

Title: CELLULAR MECHANISMS OF CARDIAC ARRHYTHMIAS INDUCED BY BUPIVACAINE

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Introduction. Cardiac arrhythmias are due to disturbances of conduction, disturbances of automaticity, or both. Bupivacaine (Marcaine) was previously reported to induce cardiac arrhythmias and death in man and animals.¹ We have investigated the effects of bupivacaine (BUP) on conduction and automaticity in isolated Purkinje fibers (PF) to explain the nature of arrhythmias induced by this drug.

Method. Purkinje fibers with attached ventricular muscle (VM) were isolated from dog ventricles and superfused in a small volume perfusion chamber with Tyrode's solution (4 mM K, 2.7 mM Ca, temp. 37°C), gassed with 95% O₂-5% CO₂. Their transmembrane potentials were recorded with intracellular glass microelectrodes. Automaticity was induced by low K solutions (1-2 mM K) or norepinephrine (0.1 mg/l). To induce depolarization similar to that which occurs in the pathological myocardium in-vivo, PF were stretched or superfused with high K (8 mM) solutions. Conduction velocity was measured with two microelectrodes impaled at a constant distance away from the stimulation electrode. In some experiments PF were placed in a double compartment chamber and the action potentials were recorded on both sides of the partition. The action potentials on one side were prolonged by removing Ca and addition of EDTA (2-5 mM). This generated electrotonic tails on the other side.² Effects of BUP on the amplitudes of those tails were tested. All fibers were stimulated at a rate 60-90/min. Preparations were exposed sequentially to BUP in concentrations of 1 - 10 mg/l for 30 sec to 45 min. Data were analyzed statistically by Student "t" test (P < 0.05 significant).

Results. Physiological automaticity (slow diastolic depolarization) was quickly suppressed (30 sec-2 min) by all concentrations of BUP used. BUP also suppressed pathological oscillations at low levels of membrane potential (-50 to -30 mV) induced by low K and norepinephrine. Duration of the action potential measured at 50% of repolarization was decreased (Fig.1). The upstroke velocity and amplitude were decreased in a dose dependent manner leading to a decrease of conduction velocity (Fig.1). In 4 out of 7 fibers, BUP (10 mg/l) led to conduction block and total inexcitability after 15 to 30 min of superfusion. In depolarized fibers (hyperkalemia, stretch), BUP abruptly induced conduction block and inexcitability even in lower concentrations. Amplitude of electrotonic tails (reflecting changes of passive membrane properties) was practically unchanged.

Discussion. Ventricular arrhythmias induced by BUP may be due to slowing of the conduction velocity, induction of unidirectional block (eg. in PF-VM

junctions), and the occurrence of reentrant excitation. BUP-induced arrhythmias certainly are not due to increased automaticity or the occurrence of pathological oscillations, which are actually suppressed by BUP. Decreased conduction velocity is apparently due to a reduction of the inward membrane currents and not to the changes in passive (cable) membrane properties. Effects of BUP were more marked in the "pathological" PF which implies that patients with ischemic heart disease and circulatory insufficiency may be much more sensitive to BUP overdose.

References.

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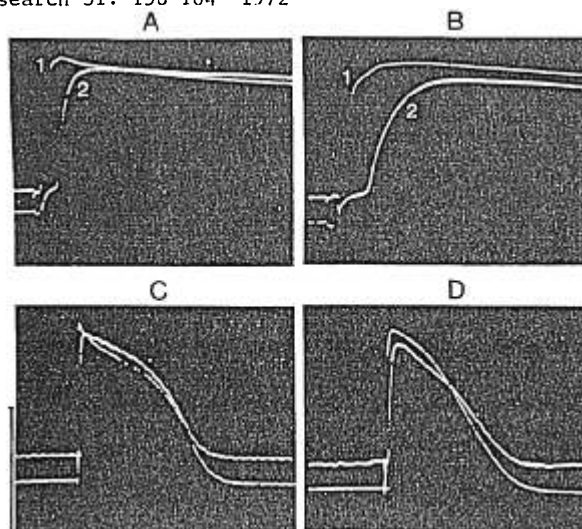


Figure 1. Effects of BUP (10 mg/l) on the interelectrode conduction time (A,B) and action potential configuration (C,D). Records A and B show upstrokes (at fast sweep speed of the oscilloscope) of the two action potentials (marked 1 and 2) shown in C and D at normal sweep speed. Vertical calibration 100 mV, horizontal 5 msec for A and B, 50 msec for C and D. Conduction time recorded in control conditions (A) was markedly prolonged by superfusion with BUP for 30 min (B). Calculated conduction velocity was decreased from 2.1 msec (A) to 0.95 msec (B).