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The effects of ropivacaine at clinically relevant doses on myocardial ischemia in pigs

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Abstract
A major risk associated with bupivacaine during myocardial ischemia is ventricular fibrillation. We investigated the influence of ropivacaine on cardiac contractility and the propensity to ventricular fibrillation before and after myocardial ischemia in a placebo-controlled pig study. Anesthetized domestic pigs were administered 1 mg·kg^{-1} of ropivacaine intravenously over 1 min and then 0.03 mg·kg^{-1}·min^{-1} as a 30-min infusion, or saline. The following endpoints were measured before and after ropivacaine administration: (1) the ventricular fibrillation threshold (VFT) before and during myocardial ischemia induced by total transient ligation of the anterior interventricular artery and (2) electrophysiological (sinus heart rate, duration of QRS and QT intervals) and hemodynamic (blood pressure, the time derivative of left ventricular pressure [peak LV dP/dt]) parameters. Ropivacaine induced no changes in sinus heart rate, QRS, and or QT before or during ischemia. In contrast, there was a mild increase in the VFT before ischemia, which was drastically and significantly reduced during ischemia. The reduction of peak LV dP/dt during ischemia was further increased by ropivacaine. We also found that the effect of ropivacaine on the VFT was coronary blood flow-dependent, with a markedly decreased threshold in the presence of ischemia. Similar effects have been observed in humans with several other local anesthetics, as well as with class I antiarrhythmic drugs. The results of this study should be taken into account by anesthesiologists when administering ropivacaine to coronary patients.

Key words Ropivacaine · Myocardial ischemia · Ventricular fibrillation · Cardiac contractility · Experimental study

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Ventricular fibrillation can occur during locoregional anesthesia, especially in the presence of myocardial ischemia. In light of the wide use of ropivacaine in elderly patients who often suffer from ischemic heart disease, we carried out this study to investigate ropivacaine-induced adverse cardiac effects in the pig during normal and altered coronary blood flow.

The study, which fully complied with the recommendations of the Claude-Bernard University Lyon-I animal ethics committee, was conducted in 12 domestic pigs of both sexes, weighing 20–25 kg. The pigs were premedicated with midazolam 0.1 mg·kg^{-1} intramuscularly, and then anesthetized with chloralose 100 mg·kg^{-1} i.v., tracheotomized, and ventilated mechanically. Ventilation and respiratory monitoring were achieved simultaneously with a Dräger SA apparatus (Lubeck, Germany).

Two groups of six animals were used; the number of animals used in this experiment was determined by the Blackwelder formula. The animals received either ropivacaine 1 mg·kg^{-1} intravenously over 1 min, and then 0.03 mg·kg^{-1}·min^{-1} as a 30-min infusion, or the same volume of saline. The ropivacaine plasma levels achieved were similar to those measured in humans on various occasions [1]: after 2 min, plasma levels were 1.3 ± 0.12 μg·ml^{-1}, and they were not significantly changed after 30 min (1.42 ± 0.25 μg·ml^{-1}).

The electrophysiological parameters of sinus heart rate (bpm), QRS complex width (ms), and the duration of the corrected QT (QTc) interval (ms) were measured from ECG recordings.

The left anterior descending artery was dissected after thoracotomy, and myocardial ischemia (MI) was obtained by total ligature for 1 min. The ventricular fibrillation threshold (VFT) was determined under electrical stimulation at a constant rate of 180 bpm to

exclude any variation of heart rate. A pacing wire was placed close to the apex of the heart in the left ventricular wall. The VFT was determined using the same device (Hugo Sachs, Freiburg, Germany) as that used for electrical stimulation, but with stimuli of longer duration (100 ms vs 5 ms). The intensity of stimulation was progressively increased by steps of 0.5 mA every 5 s until ventricular fibrillation was triggered. The VFT was measured in the following situations: (1) in basal conditions; (2) under ischemia; (3) 2 min after the end of the saline or ropivacaine intravenous bolus injection before ischemia; and (4) after the saline or ropivacaine infusion under ischemia. All parameters returned to the baseline level within 15 min after each defibrillation induced by a 360-J electrical shock.

The hemodynamic parameters of systolic, diastolic, mean arterial, and left ventricular pressures (mmHg) were recorded continuously, and the time derivative of left ventricular pressure (peak LV dP/dt) was calculated by digital treatment (Acknowledge; Biopac System, Santa Barbara, CA, USA). All hemodynamic parameters were measured immediately before VFT determination.

Each parameter was analyzed by monovariate analysis of variance (SPSS software; SPSS Science Software, Enkrath, Germany), using ischemia and the effect time-treatment before and after ropivacaine as a cofactor. When a statistically significant difference between the means was present, paired *t*-tests were used. The values for results are expressed as means ± SDs.

We found that ropivacaine administration did not induce any changes in sinus heart rate; QRS complexes; QT intervals; or systolic, diastolic, or mean arterial pressures, either before or during ischemia. In contrast, under ischemia, VFT decreased from 2.2 ± 0.80 mA before ropivacaine to 1 ± 0.42 mA after ropivacaine ($P < 0.05$; Fig. 1). There was a statistically significant protective effect of ropivacaine toward ventricular fibrillation when coronary flow was normal as VFT increased from 4 ± 1 mA (baseline value) to 8 ± 1.9 mA ($P < 0.01$). Peak LV dP/dt dropped significantly after ropivacaine infusion ($P < 0.01$) and during ischemia ($P < 0.01$; Fig. 2).

In this study, ropivacaine increased the alteration of peak LV dP/dt induced by ischemia and worsened the reduction of VFT induced by ischemia, whereas VFT was slightly, but not significantly improved by ropivacaine in nonischemic conditions.

Local anesthetic drugs are potentially cardiotoxic because they block the entry of Na^+ ions into ventricular cardiomyocytes [2,3]. However, the blocking effect of both ropivacaine and lidocaine is less than that of bupivacaine [4]. This difference seems to be related, at least partially, to differences in physicochemical properties, particularly liposolubility, which is higher for

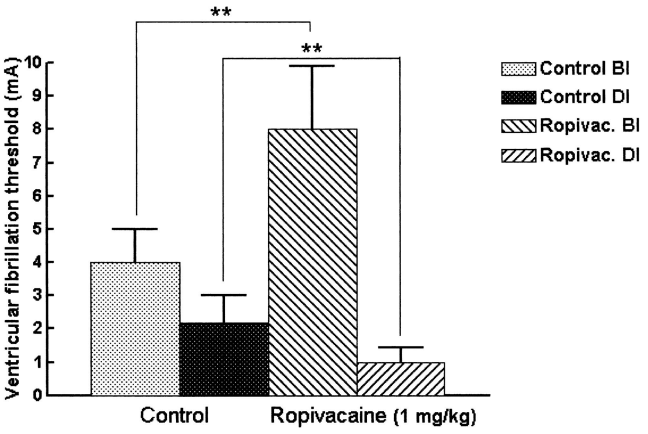

Fig. 1. Effect of ropivacaine (*Ropivac.*) on the ventricular fibrillation threshold (VFT) with and without ischemia. The VFT was measured before ropivacaine administration, then after 1 mg·kg^{-1} ropivacaine + 0.03 mg·kg^{-1}·min^{-1} over 30 min under total ischemia induced by ligature of the left anterior descending artery. Statistical significance is noted: $^{**}P < 0.01$. *BI*, before ischemia; *DI*, during ischemia

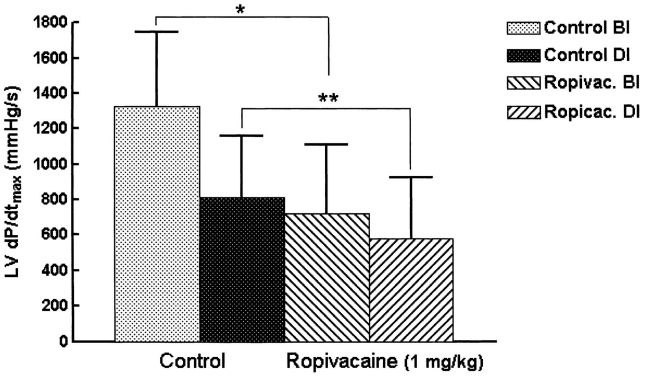

Fig. 2. Effect of ropivacaine on time derivative of left ventricular pressure (peak *LV dP/dt*) with and without ischemia. Peak LV dP/dt was measured before ropivacaine administration, then after 1 mg·kg^{-1} ropivacaine + 0.03 mg·kg^{-1}·min^{-1} over 30 min under total ischemia induced by ligature of the left anterior descending artery. Statistical significance is noted: $^{*}P < 0.05$ and $^{**}P < 0.01$

bupivacaine [5]. Of note, re-entrant arrhythmias can develop following the administration of drugs that block the entry of Na^+ ions [6]. This blocking effect has been shown for bupivacaine, and was also present with ropivacaine [7]. Furthermore, deaths reported after the intravenous injection of lidocaine, bupivacaine, and ropivacaine seemed to be closely related to myocardial tissue concentrations [8].

In this study, a synergistic effect of myocardial ischemia and ropivacaine on altered cardiac contractility was likely [9] and this may have been due to a decreased cellular content of Ca^{2+}, which could account for

decreased contractility, as there is also an inhibition of the Na^+/Ca^{2+} exchanger under such circumstances [10].

In addition, ropivacaine also induced a significant reduction in VFT under ischemia, an effect which is very similar to that shown with other local anesthetic drugs and class I antiarrythymic drugs [11,12]. Myocardial ischemia generates ventricular fibrillation, and various ischemia-related alterations are thought to be involved, including changes in the synthesis and/or degradation of sarcolemma membrane proteins [13], changes in gap junctions [14], and changes in the membrane polarity of cardiomyocytes [15]. Finally, there is an inhibition of the Na^+-K^+-dependent ATPase pumps, which results in an excess of Na^+ ions and a loss of K^+ ions during myocardial ischemia [16].

In this study, ropivacaine at plasma concentrations similar to therapeutic concentrations measured in patients, significantly decreased VFT and cardiac contractility during myocardial ischemia; These results should be taken into account by anesthesiologists when administering ropivacaine to patients with myocardial ischemia.

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