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Title: Catecholamines, renin and cardiovascular responses to fentanyl-diazepam anesthesia

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**Introduction.** Large doses of fentanyl (50 to 100 mg/kg) and diazepam (0.3 to 0.5 mg/kg) have been used in cardiac surgical patients. It has been reported that fentanyl-oxygen anesthesia produces minimal changes in cardiovascular dynamics. In addition, it has been shown that high dose fentanyl-oxygen anesthesia prevented increases of the "stress responding hormones" in cardiac surgical patients with normal catecholamine values. The present study was performed to determine if this response differs in critically ill patients with enhanced sympathetic nervous sympathoadrenal nervous activity.

**Methods:** Twelve adult patients (ASA class IV) scheduled for open heart operation were studied with their informed consent (4 females and 8 males). All patients were taking diuretics and digoxin but none was on propranolol. Anesthesia was induced with diazepam 0.4 mg/kg and fentanyl 75 mcg/kg administered intravenously over 10 minutes. Metocurine iodide (0.3 mg/kg i.v.) was given to provide muscle relaxation. Patients were ventilated with  $F_{I_{O_2}}$  1.0.

Hemodynamic measurements included heart rate (HR), arterial blood pressure (BP) pulmonary arterial pressure (PAP), pulmonary capillary wedge (PCWP), right atrial pressures (RAP), and cardiac output (CO). Cardiac index (CI), stroke volume (SV), stroke index (SI), systemic and pulmonary vascular resistance (SVR, PVR) were calculated. Plasma renin activity (PRA), epinephrine (E) and norepinephrine (NE) levels were determined using radio-immunoassay. Blood samples for NE, E, and PRA and hemodynamic measurements were taken 1) prior to anesthesia 2), with anesthesia, but prior to surgical stimulation and 3) 20 minutes from the start of operation. Results are presented as mean SEM. Significance was determined by correlated Student t-test.

**Results:** The data from this study is present in the Table. PRA, NE, and E were abnormally elevated. With anesthesia alone, HR, BP, PAP, PCW, and CI decreased significantly, while SI, SVR and PVR remained unchanged. However, only PRA increased significantly with anesthesia whereas NE and E did not change. Following

surgical incision, only SVR increased, while HR, BP, PAP, and CI remained unaltered. This increase in SVR was accompanied by a further increase in PRA. NE and E increased also.

**Discussion:** These data show that high doses of fentanyl-diazepam anesthesia produce minor cardiovascular changes in critically ill patients. Plasma renin activity increased both with anesthesia and surgery. The increase in PRA should be attributed to the fall of mean BP. E and NE increased only during surgery. The lack of significant increase in NE and E suggests that fentanyl-diazepam anesthesia alone does not produce hormonal response in critically ill patients. However, this combination of anesthetic drugs does not prevent sympathoadrenal response to surgical stimulation. Finally, this study suggests that large doses of fentanyl-diazepam do not modify the PRA response to fall in BP, observed with anesthesia alone, since PRA did increase.

	Control	Anesthesia	Surgery
HR (b/min)	94±12	74±10* **	78±11
BP (torr)	80 ±3	70 ±2 **	74 ±4
PAP (torr)	34 ±3	31 ±3 ***	31 ±5
PCWP (torr)	27 ±2	23 ±2 ***	24 ±3
RAP (torr)	9.7 ±0.5	11 ±0.8*	10.5 ±0.5
C.I. l/min/BSA	2.1 ±0.2	1.7 ±0.1*	1.7 ±0.1
SI ml/b/BSA	25 ±5	25 ±4	24 ±4
SVR dyn.sec.cm <sup>-5</sup>	1593 ±227	1538 ±157	1737 ±160**
PVR dyn.sec.cm <sup>-5</sup>	166 ±20	1.96 ±23	164 ±26
PRA ng/ml/hr	18 ±3	26 ±3***	30 ±4*
NE pg/ml	1513 ±325	1291 ±303	1710 ±411**
E pg/ml	786 ±102	812 ±98	1425 ±316***

\*P&lt;0.05, \*\*P&lt;0.02, \*\*\*P&lt;0.01