Electrocardiographic changes during continuous intravenous application of bupivacaine in neonatal pigs

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Key points

- T-elevation after intravascular injection of a small bupivacaine test dose are caused by epinephrine.
- This pig study demonstrated that higher doses of i.v. infused bupivacaine can cause T-wave elevation.
- Intravascular injection of large amounts of bupivacaine can be detected by changes in ECG.
- Bupivacaine-induced T-wave elevation is not a reliable indicator for early detection of inadvertent systemic injection.
- Bupivacaine-induced T-ware elevation is a sign of impeding cardiac toxicity, especially during fast injection.

Background. It is controversial as to whether T-wave elevation is caused by local anaesthetics, epinephrine, or their combination. It has been shown that T-elevation after intravascular injection of a small bupivacaine test dose is caused by epinephrine and not by bupivacaine. The aim of this study was to investigate ECG changes with higher doses of i.v. bupivacaine.

Methods. Thirty neonatal pigs were anaesthetized with sevoflurane and their tracheas intubated and artificially ventilated. Under steady-state conditions, bupivacaine was continuously infused (flow rate 3.2 ml kg^{-1} min^{-1}) by a syringe infusion pump through a central venous catheter. Group 1 received bupivacaine 0.125%, Group 2 bupivacaine 0.5%. The ECG was continuously printed and subsequently analysed for alterations in heart rate, ventricular de- and repolarization, and arrhythmias at 1.25, 2.5, and 5 mg kg^{-1} bupivacaine infused.

Results. Sinus rhythm persisted in all pigs. Heart rate decreased progressively in both groups, but this was significantly more pronounced in Group 1. T-wave elevation occurred in 40% and 0% (Groups 1 and 2) at 1.25 mg kg^{-1}, in 80% and 0% at 2.5 mg kg^{-1}, and in 93% and 80% at 5 mg kg^{-1} bupivacaine infused. There were significant differences between the two groups at 1.25 and 2.5 mg kg^{-1} infused.

Conclusions. Higher doses of i.v. infused bupivacaine can cause T-elevation. With slower injection technique, T-elevation can already be detected at lower bupivacaine doses administered.

Keywords: anaesthetics local, bupivacaine; heart, conduction; heart, heart rate; toxicity, local anaesthetics

Accepted for publication: 15 April 2010

Local anaesthetics (LA) for regional anaesthesia in children are usually administered under general anaesthesia.[1] Since neurological signs of LA toxicity in the event of inadvertent intravascular administration of LA are missing under general anaesthesia, ECG monitoring for the detection of LA-related changes, particularly the development of T-wave elevation, is recommended to detect inadvertent intravascular administration of LA before severe cardiovascular compromise or collapse occurs.[1–4]

It is controversial as to whether T-wave elevation is caused by LA, epinephrine, or their combination.[4] Recent research in neonatal pigs revealed that the formation of increased T-waves after injection of a common LA test dose is mainly caused by epinephrine and not by bupivacaine.[5] However, there is evidence suggesting that higher doses of bupivacaine may result in similar alterations.[5][6]

The aim of this study was to investigate the course of ECG alterations during continuous i.v. infusion of bupivacaine in neonatal pigs with special regard to the development of T-wave elevation.

Methods

After approval from the local ethics committee for animal experiments, 30 healthy male and female neonatal pigs (up to 6 weeks of age) were included. The pigs had free

access to food until 1 h before induction of anaesthesia. Anaesthesia was induced by the inhalation route using sevoflurane. After establishing venous access in an auricular vein, the trachea was intubated and the lungs were artificially ventilated using pressure-controlled ventilation. Anaesthesia was maintained using sevoflurane in oxygen/air 1:1.

Monitoring consisted of pulse oximetry, three-lead ECG, invasive arterial pressure measurement after cannulation of the carotid artery, end-tidal gas analysis (sevoflurane, O_2, CO_2), and rectal temperature control. Under steady-state conditions, bupivacaine was continuously infused (flow rate 3.2 ml kg^{-1} min^{-1}) through a central venous catheter at a dose rate of 4 mg kg^{-1} min^{-1} (Group 1: bupivacaine 0.125%) or 16 mg kg^{-1} min^{-1} (Group 2: bupivacaine 0.5%) using a syringe pump (Alaris TIVA, IVAC Corporation, Hampshire, UK).

The ECG lead with best representation of P-wave, QRS-complex, and T-wave was printed[7] and analysed after the experiment for alterations in heart rate, ventricular de- and repolarization, and arrhythmias at 1.25, 2.5, and 5 mg kg^{-1} bupivacaine infused by a blinded paediatric cardiologist and anaesthetist. Special attention was given to the appearance of T-wave elevation. T-wave elevation of $\geq 25\%$ baseline was considered a positive response.[3 8]

In each group, the percentage of heart rate change and the occurrence of positive T-wave elevation were compared between different amounts (1.25, 2.5, and 5 mg kg^{-1}) of bupivacaine administered. The Friedmann test followed by the Bonferroni corrected group comparisons using the Wilcoxon test was used for heart rate, and the χ^2 test was used to analyse the T-wave elevation data. Comparisons were made between slow and fast bupivacaine administration (Groups 1 and 2). Percentage change in heart rate was analysed using the Mann–Whitney U-tests and the occurrence of positive T-wave elevations between the groups was analysed with χ^2 tests at corresponding doses of bupivacaine administered. A P-value of ≤ 0.05 was considered to be significant. SPSS, version 16.0 (SPSS Inc., Chicago, IL, USA), was used for all analyses.

Results

Thirty male and female piglets weighing 4.5–6.2 kg (median 5.1 kg) were investigated. Changes in heart rate and T-wave elevation are shown in detail in Table 1. T-wave increases as percentage above baseline demonstrated a huge variability in degree of T-wave elevation (Fig. 1). Examples of typical and extreme T-wave increases after the infusion of 1.25, 2.5, and 5 mg kg^{-1} bupivacaine are shown in Figures 2 and 3. T-wave elevation $\geq 25\%$ baseline was considered a positive response. This occurred in 40% and 0% (Groups 1 and 2) at 1.25 mg kg^{-1}, in 80% and 0% at 2.5 mg kg^{-1}, and in 93% and 80% at 5 mg kg^{-1} bupivacaine infused. There were significant differences between the two groups at 1.25 and 2.5 mg kg^{-1} infused (Fig. 4). The probability of T-wave elevation was high at 2.5 and 5 mg kg^{-1} bupivacaine infused in Group 1, but only at 5 mg kg^{-1} in Group 2. Heart rate decreased significantly and progressively in both groups, but this was significantly more pronounced in Group 1 (Fig. 5). Sinus rhythm persisted in all animals. Neither a higher degree AV block, nor a complete bundle branch block, nor premature atrial, nor ventricular contractions were observed during bupivacaine infusion until 5 mg kg^{-1}.

Table 1 ECG alterations after i.v. infusion of 1.25, 2.5, and 5 mg kg^{-1} bupivacaine (n=30 piglets) at an infusion rate of 4 mg kg^{-1} min^{-1} (Group 1) or 16 mg kg^{-1} min^{-1} (Group 2). Results are given in median and range. ‡Significant differences between 1.25 and 2.5 mg kg^{-1} bupivacaine infused. †Significant differences between 2.5 and 5 mg kg^{-1} bupivacaine infused. *Significant differences between 1.25 and 5 mg kg^{-1} bupivacaine infused. #Significant differences between Groups 1 and 2. Infusion time, the time needed to fill the catheter with bupivacaine was 1.3 s for both drug rates (same infusion rate) and is therefore neglected

| Bupivacaine infused	Parameters	All (n=30)	Group 1 (n=15)	Group 2 (n=15)
1.25 mg kg^{-1}	Infusion time (s)		18.8	4.7
	Change in heart rate (beats min^{-1})		−5 (0 to −23)	0 (0–0)
	Change in heart rate (%)#	0 (0 to −14)	−4 (0 to −14)	0 (0–0)
	T-elevation (mm)		2 (1–6)	3 (1–5)
	T-elevation (%)	0 (0–100)	0 (0–100)	0 (0–0)
	T-elevation (yes/no)#	6/24	6/9	0/15
2.5 mg kg^{-1}	Infusion time (s)		37.5	9.4
	Change in heart rate (beats min^{-1})		−11 (−2 to −26)	−2 (0 to −13)
	Change in heart rate (%)#	−4 (0 to −16)	−8 (−1 to −16)‡	−1 (0 to −11)‡
	T-elevation (mm)		3 (1–8)	3 (1–5)
	T-elevation (%)	0 (0–40)	50 (0–400)	0 (0–0)
	T-elevation (yes/no)#	12/18	12/3	0/15
5 mg kg^{-1}	Infusion time (s)		75	18.8
	Change in heart rate (beats min^{-1})		−26 (0 to −45)	−10 (0 to −33)
	Change in heart rate (%)#	−13 (0 to −29)	−20 (0 to −29)†,*	−6 (0 to −28)†,*
	T-elevation (mm)		3.5 (1–13)	4 (1–11)
	T-elevation (%)	100 (0–800)	133 (0–800)	67 (0–200)
	T-elevation (yes/no)	26/4	14/1	12/3

Discussion

This study investigated whether bupicavaine alone can cause T-wave alteration in the ECG when systemically administered. The main findings were that i.v. administered bupivacaine alone causes T-wave elevation in a high percentage of subjects particularly at larger doses and with slower injection, T-elevation can already be detected at lesser bupivacaine doses.
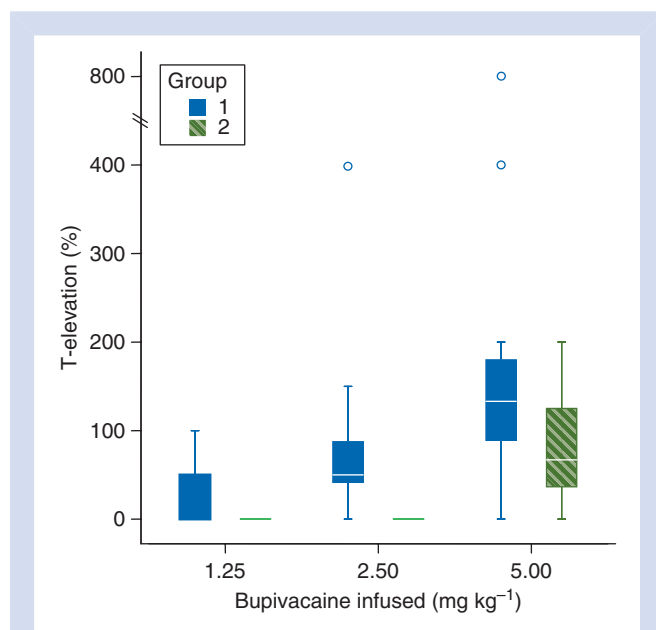
Fig 1 T-wave increase in percentage above baseline at different amounts of bupivacaine infused. $n=15$ in both groups.

Reliable signs of inadvertent systemic application of LA in anaesthetized children are of importance in order to avoid severe systemic LA toxicity, in particular haemodynamic collapse. The results of this study clearly indicate that not only systemically administered epinephrine[5] but also bupivacaine cause T-wave elevation, particularly at larger doses. This explains the confusion about origin and reported varying sensitivity of ECG for the detection of systemic administration of LA.[4] However, as shown by the current animal model, the sensitivity of bupivacaine-induced T-wave elevation for detecting inadvertent systemic LA administration is not 100%, demonstrates a large variability in T-wave elevation, and becomes mainly visible after doses corresponding to the maximum recommended dose for humans.[9] [10] Therefore, bupivacaine-induced T-wave elevation is a sign for impending cardiac toxicity and not helpful for early detection of inadvertent intravascular administration. In contrast, T-elevation caused by an epinephrine containing standard test dose of LA is the effect of epinephrine and has a sensitivity of 93%.[5] In this situation, no adverse consequences have to be anticipated.[5] [11] [12]

The study results confirm the previously reported observation that not only epinephrine in a normal test dose alone or in combination with bupivacaine but also bupivacaine systemically administered in a twice fold test dose can evoke T-wave elevation.[5] Nyström and colleagues[13] investigated acute bupivacaine overdose until near cardiac arrest in 12 adult male pigs (23–25 kg) sedated with ketamine and then anaesthetized with halothane. They also found significant increases in T-wave amplitude [+66% above baseline in maximum (mean)]. Tanaka and colleagues[6] reported a 2-month-old healthy infant demonstrating significantly increased T-wave amplitude after the
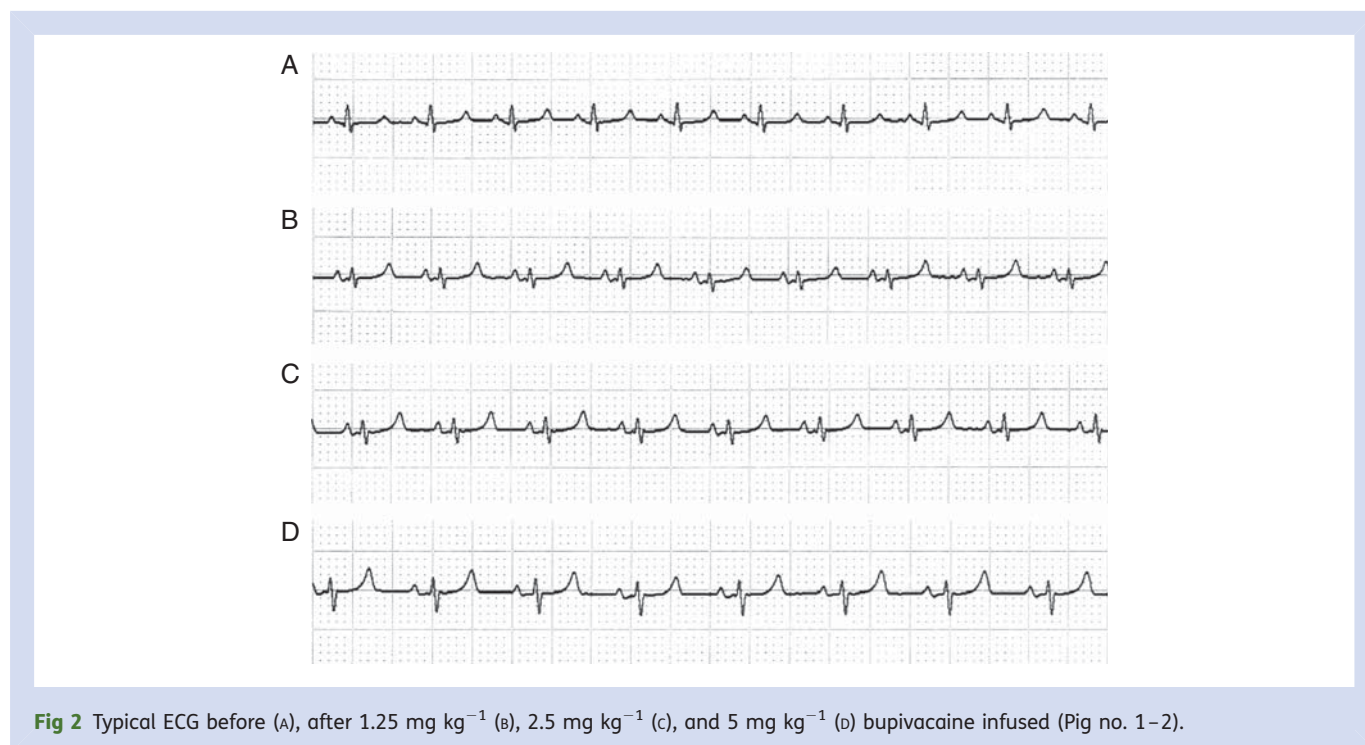
Fig 2 Typical ECG before (A), after 1.25 mg kg^{-1} (B), 2.5 mg kg^{-1} (C), and 5 mg kg^{-1} (D) bupivacaine infused (Pig no. 1–2).
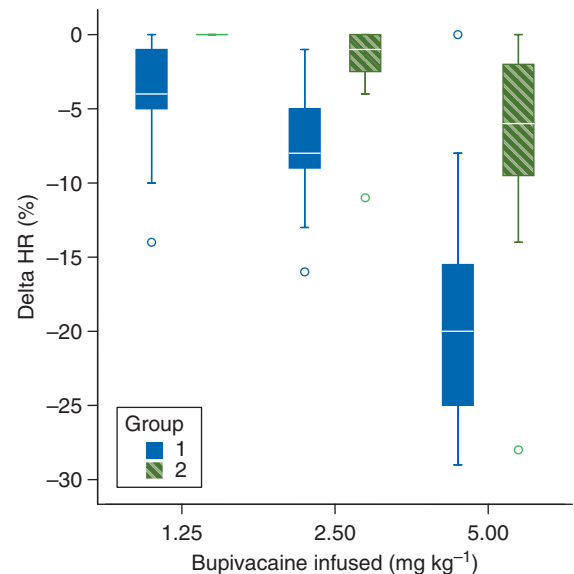
Fig 3 ECG with extreme T-elevation caused by bupivacaine. Trace before (A), after 1.25 mg kg^{-1} (B), 2.5 mg kg^{-1} (C), and 5 mg kg^{-1} (D) bupivacaine infused (Pig no. 2–9).
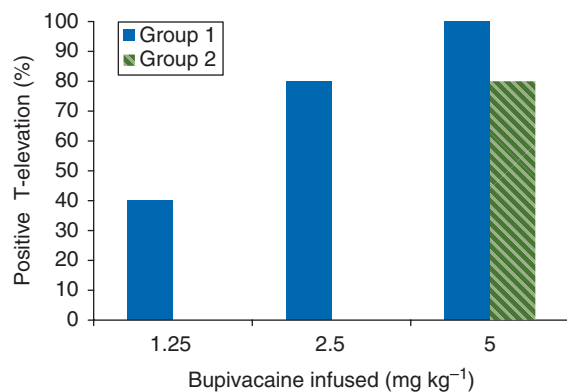
Fig 4 Percentage of pigs with positive T-wave elevation ($\geq$25% baseline) at different doses bupivacaine infused. n=15 in both groups.

Fig 5 Changes in heart rate (%) after i.v. infusion of 1.25, 2.5, and 5 mg kg^{-1} bupivacaine. n=15 in both groups.

accidental systemic administration of a near full-dose lidocaine plus bupivacaine when performing a caudal block.

The QT interval is a measure from the body surface of the time required for ventricles of the heart to repolarize. Prolongation or abbreviation of the QT interval occurs when the action potential of a significant number of cells in the ventricular myocardium is prolonged or abbreviated, as a result of an alteration in one or more ion channel currents. T-waves are in large part inscribed as a consequence of the voltage gradients that develop as a result of transmural differences in the time course of repolarization. When the T-wave is upright, the epicardial action potential is the earliest to repolarize and the M cell (mid-myocardium, papillary muscles, interventricular septum) action potential is the last. Full repolarization of the epicardium coincides with the peak of the T-wave. The $T_{peak}-T_{end}$ interval provides an index of transmural dispersion of repolarization.[14] The cardiac toxicity of LA is attributed to a blockade of sodium channels in the heart,[15] leading to a prolonged conduction

time with widening of QRS complexes, changes in QRS morphology, prolongation of PR interval, AV block, and arrhythmias. Owing to altered function of ion channels (mainly sodium channels, but also calcium and potassium channels),[16] [17] not only depolarization but also repolarization is affected. The exact mechanism for T-wave elevation caused by intravascular LA administration is not clear.[4] [6] Also, there is no clear explanation for the huge variability in the relative increase of T-wave in this study.

The current study included a slow (Group 1) and a fast dose rate (Group 2) of bupivacaine administration. One would expect that with slow injection of bupivacaine, a drug known to have a high first pass lung uptake,[18] [19] ECG alterations are reduced, in contrast to fast injection, causing an excess in plasma concentration of bupivacaine and related toxicity.[20] Interestingly, with slower infusion rates, ECG changes appeared at lower doses administered. We hypothesize that although the LA solution was given into a central vein, the circulation time needed to distribute the drug from the injection site into cardiac tissue is responsible for the delay in ECG alteration in the fast group. This reinforces the necessity that LA should be administered slowly. Not only to avoid high plasma peak levels but also not to miss LA-related ECG alterations for early cessation of LA injection.

On the basis of the fact that epinephrine early after a single LA test dose and bupivacaine alone only later and after higher doses leads to ECG alterations, for usual clinical practice, the test dose should contain epinephrine. Whether a change from an epinephrine containing LA solution after the test dose to a plain LA solution should be done is much discussed. Since regional anaesthesia needles or cannulas may migrate into a vessel,[21] our view is that the full LA dose administered should contain epinephrine to detect systemic injection at any period of injection.

In conclusion, this newborn animal model demonstrates that higher doses of systemically applied bupivacaine can cause T-elevation. However, bupivacaine-induced T-elevation is not a reliable indicator to early detect inadvertent systemic injection of LA and is rather a sign for impeding cardiac toxicity, especially during fast injection of LA.

Conflict of interest

None declared.

Funding

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