±2374.6†#	10877.8 ±2846.6†#	11375.0 ±3127.2†#	11786.0 ±3112.5#	11875.7 ±2838.1†#	12392.2 ±3264.5†#	13021.3 ±3703.8#	13275.8 ±3974.5#	13293.8 ±3454.7
	PRO-TEA	14502.7 ±2583.4	15604.2 ±2719.3	15555.3 ±2642.1#	15392.8 ±32373.1†#	16505.0 ±2264.3†#	17685.2 ±2541.7†#	18824.2 ±2347.1†	19063.2 ±3124.4†	19229.7 ±4038.7†	20809.0 ±5097.8†	20259.5 ±4543.4†	21478.0 ±7180.2†	20591.83 ±5284.5†	21424.5 ±6232.5†
	PRO-LEA	14612.0 ±3874.9	14385.8 ±2846.7	11938.2 ±2861.1	11398.2 ±3156.1	12205.8 ±3539.1	13661.0 ±4481.8	15465.3 ±5143.3	16377.8 ±5341.7	15688.7 ±4883.4	17031.7 ±5079.7	17345.2 ±6697.7	18087.8 ±6414.1	18046.7 ±6288.3	19226.2 ±8193.4

LVWI (mmHg·L/beat/kg) $\times 10^{-3}$	ISO-TEA	2.99±0.67	2.72±0.89	2.48±0.98	2.79±1.00	2.94±1.09	3.06±0.85	3.14±1.13	3.40±0.84	3.65±1.13	3.23±0.64	2.94±0.74	3.14±1.00	3.46±0.88	3.36±0.71
	ISO-LEA	2.09±0.45	1.59±0.23	1.56±0.27	1.44±0.30	1.59±0.40	1.92±0.63	1.95±0.69	2.06±0.69†	2.18±0.55	2.26±0.60	2.40±0.54	2.34±0.50	2.10±0.53†	2.46±0.50
	PRO-TEA	4.04±0.35†	3.93±0.64#	3.15±0.48*	3.50±0.53#	3.83±0.31#	3.96±0.33#	4.16±0.25#	4.14±0.12#	4.05±0.24#	4.00±0.31†#	4.16±0.36†#	4.16±0.26†#	4.15±0.47#	4.05±0.22
	PRO-LEA	3.19±0.51	2.68±0.39	2.30±0.40*	2.35±0.41*	2.25±0.30*	2.27±0.47*	2.53±0.47	2.52±0.45	2.42±0.33	2.58±0.47	2.67±0.48	2.38±0.40*	2.63±0.60	2.79±0.35
RVWI (mmHg·L/beat/kg) $\times 10^{-4}$	ISO-TEA	5.37±1.25	4.78±1.50	3.97±2.12	4.03±1.87	4.44±1.56	4.85±1.59	5.08±2.09	5.16±1.41	5.65±1.17	5.96±1.64	5.39±1.32	5.50±2.39	5.86±1.84	5.91±1.75
	ISO-LEA	3.88±0.81	3.88±0.88	3.15±0.72	2.64±0.67	3.12±0.60	3.56±0.83	3.76±0.85	3.69±1.00	3.99±0.90	4.59±1.00	4.31±0.75	4.71±1.00	4.37±1.17†	4.79±1.00
	PRO-TEA	4.10±0.51	4.01±0.67	3.31±0.49	3.32±0.51	3.74±0.60#	3.55±0.74	3.82±0.65	3.60±0.57†	3.34±0.33†	3.46±0.73†	3.65±0.50	3.48±0.36	3.43±0.38†	3.39±0.33†
	PRO-LEA	3.76±1.00	3.29±0.64	2.89±0.64	2.82±0.73	2.86±0.76	2.91±0.43	3.43±0.43	3.39±0.53	3.33±0.44	3.42±0.55	3.60±0.73	3.19±0.43	3.36±0.81	3.59±0.58
CPP (mmHg)	ISO-TEA	54.1±4.5	59.5±10.7	55.3±9.6	54.8±10.4	56.7±9.9	59.5±8.3	60.0±7.6	61.0±6.7	62.2±8.5	58.8±9.5	56.0±11.7	60.3±9.8	61.5±9.3	60.0±7.8
	ISO-LEA	51.2±9.8#	45.0±8.5	43.5±6.8	41.3±7.1	43.0±8.5	44.5±9.9#	47.8±10.8#	50.0±11.6#	51.2±11.3#	51.0±11.1#	55.0±11.5#	50.6±7. 3#	51.4±9.4#	50.8±6.4#
	PRO-TEA	84.0±7.8†	82.5±9.9†	78.7±12.8†	83.8±11.3†#	87.0±8.3†#	89.3±9.0†#	91.5±8.0†	93.3±6.4†	94.3±10.3†	94.5±8.7†	94.5±9.9†	95.8±10.2†	94.0±9.0†	94.7±10.0†
	PRO-LEA	87.3±7.4	80.3±5.3	67.0±9.5*	64.8±12.1*	65.5±12.1*	71.0±9.8	77.2±9.6	78.0±10.7	77.7±8.7	79.7±7.7	75.0±6.4	73.8±14.4	81.2±10.1	80.3±8.3

* $p < 0.05$ *vs*. baseline values.
† $p < 0.05$ *vs*. group ISO-TEA.
# $p < 0.05$ *vs*. group PRO-LEA

Table 3-2 Changes in arterial blood gas after epidural bolus injection of 0.2 mL/kg of 2% lidocaine in four different anesthesia regimens.

Arterial blood gas	Group		Baseline	Epidural injection of 2% lidocaine with a single dose of 0.2 mL/kg			
				T0	T10	T60	T120
pH	ISO	TEA	7.37±0.03	7.37±0.03	7.38±0.03	7.36±0.02	7.35±0.02
		LEA	7.37±0.02#	7.37±0.02	7.39±0.01#	7.37±0.02#	7.36±0.01#
	PRO	TEA	7.33±0.03	7.33±0.03†	7.33±0.02	7.33±0.02	7.35±0.02
		LEA	7.34±0.02	7.35±0.03	7.35±0.03	7.34±0.02	7.33±0.02
PCO_2 (mmHg)	ISO	TEA	41.6±1.7	40.3±2.3	37.0±7.0	40.0±1.6	40.8±1.8
		LEA	40.6±1.3	39.4±4.1	38.6±2.5	41.4±2.3	40.0±2.2
	PRO	TEA	44.6±1.0†	44.2±2.6†	43.4±1.5	42.2±1.1*†	41.4±1.6*
		LEA	43.1±4.5	41.7±1.9	40.6±2.3	41.1±2.7	41.8±2.2
PO_2 (mmHg)	ISO	TEA	581.2±31.8	478.1±193.3	483.3±126.0	547.7±23.2	536.5±29.3
		LEA	517.2±55.6†#	516.2±60.3#	520.2±81.0#	555.8±20.7#	511.0±50.9#
	PRO	TEA	640.2±19.3†	627.0±11.8	612.0±14.2	618.8±11.7†	605.8±37.2†
		LEA	627.3±14.5	647.5±15.3	630.3±18.0	618.2±28.3	621.2±29.2
BE (mEq/L)	ISO	TEA	-1.0±2.8	-1.7±2.3	-3.8±3.9	-2.5±2.1	-3.0±2.4
		LEA	-1.5±0.8	-2.5±2.0	-1.5±1.6#	-1.5±1.0#	-2.8±1.1
	PRO	TEA	-2.3±1.6	-2.8±1.6	-3.0±1.8	-3.2±1.1	-3.0±1.0
		LEA	-2.8±1.8	-2.8±2.0	-3.2±1.8	-3.8±1.6	-4.0±2.0
HCO_3^- (mmol/L)	ISO	TEA	25.7±5.9	23.3±2.0	21.3±3.9	22.6±1.8	22.1±2.0
		LEA	23.4±0.6	22.4±1.9	23.2±1.6	23.6±0.8#	22.4±1.0
	PRO	TEA	23.4±1.2	22.9±1.2	22.6±1.4	22.1±0.7	22.3±1.0
		LEA	22.8±1.8	22.6±1.6	22.3±1.3	21.8±1.5	21.6±1.6
TCO_2 (mmHg)	ISO	TEA	25.3±2.1	24.3±1.9	22.3±4.1	23.7±2.1	23.5±2.1
		LEA	24.5±0.7	23.3±2.2	24.2±1.8	24.5±0.8#	23.7±1.2
	PRO	TEA	24.7±1.2	24.0±1.2	23.8±1.8	23.2±0.9	23.5±1.0
		LEA	24.0±1.9	23.7±1.8	23.3±1.4	23.0±1.7	22.8±1.8
Lactate (mmol/L)	ISO	TEA	1.04±0.49	1.05±0.43	0.93±0.42	0.93±0.49	0.86±0.60
		LEA	1.99±0.56†#	2.02±0.55†#	2.00±0.62†#	1.46±0.34†#	1.22±0.37#
	PRO	TEA	0.77±0.19#	0.75±0.20#	0.72±0.19#	0.48±0.09*	0.39±0.07*
		LEA	0.47±0.20	0.48±0.28	0.46±0.23	0.38±0.13	0.42±0.26

* $p < 0.05$ *vs.* baseline values; † $p < 0.05$ *vs.* group ISO-TEA; # $p < 0.05$ *vs.* group PRO-LEA.

Table 3-3 Changes in plasma propofol concentration in PRO-TEA and PRO-LEA group. Data were shown as mean ± SD.

Group	Plasma propofol concentration (μg/mL)	
	Baseline	T120
TEA	13.9 ± 2.6	11.2 ± 2.6*
LEA	10.6 ± 2.8	9.8 ± 2.6

Plasma propofol concentration decreased in group PRO-TEA at T120 compared with the baseline. There was no difference of propofol plasma concentration between group TEA and LEA at each time point.

* Significant different between the baseline ($p < 0.05$).

Chapter 4

Cardiovascular effects of continuous low thoracic epidural anesthesia combined with isoflurane or propofol anesthesia in dogs

Introduction

Continuous epidural anesthesia with general anesthesia has been employed for major surgery. Except for providing potent anesthetic and analgesic effects during operation, continuous epidural anesthesia is also useful in postoperative pain relief with producing continuous analgesic effects. Additionally, the incidence of side effects tended to be reduced with the use of continuous infusion techniques (Mulroy et al. 1996).

Cardiovascular effects of epidural anesthesia may be various depending on method of drug delivery. Compared with intermittent bolus injection, continuous epidural infusion produces smaller circulatory fluctuations, which may be due to the consistent blood concentration of the drug during infusion (Kawamoto et al. 1991). Besides, epidural continuous infusion is thought to be superior to a bolus injection because it can produce a less peak concentration, which may decrease the potential for systemic toxicity (Jiang et al. 1997). Compared with human medicine, little information has been known about the cardiovascular effects of continuous thoracic epidural anesthesia with general anesthesia in dogs.

Local anesthetics absorbed via the venous plexus or lymphatic system into the circulation during continuous epidural anesthesia may cause systemic effects such as

convulsion or cardiovascular depression. Cardiovascular toxicity of local anesthetics may result from direct cardiac toxicity or systemic vasoactive effects and through the action on the autonomic nervous system. A safe dosage regimen for continuous epidural infusion of lidocaine has been established in humans (Takasaki et al. 1990; Fukuda et al. 2003). However because thoracic epidural anesthesia is not routinely used in veterinary medicine, little information is provided about cardiovascular safety of continuous thoracic anesthesia.

Besides, it has been reported that the additive used of epidural anesthesia may prolong the recovery time in humans (Inagaki et al. 1994). Similar data were only provided in dogs treated with lumbar but not thoracic epidural anesthesia (Sakonju et al. 2010).

Therefore, in this chapter cardiovascular effects of continuous thoracic epidural anesthesia of lidocaine at three infusion rates combined with isoflurane or propofol anesthesia in dogs were investigated. Besides, changes in serum lidocaine concentration, recovery quality and potential adverse events were compared among different anesthetic regimes.

Materials and methods

The present study protocol was approved by the Animal Care Committee of the Graduate School of Agricultural and Life Sciences at the University of Tokyo.

Animals

Six beagles with a mean age of 21.8 months (range, 17 to 42 months) and mean body weight of 12.0 kg (range, 10.9 to 14.0 kg) were used in this study. Dogs were housed in individual cages in which temperature and humidity were kept constant. Food was withheld for at least 12 hr before each experiment with water available ad libitum. All dogs were used repeatedly in different treatments separated by a washout period at least 7 days.

Animal preparation and anesthesia protocol

General anesthesia and monitoring were performed in the same way as described in chapter 3. A 22G IV catheter was placed into the cephalic vein for intravenous administration. Anesthesia was induced by either inhalation of 5% isoflurane (group ISO) or intravenous bolus injection of propofol (group PRO) with a dose of 6 to 10 mg/kg, and maintained with the end-tidal concentration of isoflurane (EtISO) at 1.8% or continuous infusion of propofol at a rate of 30 mg/kg/hr for 2 hrs in ISO and PRO group, respectively. The respiratory rate and the tidal volume were adjusted to

maintain the end-tidal concentration of CO_2 ($EtCO_2$) between 35 and 40 mmHg by intermittent positive pressure ventilation (KV-1a; Kimura Medical Instrument Co. Ltd., Tokyo). Pure oxygen was delivered at 2 L/min and arterial oxygen saturation (SpO_2) was maintained above 98%. A 24G catheter was placed percutaneously in a dorsal pedal artery for measuring direct systolic, diastolic and mean arterial blood pressure (SAP, DAP, MAP) and collecting blood samples. Esophageal temperature was maintained within a range of 37.5 to 38.5℃ using a warm air blanket (Bair Hugger Mode 1505; Arizant Healthcare Inc; MN, USA). Lactated Ringer's solution was used for intravenous infusion and the total infusion rate was adjusted at 10 mL/kg/hr throughout the experiment in both ISO and PRO groups.

Epidural catheterization

Procedures of the epidural puncture and catheterization were similarly to those in experiment 2 of chapter 2. Briefly, dogs were kept in sternal recumbency. Hair was clipped and the skin surface around the puncture site was sterilized according to a surgical preparation procedure. A Tuohy needle was inserted into the epidural space at T12 to L1 vertebral level. After confirming the correct needle placement by a positive loss of resistance test with saline, an epidural catheter was introduced cephalad 10 cm through the needle and indwelled in the thoracic epidural space.

Catheter tip location in the epidural space was immediately confirmed by fluoroscopy after injecting a volume of iohexol (Omnipaque 300, Daiichi Seiyaku Co. Ltd., Tokyo).

Swan-Ganz catheterization and cardiovascular measurements

The Swan-Ganz thermodilution (TD) catheter was used for measuring pulmonary arterial blood pressure (PAP), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP) and cardiac output (CO). Values of PAP, PCWP and CO were monitored by the same equipment (BSM-8301; Nihon Konden Corp., Tokyo). HR, MAP, CVP, EtISO, $EtCO_2$, SpO_2, lead II ECG and esophageal temperature were measured with a multifunction monitor (BP-508; Colin Medical Technology Corp., Aichi). Derived cardiovascular variables including RPP, CI, SI, SVRI, PVRI, LVWI, RVWI and CPP were calculated based on the above variables. All variables were recorded before (the baseline) and 0, 10 min, followed by a 10-minute interval until 120 min after the beginning of lidocaine continuous infusion (T0-T120).

Arterial blood gas

Arterial blood pH, PO_2, PCO_2, $[HCO_3^-]$ and lactate level were analyzed by a commercial cartridge with 0.5 mL arterial blood sample. Values were recorded at the baseline and 0, 10, 60, 120 min after starting epidural lidocaine infusion.

Lidocaine serum concentration

Arterial blood samples were collected at 15 and 120 min after starting continuous epidural infusion. Serum was separated by centrifugation. A minimum of 0.3 mL of serum was stored in a special tube and frozen at -80℃ until assayed. Serum concentration of lidocaine was evaluated by enzyme immunoassay (EIA) through a company (SRL, Inc. Tokyo).

Propofol plasma concentration

Under propofol anesthesia, plasma concentration of propofol was measured at the baseline and 120 min after the beginning of lidocaine epidural infusion by high performance liquid chromatography/fluorescence (FL-HPLC) method.

The recovery duration from extubation until sternal recumbency, and until the first instance of standing upright were recorded.

Experiment procedures

After completing of instrumentation and achieving a hemodynamic steady state, a volume of 2% lidocaine with dose of 0.2 mL/kg was injected through the catheter into the epidural space manually over one minute. Then a continuous epidural infusion was immediately started by using a syringe pump (top syringe pump Top-5500, TOP Corporation, Tokyo) at three infusion rates; 0.1, 0.2 and 0.4 mL/kg/hr,

which were regarded as group 0.1, group 0.2 and group 0.4 respectively. The epidural infusion of lidocaine was continued for 120 min. Cardiovascular variables, arterial blood gas, lidocaine and propofol concentration, as well as the recovery duration were record at their respective time points.

Statistical analysis

Values were expressed as mean ± SD unless otherwise stated. One-way repeated analysis of variance (ANOVA) was used for analyzing time-related differences followed by Dunnett's (between the baseline and following time points within each group) and Tukey-Kramer's (among groups) multiple comparison post-hoc test. A value of $p < 0.05$ was counted as statistically significant.

Results

In group ISO-0.1 and ISO-0.2, cardiovascular variables did not change significantly throughout the infusion period. In group ISO-0.4, RVWI decreased significantly from 50 to 120 min (except 80 min) after starting epidural infusion. While PCWP increased gradually over time, with significantly high values at 90 and 120 min compared with the baseline value. There were no differences between the baseline values and values at following time points in other cardiovascular variables (Table 4-1). MAP was generally comparable among three groups. It was significantly lower in ISO-0.1 group than ISO-0.2 group (75.0 ± 10.8 *vs.* 82.7 ± 7.2) at 10 min, in group ISO-0.4 than ISO-0.2 (69.8 ± 6.8 *vs.* 75.2 ± 8.4 and 66.5 ± 5.9 *vs.* 74.5 ± 7.3) at 60 and 100 min, and in group ISO-0.4 group than ISO-0.1 (66.0 ± 6.7 *vs.* 77.2 ± 8.5) at 110 min. Between group ISO-0.2 and ISO-0.4, significant differences in CI and SI were observed at the baseline, but no differences were found at the following time points after starting epidural infusion. SVRI was generally comparable among groups, but it was significantly higher in group ISO-0.4 than ISO-0.2 at 60 and 70 min No differences in HR, RPP were found among three (Fig.4-1).

Under propofol anesthesia, there were no differences in cardiovascular variables from their baseline values and values throughout following time points after starting

epidural anesthesia (Table 4-1). Among three infusion rate groups, HR was significantly lower at 10 min in group PRO-0.4 (100.3 ± 15.4) than those in PRO-0.1and PRO-0.2 groups (129.5 ± 36.2 and 113.7 ± 17.0), but all of them were within the normal range. MAP was more depressed in PRO-0.4 group than PRO-0.1 and PRO-0.2 groups. Significantly lower values in group PRO-0.4 were observed from 30 to 70 min than those in group PRO-0.1, and from 40 to 120 than those in group PRO-0.2. CI was also significantly depressed in group PRO-0.4, with significantly low values at the baseline, from 10 to 70 min, 90 and 120 min compared with those in group PRO-0.2. SI was less affected by different infusion rates. At 20 min, SI was slightly but significantly higher in group PRO-0.2 than those in PRO-0.1 and PRO-0.4 groups. At 120 min, SI was significantly depressed in PRO-0.4 group compared with the other two groups. At 40 min a significant higher SVRI was found between group PRO-0.1 and the other two infusion groups. RPP changed in a dose-dependent manner, with significantly lower values in PRO-0.4 group compared with other two groups throughout measurement time points (Fig. 4-2).

The overall values of MAP, LVWI and CPP were relatively high in three PRO groups than those in three ISO groups. CI and SI were less affected by the different general anesthetics. There were no differences between ISO-0.1 and PRO-0.1 groups

throughout measurement time points. In PRO-0.2 group, significantly higher values of SI were observed at the baseline, 0, 20, 70, 110 and 120 min than those in ISO-0.2 group. No differences were observed in CI between two groups. Between two 0.4 groups, the baseline value of CI was significantly higher in ISO-0.4 group, while SI values at 90, 100 and 120 min were significantly lower in ISO-0.4 group, compared with those in PRO-0.4 group. Differences of SVRI were more obvious between two 0.2 groups, with significantly higher values at the baseline, from 30 to 70, 90, 110 and 120 min in group PRO-0.2 than those in group ISO-0.2. RPP was more affected between two 0.1 groups, with significantly high values from 10 to 120 min (expect 60 min) in PRO-0.1 group compared with ISO-0.1 group (Table 4-1).

Arterial blood gas parameters were generally stable throughout measurement and changed within a clinical acceptable range. Under isoflurane anesthesia, arterial blood pH was higher than those under propofol anesthesia. There was a decreasing trend of lactate in all three infusion rate groups under either isoflurane or propofol anesthesia, but significant differences were only observed at in PRO-0.1 group, in which lactate was lower at 60 and120 min than the baseline value. Between groups, lactate was higher in three ISO groups than those in three PRO groups but no significant differences were found (Table 4-2)

In ISO-0.1 group, lidocaine concentration reached 2.4 ± 0.6 μg/mL at 15 min and decreased significantly at 120 min (1.4 ± 0.4 μg/mL, $p = 0.028$). No differences were observed between two time points in ISO-0.2 and ISO-0.4 group. Among three ISO groups, at 15 min after starting epidural continuous infusion, lidocaine concentration in group ISO-0.1 was significantly lower than that in group ISO-0.2 and ISO-0.4 (3.2 ± 0.9 and 3.0 ± 0.6 μg/mL). At 120 min, lidocaine concentration was significantly different among three groups, with its concentration of 1.4 ± 0.4, 2.4 ± 0.8 and 3.3 ± 0.7 μg/mL in group ISO-0.1, ISO-0.2 and ISO-0.4, respectively. In three PRO groups, changes in serum concentration of lidocaine were similar to those in three ISO groups. In group PRO-0.1, serum concentration of lidocaine decreased significantly at 120 min compared with that at 15 min ($p = 0.004$), but no differences were observed in PRO-0.2 and PRO-0.4 groups. Among three PRO groups, at 15 min, lidocaine concentration in group PRO-0.1 (2.4 ± 0.5 μg/mL) was significantly lower than that in group PRO-0.2 and PRO-0.4 (3.3 ± 0.8 and 3.5 ± 0.6 μg/mL). At 120 min lidocaine concentration was 1.2 ± 0.3, 2.4 ± 0.6 and 3.5 ± 0.5 μg/mL in group PRO-0.1, PRO-0.2 and PRO-0.4, respectively, which was significantly different among three groups. There were no differences in lidocaine concentration between two groups at the same lidociane infusion rate under isoflurane and propofol

anesthesia (Table 4-3).

At the baseline and 120 min, plasma concentration of propofol was 9.2 ± 2.9 and 8.0 ± 2.5, 12.7 ± 3.1 and 11.7 ± 3.4, 14.4 ± 4.0 and 14.1 ± 4.0 μg/mL in group PRO-0.1, PRO-0.2 and PRO-0.4, respectively. No difference was found between two time points in each of the three groups. There were no differences of propofol concentration among three groups at the baseline, but it was significantly higher in group PRO-0.4 than PRO-0.1 at 120 min ($p = 0.031$, Table 4-4).

In three ISO groups, time needed from extubation until sternal recumbency tended to increase concordantly with three incremental lidocaine infusion rates, but not significantly. Time needed from sternal recumbency until standing up and walking without aids increased dose-dependently. It was significantly longer in group ISO-0.4 than the other two groups ($p < 0.05$). Under propofol anesthesia, time from either extubation until sternal recumbency or from sternal recumbency until standing up and walking without aids was comparable among three infusion groups. Horner's syndrome was found in one dog in PRO-0.1 group, in 4 and 3 dogs in ISO-0.2 and PRO-0.2 group, respectively, and in all 6 dogs in both ISO-0.4 and PRO-0.4 groups. Muscle tremors and myoclinic twitching were found in 2 special dogs under propofol anesthesia, but not found in any dog under isoflurane anesthesa. One of the affected

dogs presented only in PRO-0.1 group, and the other tremored in all three infusion rate groups (Table 4-5).

Discussion

Under isoflurane anesthesia, except for right ventricular work index in group ISO-0.4, no significant changes were found in cardiovascular variables in three groups after the beginning of epidural continuous infusion compared with the baseline values over time. No significant incremental cardiovascular changes caused by continuous infusion of lidocaine were observed in any group. However, MAP was generally lower in ISO-0.4 group than in ISO-0.1 and ISO-0.2 group. Arterial blood pressure in ISO-0.4 group decreased about 15% from the baseline value at 90 to 120 min, but was still kept within the clinically acceptable range. There were no significant differences in heart rate, cardiac output index and stroke volume index among three groups after the beginning of epidural lidocaine infusion. In terms of cardiovascular effects, continuous thoracic epidural infusion of lidocaine at any rate of 0.1 to 0.4 mL/kg/hr is clinically acceptable. A temporary increase in systemic vascular resistance was observed in all three groups in the early period after starting epidural lidocaine infusion. This slight increase may be due to the stimulation of lidocaine injected into the epidural space.

A significant systemic accumulation of lidocaine was observed in ISO-0.2 (2.4 ± 0.8 μg/mL) and ISO-0.4 groups (3.3 ± 0.7 μg/mL) compared with ISO-0.1 group (1.4

± 0.4 μg/mL) at 120 min. It has been reported that lidocaine even at relatively low blood levels ranging from 3-7 μg/mL may induce mild myocardial toxicity in conscious humans (Reynolds et al. 1987). This finding suggests that blood concentrations should be maintained less than 3 μg/mL to secure a saftety margin under continuous administration. Hence, lidocaine continuous infused at the rate of 0.4 mL/kg/hr may be unsuitable for clinical use because of its potential toxicity. Besides, it has been reported that local therapeutic anesthetics at modest effective concentrations act as vasoconstrictors (Aps et al. 1975; Blair 1975). Moreover, the blood levels of lidocaine less than 4 μg/mL following epidural anesthesia could produce a slight blood pressure elevation due to the increased cardiac output (Bonica et al. 1970). It is suggested that in group ISO-0.4, a systemic lidocaine absorbed from the epidural space may impair the depression on arterial blood pressure by its vasoconstrictive effect and/or improving cardiac output.

Under propofol anesthesia, cardiovascular variables in three infusion rate groups changed similarly to those under isoflurane anesthesia, which were generally stable during continuous infusion and changed within the clinical normal range. However, a significant dose-dependent depression in arterial blood pressure, cardiac output and rate pressure product was observed among three groups, particularly between

PRO-0.4 group and the other two lower infusion rate groups. This is partly because of less cardiovascular depression by propofol which resulted in higher level of baseline values. The cardiovascular effects of higher dose of lidocaine may have become more apparent in PRO groups.

The serum concentrations of lidocaine in three PRO groups were comparable with those in three ISO groups, which indicated that propofol dose not inhibit lidocaine metabolism during epidural anesthesia. This finding is consistent with the result of a previous study (Nakayama et al. 2004). In another aspect, plasma concentration of propofol was significantly higher in PRO-0.4 than PRO-0.1 group at 120 min. It may be speculated that there is more propofol in the circulation in PRO-0.4 group, which may further deteriorate the relatively low blood pressure in this group.

Horner's syndrome (HS), charactered by miosis, ptosis and enophthalmus, was observed following continuous thoracic epidural anesthesia, and number of affected dogs tended to increase with the incremental infusion rate of lidocaine. In human, the HS occurring after epidural local anesthetic injection is though to be caused by interruption of ocular pre-ganglionic sympathetic neurons as the leave the spinal cord from C8 to T1 ventral roots. In dogs, the spinal sympathetic innervation of the eyes

synapses with neurons of the intermediolateral grey column nuclei (pre-ganglionic nuclei) at T1 to T3 level (Bosmans et al. 2009). Hence, results indicate that the neural blockade under continuous thoracic epidural infusion with lidocaine at a high rate may possibly achieve T3 or more cranial level, consequently blocking sympathetic nerves in those anesthetized segments. Besides, uni- or bilateral forelimb paralysis was observed in dogs in 0.2 and 0.4 groups under either isoflurane or propofol anesthesia, which is also suggested that the epidural blockade may have achieved C6 to T2 level when lidocaine was infused at a relatively high rate (Wayne 1999). The time from extubation until the position change (from left lateral recumbency to sternal recumbency) was not prolonged in any infusion rate group under either isoflurane or propofol anesthesia. But the time from the sternal recumbency to the first instance of stranding and walking was prolonged in both ISO-0.4 and PRO-0.4 groups, and it tended to be more substantial in the former (Table 4-5). It is suggested that blockade motor nerves may recover relatively rapidly after ceasing epidural lidocaine infusion at a rate lower than 0.2 mL/kg/hr.

In conclusion, under continuous thoracic epidural anesthesia of 2% lidocaine in combination with isoflurane or propofol general anesthesia, cardiovascular variables did not change significantly when lidocaine was infused at the rate of 0.1 and 0.2

mL/kg/hr. Arterial blood pressure tended to be depressed when lidocaine was infused at the rate of 0.4 mL/kg/hr, but it was still within the clinically acceptable range. A significant systemic accumulation of lidocaine was observed particularly in high infusion rate group. In the present study, cardiovascular changes may be due to both the sympathetic blockade of epidural anesthesia and a potential systemic effect of lidocaine absorbed from the epidural space during continuous epidural infusion.

With respect to cardiovascular effects, the use of combined isoflurane or propofol anesthesia with continuous thoracic epidural anesthesia of lidocaine may be applied in the clinical setting. However, caution should be advised when a high fusion rate is used because of its potential systemic accumulation and toxicity. Besides, since muscle tremors caused by an enhanced muscular tone may occur under propofol anesthesia, some adjuvant such as systemic opioids may be necessary.

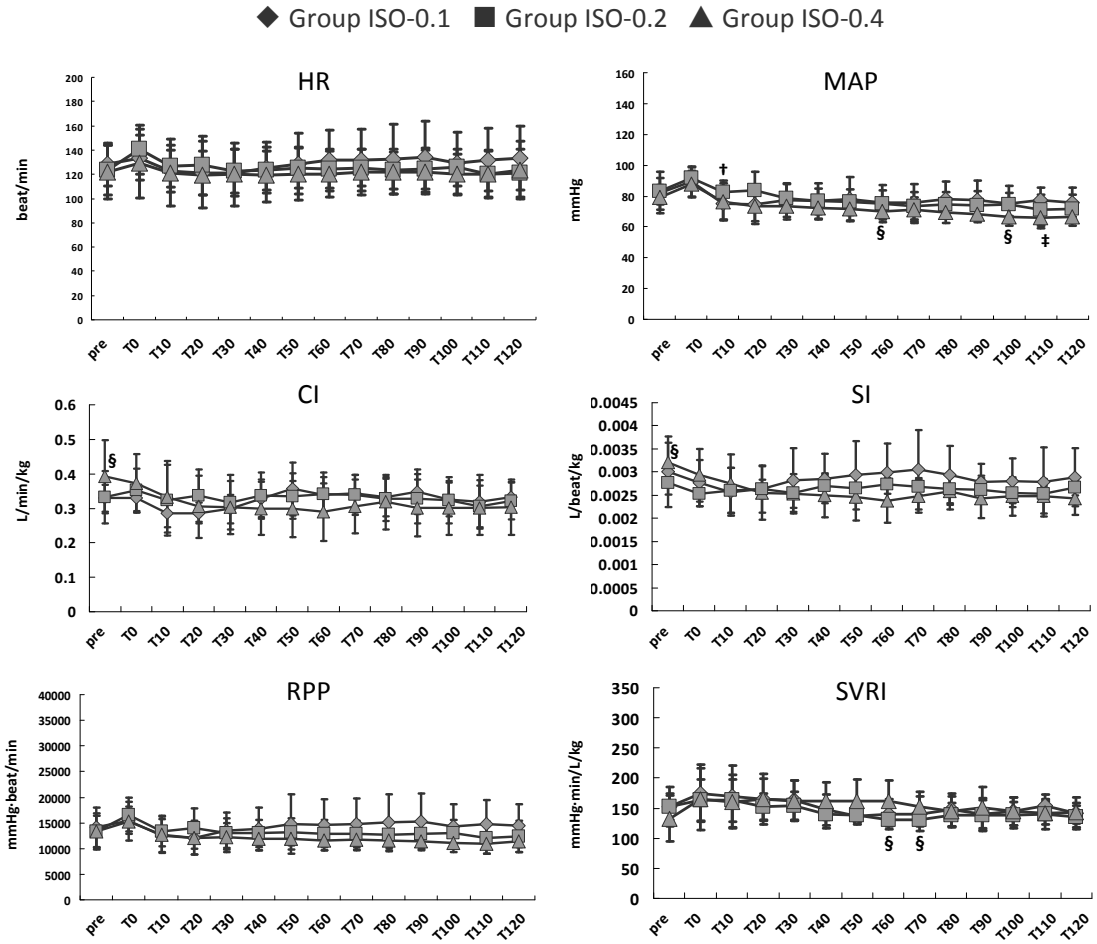

Fig. 4-1 Changes in heart rate (HR), mean arterial blood pressure (MAP), cardiac output index (CI), stroke volume index (SI), rate pressure product (RPP) and systemic vascular resistance index (SVRI) among three infusion rate groups under isoflurane anesthesia.

Cardiovascular variables were generally stable throughout measurement period. MAP was significantly lower in ISO-0.1 group than ISO-0.2 group at 10 min, in group ISO-0.4 than ISO-0.2 at 60 and 100 min, and in group ISO-0.4 group than ISO-0.1 at 110 min. The baseline values of CI and SI were significantly different between group ISO-0.2 and ISO-0.4. SVRI was generally comparable among groups, but it was significantly higher in group ISO-0.4 than ISO-0.2 at 60 and 70 min. No differences were found in HR and RPP.

† Significant difference between group ISO-0.1 and ISO-0.2, ‡ Significant difference between group ISO-0.1 and ISO-0.4, § Significant difference between group ISO-0.2 and ISO-0.4 ($p < 0.05$).

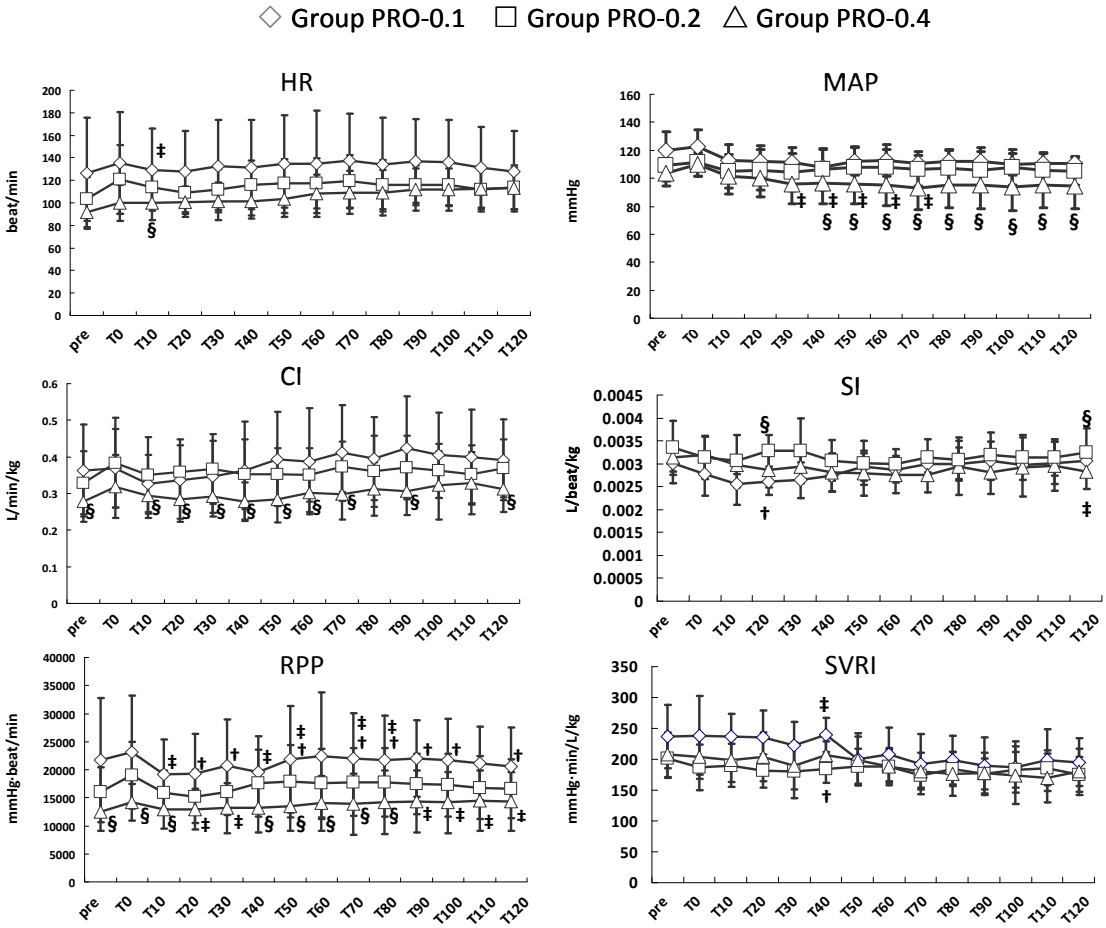

Fig. 4-2 Changes in heart rate (HR), mean arterial blood pressure (MAP), cardiac output index (CI), stroke volume index (SI), rate pressure product (RPP) and systemic vascular resistance index (SVRI) among three infusion rate groups under propofol anesthesia.

There were no differences in cardiovascular variables from their baseline values and values throughout following time points. HR was significantly lower at 10 min in group PRO-0.4. MAP was more depressed in PRO-0.4 group. Significantly lower values in group PRO-0.4 were observed from 30 to 70 min and from 40 to 120 min compared with group PRO-0.1 and PRO-0.2, respectively. CI was significantly depressed in group PRO-0.4, but SI was less affected by different infusion rates. At 40 min a significant higher SVRI was found between group PRO-0.1 and the other two infusion groups. RPP changed in a dose-dependent manner, with significantly lower values in PRO-0.4 group throughout measurement time points.

† Significant difference between group PRO-0.1 and PRO-0.2, ‡ Significant difference between group PRO-0.1 and PRO-0.4, § Significant difference between group PRO-0.2 and PRO-0.4 ($p < 0.05$).

Table 4-1 Changes in cardiovascular variables after thoracic epidural administration of 2% lidocaine with a bolus injection of 0.2 mL/kg followed by continuous infusion at three rates of 0.1, 0.2 and 0.4 mL/kg/hr. Data were shown as mean ± SD.

Cardiovascular variables	Groups	Baseline	Thoracic epidural administration a single dose of 0.2 mL/kg of 2% lidocaine followed by epidural 2% lidocaine continuous infusion at different infusion rates												
			T0	T10	T20	T30	T40	T50	T60	T70	T80	T90	T100	T110	T120
HR (beat/min)	ISO-0.1	128.1±17.4	133.7±18.3	122.5±17.4	120.8±18.2	121.3±19.0	125.3±21.0	128.7±24.9	131.3±25.2	131.8±25.6	132.5±28.6	134.3±29.3	129.3±25.6	132.0±25.9	133.3±26.2
	ISO-0.2	123.1±20.6	140.3±20.5	126.8±17.3	127.2±24.0	122.5±17.9	123.3±16.1	125.5±16.9	124.5±15.8	125.5±15.3	123.3±15.3	124.7±16.8	125.7±15.2	120.1±19.5	121.2±19.9
	ISO-0.4	121.9±22.3§	129.0±28.3§	121.3±27.4	119.7±27.3	119.8±25.9	119.7±22.6	120.5±21.4	120.2±19.2	122.0±18.8	122.0±18.6	121.5±18.0	120.0±16.8	120.0±19.0	123.5±23.6
	PRO-0.1.	126.4±49.2	135.2±45.2	129.5±36.2	127.8±35.9	132.5±41.2	131.0±42.4	134.5±43.4	134.7±47.3	137.3±42.1	133.8±41.8	137.0±37.1	135.8±37.7	131.5±35.6	128.0±35.7
	PRO-0.2	103.4±19.2	121.0±30.4	113.7±17.0§	108.8±18.5	111.8±18.1	116.2±21.6	117.3±21,4	117.7±22.2	119.2±23.5	116.2±21.9	115.7±17.9	115.8±18.7	111.7±19.4	113.8±19.6
	PRO-0.4	92.0±13.6	100.2±15.9	100.3±15.4¶	101.0±13.5	101.7±16.7	101.3±15.4	103.5±15.9	108.0±17.0	109.3±19.1	109.0±19.9	111.7±18.7	111.5±18.7	112.8±18.7	113.0±18.3
MAP (mmHg)	ISO-0.1	82.2±13.5	89.3±9.4	75.0±10.8	74.3±10.6	77.2±10.9	76.7±11.6	77.8±14.3	75.8±11.3	75.8±12.0	78.0±11.5	77.5±12.5	75.3±11.5	77.2±8.5	75.8±9.5
	ISO-0.2	83.0±8.6	92.0±7.1	82.7±7.2†	83.5±12.1	78.7±8.8	76.8±8.3	76.0±8.1	75.2±8.4	73.7±8.7	74.3±8.0	73.8±9.1	74.5±7.3	70.8±10.3	71.8±9.1
	ISO-0.4	79.0±8.1§	87.8±8.6§	76.5±11.5§	73.5±11.4§	73.2±8.6§	72.2±6.6§	71.5±7.1§	69.8±6.8‡§	70.8±8.1§	69.5±7.0§	68.2±5.1§	66.5±5.9‡§	66.0±6.7†§	66.5±5.5§
	PRO-0.1	120.0±13.0†	122.7±11.7†	112.5±11.4†	112.2±11.2†	111.3±10.4†	108.2±12.1†	112.3±9.9†	112.7±11.1†	111.0±5.4†	111.8±7.8†	112.2±9.7†	110.0±7.6†	110.3±7.2†	110.7±5.2†
	PRO-0.2	109.0±11.1‡	111.3±9.7‡	105.2±11.8‡	105.8±14.4‡	104.3±13.1‡	106.5±14.6‡§	107.7±15.0‡§	107.7±13.0‡§	106.5±12.4‡§	107.2±13.4‡§	106.0±12.9‡§	107.7±12.7‡§	106.0±12.7‡§	105.2±10.0‡§
	PRO-0.4	103.7±8.9	109.8±8.5	101.2±12.3	100.0±13.5	96.2±14.3¶	96.5±14.6¶	96.2±14.7¶	95.3±14.7¶	93.2±15.6¶	95.3±16.5	95.0±16.7	93.5±16.3	94.8±15.7	94.5±16.2
PAP (mmHg)	ISO-0.1	13.5±1.6	14.2±1.5	12.8±0.7	12.5±1.0	12.8±1.1	13.0±1.2	13.3±1.2	13.3±1.1	13.3± 1.1	13.5± 1.7	13.7± 1.2	13.5± 1.0	13.5±1.3	13.5±1.4
	ISO-0.2	14.8±2.4	15.3±1.2	13.8±1.7	14.3±1.7	14.2±1.1	13.8±0.9	14.3±0.9	14.3±1.4	14.2±1.3	14.2±1.1	14.2±0.9	14.2±0.9	14.5±1.3	14.3±1.2
	ISO-0.4	14.3±1.5§	15.0±0.8§	13.7±1.1§	13.3±0.9	13.3±0.7§	13.5±0.5	13.5±0.8§	13.7±0.7	14.0±0.8	14.2±0.7	14.3±0.5§	14.2±0.4§	14.0±0.6	14.3±0.5§
	PRO-0.1	16.0±2.8	16.0±2.4	15.3±1.4	16.0±1.3	16.0±1.0†	15.7±1.2	15.2±2.5	15.7±1.4	16.0±1.5	15.7±1.4	15.3±1.4	15.5±1.3	15.2±1.9	15.7±1.7
	PRO-0.2	11.8±1.6	12.2±1.7‡	12.5±2.2	12.0±2.2¶	12.2±2.0¶	12.0±2.2¶	12.3±2.1¶	12.0±1.8	12.3±2.1¶	12.5±2.4	12.7±1.9¶	12.5±1.9¶	12.3±2.0	12.8±2.0¶
	PRO-0.4	12.8±0.9¶	12.8±0.7	12.7±0.7¶	13.0±1.2¶	12.5±1.1¶	12.5±1.0¶	12.2±1.3¶	12.7±1.7	12.2±1.3¶	12.7±1.2¶	12.5±1.3¶	12.8±1.5¶	12.8±1.6	12.8±1.2¶
PCWP (mmHg)	ISO-0.1	5.5±2.1	5.7±2.2	5.3±2.2	5.5±2.0	5.5±2.4	5.2±2.0	5.5±2.2	5.6±2.4	5.3±2.5	5.3±2.7	5.8±2.3	6.0±2.6	6.0±2.3	5.7±2.4
	ISO-0.2	8.7±1.2	8.2±1.3†	8.2±1.7†	9.0±2.7†	8.7±1.8†	8.3±1.1†	8.5±1.4†	9.2±1.3†	9.2±1.6†	8.2±1.8	9.0±1.3†	8.7±1.1	9.2±2.0	9.0±1.7†
	ISO-0.4	6.3±1.9‡	6.8±1.7‡	7.7±1.4§	7.3±1.8	7.2±1.5	7.8±1.2†§	8.2±1.3§	8.6±0.8§	8.4±1.5§	8.6±1.5§	9.4±2.1*§	9.0±1.1§	9.0±1.4§	9.6±1.7*§
	PRO-0.1	6.8±1.2	6.7±1.4	6.6±1.9	7.2±1.8	7.5±1.7	6.7±1.7	7.5±2.1	7.0±1.7	7.3±2.0	6.8±1.5	6.7±1.5	7.2±1.6	6.8±1.6	6.8±2.0
	PRO-0.2	5.3±0.7¶	5.3±1.1¶	5.8±2.0	6.0±1.5¶	5.8±1.8¶	5.7±1.8	5.5±1.7	5.8±1.5¶	6.2±1.7¶	6.3±1.8	6.2±2.0	6.2±1.6	6.2±2.0	6.3±2.1
	PRO-0.4	5.7±1.5	5.3±1.1¶	5.8±1.3	5.6±1.5	5.8±1.5	5.7±1.7	5.5±1.9	5.3±1.6	5.7±1.2	5.7±1.4¶	5.4±1.5	5.5±1.4	5.7±1.5	5.5±1.4
CVP (cmH_2O)	ISO-0.1	1.8±2.5	1.3±1.6	1.2±1.5	1.5±1.4	1.5±1.8	1.3±18	1.5±1.9	1.3±1.8	1.3±2.6	1.8±2.1	1.8±2.1	1.7±2.2	2.0±2.4	1.8±2.1
	ISO-0.2	2.2±1.7	2.2±1.7	2.8±1.5	2.7±1.5	2.8±1.6	2.8±1.9	3.0±2.0	3.5±1.7†	3.0±1.9	3.4±2.7	3.3±2.1	3.3±2.1	4.2±2.5	3.3±2.1
	ISO-0.4	2.0±1.3	2.0±0.6	2.3±1.2	2.8±1.6	3.2±1.2§	3.5±1.5§	3.5±1.5§	3.8±2.1§	3.8±2.0§	3.7±2.2	4.3±2.4§	4.5±2.1§	4.7±2.2§	4.5±2.6§
	PRO-0.1	3.2±1.3	3.0±1.5	3.5±1.1†	3.2±1.1†	3.2±1.3	4.2±1.6†	3.3±1.1	3.7±1.2†	3.5±1.3†	3.3±1.6	3.8±1.3	3.5±1.4†	3.8±1.3	3.7±1.4†
	PRO-0.2	1.7±1.2	1.3±1.1	1.5±1.3¶	1.8±1.2	1.7±1.4	2.0±1.4	2.2±1.3	2.0±1.4	2.5±2.1	2.3±1.2	2.3±1.5	2.5±1.7	2.3±1.5	2.7±1.8
	PRO-0.4	1.8±1.2	1.5±1.4	1.8±1.1¶	1.7±1.5	1.8±1.3	2.0±1.4¶	1.8±1.7	2.0±1.4¶	2.0±1.6	2.2±1.8	2.2±1.8¶	2.2±1.5	2.2±1.5	2.2±1.5
SVRI (mmHg·min/L/kg)	ISO-0.1	152.1±32.5	174.9±47.5	169.8±51.4	164.8±42.1	163.0±32.2	147.2±25.1	137.3±13.8	140.6±24.7	140.2±28.8	147.4±27.0	139.3±27.7	144.6±22.6	154.1±19.4	141.6±17.3
	ISO-0.2	151.8±21.7	163.5±33.9	162.8±35.4	152.5±22.2	153.9±24.2	139.8±22.5	138.7±9.9	131.3±11.1	131.4±11.0	138.5±20.0	139.0±25.1	138.6±21.3	140.0±25.5	134.7±20.0
	ISO-0.4	132.6±37.8§	164.7±51.0	160.6±44.0	164.6±34.8	162.2±33.3	161.6±31.2§	162.2±35.8	162.0±33.9‡	152.6±24.0‡	144.7±25.5	151.6±34.2	144.5±23.3	141.7±19.6	142.9±24.6
	PRO-0.1	236.5±51.5	238.3±64.0	236.2±37.9	235.3±44.3	222.6±37.9	239.3±27.7†	200.0±42.2	207.7±43.1	192.0±48.5	198.7±39.5	188.9±47.1	187.4±41.6	198.6±49.5	195.2±39.0
	PRO-0.2	201.7±31.7‡	187.0±36.6	189.6±34.9	181.4±27.1	180.4±43.5‡	184.5±23.2‡¶	187.7±29.9‡	188.6±26.9‡	173.9±20.6‡	184.3±27.5	176.2±24.9‡	183.0±28.6	185.7±28.1‡	175.6±28.2‡
	PRO-0.4	207.4±36.3	204.0±35.0	198.3±34.9	203.8±39.9	189.4±37.9	206.5±22.9¶	198.2±38.2	187.5±0.3	180.4±29.7	176.6±35.5	177.7±33.4	174.0±46.6	170.0±39.7	179.9±37.8
PVRI (mmHg·min/L/kg)	ISO-0.1	15.9±3.4	16.8±3.7	16.8±4.4	15.6±3.8	15.6±3.1	16.3±4.5	15.8±4.8	16.4±4.8	16.0±4.5	16.8±4.3	15.3±3.6	16.4±5.7	16.6±3.5	16.2±4.7
	ISO-0.2	11.3±1.9†	12.7±2.8	11.6±3.3	10.1±2.2†	10.8±1.9†	9.8±1.8†	10.6±2.8	9.4±2.4†	9.3±3.2†	11.7±3.6†	9.5±2.7†	11.0±3.3†	10.7±3.4†	10.3±4.0†
	ISO-0.4	13.8±2.3‡	15.5±3.3	13.0±3.2	14.6±5.6	14.1±3.1	13.7±5.0	12.7±3.1	12.9±3.9	12.7±3.1	12.3±3.1†	11.7±4.3	12.8±3.0	11.9±1.9†	11.6±4.5
	PRO-0.1	17.0±4.2	17.1±5.4	15.5±4.3	17.6±5.4	16.5±4.0	16.7±5.5	15.2±4.0	14.8±4.1	14.3±5.1	15.0±5.0	14.3±5.7	13.6±4.6	13.5±3.8	14.5±3.7
	PRO-0.2	12.8±3.6§	11.7±3.4¶§	12.3±3.0	10.5±3.1¶	11.1±2.1¶§	11.2±2.7¶§	12.2±1.6	11.1±3.2	10.4±2.1§	11.1±3.9	11.1±2.2	11.2±2.6	11.1±2.1	11.3±2.8§
	PRO-0.4	16.3±5.7	15.1±5.3	14.6±5.1	16.7±6.3	14.2±4.3	15.7±6.7	15.4±6.6	15.6±6.5	13.9±4.7	14.4±5.4	15.3±4.9	15.0±6.6	14.1±5.6	14.7±4.9
CI (L/min/kg)	ISO-0.1	0.33±0.04	0.33±0.04	0.26±0.04	0.29±0.03	0.30±0.04	0.33±0.05	0.36±0.08	0.34±0.05	0.34±0.05	0.33±0.05	0.35±0.07	0.33±0.05	0.32±0.08	0.33±0.04
	ISO-0.2	0.33±0.08	0.35 ±0.06	0.32±0.10	0.34±0.08	0.32±0.08	0.34±0.07	0.34±0.07	0.34±0.06	0.34±0.05	0.33±0.06	0.33±0.07	0.32±0.07	0.31±0.06	0.32±0.05
	ISO-0.4	0.39±0.11‡§	0.37±0.09	0.33±0.10	0.31±0.09	0.30±0.08	0.30±0.08	0.30±0.08	0.29±0.08	0.31±0.08	0.32±0.08	0.30±0.08	0.30±0.08	0.30±0.08	0.30±0.08
	PRO-0.1	0.36±0.13	0.37±0.11	0.33±0.08	0.34±0.11	0.35±0.10	0.36±0.13	0.39±0.13	0.39±0.14	0.41±0.13	0.40±0.11	0.42±0.14	0.41±0.12	0.40±0.13	0.39±0.11

	PRO-0.2	0.33±0.09§	0.38±0.12	0.35±0.10§	0.36±0.07§	0.37±0.10§	0.35±0.10§	0.35±0.07§	0.35±0.07§	0.37±0.07§	0.36±0.10	0.37±0.09§	0.36±0.07	0.35±0.08	0.37±0.08§
	PRO-0.4	0.28±0.06	0.32±0.09	0.30±0.06	0.28±0.05	0.29±0.06	0.28±0.05	0.28±0.06	0.30±0.05	0.30±0.070	0.31±0.07	0.31±0.067	0.32±0.09	0.33±0.09	0.31±0.06
SI (L/beat/kg) $\times10^{-3}$	ISO-0.1	3.00±0.76	2.77±0.50	2.57±0.52	2.63±0.51	2.83±0.69	2.86±0.54	2.93±0.73	2.99±0.63	3.05±0.86	2.94±0.62	2.78±0.41	2.81±0.48	2.79±0.75	2.89±0.63
	ISO-0.2	2.76±0.25	2.53±0.28	2.60±0.48	2.63±0.20	2.55±0.32	2.71±0.24	2.65±0.30	2.73±0.21	2.69±0.18	2.63±0.34	2.62±0.30	2.56±0.31	2.52±0.17	2.66±0.17
	ISO-0.4	3.21±0.43‡	2.93±0.57	2.74±0.63	2.55±0.58	2.53±0.42	2.50±047	2.46±0.51	2.38±0.48	2.47±0.6	2.58±0.39	2.44±0.43§	2.47±0.42§	2.48±0.37	2.44±0.37§
	PRO-0.1	3.01±0.43	2.79±0.48	2.56±0.45	2.60±0.29	2.65±0.39	2.75±0.35	2.93±0.29	2.87±0.26	2.99±0.17	3.00±0.36	3.07±0.42	2.98±0.07	3.02±0.47	3.07±0.27
	PRO-0.2	3.35±0.59‡	3.13±0.47‡	3.06±0.57	3.28±0.35¶‡§	3.28±0.71	3.07±0.45	3.02±0.48	2.99±0.35	3.15±0.39‡	3.08±0.416	3.20±0.49	3.13±0.49	3.14±0.40‡	3.25±0.52‡§
	PRO-0.4	3.15±0.31	3.20±0.41	2.97±0.19	2.87±0.37	2.93±0.31	2.81±0.42	2.79±0.49	2.76±0.41	2.76±0.39	2.95±0.62	2.82±0.48	2.93±0.65	2.95±0.53	2.82±0.37¶
RPP (mmHg·beat/min)	ISO-0.1	14120.1 ±3802.0	15495.0 ±2656.9	12552.2 ±3186.4	12123.2 ±3351.7	13432.2 ±3642.4	13827.3 ±4163.8	14754.7 ±5799.7	14582.5 ±4990.6	14758.2 ±5013.8	15047.7 ±5589.9	15199.0 ±5556.0	14323.5 ±4381.4	14823.2 ±4539.3	14467.2 ±4210.6
	ISO-0.2	13315.1 ±3559.3	16611.0 ±3312.9	13392.7 ±2933.4	13940.0 ±3937.1	13081.2 ±2881.1	12990.3 ±2668.5	13184.2 ±2656.3	12903.8 ±2619.2	12814.8 ±2529.7	12641.3 ±2584.8	12776.7 ±2842.7	13001.3 ±2545.5	12103.2 ±3170.3	12312.0 ±3047.9
	ISO-0.4	13266.3 ±3107.9	15301.7 ±3739.0	12643.0 ±3565.3	12032.2 ±3123.8	12150.8 ±2835.9	11924.5 ±2252.6	11888.2 ±2159.0	11599.5 ±2027.9	11743.0 ±2112.5	11587.2 ±2020.9	11475.7 ±1701.7	11108.0 ±1793.6	10993.5 ±1968.3	11328.0 ±2086.1
	PRO-0.1	21715.3 ±11039.0	23123.0 ±10074.0	19127.5 ±6276.0†	19238.8 ±7113.3†	20773.7 ±8147.4†	19548.2 ±6338.4†	21814.2 ±9525.2†	22455.3 ±11304.4	21926.2 ±8132.8†	21663.5 ±7931.3†	22015.2 ±6793.7†	21673.0 ±7373.1†	21083.5 ±6514.3†	20565.3 ±6991.0†
	PRO-0.2	16009.8 ±4427.5§	19077.2 ±5871.7§	15922.5 ±3936.5§	15210.2 ±4736.1¶	16071.2 ±4133.2¶	17600.5 ±6004.8§	17918.3 ±6473.7¶§	17634.2 ±6075.7§	17788.7 ±6006.7¶§	17784.5 ±6091.5¶§	17452.7 ±5405.7¶	17265.0 ±5599.5¶	16764.7 ±5604.2¶	16558.8 ±5269.8¶
	PRO-0.4	12412.1 ±3269.7	14199.3 ±3255.9	12841.2 ±3362.0¶	12968.5 ±3667.4¶	13149.3 ±4455.5¶	13261.0 ±4522.1¶	13534.0 ±4515.1¶	14006.7 ±4880.2	13856.0 ±5422.4¶	14186.3 ±5725.5¶	14354.8 ±5532.7¶	14142.7 ±5445.5¶	14432.8 ±5363.8¶	14359.7 ±5253.2¶
LVWI (mmHg·L/beat/kg) $\times10^{-3}$	ISO-0.1	2.61±0.33	2.77±0.26	2.17±0.31	2.19±0.27	2.38±0.46	2.53±0.50	2.69±0.68	2.38±0.44	2.44±0.39	2.40±0.41	2.45±0.43	.2.33±0.44	2.38±0.38	2.35±0.45
	ISO-0.2	2.78±0.53	2.88±0.41	2.66±0.68	2.68±0.53	2.46±0.57	2.52±0.43	2.46±0.44	2.46±0.47	2.39±0.41	2.40±0.52	2.36±0.53	.2.29±0.49	2.15±0.43	2.28±0.35
	ISO-0.4	2.98±0.67	3.24±0.75§	2.58±0.77§	2.35±0.82§	2.28±0.50§	2.21±0.55§	2.14±0.56§	2.02±0.60§	2.11±0.57§	2.14±0.59§	1.98±0.54§	.1.94±0.49§	1.93±0.50§	1.88±0.47§
	PRO-0.1	4.62±0.72†	4.34±0.68†	3.85±0.84	3.70±0.64†	3.71±0.58†	3.75±0.58†	4.15±0.54†	4.08±0.59†	4.19±0.45†	4.25±0.63†	4.40±0.92†	.4.16±0.31†	4.21±0.74†	4.18±0.42†
	PRO-0.2	4.61±1.11‡	4.52±0.73‡	4.18±1.12‡	4.49±0.96‡	4.43±0.19‡§	4.23±0.90‡	4.20±0.84‡	4.13±0.65‡§	4.31±0.79‡§	4.25±0.90‡	4.37±0.94‡§	.4.34±0.88‡§	4.28±0.80‡§	4.38±0.82‡§
	PRO-0.4	4.06±0.67	4.56±0.79	3.86±0.58	3.54±0.62	3.60±0.57	3.49±0.78	3.45±0.78	3.46±0.65¶	3.30±0.2¶	3.57±0.80	3.40±0.71	.3.48±0.77¶	3.56±0.72	3.40±0.59¶
RVWI (mmHg·L/beat/kg) $\times10^{-4}$	ISO-0.1	4.14±0.65	4.32±0.85	3.66±0.34	3.54±0.37	3.81±0.76	4.17±0.89	4.46±1.04	4.24±0.71	4.26±0.86	4.04±0.87	4.18±0.60	4.05±0.65	3.78±1.01	3.98±0.44
	ISO-0.2	4.36±0.82	4.54±0.94	4.14±1.60	4.20±1.14	4.02±1.36	4.09±0.97	4.07±0.79	4.07±1.22	4.13±1.00	4.00±1.17	3.94±1.20	3.81±0.99	3.58±0.89	4.00±0.80
	ISO-0.4	5.45±1.24‡	5.03±1.21	4.20±1.20	3.85±1.12	3.65±0.86	3.63±1.06	3.42±0.92*	3.42±1.14*	3.44±0.92*	3.60±1.14	3.29±1.03*	3.24±0.90*	3.21±0.86*	3.36±1.14*
	PRO-0.1	5.20±1.17	4.93±1.42	4.08±0.54	4.54±0.52†	4.66±0.99	4.32±0.79	4.82±0.29	4.68±0.81	5.07±0.62†	4.99±0.60	4.81±1.00	4.77±0.58†	4.60±0.83	5.02±1.08
	PRO-0.2	4.65±1.02	4.62±0.88	4.57±0.95	4.54±0.71	4.72±1.25	4.12±0.84	4.24±1.14	4.08±0.69¶	4.21±0.58¶	4.27±0.88¶	4.54±1.04	4.33±1.09	4.30±0.81	4.55±1.02
	PRO-0.4	4.72±0.96	4.85±0.45	4.38±0.73	4.42±1.08	4.27±0.91	3.96±0.56	3.96±1.27¶	4.08±0.76	3.79±0.84¶	4.16±0.91¶	3.91±0.83¶	4.24±1.27	4.25±1.10	4.07±0.76¶
CPP (mmHg)	ISO-0.1	61.3±16.0	69.3±12.1	56.7±12.0	56.8±11.6	57.5±12.1	57.3±12.7	57.8±14.0	56.7±12.8	55.7±13.2	57.0±12.2	55.8±12.5	54.3±12.4	54.8±9.5	55.2±11.2
	ISO-0.2	61.0±9.5	66.8±6.9	61.6±6.2	61.1±11.3	57.1±9.1	56.7±8.1	56.0±7.8	54.8±8.0	54.3±8.6	55.3±8.1	53.7±9.3	54.8±7.7	51.2±10.3	51.5±9.6
	ISO-0.4	52.8±8.8§	66.5±10.0§	55.0±10.1§	53.5±9.3§	53.2±7.9§	52.2±6.9§	51.2±7.3§	49.8±7.3§	50.4±9.2§	49.6±8.5§	48.6±6.8§	47.2±7.0§	46.0±7.9§	47.6±8.0§
	PRO-0.1	91.3±13.1†	94.8±9.3†	89.2±10.6	86.3±10.5†	83.7±10.5†	84.4±10.9†	82.5±9.7†	83.5±10.9†	81.7±6.9†	82.3±10.8†	81.2±9.1†	80.0±8.0†	80.5±8.3†	80.8±6.7†
	PRO-0.2	80.2±9.0‡	85.3±8.0¶‡	82.8±10.9‡	81.6±15.1‡	81.3±12.7‡	82.8±13.4‡	83.5±13.0‡	83.2±11.6‡	81.5±12.2‡	82.0±11.1‡	80.7±11.6‡	82.2±10.9‡	80.8±11.6‡	80.2±10.0‡
	PRO-0.4	78.2±4.2	86.7±6.2	80.0±10.0	79.0±11.4	74.3±10.9	74.8±10.6	74.3±10.4	73.8±11.1	72.3±12.0	73.3±12.4	73.8±13.4	73.0±12.0	74.2±11.5	73.8±11.9

* $p < 0.05$ *vs.* baseline values.
† $p < 0.05$ *vs*. group ISO-0.1.
‡ $p < 0.05$ *vs*. group ISO-0.2.
¶ $p < 0.05$ *vs*. group PRO-0.1.
§ $p < 0.05$ *vs*. group PRO-0.4.

Table 4-2 Changes in arterial blood gas after thoracic epidural administration of 2% lidocaine with a bolus injection of 0.2 mL/kg followed by continuous infusion at three infusion rates. Data were shown as mean ± SD.

Arterial blood gas variables	Group		Baseline	Thoracic epidural bolus injection of 0.2 mL/kg of 2% lidocaine followed by continuous epidural infusion at different infusion rates			
				T0	T10	T60	T120
pH	ISO	0.1	7.37±0.03	7.38±0.01	7.39±0.02	7.38±0.01	7.37±0.01
		0.2	7.38±0.03	7.38±0.02	7.38±0.02	7.36±0.03	7.36±0.02
		0.4	7.38±0.03	7.38±0.02	7.38±0.02	7.37±0.03	7.36±0.02
	PRO	0.1	7.32±0.03†	7.31±0.02†	7.32±0.02†	7.32±0.02†	7.31±0.02†
		0.2	7.34±0.02	7.33±0.02	7.34±0.02‡	7.33±0.02	7.33±0.02
		0.4	7.36±0.02	7.35±0.03	7.34±0.02¶	7.35±0.02	7.34±0.02
PCO_2 (mmHg)	ISO	0.1	44.1±2.1	42.7±2.3	39.4±2.4*	42.0±1.5	43.8±1.1
		0.2	42.7±3.0	41.7±2.0	40.8±1.0	43.0±2.4	42.9±1.6
		0.4	44.3±1.5	41.8±1.2*	41.3±1.5*	42.0±1.3*	41.9±1.0*
	PRO	0.1	44.4±1.5	45.1±0.9	43.9±2.1	42.2±2.0†	44.2±2.3
		0.2	45.5±0.8	43.8±1.4	43.1±1.3	42.7±2.0*	45.2±2.1
		0.4	42.3±1.0	41.5±2.4	42.1±1.8¶	40.5±3.4	42.8±2.3
PO_2 (mmHg)	ISO	0.1	570.7±50.5	577.2±44.9	528.0±45.4	543.3±55.4	542.8±89.8
		0.2	547.2±30.4	557.2±18.9	536.3±32.2	556.3±47.0	551.2±32.1
		0.4	601.2±32.6	606.8±27.0	561.0±39.4	581.0±35.3	537.8±40.3*
	PRO	0.1	645.0±13.5	625.3±29.5	607.2±26.9	583.2±57.8†	609.3±34.5
		0.2	616.5±16.5‡	604.5±23.9‡	607.7±12.9	592.8±8.3‡	621.5±22.2
		0.4	616.5±25.2	610.0±11.3	603.3±17.1	570.5±42.9	583.7±43.1
BE (mEq/L)	ISO	0.1	0.5±2.0	0.2±1.2	-1.2±1.6	-0.5±1.7	0.3±1.3
		0.2	-0.3±2.0	-0.2±1.2	-1.2±1.8	-1.3±2.5	-1.2±1.8
		0.4	0.8±2.0	-0.2±2.1	-0.7±2.3	-1.3±1.7	-1.7±1.5
	PRO	0.1	-3.3±1.0†	-3.5±1.0†	-3.3±0.9†	-4.0±0.8	-3.8±1.0†
		0.2	-1.3±1.5	-2.7±1.0	-2.7±1.3	-3.5±1.8*	-2.2±0.7
		0.4	-1.7±1.1	-2.3±1.4	-2.8±1.7	-3.5±2.2	-2.8±0.9
HCO_3^- (mmol/L)	ISO	0.1	25.5±1.4	24.9±1.2	23.5±1.4	24.5±1.5	25.2±1.1
		0.2	24.7±1.6	24.5±1.1	23.6±1.5	24.0±2.1	24.1±1.6
		0.4	25.8±1.3	24.6±1.6	24.2±1.7	23.7±1.4	23.5±1.1
	PRO	0.1	22.5±0.5†	22.5±0.8†	22.4±0.7†	21.5±0.7	22.1±0.5†
		0.2	24.1±1.0	23.0±0.8	22.8±1.0	22.2±1.8*	23.3±0.7
		0.4	23.6±0.9	22.9±1.2	22.6±1.3	21.9±1.9	22.5±0.8
TCO_2 (mmHg)	ISO	0.1	26.7±1.4	26.2±1.2	24.7±1.5	25.7±1.4	26.3±1.3
		0.2	26.0±1.6	25.7±1.4	24.7±1.5	25.3±2.3	25.5±1.8
		0.4	27.0±1.3	25.7±1.7	25.2±1.7	24.7±1.5	24.7±1.1
	PRO	0.1	23.8±0.4†	23.7±0.9†	23.8±0.7†	22.7±0.8	23.3±0.8†
		0.2	25.5±1.0	24.3±0.9	24.3±0.9	23.7±1.8*	24.8±0.7
		0.4	24.8±0.9	24.0±1.0	23.8±1.3	23.0±2.2	23.8±0.9
Lactate (mmol/L)	ISO	0.1	1.15±0.33	1.18±0.38	1.04±0.37	0.92±0.29	0.83±0.29
		0.2	1.36±0.68	1.50±0.78	1.46±0.75	1.14±0.56	0.99±0.48
		0.4	1.39±0.57	1.49±0.49	1.38±0.48	1.13±0.60	1.05±0.52
	PRO	0.1	0.69±0.17	0.71±0.19	0.68±0.20	0.43±0.04*	0.30±0.00*
		0.2	0.66±0.33	0.61±0.31	0.57±0.30	0.41±0.14	0.32±0.03
		0.4	0.68±0.29	0.65±0.27	0.62±0.24	0.50±0.26	0.32±0.02

* $p < 0.05$ *vs*. baseline values; † $p < 0.05$ *vs*. group ISO-0.1; ‡ $p < 0.05$ *vs*. group ISO-0.2; ¶ $p < 0.05$ *vs*. group PRO-0.1; § $p < 0.05$ *vs*. group PRO-0.4.

Table 4-3 Changes in serum concentration of lidocaine in group 0.1, 0.2 and 0.4 under isoflurane and propofol anesthesia. Data were shown as mean ± SD.

Group		Serum concentration of lidocaine (μg/mL)	
		T15	T120
ISO	0.1	2.4 ± 0.6†‡	1.4 ± 0.4*†‡
	0.2	3.2 ± 0.9	2.4 ± 0.8 §
	0.4	3.0 ± 0.6	3.3 ± 0.7
PRO	0.1	2.4 ± 0.5†‡	1.2 ± 0.3*†‡
	0.2	3.3 ± 0.8	2.4 ± 0.6 §
	0.4	3.5 ± 0.6	3.5 ± 0.5

No differences of lidocaine concentration were observed between isoflurane and propofol anesthesia groups at the same infusion rate. Under either isoflurane or propofol anesthesia, in group 0.1, lidocaine concentration significantly decreased at T120 compared with T15. No differences were found in group 0.2 or 0.4. At T15, lidocaine concentration was significantly lower in group 0.1 than the other two groups. At T120, significant differences of lidocaine concentration were found among three infusion rate groups.

* Significant difference compared with T15; † Significant difference between group 0.1 and 0.2; ‡ Significant difference between group 0.1 and 0.4; § Significant difference between group 0.2 and 0.4 ($p < 0.05$).

Table 4-4 Changes in plasma concentration of propofol in group 0.1, 0.2 and 0.4 under propofol anesthesia. Data were shown as mean ± SD.

Group	Plasma concentration of propofol (μg/mL)	
	Baseline	T120
0.1	9.2 ± 2.9	8.0 ± 2.5‡
0.2	12.7 ± 3.1	11.7 ± 3.4
0.4	14.4 ± 4.0	14.1 ± 4.0

Within each group, no difference of propofol concentration was found between two measurement time points. The propofol plasma concentration was higher in group 0.4 than group 0.1 at 120 min after the beginning of lidocaine epidural infusion.
‡ $p < 0.05$ *vs.* group 0.4.

Table 4-5 Anesthesia recovery characteristics.

Group		Time (minutes)		Horner's Syndrome (number of dogs)	Forelimb paralysis (number of dogs)	Muscle tremors (number of dogs)
		From extubation until sternal recumbency	From sternal recumbency until standing upright			
ISO	0.1	6.8 ± 4.6	10.3 ± 12.2*	0	0	-
	0.2	11.5 ± 4.8	31.2 ± 20.6*	4	2	-
	0.4	14.8 ± 6.9	147.4 ± 67.2	6	4	-
PRO	0.1	19.7 ± 16.8	15.3 ± 8.3	1	0	2
	0.2	14.2 ± 4.8	15.7 ± 6.5	3	3	1
	0.4	17.7 ± 11.1	29.8 ± 12.0*	6	3	1

*$p < 0.05$ *vs.* group ISO-0.4.

Conclusion

In the present study, a series of experiments were conducted to investigate the feasibility and safety of thoracic epidural anesthesia in dogs.

First, in Chapter 1, the technical safety and difficulty of thoracic epidural anesthesia (group TEA) was investigated by comparing with the lumbar epidural anesthesia (group LEA) using healthy dogs. In group TEA, the catheter was inserted into the epidural space from cranial lumbar segments (L1 to L3) with its tip placed in the thoracic vertebral region (T11 to T13); in group LEA, the catheter was inserted from caudal lumbar segments (L6 to S1) with its tip placed at mid lumbar vertebral segments (L3 to L5). Epidural catheter was placed into the target epidural space successfully in all dogs. No statistical differences were observed in the time consumed for the whole process of epidural catheterization (needle puncture, catheter placement and saline injection) between two groups. Subcutaneous bleeding was detected in 3 dogs of group TEA, but in no dog of group LEA. Neither macroscopic injuries, such as spinal tissue bleeding, dural puncture and catheterization nor histopathological changes were observed in any dog. Subjective evaluation score of the overall technical difficulty was significantly higher in group TEA, however the

difference was slight. Moreover the technique of epidural catheterization in thoracolumbar vertebral region could be improved after being well practiced. The findings obtained in this study suggest that the thoracic epidural anesthesia is feasible to be performed in medium or large-sized dogs in clinical settings.

In chapter 2, the spreading pattern of contrast medium epidurally injected at thoracic (group TEA) and lumbar (group LEA) vertebral level was studied using CT epidurography. After injecting a single dose of 0.2 mL/kg contrast medium, no difference in the cranial number of vertebral segments reached by contrast medium was observed between two groups. Three possible causes may contribute to this result. First, there was less caudal space for contrast medium spreading in group LEA because of its caudal epidural injection site. Second, potential different pressure gradients between thoracic and lumbar vertebral segments, which was presumably lower at thoracic vertebral segments, may facilitate the cranial spreading in group LEA. Third, contrast medium was more likely to leak out of the epidural space through the enlarged intervertebral foramina in cervicothoracic region, consequently resulting in the cranial epidurographic distribution generally limited to 5th and 6th cervical vertebral segments in both groups. In the other aspect, changes in the maximal CT value of the epidural space indicate that contrast medium may mainly

distribute at thoracic vertebral segments in group TEA, while distribute at lumbar vertebral segments in group LEA. It is implied that epidural anesthesia performed at low thoracic level may be effective for surgeries involving thoracic and upper abdominal regions. It has also proved that lumbosacral epidural anesthesia is suitable for surgeries caudal to the umbilicus.

In the second part of this chapter, a comparison of the epidural distribution of contrast medium administered at thoracic vertebral level between a single dose (group Bolus) and a continuous infusion (group CRI) was conducted. There was no difference in the number of vertebral segments reached by contrast medium between two groups. However, the contrast medium was more likely to leak out of the epidural space when drug was continuously infused. Although differences were not significant, the maximal CT value decreased generally in a time-related manner in group Bolus, whereas, it tended to be kept stable in group CRI. This finding indicates that epidural continuous infusion is superior to a single dose injection in keeping a stable concentration of drugs distributed to the target spinal cord segments for the long time surgery and postoperative analgesia.

As epidural anesthesia is usually used combined with general anesthesia in dogs especially during surgery, the evaluation of cardiovascular changes under general

anesthesia is clinically important. Therefore, in chapters 3 and 4, cardiovascular effects of thoracic epidural anesthesia were studied in dogs anesthetized with inhalation anesthesia (isoflurane) or intravenous anesthesia (propofol).

In chapter 3, cardiovascular effects of two epidural techniques: thoracic epidural anesthesia (group TEA) and lumbar epidural anesthesia (group LEA) were compared after epidurally injecting a single dose of lidocaine (4 mg/kg). Under isoflurane anesthesia, arterial blood pressure mildly decreased in group TEA, with less decreasing degree than that in group LEA. Since results showed a comparable systemic vascular resistance between two groups, changes in the stroke volume is supposed to be the major determined factor in the changes of arterial blood pressure. Overall, under isoflurane anesthesia, the myocardial function was less depressed by thoracic epidural anesthesia compared with lumbar epidural anesthesia. Under propofol anesthesia, changes in arterial blood pressure showed a similar trend but with significantly high levels in both two groups compared with those under isoflurane anesthesia, which nay be related to the different cardiovascular effects of these two general anesthetics. Regardless of general anesthetics, arterial blood pressure was only mildly depressed after a single dose of lidocaine epidurally injected in thoracic compared with lumbar vertebral region. Hence, in terms of

cardiovascular effects, thoracic epidural anesthesia epidural is safe to be used in clinical settings. Under propofol anesthesia, although the arterial blood pressure was well preserved, moderate, or occasionally severe muscle tremors were observed in some dogs in both TEA and LEA groups. Therefore, propofol infusion combined with epidural anesthesia seems hardly to provide a stable condition for surgical manipulations. Some adjuvant such as systemic opioids which is commonly used for the "balanced anesthesia" may be necessary. While isoflurane inhalation combined with epidural anesthesia, under which arterial blood pressure was lower but within a clinically acceptable range, could provide a stable condition for surgical manipulations.

Finally, in chapter 4, cardiovascular effects of continuous epidural infusion of 2% lidocaine in thoracic vertebral region was compared at three infusion rates: 0.1, 0.2 and 0.4 mL/kg/hr (group 0.1, 0.2 and 0.4), respectively. Under isoflurane anesthesia, differences were not significant, but heart rate, arterial blood pressure, cardiac output and stroke volume tended to be depressed dose-dependently. However, it was not found in systemic vascular resistance. Compared with other two infusion rates, cardiovascular variables were more depressed when a high infusion rate (0.4 mL/kg/hr) was used. Similar cardiovascular changes were also obtained in three

groups under propofol anesthesia. However, arterial blood pressure was significantly higher under propofol anesthesia in each group, which was thought to be attributed to the high systemic vascular resistance under propofol anesthesia. In the present study, changes in serum lidocaine concentration were similar between isoflurane and propofol anesthesia. Under either isoflurane or propofol anesthesia, the concentration reached a steady state approximately at 15 min after the beginning of continuous infusion in all three infusion rate groups, and then decreased at 120 min in 0.1 and 0.2 groups, but was maintained in group 0.4. The lidocaine concentration was higher than 3.0 μg/mL in both ISO-0.4 and PRO-0.4 groups at all measurement points, which may induce a mild myocardial toxicity in conscious humans. Considering cardiovascular effect, epidural continuous administration of 2% lidocaine should be infused at a rate less than 0.4 mL/kg/hr in dogs.

Comparing with the lumbar epidural anesthesia, thoracic epidural anesthesia was not technically difficult, and was feasible to be performed in medium or large-sized dogs. After epidurally injecting a single dose of lidocaine, thoracic epidural anesthesia only mildly depressed cardiovascular variables. During continuous epidural anesthesia, there was a mild to moderate dose-dependent cardiovascular depressant effect. A potential systemic lidocaine absorbed from and/or leak out of the

epidural space may also contribute to cardiovascular changes when it was infused at a high rate. Results in the present study implied that, with respect to cardiovascular effects, the use of thoracic epidural anesthesia with lidocaine combined with isoflurane or propofol general anesthesia may be applied in the clinical setting. However, caution should be advised when lidociane is infused continuously, particularly at a high fusion rate, because of its potential systemic accumulation and toxicity. Besides, muscle tremors caused by an enhanced muscular tone may occur under propofol anesthesia. Some adjuvant such as systemic opioids may be necessary.

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