In general, much greater doses of local anesthetics are required to produce cardiovascular (CV) toxicity than CNS toxicity. Similar to CNS toxicity, potency for CV toxicity reflects the anesthetic potency of the agent. Recent attention has focused on the apparently exceptional cardiotoxicity of the more potent, more lipid-soluble agents (bupivacaine, levo-bupivacaine, etidocaine, ropivacaine). These agents appear to have a different sequence of CV toxicity than less potent agents. For example, increasing doses of lidocaine leads to hypotension, bradycardia, and hypoxia, whereas bupivacaine often results in sudden cardiovascular collapse due to ventricular dysrhythmias that are resistant to resuscitation. Subsequent studies have identified multiple mechanisms in the CNS and CV system for increased cardiotoxicity from potent local anesthetics.

**Cardiovascular toxicity mediated at the CNS:**

It has been demonstrated that the central and peripheral nervous systems may be involved in the increased cardiotoxicity with bupivacaine. The nucleus tractus solitarii in the medulla is an important region for autonomic control of the cardiovascular system. Neural activity in the nucleus tractus solitarii of rats is markedly diminished by intravenous doses of bupivacaine immediately prior to development of hypotension. Furthermore, direct intracerebral injection of bupivacaine can elicit sudden dysrhythmias and cardiovascular collapse.

**Cardiovascular toxicity mediated at the heart:**

The more potent local anesthetics appear to possess greater potential for direct cardiac electrophysiologic toxicity. A previous study examining lidocaine, bupivacaine, and ropivacaine in rats has demonstrated equivalent peak effects on myocardial contractility but much greater effects on electrophysiology (prolongation of QRS) from bupivacaine and ropivacaine than lidocaine. Although all local anesthetics block the cardiac conduction system via dose-dependent block of sodium channels, two features of bupivacaine’s sodium channel blocking abilities may enhance its cardiotoxicity. First, bupivacaine exhibits a much stronger binding affinity to resting and inactivated sodium channels than lidocaine. Second, local anesthetics bind to sodium channels during systole and dissociate during diastole. Furthermore, bupivacaine inhibits calcium channels, release of calcium from sacroplasmic reticulum, and mitochondrial energy metabolism, thus multiple direct effects of bupivacaine on activity of the cardiac myocyte may enhance the cardiotoxicity of bupivacaine. The multitude of different cardiac and neural mechanisms of cardiotoxicity may in part explain the reported difficulties of resuscitation after cardiovascular collapse from bupivacaine.

**References:**