Hemodynamic effects of ropivacaine and levobupivacaine intravenous injection in swines[1]

Efeitos hemodinâmicos da injeção endovenosa de ropivacaína e levobupivacaína em suínos

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ABSTRACT

Purpose: To compare the hemodynamic effects following a toxic dose of either agent after intravenous injection in swines, as might accidentally occur during regional anesthesia in humans. **Methods**: Large White pigs were anesthetized with thiopental, tracheal intubation was performed and mechanical ventilation was instituted. Hemodynamic variables were recorded with invasive pressure monitoring and pulmonary artery catheterization. After a 30-minute resting period, the animals were randomly divided into two groups in a double-blinded fashion and received a bolus intravenous injection of 4 $mg.kg^{-1}$ of either agent. Hemodynamic results were evaluated at rest and 1, 5, 10, 15, 20 and 30 minutes after intoxication. **Results**: Hemodynamic repressions of acute intoxication with levobupivacaine were more important and more prolonged than those of ropivacaína. **Conclusion**: In pigs, levobupivacaine was shown to be more toxic than ropivacaine when the same large doses are injected intravenously.
Key words: Poisoning. Hemodynamics. Anesthetics, Local. Swine.

RESUMO

Objetivo: Comparar as repercussões hemodinâmicas após a injeção endovenosa dos dois agentes em suínos simulando a intoxicação que pode ocorrer durante uma anestesia locorregional em humanos. **Métodos**: 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 e em duplo-cego divididos em dois grupos e receberam por via endovenosa 4 $mg.kg^{-1}$ de um ou outro agente. 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 levobupivacaína foram mais importantes e mais prolongadas do que as com ropivacaína. **Conclusão**: Em suínos, a levobupivacaína foi mais tóxica do que a ropivacaína quando as mesmas grandes doses são injetadas por via endovenosa.
Descritores: Envenenamento. Hemodinâmica. Anestésicos Locais. Suínos.

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Introduction

Regional anesthesia might require high doses of local anesthetic agents for surgery and there is always the potential risk for toxic reactions. Both the cardiovascular and central nervous systems are the primary target organs of local anesthetic toxicity in case of intravascular injection. Bupivacaine was one of the most widely used local anesthetics, due to its quality of anesthesia and prolonged duration of action[1,2]. Nevertheless, an Anesthesiology editorial on the severe cardiovascular effects of bupivacaine intoxication was published in 1979[3] and since then research has focused on discovering new long-acting local anesthetics with lower toxicity. Although bupivacaine is synthesized in the form of its two dextrorotatory R(+) and levorotatory L(-) isomers[4], evidences that the levorotatory isomers caused less toxicity was already known since 1972[5,6]. In the last decade the levorotatory isomers ropivacaine and levobupivacaine were developed as safer alternatives. Ropivacaine is the S(-) isomer of the propyl analogue of mepivacaine and bupivacaine, whereas levobupivacaine is the S(-) enantiomer of bupivacaine. Indeed, experimental and clinical data have demonstrated these two agents may be less toxic than bupivacaine[7]. In some animal models, the lethal dose of levobupivacaine was shown to be up to 1.6 times higher than that of the racemic mixture[8]! In humans, levobupivacaine would be less potent at producing negative inotropic effects and prolonging the PR and QT intervals of the ECG, typical of racemic mixture intoxication[9]. Despite having equal analgesic potency to racemic bupivacaína[10] the drawback with this new agents would be its less intense motor block[11], The aim of this study was to simulate an acute intoxication with either agent in pigs, as might accidentally occur during local and regional anesthesia with high doses of local anesthetics and to evaluate its hemodynamic repercussions.

Methods

After approval from the Ethics Committee for Animal Experiments, 40 healthy Large White pigs (both sexes, body weight 20-27 kg) underwent the following protocol and follow the Council for International Organization of Medical Sciences ethical code for animal experimentation and the principles of the Brazilian College on Animal Experimentation. The pigs were fasted the night before and had free access to water. The morning, the animals were weighed, an auricular vein was cannulated and anesthesia was induced with a 25 mg.kg^{-1} IV dose of sodium thiopental[12]. The body surface area of the animal (BSA) was calculated using the formula[13]: BSA= (9 x weight in grams $^{2/3}$) x 10^{-4} m^2, introducing the result into the multiparametric Engstrom AS/3 monitor to calculate body index values. Intubation was performed and the animals were ventilated by a pneumatically driven ventilator using a partial re-breathing system and CO_2 absorbent with tidal volume of 15ml.kg^{-1} and respiratory rate to obtain $ETCO_2$ 32 – 34 mmHg. Fresh oxygen flow was 1 l.min^{-1} and hemoglobin oxygen saturation was measured and kept above 97%. ECG was also monitored. Anesthesia was maintained with an intravenous infusion of sodium thiopental 5mg.kg^{-1}.h. In the medial left hind limb of the animal, dissection and cannulation of the femoral artery was performed for continuous arterial pressure measurement. A Swan-Ganz catheter was inserted into the femoral vein and hemodynamic measurements were made by the Datex Engstron AS/3 multiparametric monitor. Cardiac index (CI) mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP) stroke index (SI), systemic vascular resistance index (SVRI), pulmonary vascular resistance pulmonary index (PVRI), left ventricular stroke work index (LVSWI), right ventricular stroke work index (RVSWI) were measured. After a resting period of 30 minutes to ensure stabilization, baseline hemodynamic measurements were recorded (T_0). The animals were then randomly and in a double-blinded fashion divided in 2 groups: ropivacaine group (R) and levobupivacaine group (L). The animals received intravenously a toxic dose of 4 mg.kg^{-1} of the local anesthetic[14] during 30 seconds and the experimenter was blinded about the group. Additional hemodynamic measurements were recorded at 1, 5, 10, 15, 20 and 30 minutes after intoxication. At the end the animals were sacrificed while still under anesthesia by a 10 ml intravenous injection of 19.1% potassium chloride solution. Then the double-blinded protocol was disclosed and data were statistically treated. For categorical variables the chi-square test was used and to compare the distribution of single numerical variables (measured at a single time point) the Student's t-test. To study changes in numerical variables measured at several time points, repeated-measures analysis of variance was performed (ANOVA). Furthermore, the Duncan test was used to compare the groups at each time point and the profile contrast test was applied to analyze the time course of each group. The significance level was set at 5%, i.e., $p \leq 0.05$.

Results

The following Table 1 shows the distribution by sex, mean and standard deviations of weight and body surface areas in both groups. There were no statistic differences.

TABLE 1

GROUP	L	R
female	6 (30%)	9 (45%)
male	14 (70%)	11 (55%)
weight ± SD (Kg)	22,7 ± 2,75	21,96 ± 2,08
BSA ± SD (m^2)	0,71 ± 0,06	0,69 ± 0,05

sex p = 0,327; weight p = 0,344; BSA p = 0,3

There were no difference in any of the hemodynamic parameters measured at rest between groups.

Following intoxication, there was a reduction in cardiac index (Figure 1 and Table 2) in both groups but L was lower than R until the end ($p<0.001$) and did not return to values similar to T_0 till the end while R returned to resting values in T_{10} ($p<0.001$).

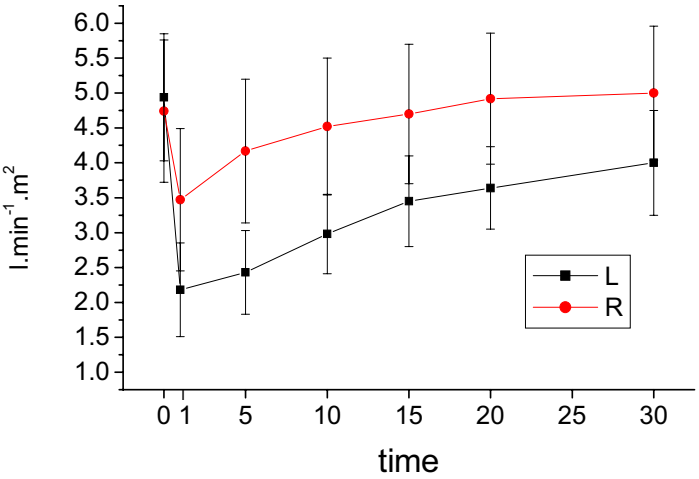

FIGURE 1 - Cardiac Index

TABLE 2 - Cardiac index ± SD (l.min^{-1}.m^2)

GROUP	T_0	T_1	T_5	T_{10}	T_{15}	T_{20}	T_{30}
L	4.9±0.9	2.2±0.7	2.4±0.6	3±0.6	3.5±0.6	3.6±0.6	4±0.7
R	4.7±1	3.5±1	4.2±1	4.5±1	4.7±1	4.9±0.9	5±1

Mean arterial pressure (Figure 2 and Table 3) decreased in both groups but L was lower than R from T_1 to T_5 and higher from T_{15} to T_{30} ($p<0.001$). In L pressure was lower than T_0 till T_{10} while in R only in T_1 ($p<0.001$).

There was a significant and similar decrease in heart rate (Figure 3 and Table 4) in both groups. L did not reach T_0 till the end but R did at T_{10} ($p<0.001$). From T_{15} till T_{30} L had lower values than R ($p<0.001$).

Central venous pressure (Figure 4 and Table 5) increased significantly in both groups but more in L which was higher than R till the end ($p=0.012$). L did not return to T_0 similar values but R did since T_5 ($p<0.001$).

TABLE 3 – Mean arterial pressure ± SD (mmHg)

GROUP	T_0	T_1	T_5	T_{10}	T_{15}	T_{20}	T_{30}
L	94.8±15	50.3±15.4	66.1±20.3	91.3±16.3	100.3±12.7	102.7±13.5	103.7±15.9
R	89.3±9.8	77.7±2.5	84.5±1.4	87.9±9.6	88±10.5	87.3±9	89.2±12.7

TABLE 4 - Heart rate ± SD (beats.min^{-1})

GROUP	T_0	T_1	T_5	T_{10}	T_{15}	T_{20}	T_{30}
L	131.9±17.4	116.6±18.7	122.5±20.2	116.8±18.6	110.1±15.1	110.2±14.4	115.3±16.7
R	128.4±24.9	118.3±25.3	122.3±28	123.6±28.9	125.2±28.1	126.2±28.3	131.6±27.3

TABLE 5 - Central venous pressure ± SD (cmH_2O)

GROUP	T_0	T_1	T_5	T_{10}	T_{15}	T_{20}	T_{30}
L	9±2	12±2.3	11.2±2	10.8±1.9	10.4±1.9	9.9±2.1	9.9±1.9
R	8.7±2.5	9.6±2	9.1±2.2	8.6±2.2	8.4±2	8.5±2	8.7±2.2

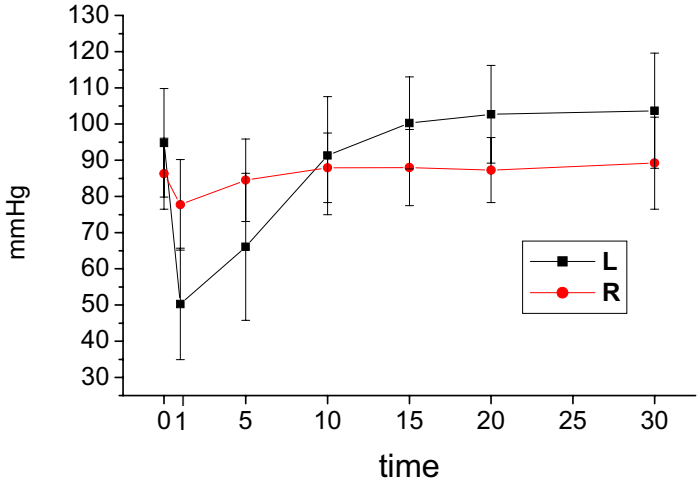

FIGURE 2 - Mean Arterial Pressure

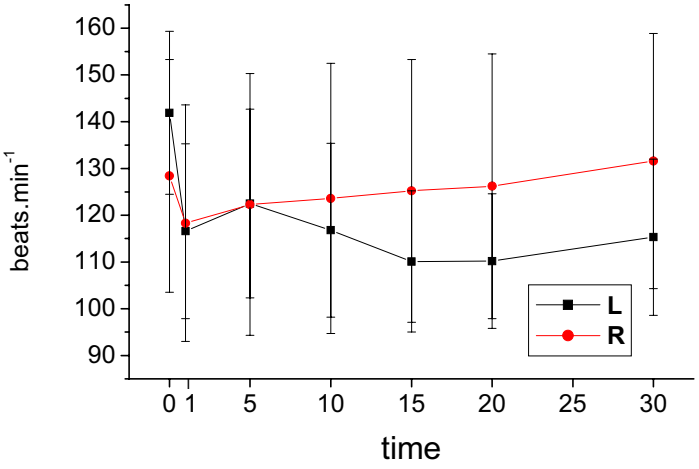

FIGURE 3 - Heart Rate

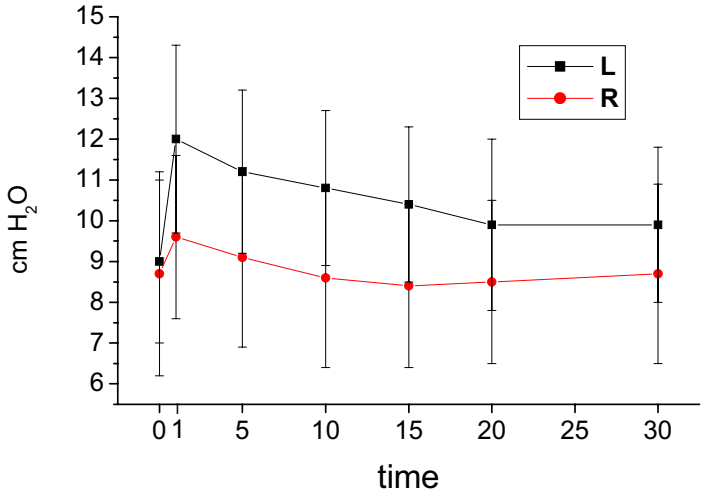

FIGURE 4 - Central Venous Pressure

Mean pulmonary artery pressure (Figure 5 and Table 6) was higher in L than R from T_5 till T_{30} (p=0.021). There were no differences in times in both groups (p=0.06).

Pulmonary capillary wedge pressure (Figure 6 and Table 7) showed increased values in both groups following intoxication but in L they were more important till T_{20} (p=0.007). L did not return to resting values but R did at T_{10} (p=0.042).

Stroke index (Figure 7 and Table 8) had a significant decline in both groups but in L these fall was more important till T_{20} (p<0.001). L returned to resting values in T_{20} while R in T_5 (p<0.001).

TABLE 6 - Mean pulmonary artery pressure ± SD (mmHg)

GROUP	T_0	T_1	T_5	T_{10}	T_{15}	T_{20}	T_{30}
L	19.1±3.9	19.3±3.2	19.6 ± 3.5	19.9 ± 4.6	19.7 ± 4.4	19.5±3.3	19.5±3.2
R	18.8±2.6	18.6±3.3	17.6±2.7	16.8±2.7	16.7±2.4	17±2.5	17.1±2.8

TABLE 7 - Pulmonary capillary wedge pressure ± SD (mmHg)

GROUP	T_0	T_1	T_5	T_{10}	T_{15}	T_{20}	T_{30}
L	8.3±2.7	11.7±2.9	11.6±2.8	10.4±2.4	9.8±2.1	9.5±2.1	9.6±2.2
R	7.5±2.1	9.6±2.5	8.6±2.4	8.1±2.2	7.9±2.2	7.8±1.9	8.2±2.8

TABLE 8 – Stroke index ± SD (ml.bat^{-1}.m^2)

GROUP	T_0	T_1	T_5	T_{10}	T_{15}	T_{20}	T_{30}
L	34.2±5	18.2±5.7	19.4±5.5	24.4±6.5	29.8±6.6	31.9±5.9	34.4±5
R	36.6±5.9	29±5.9	34.2±7.1	36.9±7.1	37.7±6.7	39.1±6.2	38.2±6.5

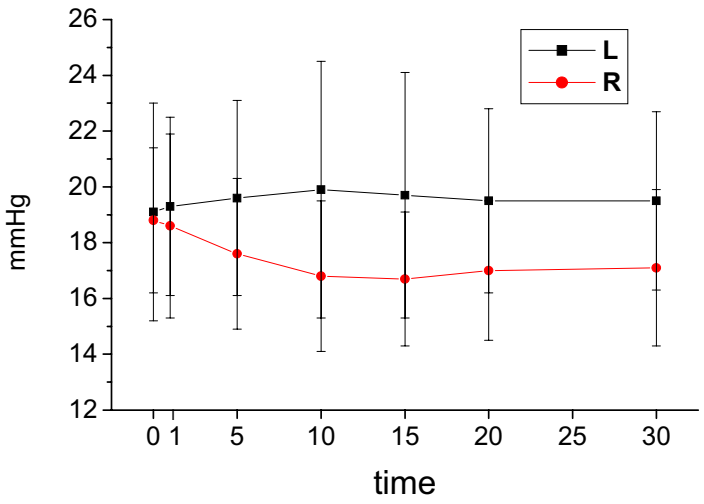

FIGURE 5 - Mean Pulmonary Artery Pressure

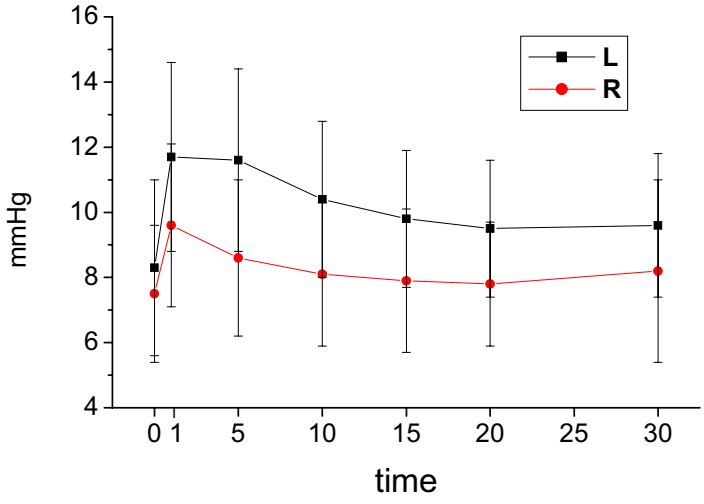

FIGURE 6 - Pulmonary Capillary Wedge Pressure

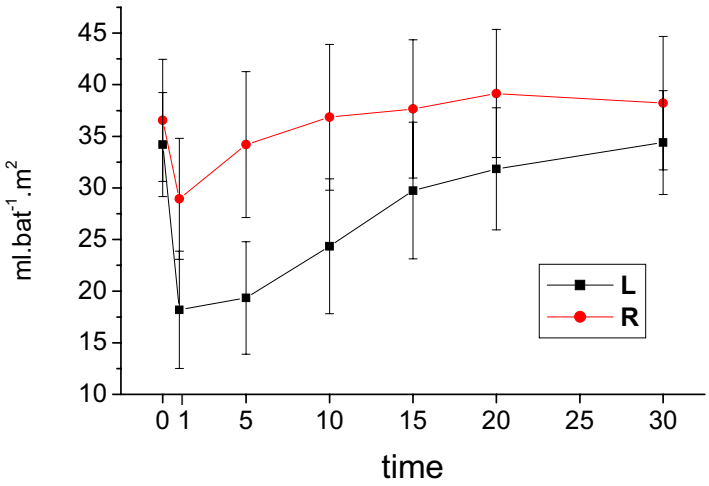

FIGURE 7 - Stroke Index

In L systemic vascular resistance index (Figure 8 and Table 9) had a fall in T_1 but from T_{10} till the end was greater than T_0, R had an increase from T_1 to T_{10} ($p<0.001$). L was greater than R from T_{10} to T_{30} ($p<0.001$).

In L pulmonary vascular resistance index (Figure 9 and Table 10) showed higher values than resting in T_1, T_5 and T_{20} ($p<0.001$) while in R only in T_1. L was greater than R from T_5 to T_{30} ($p=0.013$).

Left ventricular stroke work index (Figure 10 and Table 11) decreased after intoxication in both groups, however the fall was greater in L until T_{10} ($p<0.001$). Values returned to similar to resting at T_{20} in L and T_5 in R ($p<0.001$).

TABLE 9 – Systemic vascular resistance index ± SD (dynes.sec^{-1}.cm^5.m^{-2})

GROUP	T_0	T_1	T_5	T_{10}	T_{15}	T_{20}	T_{30}
L	1626±326.9	1409±314.8	1776±485.8	2199±409	2146±398.6	2106 ± 402.8	1945 ± 399
R	1356±283.2	1644±418	1491±267.2	1448±292.5	1396±284.7	1309±238.7	1320±273.5

TABLE 10 – Pulmonary vascular resistance index ± SD (dynes.sec^{-1}.cm^5.m^{-2})

GROUP	T_0	T_1	T_5	T_{10}	T_{15}	T_{20}	T_{30}
L	179.8±80.6	297.1±189	278.9±165.4	239.1±140	233.9±121.4	226±83.3	202.8±78.8
R	162.8±42.8	220.5±65.6	175.5±49.1	158.6±48	154.6±46	152.8±34.4	148.2±37.4

TABLE 11 – Left ventricular stroke work index ± SD (g.min^{-1}.m^2)

GROUP	T_0	T_1	T_5	T_{10}	T_{15}	T_{20}	T_{30}
L	46±11.1	10.2±6.3	15.2±7.6	28.6±10.7	38±10.4	41.6±11	44.5±11.8
R	39.4±9.6	27±8.7	36.1±12	40.6±11.4	41.6±11.4	42.7±10	42.4±11

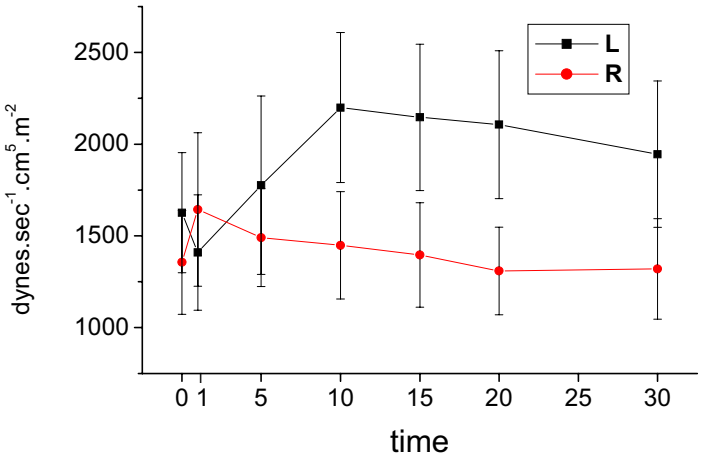

FIGURE 8 - Systemic Vascular Resistance Index

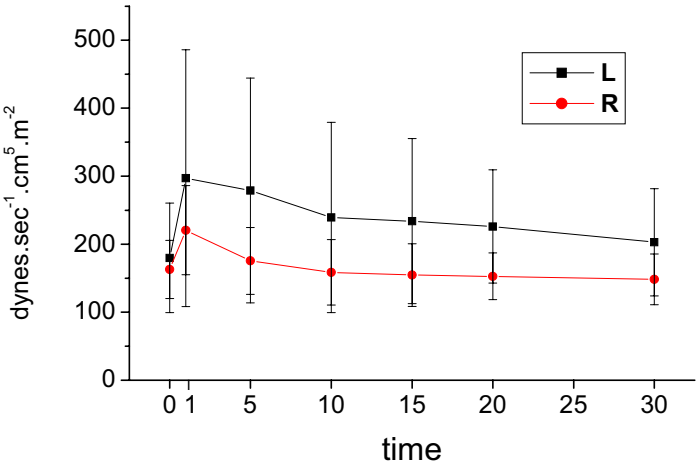

FIGURE 9 - Pulmonary Vascular Resistance Index

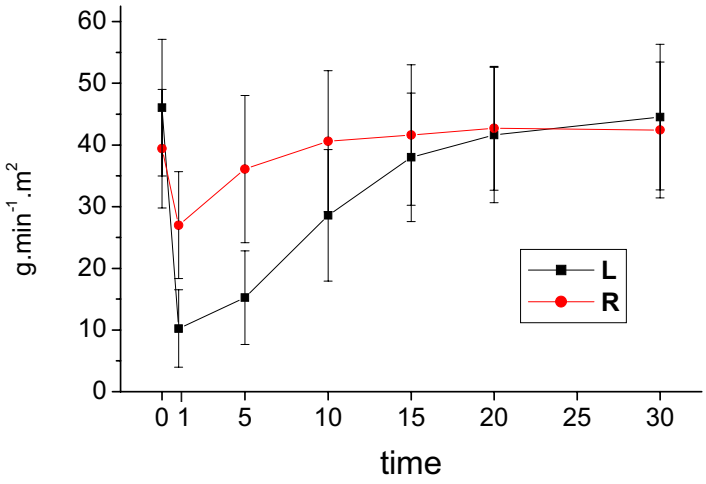

FIGURE 10 - Left Ventricular Stroke Work Index

Right ventricular stroke work index (Figure 11 and Table 12) fall in both groups, but this was more important in L until T_{10} (p=0.03). Values returned to to resting at T_{20} in L and T_5 in R (p<0.001).

TABLE 12 - Right ventricular stroke work index ± SD (g.min^{-1}.m^2)

GROUP	T_0	T_1	T_5	T_{10}	T_{15}	T_{20}	T_{30}
L	4.6±1.7	1.8±0.8	2.2±0.8	2.8±1.2	3.8±1.7	4.3±1.4	4.4±1.5
R	4.1±1.4	3.6±1.2	3.9±1.2	4.1±1.2	4.2±1.2	4.5±1.2	4.5±1.5

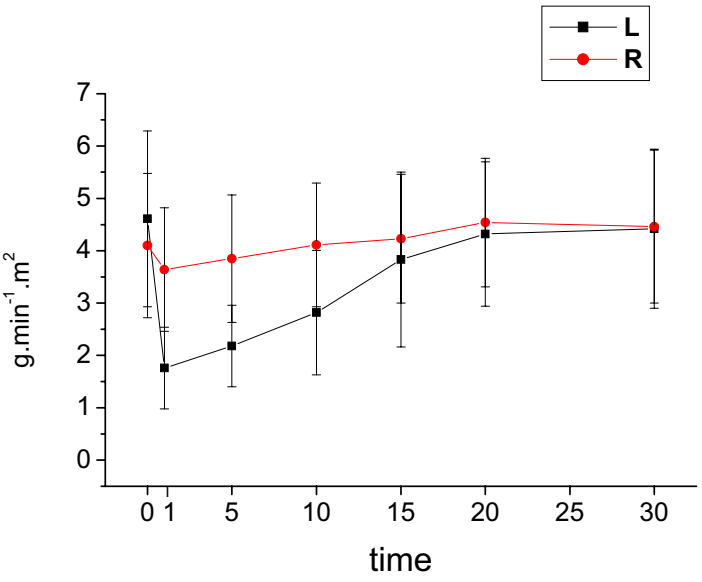

FIGURE 11 - Right Ventricular Stroke Work Index

Discussion

Cardiac toxicity of local anesthetics is attributed to a blockade of Na^+ in the heart leading to a prolonged conduction time with widening of QRS complexes, prolongation of PR interval, AV block and arrythmias[15]. These drugs cause cardiac toxicity as well by altering mitochondrial metabolism in cardiac cells and thus alter inotropism[16]. The S(-) isomer may be less cardiotoxic due to its lower affinity for cardiac Na^+ channels in comparison to the R(+)isomer as demonstrated in guinea pigs[17] and ropivacaine would be less potent than levobupivacaine to block them[18]. Overall hemodynamic variables events seen with both drugs were similar but quantitative differences were found, with ropivacaine changes were less important and turned over more quickly to the starting values. Our results demonstrated that levobupivacaine had greater hemodynamic repercussions on a swine model of acute intoxication simulating what may occur after accidental intravenous injections of local anesthetics during local and regional anesthesia. Evidence of toxicity with the same doses was shown in the significantly more important decrease in cardiac index mean arterial pressure, heart rate and left ventricular stroke work index. However, further studies must be encouraged since Polley *et al.*[19] found the drugs equipotent, Parpaglioni *et al.*[20] levobupivacaine more potent, Liisanantti *et al.*[21] ropivacaine more potent and different potencies could justify different results with the same doses. Accidental injections of high doses of local anesthetics and toxic reactions during local and regional anesthesia have decreased in the last 30 years, falling from 0.2 to 0.01%. Peripheral nerve blocks still account for the majority of these cases (7.5 per 10.000)[22]. Such considerations should intensify new efforts to discover drugs and techniques that enable to achieve a significantly low morbidity and mortality rate, protecting patients from the undesirable and unpredictable effects of local and regional anesthesia techniques with high doses of local anesthetics.

Conclusion

In pigs, levobupivacaine was shown to cause more important hemodynamic repercussions than ropivacaine when the same large doses are injected intravenously.

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