Models and Mechanisms of Local Anesthetic Cardiac Toxicity

A Review

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Abstract: Cardiovascular collapse, even death, may occur after intoxication with bupivacaine or related amide local anesthetic agents. The problem has been studied in myriad laboratories for more than 20 years. Nevertheless, there is consensus neither regarding which animal model best mimics this clinical catastrophe nor as to which ion channel, enzyme, or other local anesthetic binding site represents the point of initiation for the process. This review aimed to define the various credible mechanisms that have been proposed to explain cardiovascular collapse and death after administration of local anesthetics, particularly after bupivacaine and related agents.

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Although coca and its numbing properties were recognized in antiquity, only after cocaine was purified and injected through hypodermic needles did local anesthetic (LA) cardiac toxicity become a convenient possibility.[1,2] A report published in 1886 described the effects of cocaine on the heart and the drug's lethal dose.[3] Wider recognition that LA toxicity could have lethal consequences should have followed reports of 7 deaths in nearly 40,000 patients with the use of topical cocaine or tetracaine anesthesia to facilitate tracheobronchoscopy or esophagogastroscopy.[4] Yet, it was not until Albright[5] reported several patients who could not be resuscitated after receiving bupivacaine or etidocaine that widespread interest developed in the anesthetic and scientific communities. Despite continuing investigations using a myriad of molecular, cellular, tissue, and whole animal models, there is no consensus as to how LAs produce cardiovascular (CV) depression and mortality.

This review focused specifically on the mechanisms by which LAs could lead *directly* to severe CV depression or death. I recognize that CV depression can result from a variety of LA "secondary responses" (including anaphylaxis, coronary ischemia from inadequate treatment of hypotension during neuraxial anesthesia, or hypoxemia from LA-induced convulsions); however, I have not included such *indirect* mechanisms of LA-induced CV collapse herein. Similarly, the special circumstances surrounding cardiac toxicity with cocaine provide sufficient material for a separate article and will not be included here (see McCord et al[6] for current clinical recommendations).

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In this review, I have assumed that certain "LA issues" have been settled. Local anesthetics inhibit conduction in peripheral nerves by binding and inhibiting voltage-gated Na (Na_V) channels.[7] Lidocaine (and other class Ia antiarrhythmic agents) inhibit ventricular arrhythmias by binding and inhibiting Na_V channels in the heart.[8] Bupivacaine, etidocaine, and tetracaine are more potent at nerve blocks and toxicity than mepivacaine, lidocaine, or procaine, are more potent at producing cardiac toxicity, and likely have a reduced therapeutic index.[7] The evidence underlying these assumptions may be found in the indicated references. Finally, although I have made the assumption that cardiac toxicity is a result of *direct* LA actions on cardiac tissue, I recognize that secondary hypoxemia and acidosis play an important role and that the sympathetic response to convulsions may influence the clinical picture of LA-induced cardiac toxicity.

SEARCH METHODS

The goal was to systematically identify and assess the mechanisms that have been proposed to underlie LA cardiac toxicity. Toward this end, published studies were located and selected through the use of PubMed. Searches were performed in August 2008 with the following key words: "local anesthetic" or "bupivacaine" and "cardiac, cardiovascular, or heart," and "toxicity or toxic." A second search was conducted using "cardiac or heart" and "bupivacaine or etidocaine or tetracaine" to identify those publications of basic investigations potentially relevant to an understanding of LA toxicity that were not expressly conducted do describe the mechanisms of toxicity. Experimental studies conducted both in vitro and in vivo were included. However, this search process yielded many basic science citations that were clearly unrelated to an understanding of LA cardiac toxicity, and these were excluded. On the other hand, use of more restrictive search terms resulted in exclusion of relevant basic studies. Historical references were identified by searching under "cocaine" or "tetracaine" and limiting the search to references dating before 1950. Articles not written in English were excluded.

RESULTS

Whole Animal Studies

Is There a Standard Whole Animal Experimental Model for LA Cardiac Toxicity?

As was reviewed by Groban,[9] a wide variety of models have been used to define the mechanism(s) for LA cardiac toxicity (Table 1). Choices have varied regarding animal species (mice, rats, cats, dogs, sheep, pigs, monkeys, humans) and regarding experimental conditions (awake, sedated, or anesthetized [with any of several different agents and with spontaneous, assisted, or controlled ventilation]).[10–35] A specific set of assumptions underlies each of these models. When LAs produce convulsions in a previously conscious animal (or patient), the convulsions

TABLE 1. Examples of Whole Animal and Human Models Used to Define Local Anesthetic Cardiac Toxicity

Author	Year	Species	GA	Drug	Paradigm
de Jong and Bonin[10]	1980	Mouse	No	B, L, 2-CP	Single intraperitoneal dose to determine CD_{50} and LD_{50}
de Jong and Bonin[11]	1980	Mouse	No	B, 2-CP	Single intraperitoneal versus single subcutaneous dose to determine CD_{50} and LD_{50}
Zavisca et al[12]	1991	Rat	Yes	B	Infusion to first ventricular arrhythmia, seizure, isoelectric electroencephalogram, death
Thomas et al[13]	1986	Rat	Yes	B, L	Injection in brain to produce CV toxicity
Ohmura et al[14]	2001	Rat	Yes	LB, B, R	Infusion to asystole, then resuscitation
de Jong et al[15]	1982	Cat	Yes	L, B, E	Infusion to 3 times the convulsive dose
Chadwick[16]	1985	Cat	Yes	B, L	Infusion to produce convulsions and arrest, then resuscitation
Feldman et al[17]	1989	Dog	No	B, L, R	Twice the CD administered as bolus
Stewart et al[18]	1963	Dog	Yes	P, 2-CP, L, C, T	Infusion to reduce contractility by roughly 50%
Liu et al[19]	1982	Dog	Yes	B, E, L, M, P	Acute bolus dose to produce CV collapse
Kasten and Martin[20]	1986	Dog	Yes	B	Acute bolus to CV collapse, then resuscitation
		Sheep	Yes	B	
Riqelme et al[21]	1986	Dog	Yes	B	Dogs of varying ages administered immediate bolus to CV collapse, then resuscitation
Bruelle et al[22]	1996	Dog	Yes	B, E, L, M	Acute bolus to produce electrophysiologic and hemodynamic impairment.
Groban et al[23]	2000	Dog	Yes	B, LB, R, L	Incremental infusion with PES
Groban et al[24]	2001	Dog	Yes	B, LB, R, L	Incremental infusion to CV collapse, then resuscitation
Bernards et al[25]	1989	Pig	No	B	Bolus + infusion, then resuscitation
Nath et al[26]	1986	Pig	Yes	B	Direct bolus injection into left anterior descending coronary artery
Haasio et al[27]	1990	Pig	Yes	B	Bolus + resuscitation after premedication with antiarrhythmic (versus placebo)
Badgwell et al[28]	1990	Pig	Yes	B	Infusion to animals of varying age with varying GA
Kotelko et al[29]	1984	Sheep	No	B, L	Bolus doses to produce convulsions an arrhythmias
Santos et al[30]	1995	Sheep	No	B, R	Infusion to produce convulsions and CV collapse in pregnant and nonpregnant animals
Chang et al[31]	2001	Sheep	No	B, LB, R	Direct injection into left main coronary artery
Ladd et al[32]	2002	Sheep	No	B, LB, R	Infusion into carotid artery with CNS/CV monitoring
Copeland et al[33]	2008	Sheep	Y/N	B, LB, R, L, M, P	Defined dose infused, responses compared based on presence or absence of anesthesia
Mather et al[34]	1979	Human	No	B, E	Infusion of defined dose with CNS/CV monitoring
Scott et al[35]	1989	Human	No	B, R, L	Infusion until CNS effects with CV recording

B indicates bupivacaine; CD50, dose producing convulsions in 50% of animals; 2-CP, 2-chloropracaine; E, etidocaine; GA, general anesthesia provided to experimental animals/subjects; L, lidocaine; LB, levobupivacaine; LD50, dose producing lethality in 50% of animals; M, mepivacaine; P, prilocaine; R, ropivacaine; Y/N, both yes and no.

produce a tremendous sympathetic response that will likely influence any LA effects on the heart.[15] A choice to study anesthetized animals, whether for investigator convenience or to reduce variation in ventilation and oxygenation, removes this potentially important effect of central nervous system (CNS) excitation on the heart.

Local anesthetic drugs can also be administered in several ways: as a bolus (to mimic an unintentional intravenous injection), as a slow intravenous infusion (to define a precise toxic concentration at the effect site or to mimic gradual absorption of LA during a high dose block), or as a direct coronary artery injection (to produce isolated cardiac effects without seizures or other systemic effects; Table 1). Although the assumption behind all animal models is that the results will mimic LA cardiac toxicity in *Homo sapiens*, the lack of consensus as to the preferred species or experimental conditions has led to a confusing cacophony of experimental models and designs.

Is the Margin of Safety Between CNS and CV Toxicity the Same for All LAs?

A markedly different ratio of the LA dose producing convulsions to the dose producing CV toxic effects (CV/CNS ratio) between lidocaine and bupivacaine might support there being disproportionate CV toxicity and a reduced margin of safety in clinical practice for bupivacaine relative to lidocaine (perhaps through a toxicity mechanism not operative with lidocaine). Most recent studies have found that bupivacaine has a smaller CV/CNS ratio than other agents (Table 2).[14,16,17,36,37] One of the studies that did not report a reduced CV/CNS ratio used CV toxicity data generated in a different cohort of anesthetized ventilated dogs to calculate ratios. A more recent study from the same research group used CNS and CV data collected from the same unanesthetized animals and concluded that bupivacaine had a lower margin of safety than either ropivacaine or lidocaine. By exactly what mechanism CNS toxicity might be produced

TABLE 2. Cardiovascular-to-Central Nervous System Toxicity Ratios in Intact Animals

Author	Year	Species	Drugs and CV/CNS Ratios
Ohmura et al[14]	2001	Rat	B 4.2; R 8.1
Chadwick[16]	1985	Cat	B 4.8; L 4.0
Liu et al[36]	1983	Dog	B 4.1; L 3.5; E 5.1; T 6.7
Feldman et al[17]	1989	Dog	B 2.0; R 2.7; L 3.1
Morishima et al[37]	1985	Sheep	B 3.7; L 7.1

CV/CNS ratios calculated using administered doses causing CV collapse versus seizures.

B indicates bupivacaine; E, etidocaine, L, lidocaine; R, ropivacaine; T, tetracaine.

and whether CNS and CV toxicity have the same molecular initiation is beyond the scope of this review.

Does LA Cardiac Toxicity Arise From Effects on Electrophysiology or on Contractility, and Does it Depend on the Specific Compound?

Ultimately, cardiac death includes cessation of electrical impulses as well as cessation of contractility. 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? Finally, does the answer to the question depend on the specific LA compound? Multiple studies of LA toxicity have been performed by investigators who have assumed that the mechanism of LA toxicity is the same for all compounds (Tables 1 and 2).

There are several lines of evidence that suggest that arrhythmias may underlie LA CV toxicity. For example, in an early series of experiments comparing procaine and tetracaine at doses producing roughly 50% depression of contractility, 2 of 30 mongrel dogs died unexpectedly: one from ventricular fibrillation and the other from pulseless electrical activity.[18]

Case reports and in vivo studies in cats, dogs, and sheep described the propensity of bupivacaine for producing severe arrhythmias, concurrent with or before the onset of convulsions (supporting reduced CV/CNS margin of safety), and the greater propensity of bupivacaine than lidocaine to produce arrhythmias. de Jong et al[15] administered supraconvulsant doses of lidocaine, etidocaine, and bupivacaine to anesthetized cats. Arrhythmias were common with bupivacaine and etidocaine but not with lidocaine. Cats receiving a supraconvulsant dose of lidocaine required ephedrine to support the blood pressure, whereas cats receiving comparably supraconvulsant doses of etidocaine or bupivacaine did not require vasopressor support, suggesting that this agent might produce toxicity through depression of contractility. In a study of a small number of awake dogs, Feldman et al[17] determined the dose of lidocaine, ropivacaine, and bupivacaine that would produce convulsions. On the first experimental day, lidocaine (8 mg/kg per minute), bupivacaine (2 mg/kg per minute), or ropivacaine (2 mg/kg per minute) were infused intravenously until seizures occurred. After recovering for 24 hrs, the dogs were administered 2 times the convulsive LA dose. Approximately 83% of dogs receiving bupivacaine had ventricular arrhythmias, no dogs receiving lidocaine had ventricular arrhythmias, and 33% of dogs receiving ropivacaine had arrhythmias. These apparently different margins of safety are of particular note given that the mean convulsive doses of bupivacaine and ropivacaine were 4.3 and 4.9 mg/kg, respectively. Kotelko et al[29] administered comparable multiples of the clinical nerve blocking doses of either bupivacaine or lidocaine to unanesthetized sheep. Serious cardiac arrhythmias were seen after bupivacaine but not after lidocaine. All of the studies just described support the idea that differing LA compounds may have differing propensities to produce arrhythmias.

Several authors have considered whether cardiac toxicity per se might differ based on the LA compound. Bruelle et al[22] administered lidocaine, mepivacaine, etidocaine, and bupivacaine to anesthetized dogs, observing consistent differences in the form of cardiac toxicity that each agent produced. Etidocaine and bupivacaine produced marked cardiac electrophysiologic effects without myocardial depression, whereas (at comparable multiples of a nerve blocking dose) lidocaine markedly depressed contractility without having electrophysiologic effects. Mepivacaine produced a lesser degree of cardiac toxicity than the other agents. Groban et al[23,24] used pharmacokinetic parameters to guide incremental infusions of lidocaine, ropivacaine, levobupivacaine, or bupivacaine to anesthetized dogs. Programmed electrical stimulation (PES) was given as each new, steady-state, LA concentration in blood was achieved. Dogs receiving bupivacaine or levobupivacaine were more likely to have spontaneous or PES-induced ventricular arrhythmias than dogs receiving lidocaine. Moreover, at the onset of cardiac arrest (defined as a blood pressure <45 mm Hg), several of the bupivacaine dogs could be resuscitated by defibrillation alone, whereas all but one of the lidocaine dogs required epinephrine infusion to maintain adequate blood pressure in the face of reduced ventricular function. These studies suggest 2 things. First, bupivacaine is more prone to arrhythmias than lidocaine. Second, when given to the point of severe cardiac toxicity, lidocaine shows a consistent degree of depressed contractility without arrhythmias, whereas bupivacaine toxicity *may* take the form of arrhythmias and/or depressed cardiac conduction alone. In other words, all LA toxicity may not be expressed in the same way, particularly when different LA compounds are involved.

On the other hand, it is clear that cardiac toxicity from bupivacaine cannot only be explained by electrophysiologic actions. Royse and Royse[38] used pressure-volume loops in anesthetized open-chest rabbits to find that bupivacaine and levobupivacaine depressed cardiac contractility after a total dose of 2.66 mg/kg, whereas ropivacaine failed to depress contractility after a total dose of 4.25 mg/kg. All drugs were administered using an incremental infusion that was slowly increased in 8 defined steps. Arrhythmias were not observed.

In Vitro Models

Is LA Cardiac Toxicity From Effects on Electrophysiology or on Contractility?

Whole animal models are rarely the best way to define cellular or molecular mechanisms of toxicity. Unfortunately, as reviewed by Heavner,[39] there is very nearly the same lack of consensus regarding the best in vitro intact heart model as there is for the best in vivo model. Many in vitro studies have shown that bupivacaine (or related more potent, longer-acting LA compounds) has greater potency than lidocaine (or related less potent, shorter-acting LA compounds) at inhibiting cardiac electrophysiologic or contractile function (Table 3).[40–45] A few articles have examined the differing (or varying) LA doses required to produce effects on contractility versus cardiac conduction in isolated heart models. Block and Covino[40] measured intra-atrial conduction times, His-Purkinje conduction times, QRS duration, QT interval, and AV nodal conduction times in an in vitro, paced, Langendorff rabbit heart preparation. Bupivacaine was 8- to 15-fold more potent than lidocaine at inhibiting electrophysiologic measures

TABLE 3. In Vitro Models of Cardiac Function Used to Study Local Anesthetic Toxicity

Author	Year	Species	Technique	Drugs and Findings
Block and Covino[40]	1981	Rabbit	Langendorff	B, T, E >> M, Pr, P, L
Lacombe et al[41]	1991	Rabbit	Langendorff	B depresses conduction
Pitkanen et al[42]	1992	Rabbit	Langendorff	Greater depression by B than R or L of electrophysiologic measurements
Tanz et al[43]	1984	Guinea pig	Langendorff	More arrhythmias with B than L
Graf et al[44]	1997	Guinea pig	Langendorff	More potent block of AV conduction by *R*(+) B than *S*(−) B
Moller and Covino[45]	1988	Dog	Isolated, perfused	B more potent than L at inhibiting eletrophysiologic measurements

B indicates bupivacaine; E, etidocaine; L, lidocaine; M, mepivacaine; P, procaine; Pr, prilocaine; R, ropivacaine; R(+) B, R(+)-bupivacaine; *S*(−) B, levobupivacaine; T, tetracaine.

compared with its roughly 3- to 4-fold greater potency at nerve block. Etidocaine and bupivacaine were roughly 20-fold more potent than lidocaine at inhibiting contractility, despite being nearly equipotent (etidocaine) and 4-fold more potent (bupivacaine), than lidocaine at nerve block. Thus, Block and Covino confirmed that bupivacaine and etidocaine have greater "cardiac toxic potency" relative to their "anesthetic potency." In this model, the greater potency of bupivacaine and etidocaine relative to lidocaine is *no less* for contractility than for the various electrophysiologic measures.

Does the Form of LA Toxicity Depend on the Specific Compound?

Some in vitro studies have asked whether bupivacaine might be more likely than lidocaine to produce arrhythmias and conduction disturbances. Pitkanen et al[42] used a Langendorff rabbit heart preparation and observed conduction disturbances and arrhythmias in hearts treated with bupivacaine but not in hearts treated with lidocaine. Tanz et al[43] used a Langendorff guinea pig heart preparation to determine that bupivacaine was roughly 3-fold more potent than lidocaine at decreasing heart rate and roughly 10-fold more potent at decreasing cardiac contractility. Interestingly, arrhythmias appeared in half of the hearts that received the cardiac toxic dose of bupivacaine (3 μg/mL) but in none of the hearts that received lidocaine at any concentration. Moller and Covino[45] compared lidocaine to bupivacaine in isolated, perfused canine cardiac preparations. Bupivacaine and lidocaine both inhibited conduction and inotropy; however, bupivacaine's greater potency relative to lidocaine at inhibiting electrophysiologic measures ranged from 15:1 to 26:1, but its greater potency at inhibiting atrial contractility was only 8:1 as calculated on a weight basis.

A number of in vitro studies have attempted to define the mechanisms for bupivacaine's predisposition for arrhythmias. Multiple studies have shown that bupivacaine delays conduction.[40–45] Some studies have administered bupivacaine in sufficiently large doses that complete heart block or even pacemaker-resistant cardiac inexcitability have resulted (as would be expected for any LA administered at a sufficiently large dose). Other studies have found that bupivacaine's main effect on isolated cardiac tissue is to depress conduction, producing atrioventricular block and (potentially) reentrant arrhythmias.[41]

Graf et al[44] compared the 2 bupivacaine enantiomers to racemic bupivacaine in a Langendorff guinea pig heart preparation. At the same concentration, the *S*(−) isomer produced less delay of AV conduction than the racemic mixture, which in turn produced less delay of AV conduction than the most toxic *R*(+) enantiomer.

Studies in Isolated Cardiac Tissue

Studies in isolated heart tissue tend to support the observation in whole heart models regarding differences among LA compounds. Moller and Covino[45] compared lidocaine, ropivacaine, and bupivacaine in isolated Purkinje fibers. Ropivacaine and bupivacaine, but not lidocaine, caused premature depolarizations. Inexcitability after LA exposure was less persisting after lidocaine or ropivacaine than after bupivacaine. Bupivacaine, ropivacaine, and levobupivacaine were compared by David et al[46] for their effects on contraction and relaxation in isolated rat papillary muscles. In this model, ropivacaine was least potent, levobupivacaine was the most potent, and bupivacaine was intermediate in potency (all differences were significant) at depressing entropy (contractility). Levobupivacaine was also more potent than bupivacaine and bupivacaine was more potent than ropivacaine at inhibiting cardiac lusitrophy (relaxation) in this model.

Basic Electropharmacology of LAs

Does Cardiac Toxicity Result From Action on Na_V Channels?

Much is known about LA binding to voltage-gated Na (Na_V) channels, the integral membrane proteins responsible for action potentials in nerve and for initiating action potentials in cardiac muscle.[7] The basic mechanisms regarding LA interactions with Na_V channels were worked out in nerve tissue, so this information will be briefly summarized. In neurons, LAs bind Na_V channels preventing Na ion flux, thereby preventing generation and propagation of action potentials. Biophysical and genetic studies have localized LA binding to specific regions of the neuronal Na_V channel α-subunit.[47] Although all LAs bind Na_V channels in a similar way, binding of different LAs may induce differing conformational changes in the channel.[48] Local anesthetic inhibition of Na currents increases with repetitive depolarizations, often called "use-dependent" block.[49] Repetitive trains of depolarizations increase the likelihood that an LA will encounter a Na_V channel in the "open" or "inactivated" forms that have greater LA affinity than "resting" channels.

There are a number of reasons why LA actions on cardiac tissue cannot reliably be predicted using data collected in nerve tissue. Although heart, skeletal muscle, and nerve all have Na_V channels, there are 7 genetically distinct Na_V channel forms that are found in neural tissue, 1 additional form that is found in skeletal muscle (Na_V 1.4), and still another form that is found uniquely in cardiac tissue (Na_V 1.5 coded for by the gene *SCN5a*).[50] For years, it was assumed that only Na_V1.5 was present in cardiac tissue.[8] More recently, it has become clear that there are regions of the conduction system where neuronal forms predominate

and that neuronal forms may contribute to ventricular contractility and, potentially, to LA toxic reactions.[1–5]

It is almost certainly incorrect to assume that LAs bind the various Na_V channel forms in precisely the same way. The differing Na_V channel forms also have electrophysiologic differences. $Na_V1.5$ requires a lesser degree of depolarization to activate (commence the sequence of conformational changes that ultimately permit the channel to conduct Na ions). Calmodulin causes of hyperpolarizing shift in the voltage dependence of both activation and inactivation for $Na_V1.4$ (skeletal muscle Na_V channel) but affects only activation kinetics in $Na_V1.5$.[51] Other drugs bind the different Na_V channel forms with varying affinity. For example, $Na_V1.5$ binds the poison tetrodotoxin less avidly than neuronal and skeletal muscle Na_V channel forms.[52] Toxins isolated from tarantula venom selectively inhibit specific Na_V forms.[53] There are also profound species differences in Na_V channel function and drug binding. For example, cardiac Na_V channels from the rainbow trout (a useful species for experimentation and one which, after cardiac tissue has been removed, can be efficiently introduced into the food chain—the author recommends sauté in butter with lemon) bind the selective Na_V channel poison tetrodotoxin with 1000-fold greater affinity than mammalian cardiac Na_V channels.[54]

If we assume that the mechanism for bupivacaine cardiac toxicity relates directly to an overabundant expression on $Na_V1.5$ channels of its "usual" and desired actions on neuronal Na channels, then the best way to define such actions is by using formal electrophysiologic techniques. The initial, cardiac electrophysiologic comparisons of bupivacaine versus lidocaine were conducted by Clarkson and Hondeghem.[55] Using a sucrose gap method, they compared changes in the maximum upstroke velocity of the cardiac action potential (V_{max}) after either lidocaine or bupivacaine. Drug effects on V_{max} can be used as a guide to drug effects on Na currents. These investigators interpreted their results as showing differences between lidocaine and bupivacaine in the rate at which these compounds unbind from cardiac Na_V channels. They assumed the binding was to inactivated Na_V channels (although their results were also consistent with binding to open Na_V channels), and that bupivacaine caused greater toxicity because of the slower rate of recovery from block.

Vanhoutte et al[56] compared the effects of the 2 bupivacaine optical isomers on V_{max} in guinea pig papillary muscles. $S(-)$ bupivacaine (levobupivacaine) was less potent than $R(+)$ bupivacaine at inhibiting V_{max} and shortening action potential duration. Valenzuela et al[57] used whole-cell voltage clamp technique in isolated guinea pig ventricular myocytes. They found that the bupivacaine $R(+)$ isomer bound inactivated Na_V channels faster and with greater potency than levobupivacaine. The 2 enantiomers bound open (activated) Na_V channels with comparable potency. These results could explain the greater toxicity of the $R(+)$ enantiomers due to the large contribution of inactivated Na_V channel block during the plateau phase of the cardiac action potential.

Importance of LA Binding to Other Ion Channels

There are investigators who hypothesize that LAs cause cardiac toxicity through an electrophysiologic mechanism, but who do not believe that the cardiac Na_V channel is the only target. Szabó et al[58] compared the effects of ropivacaine and bupivacaine on ion currents in enzymatically dispersed canine ventricular myocytes. Ropivacaine produced concentration- and frequency-dependent changes in action potential configuration and also shortened action potentials duration, reduced action potential amplitude, reduced maximum velocity of depolarization, and suppressed early repolarization. Ropivacaine reduced V_{max} with an EC_{50} (the drug concentration producing 50% of the maximal drug effect) value of 81 ± 7 μm at 1 Hz. Qualitatively similar results were obtained with bupivacaine, which was nearly twice as potent (EC_{50} = 47 ± 3 μm). Under voltage clamp conditions, a variety of ion currents were blocked by ropivacaine: L-type Ca current (EC_{50} = 263 ± 67 μm), transient outward current (EC_{50} = 384 ± 75 μm), inward rectifier K current (EC_{50} = 372 ± 35 μm), rapid delayed rectifier K current (EC_{50} = 303 ± 47 μm), and slow delayed rectifier K current (EC_{50} = 106 ± 18 μm). It is notable that ropivacaine had greater potency at inhibition of Na current than of any other ionic current.

Calcium currents are critically important in cardiac contraction, so multiple investigators have wondered whether these currents might be involved in bupivacaine toxicity. Coyle and Sperelakis[59] compared lidocaine and bupivacaine effects on the Ca-mediated slow action potential in guinea pig ventricle. Their intent was to determine whether concentrations of LAs relevant to a discussion of cardiac toxicity had actions on the Ca current. Bupivacaine was approximately 10-fold more potent than lidocaine at producing 50% inhibition of this Ca current, producing this action at roughly 10-μmol/L concentration. Sánchez-Chapula[60] used the whole-cell patch clamp technique to determine that bupivacaine failed to inhibit the slow inward Ca current of single guinea pig ventriculocytes unless applied at concentrations of 10 μmol/L or greater. Shibuya et al[61] found that bupivacaine inhibited the fast inward (Na) current at concentrations much less than those that inhibited the slow inward (Ca) current, supporting the importance of Na_V channels in toxicity.

de La Coussaye et al[62] studied bupivacaine inhibition of the slow inward Ca current in frog atrial cells under voltage clamp. Even at very high concentrations (0.1 mmol/l), the peak inward current was inhibited by only 33%. This degree of inhibition of the slow inward Ca current would not be sufficient to explain a decrease in contractility—suggesting another mechanism for this finding. Zapata-Sudo et al[63] failed to identify a stereoselective L-Ca channel mechanism by which bupivacaine might cause excessive cardiac toxicity.

Repolarization of the heart does not occur in as straightforward a manner as it does in neurons, and it was conceivable that bupivacaine (and other LAs) might produce cardiac toxicity through an action on K currents. Courtney and Kendig[64] determined that bupivacaine inhibited 2 of the several K conductances in the heart and suggested that K current inhibition might contribute to bupivacaine cardiac toxicity. Castle[65] used rat ventricular myocytes and whole-cell patch clamp to observe inhibition by bupivacaine of the transient outward K current but not the inward rectifier. Valenzuela et al[66] observed stereoselective inhibition of human cardiac $K_V1.5$ currents by bupivacaine. Olschewski et al[67] found that bupivacaine at concentrations greater than those that inhibit cardiac Na_V channels would also inhibit the ATP-activated K (K_{ATP}) channel in rat cardiomyocytes.

Friederich et al[68] tested the effects of several LAs on the human "ether-a-go-go related" gene (HERG) channel. Common polymorphisms of this K channel result in an increased susceptibility to drug-induced arrhythmias. Of note, bupivacaine, levobupivacaine, and ropivacaine all bind this channel (and the genetic variant associated with drug-induced arrhythmias) at concentrations achievable after clinical regional anesthesia (10–20 μmol/L).

Friederich and Solth[69] and Solth et al[70] tested LA effects on $K_v4.3$/KChIP2.2 (transient outward K channel). Complementary DNA cloned from human heart was transfected in Chinese hamster ovary cells. The expressed K channels were studied under patch clamp. They confirmed that ropivacaine, like bupivacaine, inhibited the transient outward current in a dose- and voltage-dependent manner. The results are consistent

with the idea that these LAs, by blocking $K_v4.3$/KChIP2.2 from the open state, interfere with the gating modifying effects of KChIP2.2 on $K_v4.3$ channels. This inhibition could contribute to the deterioration of cardiac function during LA intoxication.

Siebrands et al[71] noted that most congenital long QT syndromes arise from mutations in KCNQ1 ($K_v7.1$), whereas drug-induced LQTS arise from HERG channel inhibition. They tested whether the LQT1 mutation A344V in the S6 region of KCNQ1 (this is the approximate location of the LA binding site in HERG) might render these "LA-insensitive" channels into "sensitive" ones. The mutation A344V induced voltage-dependent inactivation in homomeric KCNQ1 channels and shifted the voltage dependence of KCNQ1/KCNE1 channel activation by +30 mV. The mutation increased the sensitivity of KCNQ1/KCNE1 channels for bupivacaine 22-fold (KCNQ1wt/KCNE1, EC_{50} = 2431 ± 582 μmol/L, n = 20; KCNQ1A344V/KCNE1, EC_{50} = 110 ± 9 μmol/L, n = 24). Interestingly, effects of the mutant channels were dominant when both mutant and wild-type channels were present together. These results *could* indicate that certain forms of the LQTS may constitute a specific pharmacogenetic risk factor for arrhythmias during regional anesthesia!

Kawano et al[72] tested the effects of bupivacaine, levobupivacaine, and ropivacaine on reconstituted sarcolemmal adenosine triphosphate-sensitive K channels (K_{ATP}) from rat. They found that inhibition of these channels was stereoselective and tissue-specific: bupivacaine was more potent than levobupivacaine or ropivacaine, and bupivacaine more potently inhibited channels from the heart than from vascular smooth muscle.

Local anesthetic toxicity could relate more closely to drug actions on excitation-contraction coupling or contraction per se than to drug actions on the ion currents underlying membrane depolarization and repolarization. Chapman and Leoty[73] demonstrated that tetracaine could antagonize both the slow inward Ca current and Ca release from the sarcoplasmic reticulum (SR) in frog heart. McCaslin and Butterworth[74] reported that bupivacaine antagonized calcium oscillations in cardiomyocytes. Ca sparks are brief, spatially restricted elevations of cytosolic Ca that result from Ca release from ryanodine receptors in the SR. Ca sparks are the primary initiating events in cardiac excitation-contraction coupling. Zima et al[75] observed that tetracaine could almost completely eliminate these Ca sparks. Although tetracaine could completely inhibit the voltage-sensitive (Ca) release mechanism, tetracaine failed to antagonize Ca-induced Ca release from SR of guinea pig cardiomyocytes.[76] Mio et al[77] observed that bupivacaine could decrease the sensitivity of myofilaments to Ca in rat ventricular muscle. Local anesthetics can also interfere with events that terminate contraction. Dibucaine antagonized Ca uptake by SR vesicles from rabbit myocardium.[76]

Biochemical Actions of LAs

Not every investigator has assumed that ion channels underlie bupivacaine cardiac toxicity. Investigators have proposed multiple biochemical mechanisms that could underlie toxicity (Table 4). One result of the relatively low potency of LAs is that their relative affinity for their intended binding site (Na_V channels on peripheral nerves) is only slightly greater than their affinity for a long list of enzymes. For one example, Schönfeld

TABLE 4. Biochemical Actions of Local Anesthetics Possibly Linked to Cardiac Toxicity

Author	Year	Local Anesthetic	Enzyme or Process
Sperelakis and Lee[78]	1971	T	Na-K ATPase of chicken heart
Chapman and Miller[79]	1974	P	Antagonism of caffeine contracture in Na-free solution
de Boland et al[80]	1975	D, T, L, P	D + T Antagonize ATPase and Ca transport in rabbit skeletal muscle SR
Katz et al[81]	1975	L, PA	Antagonize calcium transport in canine cardiac SR
Suko et al[82]	1976	T, D, P, L	Antagonize Ca uptake, Ca-ATPase, Ca-dependant ATP-ADP phosphate exchange in rabbit skeletal muscle SR
Singh et al[83]	1977	T	Antagonize Ach-medicated positive cardiac inotropy in frogs
Voeikov et al[84]	1980	D, L, T, B	Antagonize catecholamine-stimulated adenylyl cyclase in frog erythrocytes
Chazotte and Vanderkooi[85]	1981	P, T, D	Antagonizes cytochrome *c* oxidase, durohydroquinone oxidase, succinate oxidase, reduced nicotinamide adenine dinucleotide oxidase, succinate dehydrogenase, succinate-cytochrome *c* oxidoreductase, NADH-cytochrome *c* oxidoreductase in beef heart
Tanaka and Hidaka[86]	1981	L, T, D	Antagonize Ca-calmodulin activation of cyclic nucleotide phosphodiesterase, myosin light chain kinase in chicken gizzard
Vanderkooi et al[87]	1981	T	Antagonizes mitochondrial F1-ATPase in bovine heart
Dorris[88]	1983	P, 2-CP, T	Antagonize monoamine oxidase in rat and mouse myocardium
Dabadie et al[89]	1987	L, B	Uncouple oxidative phosphorylation in rat liver
Schönfeld et al[90]	1992	B, QX-572	B is a protonophore in rat heart mitochondria
Butterworth et al[91]	1993	M, R, B	Antagonize basal, epinephrine-stimulated, and forskolin-stimulated cyclic AMP production in human lymphocyte adenylyl cyclase
Butterworth et al[92]	1997	M, R, B and others	Antagonize binding to β_2-receptors in human lymphocytes
Sztark et al[93]	1998	B, R	Uncoupling of oxygen consumption from phosphorylation in rat heart
McCaslin and Butterworth[74]	2000	B	Antagonizes calcium oscillations in cardiomyocytes from rat
Weinberg et al[94]	2000	B	Antagonizes acylcarnitine exchange in myocardial mitochondria from rat
Unami et al[95]	2003	B	Induce apoptosis in promyelocytic leukemia cells from human
Joseph et al[96]	2005	B	Antagonizes norepinephrine release from adrenergic nerve terminals in rat atria

B indicates bupivacaine; 2-CP, 2-chloroprocaine; D, dibucaine; L, lidocaine; M, mepivacaine; P, procaine; PA, procainamide; R, ropivacaine; T, tetracaine.

et al,[90] knowing that there was evidence for bupivacaine-induced uncoupling of mitochondrial energy mechanisms, tested whether this effect might be the result of decoupling or of proton leak. Curiously, bupivacaine increased the proton permeability of the inner membrane of rat myocardial mitochondria, most likely by serving as a protonophore itself! Of the various mechanisms listed on Table 4, some, or none of them *could* underlie the production of cardiac toxicity.

SUMMARY AND CONCLUSIONS

On the basis of these studies, we can make certain generalizations about LA cardiac toxicity and about the differences among racemic bupivacaine, *S*(−) isomer LAs, and other LAs. Clearly, if we believe clinical reports, there is something different about bupivacaine (and related potent LAs) that is not shared by less potent LAs, and this difference is not just that bupivacaine more potently inhibits cardiac Na_V channels (because it also more potently inhibits neuronal Na_V channels). In other words, if a phenomenon is to explain the findings reported in Dr. Albright's original report,[5] bupivacaine cannot merely be comparably more potent at this phenomenon as it is at clinical nerve block. More to the point, if we are to understand how bupivacaine (and related agents) differs from other LAs, we must focus on those phenomena where bupivacaine has disproportionately greater potency or where it produces an effect that other LAs usually do not produce.

Current whole animal data support the idea that bupivacaine has a reduced CV/CNS ratio for systemic toxicity. Thus, it is not surprising that case reports of cardiac toxicity from bupivacaine and related agents may report no preceding seizures. Current whole animal and isolated heart data suggest that bupivacaine is particularly prone to causing cardiac conduction system problems and arrhythmias relative to other LAs. Thus, it is not surprising that case reports specify arrhythmias as an early sign of cardiac toxicity. Current whole animal and isolated heart data also suggest that bupivacaine may cause severe negative inotropy, often at greater blood concentrations or greater doses than those sufficient to produce arrhythmias. Thus, it is not surprising that case reports often describe lack of response to prolonged resuscitative efforts with epinephrine. Current basic electrophysiologic studies provide explanations for the greater potencies of racemic bupivacaine then levobupivacaine, ropivacaine, or lidocaine at inhibiting Na_V channels with repetitive firing, providing a potential molecular explanation for arrhythmias and cardiac conduction failure. Current biochemical data describe myriad systems in which bupivacaine's greater potency than ropivacaine or lidocaine is roughly the same as its greater potency at nerve block. The importance of these many drug effects for clinical cardiac toxicity in particular, or human physiology in general, remains unknown.[97]

If we adhere to the logical tradition of William of Occam, avoiding a more complex explanation when a less complex one will do, we will select binding and inhibition of Na_V channels in the heart as the simplest explanation for cardiac toxicity from bupivacaine and related LAs. We know that bupivacaine binds more rapidly and longer than lidocaine to cardiac Na_V channels.[55] *R*(+) isomers bind cardiac Na_V channels more avidly than *S*(−) isomers (levobupivacaine and ropivacaine).[57] Local anesthetics inhibit cardiac conduction with the same rank order of potency as for nerve block and produce dose-dependent myocardial depression.[40] Nevertheless, although ascribing toxic adverse effects of LAs to their actions on Na_V channels is appealing, we do not have the data by which we can assign the toxicity to an effect on either excitation/conduction or contractility. In truth, we cannot exclude the possibility that some other mechanism may be as or more important. The fact that LAs bind and inhibit a host of cardiac ion channels and antagonize a wide array of biologic processes and enzymes may identify either one or more important mechanisms or represent an unfortunate distraction from the actual molecular mechanism of toxicity (Table 4).[7,74,77–94,97,98] Finally, although most investigators (and all animal models) assume that the mechanism(s) by which the various LAs produce CV toxicity are similar, this represents another unproven assumption. The various LAs may have subtle differences: just-barely-toxic concentrations of more potent agents (eg, bupivacaine) seem to have greater propensity for arrhythmias than just-barely-toxic concentrations of less potent agents (lidocaine); at a sufficiently great concentration, all LAs may produce myocardial depression.

It would be helpful for future investigators of LA CV toxicity to specify how their choices of (1) LA compound(s); (2) ion channel, enzyme, or assay; and (3) cell, tissue, or animal species reflect their assumptions and views about the mechanism(s). For experiments involving whole animals, our literature on LA toxicity would be improved if the assumptions regarding the following choices were routinely described: (1) general anesthesia (and specific drugs used) versus awake condition, (2) intubation and controlled ventilation versus spontaneous ventilation, and (3) suppression (versus no suppression) of seizures. Finally, different assumptions underlie differing definitions of CV toxicity and CV death.

I hope that future in vitro and in vivo studies will sort out several key issues: (1) Do LAs (and in particular bupivacaine) bind and inhibit all Na_V channel forms in the same way? (2) Do LAs have the same relative potency for each Na_V channel form? (3) Are there genetic variants (perhaps of Na_V channels) that render individuals more susceptible to bupivacaine cardiac toxicity? (4) How does myocardial damage from ischemic heart disease (or other chronic diseases) change the CV/CNS toxicity ratio? Does it increase susceptibility to cardiac toxicity? (5) What is the mechanism by which an LA concentration that would produce immediate toxicity if produced by a bolus injection can be well tolerated when reached by slow infusion? (6) Is the greater propensity for cardiac toxicity of bupivacaine (and related agents) relative to lidocaine the consequence of a single, unique process at which bupivacaine has disproportionately greater toxic potency than lidocaine or is it the result of the accumulated effects of a multiple processes in which bupivacaine has consistently greater toxic potency than lidocaine? Finally, I find it perversely amusing to consider how intravenous lipid therapy, which I regard as the most important advance in treatment of LA cardiac toxicity, has emerged despite our lack of understanding of either specific mechanisms or the best model of bupivacaine toxicity.

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