Title: IS IT POSSIBLE TO RESUSCITATE A BUPIVACAINE-INTOXICATED HEART?

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Introduction. Bupivacaine (Marcaine) may induce arrhythmias and cardiac arrest resistant to resuscitation, in man and animals, when injected intravenously.[1] Since inadvertant intravenous injection of bupivacaine (BUP) remains a possible complication of regional anesthesia, it is essential to devise methods of restoring normal electrical activity in the BUP-intoxicated heart. In this study we have tried to reverse BUP-induced suppression of primary and secondary pacemakers, slowed conduction and electrical inexcitability.

Methods. Right atria (RA) of guinea pig hearts and dog ventricular Purkinje fibers (PF) were isolated and superfused in a small volume perfusion chamber with Tyrode's solution containing either Hepes buffer or bicarbonate and saturated with 100% $O_2$ or 95% $O_2$-5% $CO_2$. Their electrical activity was recorded with intracellular glass microelectrodes. Changes in the rate of spontaneously beating RA (reflecting automatic activity of the sino-atrial node) were measured. Conduction velocity in PF was measured between two microelectrodes kept at a constant distance away from the stimulation electrode. PF were either beating spontaneously or stimulated at a rate of 60-90/min. After an equilibration period all preparations were superfused for 45-90 min with Tyrode's solution containing 10 mg/l Bup. During this time we tried to reverse BUP-induced electrical changes by applying massive doses of catecholamines (norepinephrine and epinephrine 0.5-3 mg/l), changing pH of the perfusate (by adding bicarbonate or decreasing $CO_2$ content), increasing sodium concentration (140 to 200 mM/l) or superfusing with hypertonic glucose (50 to 100 mM).

Results. BUP slowed down the spontaneous rate of RA to below 40% of the control rate. Catecholamines in increasing concentration were able to induce sustained reversal of bradycardia. Superfusion with alkalotic solutions also produced reversal of bradycardia with the spontaneous rate exceeding control values when extracellular pH was above 8. BUP in PF decreased conduction velocity, leading in 3 out of 5 fibers to conduction block and inexcitability (Fig.1). In 2 out of 5 fibers catecholamines were able to restore excitability and enabled conduction of the electrical impulses (Fig.1), although conduction velocity remained slow. While the reversal produced by catecholamines was sustained, superfusion with alkalotic solutions produced only transient improvement of the conduction velocity. Increasing extracellular sodium concentration was without effect. Superfusion with hypertonic glucose and catecholamines reinduced spontaneous automaticity in PF at a rate of 10-40/min, but those fibers could not be excited by the current pulses applied from the stimulator.

Discussion. Automaticity in the sinus node depends to a large extent on the background calcium current. Catecholamines and alkalosis are known to increase this current which may explain their beneficial effect. BUP produces slowed conduction and inexcitability in PF by suppressing fast sodium current. Reversal of this suppression may be produced by membrane hyperpolarization or a decrease in the amount of the drug bound to sodium channels. Beneficial effects of catecholamines in some fibers may be explained by hyperpolarization (see Fig.1) while alkalosis probably decreases the amount of charged form of the drug in the cells. Although it is possible to reverse the sinus bradycardia induced by BUP, improvement of conduction or restoration of excitability which was decreased by the drug, is difficult but not impossible. However, massive doses of catecholamines exceeding those used during resuscitation were necessary. In this study we have superfused the preparations with a constant concentration of BUP, which may occur in blood only transiently during overdose. Beneficial effects of the above interventions could be more pronounced with lower concentrations of BUP present.

Reference.

1. Kotelko D, Shnider S, Dailey P, Brizgys R, Levinson G, Shapiro W, Koike M, Rosen M: Bupivacaine-induced cardiac arrhythmias in sheep. Anesthesiology 60: 10-18, 1984.

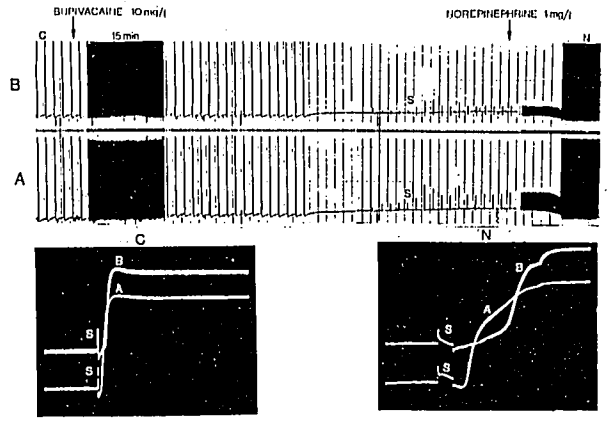


Fig.1 Upper panel - recordings of the two action potentials (B,A). After application of BUP (10 mg/l) for 15 min, PF became inexcitable. Increasing stimulus strength (s-stimulus artifact) was without effect. Subsequent application of norepinephrine (1 mg/l) restored excitability by inducing hyperpolarization. Lower panel oscilloscope photographs of upstrokes of action potentials B and A in control conditions (C) and after restoration of excitability by norepinephrine (N). Although conduction was restored, conduction time remains markedly decreased by comparison to control (C). Duration of the stimulus (S) is increased.