

# Comparação das Alterações Hemodinâmicas na Intoxicação Aguda com Bupivacaína e Ropivacaína por Via Venosa em Suínos \*

## Comparison of Hemodynamic Changes in Acute Intoxication with Intravenous Bupivacaine and Ropivacaine in Swine\*

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### RESUMO

Melo MDS, Silva WA, Moraes AC, Udelsmann A - Comparação das alterações hemodinâmicas na intoxicação aguda com bupivacaína e ropivacaína em suínos.

**JUSTIFICATIVA E OBJETIVOS:** A ropivacaína apresentada na forma levógiro pura foi introduzida para proporcionar alternativa mais segura que a bupivacaína nas anestésias locorreionais. O objetivo deste estudo foi comparar as repercussões hemodinâmicas após injeção por via venosa dos dois agentes em suínos, simulando intoxicação que pode ocorrer durante anestesia locorreional em humanos.

**MÉTODO:** Suínos da raça Large-White foram anestesiados com tiopental, realizada intubação traqueal e instituída ventilação controlada mecânica. As variáveis hemodinâmicas foram medidas através de monitorização invasiva da pressão arterial e cateterização de artéria pulmonar. Após período de repouso de 30 minutos os animais foram aleatoriamente divididos em dois grupos e receberam por via venosa 4 mg.kg<sup>-1</sup> de um ou outro agente sem conhecimento do pesquisador. Os resultados hemodinâmicos foram avaliados em repouso e 1, 5, 10, 15, 20 e 30 minutos após a intoxicação.

**RESULTADOS:** As repercussões hemodinâmicas da intoxicação aguda com bupivacaína foram mais importantes e mais prolongadas do que as com ropivacaína. Com bupivacaína o índice cardíaco teve diminuição maior e mais prolongada, a pressão arterial média e a frequência cardíaca diminuições mais prolongadas, a pressão venosa central aumento mais prolongado e a pressão capilar pulmonar aumentou mais e por mais tempo. O impacto no índice de resistência vascular sistêmica mostrou que a vasomotricidade

foi parcialmente mantida, houve aumento nos dois grupos e, paradoxalmente, maior e por mais tempo com bupivacaína.

**CONCLUSÕES:** Em suínos a ropivacaína causou menos repercussões hemodinâmicas do que a bupivacaína quando as mesmas doses foram injetadas por via venosa.

**Unitermos:** ANESTESIA, Local: bupivacaína, ropivacaína; COMPLICAÇÕES: hemodinâmica, toxicidade sistêmica.

### SUMMARY

Melo MDS, Silva WA, Moraes AC, Udelsmann A – Comparison of Hemodynamic Changes in Acute Intoxication with Intravenous Bupivacaine and Ropivacaine in Swine.

**BACKGROUND AND OBJECTIVES:** Pure levorotatory ropivacaine was introduced to provide a safer alternative to bupivacaine in regional blocks. The objective of this study was to compare the hemodynamic repercussions after the intravenous administration of both agents in swine, simulating the intoxication that can be seen during regional blocks in humans.

**METHODS:** Large-White swine were anesthetized with thiopental, followed by endotracheal intubation and controlled mechanical ventilation. Hemodynamic parameters included non-invasive blood pressure and catheterization of the pulmonary artery. After 30 minutes, animals were randomly divided into two groups, and 4 mg.kg<sup>-1</sup> of one of the agents was administered intravenously without the knowledge of the investigator. Hemodynamic parameters were evaluated at rest and 1, 5, 10, 15, 20, and 30 minutes after intoxication.

**RESULTS:** The hemodynamic repercussions of acute bupivacaine intoxication were more important and prolonged than in ropivacaine intoxication. With bupivacaine, the cardiac index showed greater and more prolonged reduction, mean arterial pressure and heart rate had more prolonged reduction, central venous pressure showed a more prolonged increase, and pulmonary wedge pressure increased more for more prolonged time. The impact on the systemic vascular resistance index showed that vasomotricity was partially maintained, increased in both groups, and, paradoxically, was greater and longer-lasting with bupivacaine.

**CONCLUSIONS:** In swine, ropivacaine caused less hemodynamic repercussions than bupivacaine when the same doses were administered intravenously.

**Keywords:** ANESTHESIA, Local: bupivacaine, ropivacaine; COMPLICATIONS: hemodynamic, systemic toxicity.

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## Comparison of Hemodynamic Changes in Acute Intoxication with Intravenous Bupivacaine and Ropivacaine in Swine

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### INTRODUCTION

Local anesthetics are capable of causing reversible block of nerve conduction. They were first used in clinical practice in 1884 when Koller<sup>1</sup> used topical cocaine in ocular anesthesia. Along with the enthusiasm with the new drugs, the first cases of alarming side effects were reported. This led to studies on new doses and drugs and, in the 1950s, bupivacaine was synthesized by Ekenstam<sup>2</sup>. Bupivacaine was a landmark in the evolution of regional anesthesia because it was the first long-acting amino-amide compound. It was introduced in the USA in 1973 and in the 1980s the first reports on its cardiotoxicity<sup>3</sup> were made; cardiovascular collapse, which was disproportional to the potency of the drug, would be caused by severe ventricular arrhythmias<sup>4</sup>. The search for long-acting, low toxicity agents, with differential sensory-motor blockade stimulated the pharmaceutical industry to investigate the enantiomers of bupivacaine when it was realized that they had different levels of biological activity. Ropivacaine, available only as the S- isomer, with lower cardiotoxic potential and greater sensory-motor dissociation in low doses, was introduced in 1990<sup>5-7</sup>. However, according to some investigators, this lower cardiotoxicity would be secondary to the lower potency of the drug, although a consensus on this hypothesis is lacking<sup>8</sup>. The objective of this study was to compare the hemodynamic repercussions of the intravascular injection of ropivacaine and bupivacaine in swine, simulating an accidental injection of large doses of local anesthetics and determine the cardiotoxicity of both drugs.

### METHODS

After approval by the Ethics on Animal Research Commission of the Biology Institute of UNICAMP, and according to the Ethics Code of the International Organization of Medical Sciences for animal studies, 40 swine of both genders, weighing 18 to 22 kg, underwent the following protocol: animals were fasting since the night before with free access to water. On the morning of the study, they were weighed, the body surface area was calculated using the following formula:  $BSA (m^2) = (9 \times \text{weight in grams}^{2/3}) \times 10^{-4}$ , and the parameters were entered in the hemodynamic Engstrom AS/3 monitor to calculate the different indices. Venipuncture was done in one of the ears of the animal and anesthesia was induced with 25 mg.kg<sup>-1</sup> of 2.5% thiopental sodium. After intubation, animals were ventilated by a pneumatic respirator with CO<sub>2</sub> absorber, tidal volume 15 mL.kg<sup>-1</sup>, and adequate respiratory rate to maintain P<sub>ET</sub>CO<sub>2</sub> between 32 and 34 mmHg.

Animals were ventilated with a mixture of air and O<sub>2</sub> to maintain hemoglobin saturation above 97% determined by a sensor placed on the tongue of the animal. Cardioscope on D<sub>II</sub> derivation was also used for monitoring. Anesthesia was maintained with continuous infusion of 5 mg.kg<sup>-1</sup>.h<sup>-1</sup> of thiopental. The internal aspect of one of the thighs of the animal was anesthetized with 5 mL of 1% lidocaine without vasoconstrictor for the dissection of the femoral artery and vein for continuous measurement of blood pressure and introduction of a 7F Swan-Ganz catheter, which was placed in a branch of the pulmonary artery by observing the morphology of the pressure curve. The following parameters were measured: cardiac index, heart rate, mean arterial pressure, central venous pressure, mean pulmonary artery pressure, pulmonary wedge pressure, peripheral and pulmonary vascular resistance, and left and right ventricular systolic load. After 30 minutes for stabilization and rest, the first series of hemodynamic parameters were determined (M<sub>0</sub>). Afterwards, animals were randomly divided into two groups and the investigator was not aware of the group distribution; 20 animals received intravenous bupivacaine 4 mL.kg<sup>-1</sup> (B group)<sup>9</sup>, and the remainder received the same dose of ropivacaine (R group). New hemodynamic parameters were determined 1, 5, 10, 15, 20, and 30 minutes after intoxication (M<sub>1</sub> to M<sub>30</sub>). At the end of the study animals were killed under anesthesia with the intravenous injection of 10 mL of 19.1% potassium chloride. The Chi-square test was used for the analysis of categorical parameters. The Student *t* test was used to compare the distribution of numerical parameters measured at one moment. Analysis of Variance (ANOVA) was used to analyze numerical parameters measured on several moments, the Duncan test was used to compare both groups in each moment, and the profile contrast test was used to analyze the evolution of each group among the different moments. It was adopted a level of significance of 5% ( $p < 0.05$ ).

### RESULTS

Groups were homogenous regarding gender, weight, and body surface area, which can be seen in table I.

Table I – Distribution by Gender, Weight, and Body Surface Area

Group	R	B
Gender		
Female	9	7
Male	11	13
Weight (kg) *	21.96 ± 2.08	22.7 ± 1.87
BSA (m <sup>2</sup> ) *	0.69 ± 0.05	0.71 ± 0.04

\*Results expressed as Mean ± SD

Gender  $p = 0.519$ ; Weight  $p = 0.243$ ; Body surface area (BSA)  $p = 0.194$

Baseline hemodynamic parameters did not differ between the groups. After intoxication, the cardiac index decreased in both groups (Figure 1). In group B, this reduction continued until the end of the study, and in R they returned to levels similar to baseline from M<sub>10</sub> on (p = 0.002). Levels in the B group were lower than in the R group from M<sub>1</sub> to M<sub>30</sub> (p = 0.032). Mean arterial pressure (Figure 2) showed significant reduction in both groups, but in the B group this lasted up to M<sub>5</sub>, while in the R group, it was observed only in M<sub>1</sub> (p = 0.01). Levels in B were higher than in R from M<sub>10</sub> on (p < 0.001). After intoxication, the heart rate (Figure 3) in B remained lower than baseline levels until M<sub>30</sub>, while in R they remained below baseline levels until M<sub>5</sub> (p < 0.001). Differences were not observed between both groups (p = 0.184). In B, central venous pressure (Figure 4) was increased from M<sub>1</sub> to M<sub>10</sub>, while in R it was increased only in M<sub>1</sub> (p < 0.001). Differences were not observed between both groups (p = 0.113).

Pulmonary wedge pressure increased in both groups (Figure 5); in B it remained increased until M<sub>30</sub>, while in R it remained so until M<sub>10</sub> (p < 0.001). Levels in B were higher than in R from M<sub>1</sub> to M<sub>20</sub> (p = 0.049). Mean pulmonary artery pressure (Figure 6) in both groups did not vary in relation to baseline levels (p = 0.381); however, levels in B were higher than those in R from M<sub>5</sub> to M<sub>30</sub> (p = 0.002). Systemic vascular resistance index (Figure 7) increased in both groups; in B it was increased until M<sub>30</sub>, while in R it remained increased until M<sub>10</sub> (p = 0.004). After intoxication, levels in B were higher than in R until the end (p < 0.001). The pulmonary vascular resistance index (Figure 8) in B did not change, and in R it was increased only in M<sub>1</sub> (p = 0.003). Levels in group B were higher than in group R from M<sub>5</sub> to M<sub>30</sub> (p = 0.007).

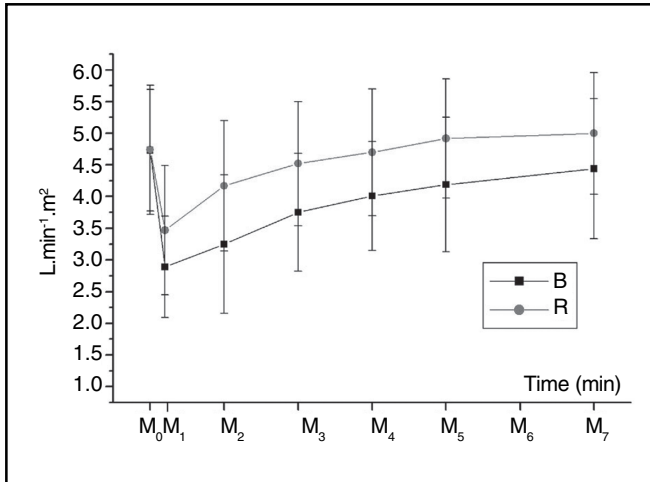


Figure 1 – Cardiac Index.

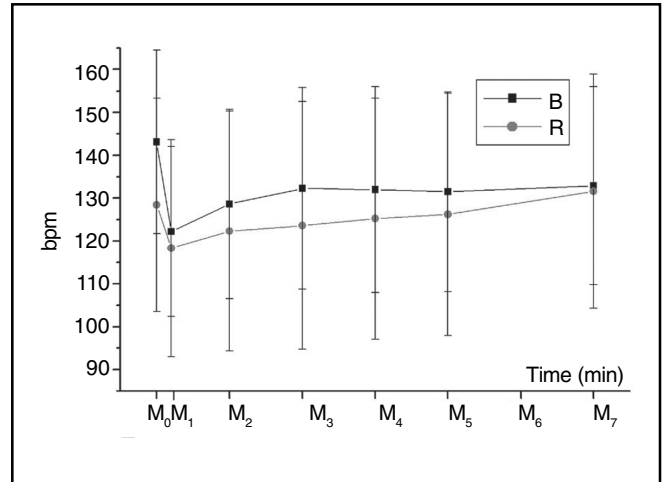


Figure 3 – Heart Rate.

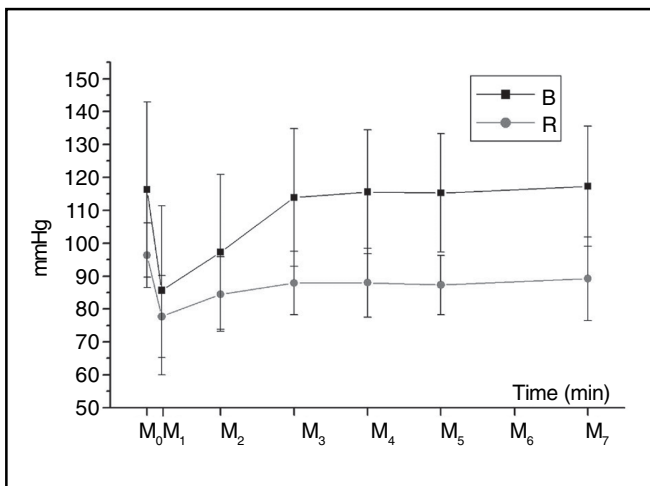


Figure 2 – Mean Arterial Pressure.

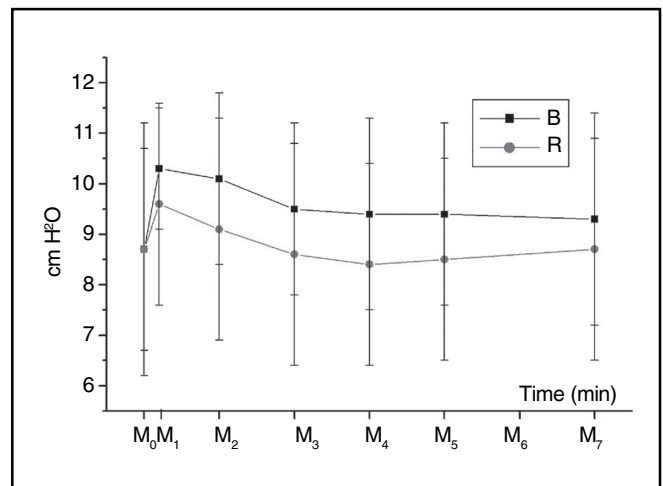


Figure 4 – Central Venous Pressure.

Left ventricular systolic load index (Figure 9) decreased in B from  $M_1$  to  $M_{10}$ , while in R it was decreased from  $M_1$  to  $M_5$  ( $p = 0.005$ ). Differences were not observed between both groups ( $p = 0.992$ ).

Right ventricular systolic load index (Figure 10) decreased in B from  $M_1$  to  $M_5$ , and in R levels did not change ( $p = 0.004$ ). Levels in B were higher than those in R at  $M_{10}$  and  $M_{30}$  ( $p < 0.001$ ).

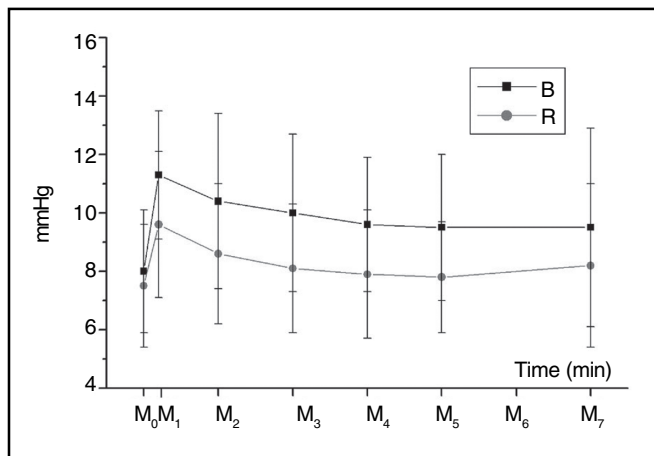


Figure 5 – Pulmonary Capillary Wedge Pressure.

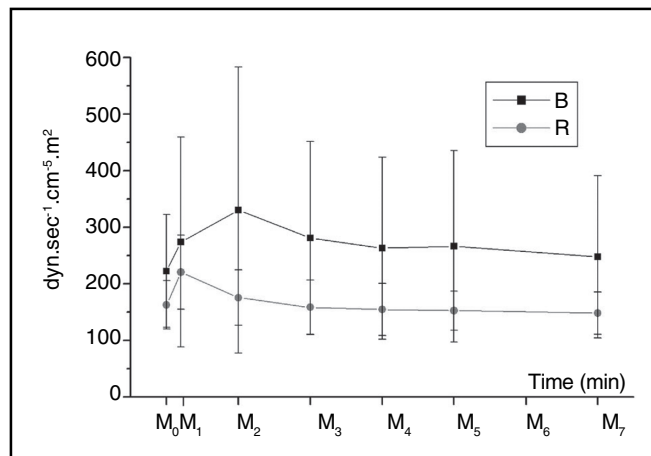


Figure 8 – Pulmonary Vascular Resistance Index.

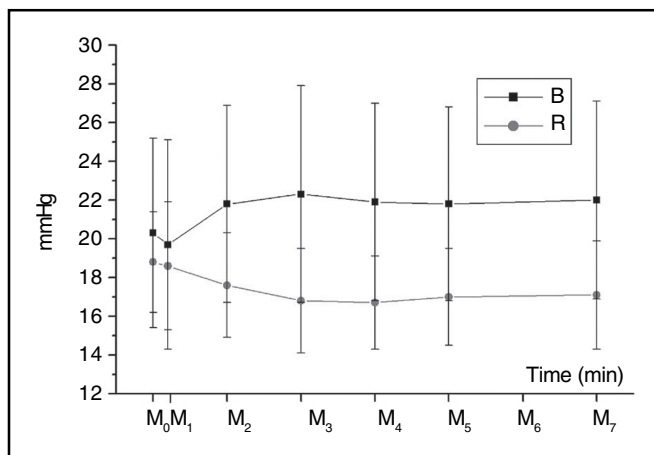


Figure 6 – Mean Pulmonary Artery Pressure.

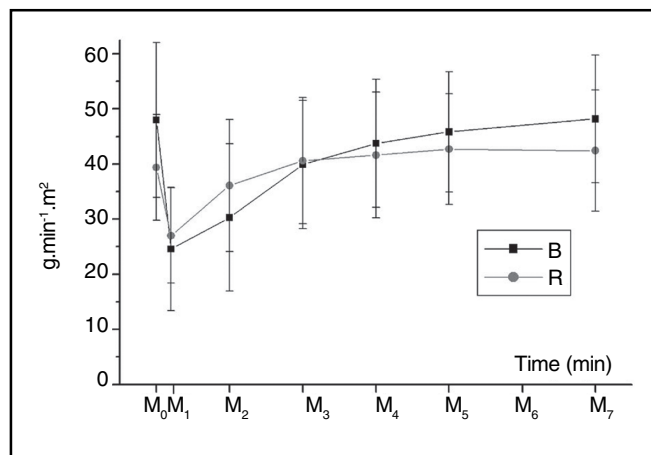


Figure 9 – Left Ventricular Systolic Load Index.

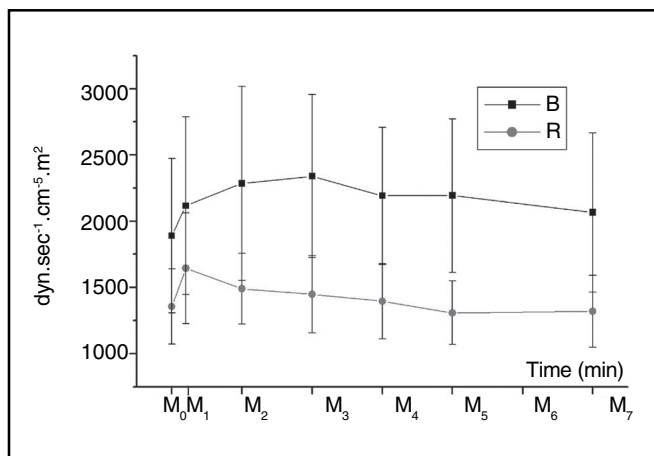


Figure 7 – Systemic Vascular Resistance Index.

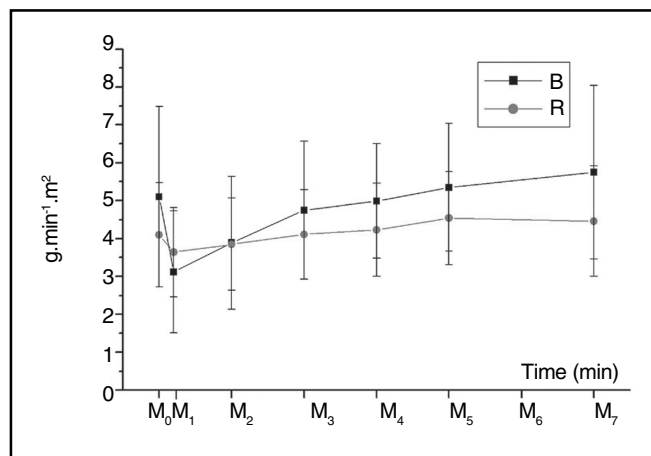


Figure 10 – Right Ventricular Systolic Load Index.

## DISCUSSION

Intravascular injection of local anesthetics is worrisome because of the severity of the consequences. Bupivacaine was a steppingstone in regional blocks due to the quality and duration of the blockade. This study compared the acute intoxication of bupivacaine to that of ropivacaine with the intravascular injection of both drugs in swine, and the results were similar to those reported in the literature<sup>4,8,10</sup>. Hemodynamic parameters were significantly affected by both agents; however, changes caused by ropivacaine were transitory and eventually several parameters returned to normal; with bupivacaine, the study parameters did not return to baseline levels and it was only temporary in those that did; parameters returned to normal after a significantly longer time than with ropivacaine. The cardiotoxicity of bupivacaine<sup>11</sup> is secondary to direct and indirect effects on the heart, with negative inotropism and conduction blockade. Bupivacaine reduces the concentration of calcium in the endoplasmic reticulum, affects the Na<sup>+</sup>/Ca<sup>2+</sup> pump in the membrane, the transduction of mitochondrial energy, and inhibits the production of cAMP<sup>10</sup>. Conduction is disrupted by the blockade of Na<sup>+</sup>, K<sup>+</sup>, and Ca<sup>2+</sup> channels, with the consequent development of arrhythmias<sup>13</sup>. The indirect effects are secondary to effects mediated by the central nervous system and blockade of autonomous innervation. *In vivo* studies demonstrated that local anesthetics inhibit voltage-dependent Na<sup>+</sup> channels in neural membranes with a delay in the conduction of the cardiac impulse, increased of the P-R interval, narrowing and increased voltage of the QRS complex, and AV block, leading to ventricular arrhythmias<sup>10</sup>. Studies that compared the R+ and S- isomers of bupivacaine demonstrated that ability of R-bupivacaine to block Na<sup>+</sup> conductance is twice as great as that of S-bupivacaine<sup>14</sup>. *In vitro* studies showed that ropivacaine produced smaller and more transitory inhibition of Na<sup>+</sup> current than bupivacaine<sup>15</sup>. In a study with swine myocytes, the authors observed that R-bupivacaine interacted with both active and inactive Na<sup>+</sup> channels, producing faster and more potent blockade of inactive channels than S-bupivacaine<sup>14</sup>. The blockade of an inactive channel plays a more significant role during the plateau phase of the cardiac action potential and this can explain the high toxicity of R-bupivacaine<sup>16</sup>. The R+ isomer was also more potent the S- isomer as well as ropivacaine in reducing the frequency of maximal depolarization, an indication of Na<sup>+</sup> influx and the duration of the action potential in papillary muscles of swine, and Purkinje fibers are not excitable for a shorter period of time with ropivacaine than with R-bupivacaine in a study with guinea pigs<sup>10</sup>. Compared to ropivacaine, bupivacaine produces more important negative inotropism due to greater inhibition of the release of Ca<sup>2+</sup> from the sarcoplasmic reticulum, greater changes in the transduction of mitochondrial energy, and greater inhibition of cAMP<sup>17,18</sup>. Animal studies seem to explain the

results of the present study, in which all hemodynamic parameters evaluated were affected by both local anesthetics, but not as intensely and more transitory by ropivacaine. The notion of decreased cardiotoxicity of levorotatory isomers, described by Aberg in 1972<sup>19</sup>, directed the investigation to search agents with those characteristics, culminating with the synthesis of ropivacaine, introduced as its levorotatory isomer and for this reason it found its place in the therapeutic armamentarium. But the comparing the cardiovascular toxicity of local anesthetics demands the knowledge of the equivalence, or potency, of the drugs used. Several methods were proposed, and MLAD (minimum local analgesic dose), which corresponds to the concentration in 20 mL of local anesthetic injected in the epidural space to provide adequate analgesia in the first phase of labor, is the more common notion. Results are still conflicting since for some investigators ropivacaine has shown to be equivalent to bupivacaine in the relief of pain, side effects, type of delivery, and consequences for the newborn<sup>20</sup>. However, using this method, other authors<sup>21</sup> stated that the analgesic potency ratio of ropivacaine:bupivacaine would be 0.65. But the notion of MLAD itself as a method to determine the potency of local anesthetics has been criticized<sup>22</sup>. Other methods that evaluate the quality of clinical anesthesia demonstrated that the quality of the sensory-motor blockade of ropivacaine would be better<sup>23</sup>. In a recent editorial, it was stated that, with the current level of knowledge it is not possible to quantify the potency of ropivacaine in relation to that of bupivacaine<sup>8</sup> and, for this reason, it was decided to use equivalent doses in the present study. Although there is evidence of the greater safety of ropivacaine in experimental studies, the real impact in clinical practice is still uncertain. The results of the present study demonstrated more intense and prolonged reperfusion with the use of bupivacaine. According to some investigators, the lower toxicity of ropivacaine would be secondary to the lower potency of this drug and, therefore, one should not compare equivalent doses; however, others understand that the lower molecular weight, lower liposolubility, and the substitution of the butyl radical of bupivacaine by a propyl radical have a greater contribution than the levorotatory state for the decreased cardiotoxicity<sup>24</sup>. Local anesthetics still have much to be investigated. Compared to racemic bupivacaine, ropivacaine seems to be safer, but, similar to other drugs, the intravascular injection of large doses has an intrinsic potential for danger<sup>25-28</sup>.

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#### RESUMEN

Melo MDS, Silva WA, Moraes AC, Udelsmann A - Comparación de las Alteraciones Hemodinámicas en la Intoxicación Aguda con Bupivacaína y Ropivacaína por Vía Venosa en Cerdos.

**JUSTIFICATIVA Y OBJETIVOS:** La ropivacaína, presentada bajo la forma de levógira pura, se introdujo para proporcionar una alternativa más segura que la bupivacaína en las anestésias locorre-gionales. El objetivo de este estudio fue el de comparar las repercusiones hemodinámicas después de una inyección por vía venosa de los dos agentes en cerdos, simulando una intoxicación que puede ocurrir durante la anestesia locorre-gional en los humanos.

**MÉTODO:** Se utilizaron cerdos de la raza Large-White, los cuales fueron anestesiados con tiopental, y fue realizada intubación traqueal e instituida la ventilación controlada mecánica. Las variables hemodinámicas se midieron a través de la monitorización invasiva de la presión arterial y de la cateterización de la arteria pulmonar. Después del período de reposo de 30 minutos, los animales fueron aleatoriamente divididos en dos grupos y recibieron por vía venosa 4 mg.kg<sup>-1</sup> de uno u otro agente, sin que el investigador lo supiese. Los resultados hemodinámicos fueron evaluados en reposo y 1, 5, 10, 15, 20 y 30 minutos después de la intoxicación.

**RESULTADOS:** Las repercusiones hemodinámicas de la intoxicación aguda con bupivacaína fueron más importantes y más prolongadas que las de la ropivacaína. Con la bupivacaína, el índice cardíaco se redujo más y fue más prolongado, la presión arterial promedio y la frecuencia cardíaca registraron reducciones más prolongadas, la presión venosa central aumento más y la presión capilar pulmonar también aumentó más y durante más tiempo. El impacto en el índice de resistencia vascular sistémica mostró que la vasomotricidad se mantuvo parcialmente. También se registró un aumento en los dos grupos y, paradójicamente, un tiempo mayor con la bupivacaína.

**CONCLUSIONES:** En los cerdos, la ropivacaína causó menos repercusiones hemodinámicas que la bupivacaína, cuando las mismas dosis se inyectaron por vía venosa.