



Original Contribution

EFFECT OF THREE DIFFERENT ANAESTHETIC SCHEMES ON THE ELECTROCARDIOGRAPHIC PARAMETERS IN DOGS

Galina Simeonova*

*Department of Veterinary Surgery, Faculty of Veterinary Medicine,
Trakia University, Stara Zagora, Bulgaria

SUMMARY

The present study investigates the effects of three different anaesthetic schemes – volatile anaesthesia using halothane, balanced anaesthesia using pancuronium and epidural anaesthesia using lidocaine, on the electrical activity of the heart in healthy dogs. Standard electrocardiographic parameters, serving as autocontrol, were reported just prior to each anaesthetic scheme, and were reported 120 minutes later. The halothane and balanced anaesthesia resulted in QT-interval prolongation which makes them potent arrhythmogenic agents. The lumbosacral epidural anaesthesia with 2% lidocaine did not provoke ECG changes, suggesting a less danger in cardiovascular complications.

Key words: Anaesthesia, ECG, QT-interval, dog

INTRODUCTION:

Many cardiovascular disturbances leading to shock, life-threatening arrhythmias or other cardiac emergencies can occur following the administration of chemical restraining drugs and anaesthetics. The potential for these critical events is increased in severely debilitated or traumatized patients. Cardiovascular complications account for 25-50% of deaths following noncardiac surgery (1). Management of patients in critical cases continues to challenge the anaesthesiologist. Anaesthetic management should be tailored to the severity of the condition, to the nature of surgical procedure, and to successful outcome. Intraoperative detection of early signs of cardiovascular emergencies depends on electrocardiographic changes. The goal of the present study is to investigate the effects of three different anaesthetic schemes on the electrical activity of the heart in healthy dogs.

MATERIALS AND METHODS:

Twenty dogs of both genders, aged between 3 and 5 years, and mean body weight 17.4 ± 2.7 kg were used. They were divided in three groups; each group received a determined anaesthetic scheme. All animals received uniform premedications in order to investigate the effect of the principal anaesthetic schemes. Acepromazine maleas (*Combistress*®, *Kela-Belgium*), 0.1 mg/kg.m. was injected i.m. 10

minutes after 0.02mg/kg.m subcutaneous application of atropine sulfas (*Sopharma-Bulgaria*). For induction of anesthesia the animals subjected to general anaesthesia received, 20 minutes later, i.v thiopental natrium (*Biochemie GmbH-Austria*) 2.5% solution at 10 mg/kg.m.

The first group of 6 animals was intubated and anesthesia was maintained using Halotan (*Narcotan*®, *Leciva-Czech Republic*) 2.5-3 vol% and oxygen flow 2-3l/min. The Fluotec Mark III halothane vaporiser and semiclosed circle breathing system were used.

The second group of 7 dogs was subjected to balanced anesthesia. For maintenance of anesthesia the following regimen was used: halothane – 0.5vol%; oxygen - 2-3l/min given 20ml/kg.m. through artificial ventilation in frequency 12min^{-1} ; i.v pancuronium bromide (*Pavulon*®, *Troyapharm-Bulgaria*) at 0.06 mg/kg.m, by repeating a half of the initial dose when one spontaneous respiratory movement was restored; i.v. fentanyl citrate (*Stobium*®, *Research Institute of Chemistry and Pharmacology-Bulgaria*) at 0.01mg/kg.m.,

*Correspondence to: Galina Simeonova

Department of Veterinary Surgery,

Faculty of Veterinary Medicine,

Trakia University, Stara Zagora 6000, Bulgaria

e-mail: galinavet@abv.bg

with a booster dose every 30 minutes. Intravenous Nivalin P (*Sopharma-Bulgaria*) at 10 mg pro dosi was applied after restoration of four spontaneous respiratory movements for reversing from respiratory block.

In the third group of 7 dogs epidural anesthesia was applied through the epidural space between L7 and S1 by inserting Tuohy needle (22-gauge, 6.36cm) and Lidocaine 2% 0.3ml/kg.m (*Sopharma-Bulgaria*) was injected through spinal catheter.

In all animals electrocardiograms during two periods were obtained in the following manner: prior to (0 min) and during deep anesthesia (120 min). For that purpose a one-channeled microcomputer electrocardiograph MAIMEX-ECG 1222 ASB (Bulgaria) was used. Needle electrodes were placed under the skin in right lateral recumbency of the dogs. Six leads (3 standard and 3 augmented) were recorded over thermopaper with speed 50mm/sec.

Since it was difficult to detect the beginning of T-wave, the length of the QT-interval was measured. Since the normal duration of QT-interval depends on the heart rate its objective assessment was done using the corrected QT-interval obtained by Bazett's formula: $QT_c = QT/RR^{1/2}$ (2).

standardized so that 1mV signal produced a deflection of 10 mm. This was necessary to take care of either proportionate alterations in voltage of complexes or lack of false elevations and depressions. Before reading of duration, amplitude and shape of each element of electrocardiogram deciphering began with determination if the heart rhythm was sinus. Most cases showed sinus rhythm while few cases showed sinus arrhythmia. The electrical axis was normal in all animals and the voltage was high enough. There were no signs of enlarged atria or ventricles, atrioventricular blocks, ischemic or rhythm disturbances including premature supraventricular and ventricular complexes. Significant differences were established in relation to corrected QT-interval duration. Its values were elevated during the period of deep halothane (0.331 ± 0.019 sec, $p < 0.001$) and balanced anesthesia (0.331 ± 0.053 sec, $p < 0.001$) in comparison with initial levels in the two groups (0.256 ± 0.023 sec and 0.258 ± 0.024 sec, respectively). Measured QT-interval was elongated (**Figure 1**) only in the halothane group at 120 minute (0.245 ± 0.018 sec, $p < 0.001$) compared to the initial period (0.203 ± 0.023 sec). Epidural anesthesia did not make any impact upon ECG parameters measured in the present study.

RESULTS:

The results of measuring ECG parameters are presented on **Table 1**. The ECGs were

Parameter	Unit	Halothane anesthesia		Balanced anesthesia		Epidural anesthesia	
		Minute 0	Minute 120	Minute 0	Minute 120	Minute 0	Minute 120
Heart rate	min ⁻¹	88.3± 20.4	101.6± 9.8	95.7± 29.3	121.4± 33.87	92.7± 31.5	100.4± 18.6
P-amplitude	mV	0.158± 0.080	0.175± 0.075	0.207± 0.105	0.242± 0.097	0.184± 0.026	0.198± 0.037
P-duration	Sec	0.041± 0.004	0.053± 0.015	0.052± 0.017	0.054± 0.005	0.042± 0.006	0.054± 0.02
PQ- duration	Sec	0.098± 0.025	0.101± 0.009	0.100± 0.023	0.097± 0.022	0.099± 0.019	0.102± 0.022
QRS- amplitude	mV	1.050± 0.550	1.033± 0.422	0.964± 0.394	1.085± 0.422	0.984± 0.416	1.033± 0.415
QRS- duration	Sec	0.040± 0.012	0.043± 0.012	0.032± 0.007	0.037± 0.009	0.040± 0.008	0.044± 0.007
T- amplitude	mV	0.191± 0.237	0.141± 0.237	0.164± 0.363	-0.050± 0.264	0.153± 0.211	0.086± 0.314
QT- duration	Sec	0.203±	0.245±	0.200±	0.222±	0.204±	0.207±

		0.015	0.018***	0.023	0.026	0.013	0.022
QT-corrected duration	Sec	0.256± 0.023	0.331± 0.019***	0.258± 0.024	0.331± 0.053**	0.257± 0.023	0.263± 0.034

Table 1. ECG parameter measurements prior to (minute 0) and during deep anesthesia (minute 120) in three groups of dogs receiving halothane (n=6), balanced (n=7) and epidural lumbosacral (n=7) anesthesia. The values are presented as mean ± standard deviation.

- * p<0.05 – compared to the initial period (minute 0)
- ** p<0.01 – compared to the initial period (minute 0)
- *** p<0.001 - compared to the initial period (minute 0)

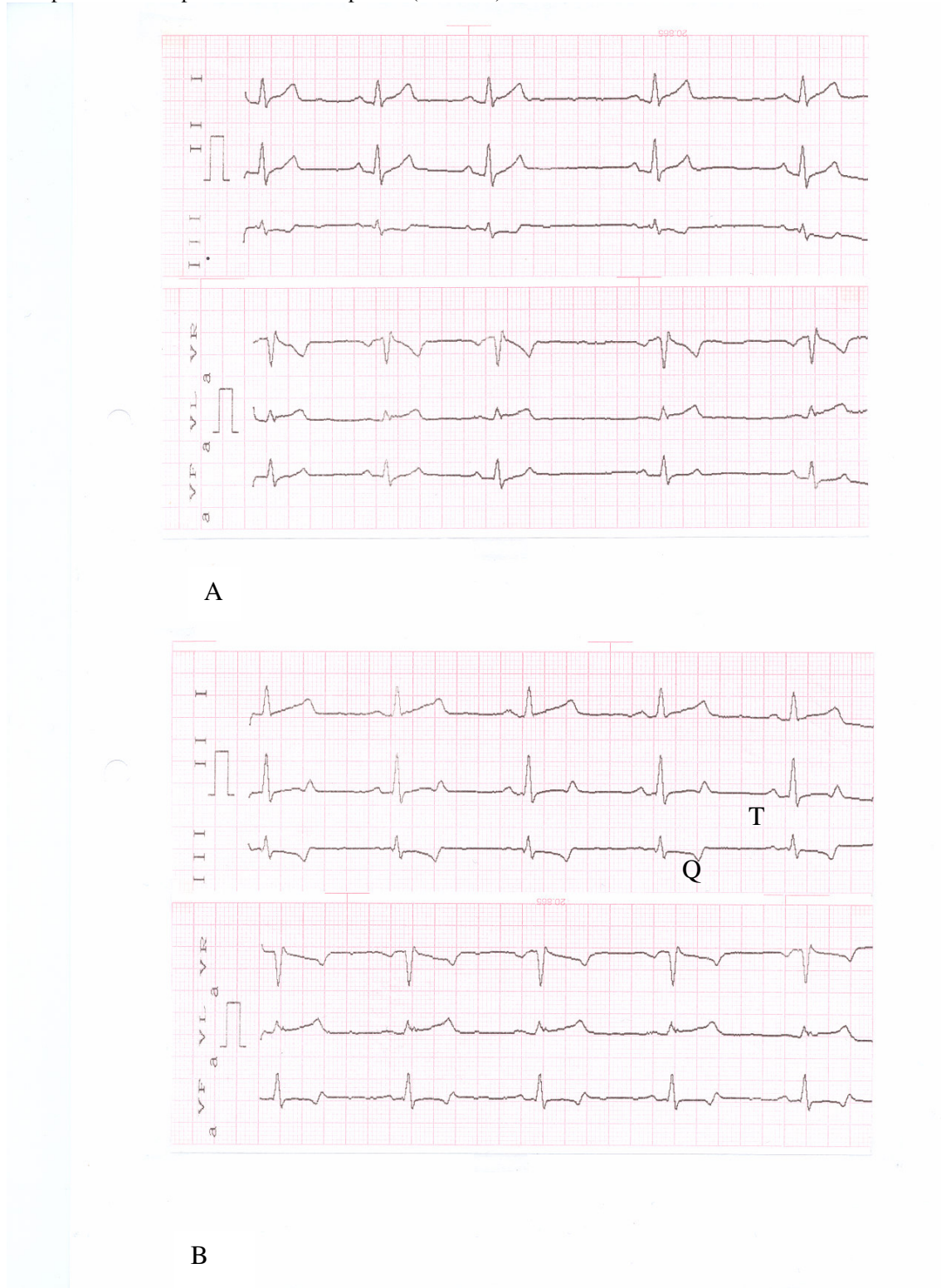


Fig.1. Electrocardiograms of dog just prior to (A) and during deep (B) halothane anesthesia

DISCUSSION:

Electrocardiographic alterations in halothane and balanced anesthesia were brought to QT-interval elongation whereas epidural anesthesia with lidocaine did not affect ECG parameters considerably.

As is well known, QT-interval reflects the electrical systole of the heart, namely, it registers the process of excitation of different parts of the chambers (QRS-peak, ST-segment) as well as their restoration (T-wave). Delayed repolarization results in QT-interval elongation that predisposes to late post-depolarizations. Therefore, the long QT-interval is a mark of increased risk of rhythm disturbances and precondition for sudden cardiac death even in seemingly healthy individuals.

The underlying molecular mechanism of the QT-interval elongation has been shown in studies of the long QT syndrome (LQTS) in humans (3-5). It is based on the malfunction of ion channels in the plasma membrane of cardiomyocytes. The inherited form of LQTS is due to mutations in the fast sodium channels, in the rapid and in the slowly activating potassium currents (3). Several drugs (including anesthetics), have shown to induce LQTS as their main targets are the fast sodium channels (6). These channels play a major role during cell repolarization, thereby determining the length of the action potential.

Other views posited a positive correlation between QT-interval elongation, QT-dispersion and serum catecholamine levels but these ECG parameters correlated negatively with serum potassium (5).

The three fundamental properties of the nodal tissue, that is, excitability, automaticity and conduction of the depolarization wave, are directly dependent on ionic transmembrane currents. These currents, either active or passive, determine the characteristics of the membrane action potential. Passive ionic movements across gated transmembrane channels could be activated by voltage-dependent and, sometimes, by time-dependent means; and for Ca^{2+} channels, is dependent on intracellular cyclic AMP content. Both intra and extra-cellular ionic concentrations (K^+ , Ca^{2+} and Mg^{2+}) alter these passive movements. Active ionic movements require ATP hydrolysis and depend only on cellular

metabolism. The neurovegetative system and its transmitters modulate the nodal tissue function thereby altering passive ionic currents. Drugs employed during anesthesia change this function either by direct action on the ionic currents or by indirect action on the neurovegetative system or on histamine liberation. Thus, local anesthetics block selectively fast sodium channels; halogenated volatile anesthetics inhibit slow calcium channels and narcotics are quite always vagomimetics, sometimes sympatholytics; they often release histamine. Nevertheless, definitive mechanisms of action of these various drugs still remain unclear (7).

Cardiovascular effects of the volatile anesthetics are due mainly to increase in heart rate which is determined primarily by cardiac vagal activity (8). Picker et al. (9) investigated the influence of 5 volatile anesthetics on the activation of the autonomic nervous system in the heart and showed that each of them suppressed vagal tone in a concentration-related manner. Halothane showed the least effect while desflurane showed the strongest. The changes of heart rate are related to the fluctuations of the arterial blood pressure as well. These alterations are detected by the baroreceptors in the carotid body and aortic arch and these cause information to be sent to the brain thus provoking a response through sympathetic drive. The volatile anesthetics interfere with this reflex arch by depressing perception of baroreceptors to some extent (10). As minimal alveolar concentration (MAC) increased, both arterial blood pressure and cardiac output decreased without any differences between anaesthetics. The substance-specific differences in the level of heart rate are related to the state of vagal activity.

Antiarrhythmic or arrhythmogenic properties characterize the influence of volatile anesthetics upon cardiac rhythm. The former may be due to direct inhibition of the calcium influx, whereas the latter is associated with their impact on catecholamines. It is known that halothane sensitizes the myocardium to circulating catecholamines. In the absence and, in the presence of autonomic nervous system blockade, halothane and isoflurane significantly prolonged the QT interval. These results as shown by Riley et al. (11) demonstrate that ventricular repolarization is

directly altered by the volatile anesthetics independent of changes in autonomic nervous tone.

Halothane has been reported to cause prolongation of the Q-T interval. Q-T interval prolongation constitutes a risk of ventricular tachycardia, including torsade de points. This should be taken into consideration when contemplating the use of halothane in patients with existing Q-T prolongation or in patients receiving other drugs known to prolong the Q-T interval. These reports confirm the pro-arrhythmic potential of halothane. Halothane administration is commonly associated with arrhythmias, some of which may be fatal. The risk of arrhythmias during halothane anaesthesia may be increased in certain procedures (e.g., dental surgery), clinical states (metabolic abnormalities, hypoxia and/or hypercapnia, pre-existing Q-T prolongation or history of arrhythmias), and in some other susceptible populations such as children (12).

Yamada et al. (13) examined the mechanism of QT interval prolongation induced by sevoflurane by means of electrophysiological technique in guinea-pig ventricular myocyte. Their conclusions were as follows: Sevoflurane 2% inhibited the fast potassium currents (IKr), but it showed only slight inhibition on calcium currents (ICa). Because the duration of action potential (AP) is regulated by ICa (plateau phase) and IKr (repolarization), greater inhibition of IKr than ICa could result in prolongation of AP. It is suggested that this mechanism may play a role in QT interval prolongation under sevoflurane anaesthesia.

As a rule, balanced anaesthesia is accompanied by increased heart rate which is mainly due to the effect of muscle relaxants. Opioids and drugs commonly used for induction of anaesthesia do not affect cardiovascular function significantly. Because of the resemblance of muscle relaxants to acetylcholine, it is not surprising that they have to do with cholinergic receptors in addition to those in the neuromuscular junctions. The entire parasympathetic nervous system and parts of the sympathetic nervous system (sympathetic ganglions, adrenal medulla, and sweat glands) depend on acetylcholine as a neurotransmitter. Since autonomic nervous system plays an essential role in the regulation of cardiovascular function, it is easy to explain the influence of the muscle

relaxants on this function. In contrast to depolarizing muscle relaxants, nondepolarizing muscle relaxants are incapable of inducing the conformational change in the cell membrane necessary for ion channel opening. Pancuronium that was used in the present study increases heart rate by amplification of the release of and blocking the re-uptake of catecholamines to the adrenergic nerve endings (14). Its use for intubation in human has resulted in electrocardiographic signs of myocardial ischemia (15). The acceleration of atrioventricular conduction and the release of catecholamines increase the probability of ventricular arrhythmias. The combination of pancuronium and halothane is considered to be rather arrhythmogenic (16). There are some studies that reported QT-interval elongation caused by muscle relaxants and, in particular, by pancuronium (17).

Local anesthetics act in the same way – they block the fast sodium channels in the cell membrane (18). In the peripheral nerves this mechanism is responsible for the anesthetic effect by preventing the conduction of the stimulus. Similar effects can be observed in the cardiac musculature. Local anesthetics affect myocardial depolarization by decreasing the inward sodium current and, likewise, prolonging the recovery time of the fast sodium channel and consequently increasing the refractory period (19). Cardiovascular effects of the local anesthetics occur at blood concentrations of systemic toxicity. Cardiovascular toxicity of local anesthetics is due to sino-atrial and AV-nodal depression resulting in bradycardia and AV block. The high blood levels of bupivacaine predispose the heart to re-entry arrhythmias whose feature is elongation of the QT-interval (20). The high affinity of bupivacaine to the membrane channels may result in toxic electrophysiologic effects which may be blunted by preliminary application of hypertonic saline solution (21). Although lidocaine binds to the inactive sodium channels too, the hypertonic solution of sodium chloride did not protect cells against this effect because lidocaine and sodium bind to the different sides of membrane thus making competition between them not possible. Lidocaine does not change the length of the QT-interval (22). On the other hand, it is one of the drugs of choice in the treatment of LQTS (23). The combined lidocaine/potassium infusion can be used as a diagnostic test for LQTS with accuracy of

94% (24). Following the infusion the length of the QT-interval and QT-dispersion decreased in the patients suspected for LQTS (with borderline QT-interval prolongation). Lidocaine used in thoracic epidural anesthesia can blunt circulatory response to isoflurane (it decreases the increased heart rate by isoflurane) but not in lumbal epidural application (25). The sympathetic neural activity contributes to the genesis of ventricular ectopic impulses, particularly in the setting of myocardial ischemia and infarction. This enabled Hogan et al. (26) to mimic myocardial infarction in dogs in order to investigate the possible antidysrhythmic effect of the thoracic epidural anesthesia thought to diminish ventricular ectopy by blocking the sympathetic innervation of the heart. Their results showed that lidocaine applied either intravenously or epidurally decreased total ectopic beats but did not alter ventricular tachydysrhythmia which remained the predominant rhythm in severe infarction. Other studies demonstrated that thoracic epidural lidocaine suppressed intracardiac conduction by blocking sympathetic efferent activity, whereas continuous intravenous lidocaine in the same plasma concentration did not have such effect (27). Another expression of cardiovascular toxicity of the local anesthetics was the dose-dependent decrease in the myocardial contractility resulting in decrease blood pressure, inotropism and cardiac output. These effects are proportional to the strength of the nervous blockade; this explains why lidocaine has the lowest and bupivacaine the highest cardiovascular toxicity (20).

In conclusion, the results of the present study confirm the evidence of the proarrhythmogenic effect of halothane and balanced anesthesia using pancuronium whose effect was QT-interval elongation. Lidocaine lumbosacral epidural anesthesia did not affect the cardiac action potential; hence it could be considered suitable in cardiovascular disturbances.

REFERENCES:

- Morgan, G.E., Mikhail, M.S., Murray, M.J., Clinical Anesthesiology, *McGraw-Hill Companies Inc.*, New York, USA, 2002.
- Marchev, S., How to interpret an electrocardiogram, *4xM*, Sofia, Bulgaria, 2002.
- Sanguinetti, M.C., Jiang, C., Curran, M.E., Keating, M.T., A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the I_{Kr} potassium channel. *Cell*, 81: 299-307, 1995.
- Curran, M.E., Splawski, I., Timothy, K.W., Vincent, G.M., Green, E.D., Keating, M.T., A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. *Cell*, 80: 795-803, 1995.
- Sato, K., Kato, M., Yoshimoto, T., QT intervals and QT dispersion in patients with subarachnoid hemorrhage. *J Anesth*, 15: 74-77, 2001.
- Chouabe, C., HERG and Kv LQT1/IsK, the cardiac K⁺ channels involved in long QT syndromes, are targets for calcium channel blockers. *Mol Pharmacol*, 54: 695-703, 1998.
- Sfez, M., Pierrot, M., Le Mapihan, Y., Physiology of nodal tissue and effect of products used in anesthesia. *Can Anesthesiol*, 33: 701-12, 1985.
- Scher, A.M. and Young, A.K., Reflex control of heart rate in the unanesthetized dog. *Am J Physiol*, 218: 780-9, 1970.
- Picker, O., Scheeren, T.W.L., Arnolt, J.O., Inhalation anaesthetics increase heart rate by decreasing cardiac vagal activity in dogs. *Br J Anaesth*, 87: 748-754, 2001.
- Saeki, Y., Hasegawa, Y., Shibamoto, T., The effect of sevoflurane, enflurane and isoflurane on baroreceptor-sympathetic reflex in rabbits. *Anesth Analg*, 82: 342-8, 1996.
- Riley, D.C., Schmeling, W.T., al-Wathiqui, M.H., Kampine, J.P., Warltier, D.C., Prolongation of the QT interval by volatile anesthetics in chronically instrumented dogs. *Anesthesia & Analgesia*, 67: 741-749, 1988.
- Blayney, M.R., Malins, A.F., Cooper, G.M., Cardiac arrhythmias in children during out-patient general anesthesia for dentistry: A prospective randomized trial. *Lancet*, 354: 1864-1866, 1999.
- Yamada, M., Hatakeyama, N., Shibuya, N., Momose, Y., Yamazaki, M., Mechanism of QT interval prolongation induced by sevoflurane in guinea-pig ventricular myocyte. *Masui*, 52: 482-8, 2003.
- Shorten, G.D., Uppington, J., Comunale, M.E., Changes in plasma catecholamine concentrations and haemodynamic effects of rocuronium and vecuronium in elderly

- patients. *Eur J Anaesthesiol*, 15: 335-341, 1998.
15. Neidhart, P.P., Champion, P., Vogel, J., Zsigmond, E.K., Tassonyi, E., A comparison of piperocuronium with pancuronium on haemodynamic variables and plasma catecholamines in coronary artery bypass patients. *Can J Anaesth*, 41: 459-464, 1994.
 16. Haywood, P.T., Divekar, N., Karalliedde, L.D., Concurrent medication and the neuromuscular junction. *Eur J Anesthesiol*, 16: 77, 1999.
 17. Saarnivaara, L., Klemola, U.M., Lindgren, L., QT interval of the ECG, heart rate and arterial pressure using five non-depolarizing muscle relaxants for intubation. *Acta Anaesthesiol Scand*, 32:623-8, 1988.
 18. Convino, B.G. and Vassallo, H.G., Local anaesthetics: Mechanisms of actions and clinical use. *Gruinne & Stratton Inc.*, New York, 29-55, 1986.
 19. Kasten, G.W., Amide local anaesthetic alterations of effective refractory period temporal dispersion: relationship to ventricular arrhythmias. *Anesthesiology*, 65: 61-66, 1986.
 20. Groban, L., Central nervous system and cardiac effects from long-acting amide local anesthetic toxicity in intact animal model. *Reg Anesth Pain Med*, 28: 3-11, 2003.
 21. Scalabrini, A., Corregiari, F., Rocha e Silva, M., Effects of hypertonic sodium chloride solution on the electrophysiologic alterations caused by bupivacaine in the dog heart. *Braz J Med Biol Res*, 36: 531-539, 2003.
 22. Ast, I., Heydeck, D., Mothes, E., Christ, B., Standardised in vitro electrophysiologic measurements using isolated perfused porcine hearts – assessment of QT interval alterations. *ALTEX*, 19: 3-8, 2002.
 23. Viskin, S., Torsades de pointes. *Curr Treat Options Cardiovas Med*, 1: 187-195, 1999.
 24. Chauhan, V.S., Krahn, A.D., Klein, G.J., Skanes, A.C., Yee, R., Utility of a simplified lidocaine and potassium infusion in diagnosing long QT syndrome among patients with bordering QTc interval prolongation. *Ann Noninvasive Electrocardiol*, 9: 12-8, 2004.
 25. Nakayama, M., Tsuchida, H., Kanaya, N., Namiki, A., Effects of epidural anesthesia on the cardiovascular response to a rapid increase in isoflurane concentration. *J Clin Anesth*, 12: 14-8, 2000.
 26. Hogan, O.H., Novalija, E., Kulier, A.H., Turner, L.A., Bosnjak, Z.J., Effect of thoracic epidural anesthesia on spontaneous postinfarction ventricular dysrhythmia in awake dogs. *Reg Anesth*, 22: 318-324, 1997.
 27. Sato, K., Yamamura, T., Murakami, F., Yokota, S., Kemmotsu, O., Thoracic epidural anaesthesia combined with enflurane anaesthesia reduces atrioventricular conduction in dogs. *Can J Anaesth*, 37: 813-8, 1990.