

Anesthetic Time-Dose Curves

4. The Influence of Respiratory Parameters upon Intravenous Drug Requirements During Surgical Procedures

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It has been noted¹ that hyperventilation during anesthesia tends to reduce the patients' anesthetic drug requirements. While this would appear desirable, opinions have been voiced²⁻⁴ that such a reduction is due to cerebral vasoconstriction and to a degree of cerebral anoxia, which, if true, would put the matter in a different light.

Since much of the work on this subject is hard to relate directly to the conditions facing the practicing anesthesiologist, it appeared of interest to record observations that would resemble the clinical situation. The present study was conducted with this purpose in mind.

Material and Methods

The subjects were drawn from the adult population of two general hospitals, unselected beyond the requirement of facing operations that were expected to last longer than three hours. They were premedicated with promethazine 50 mg. and scopolamine 0.4 mg., intramuscularly, 60 minutes before the start of anesthesia. An effort was made to keep the timing of the premedication constant while the dosage was scaled up or down when extremes of age, weight or physical condition were encountered.

An equipotent thiopental-oxymorphone mixture (PN) was prepared by adding, in a 30 ml. syringe, 1.5 mg. (1 ml.) oxymorphone (Numorphan) to 29 ml. thiopental, 2.5 per cent solution. Anesthesia was induced by increments of PN, the patient's trachea was intubated and anesthesia was maintained with

nitrous oxide (2 l. + 1 l. oxygen per minute in a semiclosed system) and additional PN. Muscle relaxants were employed as required.

In patients whose respirations were controlled, ventilation, about 25 per cent in excess of the predicted value from Radford's nomogram, was provided by a mechanical respirator at a rate of 12-15 per minute. In the assisted respiration series, the patients were connected to an assistor-type ventilator (Bird or Emerson) and their exchange was monitored by a Wright anemometer in the anesthetic circuit.

Anesthetic time-dose curves⁵ were constructed for each subject by plotting the cumulative dose of the intravenous anesthetic against the time when each successive increment was administered. Alveolar ventilation was calculated in subjects of the assisted series whose respiration rate and respiratory minute volume was known after 175 minutes of anesthesia, by assuming 1 ml. dead space for each pound of body weight in the closed-chest patient and by using Nunn's graphs⁶ in open-chest patients. The interval was chosen to allow enough time for the establishment of an anesthetic steady state.

In the last 34 cases (17 from each series) a blood sample was also drawn after 175 minutes of anesthesia, at least five minutes after the last injection of PN, through a fresh venipuncture. The plasma thiopental level was determined by UV-spectroscopy.

This study started with the collection of data from 44 cases with controlled respirations. The drug requirements of that series were evaluated in another context.⁷ Subsequently we observed patients whose respirations were assisted. After about 30 cases, it became evident that more controlled cases were needed.

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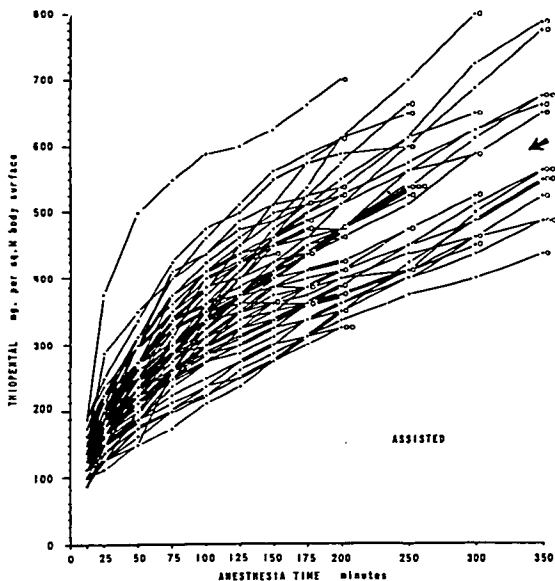


FIG. 1. Assisted time-dose curves. The arrow points to the gaps between high and low consumption groups.

since then cases were assigned alternately to one of the two series before being seen on preoperative rounds.

Results

The relevant data about the subjects and the operations from which our observations were drawn are presented in table 1. The families of time-dose curves from patients with assisted or with controlled respirations are set out in figures 1 and 2. There is a definite subdivision of the assisted cases into a high consumption and a low consumption group. Closer inspection of the controlled group reveals a similar subdivision, splitting the population in roughly the same proportion as in the assisted series—55 and 45 per cent, respectively. The mean time-dose data for the curves are listed in table 2 and the curves are shown in figure 3.

Drug requirements for the first 175 minutes of anesthesia and the plasma thiopental levels at the end of this period for those 34 cases

in which these values have been determined are shown in figure 4. Table 3 provides the numerical information for the same cases. The drug requirements of the 'assisted' group are probably significantly ($P = 0.05$) higher.

In figure 5 drug requirements during the first 175 minutes of anesthesia are plotted against the 'assisted' subjects' alveolar ventilation.

TABLE 1. Composition of Patient Material, Duration of Anesthesia and Sites of Surgery

	Assisted	Controlled
Average age, years	46.8	46.6
Sex, male/female	29/21	29/35
Mean anesthesia time, minutes	274	230
Site of surgery:		
Upper abdomen	8	11
Mid-abdomen	8	14
Lower abdomen and pelvis	5	7
Open chest	7	8
Intracranial	5	8
Major orthopedic	11	9
Others	6	7
	50	64

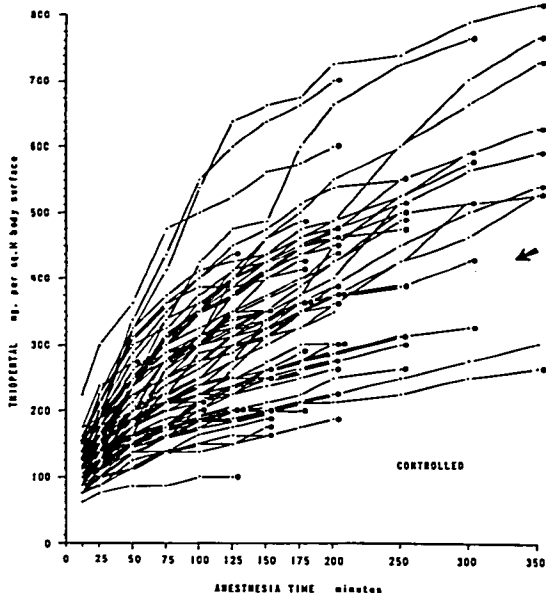


FIG. 2. 'Controlled' time-dose curves. Arrow points to gap between high and low consumption groups.

tion in 38 cases. A highly significant ($P < 0.001$) positive linear correlation was found to obtain between the two parameters in this study, the equation of the best fitting straight line being

$$Y = 0.16X + 49 \quad (1)$$

Comment

The observations in figures 1 and 2, and the mean time-dose curves which have been derived from them in figure 3 conform to the

general equation:

$$Y = At + B(1 - e^{-kt}) \quad (2)$$

This is the simplest mathematical expression of the statement that during anesthesia the anesthetist maintains a constant plasma level of the anesthetic in the face of simultaneous transformation (constant A of the equation—metabolization) and translocation (constant B —equilibration, etc.). The use of such an equation has been validated previously.⁵

It may be seen in figures 1 and 2 that the scatter of the 'controlled' series is much larger than that of the 'assisted' group—the difference between the standard deviations is significant ($P < 0.05$) past 175 minutes. Furthermore, the scatter does not follow the expected Gaussian normal distribution but there is discernible in both series a division into high and low consumption groups (indicated by the arrows in figures 1 and 2). When the mean

TABLE 2. Comparison of Mean Time-Dose Curve Constants (A , B and k , Equation 2) in the Sub-division of Assisted and Controlled Groups

	No. of Cases	A (mg./ml. ² /minute)	B (mg./m. ²)	k^{-1} (minutes)
Ass.-high	27	1.34	2.50×10^6	4.41×10^{-2}
Ass.-low	23	0.97	1.79×10^6	5.80×10^{-2}
Contr.-high	38	1.25	2.04×10^6	4.75×10^{-2}
Contr.-low	26	0.61	1.20×10^6	8.00×10^{-2}

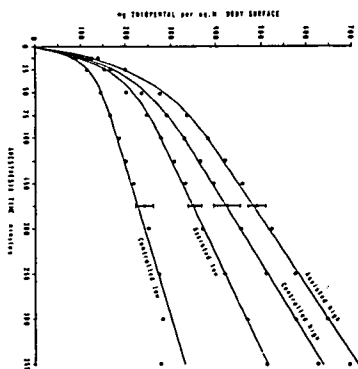


FIG. 3. Best fitting mean time-dose curves for the four groups. Vertical bars represent $\pm \sigma_M$ at 175 minutes.

time-dose curves for the four groups are calculated and compared (fig. 3), it is apparent that the difference between the two high consumption groups is less impressive ($P < 0.05$) than it is between the low consumption groups ($P < 0.01$). The distribution pattern of figures 1 and 2, the fact that in both series the high and low consumption groups have the same relative size (table 2) and the different behavior of the mean time-dose curves in figure 3 leads us to believe

that the relationship between respiratory parameters and drug requirements is subject not only to quantitative variations, but that, in addition, our hospital population is not homogeneous in its response to hyperventilation. In 55 per cent, controlled respirations produce only a moderate economy in drug requirements while in the remaining 45 per cent drug consumption can be cut drastically by this technique.

We do not know of previous mention of heterogenous response to hyperventilation in anesthetized subjects. Relevant observations have been reported however in athletes as well as in medical students and mental patients⁹ subjected to voluntary hyperventilation or CO_2 inhalation. The alterations of EEG, consciousness and ventilation in these patients suggests a heterogenous response to changes in respiratory parameters.

The data presented in figure 5 and table 4 give some indication how the drug-sparing action of hyperventilation is achieved. As can be seen, the critical mean plasma level (and thus presumably also the critical brain concentration of the drugs) was essentially the same in 17 'assisted' as in 17 'controlled' patients—yet the mean drug requirement of the 17 'assisted' patients was probably significantly ($P = 0.05$) higher. This finding suggests that controlled respirations slow the transformation of the intravenous agents (column A, table 3) and reduce their apparent distribution

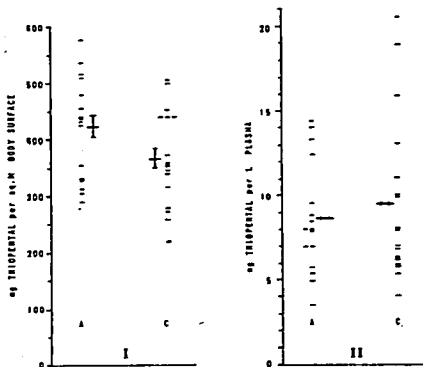


FIG. 4. (I) Drug requirements for the first 175 minutes of anesthesia in the last 34 cases. Vertical bars indicate $\pm \sigma_M$. (II) Plasma thiofental levels in the same cases. Arrows indicate mean values.

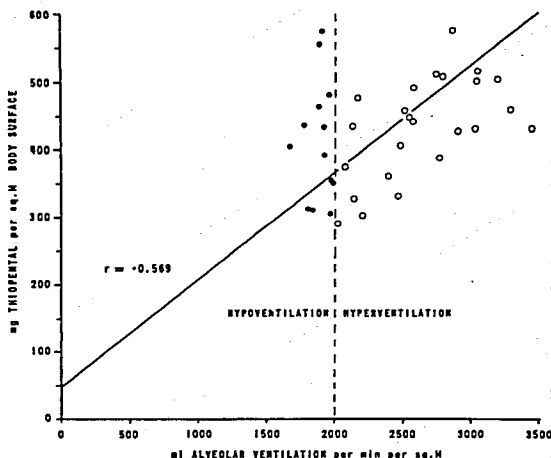


FIG. 5. The volume of patient-triggered alveolar ventilation plotted against drug requirements during the first 175 minutes of anesthesia. The best-fitting straight line and the coefficient of linear correlation are indicated.

bution space (column B, table 3). This effect is probably due to some interference with perfusion of the liver and muscles.¹⁰ At the same time the fact that the critical plasma level of the anesthetic remained unchanged would argue against any significant interference with cerebral perfusion.

Figure 5 shows the relationship between drug requirements and alveolar ventilation in 38 'assisted' patients. A highly significant ($P < 0.001$) positive correlation exists between these two functions in our series. If it appears surprising at first sight that patients who received larger doses of anesthetics should ventilate better than those who were given only small doses, one must remember that in this study the anesthetists tried to maintain all patients at essentially the same level of light clinical anesthesia. To achieve this, some 'resistant' subjects required more anesthetic than other 'easily anesthetized' patients. The same 'resistance' or lack of it must have also been reflected in the arterial oxygen and carbon dioxide values at which the patients' respiratory regulation reached a new equilibrium. Figure 5 simply indicates that in any one subject respiratory regulation shows the same degree of responsiveness to thiopental, oxymorphone and nitrous oxide than

those other cerebral mechanisms which are implicated in the achievement and maintenance of the anesthetic state.

The value of 2,000 ml. per m.² per minute was set somewhat arbitrarily as normal alveolar ventilation for our anesthetized subjects without regard to sex, age or build. If this approximation is accepted as valid, it will be seen from figure 5 that during surgery fully two thirds of our patients hyperventilated, and significant hypoventilation did not occur at all even though respiratory depressants and muscle relaxants were used freely and all our patients appeared properly anesthetized. Thus in our 'assisted' series the governing element of the respiratory servo-loop, the 'respiratory drive' must have been functioning adequately in most patients in

TABLE 3. Comparison of Mean Drug Requirements (\bar{Y}_{175}), Plasma Thiopental Levels (P_{175}) and Time-Dose Curve Constants (A and B , Equation 2) in the final 34 Cases of the Study After 175 Minutes of Anesthesia

	No. of Cases	\bar{Y}_{175} (mg./m. ²)	A (mg./m. ² /minute)	B (mg./m. ²)	P_{175} (mg./l. plasma)
Assisted	17	421 ± 19.7	1.26	2.00 × 10 ²	8.6
Controlled	17	367 ± 18.0	1.06	1.81 × 10 ²	9.5

spite of the medication received. This behavior conflicts with data obtained from healthy volunteers at rest^{11,12} in whom narcotics caused either frank CO₂ accumulation or, in weaker doses, failure to respond adequately to the challenge of CO₂ inhalation and respiratory resistance. To conclude from such data directly to the respiratory changes that might occur during surgery, as most anesthetists have done, implies the assumption that a patient's respiratory drive is fully characterized by the oxygen and carbon dioxide tension of the blood reaching the brain stem. This has been disproven for a variety of circumstances,¹³⁻¹⁵ and it does not hold in the operating room either, where the surgical stimulus becomes incorporated in the respiratory drive. The data in figure 5 furnish additional proof for this thesis, which has been mentioned previously in the literature,^{16,17} if such proof were needed. All anesthetists will recall personal experiences consistent with such a theory: there is the case of the hyperventilated patient who resumes spontaneous respirations at the precise moment of skin incision and the more serious case of the patient breathing tolerably well during surgery who lapses into potentially fatal respiratory depression post-operatively when all anesthetic agents have been discontinued.

Observation of our 'assisted' patients furnished qualitative data that conflict to some extent with the prevalent concepts of 'respiratory servocycling'.¹⁸ Patients anesthetized accordingly¹⁸ exhibit a spontaneous respiration rate in the vicinity of thirty per minute. The anesthetist can influence the force of these respiratory efforts by manipulating the sensitivity of the assistor and the tidal volume furnished by each successful triggering. The patient keeps his alveolar ventilation within normal limits under the imposed conditions by adapting not his own respiration rate but the recruitment of the central signal into an effective centrifugal impulse. These two modalities—signal formation of the respiratory center proper and the recruitment of the inspiratory impulse—stand in different relationship to each other in our patients. In our 'assisted' series the median respiration rate was 9 per minute and unsuccessful attempts at triggering the respirator were exceptional. In-

creasing the tidal volume slowed the respiration rate but would not lead to respiratory arrest even though ventilation 50 per cent higher than predicted from the Radford monogram was maintained for prolonged periods. Conversely, our patients did not compensate efficiently for reduction of their tidal volume by increasing their respiration rate: by the time a rhythm of 20 breaths per minute had been achieved, frank hypoventilation resulted. Thus, in our series respiratory regulation depended mainly on changing the frequency of impulses from the respiratory center proper and recruitment was hardly ever a limiting factor.

Our observations indicate that the effect of thiopental-oxymorphone-nitrous oxide-relaxant anesthesia on respiratory regulation is different from that of most inhalation anesthetics—they do not justify as yet conclusions about their relative merits of the techniques. We have reported previously that in our hands (that is to say, with constant respiratory assistance or control) the equipotent mixture of thiopental and oxymorphone proved to be a better supplement of nitrous oxide than other agents we have used for this purpose.^{19,20} We find this impression confirmed as our experience approaches 1,000 major interventions.

Summary

The effect of mechanical hyperventilation and of patient-triggered assisted respiration upon intravenous anesthetic requirements was investigated. Two series of patients for major surgical procedures, comprising 114 subjects altogether, have been compared. They were anesthetized with nitrous oxide, thiopental-oxymorphone mixture and muscle relaxants.

The drug-sparing effect of hyperventilation has been confirmed under actual operating room conditions. This is achieved not through a reduction of the anesthetics' critical plasma level but by diminution of their apparent distribution volume and transformation rate.

Evidence is presented that the hospital population is heterogenous in its response to hyperventilation. Observations are also presented which indicate that while during 'respiratory servocycling' the patients regulate their ventilation through changes in the recruitment of their respiratory impulses, in the present

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series recruitment was rarely the limiting factor and regulation was achieved through changes in the patients' respiration rate.

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