

The Uptake of Ethylene in Man

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Uptake of 1 per cent ethylene was studied in eight healthy, awake, unpremedicated adults. End-expiratory concentrations of ethylene were measured by gas chromatography, and CO₂ by infrared analysis. In all subjects, end-tidal concentration of ethylene was at least 95 per cent of equilibrium at the end of five minutes, 97 per cent by 10 minutes and 99 per cent at the end of 20 minutes. Studies were terminated at 30 minutes because of inability to detect differences between inspired and expired ethylene concentrations. It was unlikely that total body saturation had occurred in that time. Ordinate-derivative analysis of the individual experimental curves yielded two exponentials of the general form ae^{-kt} . Neither exponential could be related to a specific body compartment. Comparison of two separate studies done on the same subject, measuring "wet" end-tidal samples in one and "dry" samples in the other, showed no essential differences between the two uptake curves, indicating that the diluting effect of pulmonary water vapor on the dry inspired gas mixture could be ignored.

THE blood/gas partition coefficient for ethylene ($\lambda = 0.14$) is the lowest of all the inhalation anesthetic agents. This value is about one third that of comparable values for the next two least soluble gases, nitrous oxide ($\lambda = 0.47$) and cyclopropane ($\lambda = 0.42$). Using this single property of gases, and considering the body as a single compartment, Kety¹ represented the time course of ethylene uptake as the most rapid of the anesthetic gases. Predictions from mathematical models and electric analogs^{2,3} also suggest rapidity of ethylene uptake. Clinical observations of eth-

ylene anesthesia support these theoretical predictions. Complete understanding of inert gas exchange must depend, however, upon quantitative *in vivo* measurements.

This study was designed to measure pulmonary uptake of ethylene in man at a constant inspired concentration of about 1 per cent. The concentration selected fulfilled the double objective of producing a nonflammable respiratory mixture and of minimizing possible pharmacologic effects of the test agent.

Methods

Eight healthy, unpremedicated subjects were given a constant mixture to breathe, containing approximately 1 per cent ethylene, 52 per cent oxygen and 47 per cent nitrogen. Premixed gases were supplied from a cylinder to an anesthetic reservoir bag and a nonbreathing system. The subject breathed through a mouthpiece attached to a Rahn-Otis sampling device.*⁴ A Steen-Lee pressure equalizing valve⁵ prevented dilution of inspiratory gases by air during inhalation and flow of inspiratory gases into the system during exhalation. Expiratory volumes were recorded from a Tissot spirometer on a direct writing kymograph. End-expiratory samples were taken from the Rahn-Otis collection chamber and injected into serially arranged analyzers by means of a manually activated single-stroke diaphragm pump. These methods are fully described in an earlier publication.⁶ Samples were dried, when desired, by passage through a 1 × 8 cm. column of 10–20 mesh anhydrous CaSO₄. The end-tidal sample was analyzed for ethylene and carbon dioxide.

Carbon dioxide concentrations were determined with a Beckman LB-1 nondispersive infrared analyzer. Breath-by-breath analysis

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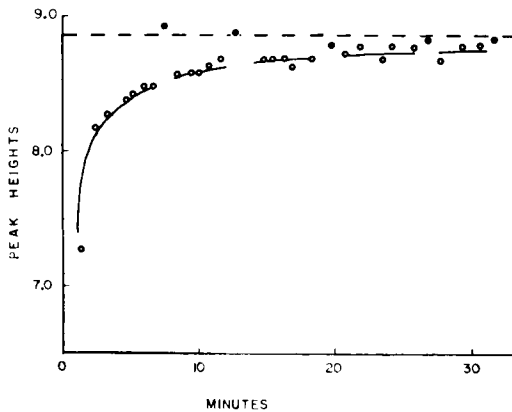


FIG. 1. Experimental values in subject 1. The plotted points represent absolute measured end-tidal C_2H_4 concentrations expressed in arbitrary chart units. The closed circles represent measured inspired C_2H_4 concentrations (approximately 1 per cent). The dashed line is the average of all the inspired C_2H_4 values.

of CO_2 was used to establish the existence of a steady state prior to the beginning of the uptake measurements and to confirm the validity of the end-tidal sample during the study.

Ethylene was measured by gas chromatography, with a Perkin-Elmer Vapor Fractometer, model 154 DG. Analysis time permitted sampling every 60–90 seconds. Ethylene was separated on a Golay capillary column (150 feet in length, 0.02 inch internal diameter) coated with Ucon polyglycol LB 550-X, a lubricating oil. The isolated fraction was detected by hydrogen flame ionization and recorded on either a Leeds-Northrup Speedomax G or a Texas Instruments Rectiriter recorder. The characteristics of the ethylene peak (sharp and symmetrical) and the constancy of operating parameters allowed direct correlation of peak height to ethylene concentration.⁷ Reproducibility of the measurement was tested by 11 consecutive analyses of a single source of 1 per cent ethylene. The range of all the values was within ± 0.3 per cent of the mean. The extreme sensitivity of the flame ionization detector permitted full scale response to 1 per cent ethylene at an overall attenuation of the output signal by 1,600:1. At this high attenuation, the baseline corresponding to zero ethylene was drift-free and free of detectable noise. A control blank of end-tidal air, taken in three subjects just before the beginning of

the uptake, showed a zero baseline at the particular instrument sensitivity needed for the study. Constancy of inspired gas concentration was indicated by measurements done before, during and after the study. Despite the presence of rubber in the breathing system, ethylene concentrations at the tank source and at a point immediately up-stream of the inspiratory valve were not detectably different.

A ten minute control period, during which the subject breathed room air, permitted baseline measurements of respiratory volumes and end-tidal P_{CO_2} . Ethylene was then introduced abruptly, sampling begun at 30 seconds and continued at intervals of 60–90 seconds thereafter for a total uptake time of approximately 30 minutes. Studies were terminated when the concentration of end-tidal gas was no longer consistently distinguishable from that of inspiratory mixture.

Empirical exponential equations were fitted to the experimental data by the ordinate-derivative method described by Perl.⁸ Briefly, the experimental points are plotted against time on Cartesian coordinates and a smooth curve drawn through them. The derivative, $\dot{F}_A(t)$, is then measured as the slope of a straight-edge placed tangentially to the curve "by eye" at one minute intervals. The value at each minute, $F_A(t)$, is then plotted against its negative time derivative, $-\dot{F}_A(t)$. At large time, a linear appearance of the plot permits the fitting of a straight line, of slope $1/k_1$, through the data in that region. This line, when extrapolated, intercepts the $F_A(t)$ axis at a point corresponding to its value at infinite time. The exponential $e^{-k_1 t}$ is then computed and plotted against $F_A(t)$; the resulting straight line, of slope a_1 , also intercepts the $F_A(t)$ axis at a point representing infinite time. The exponential expression $a_1 e^{-k_1 t}$ and its negative derivative $-k_1 a_1 e^{-k_1 t}$ may then be subtracted from $F_A(t)$ and $-\dot{F}_A(t)$, respectively, and the plotting processes repeated, thus deriving parameters for a second or "faster" exponential of the general form $a_2 e^{-k_2 t}$. Further exponential expressions may be similarly derived.

The straight line intercepts on the $F_A(t)$ axis give points whose coordinates are $F_A(\infty)$ and $\dot{F}_A(\infty)$, in which \dot{F}_A represents the rate of

TABLE 1. Average Measured Inspired C₂H₄ Concentrations and Values Derived from Ordinate-Derivative Analysis of Eight Studies

Subject	Average Derived C ₂ H ₄ Equilibrium Concentration* $F_A(\infty)$	Average Measured Inspired C ₂ H ₄ Concentration* F_I	k_1 (minutes ⁻¹)	a_1 (%)	k_2 (minutes ⁻¹)	a_2 (%)
1	8.74	8.82	0.134	7.65	1.45	48.2
2	6.34	6.40	0.191	5.66	1.03	26.0
3	6.36	6.40	0.133	10.00	1.3	94.8
4	8.82	8.86	0.130	7.68	0.646	73.3
5	5.26	5.45	0.206	8.10	0.523	9.6
6	6.08	5.94	0.110	7.22	0.540	16.5
7	9.32	9.25	0.169	9.58	0.831	48.8
8	5.57	5.50	0.159	6.67	1.04	16.2

* Arbitrary chart units.

change of alveolar concentration. Since \dot{F}_A at infinite time approaches zero, indicating arrival at equilibrium, it follows that the values $F_A(\infty)$ represent the equilibrium concentration, or that concentration of ethylene in expired air which would exist at total body saturation. The multiple values of $F_A(\infty)$ for each study so derived agreed to within 0.2 per cent or less. This manner of deriving the equilibrium concentration makes any assumption as to the effects of humidity and respiratory quotient on the inspired concentration unnecessary (see discussion). The average equilibrium value, $F_A(\infty)$ was used as the denominator in the ratio F_A/F_I for the determination of the percentage approach to alveolar equilibrium.

Results

Figure 1 shows the measured experimental values of one subject. Peak height (in arbitrary chart units) is plotted against time (in minutes). Indicated also is the smoothed curve used in the analysis. The solid circles represent the measured inspired concentration at the time indicated.

Table 1 summarizes the derived values $F_A(\infty)$, k_1, k_2, a_1 and a_2 for each uptake curve. The k_1 values have a range of 0.11 minute⁻¹ to 0.21 minute⁻¹. The values for a_1 range from 5.7 per cent to 10 per cent. The computed values for k_2 and a_2 have a much wider range, 0.52 to 1.45 minute⁻¹ and 9.6 per cent to 95 per cent, respectively. The average measured inspired concentration, F_I , is the average of

TABLE 2. Range of Respiratory Minute Volumes in Each Subject and Range of CO₂ Concentrations of the Measured End-Tidal Samples in Each Study

Subject	Height (cm.)	Weight (kg.)	Surface Area* (m. ²)	Respiratory Minute Volume (liters)		Range of CO ₂ Concentration of Samples (%)
				Average†	Range	
1	172	80	1.92	7.27	6.5-8.3	5.1-5.6
2	183	75	1.93	8.23	6.8-12.1	4.1-4.7
3	168	64	1.72	5.89	3.7-7.1	5.1-5.5
4	167	63	1.71	3.92	2.5-5.3	5.8-6.2
5	166	68	1.76	4.70	3.4-6.7	4.5-5.2
6	181	82	1.98	6.77	5.3-9.3	4.9-6.0
7	173	71	1.82	6.56	5.3-8.6	5.2-6.0
8	187	107	2.32	6.48	4.5-8.2	5.1-5.9

* Handbook of Biological Data, W. S. Spector, Editor, Philadelphia, W. B. Saunders, 1956.

† This value was obtained by averaging the individual respiratory minute volumes (approximately 30) as measured during the study period.

TABLE 3. Approach to Equilibrium Expressed as Percentage of Ethylene Equilibrium Concentration $\left[\frac{\text{Measured } F_A}{F_A(\infty)} \right]$

Subject	Minutes								
	2	4	6	8	10	16	20	26	30
1	91.5	95.5	96.7	97.4	97.9	99.1	99.5	99.8	99.9
2	92.4	97.1	98.2	98.7	99.1	99.7	99.9	99.9	100
3	74.1	93.5	95.5	96.6	97.2	98.7	99.3	99.6	99.8
4	74.3	89.6	95.4	97.2	97.8	98.9	99.3	99.6	99.7
5	91.3	95.3	97.3	98.4	98.7	99.6	99.8	100	100
6	88.4	93.5	95.7	96.8	97.5	98.7	99.1	99.5	99.7
7	84.4	93.6	96.6	97.5	98.3	99.3	99.6	99.6	99.9
8	87.6	95.5	97.4	98.1	98.7	99.5	99.7	99.9	100

inhaled C_2H_4 concentrations as measured during the uptake period. The averaged F_I and $F_A(\infty)$ values for each subject show close agreement.

Table 2 shows the average and range of respiratory minute volumes for each subject. Indicated also are the ranges of CO_2 concentrations of the measured C_2H_4 samples.

Table 3 shows the approach to alveolar equilibrium of each subject at selected identical points in time. All subjects had reached at least 95 per cent of the equilibrium concentration by the end of 5 minutes, 97 per cent at the end of 10 minutes and 99 per cent at the twentieth minute of uptake.

Table 4 shows the results of two separate studies done in the same subject, using "wet" end-tidal samples in one and "dry" samples in the other study. The pairs of values represent the same point in time and are expressed as percentage of equilibrium concentration. The closeness of the paired values indicated that the dilution effect of pulmonary water vapor could be ignored (see discussion).

Discussion

The rapid time course of total body uptake of ethylene from the lung, predictable on clinical grounds and from theoretical considerations, was experimentally confirmed. The rapid approach to apparent equilibrium made prolongation of the study beyond 30 minutes meaningless. It should be pointed out, however, that inability to detect differences between inspired and expired ethylene concentrations at the end

of the study in no way implied total body saturation. Indirect evidence, on the contrary, would indicate that saturation could not possibly have occurred in 30 minutes of uptake. Perl⁹ has stated that the probable half-time of adipose tissue uptake of N_2O is about 70 minutes, while in the case of cyclopropane the estimated uptake half-time is between 400 and 700 minutes.¹⁰ The adipose tissue/blood partition coefficient, λ_b , can be calculated † to be 2.4 for N_2O , 7.3 for C_2H_4 and 21.4 for C_3H_8 . Since to a first approximation the half-time is linear with λ_b , it is probable that the half-time for ethylene uptake in adipose tissue lies between 70 and 400 minutes. Saturation could not have been reached in any of the subjects. A similar argument applies to other body tissues. Failure to detect the continuing uptake process was instead a result of relative insensitivity of the test method, that is, inspiratory-expiratory concentration difference for a highly insoluble gas.

The same kind of difficulty is observed when correction factors are applied to the measured values. The dilution of dry inspired gas by water vapor in the lung and the concentrating effect of the respiratory quotient, assumed to be 0.8, would be expected to require corrections in the end-tidal C_2H_4 measurements. Preliminary examination of the data revealed that the application of these corrections fre-

† It is assumed (1) that fat solubility is closely related to oil solubility and (2) that adipose tissue is composed of 80 per cent fat and 20 per cent lean tissue.

quently resulted in values of F_A/F_I of unity or greater (up to 1.03) after 15 minutes of uptake. The incongruity of having corrected values of F_A larger than F_I made it reasonable to suspect the appropriateness of the correction factors. To test this in regard to the diluting effect of pulmonary water vapor (theoretically the larger of the two correction factors) one subject was studied twice, on separate days. In the first study, end-tidal measurements were made in the usual manner; in the second, end-tidal samples were passed through a calcium sulfate column before analysis. Previous experiments had confirmed the ability of the calcium sulfate drying column to remove at least 6 per cent water from a test gas mixture without interfering with ethylene analyses, as well as the ability of our analyzer to detect the resulting concentration changes. Comparison of the two uptake curves showed negligible differences between "wet" and "dry" measurements. This indicated that, under the conditions of this study, failure to correct for pulmonary water vapor dilution would not introduce an appreciable error. The reasons for this are speculative. No gross condensation in the sampling train occurred, so that it is unlikely to be due to reconcentration of the end-tidal samples prior to analysis. The concentrating effect of the assumed respiratory quotient of 0.8 was calculated to be less than 1 per cent in any subject and can not account for the theoretical water vapor volume. The decision to omit correction of F_A values in our calculations, although a concededly empirical one, was further supported by the close agreement between $F_A(\infty)$ and F_I values. The corrections which have been applied when more soluble gases have been studied^{6, 11} are no more likely to be appropriate, but as the alveolar and inspired concentration differ so greatly there is no opportunity to detect the inconsistency observed here.

The presumed lack of equilibration of body tissues with C_2H_4 must be reflected in the derived values (k_1 , k_2 , a_1 and a_2) and, consequently, results in some degree of uncertainty regarding the relationship of the expressions $a_1e^{-k_1t}$ and $a_2e^{-k_2t}$ to specific body compartments. As with the semi-logarithmic "peel-off" method of exponential curve analysis, the ordinate-derivative method here used requires

TABLE 4. Comparison of Approach to Equilibrium in the Same Subject Breathing 1 Per Cent C_2H_4 Using "Wet" End-Tidal Measurements in One Study and "Dry" End-Tidal Measurements in the Other

Minute	First Study "Wet Sample" $\frac{F_A}{F_A(\infty)}$	Second Study "Dry Sample" $\frac{F_A}{F_A(\infty)}$
2½	90.05	92.5
5	97.0	97.0
7½	97.5	97.5
10	98.2	98.3
15	99.0	98.5
20	99.0	98.5
25	100	99.1
30	98.8	99.1

properly that the tail segment of the curve predominantly reflect the kinetics of the slowest exchanging compartment, presumably adipose tissue. However, recognizing the physiological uniqueness of each subject, the relatively narrow range of the individual values would appear to indicate some common origin. This assumption may be tested in an approximate manner, by comparing the derived k values computed for each component of the familiar three compartment model: viscera, muscle-skin and adipose tissues. The theoretical values ‡ may be obtained by substituting appropriate numbers into the approximation expression $k \cong F_i/V_i \lambda_i (1)$ where F_i represents blood flow, V_i is tissue volume and λ_i is tissue/blood partition coefficient. This expression is strictly applicable only at constant arterial tension, but it may be used with only a moderate degree of error for relatively insoluble gases, because their alveolar concentration rapidly approaches a steady maximum. The theoretical k values were computed to be:

$$\begin{aligned}
 k \text{ viscera} &= 0.64 \\
 k \text{ muscle-skin} &= 0.036 \\
 k \text{ adipose} &= 0.0029
 \end{aligned}$$

‡ The values were taken from Mapleson's compilation of physiological values for a "standard" 70-kg. man (12):

viscera: $F_i = 4$ liters/minute, $V_i = 6.2$ liters, $\lambda_i = 1$
 muscle-skin: $F_i = 1.4$ liters/minute, $V_i = 39.2$ liters, $\lambda_i = 1$
 fat: $F_i = 0.26$ liter/minute, $V_i = 12$ liters, $\lambda_i = 7.3$.

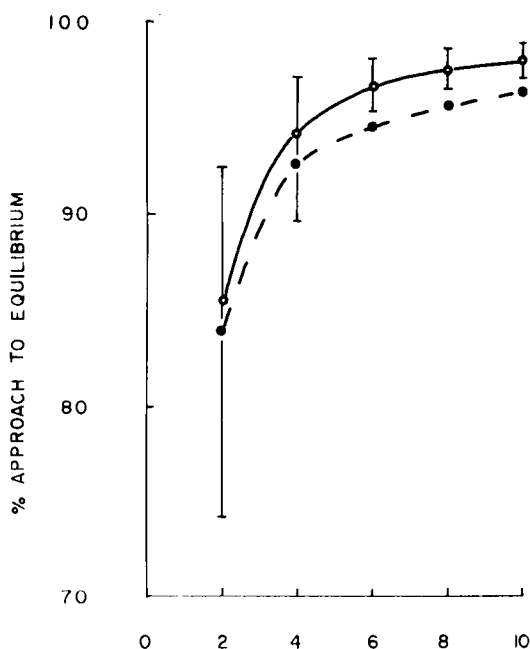


FIG. 2. Comparison of percentage approach to equilibrium of 1 per cent ethylene experimentally determined in this study (solid line) and as predicted by Mapleson (J. Appl. Physiol. **18**: 197, 1963) with electric analog (dashed line). The experimental points are averages of the ratio ($\dot{F}_A/F_A(\infty)$) of the eight studies at the times indicated; the bars show the range of values. The predicted points represent the ratio F_a/F_t and were estimated from figure 3 of Mapleson's publication.

Even assuming a certain degree of uncertainty in these computed determinations, it seems apparent that the experimental k_1 values (average: 0.15) can not be related to any of the model compartments alone. Presumably they reflect a sum of lean tissue (viscera + muscle-skin) exchange.

The interpretation of the experimental k_2 values is still more difficult, not only because of the greater spread of the individual determinations (0.50 to 1.45) but also because of the greater degree of unreliability associated with the derivation of the parameters of the second exponential. This contention is supported by the even wider range of the experimental individual a_2 constants (9.6 per cent to 95 per cent) which makes them of dubious significance. The cluster of the derived k_2 values around the value for k viscera may well be coincidental.

The inability to relate the derived expo-

ponential expressions $a_1e^{-k_1t}$ and $a_2e^{-k_2t}$ to specific body compartments points up the difficulty in determining body compartment kinetics by observing changes in the lung-compartment.⁹ The rapid approach to alveolar equilibrium of the more insoluble gases magnifies these problems because it necessitates continuous measurement of small differences between relatively large quantities, thereby requiring instruments of high sensitivity, low drift characteristics and low background noise. These gases have the advantage, however, of minimizing effects of varying ventilation. Changes in ventilation in our subjects were large enough to have significantly affected the results, had the test gas been a more soluble one.

The experimental uptake rate of 1 per cent ethylene showed fairly good agreement with the predicted uptake rate computed by Mapleson² from an electric analog "programmed" for 1 per cent ethylene at constant inspired tension and for a "standard" 70 kg. man with 6.48 liters/minute cardiac output (fig. 2). One difference between the two curves appears to be a more rapid "flattening" of the predicted curve after the fifth minute, indicating a slower approach to equilibrium as compared to the experimental curve. The difference is small but probably real since the predicted values at the sixth, eighth and tenth minutes are consistently lower than the range of all the experimental values at those times.

Because of its low solubility, the time course of ethylene uptake at clinically effective concentrations should not be much altered by the concentration effect,¹³ nor should it be accompanied by a significant second gas effect.¹⁴ For the same reason, only modest volumes of gas are available for producing alveolar dilution during washout, thus limiting the magnitude of "diffusion anoxia"¹⁵ during emergence from anesthesia.

Summary

A constant inspired mixture of approximately 1 per cent ethylene was breathed by eight healthy, awake subjects. End-expiratory samples were measured for ethylene content every 60-90 seconds. In all subjects, end-tidal concentrations had reached at least 95 per cent of equilibrium value at the end of five minutes, 97 per cent by 10 minutes and 99 per cent by

the end of 20 minutes. Ordinate-derivative analysis of the individual uptake curves yielded two exponentials, which could not, however, be related to specific body compartments. The reasons for this were discussed, as were some problems inherent in the study of multi-compartment kinetics by observation of changes in a single compartment. A comparison of the average experimental uptake curve with a predicted uptake curve computed by means of a special purpose electric analog² showed reasonably close agreement.

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EXTREMITY REPLANTATION The limbs of dogs were subjected to simulated amputation for ten hours. Re-establishment of circulation resulted in 100 per cent mortality. Neither perfusion or hypothermia of the limb altered the outcome. Blood studies showed, not a toxic factor, but acidosis. Treatment with an amine buffer reduced the mortality to only 10 per cent. (*Mahal, R. L., and others: Treatment of "Toxemia" After Extremity Replantation, Arch. Surg.* **89**: 871 (Nov.) 1964.)

AXILLARY BLOCK The axillary approach to the brachial plexus is not difficult and avoids the pulmonary and neurologic complications of the supraclavicular approach. Axillary block in 233 patients ranging in age from 8 months to 81 years resulted in an incidence of successful blocks of 97.8 per cent in adults and 96.4 per cent in children. Paresthesias were not sought. This success rate is higher than others reported in the literature. (*Modell, J. H., and Smith, B. E.: Brachial Plexus Block—Axillary Approach, GP* **30**: 120 (Nov.) 1964.)