Stereospecific Effect of Bupivacaine Isomers on Atrioventricular Conduction in the Isolated Perfused Guinea Pig Heart

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Background: The local anesthetic bupivacaine is an equal mixture of two optically active isomers known to exert different cardiotoxic profiles in vivo. Enantiomer-specific forms of bupivacaine may have differential effects on cardiovascular function, specifically on cardiac electrophysiology. The authors’ aim was to determine if there were any direct functional differences in the cardiac effects of bupivacaine isomers. The isolated heart was used to avoid possible indirect cardiac effects of bupivacaine, such as autonomic nervous and hormonal influences, as well as preload and afterload factors.

Methods: The hearts of 12 ketamine-anesthetized guinea pigs were perfused with Krebs-Ringer’s solution (97% oxygen, 3% carbon dioxide) at constant perfusion pressure using the Langendorff technique. Atrial and ventricular bipolar electrodes were placed to measure heart rate (HR) and atrioventricular (AV) conduction time. Left ventricular pressure (LVP), coronary flow, and inflow and outflow oxygen tensions were also measured. Oxygen delivery, oxygen consumption (MVO2), and percentage of oxygen extraction were calculated. Each heart was perfused with increasing randomized concentrations (0.5, 1, 5, 10 μM) of both isomers and the racemate of bupivacaine.

Results: Racemic and isomeric bupivacaine equally and dose dependently decreased cardiac function. At 10 μM bupivacaine these changes were: HR, −17 ± 2%; LVP, −50 ± 3%; coronary flow, −20 ± 4%; and MVO2, −46 ± 4%. The (+) isomer significantly prolonged AV conduction compared with the racemate and the (−) isomer at all concentrations. At 10 μM, AV time was 54 ± 6% longer with the (+) isomer and 30 ± 4% longer with the (−) racemate than with the (−) isomer. The greater delay in AV time with the (+) than the racemate or (−) isomer led to a second-degree AV dissociation in 10 of 12 of hearts treated with (+) bupivacaine.

Conclusions: This study shows that bupivacaine has an enantiomer-specific effect to delay AV conduction and to produce second-degree AV dissociation in the isolated perfused heart. This suggests that bupivacaine isomers probably have differential effects on one or more ion-specific channels regulating AV conduction. Other measured direct cardiac effects of bupivacaine appear to be independent of the isomeric form.

(Key words: Anesthetics, local; bupivacaine; stereoisomers. Heart: AV conduction; contractility; coronary flow; isolated; oxygen consumption; rate.)

The cardiotoxicity of bupivacaine and other local anesthetics is well described,1,3 yet there is increasing interest in a careful evaluation of the isomer-specific differences of local anesthetics, particularly bupivacaine.4–6 This interest derives from the lower cardiac toxicity of ropivacaine, a single isomer, at an equivalent local anesthetic potency with racemic bupivacaine.7–9 Local anesthetics act as neuronal sodium channel blockers, so an isomer-specific interaction of local anesthetics with sodium channel receptor sites appears likely. Direct application of bupivacaine isomers to vasomotor and other cardioactive areas of the rat medulla (nucleus tractus solitarius) has shown not only the importance of the central nervous system to the cardiotoxic effects of local anesthetics10 but also to the stereoselectivity of the effect.11

The current study was designed to determine whether bupivacaine isomers exhibit direct stereospecific effects on the heart, independent not only of central neuronal and humor interactions but also of dynamic ef-
fected due to changes in preload and afterload volume. Differential effects would strongly suggest that there are specific sites of action by the isomeric forms. We have used the isolated perfused heart preparation to assess, ex vivo, direct stereospecific effects of several volatile and intravenous anesthetics in recent studies.12,15

Materials and Methods

After approval was obtained from the Animal Studies Committee of the Medical College of Wisconsin, 30 mg ketamine and 1,000 units of heparin were injected intraperitoneally into each of 12 English short-haired, albino guinea pigs (weighing 300–350 g). After the animals were killed, hearts were rapidly excised during continuous retrograde aortic perfusion with cold, oxygenated, modified Krebs-Ringer’s solution equilibrated with 97% oxygen and 3% carbon dioxide (pH, 7.37 ± 0.03; P O₂, 591 ± 13 mmHg, and P CO₂, 26 ± 1.6 mmHg). A description of the surgical and preparatory methods was reported in detail previously.14,15

After placement in the Langendorff apparatus, each heart was perfused through the aortic cannula with nonrecirculated and oxygenated Krebs-Ringer’s solution at a perfusion pressure of 55 mmHg (75-cm fluid column). The perfusion solution had the following composition: 137 mm Na⁺, 4.5 mm K⁺, 1.2 mm Mg²⁺, 2.5 mm Ca²⁺, 134 mm Cl⁻, 15.5 mm HCO₃⁻, 1.2 mm H₂PO₄⁻, 11.5 mm glucose, 2 mm pyruvate, 16 mm mannitol, 0.05 mm ethylene-diamine-tetraacetic-acid, and 5 units/l insulin. Perfusion and bath temperature were maintained at 37 ± 0.2°C using a thermostatically controlled water circulator.

Isovolumetric left ventricular pressure (LVP) was continuously recorded with a transducer (Gould-Statham P23, Gould Electronics, Elk Grove, IL) connected to a thin, saline-filled latex balloon (Hugo Sachs Electronik KG, March-Hugstetten, Germany) inserted into the left ventricle through the mitral valve from a cut in the left atrium. The balloon volume was adjusted to maintain a diastolic LVP of 0 mmHg during the initial control period so that any increase in diastolic LVP reflects an increase in left ventricular wall stiffness or diastolic contracture. The volume of the balloon was unchanged during the experiment. Coronary perfusion pressure was recorded continuously with a transducer (Gould-Statham P23, Gould Electronics) connected directly to the perfusion system close to the aortic root. Two pairs of bipolar silver electrodes (Teflon-coated silver; diameter, 125 μm; Cooner Wire Co., Chatsworth, CA) were placed on the right atrium and the pulmonary conus to monitor atrioatrial and atrioventricular time. As detailed in a previous publication,16 spontaneous atrial heart rate was determined from the right atrial beat-to-beat interval. Atrioventricular (AV) conduction time was determined from the right atrial to the right ventricular pulmonary conus beat-to-beat interval (fig. 1) by an electric timer. Atrioventricular conduction time includes conduction not only through the AV node but also across Purkinje fiber and ventricular myocytes. First-degree AV dissociation (1:1 AV conduction) was defined as AV

![Fig. 1. Four original atrial and ventricular electrograms obtained during control and treatment with 1, 5, and 10 μM (+) bupivacaine. Coated silver wire recording electrodes were placed on the right atrium and on the right ventricular pulmonary conus. The electrograms were displayed on a fast-writing, high-resolution chart recorder. The dashed lines show the electric threshold limit (80% of the amplitude of the electrogram [ECG] upstroke wave) for onset of offset of the timing trigger between atrial and ventricular pulses. The time interval (solid horizontal bar) between the atrial and ventricular pulses describes AV conduction time. At 10 μM (+) bupivacaine there is no ventricular pulse following the atrial pulse, which indicates second-degree ativoventricular dissociation. With increasing bupivacaine concentration, the period between atrial pulses increases, which indicates a decrease in atrial heart rate.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931822/)}
delay greater than 70 ms (normally AV delay is 60-65 ms in the guinea pig). Second-degree AV dissociation (slowed ventricular response) was characterized as type I (Wenckebach), a progressive lengthening of the AV interval leading to a nonventricular-conducted atrial beat, or type II (Mobitz), a normal AV conduction delay with an occasional nonventricular-conducted atrial beat. All measurements were taken at the last minute of each 15-min experimental period. Coronary inflow was measured at constant pressure and at constant temperature by a transit-time in-line ultrasound flow meter (Research Flowmeter T106, Transonic Systems, Ithaca, NY). To determine maximal coronary flow and the possible effect of bupivacaine on altering coronary flow reserve, adenosine (0.2 ml of a 200-μM stock solution) was injected directly into the aortic root cannula during the initial control period and after the last control reading. Coronary sinus effluent was collected by placing a small catheter into the right ventricle through the pulmonary artery after ligating both vena cava.

Coronary inflow and outflow oxygen tension were measured continuously on-line by temperature-controlled miniature Clark electrodes (Instech 203B; Instech Laboratories, Plymouth Meeting, PA) calibrated periodically with 0%, 21%, and 97% oxygen to adjust oxygen tension (P02) to 0, 150, and 650 mmHg, respectively. The miniature Clark electrodes were placed directly into the aortic inflow cannula and pulmonary artery (coronary sinus) cannula after ligating the inferior and superior vena cava. These measurements were verified off-line with an intermittently self-calibrating gas analyzer (Radiometer ABL-2; Metron Chicago, Des Plaines, IL). Oxygen delivery was calculated as inflow oxygen tension in millimeters of mercury, multiplied by oxygen solubility (2.1 μL per ml Krebs-Ringer’s solution at 760 mmHg oxygen and 37°C), multiplied by coronary flow (coronary inflow, ml/min), and then divided by the wet weight of each heart (2.1 ± 0.2 g). Oxygen tension of the inflow perfusate was kept constant. Percentage oxygen extraction was calculated as the difference between inflow and outflow oxygen tensions multiplied by 100, divided by inflow oxygen tension. Similarly, myocardial oxygen consumption (MVO2) was calculated as oxygen solubility multiplied by the difference between inflow and outflow oxygen tensions times coronary flow per gram of wet heart tissue.

Atrial and ventricular electrograms, heart rate, spontaneuous AV conduction time, outflow oxygen tension, coronary flow, systolic and diastolic left ventricular pressure, and perfusion pressure were displayed on a fast-writing (3 kHz), high-resolution, eight-channel chart recorder (Astro-Med, West Warwick, RI).

Protocol

Maximal vasodilation was tested with adenosine and at least 30 min was allowed for stabilization before initial control measurements were obtained. The hearts were perfused with 0.5, 1, 5, and 10 μM (+), and (−) isomeric, and (±) racemic bupivacaine (Astra USA, Westboro, MA) injected directly into the preoxygenated Krebs-Ringer’s solution. Each heart was perfused for 15 min with each isomer and the racemate at each concentration. Each experimental interval was followed by a 15-min drug-free washout period, after which a different bupivacaine concentration was given. The drug-free washout period between the different isomers and between the racemate was 30 min. The concentration of a given isomer and the isomeric form (or racemic mixture) were randomized. Measurements were obtained during the last minute of exposure to each concentration and during the last minute of each control (washout) period. All variables returned to control during the drug-free periods, and these data are not presented in detail. After the last control period, adenosine was again injected at the initial concentration into the aortic root to observe any change in maximal coronary flow response.

Statistical Analysis

All data are expressed as means ± SEM. Individual statistical comparisons of the means were made following analysis of variance for repeated measures (Super Anova 1.11 software for Macintosh, Abacus Concepts, Berkeley, CA). The following comparisons were made: increasing concentrations of bupivacaine isomers and racemate versus the initial control; subsequent controls during washout versus initial control values; and each concentration of the isomers or racemate versus the same concentration of the racemate and the isomer. Least significance difference post hoc tests were used to compare means. The significance of incidence (chi-squared analysis) of AV dissociation was also determined (Statview software for Macintosh). Differences among means were considered significant when P ≤ 0.05. Atrioventricular conduction time was described as a linear function of bupivacaine concentration using
best-fit linear regression. Statistical differences in the slopes obtained were compared using homogeneity of slope comparison tests.

**Results**

**Heart Rate, Atrioventricular Conduction Delay, and Left Ventricular Pressure**

Atrial heart rate decreased on average by 17.3 ± 1% at 10 μM bupivacaine with no significant differences among the isomers or racemate at increasing equimolar concentrations (table 1). The decreases in atrial heart rate were concentration dependent, except at 0.5 μM bupivacaine, for both isomers and the racemate.

Atrioventricular conduction time (fig. 2) increased (first-degree AV dissociation) significantly with increasing concentrations of the isomers and the racemate in a concentration-dependent manner. There were significant delays in AV conduction among the (+) and (−) isomers and racemic bupivacaine at all concentrations (fig. 2). At increasing concentrations the differences in AV delay were more pronounced, such that the (+) isomer prolonged AV conduction time significantly more than the (−) isomer and the racemate prolonged AV time intermediate between the (+) and (−) bupivacaine isomers. The slope of the bupivacaine concentration-AV response curve for the (+) isomer (8.4) was more than two times the slope for the (−) isomer (3.7) at identical y intercepts. At 10 μM bupivacaine the incidence of second-degree type II (Mobitz) and second-degree type I (Wencke-

![Fig. 2. Concentration-response curves (dashed lines) for the optical isomers and the racemate of bupivacaine on atrioventricular conduction time in 12 isolated perfused guinea pig hearts beating spontaneously. Data were analyzed using best-fit linear regression. Y intercepts are nearly identical in the three groups for an average of 62.7 ms, however, the average slope of the (+) bupivacaine group is more than double that of the (−) bupivacaine group, and the slope of the racemate lays between that of the isomers. Control values between the individual concentrations are not displayed. At 10 μM only 2, 8, and 11 of 12 hearts treated with (+), (−), and (−) bupivacaine, respectively, remained in sinus rhythm and are displayed in this graph (see fig. 3).](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931822/)

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Coronary Flow and Oxygen Use

Initial and final maximal coronary flow responses to bolus injection of adenosine were similar (13.8 ± 0.7 ml·g⁻¹·min⁻¹ and 12.9 ± 0.8 ml·g⁻¹·min⁻¹, respectively). Coronary flow, initially 6.8 ± 0.6 ml·g⁻¹·min⁻¹, was decreased by bupivacaine in a concentration-dependent manner by 19 ± 4% at 10 μM, but the two isomeric and the racemic forms exhibited no differences in their effects on coronary flow (table I). Myocardial oxygen consumption, initially 72 ± 4 μl·g⁻¹·min⁻¹, decreased similarly at the higher concentrations with each isomer and the racemate of bupivacaine to 39 ± 4 μl·g⁻¹·min⁻¹ at 10 μM (fig. 5). This decrease in MVO₂, which was significant at concentrations greater than 0.5 μM, accompanied the decreases in LVP and heart rate. Percentage oxygen extraction was decreased only at 10 μM for each form of bupivacaine (table I). Oxygen supply (delivery) relative to oxygen demand (MVO₂), an index of coronary flow reserve, increased slightly only at the highest bupivacaine concentration (fig. 6). Between the (+) isomer, the (−) isomer, and the racemic mixture of bupivacaine, there were no differences in MVO₂, percentage oxygen extraction, or oxygen delivery/MVO₂ at equimolar concentrations.

Discussion

Electric, functional, and metabolic effects of optical isomeric and racemic forms of bupivacaine on the isolated heart were investigated. We observed that equimolar concentrations of the three forms of bupivacaine produced no significant differences in any measured variable except AV conduction. The (+) isomer of bupivacaine prolonged AV conduction the most and produced the greatest incidence of second-degree AV dissociation, whereas the racemic form of bupivacaine had an intermediate effect on AV conduction and on the incidence of second-degree AV dissociation between the (+) and (−) isomers. Atrial slowing was similar with each form of bupivacaine, so the sinus rate influence on AV conduction does not appear to be a factor in the AV conduction differences exhibited by the isomeric forms. Indeed, if hearts had been paced, we would have expected a more exaggerated prolongation of AV conduction time and an increase in the incidence of second-degree AV dissociation with (+) bupivacaine.

Each isomer and the racemate of bupivacaine de-
DIRECT STEREOSPECIFIC CARDIAC EFFECTS OF BUPIVACAINE

Fig. 4. Effect of four concentrations of the optical isomers and the racemate of bupivacaine on systolic left ventricular pressure in 12 isolated perfused guinea pig hearts. Values are means ± SEM of initial and final controls and individual concentrations. Control values between the individual concentrations are not displayed. There were no significant differences among the three forms of bupivacaine at a given concentration. Each value except 0.5 μM bupivacaine (each form) is significantly different from the preceding control value.

![Graph showing systolic LVP vs Bupivacaine concentration](image)

Fig. 5. Effect of four concentrations of the optical isomers and the racemate of bupivacaine on myocardial oxygen consumption in 12 isolated perfused guinea pig hearts. Values are means ± SEM of initial and final controls and individual concentrations. Control values between the individual concentrations are not displayed. There were no significant differences among the three forms of bupivacaine at a given concentration. Each value except 0.5 μM bupivacaine (each form) is significantly different from the preceding control value.

![Graph showing MVO2 vs Bupivacaine concentration](image)

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tion) was not observed with these concentrations of bupivacaine, the higher incidence of third-degree AV Mobitz type II dissociation with (+) bupivacaine could be clinically relevant because Mobitz type II blocks have a higher potential to progress to complete heart block, compared with second-degree Wenckebach type I dissociation. The only stereoselective difference in response to bupivacaine stereoisomers in isolated hearts, that on AV conduction, indicates that ion channels can be differentially effected by isomers of local anesthetics in cardiac conduction tissue, as demonstrated for neuronal transmission.13

In general, stereoselectivity is a function of the potency or affinity of the more potent isomer to its selective target site. Stereoselective effects of local anesthetics on neuronal Na⁺ channels have been well documented for more than 20 yr.17–20 Akerman and colleagues17,18 showed that neuronal tissue uptake was not a factor and that there was no stereoselectivity for serum protein binding or for membrane partitioning. Pure optical isomers appear to be useful for examining effects of local anesthetics on the cardiac conduction system. Ropivacaine, a stereoselective S (−) isomer with a chemical structure similar to that of bupivacaine, is now used clinically. Although it has a lipid solubility lower than that of bupivacaine, ropivacaine’s protein binding and anesthetic profile appear similar to that of bupivacaine.2 The potential of ropivacaine to lead to development of dysrhythmias, and other adverse cardioelectrophysiologic effects, appears less when compared with presumably equipotent concentrations of racemic bupivacaine.9 Furthermore, the duration of bupivacaine-induced cardiac effects appear to be longer than those due to ropivacaine, an effect that may depend on the higher lipid solubility of bupivacaine.

Bupivacaine more frequently slows atrial conduction,20 prolongs AV conduction time, and, at higher concentrations, results in second-degree AV dissociation compared with other local anesthetics.21–24 In addition, the time to return to sinus rhythm is slower with bupivacaine than with other local anesthetics.25 This difference in recovery time from AV dissociation and AV delay may be related to bupivacaine’s greater lipid solubility and protein binding capacity, which would tend to decrease the rate of washout from cardiac tissue. Indeed, Reiz and Nath20 have reported a slower washout of bupivacaine than of lidocaine from cardiac tissue. However, Mazoit et al.27 showed that, in isolated, paced rabbit hearts perfused at constant flow, different cardiac effects of the isomers and racemate of bupivacaine are not due to differences in myocardial uptake and disposition kinetics but rather to differences in pharmacodynamic effects. They reported that the increase in QRS duration with 25 μM bupivacaine was least with the (−) isomer, intermediate with the racemate, and greatest with the (+) isomer and that AV block occurred in each heart with each isomer except in one third of the hearts perfused with the (−) isomer. As in our model, the
bioavailability of the isomers on the target side of the channel was not investigated in their model,
but their results are qualitatively similar to ours. The observed quantitative differences may be related to the different species used, the concentrations selected, and the method of cardiac perfusion.  

Our study in the isolated guinea pig heart shows clearly that cardiac variables other than AV conduction are not differentially affected by bupivacaine isomers. But because stereoselectivity was observed for AV conduction, our study suggests that local anesthetics interact with a specific receptor site or sites involved in conducting the cardiac impulse between the atria to the ventricles. The specific site is unknown. Phases of the cardiac action potential are caused by temporal changes in the permeability of the cell membrane to Na⁺, K⁺, and Ca²⁺ ions, and the channels controlling permeability to these ions are affected by local anesthetics. Bupivacaine interacts with cardiac Ca²⁺ and K⁺ channels, and a change in cell flux of these ions affects AV conduction, but, as for neuronal tissue, the fast Na⁺ channel is probably the primary cardiac target site for the differential effect of bupivacaine isomers. Thus it appears an anomaly that bupivacaine delayed only AV conduction time in a stereoselective way, because AV delay is thought to be mediated primarily through L-type Ca²⁺ channels, and the other variables measured that depend on these L-type Ca²⁺ channels were not stereoselectively altered. Although the AV node greatly delays impulse conduction, action potential conduction may be delayed more by (+) bupivacaine than by (−) bupivacaine during conduction through atrial myocytes, Purkinje fibers, or ventricular myocytes, which have conduction properties more dependent on fast Na⁺ channels.

In ventricular myocytes, local anesthetics block Na⁺ channels in the relatively depolarized active (phase 0 upstroke) and inactive (phase 3 plateau) states. But bupivacaine blocks Na⁺ channels in the inactive state (plateau phase) much more avidly than does lidocaine. Because bupivacaine binds Na⁺ channels so tightly, the half-life for recovery is much longer. Furthermore, because the channel block is intensified with each beat, this may explain the greater occurrence of conduction block by bupivacaine than by other local anesthetics. Therefore, it is also possible that the (+) isomer of bupivacaine has a greater avidity for the Na⁺ channel in certain cardiac cells in the conduction pathway in the inactive state than does the (−) isomer. This may also explain why the clinically used (±) racemic form of bupivacaine has an intermediate effect. Bupivacaine's differential isomeric effects on AV conduction could prove useful as a tool to differentiate the ion currents responsible for the AV nodal action potential. Recently, stereoselective effects of bupivacaine have been demonstrated for the fast Na⁺ channel in guinea pig ventricular myocytes by patch-clamp techniques. We have preliminary evidence that the stereospecific effect of bupivacaine on the cardiac Na⁺ channel is dependent on cyclic adenosine monophosphate cAMP.

Two major types of cardiac action potentials are observed in the conducting system of the heart. The fast-responding action potential occurs in nearly all cardiac tissues, including the specialized conducting Purkinje fibers. This potential is due primarily to the fast inward Na⁺ current. Only in the sinoatrial node and the AV node is the slow action potential observed. Although the AV nodal potential depends predominantly on the slow inward current carried mainly by Ca²⁺, the Na⁺ channel may also play a role. It is unlikely that bupivacaine exhibits a stereoselective effect on cardiac K⁺ and Ca²⁺ channels because bupivacaine isomers and the racemate showed equivalent effects on other variables, that is, heart rate, IJV, and coronary flow, which are primarily modulated by changes in these currents.

We suggest that a specific receptor site on or within the Na⁺ channels on either side of the AV node and the fast specialized conduction tissue is blocked more by the (+) isomer than by the (−) isomer and that this causes a difference in Na⁺ conductance. A possible explanation is that atrial to AV nodal or AV nodal to ventricular coupling could be a critical transition site for cardiac impulse conduction, because the region has a low margin of safety for transmission. Bupivacaine, in blocking to Na⁺ channels at this region, may greatly delay the initial rise of the action potential, thus adding to the overall conduction time. Once the cardiac action potential begins to propagate in Purkinje and ventricular muscle cells, Vmax might be less affected and conduction more rapid. Vanhoutte et al. demonstrated stereoselective effects of enantiomers of bupivacaine on electrophysiologic properties of guinea pig papillary muscle. They found that (+) bupivacaine slowed Vmax (phase 0 upstroke) and increased action potential duration more than (−) bupivacaine. The recent study by Valenzuela et al. clearly demonstrated a stereoselectivity of bupivacaine for fast cardiac Na⁺ channels. The results of these studies correspond with our observa-
tions on bupivacaine's stereoselective effect on cardiac impulse conduction. Detailed electrophysiologic and patch-clamp studies will be necessary to test further this postulate.

In conclusion, selection of the (−) optical isomer of bupivacaine may afford a definite clinical advantage over the racemate or the (+) isomer in that one or more cardiac side effects may be eliminated or attenuated. But care must be taken when extrapolating our results to the clinical setting. Our experiments were done in isolated hearts perfused with a oxygenated crystalloid solution devoid of plasma and cells. Competitive plasma protein binding, hypoxia and acidosis, and indirect cardiac effects are factors that may shadow any stereoselective effect in vivo. In addition, central neural activation or inhibition in vivo may obscure the stereoselective effect of bupivacaine on prolonging AV conduction or on producing dysrhythmias.

References

of calcium-mediated slow action potentials in guinea pig ventricular muscle. J Pharmacol Exp Ther 1987; 242:1001–5
38. Graf BM, Bosnjak ZJ, Martin E, Stowe DF, Kwok WM: Stereoselectivity of bupivacaine on cardiac Na+ channels is dependent on cyclic adenosine monophosphate (abstract). Anesthesiology 1995; 83(Suppl):A304