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Surgical Stimulation Antagonizes the Respiratory Depression Produced by Forane

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In 15 patients anesthetized with Forane and in an additional 15 patients anesthetized with Forane and nitrous oxide, the authors found that surgical stimulation induced increases in ventilation which significantly reduced Pa_{CO_2}. The mean reductions in CO_2 from control values prior to surgical stimulation ranged from 5 to 13 torr, the magnitudes being similar in the two groups and for all depths of anesthesia. The reductions were sufficient to cause all average CO_2 values to be less than 50 torr even at deep levels of anesthesia. Prior to operation, the respiratory depression for a given anesthetic concentration appeared to be somewhat greater when Forane was given without nitrous oxide. (Key words: Forane; Nitrous oxide; Respiration; Surgical stimulation.)

FORANE •• (CF_3-CHCl-O-CHF_2) is a profound respiratory depressant. In human volunteers anesthetized with Forane with (Dolan, W. M., unpublished data) or without [1] nitrous oxide, the increase in arterial carbon dioxide partial pressure (Pa_{CO_2}) equalled or exceeded that obtained with any other anesthetic at equal multiples of MAC. This depression may be antagonized by painful stimuli. For example, we observed increases in ventilation following commencement of operation in patients anesthetized with Forane—even when anesthetic depth was increased.[2] That surgical stimulation increases ventilation has long been known to the clinician, but quantitation of the effect has not been reported, perhaps because of the difficulties in obtaining stable conditions of respiration, surgical stimulation, and anesthesia. It appeared that the effect of operation on respiration during Forane anesthesia was particularly important since respiratory depression with this agent might limit its usefulness. Accordingly, we set out to quantify the reversal of respiratory depression caused by surgical stimulation during Forane anesthesia.

Methods

Thirty healthy, unmedicated patients were studied. In 15, anesthesia was induced and maintained with Forane and 70 per cent nitrous oxide. These patients were 36 ± 3 years of age, 165 ± 4 cm tall, and weighed 70 ± 4 kg. The remaining 15 patients were anesthetized with Forane in oxygen. They were 52 ± 4 years of age, 167 ± 2 cm tall, and weighed 66 ± 3 kg. After induction of anesthesia, the trachea was intubated without muscle relaxants, and the end-tidal Forane concentration, as measured by infrared analysis, was maintained for at least 15 minutes at a predetermined level. Following this period of equilibration an arterialized venous sample from a hand or forearm vein was taken for blood–gas analysis. The arterial nature of the blood sample was confirmed by analysis of the oxygen partial pressure (P_{O_2}), which exceeded 115 torr (*i.e.*, more than 97 per cent saturated) in every patient anesthetized with Forane in oxygen. In the groups anesthetized with Forane and 70 per cent nitrous oxide, the average P_{O_2} was 86 torr, the lowest P_{O_2} was 55 torr, and 33 of the 36 total values were greater than 70

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TABLE 1. Respiratory Values (Mean ±SE) before and during Operation

	Forane–Nitrous Oxide–Oxygen			Forane–Oxygen		
Number of observations	10	12	14	7	8	7
MAC	1.0	1.4	1.8	1.1	1.3	1.5
Preoperative $Paco_2$ (torr)	44±1	52±2	56±3	52±2	62±3	57±5
$Paco_2$ during operation (torr)	39*±1	44*±2	49*±2	41*±2	49*±2	48*±3
Preoperative minute volume (l/min)	7.3±0.8	5.8±0.5	5.2±0.4	5.3±1.1	4.2±0.6	4.5±1.0
Ventilation during operation (l/min)	10.5*±1.3	8.4*±0.9	7.9*±0.8	7.8*±1.2	5.8*±0.6	6.0±0.7
Preoperative respiratory rate/min	22±1	26±2	30±1	25±4	25±2	25±3
Respiratory rate/min during operation	30*±2	33*±2	37*±2	34*±4	30*±3	31*±4
Preoperative tidal volume (ml)	323±25	223±15	172±11	209±28	174±23	179±24
Tidal volume during operation (ml)	349±38	251*±16	216*±20	234±28	196±19	208±35
Minutes from induction to first sample	67±5	50±2	38±2	55±4	43±3	41±4
Minutes from incision to sample	21±6	31±5	34±4	15±4	22±4	20±8

* Significantly different from unstimulated value ($P < 0.05$).

torr (*i.e.*, more than 92 per cent saturated). Ventilation was measured with a recording ventimeter.[3] A second, and occasionally a third, level of anesthesia was tested similarly. Care was taken not to stimulate the patient in any way (including "prepping" the patient) prior to the taking of the above samples.

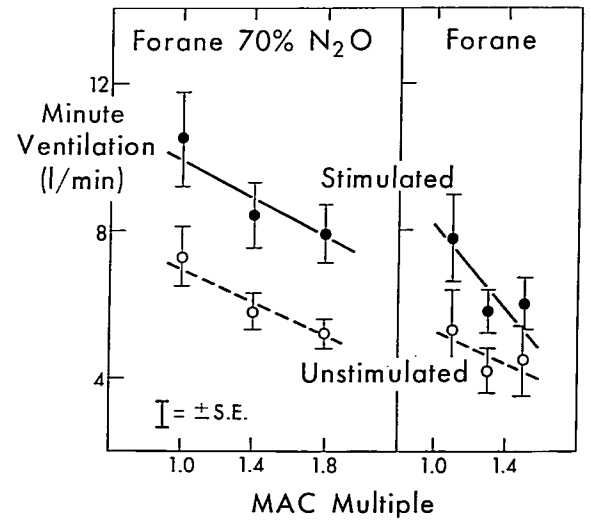
The levels of anesthesia chosen were 1.1, 1.3, and 1.5 MAC for Forane in oxygen and 1.0, 1.4, and 1.8 MAC for Forane and nitrous oxide. We assumed that the 70 per cent nitrous oxide equalled 0.75 per cent Forane (Dolan, W. M., unpublished data). Therefore, for those patients receiving 70 per cent nitrous oxide, 0.75 per cent was added to the actual concentration of Forane and then divided by the MAC for that age group to obtain the "MAC multiple." MAC for patients aged 21–30 years is 1.27 per cent Forane; for patients aged 30–55 years, MAC is 1.15 per cent; for patients more than 55 years old MAC is 1.05 per cent (Stevens, W. C., unpublished data).

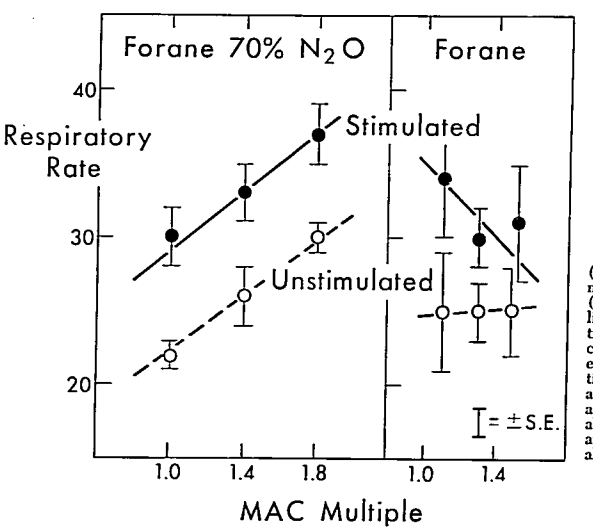
Various superficial or lower abdominal surgical procedures then were performed. We avoided neurosurgical operations or procedures requiring entry to the pleural or upper peritoneal cavities. Blood samples were taken again 12 or more minutes after the start of operation at the presurgical levels of anesthesia. As before, we required that 15 minutes or more of equilibration at a given MAC level be allowed before taking blood samples.

The results were analyzed in several ways. First, we compared the effects of age on the various respiratory measurements within the Forane–oxygen or the Forane–nitrous oxide or combined groups. Since no significant differences were found to be related to age, we ignored this factor and tested for significant differences between the values obtained in the nonstimulated (preoperative) and the stimulated (operative) portions of the study. A paired analysis using Student's t test gave us an estimate of the significance of differences between values at a given MAC multiple. We accepted as significant $P < 0.05$. We also examined the relationship of the measured variables against MAC by the method of least squares.

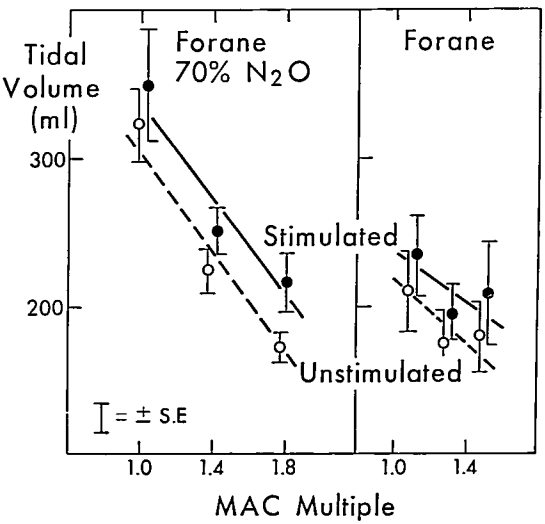
Results

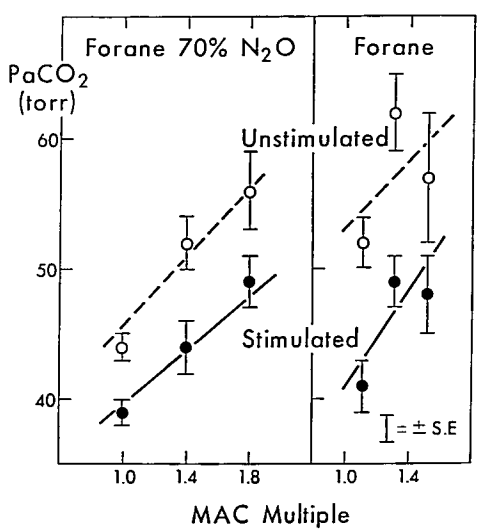
Operation induced an obvious increase in minute ventilation, achieved primarily through an increase in respiratory rate (table 1, figs. 1, and 2). Although the tidal volume also increased, this increase usually was not significant (fig. 3). As the result of the increase in minute ventilation, Pa_{CO_2} decreased significantly in all cases (table 1, fig. 4). Greater reductions in Pa_{CO_2} were achieved during Forane than during Forane–nitrous oxide an-





FIGS. 1–4. Figure 1 (*upper left*) relates the minute ventilation before (open circles and dashed lines) and after operation (closed circles and continuous lines) to anesthetic dose (MAC multiple) for both the group anesthetized with Forane–nitrous oxide (left, above) and the group anesthetized with Forane alone (right, above).





The regression analyses used to obtain the lines were performed on the raw data and not on the average points indicated in the graph. Figures 2, 3, and 4 are similar to figure 1. The differences are in the Y axis variable, being respiratory rate in figure 2 (*lower left*), tidal volume in figure 3 (*upper right*) and $Paco_2$ in figure 4 (*lower right*).

TABLE 2. Regression Analysis

	Forane–Nitrous Oxide			Forane–Oxygen		
	Slope (Value /MAC)	Y Intercept	r	Slope	Y Intercept	r
Pa_{CO_2}, prestimulation (torr)	13.1	32.0	0.53	10.4	43.9	0.18
Pa_{CO_2}, stimulation (torr)	10.4	29	0.46	18.3	22.4	0.42
Respiratory rate/min prestimulation	9.1	13.9	0.59	1.0	23.7	0.02
Respiratory rate/min, stimulation	9.8	19.5	0.46	−12.6	47.8	−0.23
Tidal volume (ml), prestimulation	−168	474	−0.70	−110	329	−0.28
Tidal volume (ml), stimulation	−158	492	−0.55	−84	320	−0.20
Minute ventilation (l/min), prestimulation	−2.2	9.2	−0.36	−2.2	7.5	−0.16
Minute ventilation (l/min), stimulation	−2.6	12.6	−0.25	−5.7	13.8	−0.39

esthesia. The effect of operation on ventilation was apparent at all depths and was unrelated to depth of anesthesia. For the most part, correlation of the variables Pa_{CO_2}, respiratory rate, volume, or minute ventilation with MAC produced low r (correlation coefficient) values (table 2); that is, only a small fraction of the total variance was due to regression. No significant differences were found in the slopes obtained from regression analysis before or after stimulation, nor were there significant differences between the slopes obtained with Forane compared with those obtained with Forane and nitrous oxide (although the slopes for Forane versus Forane–nitrous oxide for respiratory rate approached significance ($P < 0.1$).

Discussion

These results confirm our initial observation of stimulation of respiration by operation during Forane anesthesia. This stimulation is sufficient to reduce the average Pa_{CO_2} to less than 50 torr even at the deepest levels of anesthesia used (table 1, fig. 4). Thus, it would appear that surgical stimulation may bring P_{CO_2} and *p*H close to the normal range of values for man during sleep.

These results may be criticized on two bases. First, we deliberately waited at least 12 minutes after the start of operation before obtaining our first blood samples, since it appeared from increases in tidal volume and respiratory rate (blood gases not measured) that incision of the skin provided a more severe stimulus than that provided by subsequent surgical manipulation. Since the latter forms the major portion of most surgical procedures, we wished to obtain the effect of that stimulation rather than the transient effect of incision of the skin. It may be that a residual effect of the stimulus from incision of the skin influenced some of the values obtained. Arguing against this is the finding that the longer times following incision in either the Forane or the Forane–nitrous oxide group were associated with greater reductions in average Pa_{CO_2} (table 1). This suggests a second possible error, that our values may underestimate the effect of surgical stimulation. Since we began with a higher Pa_{CO_2}, at any given ventilation time would be needed to reduce Pa_{CO_2} to its final level. It might be that these represent non-steady values which would show still larger differences had longer periods been allowed prior to obtaining our samples. Serial samples might have answered these criticisms but were not obtained.

The values we obtained before operation agree with values from our previous work with human volunteers[1] (Dolan, W. M., unpublished data). We confirmed that Forane, with or without nitrous oxide, is a profound respiratory depressant whose depressant properties are dose-related. We found, as did Fourcade *et al.*,[1] that with Forane and oxygen the respiratory depression of Forane is manifested by reductions in minute ventilation and

tidal volume without the usual compensatory increase in respiratory rate (figs. 1, 2, and 3). As observed by Dolan *et al.* (unpublished data), we likewise found dose-related reductions in ventilation and tidal volume during Forane–nitrous oxide anesthesia. However, with this combination, a compensatory, dose-related tachypnea counteracted a portion of the depression achieved by the reduction in tidal volume.

There were also other differences between the group anesthetized with Forane–nitrous oxide and the group anesthetized with Forane alone. In a separate analysis, we compared the Pa_{CO_2} values obtained at 1.4 MAC for these two groups. The 1.4 MAC was obtained for the Forane group by averaging the 1.3 and 1.5 values. The average values for Pa_{CO_2} were 60 ± 3 torr for the Forane group and 52 ± 2 torr for the Forane–nitrous oxide group. The difference between these Pa_{CO_2} values was significant. This suggests that the use of Forane–nitrous oxide, as opposed to Forane–oxygen, may produce less respiratory depression. However, this conclusion should be questioned, since these groups were different in other ways (especially age), and since Dolan found no significant difference between values in his group of human volunteers anesthetized with Forane–nitrous oxide and the results obtained by Fourcade in volunteers anesthetized with Forane–oxygen.

The results we have obtained may not apply to all clinical conditions. We would expect premedication, especially with narcotics, to accent the depression achieved with Forane. Whether stimulation produced by operation would affect ventilation under these conditions is not known. Debility or advanced age may alter respiratory stimulation induced by operation. Certain forms of surgery, such as neurosurgery, were deliberately avoided, since they seem to be associated with relatively little painful stimulation. Perhaps the stimulus they produce is insufficient to reverse the respiratory depression induced by Forane.

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The Anesthesiologist's Bookshelf

Anaesthesia for Neurological Surgery. By P. B. McCORNISH AND P. O. BODLEY. Chicago, Yearbook Medical Publishers, 1971. Pp. 412. $19.00.

The authors have produced an excellent text of current neuroanesthesia practice. The qualities of terseness and lucidity characteristic of British style make the book pleasant to read and easy to comprehend.

Particularly outstanding is the authors' attention to the habitual failure of the neuroanesthetist to know exactly what the surgeon is doing. Their clear description of the order of surgical events in most of the common neurosurgical procedures will make it possible for the occasional neuroanesthetist to keep that necessary step ahead.

The book begins with an intense review of the history of neurosurgical anesthesia. The second section presents an overview of intracranial physiology. Then follows a section on basic techniques, including excellent chapters on hypotension, osmotic dehydration, and hypothermia. The final and largest section describes neuroanesthesia for various surgical procedures. Here the two introductory chapters, "Practical Details" and "Monitoring," are below the general excellence of the book. There is almost no reference to postoperative care.

The authors demonstrate a sound understanding of all of the concepts presented, although the discussion of swelling of the brain omits some important concepts. Generally, the references listed are well selected and current. The indexing is well done.

The price is high, but the book certainly is worth the money to anesthesiologists who do occasional neuroanesthesia.

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