Anesthesiology
V 37, No 4, October 1972

Cognitive Function after Hypocapnic Hyperventilation

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To investigate functional impairment subsequent to arterial hypocapnia, six healthy young men served as their own controls for two thiopental–N_2O–*d*-tubocurarine anesthesias lasting more than 125 minutes, one with and one without hypocapnia (Pa_{CO_2} 18 torr). Subjects were trained to stability on five recognized tests of cognitive function (simple and disjunctive visual reaction times, visual span of apprehension, forward letter span, and dichotic listening). Performance was evaluated daily for four days before anesthesia, 90 minutes after anesthesia, and daily thereafter until performance had reached the baseline values. No significant changes in performance were observed following either hypocapnic or normocapnic anesthesia. In part, this may have been related to the highly motivated and proficient population studied; therefore, these conclusions may not apply to hospital patients. (Key words: Hypocapnia; Hyperventilation; Cognitive function; Awareness in anesthesia.)

CONTROLLED VENTILATION is frequently associated with purposeful or inadvertent arterial hypocapnia. Proponents of such ventilatory management see benefit in its reduction in anesthetic requirements, suppression of spontaneous respiratory movements, and the rapid reversibility of these effects.[1-3] It remains to be firmly established that this practice is not without harmful sequelae both during and after the period of hyperventilation.

In order to eliminate the many variables associated with the postanesthesia study of surgical patients, six healthy cooperative subjects served as their own controls in a study to assess cognitive function in the posthyperventilation period. Anesthetic drugs were restricted to induction doses of thiopental, topical anesthesia applied to the airway, 70 per cent nitrous oxide, and *d*-tubocurarine, so that rapid return to full consciousness would be possible at the earliest interval.

Method

Six healthy male graduate students, 22–31 years old, weighing 71–84 kg, were studied. Informed consent was obtained from each subject. Financial compensation was such as to encourage complete cooperation during the periods of cognitive function testing. Each subject served as his own control for the two experimental anesthesia situations; one being ventilation at a Pa_{CO_2} of 18 torr and the other, ventilation at a Pa_{CO_2} of 40 torr. Three to four days prior to anesthesia, 90 minutes after anesthesia, and daily for four days following each of the two periods of anesthesia, performance on five tests of cognitive function was evaluated. Neither the subject nor the psychologist (G. B.) performing the test was aware of whether anesthesia had involved normocapnic or hypocapnic ventilation.

ANESTHESIA

Subjects were unpremedicated and had fasted 14 hours prior to each period of anesthesia. Using local anesthesia, plastic cannulas were inserted into the radial artery and a peripheral vein. Monitoring included telemetered ECG, direct and indirect measurements of blood pressure, and intermittent determinations of blood–gas and inspired gas tensions, tidal and minute ventilation, and nasopharyngeal temperature. Five minutes before induction each subject received 0.5 mg

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Accepted for publication March 1, 1972. Presented at the Annual Meeting of the American Society of Anesthesiologists, October 1971, Atlanta, Georgia. Supported by Grant (RR-46) from the General Clinical Research Centers Program of the Division of Resources, N.I.H. and by North Carolina Heart Association Grant 1967-70-A-42.

TABLE 1. Subjects' Ages and Weights, Doses of Thiopental and *d*-Tubocurarine, and Intervals from Induction to Testing

	Age (Years)	Weight (kg)	Thiopental Induction (mg)	Total *d*-Tubocurarine (mg)		Interval from Induction to Testing (min)
				P_{aCO_2} 18	P_{aCO_2} 40	
Subject 1	29	89	500	63	60	210
Subject 2	27	75	450	74	50	240
Subject 3	22	71	500	50	41	250
Subject 4	23	78	450	57	51	228
Subject 5	23	84	450	54	48	240
Subject 6	31	79	500	61	46	230
MEAN	25.8	79.3	475	57.5 ± SE*	49.3 ± SE*	233

* Significantly more *d*-tubocurarine was necessary during hypocapnic anesthesia ($P < 0.02$).

atropine iv. Subjects were anesthetized with thiopental (Pentothal) administered at a rate of 250 mg/min into a fast-flowing intravenous infusion of glucose in distilled water, in a dose sufficient to obtund the eyelash reflex completely (375–425 mg). This was followed by *d*-tubocurarine, 0.5 mg/kg, iv. After five minutes of assisted ventilation with 70 per cent nitrous oxide and 30 per cent oxygen, an additional 75 mg of thiopental were injected, 100 mg of lidocaine (Xylocaine) were sprayed into the larynx and trachea, and an 8.5-mm-ID endotracheal tube was inserted. An Air Shields anesthesia ventilator was then used to provide either normocapnic (Pa_{CO_2} 38–41 torr) or hypocapnic (Pa_{CO_2} 17–19 torr) ventilation at approximately 2½ times the normal ventilatory requirements, as predicted by the Radford nomogram. Normocapnic hyperventilation was accomplished by regulation of fresh gas inflow into a T-piece circuit. Minor adjustments in ventilation and per cent inspired oxygen were made on the basis of frequent blood and inspired gas determinations, Pa_{O_2} being kept between 125 and 150 torr during each period of anesthesia. Additional *d*-tubocurarine was given in 3–6-mg amounts as needed to obtund any persistent and gross muscle movement. After 120 minutes, at the predetermined Pa_{CO_2}, *d*-tubocurarine reversal was effected with 1.5 mg atropine, followed by 2.5 mg neostigmine, iv. After five more minutes the subject's ventilation was manually assisted until ventilation was judged adequate and the subject was reacting to the presence of the endotracheal tube. Half an hour after extubation, each subject responded to a questionnaire concerning the anesthesia, and approximately half an hour later he was tested as described below.

Ventilator techniques during the initial periods of anesthesia were determined randomly, so that three subjects received normocapnic hyperventilation and three, hypocapnic hyperventilation. Each subject received the same induction dose of thiopental for his second period of anesthesia, while supplemental *d*-tubocurarine was administered only as necessary during each anesthesia. The durations of nitrous oxide inhalation and the intervals from thiopental induction to onset of testing were almost identical for all subjects, ranging from 140 to 150 minutes and 210 to 250 minutes, respectively (table 1).

COGNITIVE FUNCTION TESTING

Subjects were selected following an initial screening procedure which eliminated any whose performances on any of the tests were either grossly erratic or significantly deviant from the established norms for these tests. The battery of five tests included simple and disjunctive reaction time tasks, visual span of apprehension, forward letter span, and dichotic listening. These tests were selected according to four criteria: 1) as a group they provide a fairly comprehensive survey of cognitive function; 2) they require neither extensive time periods nor continued daily testing for establishment of stable baseline levels

of performance; 3) all are standard experimental psychological techniques for which much information about effects of practice, normal scores, and experimenter technique is available; 4) the tests can be administered within a one-hour period, so that fatigue, boredom, and inattention will not influence performance.[4-7]

The *reaction time tests* (RT) measure a perceptual motor skill at two levels of complexity. In the Simple RT task a single decision is required: is the stimulus present or absent? The subject responds to the stimulus (a light) by releasing a push button. The Disjunctive RT requires more complex decision making. The subject must first decide upon the presence or absence of the stimulus, as in the Simple RT. Also, he must decide which of two possible stimuli (two different lights) is present and respond differentially.

A minimum of 300 Simple and 350 Disjunctive RT trials was given during a period of three days to achieve a stable value for the baseline measure made on the day prior to anesthesia.[7] The RT for this and every subsequent session was the mean of a block of 50 trials administered in two sets of 25 with a two-minute rest period between sets. Prior to the second administration of anesthesia, subjects were tested for two to four days until RT's had stabilized at a value equal to or less than that of the last session following the first treatment. Simple RT's of less than 120 ms and Disjunctive RT's of less than 150 ms were discarded as anticipation errors.

The test for *visual span of apprehension* consisted of the tachistoscopic presentation of random groups of black dots on a white field. Dots were presented for 100 ms via a tachistoscope (Lafayette Electronics portable tachistoscope), and subjects were required to estimate the number of dots presented. The subject initiated each stimulus presentation himself, thus eliminating the need for warning signals. The visual span of apprehension in the normal subject under the standard conditions described above is relatively stable over time, with a normal value of about seven dots.[7] Stimulus duration was held constant at the standard value of 100 ms, a period too brief to permit scanning eye movements.[7] The same set of 50 cards with one to eight dots was presented in random order in each session. The dependent variable was the number of dots which the subjects could estimate correctly on 50 per cent of the trials. Although effects of practice in this task are known to be slight, two practice trials were given before the baseline value was obtained. Before the second anesthesia, subjects were retested to insure that the level of performance remained at the baseline value. Following anesthesia, testing was conducted daily until the span was equal to or greater than the baseline span.

The *forward letter span* task tests short-term verbal memory.[8,9] The dependent variable is the length of the longest string of letters which the subject can repeat correctly 50 per cent of the time. The form of the test used in this study involves the presentation of strings of letters with four levels of approximation to actual English text.[10]

In the *dichotic listening* task two different messages are presented simultaneously, one to each ear, via stereo tape recorder and headphones. The subject's task is to repeat both of these messages, in any order. In this study the messages were two strings of three digits each, and no digit appeared more than once in any presentation. The dependent variable was the total number of digits repeated correctly. Use of this type of simultaneous testing in behavioral testing is relatively recent; however, it has been shown that such testing is much more sensitive to some physiologic variables, notably aging, than is the more traditional digit span test.[11] The test was administered to subjects three times before the baseline value was obtained, and the procedures for repeated treatments were the same as in the letter span testing. Each value obtained was the total number of digits correct for three trials of 24 triplet pairs each. The pairs were presented at a rate of one pair per 500 ms, with a break of three seconds between each triplet pair and the next. This test provides a measure of short-term verbal memory and also measures the ability to attend selectively to each of two memory stores having the same temporal characteristics. Thus, the task pro-

TABLE 2. Simple Reaction Times*

	$Paco_2$ 40 torr	$Paco_2$ 18 torr
Last preanesthesia test (day 1)	171.6 ± SE 5.77 ms	178.2 ± SE 11.66 ms
First postanesthesia test (day 2)	192.5 ± SE 6.91 ms	197.0 ± SE 16.75 ms

* Group mean values and SEM for the Simple RT test baseline and immediately postanesthesia for both anesthetic situations. No significant difference was observed.

TABLE 3. Disjunctive Reaction Times*

	$Paco_2$ 40 torr	$Paco_2$ 18 torr
Last preanesthesia test (day 1)	218.5 ± SE 5.04 ms	220.2 ± SE 14.84 ms
First postanesthesia test (day 2)	231.0 ± SE 15.60 ms	240.2 ± SE 22.08 ms
Second postanesthesia test (day 3)	217.5 ± SE 6.72 ms	206.1 ± SE 13.96 ms

* Group mean values and SEM for the Disjunctive RT test baseline and immediately postanesthesia for both anesthetic situations. RT was significantly increased 90 minutes after anesthesia ($P < 0.05$), but this increment was not significantly greater following either normocapnic or hypocapnic anesthesia.

TABLE 4. Digits Repeated Correctly in Dichotic Listening*

	$Paco_2$ 40 torr	$Paco_2$ 18 torr
Last preanesthesia test (day 1)	373.83 ± SE 23.61	378.00 ± SE 18.58
First postanesthesia test (day 2)	372.00 ± SE 23.19	377.00 ± SE 21.47

* Pre- and postanesthesia group means and SEM for the number of digits correctly repeated in the Dichotic Listening task for both anesthesias. The maximum possible score was 432.

TABLE 5. Visual Spans*

	$Paco_2$ 40 torr	$Paco_2$ 18 torr
Last preanesthesia test (day 1)	7.17 ± SE 0.27	6.67 ± SE 0.56
First postanesthesia test (day 2)	5.67 ± SE 1.09	5.00 ± SE 1.44

* Pre- and postanesthesia group mean and SEM for the visual span of apprehension task for both anesthesias. No significant differences were observed ($P > 0.10$).

vides measures of the processing and storage of auditory information, as well as the focusing of selective attention.

Results

The induction doses of thiopental and the total amounts of *d*-tubocurarine needed during each period of anesthesia are listed in table 1. Requirements for *d*-tubocurarine were significantly greater during hypocapnic anesthesia ($P < 0.02$). There were no significant differences between hypocapnic and normocapnic anesthesias with respect to measured circulatory or respiratory values, or postanesthesia replies to questions concerning memory, dreaming and awareness. No subject reported "awareness" during any period of anesthesia. On four of the 12 occasions nonspecific dreaming was reported, twice following hypocapnia and twice following normocapnia. In no instance was the dream characterized as "unpleasant," nor could details of any dream be vividly recalled. Also, the questionnaire indicated that retrograde amnesia, if any, lasted only a few seconds.

The performances on all tests of cognitive and perceptual–motor function following anesthesia with hypocapnia did not differ significantly from those following anesthesia with normocapnia. Test results (tables 2–6) were subjected to analysis of variance and to matched-pairs t testing. The only significant difference between pre- and postanesthesia values (of equal magnitude in hypocapnic and in normocapnic anesthesia) was in the Disjunctive RT task; these responses returned to baseline 24 hours after anesthesia.

Discussion

Results of tests conducted after anesthesia which involved arterial hypocapnia did not differ significantly from results of tests after anesthesia with arterial normocapnia. The type of anesthesia used in the present study appears to have little, if any, effect upon cognitive function assessed later than 90 minutes after its termination, or later than 210 minutes after thiopental induction.

The only significant ($P < 0.05$) difference between pre- and postanesthesia values was in the responses to the Disjunctive RT task, and

TABLE 6. Forward Letter Spans*

	Level of Approximation			
	0	1	2	3
$Paco_2$ 40 torr				
Last preanesthesia test (day 1)	6.83 ± SE 0.60	7.33 ± SE 0.10	7.50 ± SE 0.22	7.50 ± SE 0.22
First postanesthesia test (day 2)	6.83 ± SE 0.60	7.00 ± SE 0.26	7.33 ± SE 0.33	7.50 ± SE 0.22
$Paco_2$ 18 torr				
Last preanesthesia test (day 1)	6.83 ± SE 0.60	7.17 ± SE 0.30	7.33 ± SE 0.33	7.67 ± SE 0.21
First postanesthesia test (day 2)	7.50 ± SE 0.22	7.67 ± SE 0.21	7.50 ± SE 0.22	7.67 ± SE 0.33

* Pre- and postanesthesia and SEM group means for Letter Span of four different levels of approximation to English text for both anesthesias. No significant differences were observed.

these returned to baseline 24 hours after anesthesia. However, it is possible that the earlier postanesthesia difference was owing to residual curarization. As the increments in the Simple RT's and the Disjunctive RT's from pre- and postanesthesia values were similar, the increased latencies may have represented increases in the motor component owing to residual neuromuscular blockade. Had the increased latencies been the result of effects on cognitive functioning, it would be expected that the Disjunctive RT task would have shown a greater increase than the Simple RT. As an induction dose of thiopental reduces MAC for less than four hours, and as the intervals from induction to testing ranged from 210 to 250 minutes, a significant depressant effect attributable to the thiopental might not be expected, even though biotransformation would not have been complete.[12, 13] Wollman and Orkin [4] demonstrated prolonged reaction times in patients following hyperventilation; in some instances, reaction times were prolonged for as long as six days following anesthesia. The shorter RT's obtained in this study are probably owing to the fact that the subjects in this study were extensively practiced to insure relatively stable performance. The total number of trials in their study was less than the number of practice trials discarded in the present investigation. Furthermore, the subjects in the present study were younger and in better health, both of which would result in lower RT's.[7] The mean times in our study are within the normal limits for this population, as are the SD's, which should be in the range of 10–15 per cent of the mean.[7] According to this criterion, the SD's reported by Wollman and Orkin indicate a highly unstable performance, which probably was related to the limited experience of their subject–patients.

The failure to show significant effects on the other tests should not be taken as unequivocal evidence that anesthesia involving hypocapnia has no effects upon cognitive function when administered to hospital patients. Aside from the good health and youthfulness of the subjects in this study, the effects of practicing the tests to obtain stable performances may have made the performance more resistant to the effects of the anesthesia. Also, these subjects were highly motivated to perform well at all times. It does seem reasonable to conclude that the perceptual components of the tasks, especially the visual span and dichotic listening tasks, are not affected by the anesthesia. On the basis of Hughling Jackson's (1884) law of "descending inhibition," the cognitive aspects of the tasks should be affected first.[14] Given that these were not significantly affected, it follows that the less complex sensory components probably remained unaffected. The only exception to this conclusion is that some of the subjects did complain of "blurred" or "double" vision, which was probably the result of residual neuromuscular blockade. No subject complained of other visual problems or of problems in auditory perception. The conclusion that auditory perception remained unimpaired is supported by the fact that the anesthetic had no effect upon the difficult dichotic listening task. Negative results with our battery of

tests do not exonerate hyperventilation. Tests which look at rate of learning, attention span, intraindividual variability of performance, and other more complex and sensitive types of evaluation might have demonstrated differences, but for a variety of reasons were not employed.

In view of the fact that unpleasant dreams and "awareness" have been reported as undesirable complications of light anesthesia, particularly with nitrous oxide–*d*-tubocurarine, subjects were given a brief questionnaire to fill out at the time of the first postanesthesia testing session. The absence of "awareness," the incidence of dreaming, and the failure of hypocapnia to alter the incidence of dreaming during this light anesthesia is in agreement with previously reported observations.[15]

Requirements for *d*-tubocurarine were increased 17 per cent when anesthesia involved hypocapnia. This is in agreement with previous observations and has been explained on the basis of a reduced attachment of the *d*-tubocurarine molecule to the negatively-charged neuromuscular receptors.[16, 17]

The authors acknowledge the helpful advice of Dr. Harry Wollman and the technical assistance of Charles Marlow.

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