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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.

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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 aggravate the cardiac toxicity induced by bupivacaine

Epinephrine has been used widely 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 antagonistor, propranolol reduced bupivacaine cardiac toxicity. In 2001, Groban[4] reported that epinephrine effectively managed lidocaine induced hypotension, but induced arrhythmia in dogs received bupivacaine.[5]

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, Hasselstrøm[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 velocity and depresses spontaneous sinoatrial activity. Nav1.5, the pore forming α-subunit of the voltage-dependent cardiac Na channel, is an integral membrane protein involved in the initiation and conduction of action potentials. Mutations in the gene-encoding Nav1.5, SCN5A, have been associated with a variety of arrhythmic disorders, including long QT, Brugada, and sick sinus syndromes as well as progressive cardiac conduction defect and atrial standstill. Recently, there is accumulated evidence showing that bupivacaine potentially blocked sodium currents in cardiomyocytes as well as recombinant Nav1.5

currents. However, catecholamine showed no effect on bupivacaine mediated Na channels blockade. Therefore, it is seemly epinephrine aggravated Bupivacaine toxicity via some other way.[10-12]

In addition to blocking Na+ channels, bupivacaine affects the activity of many other channels, including Ca channel, K channel and Cl Channels. ATP-sensitive potassium channel (KATP channel) is an inward rectifier potassium channel which couples the intermediary metabolism to excitability, which highly expressed in cardiomyocytes. KATP channels are known to contribute to the shortening of action potentials during catecholaminergic stress that is mediated by β-adrenergic receptors.[13] They couple electrical and metabolic signals at the cell surface during adaptation to stress, hyperpolarizing the cells and preventing Ca entry under conditions of energy depletion. KATP channels contribute to the maintenance of myocardial electrical stability under Vigorous Adrenergic Stress. Suppression of KATP channel activity, whether by genetic deletion of channel subunits or through use of channel antagonists, predisposes to inadequate calcium handling and intracellular calcium overload.[13,14] Zingman et al.[13] reported that received 10mg/kg isoprenaline i.p., sudden death occurred in over 70% of KATP channel-deficient animals but in none of the WT mice[13] Liu et al.[15] reported that disruption of Kir6.2, the pore-forming subunit of ATP-sensitive K+ channel, predisposes to catecholamine induced ventricular dysrhythmias.[15] It has been reported that bupivacaine could inhibit KATP currents by binding to its Kir6.2 subunit.[15,16] If this is the case, bupivacaine acts as a KATP channels blocker, catecholamine will increase bupivacaine induced cardiac toxicity via β- adrenergic activation.

Cardiac contraction is initiated by the systolic Ca transient. The entry of Ca into the cell via the L-type Ca current (LTCC) triggers the release of more Ca from the sarcoplasmic reticulum (SR) through a specialized release channel known as the ryanodine receptor (RYR2). This process, known as Ca induced Ca release (CICR), is responsible for delivery of Ca to troponin C and triggering of contraction. After contraction, the Ca were reuptaken into the ER through the sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA pump). Reagents disturbing the procedure will affect myocyte contraction.

As the SERCA pump uses the chemical energy produced from the conversion of adenosine triphosphate (ATP) into adenosine diphosphate (ADP) to reuptake Ca across the membrane from the cytosol to the ER against a concentration gradient, inhibition of mitochondrial energy metabolism may depress the contraction. The effect of β- adrenergic activation mainly mediated via the adenylate cyclase–cAMP–protein kinase A (PKA) signalling pathway. PKA phosphorylates an array of important proteins involved in excitation–contraction coupling (ECC), including SERCA regulator, phospholamban, LTCC and RyR2.[17,18] This results in an elevation of Ca flux through LTCC, increase of SR Ca load, and synchronization of SR Ca release during cell systole. These modifications of Ca transport systems play an important role in positive inotropy by allowing adjustment of the strength of ECC to match the physiological demands of the heart.[19,20] To maintain cardiomyocyte Ca homeostasis, the enhanced LTCC and RYR2 activity should be accompanied by enhanced phosphorylation of phospholamban activating SERCA. In RYR2 deficient animal or clinical patients, activation of the β- adrenoceptor will worsen the heart failure.[21-23] A growing body of 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 thiols 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 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.

Conflicts of interest

There is no conflict of interest.

Acknowledgements

Funding

References

1. Tang W, Weil MH, Sun S, et al. Progressive myocardial dysfunction after cardiac resuscitation. *Crit Care Med*. 1993;21(7):1046–1050.

2. Bernards CM, Carpenter RL, Rupp SM, et al. Effect of midazolam and diazepam premedication on central nervous system and cardiovascular toxicity of bupivacaine in pigs. *Anesthesiology*. 1989;70(2):318–323.

3. Kambam JR, Kinney WW, Matsuda F, et al. Epinephrine and phenylephrine increase cardiorespiratory toxicity of intravenously administered bupivacaine in rats. *Anesth Analg*. 1990;70(5):543–545.

4. Kinney WW, Kambam JR, Wright W. Propranolol pretreatment reduces cardiorespiratory toxicity due to plain, but not epinephrine–containing, intravenous bupivacaine in rats. *Can J Anaesth*. 1991;38(4 pt 1):533–536.

5. Groban L, Deal DD, Vernon JC, et al. Cardiac resuscitation after incremental overdosage with lidocaine, bupivacaine, levobupivacaine, and ropivacaine in anesthetized dogs. *Anesth Analg*. 2001;92(1):37–43.

6. Hasselstrom LJ, Mogensen T, Kehlet H, et al. Effects of intravenous bupivacaine on cardiovascular function and plasma catecholamine levels in humans. *Anesth Analg*. 1984;63(12):1053–1058.

7. Heavner JE, Pitkanen MT, Shi B, et al. Resuscitation from bupivacaine–induced asystole in rats: Comparison of different cardioactive drugs. *Anesth Analg*. 1995;80(6):1134–1139.

8. Bernards CM, Artu AA. Hexamethonium and midazolam terminate dysrhythmias and hypertension caused by intracerebroventricular bupivacaine in rabbits. *Anesthesiology*. 1991;74(1):89–96.

9. Hanci V, Karakaya K, Yurtlu S, et al. Effects of dexmedetomidine pretreatment on bupivacaine cardiotoxicity in rats. *Reg Anesth Pain Med*. 2009;34(6):565–568.

10. Loussouarn G, Sternberg D, Nicole S, et al. Physiological and Pathophysiological Insights of Nav 1.4 and Nav1.5 Comparison. *Front Pharmacol*. 2016;6:314.

11. Stoetzer C, Doll T, Stueber T, et al. Tetrodotoxin–sensitive α–subunits of voltage–gated sodium channels are relevant for inhibition of cardiac sodium currents by local anesthetics. *Naunyn Schmiedebergs Arch Pharmacol*. 2016;389(6):625–636.

12. Liu F, Wu B, Du Y, et al. Epinephrine reversed high–concentration bupivacaine–induced inhibition of calcium channels and transient outward potassium current channels, but not on sodium channel in ventricular myocytes of rats. *BMC Anesthesiol*. 2015;15:66.

13. Zingman LV, Hodgson DM, Bast PH, et al. Kir6.2 is required for adaptation to stress. *Proc Natl Acad Sci USA*. 2002;99(20):13278–13283.

14. Brady PA, Alekseev AE, Terzic A. Operative condition–dependent response of cardiac ATP–sensitive K+ channels toward sulfonylureas. *Circ Res*. 1998;82(2):272–278.

15. Liu XK, Yamada S, Kane GC, et al. Genetic disruption of Kir6.2, the pore–forming subunit of ATP–sensitive K+ channel, predisposes to catecholamine–induced ventricular dysrhythmia. *Diabetes*. 2004;53 Suppl 3:S165–S168.

16. Olschewski A, Olschewski H, Bräu ME, et al. Effect of bupivacaine on ATP–dependent potassium channels in rat cardiomyocytes. *Br J Anaesth*. 1999;82(3):435–438.

17. Kawano T, Oshita S, Takahashi A, et al. Molecular mechanisms of the inhibitory effects of bupivacaine, levobupivacaine, and ropivacaine on sarcolemmal adenosine triphosphate–sensitive potassium channels in the cardiovascular system. *Anesthesiology*. 2004;101(2):390–398.

18. Xie Y, Grandi E, Puglisi JL, et al. β–adrenergic stimulation activates early afterdepolarizations transiently via kinetic mismatch of PKA targets. *J Mol Cell Cardiol*. 2013;58:153–161.

19. Ginsburg KS, Bers DM. Modulation of excitation–contraction coupling by isoproterenol in cardiomyocytes with controlled SR Ca2+ load and Ca2+ current trigger. *J Physiol*. 2004;556(pt 2):463–480.

20. Zhou P, Zhao YT, Guo YB, et al. Beta–adrenergic signaling accelerates and synchronizes cardiac ryanodine receptor response to a single L–type Ca2+ channel. *Proc Natl Acad Sci USA*. 2009;106(42):18028–18033.

21. Shan J, Betzenhauser MJ, Kushnir A, et al. Role of chronic ryanodine receptor phosphorylation in heart failure and β–adrenergic receptor blockade in mice. *J Clin Invest*. 2010;120(12):4375–4387.

22. Wehrens XH, Lehnart SE, Reiken S, et al. Ryanodine receptor/calcium release channel PKA phosphorylation: a critical mediator of heart failure progression. *Proc Natl Acad Sci USA*. 2006;103(3):511–518.

23. Liu N, Colombi B, Memmi M, et al. Arrhythmogenesis in catecholaminergic polymorphic ventricular tachycardia: insights from a RyR2 R4496C knock–in mouse model. *Circ Res*. 2006;99(3):292–298.

24. Mio Y, Fukuda N, Kusakari Y, et al. Bupivacaine attenuates contractility by decreasing sensitivity of myofilaments to Ca2+ in rat ventricular muscle. *Anesthesiology*. 2002;97(5):1168–1177.

25. Chedid NG, Sudo RT, Aguiar MI, et al. Regulation of intracellular calcium by bupivacaine isomers in cardiac myocytes from Wistar rats. *Anesth Analg*. 2006;102(3):792–798.

26. Communal C, Singh K, Pimentel DR, et al. Norepinephrine stimulates apoptosis in adult rat ventricular myocytes by activation of the β–adrenergic pathway. *Circulation*. 1998;98(13):1329–1334.

27. Zhang GX, Kimura S, Nishiyama A, et al. Cardiac oxidative stress in acute and chronic isoproterenol–infused rats. *Cardiovasc Res*. 2005;65(1):230–238.

28. Srivastava S, Chandrasekar B, Gu Y, et al. Downregulation of Cu Zn–superoxide dismutase contributes to β–adrenergic receptor–mediated oxidative stress in the heart. *Cardiovasc Res*. 2007;4(3):445–455.

29. Kohlhaas M, Liu T, Knopp A, et al. Elevated cytosolic Na+ increases mitochondrial formation of reactive oxygen species in failing cardiac myocytes. *Circulation*. 2010;121(14):1606–1613.

30. Andersson DC, Fauconnier J, Yamada T, et al. Mitochondrial production of reactive oxygen species contributes to the β–adrenergic stimulation of mouse cardiomycytes. *J Physiol*. 2011;589(pt 7):1791–1801.

31. Kourie JI. Interaction of reactive oxygen species with ion transport mechanisms. *Am J Physiol Cell Physiol*. 1998;275(1 pt1):C1–24.

32. Zima AV, Blatter LA. Redox regulation of cardiac calcium channels and transporters. *Cardiovasc Res*. 2006;71(2):310–321.

33. Terentyev D, Györke I, Belevych AE, et al. Redox modification of ryanodine receptors contributes to sarcoplasmic reticulum Ca2+ leak in chronic heart failure. *Circ Res*. 2008;103(12):1466–1472.

34. Yan Y, Liu J, Wei C, et al. Bidirectional regulation of Ca²+ sparks by mitochondria–derived reactive oxygen species in cardiac myocytes. *Cardiovasc Res*.2008;77(2): 432–441.

35. Bovo E, Lipsius SL, Zima AV Reactive oxygen species contribute to the development of arrhythmogenic Ca²+ waves during β–adrenergic receptor stimulation in rabbit cardiomyocytes. *J Physiol*. 2012;590(Pt 14):3291–3304.

36. Cela O, Piccoli C, Scrima R, et al. Bupivacaine uncouples the mitochondrial oxidative phosphorylation, inhibits respiratory chain complexes I and III and enhances ROS production: results of a study on cell cultures. *Mitochondrion*. 2010;10(5):487–496.

37. Hiller N, Mirtschink P, Merkel C, et al. Myocardial accumulation of bupivacaine and ropivacaine is associated with reversible effects on mitochondria and reduced myocardial function. *Anesth Analg*. 2013;116(1):83–92.

38. Calvani M, Reda E, Arrigoni–Martelli E. Regulation by carnitine of myocardial fatty acid and carbohydrate metabolism under normal and pathological conditions. *Basic Res Cardiol*. 2000;95(2):75–83.

39. Weinberg GL, Palmer JW, Vade Boncouer TR, et al. Bupivacaine inhibits acylcarnitine exchange in cardiac mitochondria. *Anesthesiology*. 2000;92(2):523–528.