Title: THE CARDIOVASCULAR EFFECTS OF MORPHINE DURING HYPOTHERMIA ARE MEDIATED BY A PERIPHERAL MECHANISM OF ACTION.

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Opiates are commonly used as main anesthetics in cardiac surgery, because they produce less cardiovascular (CV) depression than inhalation anesthetics. In these patients, systemic hypothermia (28-30°C) is also used to minimize myocardial injury. The aims of our study were to determine: 1) the CV effects of morphine (MS) during hypothermia; 2) if such effects are mediated by central or peripheral mechanisms and 3) if they are related to histamine release or a naloxone-reversible mechanism.

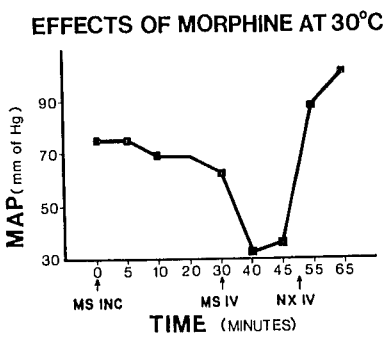
Methods: Fifteen mongrel dogs (Wt 17.2±3 kg) were used. Anesthesia was induced with IV pentothal and after intubation maintained with isoflurane-0_2. Animals were mechanically ventilated and end tidal CO_2 monitored. An arterial line, a Swan-Ganz and a cisternal CSF drain were placed. Hypothermia (30°C) was induced by surface cooling with ice and normothermia (37°C) maintained with heating blankets. After temperature was stabilized (1.5 hrs), MS was administered to the following groups: I) 37°C, 1 mg/kg MS IV (n=6); II) 30°C, 1 mg/kg MS IV (n=6) and III) 30°C, 0.1 mg/kg MS intracisternal (INC, n=3). Blood and CSF samples were taken and CV responses measured before and at different times after MS for a period of 90 min. Naloxone (NX, 1 mg/kg IV) was given 15 min after MS. Plasma and CSF levels of MS and histamine were determined by RIA. Results were compared by ANOVA followed by Student's t-test.

Results: Moderate (30°C) hypothermia increases plasma and CSF MS levels after IV administration. Moreover, a significant decrease in MAP, CO and SVR was observed when IV MS was administered at 30 but not at 37°C (Table). The correlation between decrease in MAP and MS plasma levels during hypothermia was 0.84. The CV effects of IV MS during hypothermia were reversed by IV NX (1mg/kg, Figure). Administration of MS INC to hypothermic animals did not produce significant CV depression, showing that the effects observed after IV administration are mediated by a peripheral mechanism. No significant differences in plasma histamine levels were observed in any group.

TABLE 1

GROUP	I (37°C-IV)		II (30°C-IV)		III (30°C-INC)	
	PRE	POST	PRE	POST	PRE	POST
MAP	130	125	76	29*	83	79
HR	126	109	85	69	93	83
CO	2.9	2.1	2.8	1.7*	2.7	3.1
SVR	3126	2698	2354	1091*	2130	2348
MPAP	16.5	14.0	8.5	5.3	9.0	10.5
PVR	303	368	134	172	148	129
MS (ng/ml)	-	177	-	373	-	4
HIS (ng/ml)	11.5	16.7	11.6	18.6	11.0	13.2

PRE = values before and POST = 10 minutes after MS administration. *p<0.05



Changes in MAP over time in a single experiment. MS (0.1 mg/kg INC) was given at time zero and at time 30 (1 mg/kg IV), followed by naloxone (NX) 1 mg/kg IV.

In summary, we show that: 1) MS plasma levels increase during hypothermia; 2) this increase produces a significant CV depression which is reversed by NX; 3) only IV but not INC MS produces CV depression and 4) histamine release does not play an important role in the CV depression induced by MS during hypothermia. The enhanced CV effects of opiates during hypothermia could, among other causes, contribute to the hypotension observed during cooling in cardiac surgery.