

Respiratory Effects of Clonidine Alone and Combined with Morphine, in Humans

Peter L. Bailey, M.D.,* Richard J. Sperry, M.D.,* G. Kevin Johnson, M.D.,† Stephen J. Eldredge, M.D.,† Katherine A. East, M.S.,‡ Thomas D. East, Ph.D.,§ Nathan L. Pace, M.D.,¶ Theodore H. Stanley, M.D.¶

Because only limited and controversial data exist concerning the respiratory effects of clonidine in humans, the authors evaluated the respiratory effects of clonidine alone and in combination with morphine, in 12 healthy adult males. Subjects received clonidine (0.3–0.4 mg orally), morphine (0.21 mg/kg intramuscularly), or the same doses of the two drugs combined, at three separate sessions in a randomized fashion. The study was balanced for all possible sequences of drug administration. Blood pressure, heart rate, hemoglobin oxygen saturation *via* finger pulse oximetry, and ventilatory and occlusion pressure responses to CO₂ were obtained before and 20, 40, 60, 90, 120, 180, 240, 300, and 360 min after administration of drug or drug combination. Systolic blood pressure decreased significantly only in the clonidine and clonidine plus morphine groups ($P < 0.05$). Hemoglobin oxygen saturation decreased by a statistically significant ($P < 0.05$), though clinically minor, degree only in the morphine or morphine plus clonidine groups. Clonidine alone did not depress the slope of either the ventilatory or the occlusion pressure response to CO₂. In addition, clonidine did not significantly worsen morphine-induced depression of the slope of the ventilatory and occlusion pressure responses in the drug combination group. Both the ventilatory and occlusion pressure responses to CO₂ were shifted to the right in all three drug groups ($P < 0.05$) but were shifted to a significantly lesser degree by clonidine alone than by morphine and morphine plus clonidine. In healthy young adult males, clonidine alone produces little respiratory depression and does not significantly potentiate morphine-induced respiratory depression. (Key words: Analgesics, opioid: morphine. Drug interactions: ventilation. Sympathetic nervous system, alpha-2 adrenergic agonists: clonidine.)

THE ALPHA-2 ADRENERGIC AGONISTS hold significant potential as anesthetic agents.** †† Clonidine, although not the most potent or specific alpha-2 adrenergic agonist, is the prototype of this class of drug now available for

clinical use. In humans, clonidine produces sedation^{1,*††} and analgesia,¹⁻³ decreases opioid and inhalation agent requirements for the induction or maintenance of anesthesia,⁴⁻⁶ promotes hemodynamic and adrenergic stability during anesthesia,^{6,7} and is associated with shorter times to extubation after coronary artery surgery.⁶ Although it has been suggested that minimal respiratory depression occurs with clonidine,^{6,**} other preliminary investigations report the contrary.⁸⁻¹⁰ Therefore, we designed a study to evaluate the effects of clonidine on respiration in humans. In addition, because clonidine may be administered simultaneously with other preanesthetic medications or analgesics, we also evaluated the respiratory effects of clonidine combined with morphine, to study the potential for significant drug interaction.

Materials and Methods

The investigation was approved by the University of Utah Health Sciences Center Institutional Review Board for Human Research, and written and oral informed consent was obtained from each subject. The subjects were 12 healthy adult males between the ages of 18 and 50 yr and not weighing more than 30% above ideal body weight. They had no significant medical conditions, were receiving no chronic medications, and had no history of alcohol or tobacco abuse. The subjects refrained from caffeine and aspirin consumption for at least 12 hr and had nothing to eat or drink for at least 8 hr before being studied. All study sessions began at 7:00 AM.

Each subject was evaluated at three separate sessions at least 48 hr apart. During each session, the subject received either oral clonidine in a range of 4–5 µg/kg (0.30 mg [60–69 kg], 0.35 mg [70–79 kg], or 0.40 mg [80–99 kg]) with a sip of water; intramuscular morphine, 0.21 mg/kg; or the same doses of both morphine plus clonidine. The experimental design was completely balanced for all possible sequences of drug administration. Two subjects were assigned to each of the six possible permutations of the order of drug administration. Subjects were assigned to their permutation group by a computer-generated, permuted-block, restricted randomization table; block size was six subjects. Subjects were not blinded by placebo intramuscular injections, since these may produce pain without analgesia and bias results. The study drug or drug combination was administered by one in-

* Assistant Professor of Anesthesiology.

† Anesthesia Resident.

‡ Research Associate.

§ Associate Professor.

¶ Professor of Anesthesiology.

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Address reprint requests to Dr. Bailey: Department of Anesthesiology, University of Utah School of Medicine, 50 North Medical Drive, Salt Lake City, Utah 84132.

** Bloor BC: Clonidine and other alpha₂ adrenergic agonists: An important new drug class for the perioperative period. *Seminars in Anesthesia* 7:170–177, 1988

†† Maze M, Segal IS, Bloor BC: Clonidine and other alpha₂ adrenergic agonists: Strategies for the rational use of these novel anesthetic agents. *J Clin Anesth* 1:146–157, 1988

investigator while another (blinded to drug administration) monitored the experiment.

On the morning of each study session, a 20-G catheter was inserted in an arm vein after the intradermal administration of 0.2 ml 0.5% lidocaine. Intravenous lactated Ringer's solution was then begun at a rate of 125 ml/h. Baseline systemic blood pressure (vital signs monitor, Critikon Dinamap), and heart rate and hemoglobin oxygen saturation (Sp_{O_2}) (pulse oximeter, Criticare Systems) were recorded while subjects were breathing room air. At the first session, subjects then performed an initial CO_2 rebreathing challenge to familiarize themselves with the test. Subjects wore comfortable head phones emitting white noise to standardize auditory stimuli and soft nose clips to prevent nasal breathing during each CO_2 challenge. Subjects were instructed to keep their eyes closed during each CO_2 challenge. Ten minutes later baseline ventilatory and occlusion pressure responses to CO_2 were obtained by a hyperoxic, hypercapnic technique with a computerized, modified Read rebreathing apparatus (see below). After a 10-min rest period the study drug or drug combination was administered (time 0). Blood pressure, heart rate, and Sp_{O_2} were recorded and additional CO_2 challenges were performed 20, 40, 60, 90, 120, 180, 240, 300 and 360 min later. The maximum heart rate during CO_2 rebreathing also was recorded for each CO_2 challenge.

REBREATHING CIRCUIT AND MEASUREMENT

We used a modified Read rebreathing circuit as previously described¹¹ but with upgraded software and hardware. The rebreathing apparatus had a 7.5-l neoprene rebreathing bag enclosed in a Lucite box; to measure ventilatory flow, a Validyne differential pressure transducer measured the pressure difference across a Fleisch pneumotachograph at the outlet of the box. Flow was directed either into the bag or through the pneumotachograph by a three-way valve located at the mouth of the box, permitting the subject to breathe directly into the room when not rebreathing CO_2 . Inspiratory and expiratory limbs of the circuit were separated by a Hans-Rudolph valve. CO_2 concentration was measured by an infrared CO_2 analyzer (Lifespan 100), which sampled gas at the mouthpiece at a rate of 200 ml/min and returned it to the central chamber of the Hans-Rudolph valve. Inspiratory circuit resistance was no more than $1.9 \text{ cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}^{-1}$ and expiratory circuit resistance was no more than $1.7 \text{ cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}^{-1}$ between flow rates of 15 and 135 l/min.

Flow, pressure, and CO_2 signals were sampled by a microcomputer (Samsung XTC 8088) 12-bit analog to digital (A/D) convertor (Burr-Brown MP7208 Data Acquisition System) with a resolution of 4.8 mV per A/D unit

and a range of $\pm 10 \text{ V}$. Inspiratory mouth occlusion pressure (P0.1) measurements were made at the start of every inspiration. The inspiratory occlusion valve was closed 300 msec after the start of expiration. If the shape of the occluded pressure waveform was satisfactory, inspiration pressure was sampled and stored. A signal to reopen the valve was sent 120 ms after the onset of inspiration.

REBREATHING DATA COLLECTION AND ANALYSIS

After the subject was allowed to breathe quietly through the mouthpiece with the nose clip in place, the three-way valve was switched to the rebreathing bag previously filled with 7.0% CO_2 and 93.0% O_2 . For each breath, the following data were displayed on the video terminal and stored electronically: inspiratory time (T_I); breath duration (T_{TOT}); fractional inspired CO_2 concentration ($\%IN_{CO_2}$) and end-tidal CO_2 concentration (PET_{CO_2}); tidal volume (V_T); minute ventilation (\dot{V}_E); P0.1; and elapsed time since the start of CO_2 rebreathing. All gas volumes were corrected to BTPS. Subjects were encouraged to rebreathe as long as possible but were permitted to stop at any time. The desired goal was to reach a PET_{CO_2} of 65 mmHg. The increase in PET_{CO_2} during CO_2 rebreathing tests was always at least 15 mmHg, but not more than 25 mmHg.

After completion of each CO_2 challenge, plots of \dot{V}_E versus PET_{CO_2} and P0.1 versus PET_{CO_2} were displayed on the video display terminal. To ensure that the regression line reflected only data from the linear portion of ventilatory response, data from the first 10 breaths were excluded from analysis. Data from all other breaths were used for least-squares linear regression. The slope of the ventilatory response to CO_2 (\dot{V}_E/CO_2 , $\text{l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$), the estimated \dot{V}_E at a PET_{CO_2} of 50 mmHg (\dot{V}_E50 , l/min), the slope of the occlusion pressure response to CO_2 (P0.1/ CO_2 , $\text{cmH}_2\text{O}/\text{mmHg}$), and the estimated occlusion pressure at a PET_{CO_2} of 50 mmHg (P0.1 50, cmH_2O) were the parameters chosen to depict each subject's response to CO_2 .

All values are represented as the mean \pm SEM. Inter-group comparisons were made by repeated-measurement multivariate analysis of covariance using restricted maximum likelihood estimation with a structured covariance matrix. Intragroup comparisons were made by one-way analysis of variance for repeated measures. Statistics were determined by the Wald chi-squared test with significance set at $P < 0.05$.

Results

Two subjects did not complete the study for personal reasons, and two additional volunteers were recruited to fill their random positions. No other problems or complications occurred. Mean baseline heart rates (beats per

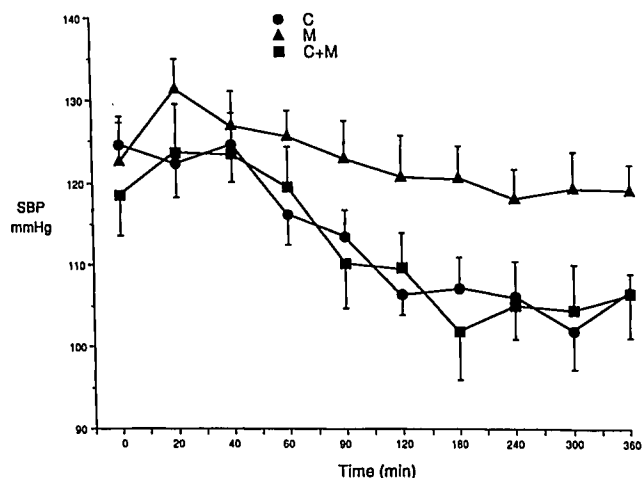


FIG. 1. Systolic blood pressure (mmHg) over time (time 0 = control) for each of the three drug groups. Significant decreases occurred only in the clonidine and clonidine plus morphine groups.

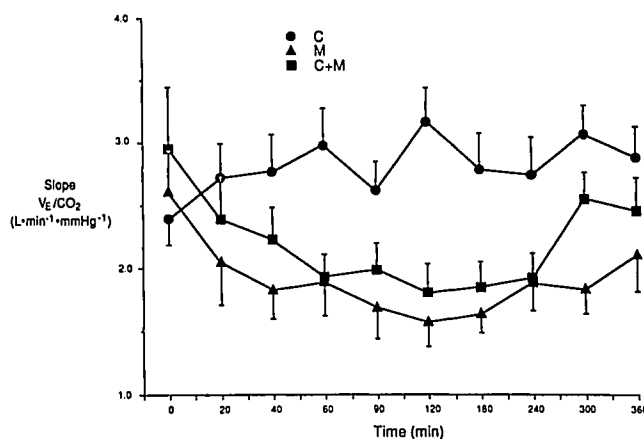


FIG. 2. Slope of the ventilatory response to CO₂ (mean ± SEM); $l \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ over time (time 0 = control) for the three drug groups. Changes were statistically significant for the morphine and morphine plus clonidine groups but not for the clonidine group.

minute) did not differ statistically between groups and ranged from 77.7 ± 2.6 in the clonidine group to 78.7 ± 3.4 in the clonidine plus morphine group and 81.0 ± 3.4 in the morphine group. Resting heart rate decreased significantly but by a similar degree in all three groups. Minimum mean resting heart rates were 65.2 ± 3.7 300 min after clonidine, 63.9 ± 2.7 240 min after morphine, and 59.5 ± 2.7 120 min after morphine plus clonidine. CO₂ rebreathing caused significant but similar increases in heart rate in all three groups.

Systolic blood pressure was similar at baseline for all three groups (fig. 1). Intergroup comparisons demonstrated statistically significant decreases in systolic blood pressure for those receiving clonidine or clonidine plus morphine but not for those receiving morphine alone ($P < 0.0001$; fig. 1). There was no significant difference in systolic blood pressure changes between the morphine plus clonidine and the clonidine groups. Intragroup comparisons demonstrated significant decreases in systolic blood pressure for both the clonidine ($P < 0.0001$) and the morphine plus clonidine groups ($P < 0.0001$). The morphine group had a small but statistically significant increase in systolic blood pressure ($P = 0.0024$). Small but statistically significant decreases in SpO₂ occurred

within the morphine group ($P = 0.0004$) and the morphine plus clonidine group ($P = 0.0012$) but not within the clonidine group (table 1). Intergroup differences in SpO₂ were not statistically significant.

Intergroup comparisons of slope of the ventilatory response to CO₂ revealed a significant and similar degree of depression in the morphine and morphine plus clonidine groups compared to the clonidine group ($P < 0.0001$) (fig. 2). Intragroup changes in the slope of the ventilatory response to CO₂ were statistically significant for the morphine ($P = 0.0001$) and morphine plus clonidine groups ($P < 0.0001$) but not for the clonidine group (fig. 2). Intergroup differences in the \dot{V}_{E50} or shift of the ventilatory response also were statistically significant, and a greater shift occurred in the morphine and morphine plus clonidine groups than in the clonidine group ($P = 0.002$) (fig. 3). Differences between the morphine and morphine plus clonidine groups were not significant. Changes in the \dot{V}_{E50} within each group were statistically significant for the morphine ($P < 0.0001$), morphine plus clonidine ($P < 0.0001$), and clonidine groups ($P = 0.0085$) (fig. 3).

Occlusion pressure response data concurred with ventilatory response data. Intergroup comparisons of the slope of the occlusion pressure response to CO₂ revealed

TABLE 1. Hemoglobin Oxygen Saturation (%) over Time

	Control	Time After Drug Administration (min)					
		20	40	60	120	240	360
Clonidine	95.8 ± 0.7	95.9 ± 0.7	95.6 ± 0.4	95.3 ± 0.5	94.8 ± 0.8	95.5 ± 0.5	95.5 ± 0.7
Morphine*	96.8 ± 0.6	95.8 ± 0.7	94.6 ± 0.9	94.9 ± 0.8	94.5 ± 1.0	95.9 ± 0.7	96.4 ± 1.0
Morphine + clonidine*	97.0 ± 0.6	96.2 ± 0.4	95.7 ± 0.4	94.6 ± 0.8	94.1 ± 1.1	95.4 ± 0.5	96.0 ± 0.5

Mean ± SEM.

* $P < 0.05$, one-way analysis of variance.

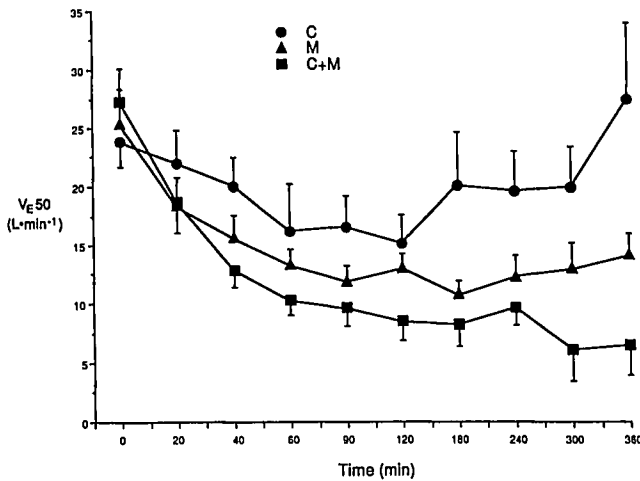


FIG. 3. V_{E50} (mean \pm SEM; l/min) over time (time 0 = control) for the three drug groups. All three groups had significant changes; statistically greater depression occurred in the morphine and morphine plus clonidine groups compared to the clonidine group.

a statistically significant and similar degree of depression in the morphine and morphine plus clonidine groups compared to the clonidine group ($P = 0.0004$, fig. 4). Intragroup changes in the occlusion pressure response were statistically significant for the morphine ($P = 0.0027$) and morphine plus clonidine groups ($P = 0.0134$) but not for the clonidine group (fig. 4). P01 50 data also concurred with the ventilatory response data. Intergroup differences in the P01 50 or shift of the occlusion pressure response were statistically significant, and a greater shift occurred in the morphine and morphine plus clonidine groups than in the clonidine group ($P = 0.0001$; fig. 5). Differences between the morphine and morphine plus clonidine group were not statistically significant. Changes in the P01 50

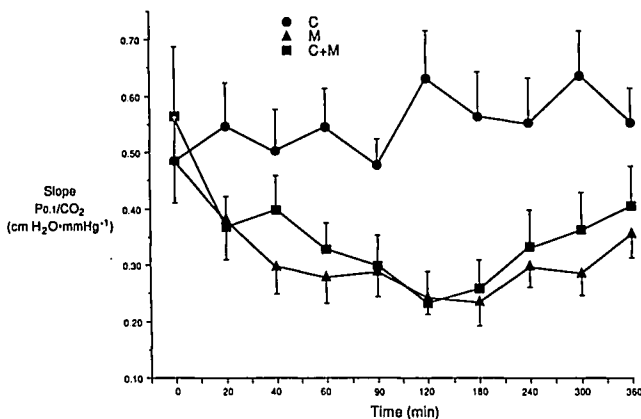


FIG. 4. Slope of the occlusion pressure response to CO_2 (mean \pm SEM; $cmH_2O/mmHg$) over time (time 0 = control) for the three drug groups. Changes were significant for the morphine and morphine plus clonidine groups but not for the clonidine group.

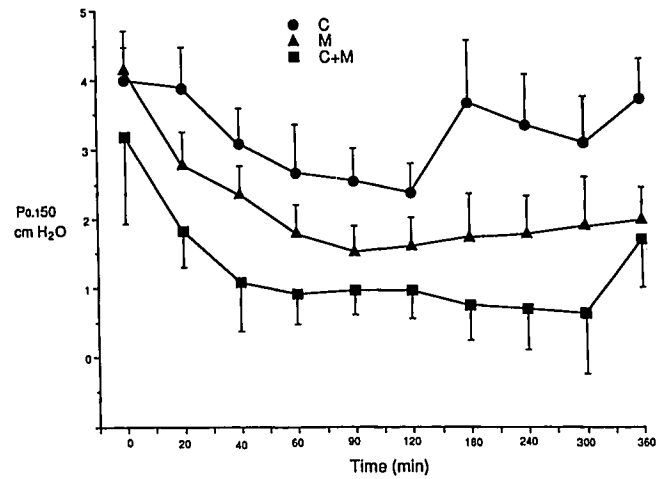


FIG. 5. P01 50 (mean \pm SEM; cmH_2O) over time (time 0 = control) for the three drug groups. All three groups had statistically significant changes; significantly greater depression occurred in the morphine and morphine plus clonidine groups compared to the clonidine group.

within each group were statistically significant for the morphine ($P < 0.0001$), morphine plus clonidine ($P = 0.0002$), and clonidine groups ($P = 0.0116$).

Discussion

Because alpha-2 adrenergic agonists produce sedation, analgesia, and reductions in anesthetic requirements while promoting hemodynamic stability, they hold considerable promise as future anesthetic adjuvants.^{**} Most of the desirable actions associated with these agents, including sedation, anxiolysis, analgesia, and hypnosis, are elicited at central alpha-2 adrenergic receptors.^{††} Clonidine is between 10 and 60 times more potent an analgesic than is morphine on a molar basis in animals and also is an analgesic in humans.^{2,12,13,14} It has been noted that alpha-2 adrenergic agonists, including clonidine, have minimal respiratory depressant properties in humans and that there is little physiologic basis for alpha-2 adrenergic receptor stimulation induced respiratory depression.¹⁵ In addition, it has been suggested that supplementing morphine analgesia with clonidine can reduce opioid requirements and lessen associated respiratory depression.¹³ Others, however, have reported that alpha-2 adrenergic agonists may indeed produce respiratory depression in humans^{8,9,10} and that alpha-2 adrenergic-mediated sedation does involve interaction with opioid neurotransmitter systems.¹⁶ Our study was designed to evaluate the effects of clonidine alone and of clonidine in combination with morphine on respiration.

A clonidine effect was achieved in our study as demonstrated by the significant decrease of systolic blood pressure in the two groups receiving the drug but not in

the group receiving morphine alone. Oral clonidine is almost completely absorbed and produces peak plasma concentrations approximately 60–90 min after injection.¹⁷ This coincides with the lower blood pressures (as seen in figure 1) starting 90 min after clonidine administration. Intramuscular morphine is also almost completely absorbed, and peak plasma concentrations occur within 20–30 min with near peak concentrations persisting beyond 1 h.^{18,19} Thus, both clonidine and morphine have onsets of effect that coincide enough to reveal significant interactions, should such interactions exist. However, decreases in blood pressure in the group receiving morphine plus clonidine were not different from decreases in the group receiving clonidine alone; this demonstrates that there is little hemodynamic drug interaction.

Sp_O₂ decreased in subjects receiving morphine alone or morphine plus clonidine (table 1). These statistically significant though clinically minor changes occurred in subjects breathing room air at altitude (approximately 5,000 ft above sea level, dry barometric pressure approximately 600 mmHg). Thus, while Eisenach²⁰ reported that clonidine produces hypoxemia in sheep, possibly through a unique peripheral alpha-2 adrenergic platelet-mediated (microembolic) action, our subjects demonstrated no hypoxemia. Eisenach *et al.*¹⁵ also reported that epidural clonidine (100–900 µg) in postsurgical patients did not produce changes in Sp_O₂ or arterial blood gases (carbon dioxide tension [PaCO₂] and oxygen tension [PaO₂]). In contrast, Veillette *et al.*⁹ concluded from a study of six volunteers that significant ventilatory disturbances could be produced by preanesthetic medication with clonidine 0.3 mg. The basis for this conclusion was that one subject who had received clonidine had an episode of airway obstruction and another subject had an apneic episode, each resulting in an Sp_O₂ of less than 90%. No statistical evidence can be drawn from this observation, especially because the mean Sp_O₂ in that study did not differ between placebo- and clonidine-treated groups. We did not observe any episodes of airway obstruction or apnea in our clonidine-treated subjects, nor did we observe any Sp_O₂ of less than 90%.

The ventilatory and occlusion pressure responses to carbon dioxide challenges are considered sensitive tests of respiratory function and are widely used to assess drug effects.^{21,22} The occlusion pressure response has the advantage of not being affected by changes in pulmonary resistance or compliance because gas flow is absent during the occlusion pressure measurement. Changes in airway resistance or chest compliance may alter the ventilatory response and yet be attributed to a central brain stem effect if only the ventilatory response is studied. In our study, both the ventilatory and occlusion pressure responses were quantified by the slope and the shift of the response. Clonidine alone did not depress either the slope

of the ventilatory or the occlusion pressure response (figs. 2 and 4). Although a tendency toward enhancement of these responses is suggested, statistical significance was not attained. In addition, morphine-induced depression of the slopes of the ventilatory and occlusion pressure responses was not worsened by combining clonidine with morphine. The slopes of these responses are an important measure of the ability of the brain and body to respond to increases in carbon dioxide: once the slope of the ventilatory response is depressed (*e.g.*, by drugs) to less than normal (less than 0.5 l·min⁻¹·mmHg),²³ CO₂ accumulation and the resulting CO₂ narcosis and worsening respiratory depression are likely to occur. Thus, it appears that clonidine has no negative impact on this important respiratory reflex.

The ventilatory and occlusion pressure responses were moderately shifted to the right in all three groups (figs. 3 and 5). When the PETCO₂ reached 50 mmHg, ventilation decreased from a mean of 24 l/min at baseline to a low mean of 15 l/min 120 min after clonidine. In a similar fashion, the occlusion pressure dropped from a mean of 4.0 cmH₂O at baseline when the PETCO₂ was 50 mmHg to a low mean of 2.4 cmH₂O 120 min after clonidine. Morphine-induced shifts were greater than those produced by clonidine. (For example, the ventilatory response decreased from a mean of 25 l/min at baseline to a low mean of 11 l/min 180 min after administration). Combining the drugs produced a tendency toward an additive effect, although the shifts induced by morphine alone were not statistically different from those produced by morphine plus clonidine. These shifts to the right of both the ventilatory and occlusion pressure responses to CO₂ are traditionally interpreted as an elevated "set point." They represent respiratory depression and would be clinically evident most likely as an increased resting PETCO₂ or PaCO₂. The significance of this increase would depend on its degree and the clinical circumstance. However, its impact is likely to be minimized, since the brain stem's and ventilatory apparatus' ability to respond to significant increases in CO₂ remains unimpaired, as demonstrated by an unaffected slope response.

Others have reported respiratory depression with clonidine in humans.^{8,9} Rougé *et al.*⁸ reported that clonidine (330 ± 15 µg) significantly reduced the ventilatory and occlusion pressure responses to CO₂. However, there was no control or comparison drug simultaneously studied; only seven subjects were evaluated; and maximum depression of the slope of ventilatory response to CO₂ was 22%, a relatively small decrease. Veillette *et al.*⁹ also suggested that clonidine depresses resting \dot{V}_E . Although these investigators did have a comparison placebo group, the number of subjects was small (n = 6); clonidine was not administered on a weight basis; and the small decreases in \dot{V}_E that they observed did not consistently differ from

placebo. In addition, the decreases in \dot{V}_E could have been due to sedation and a decreased metabolic and CO_2 production rate. More recently, Ward *et al.*^{‡‡} documented that dexmedetomidine, a more potent centrally acting alpha-2 adrenergic agonist, produced a significant increase in resting PaCO_2 and produced shift and depression of the slope of the ventilatory response to CO_2 in ten normal male subjects. Although qualified as "mild" (equivalent to 0.6 mg/kg meperidine), the depression of the slope response in that study is different from our finding and may be potency- or specificity-related.

Weaknesses of our study are in part due to our decision to perturb our subjects only minimally during the evaluation of respiratory function. Most of clonidine's actions are well documented to occur at the doses we used. Therefore, we elected not to perform concurrent evaluations of sedation and analgesia. In addition, we chose to use as a comparison a known drug, morphine, instead of a placebo. Thus the apparent (though not significant) enhancement of the slopes of the ventilatory and occlusion pressure responses to CO_2 may be more or less related to learning or time effects rather than to a clonidine effect. Our reasons for choosing morphine instead of a placebo are discussed above.

In summary, we have documented that in healthy young adult male volunteers, clonidine, in the doses studied, produces no effects on SpO_2 and no depression of the slopes of the ventilatory and occlusion pressure response to CO_2 . Although mild to moderate shifts in these response curves did occur, their physiologic impact is likely to be minimized because the slopes of the responses remain intact. In addition, clonidine-morphine interactions were minimal: clonidine-induced hemodynamic effects were not potentiated by morphine, and morphine-induced respiratory depression was not worsened by clonidine. Whether or not these results are valid for more elderly or ill patients or with other alpha-2 adrenergic agonists is not yet known.

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