

Effects of Thoracic Epidural Anesthesia with and without Autonomic Nervous System Blockade on Cardiac Monophasic Action Potentials and Effective Refractoriness in Awake Dogs

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Background: The effects of thoracic epidural anesthesia (TEA) on myocardial repolarization and arrhythmogenicity are only incompletely understood. This is primarily because of the lack of appropriate experimental models. In most of the studies performed thus far, TEA was used in anesthetized animals. Baseline anesthesia itself may have modified the effects of TEA. This study investigates right atrial and ventricular repolarization by recording monophasic action potentials after TEA in awake dogs. The authors hypothesized that an antiarrhythmic role of TEA exists, which may be related to a direct effect of TEA on myocardial repolarization.

Methods: The hypothesis was tested in an *in vivo* canine model, in which atrial and ventricular myocardial action potential duration and refractoriness are recorded by means of monophasic action potential catheters.

Results: Thoracic epidural anesthesia significantly increased ventricular monophasic action potential duration for cycle lengths shorter than 350 ms. Changes in monophasic action potential duration were paralleled by a concomitant prolongation of effective refractory period (ERP) at higher rates so that the ratio of ERP to action potential duration was unaffected.

Conclusions: This model helps to study the role of TEA on ventricular repolarization and arrhythmogenicity. Because lengthening of repolarization and prolongation of refractoriness may, in some circumstances, be antiarrhythmic, TEA may be protective against generation of ventricular arrhythmias mediated, e.g., by increased sympathetic tone. The results also imply that the beneficial role of TEA might be stronger at the ventricular site as compared with the atrium. At atrial sites there was only a trend toward prolongation of repolarization even at short cycle lengths.

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ATRIAL as well as ventricular tachyarrhythmias remain a serious problem in anesthesia. In particular, patients undergoing cardiac surgery are at great risk to develop atrial fibrillation. Sympathetic nerve activity plays a crucial role in arrhythmias, particularly tachyarrhythmias. Because thoracic epidural anesthesia (TEA) blocks the sympathetic nervous system, it has been suggested that it may be beneficial in patients with an increased propensity for cardiac arrhythmias.

The antiarrhythmic effects of a blockade of the sympathetic nervous system by TEA have been shown in anesthetized rats¹ and dogs.² As general anesthesia modulates the autonomic nervous system itself, the effects of an isolated cardiac sympathectomy by TEA have not been investigated, mostly because of the lack of an adequate method. We hypothesized that TEA, by reducing sympathetic activity, exerts an influence on refractory periods, which may have an antiarrhythmic role. To test this hypothesis, we investigated the influence of TEA in an awake animal model that offers the opportunity to record monophasic action potentials. Monophasic action potentials are extracellularly recorded waveforms that can reproduce the repolarization time course of transmembrane action potentials with high fidelity.³⁻⁵

Methods

The experimental protocol was approved by the District Government of Münster, NRW, Germany, and is in accordance with the Guiding Principles in the Care and Use of Animals as approved by the Council of the American Physiologic Society.

To test the hypothesis that the sympathetic block induced by TEA may be related to an antiarrhythmic effect on cardiac electrophysiologic properties, we studied the effects of TEA and complete blockade of the autonomic nervous system in an *in vivo* canine model. In this model, myocardial action potential duration and refractoriness are measured by means of monophasic action potential catheters. Monophasic action potential recording is an integral part of electrophysiologic studies that are concerned with understanding basic electrophysiology and arrhythmia mechanisms in the intact heart.

Cardiovascular Instrumentation

After overnight fasting, seven mongrel dogs (weight, 20–26 kg) were premedicated intramuscularly with 15 mg piritramide and 5 mg/kg ketamine. Animals were anesthetized intravenously with 5 mg/kg propofol. After tracheal intubation, anesthesia was maintained with enflurane in a mixture of oxygen in air. Cefamandole (30 mg/kg) was given as a prophylactic perioperative antibiotic.

A left thoracotomy in the fifth intercostal space was performed during aseptic conditions. Eighteen-gauge catheters (Tygon; Serpi-Erpac S.A., Wilsele, Belgium) were inserted into the descending aorta and the left atrium for measurement of pressures and withdrawal of blood. A pressure microtransducer (Janssen Pharmaceutica, Beerse, Belgium) was inserted in the left ventricle through an apical stab wound for measurement of left ventricular pressure and rate of increase of left ventricular pressure (LV dp/dt).⁶ After closure of the thorax, all catheters were tunneled subcutaneously and exited the body between the scapulae. After instrumentation, the animals were trained daily to become accustomed to the experimental environment and to lie quietly in a cage when connected to the data acquisition system.

Epidural Catheter and Sheath Insertion

After complete recovery from the thoracotomy and when blood gas values and hemodynamic parameters had returned to normal, insertion of the epidural catheter was performed during sevoflurane anesthesia with endotracheal intubation on a separate day. After lumbar puncture of the epidural space with the loss-of-resistance technique, an 18-gauge catheter (Arrow Deutschland GmbH, Erding, Germany) was advanced epidurally to the second thoracic level. The correct position of the catheter was verified by radioscopy. The spread of the local anesthetic was then determined immediately by injecting contrast solution in a volume equivalent to the calculated volume of lidocaine. A distribution of contrast solution that included all thoracic segments above the seventh thoracic level was considered adequate. The catheter was tunneled subcutaneously, brought out in the vicinity of the other leads, and secured. During the same anesthetic, two 6-French sheaths were placed percutaneously by Seldinger technique in the right external jugular vein.

Electrocardiographic and Electrophysiologic Measurements

On the following day, an electrocardiogram was recorded continuously for measurement of routine parameters, including heart rate and PQ, QRS, and QT intervals (measured as the maximal QT interval of the six electrocardiogram leads recorded [I, II, III, aVR, aVL, aVF]). To exclude electrocardiogram variation as a result of the position of the dog, all electrocardiographic recordings

were performed with dogs standing in their cages. Two quadripolar monophasic action potential catheters (EPT Technologies, Sunnyvale, CA) were placed in the right atrium and ventricle of the awake dog. The position was verified by radioscopy.

Monophasic action potential recording and pacing, as well as programmed stimulation, were accomplished simultaneously using contact monophasic action potential pacing catheters. The monophasic action potential electrograms were amplified and filtered (low pass, 0.1 Hz; high pass, 300 Hz). The signals were analyzed using software specifically designed by Franz *et al.*,⁷ permitting precise definition of the amplitude and duration of the digitized monophasic action potentials. The recordings were considered reproducible and acceptable for analysis only if they had a stable baseline, a stable amplitude with a variation of less than 20%, and a stable duration (monophasic action potential duration at 90% repolarization was reproducible within 4 ms).

Unipolar cathodal pacing at twice diastolic threshold was performed using a conventional programmable stimulator (Universal Heart Stimulator, Biotronik, Berlin, Germany) that delivered square-wave pulses of 2-ms pulse width. The monophasic action potential-pacing catheters were used for stimulation. Pacing thresholds were defined as the lowest current allowing consistent ventricular depolarization. All data were digitized at a rate of 1 kHz with 12-bit resolution and subsequently stored on a removable hard disk.

Effective refractory periods (ERPs) were determined after 1 min of ventricular stimulation at a cycle length of 400 ms. After every eighth beat, a ventricular extrastimulus was introduced. The coupling interval was initially set late in diastole and subsequently reduced by 10 ms until no capture was observed. The coupling interval was then increased by 10 ms and then decreased by 2 ms until capture was lost on two consecutive occasions. This coupling interval was defined as the ERP. Thereafter, the cycle length was shortened by 50 ms, and the ERP was again measured. This sequence was repeated up to the cycle length of 200 ms.

Aortic and left atrial pressures were measured by disposable pressure transducers (PVB Medizintechnik, Kirchseeon, Germany). Pressures were processed by a six-channel pulsed Doppler system (Baylor College of Medicine, Houston, TX). The left ventricular micromanometer was calibrated to the pressures measured in aorta and left atrium. The left ventricular pressure signal was electronically differentiated (Gould Inc., Cleveland, OH). All signals were recorded on an eight-channel thermal writing polygraph (Gould Inc.).

After baseline measurements in the awake dog, thoracic epidural anesthesia was induced by injection of 0.4 mg/kg lidocaine (4–5.2 ml lidocaine 2%). Autonomic nervous system blockade (ANS) was performed by simultaneous injection of propranolol (2 mg/kg), atropine

Table 1. Rate-dependent Effects of Partial and Complete Autonomic Nervous System Blockade in Awake Dogs (n = 7)

	CL (ms)	QT (ms)	QRS (ms)	MAP90 RV (ms)	ERP RV (ms)	ERP/MAP
Control	400	221.4 ± 14.3	82.3 ± 11.7	147.5 ± 11.9	127.3 ± 9.2	1.2 ± 0.8
	350	202.6 ± 16.1	84.5 ± 7.5	144.6 ± 11.7	122.9 ± 8.8	1.1 ± 1.0
	300	188.6 ± 17.9	81.7 ± 8.8	140.9 ± 12.8	117.9 ± 8.5	1.2 ± 0.5
	250	175.5 ± 10.9	83.5 ± 15.1	134.4 ± 9.5	109.7 ± 11.2	1.2 ± 0.8
TEA	200	166.4 ± 17.6	83.7 ± 10.7	124.5 ± 9.2	97.1 ± 11.4	1.3 ± 0.8
	400	223.3 ± 16.2	82.2 ± 9.4	151.3 ± 7.2	130.7 ± 11.5	1.1 ± 0.5
	350	207.3 ± 15.1	82.2 ± 8.3	149.0 ± 6.0	128.9 ± 12.3	1.1 ± 0.5
	300	195.0 ± 5.2*	84.4 ± 8.8	146.5 ± 8.9*	124.0 ± 6.8	1.2 ± 0.8
ANS	250	180.4 ± 13.8	84.4 ± 10.1	139.9 ± 7.3*	118.1 ± 5.9*	1.2 ± 0.4
	200	176.4 ± 7.2*	81.7 ± 11.7	134.3 ± 9.6*	108.9 ± 7.4*	1.2 ± 1.0
	400	227.1 ± 15.4	82.2 ± 10.1	155.3 ± 6.7	135.4 ± 11.8	1.2 ± 0.5
	350	212.3 ± 12.4*	83.2 ± 8.3	153.7 ± 6.3*	133.6 ± 14.9*	1.2 ± 0.8
	300	200.7 ± 4.5*	83.5 ± 9.6	151.4 ± 7.9*	130.4 ± 10.8*	1.2 ± 1.0
	250	192.3 ± 8.8*	83.1 ± 8.6	148.6 ± 8.6*†	129.7 ± 10.1*†	1.2 ± 1.0
	200	187.1 ± 7.4*	82.7 ± 9.7	146.2 ± 9.0*†	124.4 ± 10.0*†	1.2 ± 0.5

Values are shown as mean ± SD.

* $P < 0.05$ versus control. † $P < 0.05$ versus thoracic epidural anesthesia (TEA).

CL = cycle length; MAP90 RV = right ventricular monophasic action potential duration at 90% repolarization; ERP RV = right ventricular refractory period measured at twice diastolic threshold; ANS = autonomic nervous system blockade.

(3 mg/kg), and hexamethonium (20 mg/kg). Adequacy of TEA was verified by occurrence of Horner syndrome and loss of motor function in the front limbs. The measurements were repeated 30 min after initiation of TEA or after nervous system blockade.

Statistical Analysis

Data were analyzed using repeated-measures two-way analysis of variance followed by Bonferroni-corrected Student t test. $P < 0.05$ was considered significant. Data are presented as mean ± SD. Comparisons of data between the three different states (control, TEA, and ANS) was performed by a paired t test.

Results

Baseline Measurements

One day after implantation of the catheter sheaths, all dogs were without signs of local or systemic infection. Spontaneous heart rate was 118 ± 15 beats/min before introduction of TEA. Mean arterial blood pressure was 100 ± 5 mmHg, and LV dP/dt was $2,936 \pm 214$ mmHg/s. During ventricular pacing, a cycle length-dependent decrease in QT interval and duration of monophasic action potentials was observed (table 1).

Electrocardiographic and Electrophysiologic Effects of Thoracic Epidural Anesthesia

Measurements of electrocardiographic parameters were performed 30 min after introduction of TEA and are shown in table 1. All measured electrophysiologic parameters reached steady state within this period. Left ventricular systolic pressure was not affected by TEA or by ANS during TEA.

During sinus rhythm, heart rate decreased by 10% from

118 ± 15 beats/min to 108 ± 20 beats/min (nonsignificant). No significant changes in QRS, PR, and QT interval duration during sinus rhythm and at a stimulation cycle length of 400 and 350 ms were observed. For cycle lengths shorter than 350 ms, there was a significant increase in QT interval with TEA as well as ANS as compared with control (table 1).

Monophasic action potential recording and pacing thresholds remained highly reproducible throughout the experimental protocol. After an initial stabilization period of approximately 5–10 min, the monophasic action potential amplitude did not change by more than 20% for the subsequent investigation period. In test periods of 60 min, monophasic action potentials varied by no more than 10%. Ventricular pacing thresholds were not affected by TEA or ANS. Ventricular pacing thresholds were low, ranging from 0.4 to 4.0 mA at cycle lengths from 200 to 400 ms. They were stable over time (< 10% increase during 15 min of continuous pacing). Because of the close proximity of the pacing and recording electrodes, pacing artifacts nearly coincided with the monophasic action potential upstroke. As pacing thresholds were low, pacing artifacts were almost always small. Programmed ventricular stimulation was used to simultaneously determine local right ventricular refractory periods and monophasic action potential duration. Atrial pacing thresholds ranged from 0.8 to 5.0 mA at cycle lengths from 200 to 400 ms.

Refractoriness and Action Potential Duration

Thoracic epidural anesthesia increased right ventricular monophasic action potential duration at 90% repolarization over the entire range of steady state cycle lengths. Table 1 summarizes the mean values of the last 10 monophasic action potential recordings after 1 min of

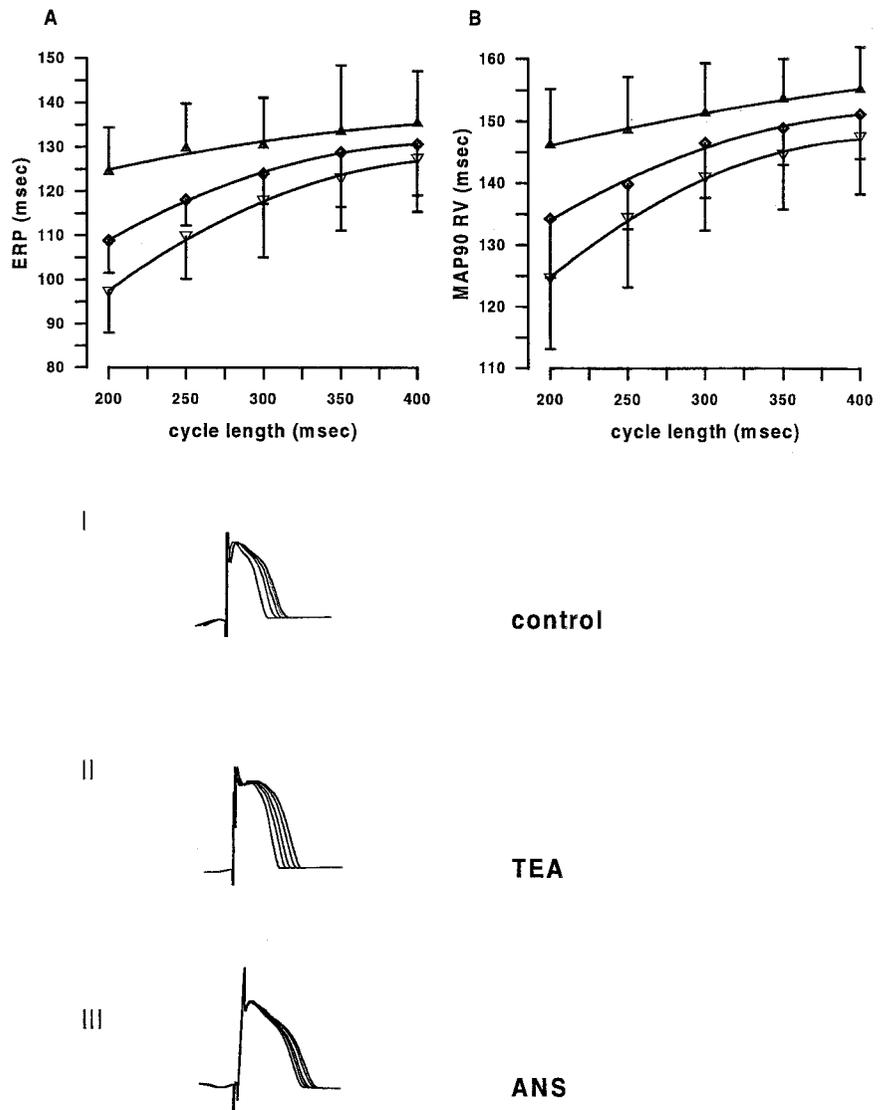


Fig. 1. Rate-dependent right ventricular electrophysiologic effects of thoracic epidural anesthesia (TEA; diamonds) and autonomic nervous system blockade (ANS) in the presence of continued TEA (triangles) in awake dogs ($n = 7$) in comparison to control (upside down triangles); mean \pm SD. Right ventricular endocardial effective refractory period (ERP; *A*) and monophasic action potential duration at 90% repolarization (MAP90 RV; *B*) are plotted against cycle length (I–III). Example of monophasic action potential shortening with decreasing cycle length during control conditions (I), with TEA (II), and with ANS in the presence of continued TEA (III).

pacing at constant rate. The increase ranged between 2.5% at a cycle length of 400 ms and 7.8% at a cycle length of 200 ms. It was significant for cycle lengths shorter than 350 ms. Changes in right ventricular monophasic action potential duration were closely paralleled by changes in ERP (fig. 1). Thus, neither TEA nor ANS blockade affect monophasic ERP-monophasic action potential duration. ANS in the presence of TEA led to a further increase in refractoriness and monophasic action potential duration (fig. 1 and table 1). This effect was significantly more marked at short cycle length than at long cycle lengths ($P < 0.05$). The action potential prolongation ranged between 5.3% at a cycle length of 400 ms and 17.4% at a cycle length of 200 ms ($P = 0.01$; fig. 1).

In the right atrium, there were no significant changes also toward a cycle length-dependent increase in refractoriness and action potential duration with TEA and ANS in the presence of continued TEA (fig. 2).

Hemodynamic Changes Induced by Thoracic Epidural Anesthesia

No significant changes in mean arterial blood pressure and LV dP/dt were observed after induction of TEA (table 2). Autonomic blockade resulted in a marked, statistically significant decrease in blood pressure (-24% , $P < 0.01$). This was accompanied by a substantial increase in heart rate ($+20\%$, $P < 0.01$). LV dP/dt significantly decreased by 33% ($P < 0.01$).

Thoracic epidural anesthesia as well as ANS were well tolerated by all dogs. Spontaneous arrhythmias were not observed on the atrial or ventricular level.

Discussion

The current study describes electrophysiologic effects of TEA and a complete blockade of the autonomic nervous system in conscious dogs. It shows that action potential duration and refractoriness are significantly

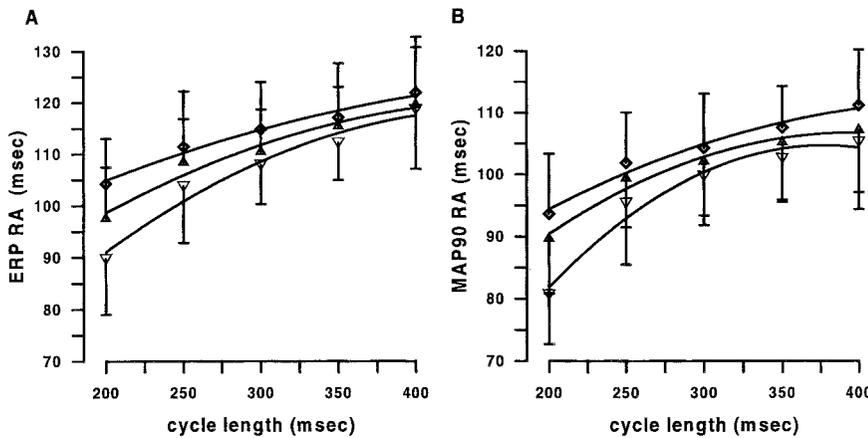


Fig. 2. Rate-dependent right atrial electrophysiologic effects of thoracic epidural anesthesia (diamonds) and autonomic nervous system blockade in the presence of continued thoracic epidural anesthesia (triangles) in awake dogs ($n = 7$) in comparison to control (upside down triangles); mean \pm SD. Right atrial effective refractory period (ERP RA; A) and monophasic action potential duration at 90% repolarization (MAP90 RA; B) are plotted against cycle length.

prolonged at fast heart rates in the presence of TEA as compared with control. Prolongation of repolarization is a well-known principle of antiarrhythmic agents. During right ventricular pacing and programmed stimulation, electrophysiologic parameters with increasingly shorter cycle lengths were significantly attenuated.

Monophasic Action Potentials to Assess Action Potential Duration and Refractoriness

Monophasic action potential recording is a unique tool that allows important insights into the presence of local inhomogeneities of repolarization. In 1986, Franz *et al.*⁴ demonstrated that stable and reliable monophasic tracings could be recorded from the human heart through the use of a catheter electrode and maintained pressure. Since then, this method has been used widely for studies on the *in situ* hearts of human and experimental animals and has provided a great deal of useful information on alterations in action potential duration, the time course of repolarization, and the occurrence of after-depolarizations as a result of physiologic conditions, disease, and drugs. Action potential duration and effective refractory periods allowed determination of both variables simultaneously at the same site. The accuracy with which monophasic action potential recordings reflect the local cellular depolarization and repolarization was examined in several studies that compared the monophasic action potentials with the simultaneously recorded transmembrane action potentials.³⁻⁵

Table 2. Hemodynamic Parameters during Partial and Complete Autonomic Nervous System Blockade (ANS) in Dogs ($n = 7$)

	Beats/min	MAP (mm Hg)	LV dP/dt (mm Hg/s)
Control	118 \pm 15	100 \pm 5	2936 \pm 214
TEA	108 \pm 20	98 \pm 6	2708 \pm 178
ANS	137 \pm 19*	76 \pm 9*	1973 \pm 96*

Values are shown as mean \pm SD.

* $P < 0.01$ versus control.

MAP = mean arterial pressure; LV dP/dt = left ventricular increase in pressure; TEA = thoracic epidural anesthesia.

Electrocardiographic and Electrophysiologic Effects of Thoracic Epidural Anesthesia and Autonomic Nervous System Blockade

Stimulation of the sympathetic nervous system facilitates the development of cardiac arrhythmias.^{2,8} Because TEA blocks the sympathetic nervous system, it has been suggested that it may be beneficial in patients with an increased propensity for cardiac arrhythmias. Until now, all investigations addressing this issue have been performed in anesthetized animals. Therefore, proper conclusions cannot be drawn from these studies. Sympathetic stimulation has been shown for pentobarbital anesthesia, and sympathetic depression has been shown for propofol and inhalation agents.⁹ This is aggravated by effects of anesthetic agents on vagal tone and baroreceptor sensitivity.^{9,10} Investigations of the effects of vagal and sympathetic stimulation *in vivo* and *in vitro* vary widely.^{11,12}

In pentobarbital-anesthetized dogs, Hotvedt *et al.*¹³ found predominantly β effects that were responsible for the effects of TEA: when TEA was induced after β blockade, a lack of additional effects on atrial and ventricular refractoriness and action potential duration was noted. The only small effect was a further prolongation of atrioventricular nodal refractoriness. However, this study is hampered by the use of pentobarbital-anesthetized dogs at a high baseline sympathetic activation with heart rates of 160 beats/min and an aortic blood pressure of approximately 137 mmHg.

Our results are in accordance with a previous study by Kamibayashi *et al.*,² who demonstrated a reduced incidence and increased threshold of epinephrine-induced arrhythmias in halothane-anesthetized dogs. An earlier study in rats found that the incidence of ventricular arrhythmias after coronary ligation was reduced when TEA was present at the time of ligation.¹

The cycle length-dependent effect of TEA on refractoriness has important implications. On the one hand, the effects on refractoriness may be small and possibly undetectable during sinus rhythm or at long cycle lengths. On the other hand, the effects of TEA, being

minor during sinus rhythm, may be clinically important at shorter cycle length or during tachycardia. When tachyarrhythmia develops, there is a shortening of action potential duration and refractoriness caused by the rate of adaptation of action potential duration. In this situation, TEA may be most relevant with regard to antiarrhythmic potency. ANS induced by injection of propranolol, atropine, and hexamethonium during TEA led to a further attenuation of the rate-dependent shortening of repolarization, suggesting that sympathetic blockade induced by TEA was incomplete.

Thoracic epidural anesthesia and ANS did not affect postrepolarization refractoriness. Even when repolarization is complete and membrane voltage has reached its previous baseline negative potential, ion channels may still not be sufficiently recovered to allow a new action potential, a phenomenon termed "postrepolarization refractoriness."¹⁴ This is quantified by the ratio of ERP to action potential duration (table 1).¹⁵

In our study, lidocaine was chosen as local anesthetic for two reasons: (1) its direct effects on the heart are well characterized; and (2) its depressant effects on cardiac excitation and conduction are lower compared with other anesthetics such as bupivacaine or ropivacaine.¹⁶ Lidocaine has been shown to shorten monophasic action potential duration in humans¹⁷ and swine.¹⁸ If absorbed lidocaine shortens repolarization, our results may underestimate the true beneficial role of TEA on repolarization, because lidocaine in the serum (although not measured) may counteract the measured prolongation of action potential duration and refractoriness. It is noteworthy that, in a study using intravenous mepivacaine and the same amount for TEA, only the epidural route was followed by an antiarrhythmic effect.²

Limitations of Measuring Monophasic Action Potential in Awake Dogs

One of the most important limitations of monophasic action potential recordings is that they may be distorted by motion artifacts caused by the beating heart as well as the movements of the dog. General limitation derives from the technique of monophasic action potential recording itself. We must be aware of the inability of monophasic action potentials to reproduce the true transmembrane action potential amplitude and upstroke velocity. Because the monophasic action potential catheter electrode is too large to enter a single cardiac cell, the monophasic action potential reflects a summation potential derived from a multitude of cells in close vicinity of the exploring monophasic action potential electrode. The present approach of monophasic action potential recording *in vivo* is limited to measurements on endocardial sites of the right atrium and ventricle, including the septum. Therefore, left ventricular changes of repolarization occurring, *e.g.*, in canine models of heart failure or ischemia cannot be studied. Our ap-

proach may overlook important epicardial changes that may result in important changes in dispersion of repolarization.

Hemodynamic Changes Induced by Thoracic Epidural Anesthesia

Sympathetic stimulation results in an increase of inotropy, cardiac output, and systemic vascular resistance. High TEA blocks cardiac sympathetic fibers originating from T1-T5. In patients with coronary artery disease, a reduction in heart rate, cardiac output, and systemic vascular resistance has been reported.^{19,20} However, other investigators reported increased heart rates with a reduction in cardiac output²¹ or no change in either variables. In a recent study, a reduction of heart rate without a change in cardiac output and perfusion pressure was reported.²² A similar variability has been reported for influences of TEA on contractility.²³ These varying results might be related to the use of different anesthetics and/or epinephrine additives, the differing number of segments blocked, and species differences. The observed effects of TEA on general hemodynamic parameters are in accordance with another study from this laboratory,²⁴ and the effects of ANS are similar to those reported by Pagel *et al.*²⁵

Clinical Relevance and Conclusions

The prolongation of action potential duration as well as the parallel increase in refractoriness suggest an antiarrhythmic role of TEA *in vivo*. Thus, TEA may have antiarrhythmic properties, especially in situations that result in a shortening of repolarization, such as ventricular and atrial (mainly atrial flutter and fibrillation) tachyarrhythmias and increased sympathetic tone or myocardial ischemia. Clinical studies need to verify if these experimental data result in antiarrhythmic effects in humans.

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