Title : HUMAN RESEARCH AND NONINVASIVE MEASUREMENT OF VENTRICULAR PERFORMANCE: AN ECHOCARDIOGRAPHIC EVALUATION OF ETOMIDATE AND THIOPENTAL

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Introduction. Federal guidelines for research with human subjects encourages the development of experimental protocols which reduce risk to the volunteer. Nowhere is this more obvious than in the field of cardiovascular pharmacology. Clinical research on new induction agents requires assessment of the circulatory component of anesthetic action. Cardiovascular data has been derived in large part with invasive monitoring of patients with significant cardiovascular disease. However, a methodologic problem exists in circulatory studies of healthy patients, where such monitoring cannot be clinically justified. In this light, Wollman and Dripps[1] proposed that the maximum acceptable risk for research with human subjects, the Pf (probability of fatality per person hour of exposure) should be less than 3×10^{-5}. In comparison, cardiac catheterization (left side) which has been used as a research tool[2] is associated with a greatly increased Pf (2×10^{-3}). Echocardiography offers a potential solution. The echocardiogram provides a safe, reliable, non-invasive method for evaluating left ventricular performance. Excellent correlation exists between echocardiographic data and simultaneous angiographic determinations. Using M-mode echocardiography, we report the cardiovascular effects of a commonly employed induction agent, thiopental, and experimental drug, etomidate. These results are compared to previously reported data obtained from left heart catheterization.[2,3]

Methods. Twenty (20) healthy patients without cardiac disease ranging in age from 17 to 71 years (mean-21) who were to undergo elective surgery were evaluated. Informed written consent, in accordance with a Human Investigation Committee approved protocol was obtained from each patient. Alternate patients were allocated to either the thiopental (n=10) or etomidate (n=10) group. Cardiovascular and ventilatory parameters were assessed with the aid of M-mode echocardiography (Picker Systems-80 Cardiac Imager) and end-tidal (ET) gas analysis (Beckman LB-2). Each series of measurements consisted of blood pressure (BP), pulse rate (P), M-mode echos of the left ventricle and aortic root and ET CO_2. Derived data included: mean blood pressure ($\overline{BP}$), cardiac index (CI), shortening fraction (SF), ejection fraction (EF), mean circumferential fiber shortening (Vcf), pre-ejection period/left ventricular ejection time (PEP/ LVET).

Measurements were made with the patient awake (control); ninety minutes following intramuscular premedication with morphine 0.1 mg/kg and scopolamine 0.005 mg/kg (=post premed.) and then 1,2 and 3 minutes following intravenous administration (injection time = 30 sec) of thiopental (4 mg/kg) or etomidate (0.3 mg/kg).

Results. (Table) Compared to awake control, CI and P were well maintained with both etomidate and thiopental. At 3 minutes, although not clinically significant, SF decreased 9% ($P < .05$) for both etomidate and thiopental. However, Vcf was significantly ($P < .05$) decreased at 1, 2 and 3 minutes following thiopental (maximal decrease = 28%). In contrast etomidate caused only a decrease of only 9% in Vcf ($P > .05$). At 3 minutes following injection, EF was decreased 12% ($P < .05$) and 7% ($P < .05$) by thiopental and etomidate respectively. Systolic time intervals (PEP/LVET) showed no significant changes. No statistically significant differences were noted between the group receiving etomidate or thiopental.

Discussion. Using M-mode echocardiography, the magnitudes of change we found in cardiovascular performance and ventricular function correlates well with previously reported data obtained a via highly invasive techniques. Sonntag,[2] using left ventricular catheterization, reported a 17% reduction in CI, a depression in left ventricular performance (↓ dp/dt) following thiopental (4 mg/kg). Using similar invasive research techniques, but with a smaller dose (etomidate = .12 mg/kg) Kettler[3] reported a modest rise in CI (13%) and maintenance of ventricular function. We have demonstrated the utility of echocardiography as a safe, non-invasive modality for the study of cardiac function during anesthesia, which may be of particular value in assessing healthy subjects.

References

1. Wollman, H., and Dripps, R.D.: Physiologic and Pharmacologic Studies in Human Volunteers. Anesthesiology 35:168-173, 1971.
2. Sonntag, K., et al: Effects of thiopental (Trapanal) on coronary blood flow and myocardiac metabolism in man. Acta Anaesth Scand 19:69-78, 1975.
3. Kettler, D., et al.: Haemodynamics, myocardial function, oxygen requirement and oxygen supply of the human heart after administration of etomidate. Anaesthesiology and Resuscitation 106:81-94, 1977.

TABLE Cardiovascular Data (Mean ± S.E.M.)

	AWAKE (CONTROL)	
	THIOPENTAL N=10	ETOMIDATE N=10
P (BPM)	61.9 ± 2.9	56 ± 2.6
$\overline{BP}$ (mmHg)	94.1 ± 2.8	88.8 ± 2.2
CI (L/M^2/min)	3.09 ± .24	2.70 ± .18
SF	0.34 ± .02	0.36 ± .01
Vcf (circs/sec)	1.18 ± .08	0.98 ± .02
EF (%)	71 ± 2	73 ± 1
PEP/LVET	.25 ± .01	.23 ± .02
	THREE MIN. POST INJECTION	
	THIOPENTAL 4 mg/kg	ETOMIDATE 0.3 mg/kg
P (BPM)	69.6 ± 6.1	62.2 ± 9.1
$\overline{BP}$ (mmHg)	92.6 ± 3.0	80.9 ± 3.0*
CI (L/M^2/min)	2.59 ± .23	2.66 ± .52
SF	0.29 ± .02*	.32 ± .03*
Vcf (circs/sec)	0.86 ± .07*	.90 ± .04
EF (%)	63 ± 3*	68 ± 2*
PEP/LVET	.29 ± .02	.25 ± .02

*$p < .05$ Student's t test for paired data.