Laboratory Reports

Thoracic epidural anaesthesia combined with enflurane anaesthesia reduces atrioventricular conduction in dogs

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Cardiac electrophysiological variables during thoracic epidural lidocaine (TEL) were compared with those during continuous intravenous lidocaine (IVL) infusion in 14 mongrel dogs anaesthetized with enflurane in order to investigate the combined effects of thoracic epidural anaesthesia (TEA) and enflurane anaesthesia on intracardiac conduction. Thoracic epidural lidocaine suppressed intracardiac conduction. Sinus cycle length (SCL) and Atrium-His (AH) interval increased by 9 and 11 per cent respectively (P < 0.05), 30 min after TEL. Intravenous lidocaine did not increase either SCL or AH. The functional refractory period of the atrioventricular node increased five per cent above the control value 15 min after TEL (P < 0.05), while it was unchanged in the IVL group. The mean plasma concentrations of lidocaine ranged from 0.48 ± 0.07 to 1.00 ± 0.14 $\mu g \cdot ml^{-1}$ in the TEL group and from 0.98 ± 0.13) to 1.21 ± 0.15 $\mu g \cdot ml^{-1}$ in the IVL group. There were no significant differences in plasma concentrations of lidocaine in both groups during the observation period. Therefore, it is concluded that the depressant effects of TEA on intracardiac conduction were caused by blocking of the sympathetic efferent activity. Caution may be advised in administering TEA when cardiac conduction is already compromised.

Les variables électrophysiologiques cardiaques lors d'une anesthésie thoracique épidurale avec la lidocaïne (TEL) ont été comparées avec celles obtenues lors d'une perfusion intraveineuse de lidocaïne (IVL) chez 14 chiens bâtards anesthésiés avec l'enflurane afin d'investiguer les effets combinés de l'anesthésie épidurale thoracique (TEA) et l'anesthésie à l'enflurane sur la conduction intracardiaque. La lidocaïne administrée par voie épidurale thoracique a supprimé la conduction intracardiaque. La longueur du cycle sinusal (SCL) et l'intervalle de His auriculaire (AH) ont augmenté de 9 et 11 pour cent, respectivement (P < 0,05), 30 minutes après TEL. La perfusion intraveineuse de lidocaïne n'a augmenté ni le SCL ni le AH. La période réfractaire fonctionnelle du nœud atrioventriculaire augmenta de cinq pour cent de la valeur de contrôle 15 minutes après TEL (P < 0,05) alors qu'elle fut inchangée dans le groupe IVL. Les concentrations plasmatiques moyennes de lidocaïne variaient entre 0,48 ± 0,07 à 1,00 ± 0,14 $\mu g \cdot ml^{-1}$ pour le groupe TEL et de 0,98 ± 0,13 à 1,21 ± 0,15 $\mu g \cdot ml^{-1}$ pour le groupe IVL. Il n'y avait aucune différence significative dans les concentrations plasmatiques de lidocaïne dans les deux groupes pendant la période de surveillance. Ainsi on conclut que les effets dépresseurs de la TEA sur la conduction intracardiaque sont causés par le blocage de l'activité efférente sympathique. La prudence est conseillée lors de l'administration de la TEA quand la conduction cardiaque est déjà compromise.

Key words
ANAESTHETICS, LOCAL: lidocaine;
ANAESTHETICS, VOLATILE: enflurane;
ANAESTHETIC TECHNIQUES: epidural, thoracic;
HEART: conduction, artioventricular.

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Decrease of heart rate (HR) and prolongation of atrioventricular (AV) nodal conduction time and refractoriness during TEA with lidocaine have been attributed to block

of cardiac sympathetic activity.[1,2] Enflurane produces prolongation of AV nodal, His-Purkinje and ventricular conduction times in dogs.[3,4] We usually combine thoracic epidural anaesthesia with inhalational anaesthetics in clinical practice. However, there is no report concerning the combined effects of TEA and inhalational anaesthetics on AV conduction time. Furthermore, the involvement of a direct pharmacological effect of the circulating local anaesthetics has not been ruled out because plasma concentrations of lidocaine can sometimes reach pharmacologically effective levels during TEA.[5] Therefore, it is uncertain whether the effects of TEA on cardiac electrophysiology are caused by diminished cardiac sympathetic activity or by direct pharmacological action of the circulating drug. To answer this, we performed TEA in dogs during enflurane anaesthesia and studied the cardiac electrophysiological variables (CEVs). The CEVs during TEA combined with enflurane anaesthesia were compared with CEVs during continuous intravenous lidocaine infusion (IVL) combined with enflurane anaesthesia. Plasma lidocaine concentrations during IVL were maintained similar to those during TEA.

Methods

The experimental protocol was approved by the Animal Care and Use Committee of Hokkaido University School of Medicine. Fourteen mongrel dogs of either sex, weighing 7–14 kg were randomly divided into two groups: eight for the TEL group and six for the IVL group. Anaesthesia was induced with thiamylal 25 mg·kg^{-1} IV and the trachea was intubated. Mechanical ventilation was performed to keep normocapnia ($PaCO_2$: 40 ± 5 mmHg) and anaesthesia was maintained with 1 MAC of enflurane (end–tidal concentration: 2.2 per cent) in 50 per cent nitrogen and 50 per cent oxygen. End–tidal anaesthetic concentrations and end–tidal CO_2 concentrations were monitored continuously with an infrared analyzer (CAPNOMAC, Datex). The animal was paralyzed with pancuronium 2 mg IM every three hours throughout the experiments. The femoral artery was cannulated for continuous monitoring of arterial blood pressure (ABP, Statham, P23ID) and measurement of plasma lidocaine concentrations. The femoral vein was cannulated for administration of fluids and drugs. Arterial blood gas tensions and acid–base balance were periodically measured throughout the procedure. Oesophageal temperature was maintained at 37 ± 0.5° C by an infrared lamp and a warming pad.

The methods used to measure CEVs were described in detail in a previous report[6] and are only briefly described here. Bipolar catheters were inserted into the right femoral vein and right external jugular vein to monitor the His bundle electrocardiogram and the high right atrium

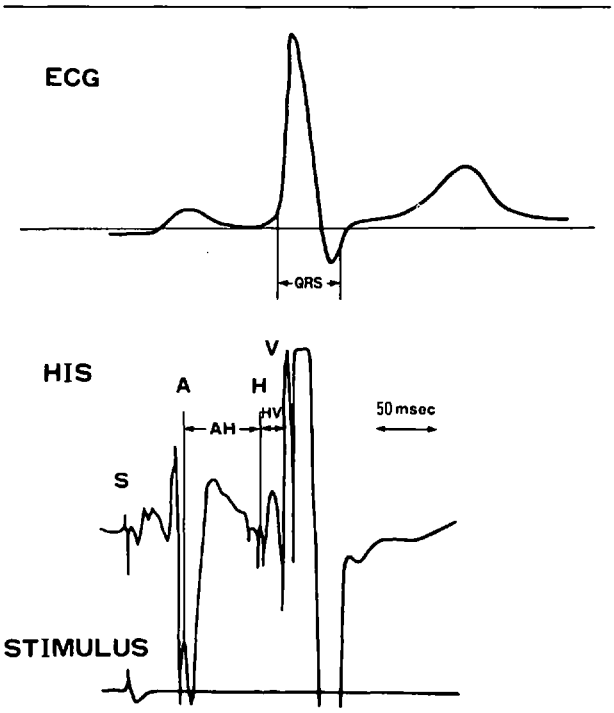

FIGURE 1 Typical His bundle electrocardiogram. S: stimulation artifact, A: atrium depolarization, H: His bundle depolarization, V: ventricle depolarization.

electrocardiogram using a polygraph system (Nihonkoden). After a right thoracotomy, bipolar pacing was performed using a stimulator (SEN-3201, Nihonkoden). The following variables were measured: sinus cycle length (SCL), atrium His (AH) interval, His ventricle (HV) interval, and effective and functional refractory periods (ERP and FRP) of the AV node. The FRP and ERP of the AV node were obtained by the atrium scanning method in which the atria were driven at a basic cycle period (A1-A2) of 330 msec, and premature atrial beats (A2) were elicited by progressively decreasing A1-A2 intervals up to the point of atrial refractoriness. The atrial, His bundle, and ventricular depolarizations during the basic atrial drive were defined as A1, H1, and V1. Those depolarizations resulting from coupled premature atrial stimulation were defined as A2, H2, and V2. The ERP of the AV node was defined as the longest A1A2 interval at which A2 did not conduct to the bundle of His. The FRP of the AV node was defined as the shortest H1H2 interval in response to two successive atrial impulses, both propagated through the AV node (Figure 1). All the variables except for SCL were measured during the basic cycle obtained by atrial pacing at 330 msec intervals. All data were recorded on a seven-channel FM magnetic tape recorder (SR-30, TEAC) for later data analysis and analyzed by a wave form controller (VD-640G, Nihonkoden) with a one msec resolution.

TABLE I Effects of thoracic epidural lidocaine (TEL) and intravenous lidocaine (IVL) on mean blood pressure and heart rate

		Control	*15*	*30*	*60*	*90*	*120 (min)*
Mean BP	TEL	104 ± 23	88 ± 17	84 ± 15*†	83 ± 14*	82 ± 12*	82 ± 14*
(mmHg)	IVL	100 ± 19	101 ± 13	98 ± 12	96 ± 14	97 ± 14	94 ± 16
HR	TEL	119 ± 24	113 ± 22	109 ± 20*	105 ± 20*	102 ± 20*	99 ± 19*
(bpm)	IVL	128 ± 17	126 ± 16	124 ± 15	123 ± 20	120 ± 21	113 ± 16*

BP: blood pressure, HR: heart rate, bpm: beats · min^{-1}.
All values are mean ± standard deviation.
*$P < 0.05$ compared with control value.
†$P < 0.05$ TEL *vs* IVL.

An epidural catheter was placed at the third thoracic vertebra by puncturing the ligamentum flavum at the T_{3-4} interspace using an 18-gauge Tuohy needle after surgical exposure of the dorsal laminar arch. The epidural space was identified by the loss of resistance technique using normal saline solution. The catheter was inserted 3 cm into the epidural space in a rostral direction. After the control measurement of variables, lidocaine was administered through the following two routes: (a) epidurally in the TEL group, lidocaine 2 mg · kg^{-1} one per cent solution (0.2 ml · kg^{-1}) containing methylene blue, or (b) by continous IV injection in the IVL group, 1 mg · kg^{-1} bolus followed by 1 mg · kg^{-1} · hr^{-1}. Measurements of CEVs and arterial plasma lidocaine concentration were repeated 5, 15, 30, 45, 60, 90, and 120 min after the administration of lidocaine in each group. After all the measurements were completed, the epidural space of each animal in the TEL group was opened, and the area of the epidural extension of methylene blue was determined by direct visual inspection.

The plasma concentrations of lidocaine were determined by high performance liquid chromatography (HPLC, Shimadzu LC-6A).

ANOVA was used to analyze progressive changes in values within each group, while a two-way ANOVA was used to compare changes between groups. A P-value < 0.05 was considered statistically significant.

Results

The epidural extension of methylene blue was observed in the area from T_1 to T_4 in every animal in the TEL group. Following the epidural administration of lidocaine, HR and ABP decreased gradually over the first 30 min (Table I), though it remained within 80 per cent of the control values. In the IVL group, on the other hand, HR and ABP remained unchanged throughout the course of the experiments.

The changes of CEVs are shown in Table II. No significant differences were seen between control values in the two groups under enflurane anaesthesia. The TEL suppressed intracardiac conduction; SCL and AH increased by 9 and 11 per cent, respectively ($P < 0.05$), 30 min after TEL. However, IVL did not increase either SCL or AH. Thoracic epidural lidocaine resulted in significant increases in SCL after 30 min and in AH after 15 min. The HV and QRS remained unchanged throughout the observation period in both groups. The FRP increased to five per cent above the control value 15 min after TEL ($P < 0.05$), while it was unchanged in the IVL group. No statistically significant differences were found in the changes of CEVs over time between the two groups. However, there were significant differences in the percentage changes of CEVs over time between the two groups (Figure 2). Statistically significant differences were found in SCL values after 30 min, in AH values after 15 min and in FRP values after 120 min ($P < 0.05$).

The peak plasma concentrations of lidocaine were observed within 5–15 min after the administration of lidocaine in both groups (Figure 3). Peak plasma concentrations were 1.57 μg · ml^{-1} in the TEL group and 1.86 μg · ml^{-1} in the IVL group. The mean plasma concentration of lidocaine ranged from 0.48 ± 0.07 to 1.00 ± 0.14 μg · ml^{-1} in the TEL group and from 0.98 ± 0.13 to 1.21 ± 0.15 μg · ml^{-1} in the IVL group. There were significant differences in plasma concentrations of lidocaine between the two groups after 5 and 120 min ($P < 0.05$), but no significant differences during the 15–90 min period.

Discussion

In the present study, anaesthesia was maintained with enflurane which has been reported to affect intracardiac conduction.[3,4] Enflurane has been reported to elicit a positive chronotropic effect on isolated rat atria in a dose-dependent manner.[3] Increasing the depth of enflurane anaesthesia from 1.0 to 2.0 MAC impaired AV nodal conduction and depressed the functional refractory period of the AV node while having minimal effects on His-Purkinje conduction in dogs.[4] Recently, Atlee *et al.* reported that 1.2–2.3 MAC enflurane prolonged AV nodal, His-Purkinje and ventricular conduction times in spontaneously beating hearts of chronically instrumented dogs.[7,8] Since atrioventricular conduction time becomes

TABLE II Sinus cycle length (SCL), atrial-His length (AH), His-venticle interval (HV), functional refractory period (FRC), effective refractory period (ERP) of atrioventricular node (AVN) and QRS-width in the two groups

		SCL	*AH*	*HV*	*FRP of AVN*	*ERP of AVN*	*QRS*
Time (min)							
Control	TEL	504 ± 49	70 ± 8	21 ± 0.6	243 ± 14	180 ± 8	59 ± 2.9
	IVL	468 ± 28	67 ± 10	21 ± 0.8	261 ± 11	180 ± 5	57 ± 4.9
5	TEL	515 ± 48	73 ± 9	21 ± 0.7	247 ± 16	182 ± 11	60 ± 3.2
	IVL	481 ± 29	65 ± 10	21 ± 0.8	261 ± 11	184 ± 4	58 ± 5.1
15	TEL	528 ± 45	74 ± 9	22 ± 0.7	256 ± 14*	188 ± 14	60 ± 3.1
	IVL	473 ± 28	66 ± 10	21 ± 0.7	257 ± 10	183 ± 4	58 ± 5.2
30	TEL	550 ± 47*	78 ± 9*	22 ± 0.7	260 ± 18*	188 ± 15	61 ± 3.4
	IVL	481 ± 27	65 ± 9	21 ± 0.7	258 ± 10	186 ± 4	58 ± 5.6
45	TEL	551 ± 49*	80 ± 12*	22 ± 0.6	258 ± 18*	188 ± 13	61 ± 3.1
	IVL	493 ± 31	67 ± 9	21 ± 0.6	255 ± 12	188 ± 4	59 ± 5.7
60	TEL	570 ± 49†	83 ± 13*	22 ± 0.6	260 ± 18†	191 ± 12	61 ± 3.5
	IVL	485 ± 37	65 ± 8	22 ± 0.8	255 ± 11	188 ± 3	60 ± 6.0
90	TEL	584 ± 52†	86 ± 13*	23 ± 0.6	266 ± 19†	191 ± 12	62 ± 3.8
	IVL	499 ± 40	66 ± 9	22 ± 0.8	258 ± 6	191 ± 4	61 ± 6.5
120	TEL	601 ± 53†	89 ± 12†	22 ± 0.5	272 ± 17†	201 ± 13	64 ± 3.7
	IVL	528 ± 34*	68 ± 9	22 ± 0.5	267 ± 6	197 ± 5	62 ± 6.7

Results are expressed as mean ± SEM (msec).
*$P < 0.05$, †$P < 0.01$ significantly different from control value. No statistically significant differences were found between the two groups.

prolonged with increasing heart rate,[9] it is important to compare AH and HV intervals at the same paced rates. Therefore, our results and the results of Atlee *et al.* are not directly comparable. However, the 1 MAC enflurane used in our study might have produced some depressant effects on AH and HV intervals, although we did not find any differences between the TEL and the IVL groups. Negative chronotropic effects observed in the TEL group included the marked prolongation of AV nodal FRP and a decreased intracardiac impulse conduction velocity. However, atrial, His-Purkinje or ventricular impulse conduction were unaffected by TEL. These findings are in accordance with those in previous reports.[1,2,10] Hotvedt *et al.* indicated that the cardiac electrophysiological effects of TEA were mainly caused by reduced sympathetic stimulation. They showed that TEA did not prolong ventricular refractoriness, action potential duration or the AV nodal conduction time any more in the dogs pretreated with atenolol.[10] Wallace and Sarnoff reported that stimulation of the left stellate ganglion did not change His-Purkinje or ventricular conduction in dogs.[11] Since sympathetic excitation shortens AV nodal refractory period and AV nodal conduction time,[12] our results further support the hypothesis that sympathetic block by TEL might cause such a prolongation.

Since lidocaine is known to reduce the maximum rate of depolarization of cardiac muscle and to shorten the action potential duration and effective refractory period in the His-Purkinje fibres and ventricular myocardium,[13–15] circulating lidocaine might be responsible for the cardiac depression after TEA. Plasma lidocaine concentration was controlled in the IVL group in ranges similar to those in the TEL group. The lack of significant change in CEVs during IVL ruled out direct cardiac depressant effects of lidocaine at these concentrations. Cardiac reflex mechanisms may also contribute to the cardiac electrophysiological effects of TEA. Cardiac vagal efferent activity has been shown to be modulated by cardiac receptor activities. The afferent fibres from such receptors travel in the sympathetic nerves towards the central nervous system.[16–18] It has been demonstrated that stimulation of the sympathetic afferent fibres produces reflex inhibition of vagal efferent activity.[19] Therefore, sympathetic block by TEA can increase cardiac vagal efferent activity and, thereby, decrease heart rate and prolong AV nodal impulse conduction and refractoriness.

It is generally accepted that beta-adrenergic blockade can protect against ischaemic or hypertensive heart disease during the operative and postoperative periods. Thoracic epidural analgesia has been shown to produce similar electrocardiac effects.[1,2] Combined TEA and beta-adrenergic blockade may have additive depressive effects on sinoatrial and AV nodal functions, as well as on left ventricular inotropy.[10] It has been reported that the potent volatile inhalation anaesthetics and calcium channel blockers affect AV conduction times.[6,20] Therefore,

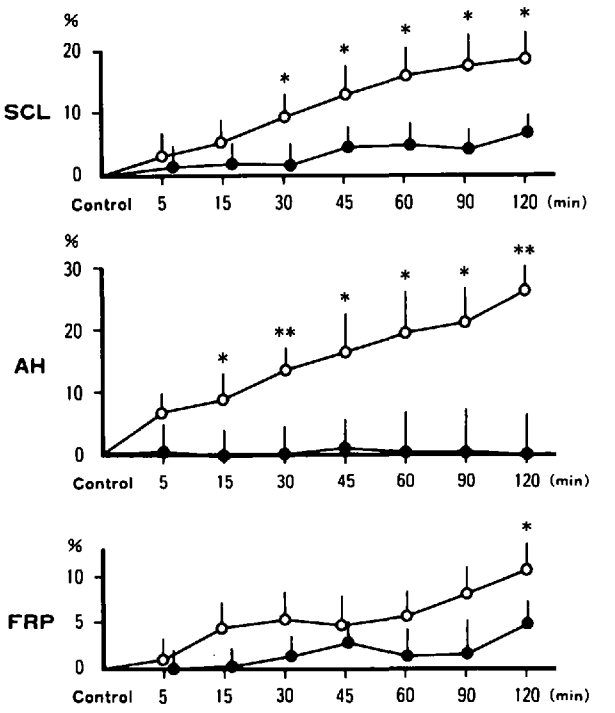

FIGURE 2 Effects of TEL and IVL on sinus cycle length (SCL), atrial-ventricle interval (AH), and functional refractory period of atrioventricular node (FRP) over two hours. Bars indicate SEM. TEL group (○), IVL group (●) (note the unequal time scale). $*P < 0.05$, $**P < 0.01$ TEL vs IVL.

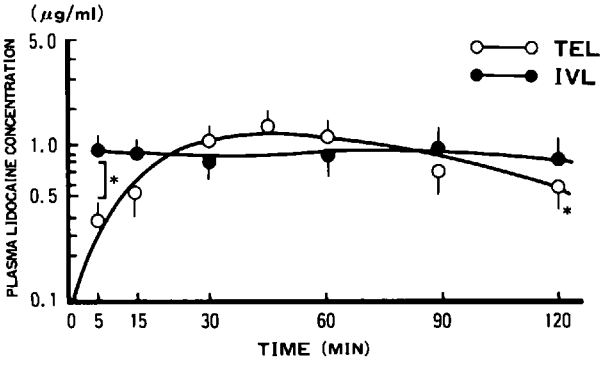

FIGURE 3 Plasma lidocaine concentration ($\mu g \cdot ml^{-1}$). Bars indicate SEM. $*P < 0.05$ TEL vs IVL.

TEA performed in patients treated with calcium channel blockers may produce heart block or nodal escape rhythm.

We conclude that the depressant effects on intracardiac conduction produced by TEA during enflurane anaesthesia were caused by the block of the sympathetic efferent activity. Caution may be advised in administering TEA when cardiac conduction is already compromised.

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