Title: **Influence of venous return on ventilatory response to CO_2 in humans**

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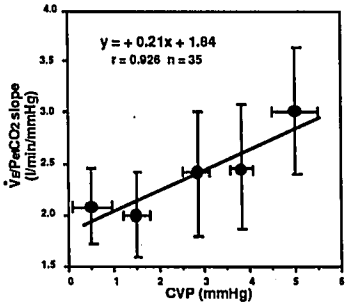
Since cardiovascular failure may reflexly result in apnea in dogs[1], we investigated the influence of a decrease in venous return induced by Lower Body Negative Pressure (LBNP)[2] on ventilatory response to CO2 in humans.

Methods. After approval by the Ethical Committee and obtaining informed consent, 7 healthy volunteers (23±2 yrs) entered the study. Ventilatory measurements were done before (control) and during 4 levels of LBNP (-5, -10, -20, -30 mmHg). Levels of LBNP were randomly applied below the iliac crests of the volunteer with a recovery period of at least 20min between each level. Systolic arterial (SAP, Finapress®), heart rate (HR, ECG), central venous pressure (CVP, basilic catheter) were continously monitored. Ventilatory measurements [respiratory rate (RR), minute ventilation ($\dot{V}E$), end tidal CO2 tension ($PetCO_2$)] were measured using a pneumo-tachograph and a capnograph (Gould®) during room air breathing and CO2 stimulation (Read circuit). Linear regression equations were computed from $\dot{V}E$ and $PetCO_2$ for each challenge curve. Data are expressed as mean ± SD and compared using ANOVA for repeated measures followed by appropriate post hoc tests. $P<0.05$ was considered as significant.

Results. As expected (table), LBNP progressively decreased CVP. A slight hypotension and mild tachycardia were only observed during the higher level of LBNP (-30 mmHg) whereas $\dot{V}E$ was reduced. A progressive decrease in $\dot{V}E/PetCO_2$ slope was significantly related to the decrease in CVP (figure).

Comments. This study shows that a selective impairment of venous return induces a decrease in the CO_2 respiratory control. Moreover a decrease in basal $\dot{V}E$ is observed when both cardiopulmonary (↓CVP) and arterial (↓SAP) baroreflexes were concerned. These results indicate that the ventilatory stimulation previously described during upright tilt[3] would be more likely related to changes in diaphragmatic function and chest wall mechanics rather than to a decrease in venous return. The present results may be due to a central interaction between cardiovascular and respiratory control mechanisms.

	control	LBNP (mmHg)			
		-5	-10	-20	-30
CVP (mmHg)	5.0±0.5	3.8±0.2*	2.8±0.3*	1.5±0.3*	0.5±0.4*
SAP (mmHg)	136±10	145±17	142±8	140±15	129±10*
HR (bpm)	58±8	57±6	57±12	63±11	64±8*
RR (cpm)	14±5	14±3	15±4	13±4	12±1
$\dot{V}E$ (L/min)	8.8±2.4	8.0±1.1	9.1±1.8	7.8±2.2	6.7±0.4*
$PetCO_2$ (mmHg)	35.8±4.4	35.1±1.9	35.6±1.9	34.8±3.9	35.5±3.0
$\dot{V}E/PetCO_2$ slope (L/min/mmHg)	3.02±0.69	2.46±0.62*	2.44±0.72*	2.01±0.41*	2.09±0.39*



References

1. Nava S, Bellemare F. J Appl Physiol 66 : 184-189, 1989.
2. Mark AL, Kerber. Hypertension 4 : 39-46, 1982.
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TITLE: SLOW INJECTION DOES NOT PREVENT MIDAZOLAM INDUCED VENTILATORY DEPRESSION

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Introduction: Single (bolus) doses of midazolam (MDZ) decrease both hypoxic and hypercarbic ventilatory drive (1,2). We conducted the present study to determine if this effect is dependent on the rate of MDZ administration.

Methods: Ten volunteers consented to participate in this IRB-approved study. We used the dual isohypercapnic technique (2) to determine the hypercarbic ventilatory response for twenty min after injecting midazolam 0.1 mg/kg over 15 sec (fast) or 5 min (slow). We analyzed data over two time periods: 0-5 min (during MDZ infusion) and 5-20 min (after infusion) using 2-way ANOVA and the protected LSD test; $P<0.05$ indicated significance.

Results: During the first 5 min, the slope of the ventilatory response to CO_2 was significantly lower in the subjects who received MDZ by fast injection ($P<0.001$). After completion of the infusion (5-20 min), the slopes did not differ between fast and slow administration (fig 1). MDZ's primary effect was a reduction in tidal volume (fig 2): During the first 5 min, tidal volume was also significantly lower in subjects who received MDZ by fast injection: it did not differ between groups during the subsequent 15 min.

Discussion: Although the onset of changes in slope and tidal volume was faster in subjects who received MDZ by fast injection, this effect was dose dependent. Once subjects in the slow injection group had received the same total dose of midazolam as those in the fast group (i.e. after 5 min), there was no difference in its effect on ventilatory control. Slow administration of midazolam, per se, did not prevent significant depression of ventilatory drive and tidal volume.

References: 1. Anesth Analg 67:377, 1988
2. Anesthesiology 58:540-544, 1983

Figure 1

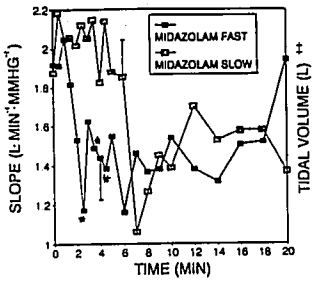
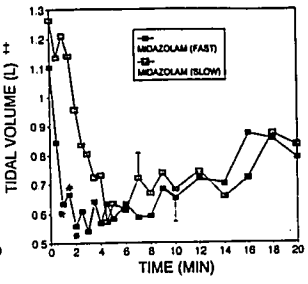


Figure 2



$\bar{X}$ ± SEM, *$P<0.05$ compared with slow injection
++ $P_{ET}CO_2$ = 46 mmHg