

The effects of dopexamine in bupivacaine and ropivacaine induced cardiotoxicity in isolated rat heart

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ABSTRACT

Objectives: To compare the inotropic and chronotropic effects of ropivacaine and bupivacaine in an isolated, spontaneously beating rat heart, and to determine the reversal effects of dopexamine on these effects.

Methods: The study was conducted at the Department of Physiology, Medical Faculty, Osmangazi University, Eskisehir, Turkey in November 2001. Fifty animals were randomly assigned to 5 groups. Hearts were perfused with a modified Krebs Henseleit solution. In group I (n=10) hearts were exposed to bupivacaine 5×10^{-6} M and in group II (n=10) hearts were exposed to ropivacaine 5×10^{-6} M for 15 minutes. Group III (n=10) was the dopexamine control group and hearts were exposed to dopexamine 1×10^{-6} M for 5 minutes. In group IV (n=10) and in group V (n=10) hearts were exposed to dopexamine in 1×10^{-6} M doses immediately after the bupivacaine and ropivacaine

infusions. Heart rates and contractile forces were recorded continuously during the study.

Results: Both of the local anesthetics had cardiac depressant effect on isolated hearts. Bupivacaine created more significant effect on heart rate and contractility than ropivacaine. Hearts receiving dopexamine after the infusion of local anesthetic, recovered more quickly.

Conclusion: Bupivacaine had more depressant effects on cardiac contractility and chronotropy than ropivacaine. Dopexamine may provide an alternative to presently recommended pharmacological therapy in cases of bupivacaine and ropivacaine induced cardiotoxicity. But, the clinical impact of the use of dopexamine in this situation deserves further evaluation.

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Systemic blood levels of local anesthetics produce a concentration dependent continuum of effects ranging from the therapeutic to toxic. Local anesthetic toxicity most frequently results from either accidental intravascular injection or administration of an excessive dose of local anesthetic. The toxic effects of local anesthetics are primarily directed at the central nervous system and cardiovascular system. Although the cardiovascular system is more resistant to local anesthetic toxicity than in the central nervous system,

cardiovascular toxicity can be severe and difficult to treat. Local anesthetics produce dose-related decreases in myocardial contractility and the rate of conduction of electrical impulses and either contract or dilate vascular smooth muscle.¹ Higher doses of local anesthetics may produce refractory dysrhythmias and cardiovascular collapse.² Bupivacaine, an amide type local anesthetic, is popular due to its high potency, dense sensory and motor blockade and long duration of action. However, bupivacaine has probably more

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cardiotoxic properties than other local anesthetics in use today.^{3,4} Several case reports have appeared indicating that accidental intravenous injection of bupivacaine may lead to cardiovascular collapse, from which resuscitation may be extremely difficult or unsuccessful. The cardiac toxicity of bupivacaine stimulated interest in developing a less toxic, long-lasting ropivacaine, a new local anesthetic that is structurally related to bupivacaine. Its potency and duration of action are similar to those of bupivacaine, but its cardiotoxicity may be less.⁵⁻⁷ Little information is available regarding the treatment of cardiovascular toxicity of local anesthetics in humans. But all researches conclude that supporting the contractility is the basis of the therapy. Dopexamine is a new inotropic agent. It is a dopaminergic receptor agonist and a β_2 adrenoreceptor agonist devoid of α and β_1 receptor activity. This profile offers some advantages due to its strong positive inotropy, usually mediated by β_1 adrenoreceptors and may be undesirable due to its effect on myocardial energy requirements and arrhythmogenicity. Dopexamine is less arrhythmogenic than other catecholamines; animal studies have demonstrated an anti arrhythmogenic effect.⁸ Its actions are to increase cardiac output while producing vasodilatation. It may have a place in treating spinal/epidural hypotension by its inotropic actions without producing vasoconstriction and this spectrum of activity may prove very useful effects in some group of patients.⁹ Presence of positive inotropic and chronotropic effects and also the absence of arrhythmogenic effect of dopexamine may provide its use in local anesthetic cardiotoxicity. The purpose of this study was to investigate the cardiac effects of bupivacaine and ropivacaine in isolated rat hearts and to determine whether dopexamine may be an alternative agent in treating these effects.

Methods. After the approval of the Osmangazi University Institutional Local Animal Care and Use Committee, the study was conducted at the Department of Physiology, Medical Faculty, Osmangazi University, Eskisehir, Turkey in November 2001. We used 50 Wistar rats of either gender weighing between 200-300 grams, in the aged of 2-3 months in all experiments. The rats were housed under standard conditions. Standard diet and water were given to the animals. They were fasted 10 hr prior to the experiments. One hour after the administration of heparin (1000 I.U., intraperitoneally) the chest was opened under anesthesia by using sodium thiopental 40 mg/kg. Hearts were rapidly removed and placed in ice cold (0-4°C) modified Krebs-Henseleit solution until contractions ceased. After the

heart was cleaned of the surrounding fat and other tissues, aorta was immediately tied to stainless steel cannula of the perfusion apparatus and heart was perfused retrogradely under constant pressure (70 mm Hg) with modified Krebs-Henseleit solution by the non-recirculating Langendorff technique. The pulmonary artery was incised to facilitate complete coronary drainage in the ventricles. The perfusion solution was modified Krebs-Henseleit solution of the following composition (mM): NaCl 118, KCl 4.7, CaCl_2 2.5, MgSO_4 1.2, KH_2PO_4 1.2, NaHCO_3 25 and glucose 11. Modified Krebs-Henseleit solution was continuously gassed with 95% O_2 and 5% CO_2 using a disposable infant oxygenator and pH of the solution was maintained at 7.4-7.5. The temperature was continuously measured in aorta cannula and kept at 37°C. Contractile force was measured by attaching one end of a piece of silk suture to the apex of the heart and other end to a force displacement transducer (Nihon Kohden TB 611T, Tokyo). Transducers were calibrated in a standardized fashion before and after measurement. A resting tension of 2 gm was applied and developed isometric tension of the heart was displayed on a polygraph (Nihon Kohden RM 6000). Heart rate was determined from the tracings of the contractile force at a paper speed of 2.5 mm/s. The hearts were allowed to equilibrate for 20 minutes before the administration of drugs and studied for a total period of 60 minutes. After the infusion of the drug. We recorded control measurements for every 10 minutes. Experiments were performed in 5 groups (**Figure 1**): Group I (bupivacaine control group) - bupivacaine (5×10^{-6} M) was infused in to the inflow perfusate for 15 minutes with an infusion pump.¹⁰ Heart rate and contractile force was recorded during the infusion. Group II (ropivacaine control group) - ropivacaine (5×10^{-6} M) was infused in to the inflow perfusate for 15 minutes as in group I. Group III (dopexamine control group) - the aim of this group was to determine the optimum dose for the positive inotropic and chronotropic effects of dopexamine. Dopexamine in doses of 1×10^{-6} M exerted an increase in cardiac contractility. Higher doses were causing severe tachycardia while lower doses exerted no effects on cardiac contractility. So we used dopexamine in doses of 1×10^{-6} M for the treatment of the effects of local anesthetics in group IV and group V. Group IV (bupivacaine-dopexamine group) - in this group, immediately after the infusion of bupivacaine (5×10^{-6} M), dopexamine (1×10^{-6} M) was infused for 5 minutes. Group V (ropivacaine-dopexamine group) - the same procedure in group IV was repeated with ropivacaine in this group. The hearts were studied during a total period of 60 minutes.

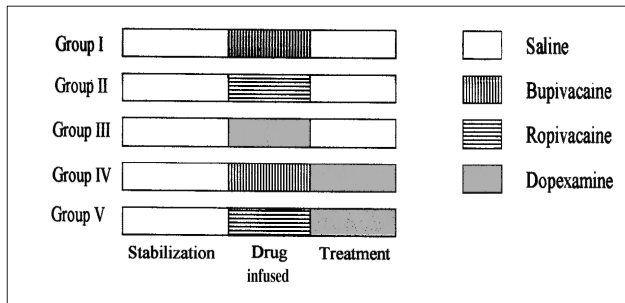


Figure 1 - Diagrammatic presentation of the experimental protocol.

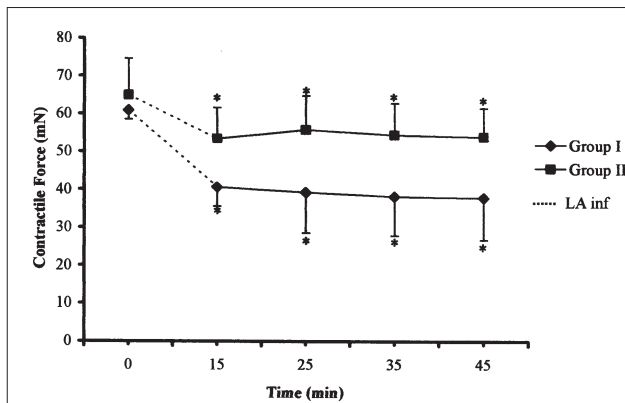


Figure 2 - Time course of the effects of bupivacaine and ropivacaine on contractile force * $p < 0.05$ significantly different from the respective control. Values are mean \pm standard error.

After the infusion of the drugs control measurements recorded for every 10 minutes.

Analysis of data. Results are presented as the means and standard errors of the means. Statistical analyses of the data were performed by 2-way Analysis of Variance followed by DUNNET variance analyze. A p -value < 0.05 was considered to be significant.

Results. Both of the local anesthetics caused a significant decrease in heart rate ($p < 0.001$). The decrease with bupivacaine was more significant than ropivacaine. Either in bupivacaine or ropivacaine group, heart rates was slightly increased after the discontinuation of the infusion. But, they were also significantly lower than control values ($p < 0.05$). Contractile forces of the hearts were influenced by bupivacaine and ropivacaine (**Figure 2**). Bupivacaine caused a significant decrease in contractile force ($p < 0.001$). Depression of myocardial contractility was persisted after the discontinuation of bupivacaine infusion. Infusion of ropivacaine also produced a significant reduction in contractile force ($p < 0.05$). Discontinuation of this drug caused a slight recovery

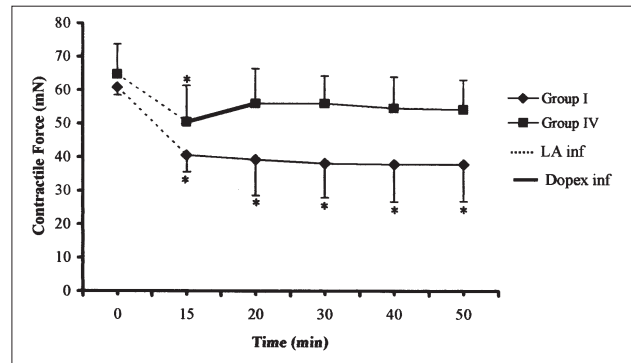


Figure 3 - Time course of the effects of only bupivacaine and bupivacaine-dopexamine on contractile force. * $p < 0.05$ significantly different from the respective control. Values are mean \pm standard error.

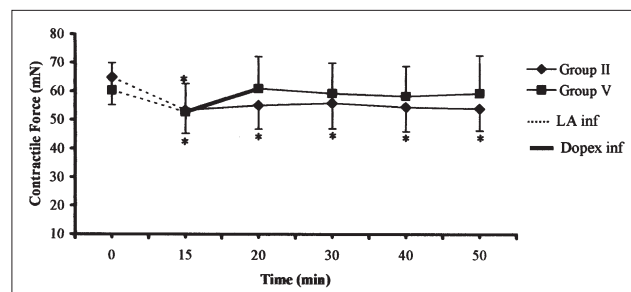


Figure 4 - Time course of the effects of only ropivacaine and ropivacaine-dopexamine on contractile force. * $p < 0.05$ significantly different from the respective control. Values are mean \pm standard error.

of contractility. In group III, dopexamine created a significant increase in heart rate and contractile force ($p < 0.001$). Although discontinuation of dopexamine caused a slight decrease in contractile force and heart rate, 30 minutes after the infusion of dopexamine contractile force was still slightly higher than control values ($p < 0.05$). In group IV and V, the treatment of hearts with dopexamine created a significant effect on heart rate and contractile force. While bupivacaine produced a significant decrease in heart rate and contractile force, dopexamine infusion treated these effects. Heart rates were nearly the same as the control values. Contractile force was also increased by dopexamine infusion, but it was still lower than the control values (**Figure 3**). Dopexamine reversed the depressant effects of ropivacaine on contractile force and heart rate. Increase in heart rate was significant after the infusion of dopexamine so that heart rates were nearly the same as the control values. In group V, contractile force was also increased by dopexamine (**Figure 4**). But at the end of the infusion of dopexamine, contractile force was not the same as the control values.

Discussion. The cardiovascular effects of local anesthetics results partly both from direct effects upon the cardiac smooth muscle membranes, and from indirect effects upon the autonomic nerves. Local anesthetics block cardiac sodium channel and thus, depress abnormal cardiac pacemaker activity, excitability and conduction.¹¹ In our study, we observed the decline in heart rate by the infusion of bupivacaine and ropivacaine. The depressant effect of bupivacaine on heart rate was significant than the effect of ropivacaine. Many of the studies demonstrate that bupivacaine has negative inotropic, negative chronotropic and arrhythmogenic effects.¹²⁻¹⁴ The effects of bupivacaine may cause severe cardiovascular collapse and cardiac arrhythmias, which have been responsible for fatalities.^{15,16} Bupivacaine more frequently slows atrial conduction, prolongs AV conduction time and at higher concentrations results second-degree AV dissociation compared with other local anesthetics.¹⁷ The durations of bupivacaine induced cardiac effects appear to be longer than those due to ropivacaine, an effect that may depend on the higher lipid solubility of bupivacaine. The time to return to control heart rate is slower after bupivacaine infusion than ropivacaine. This difference in recovery time may be related to bupivacaine greater lipid solubility and protein binding capacity, which would tend to decrease the rate of wash out from cardiac tissues. In the isolated rat heart, we demonstrated that both of bupivacaine and ropivacaine causes a marked decline in contractility. Bupivacaine exerted more significant effect than ropivacaine on myocardial contractility. Our findings are in agreement with result from previous studies showing that bupivacaine has more depressant effects on cardiac contractility than ropivacaine.^{13,18,19} Reduction in cardiac contractility was continued after the infusion of bupivacaine. In ropivacaine group, we observed an increase in contractile force by discontinuation of the local anesthetic. But, still there was a significant difference with the control values. Bupivacaine inhibition of slow channels augment sodium channel blockade. Blockade is "fast in-slow out" and may explain the difficulty by reversing toxicity in cardiac arrest caused by bupivacaine.³ The basis of the treatment of local anesthetic induced cardiotoxicity is to support the contractility and rhythm of the heart. Dopexamine is an agonist at peripheral dopamine receptors and β_2 adrenoreceptors. Little activity at α and β_1 adrenoreceptors gives dopexamine a novel pharmacological profile.²⁰ In our study, dopexamine created a significant positive inotropic effect in 1×10^{-6} mM doses. But, positive chronotropic effect was not so clear in this dose. Increasing dose of dopexamine caused a significant tachycardia that result a decrease

in cardiac contractility. Our data was in agreement with other studies that shows positive chronotropic and anti arrhythmogenic effects of dopexamine.^{8,21} This lower arrhythmogenic potential of dopexamine was explained by its relative lack of activity at β_1 adrenoreceptors, which have been implicated in dysrhythmias induced by other catecholamines. Right and left ventricular filling pressures decreased over the entire dose range of dopexamine concomitant with a demonstrable improvement in the indexes of ventricular performance. This increase in cardiac index appears to occur predominantly as a result of an increase in heart rate, as stroke volume index demonstrates only a minimal change.^{22,23} Myocardial contractility depression induced by ropivacaine treated significantly by dopexamine infusion. Contractile force was approximately same as the control values before the ropivacaine infusion. But, we observed a small decrease in contractile force later. Brown et al²⁰ demonstrated that both dopexamine and dopamine produced transient positive inotropic effects when given by bolus injection to the isolated perfused heart, followed by secondary depression of force.

In conclusion, bupivacaine has more depressant effects on inotropy and chronotropy than ropivacaine. Dopexamine may provide an alternative to presently recommended pharmacological therapy in cases of bupivacaine and ropivacaine induced cardiotoxicity. But clinical impact of the use of dopexamine in this situation deserves further evaluation.

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