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Changes in Rib Cage and Diaphragm Contribution to Ventilation after Morphine

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Ventilatory response to CO_2 was measured before and after intravenous morphine, 0.15 mg/kg, in 13 healthy adult subjects. Tidal volume response was partitioned into that component due to rib cage (RC) and that due to abdomen-diaphragm motion (AD). The response was assessed also in terms of inspiratory and expiratory durations (T_i,T_e), the ratio of T_i to total cycle duration (T_i/T_{tot}) and mean inspiratory flow (V_T/T_i).

The ventilatory response to CO_2 was displaced to the right after morphine; this was due to a decrease in both the tidal volume and breathing frequency responses. The displacement of the tidal volume response was due largely to a similar displacement of the RC response; there was no significant change in the AD response. The decrease in the frequency response after morphine was manifest by increases in both inspiratory and expiratory durations at equivalent CO_2 pressures during rebreathing; these increases occurred to equivalent extents such that no change of T_i/T_{tot} was found during rebreathing after morphine. Mean inspiratory flow per breath was significantly reduced during rebreathing after morphine. When RC, AD, T_i, T_e, V_T/T_i, and T_i/T_{tot} during rebreathing were plotted as functions of tidal volume and expressed as a per cent of vital capacity, no effect was found after morphine. The marked depression of the RC response and the relative stability of the AD response after such dissimilar ventilatory depressants as morphine and halothane may represent characteristic responses of the separate groups of intercostal and phrenic motoneurones to descending influences determined by the direct action of these drugs on respiratory neurons in the medulla. (Key words: Analgesics: morphine. Ventilation: carbon dioxide response; diaphragm; rib cage.)

HALOTHANE-INDUCED depression of the ventilatory response to CO_2 is largely the consequence of almost complete abolition of the rib cage contribution to ventilation. In contrast, the diaphragm contribution is only slightly impaired, as manifested by a displacement of the response to the right.[1] These observations raise the question as to whether these contrasting responses are due to a specific action of halothane or a general feature of the response of the physiologic control system for the regulation of breathing, thay may be manifest after the administration of other drugs known to depress central nervous system activity. In order to explore this question in more detail, experiments were designed to investigate the effects of morphine on the contribution of the rib cage and diaphragm to ventilation in normal subjects, both at rest and during rebreathing.

Materials and Methods

Ventilation and ventilatory response to CO_2 were measured before and after intravenous morphine; ventilatory responses were partitioned into tidal volume and frequency responses. Tidal volume responses were partitioned into rib cage (RC) and abdomen/diaphragm (AD) component responses, using magnetometers.[2]

Thirteen healthy adults, ten men and three women, were studied. Informed consent was obtained according to the protocol approved by the hospital research committee. All subjects were naive with regard to respiratory investigations and were not aware of the precise nature of the research questions. Subjects fasted for at least four hours before an experiment; all experiments were conducted with subjects in the supine position.

Inspired ventilation ($\dot{V}_I$) was measured with a dry gas meter (Parkinson Cowan®, CD4), with a potentiometer fitted to the output shaft; full scale deflection was precise to ±2 per cent. Breath-by-breath output was linearised to a precision of ±2 per cent.[3] Carbon dioxide was measured with an infrared analyser (Godart) with a response time of 0.1 s and precise to ±0.1 per cent over the range 0–10 per cent CO_2. End-tidal P_{CO_2} (PET_{CO_2}) and $\dot{V}_I$ were recorded on a Gould® 2400 pen recorder. The resistance of the rebreathing circuit was 1.0 cm $H_2O \cdot l^{-1} \cdot$ s at a flow rate of 4 l/s. A four-channel variable reluctance magnetometer system was used to measure changes in the anteroposterior dimensions of RC and abdomen.[4] The magnetometers were calibrated using isovolume lines, as described by Tusiewciz *et al.*[1] For experiments with the first eight subjects, magnetometer signals were conditioned via a Hewlett Packard® system, and recorded on a HP polygraphic recorder and a four-channel magnetic tape recorder (Thermionic® T-3000). For the subsequent five subjects, the Konno Mead diagram (XY plots of RC and AD) was displayed directly on a Tektronix® storage oscilloscope S64B. Breathing loops were intermittently recorded on a Hewlett Packard® pen XY recorder (Model 7035B).

Two sets of magnetometer coils were fixed to the skin with double-sided adhesive discs. Both were oriented anteroposteriorily in the midline, the upper set at the nipple level, and the lower set just below the umbilicus to monitor anteroposterior RC and AD motion, respec-

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tively. The subjects then adopted the supine posture for the duration of the experimental procedure and in this posture, the calibration procedure was conducted as described by Tusiewicz *et al.* to calibrate diameter changes in terms of volume.[1] At the end of the experimental procedure, caliper measurements of chest wall dimensions at the level of the magnetometer coils were obtained, as well as measurements of output voltage to enable linearization of the magnetometer signal.[2,4]

Control measurements of steady state resting $\dot{V}_I$, $P_{ET_{CO_2}}$ and the oxygenated mixed venous P_{CO_2} ($P_{v_{CO_2}}$), measured by rebreathing, were obtained.[5,6] Ventilatory response to CO_2 was obtained in duplicate by the method of Read, using modifications previously described to ensure "open loop" conditions during rebreathing.[7-9]

After the control CO_2 responses, each subject was given 0.15 mg/kg morphine sulfate intravenously over 2 min. Resting $\dot{V}_I$, $P_{ET_{CO}}$², $P_{v_{CO_2}}$, and the ventilatory response to CO_2, were again measured at 15- and 30-min intervals after the injection.

Mean ventilation ($\dot{V}_I$), tidal volume (V_T), and breathing frequency (f), were each calculated for successive 30-s intervals, during 3 to 4 min of rebreathing, providing 6 to 8 data points for response calculations. All gas volumes were corrected to BTPS. The slopes of ventilatory ($\Delta\dot{V}_I/\Delta P_{CO_2}$,) tidal volume ($\Delta V_T/\Delta P_{CO_2}$,) and frequency responses ($\Delta f/\Delta P_{CO_2}$) to CO_2 were calculated by least-squares regression. Relative contribution of RC and AD compartments to total ventilation during rebreathing was assessed by plotting RC and AD volume against P_{CO_2}. In order to assess morphine effect at equivalent levels of ventilation, RC and AD responses were plotted against V_T achieved during rebreathing, expressed as a per cent of VC (V_T/VC) per cent. To compare the position of response curves between control and morphine, the following procedure was adopted. For each subject, a P_{CO_2} value which represented the highest level common to all response curves for that subject was chosen (ISO-P_{CO_2}.) Ventilation, V_T and f observed at this P_{CO_2} were used as a measure of response curve position.[9] The choice of an ISO-P_{CO_2} value unique to each subject eliminated errors due to extrapolation that would result if a single P_{CO_2} was chosen the express response curve position for all subjects.[9] These variables were assigned the symbols ISO-$\dot{V}_I$, ISO-V_T, ISO-f, ISO-RC and ISO-AD, respectively.

Recently, several reports have emphasized the importance of analyzing ventilation in terms of respiratory transforms of generally accepted physiological concepts of central neural drive to breathing.[10-13] Mean inspiratory flow (V_T/T_i) is the mechanical transform of the neural drive for single breath—the central inspiratory activity (CIA). The ratio T_i/T_{tot} (inspiratory duration/total breathing cycle duration) is a transform representing central neural processes regulating both the "off switch" mechanism for the termination of inspiratory activity and the "on switch" for initiation of inspiratory activity (or control of expiratory duration).[11,12] Consequently, the results of the present study were analyzed in terms of inspiratory (T_i) and expiratory (T_e) duration and V_T/T_i and T_i/T_{tot}. Mean values of these variables were calculated for sucessive 30-s intervals during each rebreathing run, in an analogous manner to the method used to calculate $\dot{V}_I$, V_T and f responses to CO_2. The effect of morphine on all variables were tested using paired *t* tests.

Recovery of compartmental volumes, RC and AD, from linear AP diameter changes of the chest wall and abdomen, was obtained as described by Pengelly *et al.*[4] The validity of estimating volume changes of rib cage and abdomen compartments in awake humans was established by Konno and Mead[14] using linear differential transducers and confirmed in a number of subsequent studies under various experimental conditions[1,4,15-23] using magnetometer systems.[2] Konno and Mead established that volume of a part could be estimated from linear motion of a point on that part provided the system maintained only one degree of freedom.[14] The ability to recover compartmental volumes by magnetometry confirms that the system does behave in this way.[1,14] Imprecision in recovery of compartment volume indicates the extent to which distortion of the parts of the system from their relaxation characteristics and postural change introduces errors due to additional degrees of freedom.[1,14,23] In the present experiments, normal subjects with conscious states mildly depressed by morphine, were required to lie supine for up to 4 hours in one experiment. It was not possible to eliminate all postural movement during each study and this was an additional factor mitigating against precise recovery of compartmental volumes when compared to tidal volume measured at the mouth. We accepted a sum of the compartmental volumes of ±20 per cent of measured tidal volume as the acceptable limit of precision of technique of calibration and measurement of RC and AD volumes. Imprecision extending outside this limit and other technical problems led to discarding the results of magnetometer volumes of three subjects.

Results

Mean age, weight, height, and vital capacity of subjects (±SEM) were 23 ± 0.8 years, 70 ± 2.5 kg, 175 ± 1.6 cm, and 4.4 ± 0.21 l. The slope of the ventilatory response to CO_2 decreased and the curve was displaced to the right after morphine. These effects were mediated largely by changes in breathing frequency, and to a lesser extent by tidal volume changes (table 1).

TABLE 1. Mean ± SEM End-Tidal P_{CO_2} ($P_{ET_{CO_2}}$), Mixed Venous P_{CO_2} (Pv_{CO_2}), Slopes of Ventilatory, and Components of Ventilatory Responses to CO_2 and ISO-P_{CO_2} Response Curve Positions before, and 15 min (M_{15}) and 30 min (M_{30}) after Intravenous Morphine

Variable	n	Control	M_{15}	P	M_{30}	P
$P_{ET_{CO_2}}$ (torr)	13	38.9 ± 1.0	42.7 ± 1.2	<0.001	42.9 ± 0.9	<0.001
Pv_{CO_2} (torr)	13	48.4 ± 0.9	51.7 ± 1.1	<0.001	52.8 ± 0.8	<0.001
$\Delta\dot{V}_I/\Delta P_{CO_2}$* 1·min^{-1}·torr^{-1}	13	3.42 ± 0.30	1.93 ± 0.27	<0.001	2.02 ± 0.33	<0.001
$\Delta f/\Delta P_{CO_2}$* (breath/torr)	13	0.65 ± 0.06	0.27 ± 0.07	<0.001	0.27 ± 0.08	<0.001
$\Delta v_T/\Delta P_{CO_2}$* (l/torr)	13	0.117 ± 0.18	0.097 ± 0.009	N.S.	0.089 ± 0.015	<0.05
$\Delta RC/\Delta P_{CO_2}$* (l/torr)	10	0.093 ± 0.020	0.057 ± 0.008	N.S.	0.050 ± 0.010	N.S. (n = 9)
$\Delta AD/\Delta P_{CO_2}$* (l/torr)	10	0.03 ± 0.010	0.04 ± 0.003	N.S.	0.03 ± 0.010	N.S.
ISO-$\dot{V}_I$† (l/min)	13	56.0 ± 5.7	30.8 ± 3.3	<0.001	31.9 ± 4.2	<0.001
ISO-f† (breath/min)	13	20.1 ± 1.6	15.0 ± 1.2	<0.001	15.2 ± 1.0	<0.001
ISO-V_T† (l)	13	2.81 ± 0.17	2.11 ± 0.18	<0.01	2.08 ± 0.17	<0.001
ISO-RC† (l)	10	1.78 ± 0.23	1.14 ± 0.16	<0.01	1.10 ± 0.17	<0.01 (n = 9)
ISO-AD† (l)	10	1.06 ± 0.10	0.88 ± 0.10	N.S.	0.90 ± 0.09	N.S.

* Slopes of total ventilatory ($\dot{V}_I$), breathing frequency (f), tidal volume (V_T), and rib cage (RC) and abdomen-diaphragm (AD) compartment responses to CO_2.

† CO_2 response curve position variables for $\dot{V}_I$, f, V_T, RC and AD compartment responses to CO_2. See methods section for detailed explanation of these variables.

During quiet breathing, the relative contribution of RC and AD varied among subjects. In six subjects AD motion was predominant (fig. 1, left panel), in three subjects RC motion was predominant (fig. 1, right panel), and in one subject the contribution of RC and AD to tidal volume was about equal. During rebreathing the increase in tidal volume in all subjects was due largely to increased RC motion, with a lesser contribution due to increased AD motion. After morphine, RC and AD contributions to V_T were reduced during both quiet breathing and rebreathing; however, the effect of morphine was greater on the RC component of tidal volume (table 1, fig. 2).

Inspiratory and expiratory time both decreased progessively during control rebreathing runs; after morphine both were significantly increased at equivalent P_{CO_2} levels. After morphine, progressive decreases in T_i and T_e during rebreathing were less, but changes in $\Delta T_i/\Delta P_{CO_2}$ and $\Delta T_e/\Delta P_{CO_2}$ were not significant (table 2, fig. 2). Although T_e at any level of P_{CO_2} or ventilation was about 30 per cent greater than T_i, the progressive changes in both variables both before and after morphine were very nearly proportional; consequently, the ratio T_i/T_{tot} did not change appreciably during rebreathing, either before or after morphine (table 2, fig. 2). On the other hand, mean inspiratory flow per breath (V_T/T_i) was markedly diminished after morphine. Displacement of the V_T/T_i response to CO_2 to the right was very highly significant, but although the slope of the response was only 50 per cent of control after morphine, this trend was not statistically significant (table 2, fig. 2).

To further assess RC and AD contribution to tidal volume and T_i, T_e, V_T/T_i and T_i/T_{tot} responses before and after morphine, these variables were each plotted against tidal volume, expressed for each subject as a per cent of vital capacity (V_T/VC) per cent. These plots show that for a given tidal volume, morphine did not alter the relationship between these variables and V_T during rebreathing (fig. 3). Although the slope of the relationship of V_T/T_i and (V_T/VC) per cent decreased by about 40 per cent after morphine, this was not significant. No change was observed for T_i/T_{tot} as a function of V_T/VC, either before or after morphine (fig. 3).

Discussion

Morphine-induced ventilatory depression is achieved predominantly by a reduction in breathing frequency; breath size tends to be more resistant, requiring a larger dose to achieve a significant reduction of V_T.[5,24] The results of the present study confirm these older findings. The observed changes in the ventilatory response to CO_2 in the present study are attributable largely to changes in both the slope and position of the breathing frequency response to CO_2. In contrast, although a significant shift to the right of the tidal volume response to CO_2 was

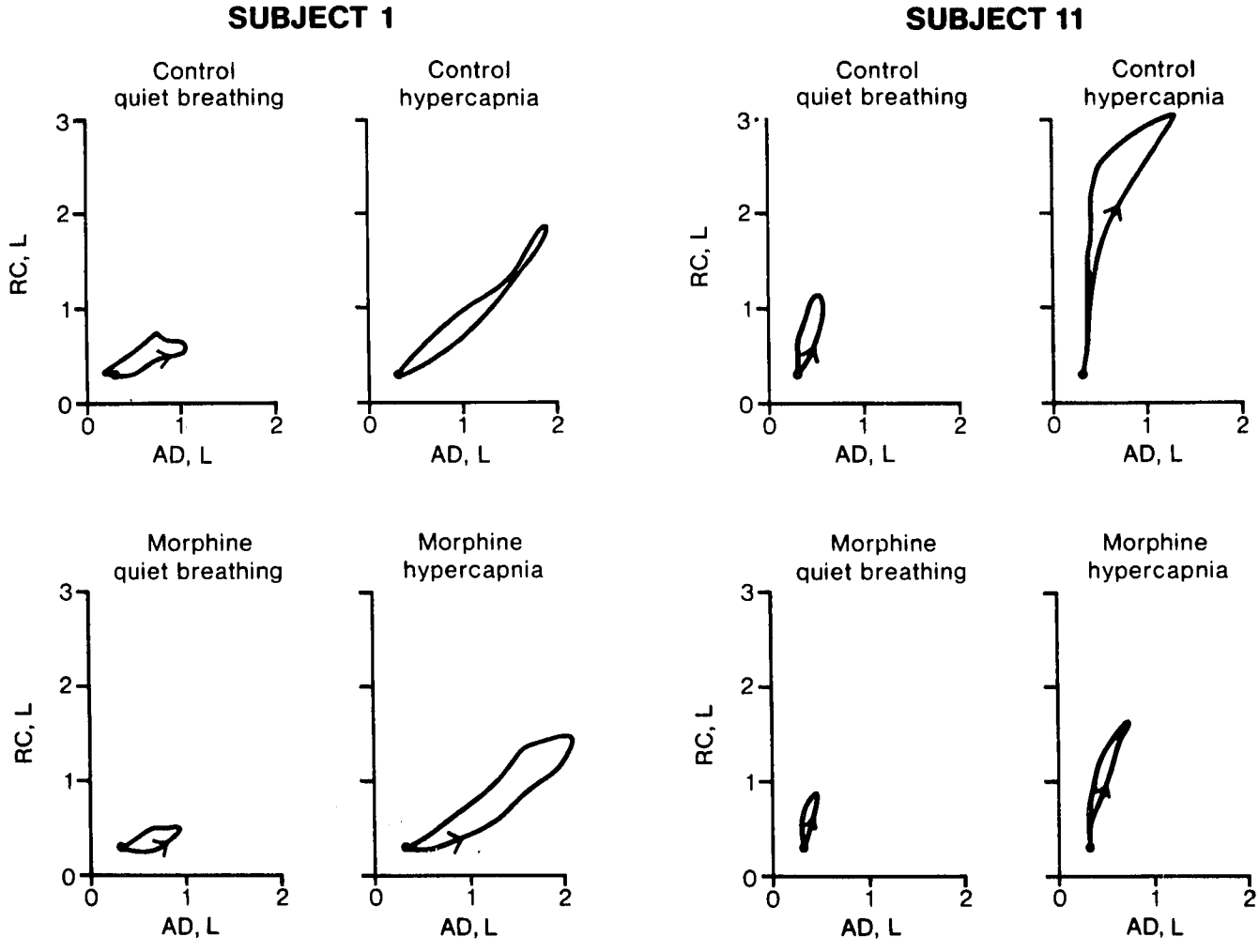

FIG. 1. X-Y plots of tidal volume loops in two subjects obtained from rib cage and abdominal motion, measured with magnetometers. Gains were adjusted so that equal displacements along each axis corresponded to equal compartment volume changes. Loops are shown for quiet breathing, and CO_2 stimulated breathing before and after intravenous morphine, 0.15 mg/kg. Closed circles indicate FRC points. RC = rib cage contribution to tidal volume, and AD = abdomen diaphragm contribution.

observed, the slope of the V_T response did not differ significantly from control (table 1, fig. 2).

When this morphine effect on V_T is analyzed in terms of the relative contribution of RC and AD components to the total response, it is evident that the effect is mediated almost entirely by depression of the RC component; no significant change of either the slope or the position of the AD response occurred after morphine. These findings are similar, but less marked, to those of Tusiewicz *et al.* during halothane anesthesia.[1] However, the implications of the findings are important since the effect of the narcotic in decreasing respiratory frequency causes a large decrease in minute ventilation comparable to that seen with halothane anaesthesia.

The findings of this study have both practical and theoretical implications. The practical implications is that morphine may be a special hazard for patients with impaired diaphragm function, particularly if the drug is administered in non-intensive-care settings without continuous nursing or medical supervision. Such patients may develop severe and life-threatening alveolar hypoventilation. Patients with hyperinflation due to chronic airways disease or increased abdominal (respiratory) load as a consequence of obesity or their surgical condition or a combination of these rely increasingly on intercostal and accessory muscle activity to maintain adequate alveolar ventilation.[1] It is possible that the sensitivity of these patients to the ventilatory depressant activity of such dissimilar drugs as halothane and morphine reflects the greater sensitivity of these muscle groups to the depressant action of the drugs and the inability of an impaired diaphragm in these patients to perform its usual

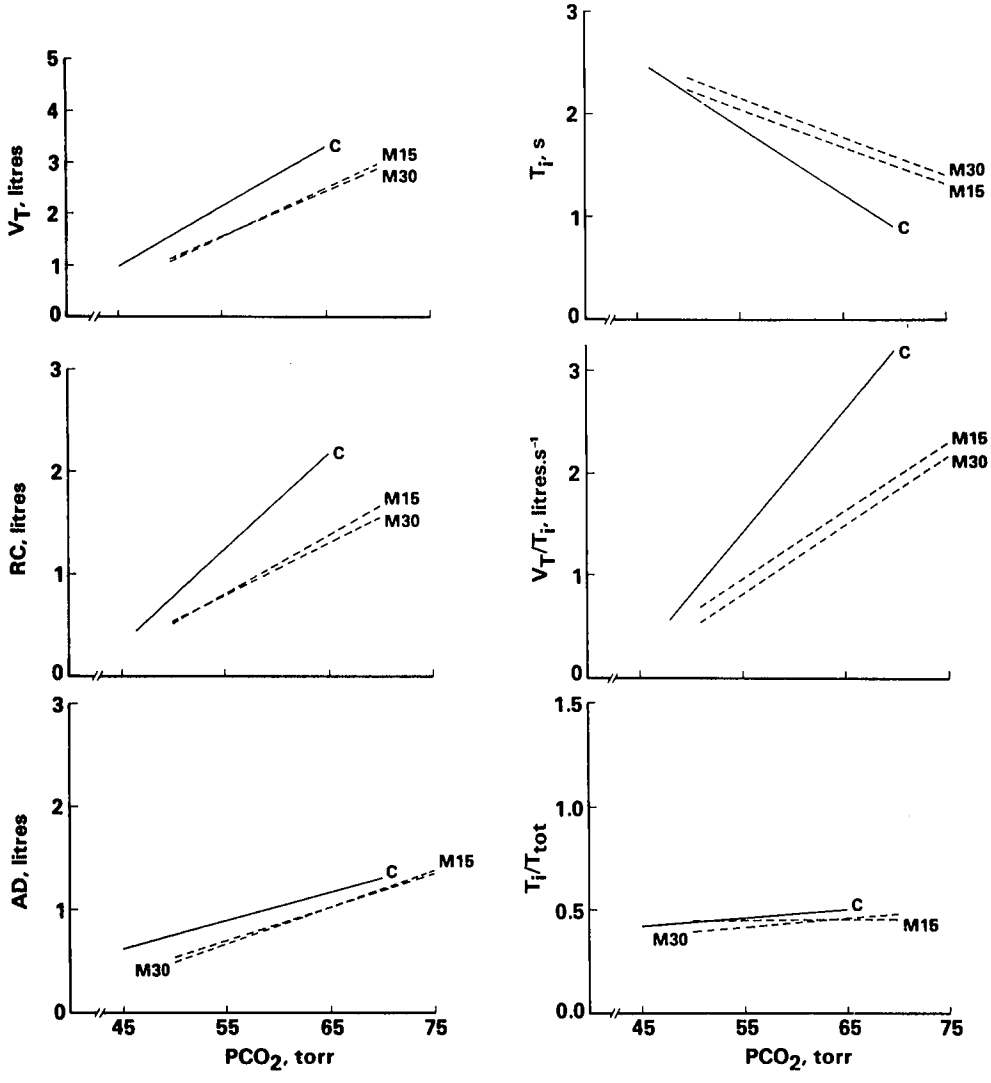

FIG. 2. Mean tidal volume (V_T), rib cage (RC), abdomen diaphragm (AD), inspiratory time (T_i), mean inspiratory flow per breath (V_T/T_i), and inspiratory time: total respiratory cycle duration (T_i/T_{tot}) responses to CO_2. C = control, M_{15} = 15 min, and M_{30} = 30 min after 0.15 mg/kg intravenous morphine.

TABLE 2. Mean Slopes of Inspiratory Time (T_i), Mean Inspiratory Flow, (V_T/T_i), and Inspiratory Time: Total Cycle Duration (T_i/T_{tot}) Responses to CO_2 and ISO-P_{CO_2} Response Curve Positions before, and 15 min (M_{15}) and 30 min (M_{30}) after Intravenous Morphine

Variable	n	Control ± SEM	M_{15}	P	M_{30}	P
$\Delta T_i/\Delta P_{CO_2}$* (s/torr)	13	0.065 ± 0.011	0.036 ± 0.014	N.S.	0.037 ± 0.014	N.S.
ISO-T_i† (s)	13	1.49 ± 0.11	1.83 ± 0.14	<0.01	1.93 ± 0.24	<0.05
$\Delta V_T/T_i/\Delta P_{CO_2}$* ($l \cdot s^{-1} \cdot torr^{-1}$)	13	0.119 ± 0.018	0.067 ± 0.010	N.S.	0.068 ± 0.009	N.S.
ISO-V_T/T_i† (l/s)	13	2.11 ± 0.21	1.35 ± 0.15	<0.001	1.21 ± 0.12	<0.001
$\Delta T_i/T_{tot}/\Delta P_{CO_2}$* $torr^{-1}$	13	0.004 ± 0.001	0.005 ± 0.001	N.S.	0.000 ± 0.001	N.S.
ISO-T_i/T_{tot}†	13	0.48 ± 0.01	0.44 ± 0.02	N.S.	0.45 ± 0.02	N.S.

* Slopes of T_i, V_T/T_i, T_i/T_{tot} responses to CO_2, respectively.
† CO_2 responses curve position variables for T_i, V_T/T_i, and T_i/T_{tot}, respectively. See methods section for detailed explanation of these variables.

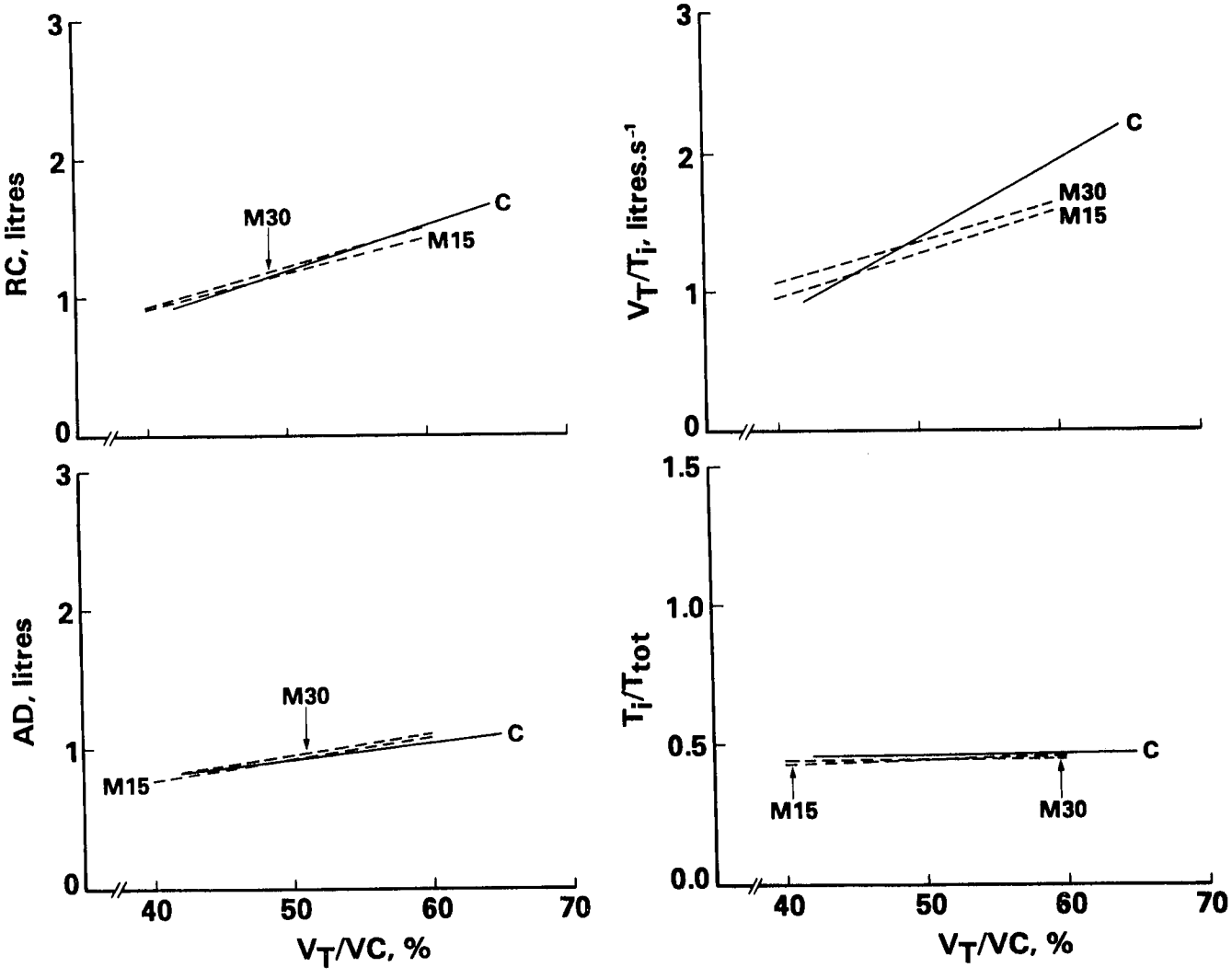

FIG. 3. Mean rib cage (RC), abdomen diaphragm (AD), mean inspiratory flow per breath (V_T/T_i), and inspiratory time: total respiratory cycle duration (T_i/T_{tot}) response as a function of tidal volume, expressed as a per cent of vital capacity (V_T/VC per cent). C = control, M_{15} = 15 min, and M^{30} = 30 min after 0.15 mg/kg intravenous morphine.

function as the principal muscle of breathing at rest.[15,16,25] The diagnosis of impaired diaphragm function is difficult and it is probable that such impairment is more common than is generally appreciated.[25] If this is so, then impaired diaphragm function may be an important cause of alveolar hypoventilation in the recovery room and of patients with chronic lung disease, neuromuscular and muscle diseases to whom narcotics may be given in various hospital settings.

From a theoretical standpoint, the similarity of these observations with morphine and halothane suggest, at first, that both drugs may affect neural mechanisms regulating tidal volume responses in a similar manner. Tusiewicz *et al.* suggested that the striking differences they observed between halothane effects of RC and AD responses might be attributable to different susceptibilites of the motor neurone pools subserving RC (the intercostal motor neuronal pool) and AD (phrenic motor neurone pool) motion.[1] This suggestion raised the novel possibility that spinal motor control systems (rather than medullary respiratory neurones) are a major site of action of ventilatory depressant drugs. However, neither the present study nor that of Tusiewicz *et al.* provides direct evidence of spinal cord effects.

In contrast, there is much neurophysiological evidence for the direct action of ventilatory depressant drugs on medullary respiratory neurones.[26-28] It is conceivable that these differential activities of phrenic and intercostal motor neurone pools may result from different descending influences of medullary respiratory neurones. An-

other possibility is that the different outputs of the RC and AD systems do not reflect specific direct drug effects, but may represent a fundamental property of the respiratory control system. In other words, drugs that reduce ventilatory responses act largely by reducing the RC component of V_T, whereas stimuli that increase ventilatory responses act largely by increasing the RC component of V_T. This interpretation suggests that the AD response to CO_2 is relatively stable and invariant and that the RC response is highly variable and more susceptible to a variety of influences. This suggestion is in agreement with that of Pengelly *et al.*,[4] who studied differences in CO_2 responses in a group of normal subjects. After correction for body size, AD responses to CO_2 in their subjects were similar, whereas all the intersubject variation in CO_2 responses was attributable to interindividual differences in RC response.[4]

When the results of the present study were expressed as functions of tidal volume as per cent of VC (V_T/VC) per cent, there was no change with morphine in the relationship of RC, or AD to tidal volume (fig. 3). This finding lends support to the possibility that compartmental response changes after a ventilatory perturbation, such as that induced by morphine, reflect not a specific effect due to the perturbing influence but the characteristic behavior of the system at that level of ventilation. The present study provides no evidence that the different RC and AD responses to CO_2 reflect different properties of either the separate populations of spinal motor neurons subserving respiratory motor functions or the separate medullary descending influences on the two motor neurone pools. However, the data suggest that these are important questions of respiratory motor control requiring neurophysiologic experimentation and elucidation.

In their study of five patients under methoxyflurane (MOF) anesthesia,[11] Derenne *et al.* found that the effects of MOF on the $\dot{V}_I$, V_T, T_i, T_e, T_T/T_i, T_i/T_{tot} responses to CO_2 were both qualitatively and quantitatively similar to the response here after morphine. The present findings support the concept that V_T/T_i is the fundamental expression of breath-by-breath ventilatory drive, a concept supported increasingly by both neurophysiologic and respirologic evidence.[1,10-13]

Although the trend towards a lower slope of the V_T/T_i relationship to V_T/VC after morphine was not statistically significant, the finding is in marked contrast to the absence of any trend for the RC and AD relationships to V_T/VC. It seems reasonable to suggest that a significant fall in $\Delta V_T/T_i/\Delta V_T/VC$ may have been demonstrated if a larger number of subjects had been studied. Since V_T/T_i is a generally accepted index of breath-by-breath inspiratory drive, and is believed to be generated primarily by medullary inspiratory neurone activity, the finding of the above trend in association with the absence of any such trend for RC and AD lends further support for the view that the different respiratory effects of morphine and halothane are due primarily to central effects of these drugs and not to different direct effects on phrenic and intercostal motor neurone pools.

Finally, the studies of Jones *et al.* in patients undergoing elective surgery also showed that the RC contribution to ventilation was more susceptible to the effects of various anesthetic drugs than the AD component.[29] Their patients exhibited a degree of variability of chest wall motion similar to that found in the present study. However, in the study of Jones *et al.*, a much greater proportion of tidal volume was attributable to the AD component.[29] This may reflect different methodology or a different sample of subjects, or both. Their patients had a mean age of 40 years, and were undergoing anesthesia and surgery.

It is clear, however, from all the studies cited in which V_T is partitioned into RC and AD components, that AD responses are stable under a variety of influences in contrast to the marked variability observed with RC responses.

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