The Possible Mechanisms Underlying Epinephrine Worsens Bupivacaine Induced Cardiac Toxicity

Abstract
Overdose bupivacaine disturbs both electrophysiologic and hemodynamic function by blocking Na channels, affecting Ca transient and reuptake, inhibiting mitochondria respiration and lipid metabolism. Adrenergic activation aggravates Ca overload, increases oxygen consumption, increases ROS production, and therefore worsens cardiac contractile dysfunction.

Introduction
Accidental intravascular or overdose injection of bupivacaine can result in serious, potentially life threatening complications. Electrophysiologic and hemodynamic disturbances, including conduction blocks, ventricular arrhythmias, and fatal cardiovascular collapse have been reported in patients and experimental animals. But which occurs first and is more important? Put another way, do patients with bupivacaine toxicity die of arrhythmias, contractile failure, or a combination of the two? Epinephrine is a first-line agent for treating cardiac arrest; but why patients who have undergone bupivacaine induced cardiac arrest are often resistant to adrenergic therapy? This article reviews the mechanism underlying bupivacaine induced cardiac collapse, and the effect of epinephrine on the toxicity.

Epinephrine aggravates the cardiac toxicity induced by bupivacaine
Epinephrine has been widely used in the treatment of heart failure and cardiogenic shock. However, epinephrine increases myocardial oxygen demand, reduces subendocardial perfusion, cause pulmonary edema, and reduces myocardial function after resuscitation [1]. In 1989, Bernards [2] reported that epinephrine decreases the dose of bupivacaine needed to cause seizures and dysrhythmias in pigs. In 1990, Kambam [3] reported that epinephrine increased the cardiorespiratory toxicity of intravenously administered bupivacaine in rats. In 1991, Kinney [4] reported that epinephrine increased, but β-adrenergic antagonist, propranolol reduced bupivacaine cardiac toxicity. In 2001, Groban [5] reported that epinephrine effectively managed lidocaine induced hypotension, but induced arrhythmia in dogs received bupivacaine.

Bupivacaine induced SNS hyperactivity, which mediated indirect cardiac toxicity
It is well known that overdose bupivacaine not only induces cardiac toxicity by directly bind to cardiomyocytes, but also produce indirect cardio toxicity via CNS. In 1984, Hasselstrom [6], reported that intravenous infusion of bupivacaine resulted in sympathetic nerve system hyperactivity. In eight healthy volunteers, after bupivacaine was intravenously infused at 2 mg/min for 3 hr, plasma epinephrine concentrations increased significantly from 0.03 to 0.08 ng/ml (p<0.05). In 1986, Heavner [7] reported that activation of the autonomic nervous system by bupivacaine could participate in its cardiotoxicity. In his report, the cats received microscale intracerebroventricular (icv) bupivacaine developed ventricular arrhythmias including premature ventricular contractions, bigeminy, quadrigeminy, and ventricular tachycardia. In 1991, Bernards [8] reported that icv bupivacaine resulted in dysrhythmias and hypertension, which can be terminated by icv midazolam and iv hexamethonium. Accordingly the author proposed that bupivacaine produced local anesthetic blockade of GABA-ergic neuron, with tonically inhibit of autonomic nerve system outflow from the brainstem. Increased sympathetic nerve system outflow to the myocardium produced dysrhythmias. Midazolam terminated dysrhythmias by potentially inhibitory GABA activity at the autonomic nerve system outflow neuron; hexamethonium terminated dysrhythmias by blockade of peripheral autonomic ganglia. Additionally, recent studies showed that bupivacaine induced cardiac toxicity can be attenuated by inhibit central nervous system sympathetic outflow. In Hancis’ work [9], sixteen Wistar-Albino male rats pretreated with dexmedetomidine, or saline as control, received bupivacaine intravenously at a rate of 3 mg/kg per minute until cardiac asystole occurred. The result showed that dexmedetomidine pretreatment significantly increased the time to the 25%, 50%, and 75% reductions in mean arterial pressure and the time to the 25% and 50% reductions in heart rate; significantly increased the time to first arrhythmia and time to asystole.

The possible mechanisms underlying epinephrine aggravated bupivacaine cardiac toxicity
As in neurons, bupivacaine bind Na channels preventing Na ion flux, thereby preventing generation and propagation of action potentials, it was thought to decrease intracardiac conduction.
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The effect of β-adrenergic activation mainly mediated via the cytosol to the ER against a concentration gradient, inhibition of diphosphate (ADP) to reuptake Ca across the membrane from the mitochondrial matrix for beta-oxidation [38]. The cardiac mitochondrion is more than 70% dependent on fatty acids for energy. Studies have demonstrated that bupivacaine inhibits fatty acid oxidation in rat myocardial mitochondria and that toxicity is related to impaired mitochondrial function [39], and recent evidence suggests that bupivacaine can not only reduces myofibrillar activation via inhibition on the Ca binding to troponin C in rat ventricular muscle [24], but also block LTCC, inhibits Ca release by RyR2 and Ca uptake by SERCA pump [25]. If this is the case, β-adrenergic activation will worsen bupivacaine induced cardiac depression, just like it in RYR2 deficient animal or clinical patients.

β-adrenergic activation increases cellular metabolism and therefore mitochondrial oxygen consumption. This results in a higher rate of mitochondrial reactive oxygen species (ROS) production [25]. Chronic β-adrenoceptor activation is commonly associated with myocardial injury induced by oxidative stress and apoptosis [26-28]. Recent studies showed that even acute β-adrenoceptor activation can rapidly increase ROS production [29] and these free radicals play a critical role in augmentation of LTCC current during β-adrenergic activation [30]. ROS also are known to alter RyR2 activity by oxidation of thiol groups of cysteine residues in the channel [31,32]. Oxidation of RyR2 thios appears able to enhance the channel’s activity, increase SR Ca leak [33] and augment Ca spark frequency [34]. Thus, β-adrenergic stimulation increases mitochondrial ROS production, which results in redox modification of RyRs, consequently increases diastolic SR Ca leak, and finally leads to the generation of arrhythmogenic Ca waves [35].

Bupivacaine produced a dose-dependent inhibition of oxygen consumption, depresses the mitochondrial respiration by inhibiting the respiratory chain complexes I and III activities, and in turn enhances ROS production [36]. Hiller et al. [37] reported that bupivacaine accumulate in the myocardium, induced a reversibly mitochondrial swelling, reduces cellular metabolism and consequently cause a negative inotropic effect [37]. In view of β-adrenergic stimulation increases cellular metabolism and therefore enhances mitochondrial oxygen consumption, we propose that β-adrenergic activation may further increase ROS production, and consequently worsen bupivacaine cardiac toxicity e.g. via oxidate RyR2.

Carnitine is a naturally occurring amino acid derivative that is essential in the transfer of long-chain fatty acids into the mitochondrial matrix for beta-oxidation [38]. The cardiac mitochondrion is more than 70% dependent on fatty acids for energy. Studies have demonstrated that bupivacaine inhibits fatty acid oxidation in rat myocardial mitochondria and that toxicity is related to impaired mitochondrial function [39], and recent evidence suggests that bupivacaine can not only reduces myofibrillar activation via inhibition on the Ca binding to troponin C in rat ventricular muscle [24], but also block LTCC, inhibits Ca release by RyR2 and Ca uptake by SERCA pump [25]. If this is the case, β-adrenergic activation will worsen bupivacaine induced cardiac depression, just like it in RYR2 deficient animal or clinical patients.

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studies showed that intravenous L-carnitine administration enhanced threshold for bupivacaine-induced cardiotoxicity in rats. This should be another mechanism underlying bupivacaine inhibit mitochondrial metabolism.

Take together, overdose bupivacaine not only block Na channels, but also affects Ca transient and reuptake, inhibits mitochondria respiration and lipid metabolism. Adrenergic activation aggravates Ca overload, increases oxygen consumption, increases ROS production, and therefore worsens cardiac contractile dysfunction.

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