

**Title:** MYOCARDIAL TISSUE UPTAKE OF BUPIVACAINE AND LIDOCAINE AFTER INTRAVENOUS INJECTION IN NORMAL AND ACIDOTIC RABBITS

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**Introduction.** Bupivacaine but not lidocaine has been reported to cause life-threatening cardiac arrhythmias in normal animals and cardiovascular collapse and death in hypoxic-acidotic animals. Although the mechanism for this increased toxicity is unknown, it may be that more bupivacaine reaches specific cardiac membrane receptors, especially during acidosis. We determined myocardial tissue/blood drug concentration ratios 30 sec. after intravascular injection in normal and acidotic rabbits, *i.e.*, at a time of maximal myocardial uptake prior to bupivacaine-induced cardiovascular collapse.

**Methods.** Under halothane/oxygen anesthesia, 20 rabbits had arterial and venous catheters inserted. After a 2 hr. recovery, an equal number of animals were randomly assigned to one of four groups: Groups I and II were unanesthetized, normoxic and nonacidotic. Groups III and IV were also unanesthetized but were rendered acidotic (pH 7.1-7.2) with CO<sub>2</sub> and mildly hypoxic (P<sub>a</sub>O<sub>2</sub> 10-20 torr below control) with nitrogen. Groups I and III received lidocaine 5.7 mg/kg and Groups II and IV received bupivacaine 2.1 mg/kg intravenously over 10 sec. These doses are equivalent (on a mg/kg basis) to those administered epidurally (or accidentally intravascularly) during cesarean section. Following arterial blood sampling 30 sec after injection, animals were killed and myocardial tissue was removed for determination of local anesthetic concentrations. Tissue and blood drug concentrations were assayed by gas/liquid chromatography. The ratios of local anesthetic concentrations in myocardial tissue to those in blood, and the effects of acidosis/hypoxia, were compared by two-way analysis of variance.

**Results.** Although the ratio of drug concentrations in myocardial tissue to those in blood were higher for bupivacaine than for lidocaine (P less than 0.05), acidosis did not increase these ratios for either drug (table).

**Discussion.** Several factors may account for the increased concentration of bupivacaine in the myocardium. These include differences in ion trapping, protein binding and lipid solubility between the two drugs. The pKa of bupivacaine is 8.1 and the pKa of lidocaine is 7.9. In the physiologic range of pH, more bupivacaine is protonated compared to lidocaine. In the cell, a further increase in protonation occurs with both drugs, but the percent change is small and favors intracellular trapping of lidocaine. Respiratory acidosis does not change ion trapping significantly since both intracellular and extracellular pH are reduced proportionately. Protein binding would not appear to account for the increased amount of bupivacaine as there is the same amount of total protein in whole blood (18%) as in myocardial tissue (14% to 19%).<sup>3</sup> Therefore, no

partitioning would be expected on the basis of differences in the absolute amount of protein. Bupivacaine is ten times more lipid soluble than lidocaine. Since the heart has 3 times as much lipid as blood,<sup>3</sup> this likely accounts for most of the increase in myocardial uptake of bupivacaine compared to lidocaine. Most of the lipid is in the myocardial cell membrane which is the presumed site of action of bupivacaine.

In conclusion, more bupivacaine than lidocaine is bound to myocardial tissue after rapid intravenous administration at a time when electrocardiographic and hemodynamic changes start to occur. Acidosis does not produce increased myocardial tissue uptake of either bupivacaine or lidocaine. Therefore, the observed increase in toxicity of intravenous bupivacaine during acidosis is not primarily caused by increased myocardial tissue uptake of the drug during acidosis.

#### References.

1. Kotelko DM, Shnider SM, Dailey PA, *et al*: Bupivacaine-induced cardiac arrhythmias in sheep. *Anesthesiology* 60:10-18, 1984
2. Thigpen JW, Kotelko DM, Shnider SM, *et al*: Bupivacaine cardiotoxicity in hypoxic-acidotic sheep. *Anesthesiology* 59:A204, 1983
3. Report of the Task Group on Reference Man ICRP number 23, 1975.

#### Heart Muscle

#### Tissue: Blood Ratios of

#### Local Anesthetic

	Lidocaine (n = 5)	Bupivacaine (n = 5)
Nonacidotic	5.4 ± 1.4	8.5 ± 1.2
Acidotic	2.5 ± 1.3	6.5 ± 2.2

Bupivacaine ratios > lidocaine ratios  
p < 0.05