

# Pulmonary Exchange of Divinyl Ether in Man

Ernest Salanitro, M.D.,\* Gerald L. Wolf, M.D.,† Herbert Rackow, M.D.‡

The published partition coefficients for divinyl ether do not seem to account, on theoretical grounds, for the clinically observed rapidity of action of divinyl ether. This question was investigated by having 6 conscious adults breathe a 0.05 per cent concentration of divinyl ether in a non-rebreathing system for a period of 60 minutes. End-tidal air was sampled and analyzed for divinyl ether and CO<sub>2</sub>. The ratios of end-expiratory and inspiratory concentrations of divinyl ether were plotted against time and equilibrium curves constructed for each study. A composite of these curves showed a relatively slow rise of alveolar concentration. At 2½ minutes F<sub>A</sub> was 40 per cent of the inspired tension, 43 per cent at 5 minutes, 51 per cent at 30 minutes and 54 per cent at 60 minutes. The degree of uneven ventilation present during the study did not appear to affect the smooth course of the equilibrium curve, but deliberate maximal hyperventilation for 1 minute at the end of the study resulted in a sharp rise of the F<sub>A</sub>/F<sub>I</sub> ratio from 0.5 to 0.8. The rapid action of divinyl ether in inducing anesthesia is not dependent upon its physical properties.

THE ABILITY of divinyl ether to produce unconsciousness rapidly appears to be firmly established.<sup>1, 2, 3</sup> It is not clear whether this property derives from its partition coefficients<sup>4, 5</sup> or depends upon the recognized potency of the agent and the use of overpressure in its administration. On theoretical grounds, because of its fairly high blood solubility, it seemed unlikely that the rapidity of action of divinyl ether is the result of a quick rise in alveolar concentration. It seemed appropriate to investigate this aspect of the ques-

tion by determining the rate of approach of end-tidal concentration to inspired concentration during the breathing of a gas mixture containing a constant subanesthetic concentration.

## Methods

Six conscious subjects, 5 male and 1 female, were studied. None had any evidence of systemic disease. Their weights ranged from 125 to 185 pounds. Each was studied in the sitting position. The subject, with noseclip in place, breathed through a mouthpiece attached to a Rahn-Otis sampler.† End-expiratory samples were taken from the Rahn-Otis sampler and injected into serially arranged analyzers by means of a manually triggered single-stroke diaphragm pump. These methods are fully described in an earlier publication.<sup>6</sup>

The test gas consisted of 0.05 per cent divinyl ether, 51 per cent oxygen and the balance nitrogen. The gas mixture was premixed in a cylinder ‡ and supplied to the subject via a nonrebreathing system.

Carbon dioxide concentrations were determined with a Beckman LB-1 nondispersive infrared analyzer, previously calibrated with 4 per cent and 6 per cent CO<sub>2</sub> in oxygen. Analysis of end-tidal air confirmed the validity of the end-tidal character of the sample. Ventilation was monitored by collecting the expired volumes in a 120 liter Tissot spirometer and recording them on a direct-writing kymograph. Constant ventilation was achieved by adjusting a Respiratory Simulator § to the subject's normal pattern of breathing and then having the subject follow the pre-set pattern throughout the study period. This apparatus can be adjusted to any respiratory pattern and translates this pattern into an audible signal easily followed by the subject.

\* Associate Professor of Clinical Anesthesiology.

† Assistant Professor of Anesthesiology.

‡ Associate Professor of Anesthesiology.

Received from the Department of Anesthesiology, College of Physicians and Surgeons, Columbia University and the Anesthesiology Service of Presbyterian Hospital, New York, New York, 10032. Accepted for publication November 7, 1967. Supported by N.I.H. Grant GM-09069-04.

\* Blood/gas = 2.8; oil/gas = 58; water/gas = 1.4.

† Anesthesia Associates, Hudson, New York.

‡ Matheson Company, Rutherford, New Jersey.

§ Model 72E-Somanetics Incorporated, Lajolla, California.

Divinyl ether was measured by gas chromatography, with a Perkin-Elmer Vapor fractometer, model 154 DG. Analysis time allowed sampling every 90 seconds. Divinyl ether was separated in a polypropylene glycol column. The isolated fraction was detected by hydrogen flame ionization and recorded on a Texas Rectiriter recorder. The area under the peak was integrated electronically.

Reproducibility of the measurement was tested by 13 consecutive analyses of a single source of 0.05 per cent divinyl ether. The range of all the values was within  $\pm 1$  per cent of the mean. The sensitivity of the detector permitted full-scale response to 0.05 per cent divinyl ether at an attenuation of 32:1. At this attenuation, there was no significant baseline drift or noise.

A control sample of end-tidal air, taken in all subjects, showed a zero baseline at the instrument sensitivity needed for the study. Constancy of inspired gas concentration was indicated by measurements done before, dur-

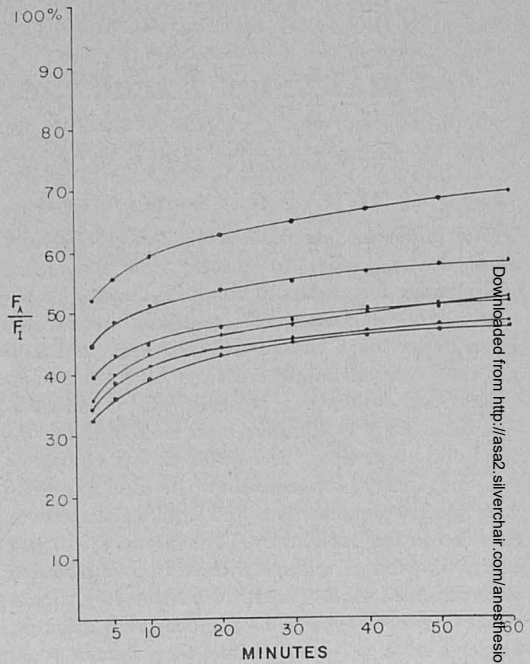


FIG. 2. Equilibrium curves for each of the 6 studies. From top to bottom (at the 5 minute mark) they represent data from subjects 4, 1, 3, 2, 6, 5.

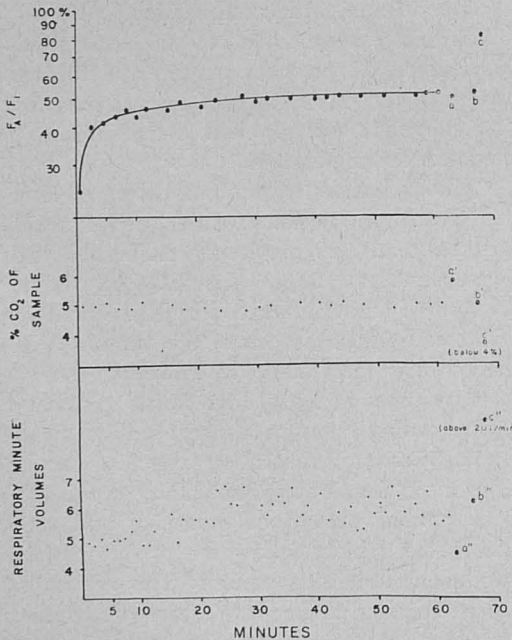


FIG. 1. Summary of experimental data obtained in subject 3. Points *a*, *a'*, *a''* were obtained after 1 minute of spontaneous hypoventilation; points *b*, *b'*, *b''* after 4 minutes of normal breathing; points *c*, *c'*, *c''* after 1 minute of maximal hyperventilation.

ing and after the study; these did not vary by more than 1 per cent.

After a 10 minute control period, the test gas mixture was introduced abruptly and the first end-tidal sample taken as closely to the 1 minute mark as possible. Sampling was done thereafter approximately every 2-3 minutes, except when the inspired concentration was recorded, or the CO<sub>2</sub> analyzer calibrated.

The ratio of the experimental, uncorrected (for pulmonary water vapor) end-tidal divinyl ether concentration,  $F_A$ , and the average inspired concentration  $\bar{F}_I$  was plotted against time on semilogarithmic coordinates, and individual  $F_A/\bar{F}_I$  equilibrium curves were constructed by drawing a smooth curve through the experimental points. Respiratory minute volumes were calculated for each minute of the 60 minute study.

At the termination of the study, 2 subjects were asked to hypoventilate spontaneously for 1 minute and then to hyperventilate maximally for 1 minute.

Downloaded from http://ajph.aphspublishers.org/ at University of Illinois at Chicago on April 9, 2013

Results

Figure 1 shows the findings of a typical study (subject 3). The  $F_A/F_I$  curve is plotted on semilogarithmic coordinates, while the  $CO_2$  values and respiratory minute volumes are plotted on arithmetic scales. The  $F_A/F_I$  curve reaches a value of about 40 per cent of equilibrium quite rapidly, and the "knee" of the curve occurs early, at about 5-7 minutes. The curve then flattens out and rises very slowly, to reach 50 per cent of equilibrium at the end of 60 minutes. The  $CO_2$  values of the analyzed samples had a narrow range (4.9 to 5.1 per cent) giving reasonable confidence in the alveolar nature of the analyzed samples. The stability of  $CO_2$  values cannot be interpreted as indicative of constant ventilation, however, because the scattergram of the respiratory minute volumes shows a somewhat uneven ventilation, with a relative hypoventilation in the initial stages of the study. Variation in ventilation occurred in all subjects, despite the seeming lack of deviation from the pre-set rhythm and the phasing of the respiratory simulator. Points *a*, *a'*, *a''* represent the values of the parameters indicated, after 1 minute of spontaneous hypoventilation; points *b*, *b'*, *b''* after 4-5 minutes of normal ventilation; and points *c*, *c'*, *c''* after 1 minute of maximal hyperventilation. Following 1 minute of hyperventilation, the respiratory minute volume fell from 5.8 l./minute at the sixty-second minute to 4.5 l./minute at the sixty-third minute,  $CO_2$  concentration rose from 5.05 per cent to 5.8 per cent, and  $F_A/F_I$  fell slightly from 50 per cent to 49 per cent. With resumption of normal breathing the values returned to pre-hypo-

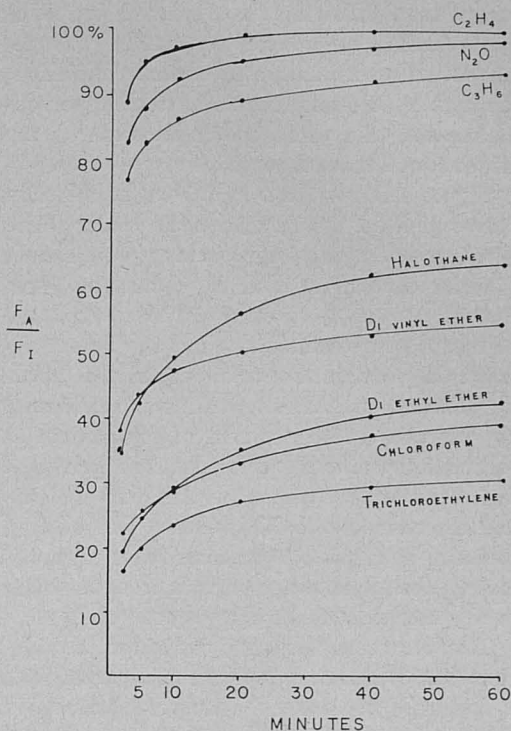


FIG. 3. A spectrum of equilibrium curves for different inhalation anesthetic agents. Each curve is a composite from a small group of subjects; some subjects participated in all the studies.

ventilation levels. After 1 minute of maximal hyperventilation, the respiratory minute volume rose to 20 l./minute,  $CO_2$  concentration dropped to an unknown value below 4 per cent, and the  $F_A/F_I$  level rose from 51 per cent to 80 per cent.

Subject 2 underwent similar hypoventilation and hyperventilation at the end of the study,

TABLE 1. Pulmonary Exchange of Divinyl Ether in Man

Subject	Weight (kg.)	Height (cm.)	Average Resp. Min. Vol. (l./min.)	Average $CO_2$ of Samples (%)	Minutes								
					2½	5	7½	10	20	30	40	50	60
					$F_A/\bar{F}_I$ (%)								
1	74	183	6.82	4.55	43.2	47.6	50.0	51.3	53.8	55.3	56.8	57.9	58.8
2	83	183	5.49	5.20	35.5	39.6	41.5	42.8	43.9	45.0	45.7	46.3	47.0
3	80	173	5.97	5.00	39.5	42.3	43.8	45.0	47.8	49.0	49.8	50.2	50.5
4	60	160	8.34	3.05	51.3	55.3	57.7	59.8	64.0	66.3	68.0	69.0	70.0
5	81	180	5.72	5.53	32.0	35.8	37.9	39.7	43.3	44.9	46.3	47.7	48.8
6	92	180	5.64	4.77	34.0	38.7	41.5	43.3	46.3	47.8	49.0	50.0	51.0

except that, following the 1 minute period of hyperventilation, normal ventilation was resumed. After 2 minutes of normal ventilation, the high  $F_A/F_I$  value resulting from hyperventilation fell to a value which placed it on the normal equilibration curve.

Figure 2 shows the 6 individual equilibrium curves plotted on an arithmetic scale. The curve most rapidly approaching equilibrium (70 per cent at the end of 60 minutes) was that of subject 4, a female, who showed the highest average ventilation and the lowest average  $\text{CO}_2$  concentrations of the samples (table 1). The second fastest uptake was manifested by subject 1 (58.8 per cent of equilibrium at the sixtieth minute) who also had the next highest average respiratory minute volume and the next lowest  $\text{CO}_2$  values. The other 4 subjects had minute volumes over approximately the same range and their equilibrium curves clustered at the same level.

The composite of the 6 individual equilibrium curves is shown in figure 3, together with a spectrum of composite curves obtained in our laboratory for other inhalation anesthetics.

### Discussion

The findings indicate that the rapidity of action of divinyl ether is not the result of an early approach of alveolar to inspired concentration. It follows, then, that potency of the agent and the use of overpressure in its administration must play important roles. The relative contribution of each factor has not been determined.

The effect of changes in ventilation upon alveolar concentration is well known. The higher the solubility of the agent in blood, the greater the influence of ventilatory changes, provided cardiac output remains unchanged. The reported blood/gas partition coefficient of 2.8 for divinyl ether indicates a moderately high solubility in blood. It could be expected, then, that variations in ventilation would markedly affect alveolar concentration and also  $F_A/F_I$  ratios. The scattergram of respiratory minute volumes (fig. 1) shows a considerable variation in ventilation during the 60 minute study. This fairly wide scatter of respiratory minute volumes, however, is not reflected in the equilibrium curve. The  $F_A/F_I$  values show

no comparable scatter and there are no sharp breaks in the shape of the curve. A lower blood solubility than that reported<sup>5</sup> would satisfactorily explain the relative insensitivity of alveolar concentration to changes in ventilation. But there is suggestive evidence that this hypothesis is untenable because: (1) the modest initial rise of the equilibrium curve as compared to the sharp initial rises associated with agents whose low blood solubilities are firmly documented— $\text{C}_2\text{H}_4$ ,  $\text{N}_2\text{O}$ ,  $\text{C}_3\text{H}_6$  (fig. 3); (2) the demonstrated sensitivity of the  $F_A/F_I$  ratio to maximal hyperventilation (fig. 1, point  $c''$ ) with a quick return to normal level following a short period of normal ventilation; (3) the observation, in this study, that the subjects with the higher ventilation showed a more rapid approach to equilibrium (fig. 2).

The lack of response of alveolar concentration to changes in respiratory minute volume may have been a result of a relatively minor effect of the observed changes in respiration upon alveolar ventilation. The narrow range of  $\text{PA}_{\text{CO}_2}$  values lend support to this thesis. However, another factor may have contributed to the smoothness of the equilibrium curve. Cander and Forster<sup>7</sup> reported that the introduction of an inert gas into the lungs resulted in equilibrium with pulmonary parenchyma in less than  $1\frac{1}{2}$  seconds. Cander<sup>8</sup> also determined that pulmonary tissue/gas partition coefficients for nitrous oxide and diethyl ether were in the same range as their water/gas partition coefficients. As a result of this phenomenon, pulmonary tissue could act as a buffer between alveolar and inspired gas tensions. The measured end-tidal concentration of an inspired test gas, therefore, may represent some value determined by equilibrium between the alveolar and pulmonary tissue tensions. The magnitude of this effect must be proportional to the gradient between the two tensions, and thus greatest during the initial stages of the uptake of the more soluble inert gases or during periods of relative hypoventilation when alveolar concentration tends to fall. The extent to which this effect contributed to the stability of end-tidal concentrations of divinyl ether is unknown but cannot be excluded, on theoretical grounds.

The location of the composite curve for di-

vinyl ether (fig. 3) between that for halothane and for diethyl ether is not surprising, considering the proximity of its blood/gas coefficient to one and its oil/gas coefficient to the other. However, because of the much lower oil/gas partition coefficient of divinyl ether compared to halothane, it might have been expected that divinyl ether would show a more rapid approach to equilibrium than halothane, at the end of 60 minutes.

It must be pointed out, on the other hand, that the curve for each agent is a composite from a relatively small group of subjects and thus cannot be representative of uptake processes of that agent in the absolute sense. Moreover, one can only speculate regarding the degree to which the adipose compartment contributes to the equilibration curve during the first 60 minutes.

However, all of the composite curves share common features. The studies were all done in the same laboratory, by the same investigators, using similar methods and instrumentation. The test gases were always in subanesthetic concentration, and some of the subjects were used in all the studies. These facts lend strong validity at least to the accuracy of the relative positions of the various inhalation agents in the spectrum.

The sharp rise in alveolar concentration following hyperventilation (fig. 1, point *c''*) emphasizes the inherent risks of hyperventilation and overpressure in the clinical use of agents with relatively high blood solubility. After arrival at a fairly "steady state," even at levels of alveolar concentration still distant from inspired concentration (the latter part of the equilibrium curves in figure 1) hyperventilation very quickly raises alveolar tension, without increase of inspired tension. Deepening of the anesthetic level by hyperventilation with maintenance concentrations can, therefore, be potentially dangerous with the agents more soluble in blood. A knowledge of an agent's physical properties and how they affect pulmonary exchange can help to avoid anesthetic overdose.

### Summary

Six subjects breathed a constant gas mixture containing 0.05 per cent divinyl ether, 51 per

cent oxygen and the balance nitrogen, for a period of 60 minutes. End-tidal air was analyzed by gas chromatography and hydrogen flame ionization for divinyl ether concentration.  $F_A/F_I$  values were calculated and plotted against time on semilogarithmic coordinates for each study. A composite curve of the 6 individual curves showed a rise to 40 per cent of equilibrium at 2½ minutes, 43 per cent at 5 minutes, 51 per cent at 30 minutes and 54 per cent at 60 minutes. Uneven ventilation had no significant effect on the uptake curve, but maximal hyperventilation for 1 minute at the end of the study period caused a rise in  $F_A/F_I$  level in 2 subjects from about 50 per cent to 80 per cent. The approach to equilibrium occurred most rapidly in the subject with the highest average respiratory minute volume (8.34 l./minute). In the 4 subjects whose average respiratory minute volumes were in the same range (5.49–5.97 l./minute), the  $F_A/F_I$  curves clustered at the same level. The composite curve for divinyl ether lies between those for diethyl ether and halothane in the spectrum of uptake curves, and confirms, in a broad sense, its location as predicted from its partition coefficients.

### References

1. Gelfan, S., and Bell, I. R.: The anesthetic action of divinyl oxide in humans, *J. Pharm. Exp. Ther.* 47: 1, 1933.
2. Martin, S. J., and Rovenstine, E. A.: Vinethene: Recent laboratory and clinical evaluation, *ANESTHESIOLOGY* 2: 285, 1941.
3. Wyler, W. D., and Churchill-Davidson, H. C.: *A Practice of Anaesthesia*, ed. 2. London, Lloyd-Luke, Ltd., 1966.
4. Larson, C. P., Eger, E. I., and Severinghaus, J. W.: Ostwald solubility coefficients for anesthetic gases in various fluids and tissues, *ANESTHESIOLOGY* 23: 686, 1962.
5. Munson, E. S.: Blood/gas partition coefficient of divinyl ether, *ANESTHESIOLOGY* 25: 406, 1964.
6. Salanitre, E., Rackow, H., Greene, L. T., Klonyms, D., and Epstein, R. M.: The uptake and excretion of subanesthetic concentrations of  $N_2O$  in man, *ANESTHESIOLOGY* 23: 814, 1962.
7. Cander, L., and Forster, R. E.: Determination of pulmonary parenchymal tissue volume and pulmonary capillary blood flow in man, *J. Appl. Physiol.* 14: 541, 1959.
8. Cander, L.: Solubility of inert gases in human lung tissue, *J. Appl. Physiol.* 14: 538, 1959.