

**TITLE:** NALOXONE POTENTIATES INOTROPIC BUT NOT CHRONOTROPIC EFFECTS OF ISOPROTERENOL *IN VITRO*

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Naloxone (NAL) potentiates the effects of adrenergic agonists when administered to dogs subjected to hemorrhagic shock, and this effect has been attributed to naloxone's actions at opiate receptors. Recently we reported that in the absence of opioids, naloxone potentiated the inotropic effects of high doses of isoproterenol in guinea pig papillary muscles paced at 0.1 Hz.<sup>1</sup> We postulate that NAL might be useful as an adjunct to adrenergic therapy if it potentiates the inotropic but not chronotropic effects of low dose isoproterenol.

To determine the effects of NAL on paced papillary muscles and spontaneously contracting atria in the presence or absence of isoproterenol  $2 \times 10^{-8}$  M, muscles were removed from anesthetized guinea pigs, superfused with modified Tyrode solution at 36.5°C and bubbled with O<sub>2</sub>:CO<sub>2</sub> (95%:5%). After stabilization, atria were assigned to one of four groups (n=7 per group). Groups I & II received vehicle pretreatment, and groups III and IV received isoproterenol pretreatment. After pretreatment, vehicle (groups I & III) or NAL  $10^{-6}$  M to  $3 \times 10^{-5}$  M was added (groups II & IV). After stabilization, papillary muscles were pretreated with isoproterenol, paced at 0.1 Hz and then

treated with vehicle (group V) or NAL (group VI). Changes in rate of tension development (dT/dt) were determined as percent of control. Comparisons between vehicle and NAL treated groups were made for heart rate (HR) and dT/dt using unpaired Student's t tests.

In atria without isoproterenol pretreatment (groups I & II), NAL decreased HR by 13 beats/min relative to vehicle (p=.03), and had no significant effect on dT/dt. In atria, pretreatment with isoproterenol (groups III & IV) increased HR by  $122 \pm 19$  beats/min and increased dT/dt to  $278 \pm 60$  % of control. In these atria, NAL increased dT/dt an additional 32% relative to vehicle (p=.0002), and had no significant effect on HR. In papillary muscles, with isoproterenol pretreatment (groups V & VI), NAL increased dT/dt by 89% relative to vehicle (p=.05).

From these data, we conclude that naloxone does not have any significant intrinsic inotropic effect in atria, and previously we showed that it had no intrinsic effect on ventricular tissue.<sup>1</sup> Naloxone does however potentiate the inotropic effects of isoproterenol in both atrial and ventricular tissue, without potentiating isoproterenol's chronotropic effects. Since naloxone exerts these effects in the absence of opioids, naloxone might be acting at a sight other than the opiate receptor. Though extrapolation of our findings to the clinical situation is premature, naloxone (or it's stereoisomer) may be useful as an adjunct to adrenergic administration when increased inotropy without increased chronotropy is desired.

1. FASEB J 4:A953, 1990.

## A588

**Title:** ACTIONS OF HALOTHANE, ENFLURANE AND ISOFLURANE ON PURKINJE FIBERS IN NONINFARCTED AND INFARCTED CANINE HEARTS

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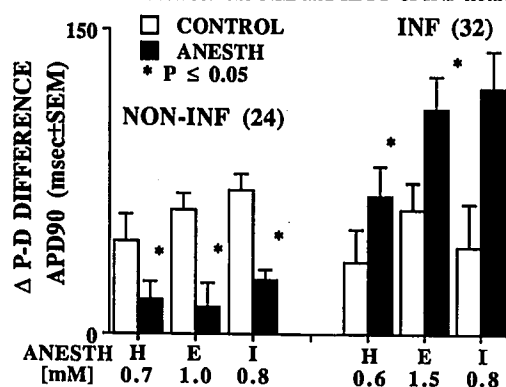
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The actions of anesthetics on the repolarization characteristics of Purkinje fibers (PF) may differ in noninfarcted (NIF) and infarcted (INF) hearts and have an important influence on conduction and the generation of re-entrant activity<sup>1</sup>. The present study compares the *in vitro* actions of halothane (H), enflurane (E) and isoflurane (I) on regional differences of action potential duration (90% repolarization-APD<sub>90</sub>) of PF derived from normal and 1-day-old infarcted canine hearts.

56 left ventricular preparations were superfused and paced at 75 bpm. Action potentials from 10 proximal (false tendon-ant. papillary muscle junction) and 10 distal (apical) PF were analyzed under each condition to develop average values of APD<sub>90</sub> for analogous regions in 4 groups of 6 NIF hearts (H, E, I, No-Anesth Control) and 4 similar groups of 8 INF hearts. The distal fibers of INF hearts were always located within the ischemic zone (IZ) while the proximal fibers were located in the nonischemic zone (NIZ). In anesthetic groups the agents were superfused at high followed by low dose (1:1 dilution) with pre- and post controls. Equilibrium bath anesthetic concentrations were measured by gas chromatography. Mean values for each type of preparation were compared by LSD and ANOVA. The average

difference between proximal and distal PF APD<sub>90</sub> ( $\Delta$  P-D, msec) for each anesthetic group and type of preparation is indicated in the Figure. A P level  $\leq 0.05$  was considered significant.

In NIF hearts proximal APD<sub>90</sub> always exceeded distal APD<sub>90</sub>. H, E, and I each reduced the differences in APD between the two regions. In INF hearts proximal (NIZ) APD<sub>90</sub> was shorter than distal (IZ) APD<sub>90</sub>. H, E, and I each accentuated the differences in APD between the NIZ and IZ PF of INF hearts.



The actions of enflurane and isoflurane in infarcted hearts resemble those of halothane and should promote decremental conduction of impulses from the NIZ into the more refractory IZ PF. The results suggest that enflurane and isoflurane may facilitate re-entrant activity in the *in vitro* canine infarction model in a manner similar to that reported for halothane<sup>1</sup>.

Reference: 1) *Anesthesiology* 67:619, 1987