

Title : CHANGES IN BREATHING PATTERN INDUCED BY MIDAZOLAM IN NORMAL SUBJECTS  
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**Introduction.** Several recent investigations have emphasized the importance of the changes in breathing pattern induced by anesthetic agents (1,2). Since benzodiazepines are commonly administered in spontaneously breathing patients, we evaluated the influence of midazolam on the respiratory pattern in normal subjects with a non-invasive technique.

**Methods.** 8 healthy men accustomed to investigational environment, mean age  $30 \pm 4$  years ( $\bar{x} \pm SD$ ), mean weight  $76 \pm 8$  kg volunteered for the study. None of them had a previous medical history or did take regular medication or alcohol. Informed consent was obtained and the Committee for Ethics and Human Research of our institution approved the study. Tidal volume ( $V_T$ ) and respiratory rate were continuously measured with a non-invasive method using 2 bellows pneumographs (Hewlett-Packard (HP) model 108 pneumograph) attached circumferentially around the rib cage and the abdomen. The bellows were connected to differential pressure transducers (HP 267BC) and their signals stored on a microcomputer (Appel II plus). Any change in circumference of the rib cage (RC) and the abdomen produces a linear variation of pressure within the bellows. Calibration was done before each experiment by adjusting these signals to match the volumes measured with a pneumotachograph (Godart type 17212) according to a computer-aided procedure (3). The calibration was judged satisfactory when the mean differences between the volumes obtained by the non-invasive technique and those obtained with the pneumotachograph were less than 10% with various breathing patterns. The calibration procedure was repeated at the end of the experiment to test the reliability of our results. The percentage error remained always below 10%. Minute volume ( $\dot{V}_E$ ), inspiratory time ( $T_i$ ), expiratory time ( $T_e$ ), the ratio of  $T_i$  on total respiratory cycle ( $T_i/T_{tot}$ ) and the ratio of the RC contribution to  $V_T$  ( $RC/V_T$ ) were computed from the data stored in the microcomputer. Changes in thoracic gas volume (TGV) were derived from changes in end-expiratory positions. The experiments were performed twice randomly, in a double-blind fashion. At least 4 days apart, each subject received either placebo or midazolam 0.1 mg/kg intravenously over a 15-sec period. The subjects were studied in a supine position, in a quiet dark room, disconnected from the pneumotachograph, comfortably installed with ear phones listening to music and with the eyes covered with a cloth. A Wilcoxon rank sum test was used to detect statistical significance. All results are expressed as mean  $\pm$  SEM and are the mean data of values recorded between 5 and 7 minutes after the injection; this time corresponded to the peak effect of the drug.

**Results.** The results are summarized in table 1, fig 1 and 2. When compared with placebo, midazolam produced a significant decrease in  $V_T$  associated with an increase in respiratory rate (f), so that the minute volume did not change statistically. The increase in

f was due to a reduction of  $T_e$  since  $T_i$  remained stable. The decrease in mean inspiratory flow ( $V_T/T_i$ ) was related to a decrease in  $V_T$ , which was mainly produced by a reduced abdominal contribution to the ventilation as indicated by the significant increase in  $RC/V_T$ . TGV remained stable throughout the study.

**Discussion.** The effects of midazolam on the respiratory pattern in healthy subjects differ from other anesthetic agents. Our most interesting result is the increase in  $RC/V_T$  seen after midazolam, whereas halothane (1) or morphine (2) suppress the RC contribution to ventilation while sparing the diaphragmatic activity. This phenomenon may have clinical implications in COPD patients, who have minimal RC contribution to ventilation, in whom midazolam produces a more profound ventilatory depression than in normal subjects (4).

**References.**

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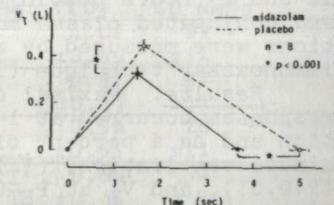
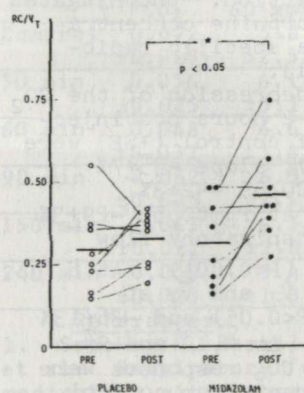


Fig. 1 Individual (o,\*) and mean (—) changes of  $RC/V_T$  before and after injection of placebo or midazolam. ( $p < 0.05$ )  
 Fig. 2 Mean  $\pm$  SEM respiratory cycle time components, five minutes after i.v. injection of placebo or midazolam (0.1 mg/kg). Inspiratory flow ( $V_T/T_i$ ) is represented by the slope of the ascending limb of the spirogram  
 n = 8  
 \* p < 0.001

TABLE 1 MEAN  $\pm$  SEM CHANGES IN RESPIRATORY PATTERN 5 MINUTES AFTER I.V. PLACEBO OR MIDAZOLAM 0.1 MG/KG (n = 8)

Variables	PLACEBO	MIDAZOLAM	P
$V_T$ (s)	- 4.0 $\pm$ 3.6	- 32.3 $\pm$ 3.3	<0.001
f (s)	- 2.6 $\pm$ 3.3	+ 36.5 $\pm$ 6.5	<0.001
$\dot{V}_E$ (s)	- 6.8 $\pm$ 4.5	- 9.9 $\pm$ 3.9	N.S.
TGV (s)	+ 0.4 $\pm$ 0.7	- 2.7 $\pm$ 1.2	N.S.
$T_i$ (s)	+ 8.9 $\pm$ 4.2	+ 0.8 $\pm$ 2.9	N.S.
$T_e$ (s)	+ 8.6 $\pm$ 8.7	- 33.4 $\pm$ 6.4	<0.01
$V_T/T_i$ (s)	- 9.5 $\pm$ 3.3	- 30.5 $\pm$ 3.0	<0.001
$T_i/T_{tot}$	+ 0.01 $\pm$ 0.01	+ 0.10 $\pm$ 0.02	<0.001
$RC/V_T$	+ 0.03 $\pm$ 0.03	+ 0.14 $\pm$ 0.03	<0.05