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The Effects of Lidocaine on Bupivacaine-Induced Cardiotoxicity in the Isolated Rat Heart

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Summary

Bupivacaine is a widely used long-acting local anaesthetic. In clinical practice, a mixture of bupivacaine and lidocaine is often used in order to combine the faster onset of sensory blockade of lidocaine with more profound and longer duration of blockade by bupivacaine. The aim of this study was to compare the cardiotoxicity of large doses of bupivacaine and mixture of bupivacaine with lidocaine in the isolated rat heart and to estimate whether or not the addition of lidocaine in clinically relevant concentration increases bupivacaine-induced toxicity. Experiments were performed on 21 adult male rats divided into three groups: B (6 μg/ml bupivacaine), BL (6 μg/ml bupivacaine and 12 μg/ml lidocaine) and L (12 μg/ml lidocaine). The experiment consisted of three 30 min periods: stabilisation, perfusion and washout. The isolated hearts were perfused according to Langendorff with Krebs-Henseleit solution at constant pressure (80 mmHg) and 37 °C ($CaCl_2$ 1.25 mM) and the heart rate (based on RR interval assessment), PQ and QRS intervals were measured. The present study shows that the mixture of tested anaesthetics – bupivacaine and lidocaine – impairs the intraventricular conduction parameters (QRS interval prolongation) to a lesser extent than bupivacaine itself, and that this effect is marked mainly at the beginning of perfusion.

Key words

Bupivacaine • Lidocaine • Isolated rat heart • Cardiotoxicity • QRS duration

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Introduction

Bupivacaine has become a widely used local anaesthetic due to its long duration of action and outstanding sensory anaesthesia. Unfortunately, bupivacaine exhibits a strong tendency to cardiac toxicity when accidentally administered intravenously. Fatal cases of cardiac arrest associated with the use of bupivacaine have been reported repeatedly (Albright 1979, Davis and de Jong 1982).

In clinical practice, a mixture of bupivacaine and lidocaine is often used in order to combine the faster onset of sensory blockade of lidocaine with more profound and longer duration of blockade by bupivacaine (Křikava *et al.* 2008). Bupivacaine leads to enhanced myocardial sodium channel block because it dissociates from channels slowly during diastole in contrast to lidocaine which binds and dissociates fast (Clarkson and Hondeghem 1985). Previously published studies showed that lidocaine could displace bupivacaine from its receptor site and some authors suggested symptomatic treating of bupivacaine cardiotoxicity with lidocaine. Namely the animal trials supported this receptor theory (Lefrant *et al.* 2003, Fujita *et al.* 1998). However, studies in isolated animal hearts did not confirm this positive effect of lidocaine and thus the role of lidocaine in affecting bupivacaine-induced cardiotoxicity remained unresolved (Simon *et al.* 2002).

The aim of this study was to compare the

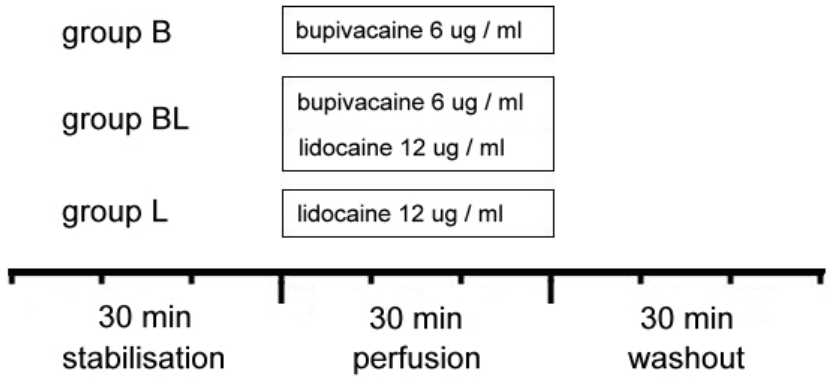

Fig. 1. Flowchart of the experiment. Bupivacaine was applied in groups B and BL and lidocaine in groups BL and L during perfusion period.

cardiotoxicity of large doses of bupivacaine and mixture of bupivacaine with lidocaine in the isolated rat heart and to estimate whether or not the addition of lidocaine in clinically relevant concentration increases bupivacaine-induced toxicity.

Materials and methods

All animal experiments were carried out with respect to the recommendations of the European Community Guide for the Care and Use of Laboratory Animals and followed the guidelines for animal treatment approved by local authorities.

Twenty-one adult Wistar rats were divided into three experimental groups. The hearts from group B were exposed to bupivacaine, group BL – mixture of bupivacaine and lidocaine, and in group L lidocaine was administered.

Animals were sacrificed by cervical dislocation under deep ether anaesthesia. The heart was rapidly removed and placed in a cold (5 °C) Krebs-Henseleit solution of the following composition: 118 mM NaCl, 25 mM $NaHCO_3$, 4.7 mM KCl, 1.2 mM KH_2PO_4, 1.2 mM $MgSO_4$, 1.25 mM $CaCl_2$, and 7 mM glucose. Aorta was then cannulated and fixed to the Langendorff set up. The heart was perfused with Krebs-Henseleit solution of the abovementioned composition at constant perfusion pressure of 80 mmHg.

The experiment consisted of three periods, each lasting 30 minutes (Fig. 1). After a 30 min stabilisation period, the perfusion with the tested substance started: bupivacaine 6 μg/ml (21 μM) in group B, bupivacaine 6 μg/ml (21 μM) and lidocaine 12 μg/ml (51 μM) in group BL and with lidocaine 12 μg/ml (51 μM) in group L (control). This period lasted again 30 minutes and was followed by 30 minutes washout phase of the experiment. The concentrations of bupivacaine and lidocaine were estimated according to the results of our pilot study (Křikava *et al.* 2008) as well as of other studies (Lefrant *et al.* 2003, Fujita *et al.* 1998). In this study, higher concentrations were used which simulate high plasmatic levels of local anaesthetics during inadvertent intravenous administration. Since the mixture of local anaesthetics mostly used in clinical practice contains bupivacaine and lidocaine concentrations in ratio 1:2, the same proportion was used in this study.

Continuous electrographic recordings were obtained by touchless method during the entire experiment (Nováková *et al.* 2000). Three bipolar leads in orthogonal arrangement were used. The electrodes were placed in the bath in which the heart was immersed during the experiment. The sampling rate was 2 kHz. The recorded electrograms were stored in PC and subsequently off-line analyzed.

The heart rate (based on RR interval assessment), PQ and QRS intervals were measured and counted during the processing of records. Coronary flow in each group was monitored by collecting the perfusate leaving the bath via the outlet as a corroboratory parameter.

Standard nonparametric descriptive statistics was adopted for the analysis. Continuous variables were described by median and scatter; categorical parameters were described by percentage of categories. Statistical significance of differences between the groups of experimental subjects was analyzed by means of Mann-Whitney U test; no correction for multiple testing was applied. Wilcoxon rank test for paired data was applied for analysis of statistical significance of variables changes in time. Relationship of categorical variables in contingency tables was analyzed using Fisher exact test. Statistical analysis was performed using SPPS 18.0.0.

Results

Eight, eight and five rats were included in the bupivacaine (B), mixture of bupivacaine and lidocaine

Table 1. Basic characteristics of animals in particular experimental groups. Data are shown as median and scatter. No statistical difference among groups was found.

	B (N = 8)	BL (N = 8)	L (N = 5)
Weight	265 (150; 351)	263 (229; 295)	255 (235; 260)
Sex (males)	N = 5 (62.5 %)	N = 6 (75.0 %)	N = 2 (40 %)

(BL) and lidocaine (L) groups, respectively. The animal weight and male/female ratio in the experimental groups did not differ statistically. Biological parameters of the respective groups are summarized in Table 1.

The heart rate significantly decreased in groups B and BL as compared to control group L, without any difference between groups B and BL. The heart rate in all groups did not return to initial value even at the end of washout period (significant difference in each particular group). As shown in Figure 2, bupivacaine application induced a significant widening of QRS complex in both bupivacaine groups. Moreover, prolongation of PQ was observed. However, PQ interval couldn't be compared and statistically evaluated due to a small number of measured values during perfusion period. Severe arrhythmias (mainly atrioventricular dissociation) in three hearts and profound flattening of P wave in two hearts did not allow valid statistical analysis of this parameter either. Significant prolongation ($p<0.05$) of QRS was found in the group B in comparison with the group BL at the 5^{th} and the 10^{th} minute of the perfusion period. Significant QRS widening as compared to the control group L persisted till the beginning of the washout period. In the rest of perfusion period, no difference between groups B and BL in this parameter was found. During washout, QRS widening reversed quickly in both bupivacaine groups. At the 5^{th} minute of washout, significant difference in QRS duration between groups BL and L was found, but the statistical analysis showed much faster return to the initial value in group BL than in group B (tested as comparison of variables in time inside each particular group to the end of stabilisation period). QRS duration at the end of washout period was comparable to the initial value (e.g. end of stabilisation) in all experimental groups.

Coronary flow was significantly lower in group B at the 5^{th} minute of perfusion period as compared to group BL. Subsequent decrease of the coronary flow in both bupivacaine groups without return to initial values after termination of bupivacaine application was observed at statistically significant level ($p<0.05$). This decrease was not observed in lidocaine group (group L).

Discussion

In the present study, toxic effects of local anaesthetics were studied on a model of spontaneously beating isolated rat heart. Since ventricular conduction depends on fast sodium channels, QRS widening – directly reflecting the slowing of ventricular conduction velocity – allows the accurate evaluation of the effect of various drugs on ventricular conduction in the Langendorff-perfused heart (Clarkson and Hondeghem 1985, Mazoit *et al.* 2000, de La Coussaye *et al.* 1992). After acute exposure of isolated rat hearts to bupivacaine, lidocaine or their mixture, QRS duration and other electrophysiological parameters were followed. The experimental design was set up to simulate organ specific action of bupivacaine during the unintentional intravenous injection and to study possible additive or protective effects of lidocaine.

Cardiotoxic effects of bupivacaine are relatively well documented. Clarkson and Hondeghem (1985) described the mechanism for bupivacaine-induced depression of cardiac conduction in guinea pig ventricular muscle in comparison with lidocaine. Since both compounds exert hypothetically their effect at the same site of sodium channel and they compete for it, the effect of their mixture was studied as well. De Jong and Bonin (1981) found in his experiments on *in vivo* mice that the effect of a mixture of bupivacaine and lidocaine is not synergistic and their additive effect was suggested. Other animal studies proved protective effect of lidocaine in combination with bupivacaine. Lefrant *et al.* (2003) described lesser alterations of ventricular conduction in anesthetized piglets. Fujita *et al.* (1998) found increased threshold for bupivacaine-induced ventricular fibrillation in pigs if lidocaine was added. However, in isolated rabbit heart model, Simon *et al.* (2002) described significantly increased QRS duration after adding

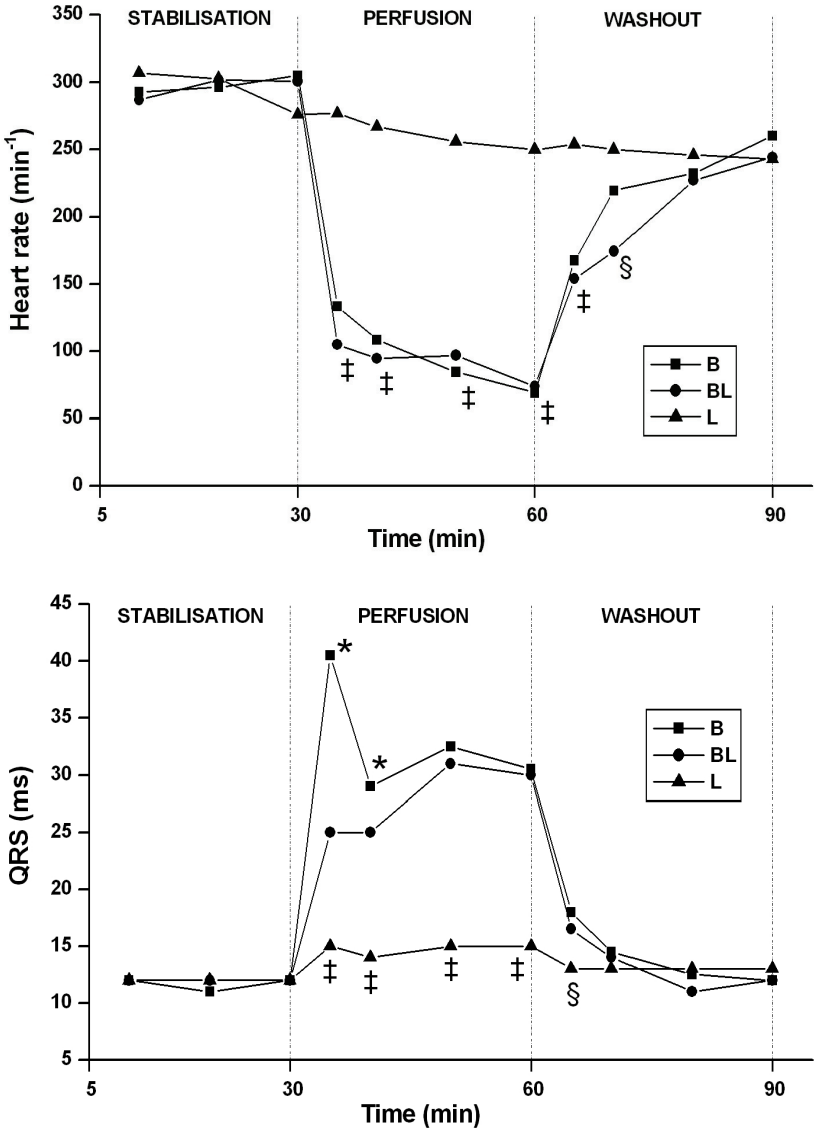

Fig. 2. Effect of 6 μg/ml bupivacaine (squares, group B), mixture of 6 μg/ml bupivacaine and 12 μg/ml lidocaine (circles, group BL), and 12 μg/ml lidocaine (triangles, group L) on electrophysiological parameters (**top** – Heart rate, **bottom** – QRS duration). Values are expressed as medians. Symbols indicate statistically significant difference at $p<0.05$ between groups: * B vs. BL, § BL vs. L, ‡ B and BL vs. L.

lidocaine to bupivacaine. The heterogeneity of results obtained may be explained by species diversity and methodological differences.

The effect on QRS prolongation and observed differences during perfusion with lidocaine mixture are presumably caused by competition of bupivacaine and lidocaine on fast voltage-operated sodium channel and different farmacodynamics of both drugs (slower bupivacaine dissociation). Although spontaneously beating heart model was used, the difference in toxicity between groups B and BL cannot be explained by different heart rate, which did not differ between both groups. Significant decrease in coronary flow was recently described as a direct coronary vascular effect of bupivacaine, possibly via K_{ATP} channel blockade (Burmester *et al.* 2005). However, in our study mean coronary flow served only as a subsidiary parameter, since it depends on numerous factors. The only plausible conclusion which can be done from present experiments is that the mean coronary flow significantly decreased after the bupivacaine administration. Since the inotropic parameters were not followed, the effect of bupivacaine and the mixture with lidocaine on contractility and consequently on myocardial metabolism cannot be estimated.

The present study shows that the mixture of tested anaesthetics – bupivacaine and lidocaine - impairs the intraventricular conduction parameters (QRS interval prolongation) to a lesser extent than bupivacaine itself, and that this effect is marked mainly at the beginning of perfusion. The elucidation of the fact that this effect is most pronounced during first couple of minutes of drug application needs further examination.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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