

Continuous mixed venous oxygen saturation, not mean blood pressure, is associated with early bupivacaine cardiotoxicity in dogs

[La saturation en oxygène du sang veineux mêlé, mais non la tension artérielle moyenne, est associée à une cardiotoxicité précoce à la bupivacaine chez les chiens]

Jin-Tae Kim MD, Ka-Young Rhee MD, Jae-Hyon Bahk MD, Sang-Hwan Do MD, Young-Jin Lim MD, Hong Ko MD, Kook-Hyun Lee MD

Purpose: To investigate changes of continuous mixed venous oxygen saturation ($cSvO_2$) and mean arterial blood pressure (MBP) in dogs with bupivacaine-induced cardiac depression.

Methods: Bupivacaine was infused into pentobarbital-anesthetized mongrel dogs ($n = 8$) at a rate of $0.5 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ until the MBP was 40 mmHg or less (end of bupivacaine infusion; BIE). The infusion time was divided into the early period, first 30 min of bupivacaine infusion and the late period, which was from 30 min of bupivacaine infusion until BIE. $cSvO_2$ was monitored using a fibre-optic pulmonary artery catheter, and MBP and cardiac output (CO) were measured every ten minutes after the initiation of bupivacaine infusion. Arterial blood gas, serum electrolyte and bupivacaine concentration were measured simultaneously. The relationships between CO and $cSvO_2$, and of CO vs MBP were compared by regression analysis in the early and late periods.

Results: The Pearson's correlation coefficients between CO and $cSvO_2$ were 0.782 ($P = 2.1 \times 10^{-7}$) in the early period and 0.824 ($P = 1.3 \times 10^{-6}$) in the late period. The correlation coefficients between CO and MBP were 0.019 ($P = 0.921$) in the early period and 0.799 ($P = 4.8 \times 10^{-6}$) in the late period.

Conclusions: $cSvO_2$, but not MBP, is associated with CO changes in bupivacaine-induced cardiac depression during the early period of bupivacaine intoxication. Decrease of MBP with low $cSvO_2$ observed during the late period might imply severe cardiac depression induced by bupivacaine infusion.

Objectif : Examiner les modifications de la saturation continue en oxygène du sang veineux mêlé (ScO_{2v}) et de la tension artérielle moyenne (TAM) chez des chiens qui présentent une dépression cardiaque induite par la bupivacaine.

Méthode : La bupivacaine a été administrée chez des chiens de race commune ($n = 8$), anesthésiés au pentobarbital, selon un débit de $0,5 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ jusqu'à ce que la TAM soit de 40 mmHg ou moins (fin de la perfusion de bupivacaine ; FPB). Le temps de perfusion a été divisé en une période précoce pour les 30 premières min et tardive, à partir de 30 min jusqu'à la FPB. La ScO_{2v} a été enregistrée avec un cathéter artériel pulmonaire fibroscopique. La TAM et le débit cardiaque (DC) ont été mesurés toutes les dix minutes après le début de la perfusion de bupivacaine. La gazométrie du sang artériel, la concentration sérique d'électrolytes et de bupivacaine ont été mesurées simultanément. La relation entre le CO et la ScO_{2v} , et entre le CO et la TAM a été comparée par une analyse de régression pendant les deux périodes de perfusion déterminées.

Résultats : Les coefficients de corrélation de Pearson entre le CO et la ScO_{2v} ont été de 0,782 ($P = 2,1 \times 10^{-7}$) pendant la période précoce de la perfusion et de 0,824 ($P = 1,3 \times 10^{-6}$) pendant la période tardive. Les coefficients de corrélation entre le CO et la TAM ont été de 0,019 ($P = 0,921$) pendant la période précoce et de 0,799 ($P = 4,8 \times 10^{-6}$) pendant la période tardive.

Conclusion : La ScO_{2v} , mais non la TAM, est associée aux variations de CO de la dépression cardiaque induite par la bupivacaine pendant la période précoce de l'intoxication à la bupivacaine. Une baisse de la TAM, accompagnée d'une faible ScO_{2v} , observée pendant la période tardive, peut correspondre à une dépression cardiaque sévère induite par la perfusion de bupivacaine.

From the Department of Anesthesiology and Pain Medicine, College of Medicine, Seoul National University, Seoul, Korea.

Address correspondence to: Dr. Kook Hyun Lee, Department of Anesthesiology, Seoul National University Hospital, 28 Yongon-Dong, Chongno-Gu, Seoul, Korea 110-774. Phone: 82-2-760-2567, 1720; Fax: 82-2-747-5639; E-mail: leekh@plaza.snu.ac.kr
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BUPIVACAINE can provoke cardiovascular complications such as arrhythmia, hypotension and cardiac arrest when large doses are administered or intravascular injection occurs accidentally. The mechanism of bupivacaine-induced cardiac depression has been associated with the inhibition of cardiac muscle depolarization resulting from the Na⁺ channel block¹ and the inhibition of repolarization because of the presence of an outward K⁺ current (Ito) block.² Bupivacaine also inhibits calcium release from the sarcoplasmic reticulum³ and bupivacaine induced-cardiovascular collapse is resistant to conventional treatment.^{4,5} Therefore, the early recognition of bupivacaine-induced cardiac depression is vital to recovery. Though blood pressure is useful for the evaluation of cardiovascular status during clinical anesthesia, prior studies have shown that blood pressure changes little when bupivacaine is injected.^{6,7} Therefore, we expected that it would be difficult to detect bupivacaine-induced cardiac depression at an early stage by monitoring blood pressure.

Mixed venous oxygen saturation (SvO₂) is closely related to oxygen consumption (VO₂) and oxygen delivery (DO₂). VO₂ is known to be independent of DO₂ if the latter is above a critical level.^{8,9} If VO₂ is constant under general anesthesia with controlled ventilation, cardiac output (CO) changes can be predicted by continuously monitoring SvO₂ (cSvO₂). cSvO₂ is rarely used in most cases where bupivacaine toxicity is likely to occur, however, epidural anesthesia or analgesia is sometimes recommended for major operations that may require pulmonary artery catheterization.¹⁰⁻¹⁴

We hypothesized that cSvO₂ monitoring would reflect CO changes induced by bupivacaine infusion better than mean arterial blood pressure (MBP). The purpose of this study was to investigate changes of cSvO₂ and MBP when CO decreases and, ultimately, to compare the correlation between CO and cSvO₂ or MBP in dogs with bupivacaine-induced cardiac depression.

Methods

The study received approval from the Animal Care and Use Committee of the Seoul National University College of Medicine. The subjects consisted of eight male mongrel dogs (19–20 kg). Anesthesia was induced with sodium pentobarbital 25 mg·kg⁻¹ *iv* and maintained with a continuous infusion of 5 mg·kg⁻¹·hr⁻¹ sodium pentobarbital. The trachea was intubated with an internal diameter 7.0-mm cuffed endotracheal tube. Vecuronium was injected as a bolus of 0.2 mg·kg⁻¹, and this was followed by the administration of 0.02 mg·kg⁻¹ at 30-min intervals. Mechanical ventilation was performed using a Royal ventilator (Royal Medical Co,

Seoul, Korea) to maintain normocarbida at a fraction of inspired oxygen of 1.0. Normal saline was infused at a rate of 5 mL·kg⁻¹·hr⁻¹ throughout the experiment.

Cardiac rhythm and heart rate (HR) were monitored continuously by using standard lead II of the electrocardiograph (ECG). A percutaneous 20G polyvinyl catheter was inserted into the femoral artery to obtain blood samples and to monitor arterial blood pressure. A fiberoptic pulmonary artery catheter (Opticath®, P 7110-EH, Abbott, Chicago, IL, USA) was inserted via the external jugular vein to continuously monitor cSvO₂ (Oximerix® 3, Abbott, Chicago, IL, USA) and central venous pressure (CVP). CO was measured three times using the thermodilution method at ten-minute intervals and pulmonary capillary wedge pressure (PCWP) was monitored simultaneously. ECG lead II and the femoral arterial pressure were monitored continuously and recorded at ten-minute intervals throughout the experiment with a HP Component Monitoring System™ (Hewlett-Packard Model 54S, Andover, MA, USA). The PR interval, the QRS duration and the QTc interval were also measured. The QTc interval was calculated using the formula of Van de Water *et al.*,¹⁵ which is appropriate for a rapid HR: QTc (msec) = QT – 0.087 (RR – 1000). Temperature was maintained at 37°–38°C using a warming blanket. The dogs were stabilized for 30 min before the start of the experiment.

After having measured the baseline variables, 0.5% bupivacaine was administered at a rate of 0.5 mg·kg⁻¹·min⁻¹ via a venous catheter. At the same time, sodium bicarbonate was infused at a rate of 2–4 mEq·kg⁻¹·hr⁻¹ via another venous catheter to maintain arterial pH 7.35–7.45. Bupivacaine was infused continuously until the MBP decreased to 40 mmHg or less (BIE: end of bupivacaine infusion). We defined the early period as the first 30 min of bupivacaine infusion, and the late period as the interval from 30 min of bupivacaine infusion until BIE (Figure 1). MBP, HR, CVP, PCWP, cSvO₂ and CO were measured every ten minutes until BIE. Systemic vascular resistance (SVR) was calculated using a standard formula with MBP, CVP and CO, whereas DO₂ and VO₂ were calculated as the products of CO and arterial oxygen content, and CO and arterial-venous oxygen content difference, respectively, every ten minutes.

Hemoglobin concentration was measured using a blood sample taken at baseline. Arterial blood samples were obtained for blood gas analysis every ten minutes, and these were also analyzed for serum Na⁺, K⁺, calcium and plasma bupivacaine. In five dogs, pulmonary arterial blood was withdrawn to perform mixed venous blood gas analysis and measurement of SvO₂ with co-

TABLE I Changes in hemodynamic variables, oxygen delivery (DO₂) and oxygen consumption (VO₂)

	0 min (Baseline) (n = 8)	10 min (n = 8)	20 min (n = 8)	30 min (n = 8)	40 min (n = 6)	50 min (n = 4)	60 min (n = 4)	BIE (n = 8)
CSvO ₂ (%)	90 ± 8	82 ± 12*†	76 ± 15*†	73 ± 18*	70 ± 22	77 ± 15	62 ± 15	41 ± 7*
MBP (mmHg)	110 ± 13	109 ± 12	104 ± 9	101 ± 19	90 ± 18	94 ± 10	74 ± 17	40*
HR (beats·min ⁻¹)	125 ± 29	107 ± 31*†	107 ± 16*	104 ± 16*	100 ± 19	103 ± 12	91 ± 13	70 ± 8*
CVP (mmHg)	5 ± 3	5 ± 2	7 ± 2	7 ± 3	7 ± 2	7 ± 1	7 ± 2	8 ± 3*
PCWP (mmHg)	8 ± 2	11 ± 2	13 ± 3*	14 ± 3*	14 ± 3	14 ± 3	15 ± 3	12 ± 2*
CO (L·min ⁻¹)	3.84 ± 1.33	2.42 ± 1.07*†	2.11 ± 0.83*†	2.03 ± 0.88*	1.84 ± 1.03	2.06 ± 0.75	1.34 ± 0.68	0.76 ± 0.35*
SVR (dyn·sec·cm ⁻⁵)	2445 ± 990	4134 ± 1977	4233 ± 1708*	4120 ± 1438*	3949 ± 1717	3682 ± 1249	4709 ± 2218	3930 ± 1442*
DO ₂ (mL·kg ⁻¹ ·min ⁻¹)	24.7 ± 8.7	15.6 ± 7.1*†	13.5 ± 5.2*	12.9 ± 4.8*	11.5 ± 6.4	12.7 ± 5.7	8.1 ± 3.8	4.8 ± 1.7*
VO ₂ (mL·kg ⁻¹ ·min ⁻¹)	3.7 ± 1.2	3.1 ± 0.7	3.4 ± 0.7	3.6 ± 1.4	2.9 ± 0.4	3.2 ± 1.3	3.2 ± 1.3	3.0 ± 1.1

Values are expressed as mean ± SD. BIE = end of bupivacaine infusion; MBP = mean arterial blood pressure; HR = heart rate; PCWP = pulmonary capillary wedge pressure; CO = cardiac output; cSvO₂ = continuous mixed venous oxygen saturation; SVR = systemic vascular resistance; DO₂ = oxygen delivery; VO₂ = oxygen consumption.

The comparisons were omitted when a dog reached BIE, resulting in a number of dogs less than eight ($n = 6$, $n = 4$) and data ($n < 4$) are not presented. * $P < 0.05$ vs baseline; † $P < 0.05$ vs previous value.

TABLE II Arterial blood gas analysis, plasma electrolytes, bupivacaine concentration and ECG intervals

	0 min (Baseline) (n = 8)	10 min (n = 8)	20 min (n = 8)	30 min (n = 8)	40 min (n = 6)	50 min (n = 4)	60 min (n = 4)	BIE (n = 8)
<i>Arterial</i>								
pH	7.39 ± 0.08	7.43 ± 0.07	7.44 ± 0.04	7.44 ± 0.07	7.40 ± 0.11	7.45 ± 0.03	7.42 ± 0.04	7.43 ± 0.08
PO ₂ (mmHg)	415 ± 97	474 ± 116	532 ± 46	514 ± 104	475 ± 137	553 ± 31	571 ± 16	531 ± 48
PCO ₂ (mmHg)	34 ± 9	34 ± 8	35 ± 7	34 ± 5	35 ± 8	31 ± 3	34 ± 4	34 ± 8
<i>Plasma</i>								
Na ⁺ (mM)	152.3 ± 2.7	152.1 ± 3.2	153.0 ± 3.0	152.4 ± 3.6	153.5 ± 3.3	153.3 ± 3.8	153.4 ± 3.9	152.8 ± 3.2
K ⁺ (mM)	4.1 ± 0.3	3.7 ± 0.4	3.7 ± 0.4	3.7 ± 0.4	3.5 ± 0.4	3.4 ± 0.3	3.4 ± 0.3	3.9 ± 0.4
Calcium (mM)	2.65 ± 0.16	2.59 ± 0.16	2.42 ± 0.13*	2.34 ± 0.10*	2.25 ± 0.06	2.20 ± 0.04	2.16 ± 0.05	2.22 ± 0.14*
Bupivacaine (µg·mL ⁻¹)	0	9.2 ± 4.0*†	10.5 ± 4.5*	10.0 ± 3.2*	14.1 ± 9.1	12.8 ± 4.4	14.7 ± 3.8	20.2 ± 7.5*
<i>ECG</i>								
PR (msec)	93 ± 16	110 ± 24*†	123 ± 22*†	134 ± 21*	137 ± 18	146 ± 17	153 ± 12	156 ± 14*
QRS (msec)	57 ± 10	66 ± 12*†	78 ± 13*†	90 ± 16*†	98 ± 17	107 ± 20	111 ± 19	119 ± 16*
QTc (msec)	327 ± 27	347 ± 30*†	369 ± 31*†	378 ± 18*	390 ± 27	395 ± 41	414 ± 30	412 ± 22*

Values are expressed as mean ± SD. BIE = end of bupivacaine infusion. The comparisons were omitted when a dog reached BIE, resulting in a number of dogs less than eight ($n = 6$, $n = 4$) and data ($n < 4$) are not presented. * $P < 0.05$ vs baseline; † $P < 0.05$ vs previous value.

oxymetry method (ABL™ 520, Radiometer, Copenhagen, Germany) at the same times to compare SvO₂ and cSvO₂. Blood samples for bupivacaine concentration assay were centrifuged at 2500 rpm for 15 min to collect the plasma, which was then stored at -20°C until required for analysis. The bupivacaine concentration was measured by high-performance liquid chromatography.

We compared changes with baseline values at ten-minute intervals. The comparison was omitted when a dog reached BIE (MBP ≤ 40 mmHg), resulting in a number of animals less than eight. Analysis of variance for repeated measures was used to evaluate changes

over time. Linear regression analyses of CO vs cSvO₂, and CO vs MBP were recorded for the early and late periods. The linear regression plots for each period were analyzed and compared by t test. Linear regression analysis between SvO₂ and cSvO₂ was performed using the data from five dogs. Data are expressed as means ± SD. A P value < 0.05 was accepted as significant.

Results

The amount of bupivacaine administered before reaching BIE was 29 ± 10 mg·kg⁻¹, and it took 57 ± 19 min for the MBP to decrease to 40 mmHg. The hemoglobin concentration at baseline was 8.7 ± 1.1 g·dL⁻¹.

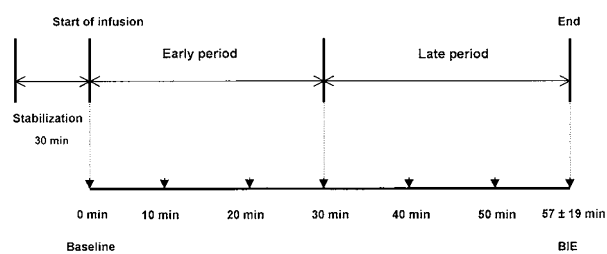


FIGURE 1 Time sequence of the experiment. BIE (end of bupivacaine infusion). Arrow = blood sampling and measurement of cardiac output, mean arterial blood pressure and continuous mixed venous oxygen saturation.

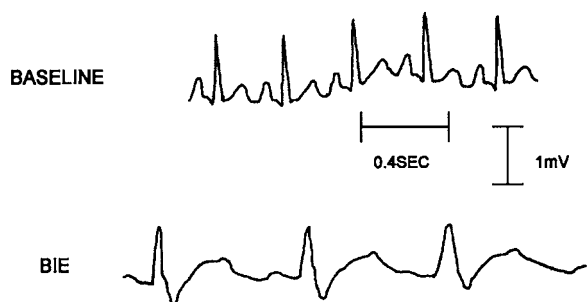


FIGURE 2 Electrocardiographic changes (lead II) induced by bupivacaine infusion. In one of the experimental dogs, during the baseline period, the values were: heart rate, 150 beats·min⁻¹; PR interval, 90 msec; QRS duration, 65 msec; and QTc interval, 320 msec. Bupivacaine administration at a concentration of 20.2 µg·mL⁻¹ at BIE (end of bupivacaine infusion) resulted in the following alterations: heart rate, 72 beats·min⁻¹; PR interval, 180 msec; QRS duration, 160 msec; and QTc interval 400 msec.

The bupivacaine infusion produced a decrease of cSvO₂ and CO from baseline values ten minutes after the infusion started. No significant changes in MBP occurred during the first 30 min after the initiation of the bupivacaine infusion. HR began to decrease from baseline value at ten minutes. PCWP and SVR increased from their baseline values after 20 min. DO₂ was lower than the baseline value after ten minutes, but VO₂ remained constant throughout the experiment. There were significant differences in MBP, HR, CO, cSvO₂, PCWP, CVP, SVR and DO₂ at baseline and at BIE (Table I). pH, PaCO₂, and PaO₂ remained in the physiologic range throughout the experimental period. No statistical differences in serum Na⁺, or K⁺ were found. Serum calcium concentration differed significantly from

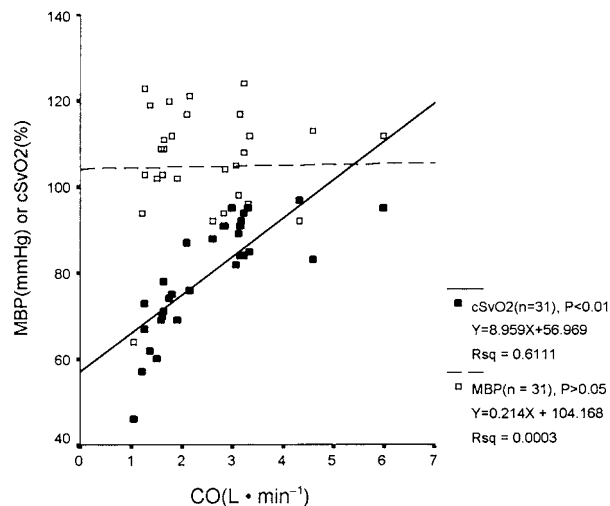


FIGURE 3 Relationship between cardiac output (CO) vs continuous mixed venous saturation (cSvO₂) or mean arterial blood pressure (MBP) in the early period. These two plots were statistically different from each other in terms of slope and intercept. Rsq = r².

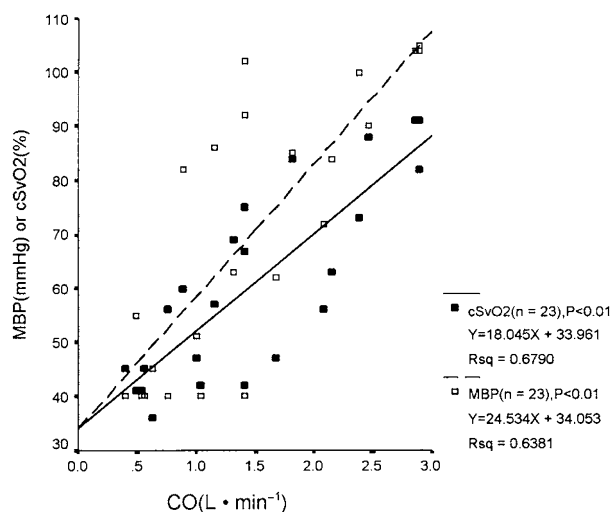


FIGURE 4 Relationship between cardiac output (CO) vs continuous mixed venous saturation (cSvO₂) or mean arterial blood pressure (MBP) in the late period. These two plots were not significantly different from each other in terms of slope and intercept. Rsq = r².

baseline value after 20 min. At BIE, the plasma bupivacaine concentration was $20.2 \pm 7.5 \mu\text{g}\cdot\text{mL}^{-1}$. All animals had a normal sinus rhythm before starting the bupivacaine infusion. Significant increases were seen in the PR interval, the QRS duration and the QTc interval after ten minutes (Table II). At BIE, significant changes had occurred in the PR, QRS, and the corrected QT (QTc) intervals on the ECG (Figure 2).

During the early period, cSvO_2 and CO were linearly correlated ($r = 0.782$, $P = 2.1 \times 10^{-7}$) while MBP and CO were not ($r = 0.019$, $P = 0.921$). The two linear regression lines of the early period differed in terms of slope and intercept ($P = 9.5 \times 10^{-4}$, $P = 6.8 \times 10^{-9}$) (Figure 3). During the late period, cSvO_2 was correlated with CO ($r = 0.824$, $P = 1.3 \times 10^{-6}$) and MBP correlated with CO ($r = 0.799$, $P = 4.8 \times 10^{-6}$). The two linear regression plots of the late period were not significantly different in terms of slope and intercept ($P = 0.188$, $P = 0.991$; Figure 4). SvO_2 and cSvO_2 were found to be well correlated ($r = 0.992$, $P = 1.9 \times 10^{-17}$).

Discussion

We designed this study to compare changes in cSvO_2 and MBP during bupivacaine-induced cardiac depression in dogs. The results showed that cSvO_2 was associated with CO decrease in dogs with bupivacaine-induced cardiac depression during the early stages of bupivacaine intoxication, while MBP was not. Two conditions should be satisfied for cSvO_2 to be useful to monitor CO changes in bupivacaine-induced cardiac depression. Firstly, VO_2 must be constant during monitoring, as was the case in our experiment. Secondly, there must be strong correlation between SvO_2 and cSvO_2 , and our results show that SvO_2 and cSvO_2 are significantly correlated.

Both pulmonary artery catheterization and epidural anesthesia or analgesia are sometimes recommended for clinical cases such as aortic surgery, coronary artery bypass graft and thoracotomy.¹⁰⁻¹⁴ For such cases, cSvO_2 can be a useful monitor. In the absence of a pulmonary artery catheter, the arterial lactate variation, end-tidal CO_2 and ECG changes may be useful variables for detecting the cardiac toxicity of bupivacaine.¹⁶⁻¹⁸ In this study, we compared cSvO_2 and MBP because CO is directly related to these variables. Though the experimental setting of fixed bupivacaine infusion may not represent an accidental bolus *in vivo* injection, it can be useful to analyze the early changes associated with hemodynamic and cardiovascular toxicity.

Bupivacaine is a potent and long acting local anesthetic and, if accidentally injected into the systemic circulation, it can cause lethal cardiotoxic effects. Moreover, the cardiotoxic effect of bupivacaine is

enhanced by hyperkalemia-induced blocking of the inward sodium current.¹⁹ Therefore, we maintained serum potassium levels within a normal range. In addition, bupivacaine is known to inhibit Ca^{2+} release from the sarcoplasmic reticulum.³ Although the serum calcium concentration changed significantly 20 min after bupivacaine administration in this experiment, the observed decrease probably had little effect on decreased CO because serum calcium was maintained within the normal range. Acidosis is known to be associated with increased levels of free forms of bupivacaine and thus to increase cardiotoxicity.²⁰ Therefore, we infused sodium bicarbonate to maintain the arterial pH within the normal range.

In this study, cardiovascular collapse was defined hemodynamically as a MBP of 40 mmHg. We intended to induce a severe but recoverable cardiovascular collapse to allow observation of the hemodynamic changes in severe bupivacaine-induced cardiac depression. Cho *et al.* demonstrated that control dogs recovered spontaneously after MBP had been reduced to 65 mmHg by a bupivacaine infusion for an average of 30 min.²¹ Epinephrine treatment allowed the recovery of half of the dogs with bupivacaine-induced cardiac depression, which had a MBP of less than 40 mmHg.²² Pilot studies showed that no dog recovered from bupivacaine-induced cardiac depression in two dogs with MBPs of 40 mmHg in the presence of acidosis and hypothermia. However, we succeeded in resuscitating all eight dogs with epinephrine when arterial pH was maintained normal after severe cardiovascular collapse.

We analyzed results during the early (baseline - 30 min of infusion) and late (30 min - BIE) periods of bupivacaine infusion. The early period represents the time during which spontaneous recovery is thought to be possible when the infusion of bupivacaine is stopped.²¹ The results showed that MBP was poorly correlated with decreased CO in the early period. However, in contrast to MBP, cSvO_2 was well correlated with CO during the early period. The late period represents times close to impending cardiovascular collapse. In the late period, bupivacaine caused a significant decrease in MBP. Thus, a decrease in MBP means that bupivacaine overdose has already occurred.²²

The mechanism responsible for the maintenance of MBP in the early period is not clear. Increased SVR could be suggested as one of the causes. Jorfeldt *et al.*²³ showed a 20-40% increase in systemic resistance in humans at a plasma bupivacaine concentration of $2 \mu\text{g}\cdot\text{mL}^{-1}$. Although SVR increased during the early administration of bupivacaine, this might not persist during impending cardiovascular collapse since tissue hypoxia tends to cause arterial vasodilatation.^{24,25}

In conclusion, MBP is not an appropriate monitor of early bupivacaine toxicity in dogs. If the same applies to the human situation, a stable MBP may give the clinician a false sense of security during early bupivacaine toxicity. Our results show that $cSvO_2$ is superior to MBP for monitoring decreased CO, regardless of the amount of bupivacaine infusion, especially in the early period. A profound reduction of CO is expected when the MBP begins to decrease during the late period of bupivacaine-induced cardiotoxicity.

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