

Date :

Title : SYMPATHETIC RESPONSES TO MORPHINE ANESTHESIA AND SURGERY

Authors : P. F. Hoar, Ph.D., M.D., N. T. Nelson, Ph.D., D. T. Mangano, Ph.D., M.D., R. F. Hickey, M.D., and C. R. Bainton, M.D.

Affiliation: Department of Anesthesia, University of California, San Francisco 94143, and Veterans Administration Medical Center, San Francisco, California 94121

**Introduction.** Plasma catecholamine levels increase after administration of large doses of morphine sulfate (MS), while addition of sedative-hypnotic adjuvants ablates this response. Superimposition of a surgical stimulus results in elevations of blood pressure and vasoconstriction. Although the latter circulatory responses are presumed to be related to sympathoadrenal activation, total catecholamine concentrations with surgery are lower than those measured following MS. To address this apparent paradox, the epinephrine/norepinephrine ratio (E/NE), which delineates adrenal from peripheral sympathetic nervous system activity, can be employed. We applied this ratio to the plasma catecholamine response of patients following MS-diazepam anesthesia and surgery for myocardial revascularization.

**Methods.** We obtained informed consent and approval of the Committee on Human Research to study 10 patients with coronary artery disease. All patients had angina unresponsive to various combinations of nitrates, propranolol, and/or diuretics. Following premedication with MS, 10 mg, and scopolamine, 0.4 mg im, monitoring devices (ECG, radial and pulmonary artery catheters) were placed. When the patients' hemodynamic status was stable, control measurements of standard hemodynamic variables were obtained (Period I). At the same time, arterial blood was withdrawn for analysis of plasma E and NE (by radioenzymatic assay) and blood gases. Anesthesia was induced with MS, 3 mg/kg, at rates of 5-10 mg/min. Ventilation was assisted throughout induction, the patients inspiring 100% O<sub>2</sub>. After MS, repeat measurements were performed (Period II). Further measurements were obtained upon addition of intravenous diazepam (0.25-0.35 mg/kg) (Period III). With loss of lid reflex, ventilation was controlled and the trachea intubated, facilitated by succinylcholine. Final sets of measurements were taken after intubation (Period IV) and sternal skin incision (Period V).

**Results.** Morphine sulfate, 3 mg/kg, produced reductions in mean arterial pressure (MAP) associated with decreases in systemic vascular resistance index (SVRI) (from control values of  $38 \pm 3$  to  $30 \pm 5$  units,  $P < 0.05$ ). Mean plasma E concentrations increased four-fold ( $129 \pm 20$  to  $570 \pm 182$  pg/ml,  $P < 0.01$ ), while plasma NE doubled ( $246 \pm 31$  to  $488 \pm 85$  pg/ml,  $P < 0.01$ ). The E/NE ratio increased from  $0.6 \pm 0.1$  to  $1.0 \pm 0.2$  ( $P < 0.05$ ) (fig. 1). Addition of diazepam reduced MAP further. This reduction was associated with significant decreases in cardiac index (CI) when compared with values obtained following MS. Increases in plasma E and NE measured after MS were totally ablated by diazepam, and the E/NE ratio decreased from  $1.0 \pm 0.2$  to  $0.6 \pm 0.2$  ( $P < 0.05$ ). Endotracheal

intubation produced negligible circulatory effects and no alterations in plasma catecholamines. Surgical incision elicited a response. Increases in MAP to control levels were associated with marked increases in SVRI ( $50 \pm 5$  units) and decreases in CI ( $2.02$  l/min/m<sup>2</sup>) ( $P < 0.01$ ). Plasma NE increased modestly above levels measured following induction ( $202 \pm 29$  to  $321 \pm 63$  pg/ml,  $P < 0.05$ ), while plasma E did not change, and E/NE ratio remained at  $0.6 \pm 0.2$ . During the study, PaO<sub>2</sub> ranged from 200 to 450 torr, and PaCO<sub>2</sub> from 37 to 41 torr. The pH was stable at 7.38.

**Conclusions.** Large-dose MS induces systemic vasodilatation and stimulates sympathoadrenal activity. Increases in the E/NE ratio indicate that the adrenal medulla is an important contributor to this response. Patients demonstrate varying levels of awareness despite 3 mg/kg MS, so that baroreceptor reflex mechanisms may be intact and can respond to changes in MAP with liberation of endogenous catecholamines. Diazepam produces central sedation and loss of consciousness and ablates this reflex activity. It also exacerbates the hypotension produced by MS. In contrast, surgical incision causes peripheral vasoconstriction and increases only plasma NE, suggesting that only peripheral sympathetic activity is enhanced. Since this neurotransmitter is thought to be rapidly metabolized locally, circulating levels of NE will represent only spillover of excess catecholamine and will not accurately reflect the magnitude of the observed circulatory changes. Thus, the possibility of a strong correlation between changes in plasma NE and SVRI is unlikely.

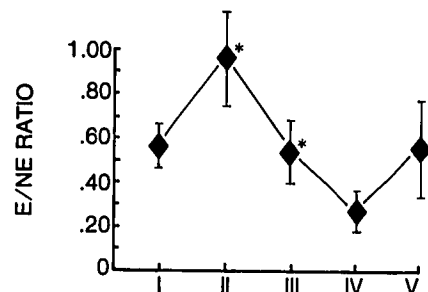


Fig. 1. Data analyzed by analysis of variance, \* $P < 0.05$ , when each period is compared with the one immediately preceding.