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PART I

FLUCTUATIONS IN O_2 STORES AND GAS EXCHANGE WITH PASSIVE CHANGES IN POSTURE

ABSTRACT

To clarify the role of O_2 stores in the fluctuations in $\dot{V}_{O_2}$ observed with changing posture, O_2 intake ($\dot{V}_{O_2}E$) and pulmonary capillary O_2 transfer ($\dot{V}_{O_2pc}$) were calculated breath-by-breath with a box-balloon spirometer and mass-spectrometer. Changes in O_2 stores of the lungs (O_2L) and blood (O_2B) were computed assuming metabolic rate ($\dot{V}_{O_2}C$) constant ($O_2L = \dot{V}_{O_2}E - \dot{V}_{O_2pc}$; $O_2B = \dot{V}_{O_2pc} - \dot{V}_{O_2}C$). Measurements were made before, during, and after passive tilt to 60° and on return to recumbency after 10 min erect. From supine to upright O_2L increased rapidly and O_2B dropped slowly, creating a net deficit in $\dot{V}_{O_2}E$ of 130 ml in 10 min. Return to supine caused rapid loss in O_2L and gain in O_2B with a net $\dot{V}_{O_2}E$ excess of 117 ml. Shifts in O_2B were 2.5 times greater but opposite to shifts in O_2L. Changes in O_2B result from shifts in blood volume and flow more than from changes in cardiac output. Refilling of O_2B, matching loss while upright, caused transient hypoxia with significant hyperpnea.

Previous studies have reported finding a reduction in oxygen uptake ($\dot{V}_{O_2}$) shortly after subjects were moved to an upright position from supine, and a transient increase in $\dot{V}_{O_2}$ when they were returned to the supine posture (7, 8, 11). These changes undoubtedly result to a large extent from changes in the O_2 stores of the lungs and blood which are associated with the gravitational effects on lung volume, total cardiac output, and the distribution of blood volume and flow. Studies to date have not emphasized the time course of these changes; nor have they attempted to separate the individual contributions of the lung and blood O_2 stores to the alterations noted in gas exchange during and immediately following changes in posture. Measurements of metabolic gas exchange by open circuit methods during, and shortly after changes in posture may be invalid because of changes in lung volume occurring during the course of measurement. By measuring $\dot{V}_{O_2}$ breath-by-breath with a closed system with continuous and simultaneous measurements of end-tidal gases and lung volume (FRC), O_2 stores in the lung and O_2 passing the pulmonary capillary membrane can be calculated for each breath. The object of this study was to determine the effects of changes in posture on O_2 transfer at the mouth and pulmonary capillary membrane and to observe concomitant subtle changes in ventilation.

A number of assumptions are necessary to quantitate the changes in O_2 stores in the lung (O_2L) and O_2 stores in the blood (O_2B).
1) In a true steady state, O_2 transfer at the mouth ($\dot{V}_{O_2}E$) is equal to O_2 transfer across the pulmonary capillary membrane ($\dot{V}_{O_2pc}$) and these in turn are equal to the cellular O_2 consumption or metabolic rate ($\dot{V}_{O_2}C$).

$$\dot{V}_{O_2}E = \dot{V}_{O_2pc} = \dot{V}_{O_2}C \qquad (1)$$

In the present study $\dot{V}_{O_2}C$ was assumed to remain constant during and for 3 min after changes in posture since the subjects were passively tilted and minimal muscle involvement was required to maintain the upright position. Wether this assumption is valid or not, it must be accepted here in order to discuss whether shifts in O_2 stores can account for the observed changes in $\dot{V}_{O_2}E$ and $\dot{V}_{O_2pc}$.

2) If $\dot{V}_{O_2}E < \dot{V}_{O_2}C$, then some of $\dot{V}_{O_2}C$ is obtained from either O_2L or O_2B or both.

3) If $\dot{V}_{O_2}E > \dot{V}_{O_2}C$, then O_2L and O_2B or both are being replenished.

4) Changes in O_2L are indicated by differences between $\dot{V}_{O_2}E$ and $\dot{V}_{O_2pc}$. When $\dot{V}_{O_2}E > \dot{V}_{O_2pc}$, then O_2 is being stored in the lung and vice-versa.

5) Changes in O_2B are indicated by differences between $\dot{V}_{O_2pc}$ and $\dot{V}_{O_2}C$. When $\dot{V}_{O_2pc} > \dot{V}_{O_2}C$, then O_2 is being stored in the blood and vice-versa.

Although both standing up and lying down result in transient increases in ventilation (12), the time course of these changes has not been carefully studied. It is also necessary to account for the time-related changes in lung volume (FRC) which are known to occur with posture changes (6). It would seem reasonable to postulate that the increased lung volume when subjects are upright should influence the tidal volume-frequency relationship in changing or maintaining pulmonary ventilation.

METHODS

Subjects and Equipment

Six healthy males were the subjects in the study. Their ages ranged from 29 to 63 yrs (mean: 40) and the weight range was 60 to 80 kg (mean: 73).

The tilt-table was a converted x-ray table with a foot-board and foam rubber mattress. The tilt maneuver from supine to 60° upright or vice-versa took 15 sec to complete. The angle of tilt was chosen so that a major part of body weight was supported by friction on table top in order to minimize leg muscle involvement.

Subjects breathed continuously through a Rudolph valve and rubber mouthpiece. The unidirectional valve was attached to a 110 L bag-in-box apparatus, the subject inspiring from the bag and exhaling into the box via corrugated plastic tubing. The inspiratory line was connected to a 6 L Krogh spirometer with an electrical signal. The bag was filled with air saturated with vapor well before the experiments began to prevent erroneous volume measurements resulting from increases in water vapor pressure during the experiments. Two-way stopcocks were inserted in the inspiratory

and expiratory lines to allow for periodic collection of expired gas for conventional open-circuit gas exchange determinations. Concentrations of O_2, CO_2, N_2 and argon were recorded continuously with a respiratory mass-spectrometer (SRI-MEDSPECT MS8) from a sampling capillary in the Rudolph valve, about one inch from the subject's mouth in midstream. The response time of the instrument was 90% of a step change in 100 milliseconds at a sampling rate of about 40 ml/min. The time lag between the volume and gas concentration recordings was determined by bursting a rubber membrane with 100% O_2 under pressure where the mouthpiece attached to the Rudolph valve, thus producing a simultaneous increase in volume and O_2 concentration. The mean time lag was 1.23 sec and was periodically measured between experiments. The electrical outputs for the 4 gases and the spirometer were connected to a Visicorder (Honeywell-1508A), providing a breath-by-breath recording on a time base. Lung volumes were determined from a short argon rebreathing procedure (gas dilution method). The gas mixture employed was approximately 6% argon in 3 L of air, contained in a 5 L capacity rubber bag with stopcock and mouthpiece attached.

Validation and Calibration Procedures

Mixed expired O_2 and CO_2: After the time lag was known, the areas under the gas curves during expiration were determined by planimetry and divided by the time from start to end of expiration and the mixed-expired gas concentration calculated for each breath. In preliminary trials, the cumulative breath-by-breath mixed-expired O_2 and CO_2 concentrations over a one min period were compared to the mean mixed-expired values of the same gases after the expired air was collected and mixed in one bag. The O_2 and CO_2 concentrations from these two methods were within 0.09% in each of three trial runs on three subjects. The effect of the small deadspace in the valve was subsequently ignored as the inspired and expired deadspace time lags were assumed to be equal in these trial calculations.

The mass-spectrometer was calibrated before and after each run with gas mixtures analyzed by the Scholander method. The deflections of the Visicorder for 1.0% of each of the gases was in the following range: O_2 and CO_2 = 8 mm, N_2 = 2.5 mm, argon = 22 mm.

Gas volumes: The sampling rate of the mass-spectrometer was measured before the runs (about 40 ml/min). After each run the system was closed and the "leak" rate was determined over a 5 to 10 min period (usually amounting to about 14 ml/min). Similarly, any change in the volume of the system, because of flexing of the tubing during tilt from horizontal to 60° was measured after each run (approximately 80 ml). These three artifacts could thus be eliminated from the volume recording.

The spirometer was calibrated before and after each run with a 1.0 L syringe and volumes were calculated accordingly. The sensitivity was such that approximately 1.0 mm deflection represented about 33 ml (BTPS) in volume. The barometric pressure and ambient temperature during the experiments were near 630 mm Hg and 22°C, respectively.

Protocol and Calculations

The subjects were placed in the supine position (SUP I) for 5 min and then breathed through the open circuit for 3 to 5 min more before measurements were started. Expired gas was then collected for 2 min in a Douglas bag for the calculation of gas exchange for comparison with breath-by-breath measurements. During the following 15 sec the subject was switched into the bag-in-box system; baseline measurements of gas concentrations and volumes were then made for one min before the subject was tilted up to 60° (UP) and continued for 3 min. The subject then closed his glottis after a normal exhalation and transferred to another adjacent mouthpiece attached to the rebreathing bag for FRC. After 7 or 8 breaths with a large tidal volume he returned to the other mouthpiece. The mixed argon concentration reached a plateau after 3 or 4 breaths.

The subject remained at 60° while the bag-in-box was refilled with moist air. Another Douglas bag was collected during the 7th and 8th min and, as before, one min of breath-by-breath recordings were taken for baseline before tilt down and continued for 3 min after the return to supine (SUP II). Another rebreathing maneuver followed for FRC.

Any pre-, mid-, or post-expiratory pauses noted on the spirometer tracing were not included in the area or time of that breath. The FRC for each breath was calculated from the volume obtained by the subsequent argon rebreathing maneuver adjusted for changes in end-tidal volume on

the spirometer. Oxygen uptake was calculated both at the mouth ($\dot{V}_{O_2}E$) and at the pulmonary capillary membrane ($\dot{V}_{O_2pc}$) as described by Auchincloss et al. (1).

$$\dot{V}_{O_2}E = F_{I_{O_2}} \cdot V_I - F_{E_{O_2}} \cdot V_E \tag{2}$$

where F_I and F_E refer to inspired (.2094) and mixed-expired gas fraction and V_I and V_E refer to inspired and expired tidal volumes (STPD).

$$\dot{V}_{O_2pc} = F_{I_{O_2}} \cdot V_I - F_{E_{O_2}} \cdot V_E - (F_{A_{O_2}} \cdot V_A - \tilde{F}_{A_{O_2}} \cdot \tilde{V}_A) \tag{3}$$

where $F_{A_{O_2}}$ and V_A represent end-tidal gas fraction and lung volume (FRC) at the end of the breath and $\tilde{F}_{A_{O_2}}$ and $\tilde{V}_A$ represent the same quantities at the beginning of the breath. $F_A \cdot V_A$ for breath n is $\tilde{F}_A \cdot \tilde{V}_A$ for breath n + 1. $\dot{V}_{CO_2pc}$ was calculated from the following equation.

$$\dot{V}_{CO_2pc} = F_{ECO_2} \cdot V_E - F_{ICO_2} \cdot V_I + (F_{ACO_2} \cdot V_A - \tilde{F}_{ACO_2} \cdot \tilde{V}_A) \tag{4}$$

The respiratory exchange ratio at the pulmonary capillary membrane was computed as follows:

$$R_{pc} = \frac{\dot{V}_{CO_2pc}}{\dot{V}_{O_2pc}} \tag{5}$$

Oxygen uptake and carbon dioxide output were computed on a per second basis with the value computed for each expiration being divided by the time of the respiratory cycle (inspiration and expiration).

The lung O_2 content (O_2L) at the end of each breath was computed as the product of $F_{A_{O_2}}$ and FRC. The respiratory frequency (f) was calculated on a per minute basis from the time between successive end-expirations and each of the values for f was multiplied by the corresponding values for inspired V_T to obtain ventilation ($\dot{V}_I$) on a per minute basis.

All the above values were plotted for each individual on a time base at the mid-point of each respiratory cycle. From these individual graphs

mean values were computed at 5 or 10 sec intervals and these means were then replotted. Averaging the data in this fashion served to smooth out some breath-by-breath fluctuations in a few subjects so that overall characteristics in gas exchange and breathing patterns were more easily seen. Portions of the area under these mean curves were also determined by planimetry to quantitate changes in gas stores. All testing for statistical significance ($p < 0.05$) was done with the t-test for paired samples.

RESULTS

Lung O_2 Stores

Tilt up resulted in an immediate rise in $\dot{V}_{O_2}E$ (Fig. 1), while $\dot{V}_{O_2pc}$ dropped simultaneously. After 30 sec $\dot{V}_{O_2}E$ dropped to a level essentially equal to $\dot{V}_{O_2pc}$, with both remaining below, but approaching the $\dot{V}_{O_2}C$ value during the first three min. $\dot{V}_{O_2}E$ showed more marked fluctuations than $\dot{V}_{O_2pc}$, being more sensitive to irregularities in respiratory pattern than the latter. The increase in O_2L during the first 30 sec, represented by the area between the $\dot{V}_{O_2}E$ and $\dot{V}_{O_2pc}$ curves, amounted to 116 ml. This is almost identical to the 114 ml increase in O_2L which was computed independently from the rise in FRC (0.88 L BTPS) and $P_{A_{O_2}}$ (9.0 mm Hg) indicated in Fig. 1 for the same time. The rise in $P_{A_{O_2}}$ and FRC, which are interrelated, made up about 80% of the increase in O_2L, while the remainder (22 ml) was the result of reduced O_2 transfer ($\dot{V}_{O_2pc}$) across the pulmonary capillary membrane.

On return to the supine position after 10 minutes (Fig. 2) $\dot{V}_{O_2}E$ and $\dot{V}_{O_2pc}$ again took a widely separate course. This time $\dot{V}_{O_2}E$ dropped momentarily below zero while $\dot{V}_{O_2pc}$ rose well above $\dot{V}_{O_2}C$, reaching a peak at 20 sec. However, $\dot{V}_{O_2}E$ showed a rapid rebound shortly after tilt down and surpassed $\dot{V}_{O_2pc}$ again after 35 sec. Then both gradually returned close to the baseline after about 90 sec. The loss of O_2L calculated from the area between $\dot{V}_{O_2}E$ and $\dot{V}_{O_2pc}$ for the first 35 sec (-120 ml) was again in good agreement with the value derived from the change in FRC and $P_{A_{O_2}}$ (-117 ml) and also closely matched the gain in O_2L observed during the first 30 sec of tilt up (Fig. 1). Approximately half of the decrement in O_2L during the first 35 sec was attributable to the decline in FRC (0.77 L) while the remainder was due to increased oxygen transfer into the blood.

However, during the second half of the first minute back to supine part of the loss in O_2L was regained as $\dot{V}_{O_2}E$ exceeded $\dot{V}_{O_2pc}$ associated with an increase in ventilation at this time (Fig. 4).

Blood O_2 Stores

The O_2 stores in the blood (O_2B) as calculated from the difference between $\dot{V}_{O_2pc}$ and $\dot{V}_{O_2}C$ (Figs. 1 & 2) did not change as rapidly with posture as O_2L. Nevertheless $\dot{V}_{O_2pc}$ dropped below $\dot{V}_{O_2}C$ immediately upon tilt up and reached a minimum at 60 sec where it was 30% less than $\dot{V}_{O_2}C$. The total loss in O_2B for the first 3 min in the upright posture was estimated at 169 ml, of which 60 ml occurred during the first, 58 ml in the second, and 51 ml in the third minute. It must be assumed that this drain of the blood oxygen stores continued after this time, because $\dot{V}_{O_2pc}$ remained slightly below $\dot{V}_{O_2}C$ over the entire 10 minute period until the subjects were returned to recumbency. Assuming a linear course for $\dot{V}_{O_2pc}$ and $\dot{V}_{O_2}C$ between the end of the third minute (Fig. 1) and the points of measurement during the 10th minute (Fig. 2) one can interpolate that an additional 50 ml of oxygen were taken from the blood stores, giving a total loss of 219 ml in the upright posture (Table 1).

On reassuming the supine posture $\dot{V}_{O_2pc}$ exceeded $\dot{V}_{O_2}C$ by close to 100% after 20 sec (Fig. 2), gradually tapering off until the difference was minimal after 2.5 min. This reflects a rapid replenishment of O_2B amounting to a total of 202 ml in the three minutes, of which 154 ml were regained in the first, 37 ml in the second, and 11 ml in the third minute. Table 1 gives a summary of the average shifts in oxygen stores in the lungs (ΔO_2L) and in the blood (ΔO_2B) separately. The balance of the two represents the discrepancy between $\dot{V}_{O_2}E$ measured externally and the assumed true metabolic rate ($\dot{V}_{O_2}C$).

Ventilation and Alveolar Gases

There was a temporary increase in ventilation both on transition from the supine to the upright position (Fig. 3) and on return to recumbency (Fig. 4). Before the tilt up maneuver was complete ventilation had risen by 35% and most of this (80%) could be accounted for by the expansion of the FRC (+0.88 L) during this time. After 30-35 sec at 60° both V_T and f had subsided to the pre-tilt baseline, but during the second minute there

was an alteration in breathing pattern characterized by a significant 31% increase in V_T and an 11% drop in f, resulting in a slight increase in $\dot{V}_I$ (14%). At the end of three minutes upright all three parameters had returned to the initial level before tilt. During the remaining period at 60° f increased significantly while V_T declined with little change in $\dot{V}_I$.

Upon tilt down $\dot{V}_I$ again rose significantly during and after the change in posture but did not reach its peak (+40%) until 40 sec. This was achieved entirely by a significantly greater V_T (+67%) while f was significantly reduced. By the end of the third minute supine all ventilatory measurements were close to their control levels before the experiment. Incidentally, the change in FRC during tilt down (-.77 L) is not reflected in $\dot{V}_I$ (Fig. 4) but was manifested by a greater expired volume on the spirometer record.

Alveolar (end-tidal) P_{CO_2} (Fig. 3) dropped first rapidly then more slowly in all subjects during the tilt up with the mean value levelling off 4.5 mm Hg below the supine control after 60 sec. It remained remarkably stable at this level for the entire period at 60°. $P_{A_{O_2}}$ (Fig. 1) gained 9 mm Hg during the same period that $P_{A_{CO_2}}$ was falling during the transition to the upright position, but subsequently showed a downward trend, ending up 4 mm Hg above the initial supine value after 10 min upright. The initial disparity between the rise in $P_{A_{O_2}}$ and fall in $P_{A_{CO_2}}$ is closely reflected in the alveolar-respiratory exchange ratio ($\dot{V}_{CO_2pc}/\dot{V}_{O_2pc}$), which rose from a control value of 0.91 before tilt to nearly 1.20 shortly after tilt up, but gradually dropped to 0.82 after three minutes. On return to supine $P_{A_{CO_2}}$ reverted to the pre-tilt control value after one minute after a slight overshoot of 1.5 mm Hg during the first 30 seconds. On the other hand, $P_{A_{O_2}}$ lost 14 mm Hg on tilt down reaching its lowest level at 30 seconds where it was 10 mm Hg lower than in the supine position before the experiment. The extremely unsteady state of alveolar gas exchange during and after tilt down can be visualized from the rapid changes in the alveolar R (Fig. 2) which dropped to 0.64 during the first 25 sec, then fluctuated between 0.8 and 0.9 during the second and third minutes.

The steady state measurements of gas exchange (Douglas bag) for two minutes during the pre-tilt control period and during the 7th and 8th minutes at 60° were not significantly different statistically, but both $\dot{V}_{O_2}$

and $\dot{V}_{CO_2}$ were on the average slightly (6%) lower in the erect posture, while R from the mixed expired air was 0.82 supine before and 0.80 at the end of 10 min upright.

DISCUSSION

The O_2 stores in the lungs and the blood are believed to comprise 80% of an estimated 1500-1600 ml total ordinarily present in the body (10). The remainder is in physical solution in the tissues (5%) and in the form of oxymyoglobin (15%). In the erect position, P_{O_2} in the muscles of the lower extremities must be considerably lower than in the supine posture (vide infra) and it is conceivable that tissue O_2 stores are affected when going from one position to the other. However, this contribution is very small in view of the minimal amount of physically dissolved O_2 and the fact that myoglobin is still 90% saturated with O_2 at a P_{O_2} of 25 mm Hg (13). On the other hand, the effect of changing posture on the O_2 stored in the lungs and blood is apparently of sufficient magnitude to alter overall gas exchange significantly as measured by conventional open or closed system methods, not only during the actual movement of the body but for several minutes thereafter.

Lung O_2 Stores

Lung O_2 stores are liable to change whenever the amount of the gas supplied to the lungs by ventilation ($\dot{V}_{O_2}E$) does not match the amount being transferred to the pulmonary capillary blood. Such a discrepancy was seen in these experiments during and shortly after tilt up (Fig. 1) where $\dot{V}_{O_2}E$ increased momentarily by more than 100%, while $\dot{V}_{O_2pc}$ declined below the preceding supine level. The immediate rise in $\dot{V}_{O_2}E$ can be accounted for quantitatively by the increase of the inspired over the expired tidal volume associated with the caudad shift of the diaphragm and increase in functional residual capacity. At the same time less O_2 was transferred into the blood than previously, also contributing to a net gain of O_2L. In less than 30 sec after starting the tilt $\dot{V}_{O_2}E$ again approximated $\dot{V}_{O_2pc}$, both of them continuing below the supine baseline, while O_2L stabilized 50% higher than before thanks not only to the larger FRC but also to a rise in alveolar P_{O_2} from increased ventilation. During and after tilt down the discrepancy between $\dot{V}_{O_2}E$ and $\dot{V}_{O_2pc}$ was even more drastic, this time in reverse direction. During the tilting process $\dot{V}_{O_2}E$ dropped abruptly and the record (Fig. 2) actually indicates

a loss of oxygen to the environment for a few seconds, because the expired volume exceeded the inspired with the cephalad shift of the diaphragm reducing the functional residual capacity. Simulteneously $\dot{V}_{O_2pc}$ increased rapidly and at 20 sec was twice as great as before, further depriving the lungs of O_2. As a result O_2L dropped well below its initial supine value (SUP I) and did not return to that level for 60 sec. The recovery of O_2L during this time was due to the biphasic course of $\dot{V}_{O_2}E$ with a sharp rebound after returning to the supine position overtaking and surpassing $\dot{V}_{O_2pc}$ after 30 sec thanks to a prompt increase in ventilation (Fig. 4, $\dot{V}_I$). Subsequently $\dot{V}_{O_2}E$ and $\dot{V}_{O_2pc}$ followed each other more closely but did not return to the baseline for more than two minutes pointing to a continuing replenishment of O_2 stores beyond the alveolar membrane.

Blood O_2 Stores

The estimation of shifts in blood O_2 stores from changes in $\dot{V}_{O_2pc}$ is open to question, because it is based on the assumption that metabolic O2 consumption does not change appreciably with passive changes in posture. Our apprehension that some isometric muscle activity in the 60^o upright posture might increase O_2 consumption proved to be unfounded since metabolic rate (open circuit method) after 7 minutes upright was actually 6% below the control values after 8 minutes complete rest supine. This difference was not statistically significant. In order to obtain some information concerning blood O_2 stores the assumption of a constant metabolic rate using these two reference points appeared justified.

There is general agreement that cardiac output at rest is 20-25% lower in the erect standing than in the supine position (14). This must be associated with an increased arteriovenous O_2 difference and a reduction in venous O_2 stores. For example, an individual with a $\dot{V}_{O_2}$ of 300 ml/min, an arterial O_2 content of .20 ml/ml, a supine $\dot{Q}$ of 5000 ml/min and a venous blood volume of 4500 ml would have 630 ml of O_2 in venous stores. In the erect position with a loss of 25% in $\dot{Q}$ the venous store would be 540 ml. The difference of 90 ml is far short of the total changes in O_2B calculated for these experiments from the difference between $\dot{V}_{O_2pc}$ and $\dot{V}_{O_2}C$ in Fig. 1 and shown in Table 1. There must be other factors effecting O_2B with changes in posture than $\dot{Q}$ alone.

Pooling of blood in the dependent parts of the body during passive tilt to the upright position involves a shift of blood volume in the order of 500 ml (4) as well as a reduction of blood flow through the lower extremities. The latter can be inferred from the observations of Reeves et al. (12) that the arteriovenous O_2 difference between femoral arteries and veins increased from .041 to .123 ml/ml from the supine to the erect posture. In addition, total cardiac output drops by 20-25% during 10 minutes passive tilt at 60° (14). All three of these factors must affect the O_2 stores of the blood. In order to assess the relative contribution of redistribution of blood volume and flow, and of changes in cardiac output, a simplified analog of the cardiovascular system, consisting of two compartments in parallel, was calculated to estimate changes in blood O_2 stores with changes in posture (Table 2). The following assumptions were made: a total blood volume of 5500 ml of which 4500 ml are contained in the venous system (BV), a blood flow ($\dot{Q}$) of 5000 ml/min, a metabolic O_2 consumption ($\dot{V}_{O_2}$) of 300 ml/min, and arterial O_2 content (Ca_{O_2}) of .20 ml/ml. Since the O_2 store of arterial blood probably does not change appreciably with posture the following calculations were limited to the venous O_2 stores (O_2B) only and derived as:

$$O_2B = BV \left(Ca_{O_2} - \frac{\dot{V}_{O_2}}{\dot{Q}} \right) \qquad (6)$$

In the supine reference position (Table 2, I) BV and $\dot{Q}$ are equally distributed between compartment A and B, each of them having the same $\dot{V}_{O_2}$ (150 ml/min). In this case the total O_2B of 630 ml is equally distributed between A and B. On going to the upright position (II) 500 ml of venous blood are shifted from A to B while 1250 ml/min of blood flow are transferred from B to A without altering cardiac output. As a result O_2B is reduced in both compartments and the sum of both is 130 ml less than under I. It is apparent that the actual loss of O_2B is not revealed if calculated as usual from the total volume and the mixed venous O_2 content as shown in parentheses. Under III (Table 2) a reduction in cardiac output of 24% after 10 minutes at 60° is taken into account and applied in proportion to $\dot{Q}$ in each compartment. Under these conditions total O_2B is reduced by 257 ml as compared to the supine reference (I). This figure is of the same order of magnitude as those derived for O_2B

from the difference between $\dot{V}_{O2pc}$ and $\dot{V}_{O2}C$ shown in Table 1 for the same period upright and approximately the same amount of O_2 is restored to the blood on return to recumbency (Table 1, SUP II). The analog also shows that a drop in cardiac output by 24% without any redistribution of volume and flow (figures in parentheses) would reduce O_2B by only 85 ml or one-third of the difference caused by all three factors.

Further manipulations with the two compartment model with constant cardiac output (Table 2, I and II) permit the following interesting conclusions. 1) Shifts in BV between A and B without redistribution of $\dot{Q}$ do not affect venous O_2 stores. 2) If $\dot{Q}$ and BV shift in the same direction by the same proportion, O_2 stores do not change. 3) Redistribution of $\dot{Q}$ without shifts in BV always reduce O_2B, whereby loss of O_2B increases exponentially the greater the shift in $\dot{Q}$. 4) Loss of O_2B is greatest when BV and $\dot{Q}$ both shift in opposite directions, as in the example in Table 2, whereby changes in BV contribute linearly and shifts in $\dot{Q}$ exponentially to the resulting loss in O_2B. 5) When BV and $\dot{Q}$ move in the same direction simultaneously, total O_2 stores decrease as long as the shift in BV is smaller than that of $\dot{Q}$, but increase when ΔBV exceeds $\Delta\dot{Q}$.

Granted the inadequacy of the simple two compartment model to describe events in the complex cardiovascular system, the concept may well be applicable to other conditions associated with massive redistribution of blood volume and flow such as clinical shock and gravitational stress in aviation. Thus Glaister (5) reported a reduction of apparent $\dot{V}_{O_2}$ during a three minute exposure to $+3G_z$ on a centrifuge and an excess $\dot{V}_{O_2}$ of 560 ml above control immediately thereafter and he interpreted these as transient depletion and replenishment of O_2 stores.

The preceding discussion has pointed out that O_2L increases on transition from supine to upright posture while O_2B is reduced and vice-versa on return to supine. The arithmetic sum of these changes should result in the excess or deficit in $\dot{V}_{O_2}E$ of the body at any given time. Table 1 presents the changes in each of the two stores during the first 3 minutes tilt up separately, the sum during the 4th-10th minute, and the total for 10 minutes followed by the same calculations for the first three minutes supine. The cumulative loss or gain in each store when balanced for the 10 minutes

at 60° shows a deficit of 130 ml with the negative contribution of O_2B being 2.5 times greater than the positive one of O_2L. On return to supine the gain in O_2B is much greater than the loss of O_2L in the first minute resulting in about the same excess in total $\dot{V}_{O_2}E$ as in the first minute after tilt up. In the following two minutes O_2B continues to gain while O_2L changes very little. The total amount of O_2 restored three minutes after return to supine was very close to the amount lost in 10 min at 60°. These results strongly suggest that the reduced O_2 intake during the first few minutes of orthostasis and the excess on return to recumbency seen in this study, confirming several earlier investigators (7, 8, 11), can be adequately accounted for by the interaction of changing lung and blood O_2 stores, thus discounting the presence of a true oxygen debt in the tissues as invoked by Rahn and Ament (11). As can be seen from Table 1 and inferred from the changes in $\dot{V}_{O_2pc}$ in Figs. 1 & 2, the replenishment of O_2B after tilt down was accomplished much more rapidly than the preceding depletion of O_2B at 60°. Indeed 75% of the O_2 deficit in O_2B was regained after the first minute tilted down, while it took three minutes to lose about the same amount during orthostasis. An explanation for this may be the fact that the depletion of venous O_2B is a function of metabolic rate of poorly perfused dependent parts of the body and is therefore a relatively slow process. Reeves et al. (12), who followed venous O_2 content in femoral venous blood after moving from supine to erect, noted that the fall in O_2 content took 5-7 minutes to stabilize. Conversely, on return to supine a large amount of blood with very low O_2 content is rapidly moved centrally by gravity and resaturated with O_2 in a single passage through the lungs. In our experiments the tilt itself took 15 sec to complete. With faster changes in posture as employed by others (8), the repletion of O_2B reflected in an excess $\dot{V}_{O_2}E$ is apparently even more rapid.

Ventilation and Alveolar Gases

In contrast to numerous previous investigations where pulmonary ventilation was higher while standing than in the supine position, very little change in $\dot{V}_I$ was observed in the present study with the exception of the initial rise during the first 30 sec upright, directly associated with the increase in FRC (Fig. 3), and again a transient increase lasting about two minutes after return to recumbency (Fig. 4); yet our results are in close

agreement with those of other authors in that alveolar P_{CO_2} drops on the average 4 mm Hg in the upright posture and remains low until returning to supine. Furthermore, the alveolar ventilation calculated from $\dot{V}_{CO_2}E$ and $P_{A_{CO_2}}$ remained practically constant regardless of changes in posture and $P_{A_{CO_2}}$, except for the first two minutes after changing position. However, CO_2 output was consistently lower in the erect than in the supine position. Therefore, in spite of the fact that $\dot{V}_A$ did not change with posture there was indeed alveolar hyperventilation relative to the reduced $\dot{V}_{CO_2}$ when standing up resulting in a lower $P_{A_{CO_2}}$. Bjurstedt et al. (2) found that the arterial-alveolar gradient for CO_2 increases about 2 mm Hg while standing and attributed this to a redistribution of blood flow in the lungs where apical regions are less well perfused than the basal ones (15), thus contributing to an alveolar deadspace effect. This gradient calls for more alveolar ventilation to maintain a given arterial P_{CO_2} and partly explains the relative hyperventilation. Nevertheless, the remaining reduction in arterial P_{CO_2} observed by these authors and presumably present in our study remains to be accounted for. A possible explanation invoked earlier by McMichael (7) and later advocated by Rahn and Ament (12) points to the reduction of cerebral blood flow in the erect position (9) leading to a rise in P_{CO_2} at the central chemoreceptors. This calls for more ventilation resulting in a lower arterial P_{CO_2} to restore its proper level in the brain.

The attenuation of CO_2 output during the erect period reflects CO_2 retention in the blood and tissue as a corollary to the loss of O_2 stores discussed above. On return to the supine position a marked surge in $\dot{V}_{CO_2pc}$ was noted similar to $\dot{V}_{O_2pc}$, but not quite as great (R_{pc}: 0.64), signifying release of stored CO_2.

The only time during the entire protocol when a statistically significant increase in $\dot{V}_I$ occurred was immediately after returning to the supine position with a striking rise in V_T at reduced frequency (Fig. 4). The transient hyperpnea reached its peak at 40 sec and had subsided by the end of the second minute. It is most likely that this transient ventilatory response was elicited via the peripheral chemoreceptors by the drastic changes in alveolar P_{O_2} and P_{CO_2} when the hypoxic and hypercapnic pooled blood reached the lungs. By

30 sec $P_{A_{O_2}}$ dropped to 71 mm Hg which, assuming a normal A-aO_2 gradient of 12 mm Hg at this elevation, would correspond to an arterial P_{O_2} of less than 60 mm Hg. According to Witzleb (16) impulse frequency from the carotid sinus nerve increases markedly when Pa_{O_2} drops below 60 mm Hg and the central response may have been reinforced by the rising P_{CO_2} at this time. Bjurstedt et al. (2) also noted hyperpnea in the first minute after tilting down and commented that in spite of this a marked drop in arterial O_2 saturation occurred. However the time sequence in our records speaks in favor of a cause and effect relationship. Pertinent in this context are recent studies by Edelman et al (3) on the response to transient hypoxia and hypercapnia in man. Their records show a lag time of 5-10 sec between the first breath of N_2 and the response in tidal volume.

Considering that our experiments were conducted at an elevation of 5400 ft. ($P_{I_{O_2}}$ 122 mm Hg), it is conceivable that the hypoxic stimulus and the ventilatory response might not be as great nearer sea level, where alveolar P_{O_2} would not reach as low levels as here. Conversely, patients suffering from cardiopulmonary disorders with pre-existing hypoxemia might encounter transient severe hypoxia with acute respiratory embarrassment on lying down after standing still for some time.

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LEGENDS - FIGURES

Fig. 1. O_2 intake by the lungs ($\dot{V}_{O_2}E$) and by the pulmonary capillaries ($\dot{V}_{O_2pc}$), alveolar (end-tidal) oxygen pressure ($P_{A\,O_2}$), exchange ratio at the pulmonary capillaries (R_{pc}), lung O_2 stores (O_2L), and functional residual capacity (FRC) at supine and during and after tilt to 60^{o} upright. Gas exchange was measured by open circuit method during the 2nd and 3rd minutes before tilt (Douglas bag). Note: Average barometric pressure on location was 630 mm Hg.

Fig. 2. Same as Fig. 1 for last three minutes upright and during and after return to supine posture.

Fig. 3. Inspired ventilation ($\dot{V}_I$), tidal volume (V_T), frequency (f), and alveolar (end-tidal) CO_2 pressure ($P_{A\,CO_2}$) corresponding to Fig. 1 in time.

Fig. 4. Same as Fig. 3 corresponding to Fig. 2 in time.

Fig. 1

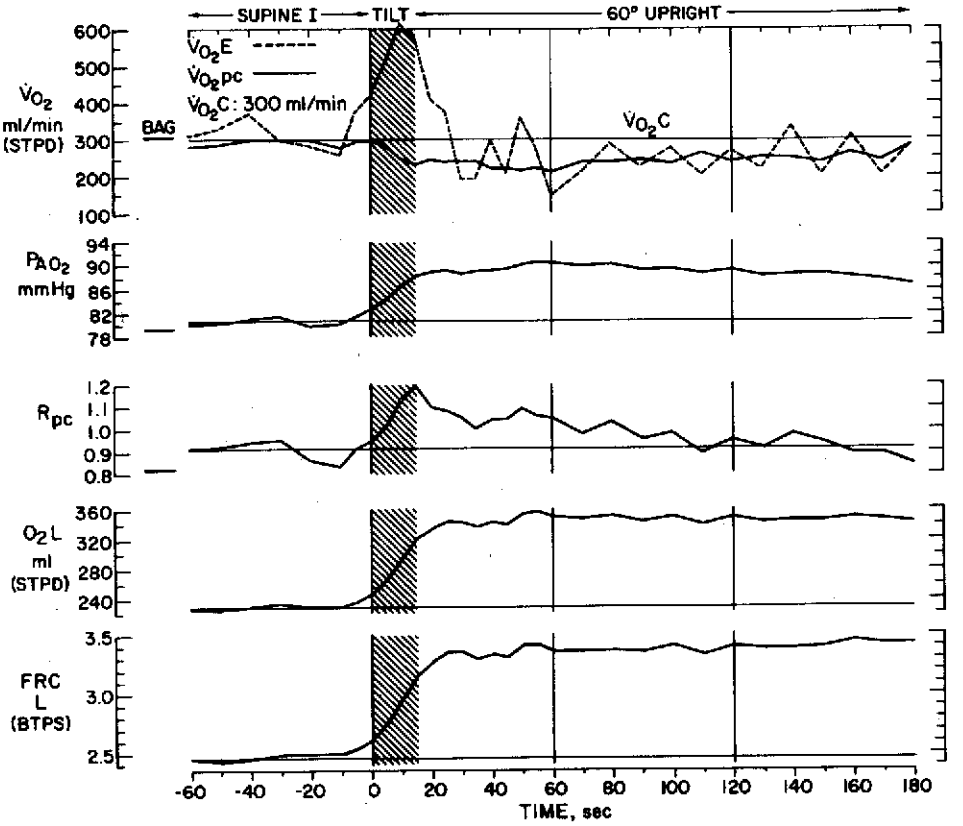
SUPINE I
TILT
60° UPRIGHT
$\dot{V}_{O_2}$E
$\dot{V}_{O_2}$pc
$\dot{V}_{O_2}$C: 300 ml/min
$\dot{V}_{O_2}$C
BAG
$\dot{V}_{O_2}$ ml/min (STPD)
P_{AO_2} mmHg
R_{pc}
O_2L ml (STPD)
FRC L (BTPS)
TIME, sec

Fig. 3

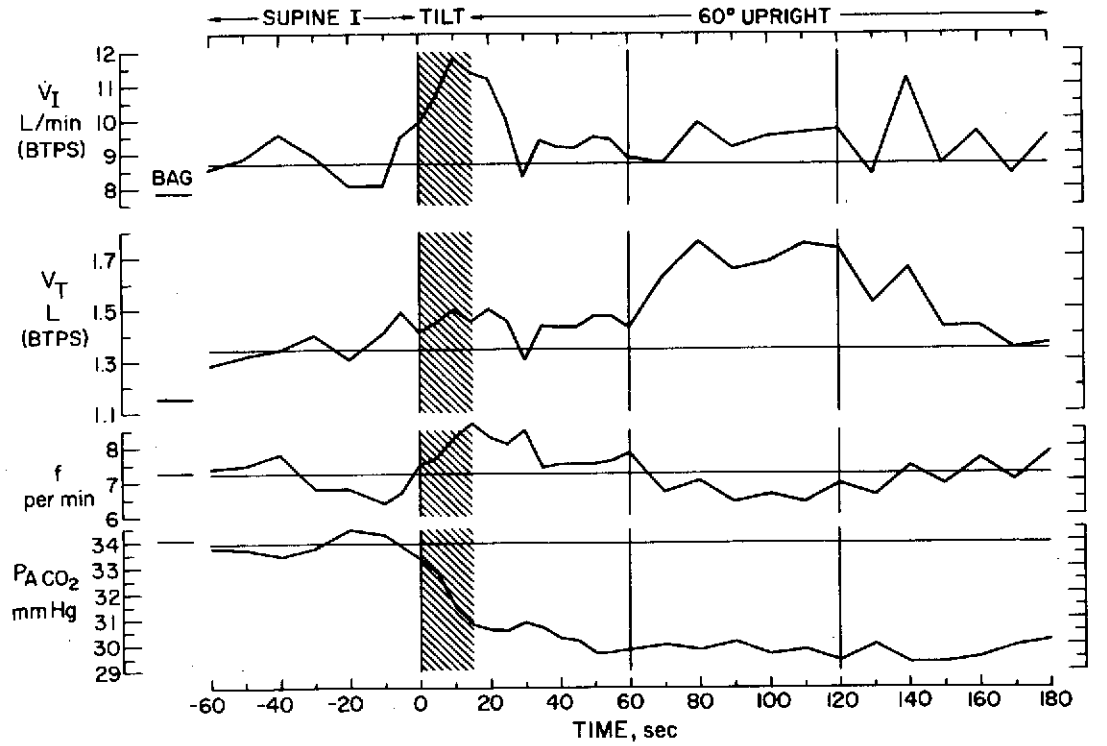
SUPINE I
TILT
60° UPRIGHT
$\dot{V}_I$ L/min (BTPS)
BAG
V_T L (BTPS)
f per min
P_{ACO_2} mmHg
TIME, sec

Fig. 2

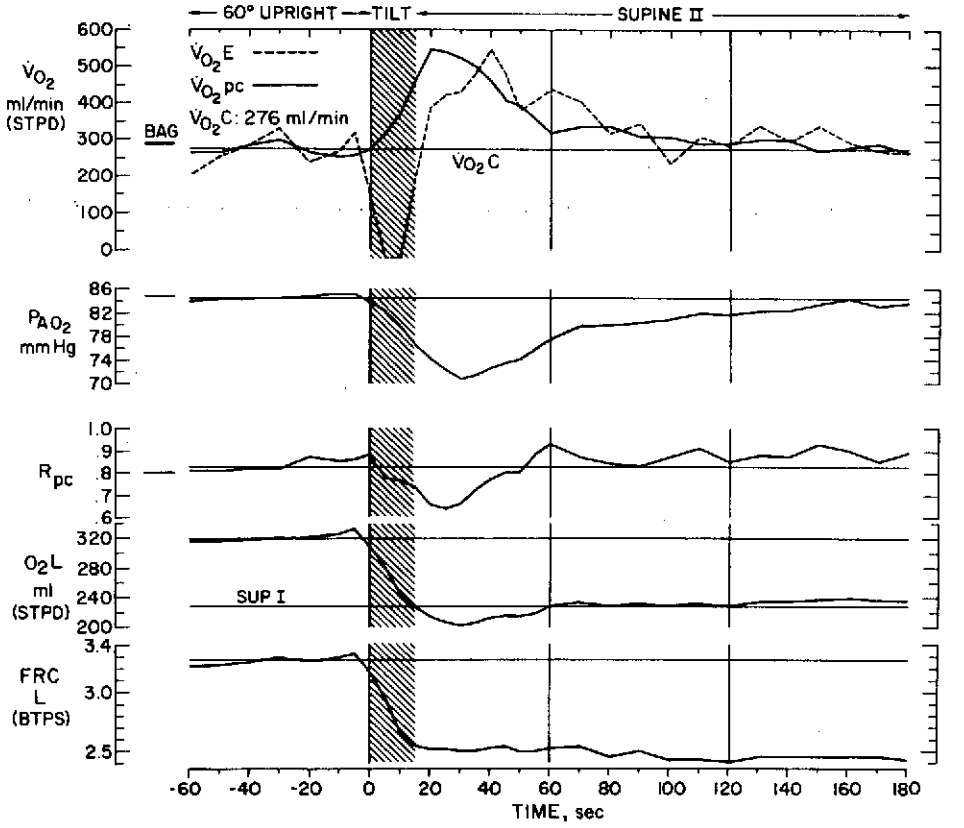
60° UPRIGHT
TILT
SUPINE II
$\dot{V}_{O_2}$ ml/min (STPD)
$\dot{V}_{O_2}E$
$\dot{V}_{O_2}pc$
$\dot{V}_{O_2}C$: 276 ml/min
BAG
$\dot{V}_{O_2}C$
P_{AO_2} mm Hg
R_{pc}
O_2L ml (STPD)
SUP I
FRC L (BTPS)
TIME, sec

Fig. 4

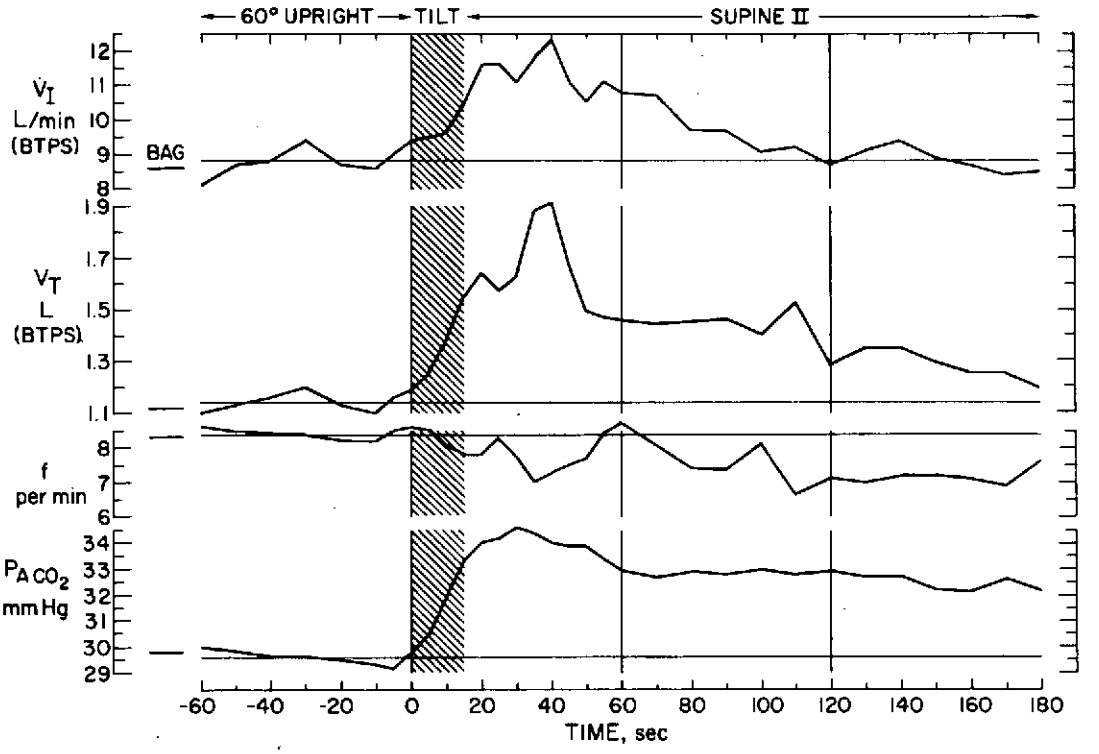
60° UPRIGHT
TILT
SUPINE II
$\dot{V}_I$ L/min (BTPS)
BAG
V_T L (BTPS)
f per min
P_{ACO_2} mm Hg
TIME, sec

Table 1

BALANCE OF OXYGEN STORES (ml)

	60° Upright					Supine II			
	1'	2'	3'	4-10'	Total 1-10'	1'	2'	3'	Total 1-3'
ΔO_2L	+120	-1	-7	-23	+89	-92	+1	+6	-85
ΔO_2B	-60	-58	-51	-50	-219	+154	+37	+11	+202
Balance	+60	-59	-58	-73	-130	+62	+38	+17	+117

Cumulative gains or losses in lung (O_2L) and blood stores (O_2B) for the first three minutes at 60° separately, for the 4th to 10th minute combined and the total for 10 minutes, followed by 3 minutes supine. The balance of ΔO_2L and ΔO_2B shows excess (+) or deficit (-) in apparent O_2 intake.

Table 2

	I			II			III		
	A	B	A+B	A	B	A+B	A	B	A+B
$\dot{V}_{O_2}$ (ml/min)	150	150	300	150	150	300	150	150	300
BV (ml)	2250	2250	4500	1750	2750	4500	1750	2750	4500
$\dot{Q}$ (ml/min)	2500	2500	5000	3750	1250	5000	2850	950	3800
a-vD_{O_2} (ml/ml)	.060	.060	.060	.040	.120	.060	.053	.158	.079
Cv_{O_2} (ml/ml)	.140	.140	.140	.160	.080	.140	.147	.042	.121
O_2B (ml)	315 +	315 =	630	280 +	220 =	500(630)	257 +	116 =	373(545)

Hypothetical calculations with a two compartment circulatory system to demonstrate the effects of shifts in venous blood volume (BV) and flow ($\dot{Q}$) on venous O_2 stores. Compartments A and B have constant and equal $\dot{V}_{O_2}$. Under I BV and $\dot{Q}$ are equally distributed in A and B. Under II BV and $\dot{Q}$ are skewed between A and B in opposite directions, simulating blood pooling. Combined $\dot{Q}$ is the same as I. Under III distribution of BV and $\dot{Q}$ is the same as in II, but $\dot{Q}$ is 24% less in each compartment. Numbers in parentheses indicate total O_2L from mixed venous C_{O_2} and total BV assuming uniform Cv_{O_2}.

PART II

A COMPARISON OF THE CLOSING VOLUME TEST WITH OTHER PULMONARY FUNCTION MEASUREMENTS

ABSTRACT

The closing volume (CV) test was compared with measurements of forced expired volume in one second (FEV_1), maximal mid-expiratory flow (MMEF, flow-volume loop), maximal expiratory flow at 25% VC ($MEF_{25\%VC}$) and nitrogen clearance equivalent (N_2 Cl. Equiv.) from the N_2 washout in 70 subjects. A group comparison between healthy smokers and non-smokers revealed statistically significant differences for CV ($p < .01$) CV/VC% ($p < .001$) and CC/TC% ($p < .001$) (CC: closing capacity = CV + RV). The difference was also significant for the N_2 Cl. Equiv. ($p < .01$) but not for MMEF, $MEF_{25\%VC}$ nor FEV_1. While the CV test is apparently more sensitive as a screening test than the FEV_1 or the flow-volume loop, it has the disadvantage of great variability in healthy non-smokers both within and between individuals. The N_2 washout test also has good discriminating capability but has a much smaller coefficient of variation which makes it preferable for evaluating individual cases.

In 34 patients with different types of pulmonary disease there was a strong correlation between CC/TC% and MMEF ($r = -.67$, $p < .01$) and a lesser one with FEV_1 ($r = -.58$, $p < .01$). The correlation between the N_2 clearance equivalent and the slope of Phase III in the CV test was statistically highly significant ($r = .73$, $p < .001$) which implies that the slope of Phase III deserves as much attention as the CV for screening purposes. In 25% of the patients CC was greater than FRC, thus encroaching upon the tidal volume and interfering with gas exchange.

A COMPARISON OF THE CLOSING VOLUME TEST WITH OTHER PULMONARY FUNCTION MEASUREMENTS

Recent advances in respiratory pathophysiology have led to the conclusion that in the early stages of chronic obstructive lung disease the primary site of pathology is in the small caliber peripheral airways (ID $\leq$ 2 mm) (11). Since the resistance of these small airways represents only a small part of total pulmonary resistance because of their large number, (17) a considerable increase in peripheral resistance may occur without producing any detectable change in total pulmonary resistance when measured by the usual dynamic tests such as maximal breathing capacity (MBC), forced expired volume in one second (FEV_1) or specific airway conductance (SGaw) measured in the body plethysmograph. Maximal expiratory flow rates measured at 50% (MMEF) or less ($MEF_{25\%VC}$) on the flow volume loop are apparently the most sensitive criteria of dynamic ventilatory impairment available so far (5). In the search for more specific methods for detecting small airways involvement, several different procedures have been advocated and are currently under study. The most reliable of these is the test for frequency dependence of dynamic pulmonary compliance (23). Unfortunately, the procedure is too complicated and time consuming for routine clinical use. However, experience has shown that a significant drop in dynamic compliance with increasing frequency of breathing is invariably associated with unequal distribution of ventilation (6, 13) as reflected in the N_2 washout test, a procedure more practicable with patients. Another test that may be even more suitable for screening purposes and epidemiological surveys is based on the closure of small airways in the dependent parts of the lungs as one approaches residual volume on deep expiration. This gravity dependent phenomenon can be demonstrated either by introducing a bolus of foreign gas (xenon, helium, or argon) early during inspiration

from RV, or by the dilution of N_2 with a single maximal inspiration of O_2. When N_2 concentration is plotted against volume during the following controlled maximal expiration a tracing as shown in Fig. 1 is usually obtained. The abrupt upward deflection of N_2 toward the end of expiration defines Phase IV and the subtended closing volume (CV). This pattern has been interpreted by the following sequence of events. When starting the maneuver from maximal expiration a larger fraction of the residual volume is contained in the upper parts of the lungs than in the dependent regions. During the following inspiration with O_2 the N_2 in the lower parts becomes more diluted than in the upper ones. During the following slow expiration the upper and lower regions both contribute to the alveolar plateau (Phase III) but toward the end of expiration some of the airways in the dependent zone collapse due to compression and reduce the contribution with low N_2 to the expirate. At this point the contribution from the upper regions with high N_2 predominates producing the upward deflection of N_2. The closing volume becomes larger when the elastic recoil of the lungs and/or the caliber of the small airways are reduced.

The following study had several objectives: 1) to establish the reproducibility of the CV test in one and the same individual, 2) to define the range and variability of the CV in subjects of different ages with no pulmonary pathology, 3) to assess the ability of the CV test to discriminate between smokers and non-smokers in a normal group as compared to standard pulmonary function tests, 4) to compare pulmonary function data from a group of patients with different forms of clinically established cardiorespiratory disease with the measurements of CV and to evaluate its functional significance.

Methods and Procedures:

Closing volumes were measured by the single breath N_2 dilution method closely following the standard procedure suggested by the Division of Lung Disease, National Heart and Lung Institute (1972). This is a modification of the original single breath N_2 dilution method proposed by Fowler (10) for assessing uneven pulmonary ventilation. It consists of a slow maximal inspiration of O_2 starting from residual volume, immediately followed by a slow complete expiration to residual

volume at a flow rate of not more than 0.5 liters/sec. All tests were performed sitting erect. Nitrogen concentration during expiration was recorded from a needle valve at the mouth piece with a Nitralyzer (Med-Science, Model 505). The subject breathed through a low-dead-space (28 ml) Rudolph valve directly attached to a 3-way stopcock upstream giving access to either room air or 100% O_2 from a 13 liter rubber bag. Another stopcock on the expiratory side led either to room air or to a recording WEDGE spirometer (Med-Science, Model 170). The signal from the Nitralyzer was plotted on the y-axis and the volume on the x-axis of a Bryan's Autoplotter (Series 22,000). The scale was on the average 2 mm deflection for one percent N_2 and 32 mm per liter volume. The Nitralyzer was calibrated regularly with N_2-O_2 mixtures analyzed by the method of Van Slyke and the deflection for air and tank O_2 ($< 0.2\% N_2$) were inscribed on each record as well as the calibration signal from the spirometer. The latter was checked frequently with a one liter Hamilton precision syringe. The expiratory flow rate was maintained at approximately 400 ml/sec in adults by having the subject control his expiration to follow a prescribed deflection of the flow signal from the WEDGE spirometer on an oscilloscope in front of him. In children a lower flow rate was used depending upon the size of their vital capacity measured previously. Tests in which the flow rate exceeded 500 ml/sec were discarded. Each subject performed three single breath maneuvers at intervals sufficient to restore the initial N_2 concentration in the expired air as shown by the Nitralyzer. The average of these tests was taken.

On two normal subjects 21 consecutive measurements of closing volume were made at 3-5 minute intervals to determine the individual coefficient of variation. The range of variability as seen in Table VI was quite large and the coefficient of variation was 28% in the younger and 21% in the older subject. In an attempt to minimize the variation in each individual the results of three tests were averaged for each subject in this study.

The N_2/volume expirogram (Fig. 1) was divided into four phases as described by Dollfuss et al. (9), whereby Phase I represents deadspace gas, Phase II the mixture of deadspace and alveolar gas and Phase III alveolar gas only. In most instances there is an abrupt

change in slope toward the end of expiration which defines the beginning of Phase IV and the closing volume (CV) projected on the x-axis under it. Subsequently the CV was related to the vital capacity (CV/VC%), and the closing capacity (CC = CV + RV) to the total capacity (CC/TC%) and to the functional residual capacity (CC/FRC%) using the values for FRC and TC obtained previously by the N_2 washout method. The average slope of Phase III was determined for each subject and expressed as change in $\%N_2$ concentration per liter change in volume.

A total of 70 subjects between 9 and 68 years old was studied. Of these 34 (24 men, 10 women) were healthy volunteers without any complaints, clinical signs or history of pulmonary disease. As it happened 9 of the normals were smokers. The 36 patients (25 men and 11 women) were taken at random as they came to the laboratory for routine tests regardless of the type or severity of their disease. However, the majority (66%), turned out to be suffering from some form of airway disease and half of them happened to be smokers. The routine pulmonary function tests consisted of measurements of total lung capacity and all its subdivisions using direct spirometry and the N_2 washout method (16). From the latter mixing efficiency was determined from the N_2 clearance equivalent, which is the ventilation with O_2 required to clear one liter of lung volume to less than 1% of N_2. The forced vital capacity and forced expired volume in one second (FEV_1) were measured three times and the best effort was taken. The maximal flow volume loop was performed on a WEDGE spirometer and a SANBORN x-y recorder (670A). The maximal mid-expiratory flow (MMEF) and the maximal flow at 25% of vital capacity ($MEF_{25\%VC}$) were measured. Diffusing capacity was estimated by the steady state carbon monoxide method after Bates et al. (1962) using end-tidal samples for alveolar carbon monoxide pressure.

Results and Discussion:

No closing volume could be demonstrated in six (9%) of the 70 subjects studied, although the maneuver was properly performed and repeated at least three times. Four of the normals and two of the patients did not show a CV. It was remarkable that only one of these

was over 20 years old, the other five were between 13 and 19. It has been reported by Mansell (18) that CV/VC% falls from 20% at age 6 to 2% at age 19. This may be related to the increase in elastic recoil of the lungs with growth, so it is understandable that CV may be more difficult to obtain in adolescents. In general CV increases with age in adults. A statistically significant positive correlation was obtained on our normal group between CV/TC% (y) and age (x):

$$y = 20.76 + 0.27x$$
$$SEE = 7.2\%$$

This finding is in agreement with several previous investigations (1, 4, 7, 15, 20) and is generally attributed to the loss of elastic recoil of the lungs over the years.

In Table I the closing volumes and capacities on the normal group are presented according to age and sex and in relation to vital capacity, total lung capacity and functional residual capacity. Table II shows the slope of Phase IV on the single breath N_2 test, the nitrogen clearance equivalent and the conventional measurements of dynamic characteristics of the airways (MMEF and FEV_1).

Smokers v. non-smokers

The fact that 9 of 34 normals were smokers provided an opportunity to test the sensitivity of the closing volume as compared to the other tests in discriminating these from the non-smokers under the assumption that the former might have some manifestations of small airway disorder that were not symptomatic clinically.

A statistical analysis was performed by group comparison between the normal smokers and non-smokers and the results are shown in Table V. All measurements relating to the closing volume were on the average higher in the smokers and the mean differences were statistically significant for CV and CC/FRC% ($p < 0.01$) and highly significant for CV/VC% and CC/TC%. Of the other tests only the results of the N_2 washout test (N_2 Cl. Equiv.) were significantly different in the two groups ($p < 0.01$), while neither the flow volume loop (MMEF and $MEF_{25\%VC}$) nor the FEV_1 showed a significant difference although the

mean values were all lower in the smokers. The coefficients of variation (cv) given for each test in Table V indicate that the scatter of the individual data is much greater for CV alone than when it is coupled with VC or TC, so that the latter appear to be more sensitive for evaluating an individual case. In comparison the N_2 Cl. Equiv. has a considerably smaller coefficient of variation than any of the other tests except the FEV_1. The relative discriminating power of the different tests can also be derived from the percentage of smokers that showed values of more than 1 SD from the mean value for the non-smokers. Thus 78% of the smokers had a CV and CV/TC% of more than 1 SD higher, whereas none of the smokers had an MMEF or FEV_1 more than 1 SD lower than the average non-smoker. On the other hand 56% of the smokers were beyond the 1 SD margin in their N_2 Cl. Equiv. and in the slope of Phase III. Although it is not related directly to the mechanics of breathing, diffusing capacity (DL_{CO}) was included in Table V, because it is adversely affected by smoking (12). The mean for the smokers was 25% lower than for the non-smokers, but this difference was not statistically significant and only 43% of the smokers were more than 1 SD below the average for non-smokers.

In appraising the relative discriminating power of the different tests listed in Table V it appears that either CV/VC% or CC/TC% are most suitable for differentiating between populations with and without mild abnormalities in respiratory mechanics in epidemiological surveys. However, the N_2 Cl. Equiv. is nearly as effective in this regard and may be more useful for evaluating the individual case, because of its narrower range of variation in the healthy non-smoking population. Several recent publications have drawn attention to the close association between distribution of ventilation, as measured by N_2 washout test, and disturbance of the mechanics of breathing in small airways, as determined from the frequency dependence of dynamic lung compliance (6, 13, 22). The latter is generally accepted as the only technique currently available for specifically detecting disease in the small, peripheral airways during life (14). These empirical observations confirm the concept developed earlier by Otis et al. (21) that unequal time constants (time constant = compliance x resistance) in parallel lung units cause not only frequency dependence of compliance but also uneven distribution of ventilation. For this reason the non-invasive N_2 washout test is capable of providing

important indirect indications of disturbance in the mechanics of breathing. Our results show that the N_2 washout can indeed distinguish between groups of smokers and non-smokers as well as the CV test (Table V).

Patients

So far the CV test has been advocated primarily as a screening test for incipient airway disease and it has been used in several recent studies to demonstrate a larger CV in smokers as compared to non-smokers (3, 15, 19, 20) and the age dependence of the CV (vide supra). It stands to reason that if this test is particularly sensitive for detecting early pathology in the airways, it could also be useful in the evaluation of more advanced stages of pulmonary disease with respect to progression or regression of the disorder or the effects of therapeutic measures. So far relatively few reports have been forthcoming concerned with the CV phenomenon in various forms of clinically and functionally established cases of cardiopulmonary disease and its relation to other tests of pulmonary function.

The randomly selected group of patients described in Tables III and IV was purposely inhomogeneous with regard to clinical diagnosis as well as the severity of their condition. In only two of the patients could the CV not be identified. One of them (#40) was an 18 year old case of cystic fibrosis with severe mixing impairment showing the largest slope of Phase III recorded in this study (20.4% N_2/liter). The second was a 17 year old patient with asthma (#61) also with a large slope of Phase III and an abnormal N_2 washout. Similar difficulties in differentiating between Phase III and IV on the expirogram were encountered by McCarthy et al. (20), who failed to identify a CV in 15% of a group of heavy smokers. In the remaining 34 patients CC/VC% was significantly higher (M = 47%) than in our normal group including the smokers (M = 20.8%) and only three patients had a CC/TC% below the average of the normals. On the other hand, 21 (62%) of the patients with an identifiable CV had values for CC/TC% that were more than 2 SD (95% limit) beyond the mean for the normal group, indicating a significant degree of abnormality.

The maximal flow rate at 50% and less of vital capacity measured on the maximal flow volume loop is generally considered to be a reliable index of peripheral airway obstruction. As shown in Fig. 2, a fairly good inverse correlation was found between MMEF and CC/TC% in our patients ($r = -.67$, $p < 0.01$). Considering that the MMEF may also reflect some obstruction in medium size and larger airways, the measurements of maximal flow at a lower lung volume, i.e. at 25% VC (5) were also correlated with CC/TC%. The correlation obtained ($r = -0.66$, $p < 0.01$) was statistically significant but not any better than that with MMEF.

As was expected, the correlation between CC/TC% and FEV_1 ($r = -.58$, $p < 0.01$) was not as good as with MMEF, but nevertheless statistically significant. The FEV_1 is not greatly affected by obstruction located primarily in the small peripheral airways unless it is quite severe, because the resistance of that part of the bronchial tree contributes only 20-30% of total pulmonary resistance (17). However FEV_1 is quite sensitive to changes in caliber of the medium size and larger airways that are the site of bronchoconstriction in asthma. The fact that FEV_1 showed a significant correlation with CC/TC% is possibly due to the fact that 32% of our patient population were asthmatics in whom both small and larger airways are usually involved.

Craig et al. (8) have pointed out that the CV may have adverse effects on gas exchange whenever the CC (RV + CV) becomes greater than the end tidal lung volume (FRC). Under these circumstances a certain number of airways must remain closed during part of the respiratory cycle and thus create areas with low ventilation/perfusion ratios. According to Leblanc et al. (15) this occurs even in healthy individuals over 65 years of age in the sitting position and over 44 years lying down. In the supine posture FRC is smaller but CV remains unchanged. None of our normal subjects had a CC greater than FRC, but none of them were over 60 years old. However CC exceeded FRC in 8 of the patients (Table IV). In two cases (#55 & #58) the CC was nearly one liter greater than FRC which was more than their usual tidal volume.

Apart from the CV derived from Phase IV of the single breath N_2 test (Fig. 1), the slope of Phase III can provide useful information about mixing and distribution of ventilation in the lungs similar to the nitrogen

washout test. The slope of Phase III corresponds to the single breath N_2 test of Fowler (10), who measured the change in N_2 concentration between 750-125 ml of expiration. In this study the slope was obtained over the entire Phase III as shown in Fig. 1. Our data on the patients gave a good correlation ($r = .73$, $p < 0.001$) between the N_2 clearance equivalent from the N_2 washout test and the slope of Phase III shown in Fig. 4. Although a good agreement between the two methods is not surprising, the data in Fig. 4 shows a considerable scatter. For instance in three patients (#39, 41 and 42 Table IV) the N_2 Cl. Equiv. was quite high, indicating very uneven ventilation, whereas the slope of Phase III was within the normal range or slightly elevated (Fig. 4). On the other hand there were fewer cases where the slope of Phase III was greater than might be expected from N_2 Cl. Equiv. Whether or not this implies that the latter is a more sensitive measure of uneven ventilation is debatable. One important difference between the two tests should be emphasized. The N_2 washout test reveals uneven ventilation as it prevails during spontaneous resting breathing rather than during a vital capacity maneuver as in the single breath N_2 test, where the distribution of ventilation may be quite different, particularly in patients with severe disease. The results of the N_2 washout test are probably more representative of the actual distribution of ventilation as it effects gas exchange under natural conditions. Nevertheless, the slope of Phase III should not be neglected whenever the CV test is performed. In many cases it can provide as much or more information about a patients condition than the CV itself.

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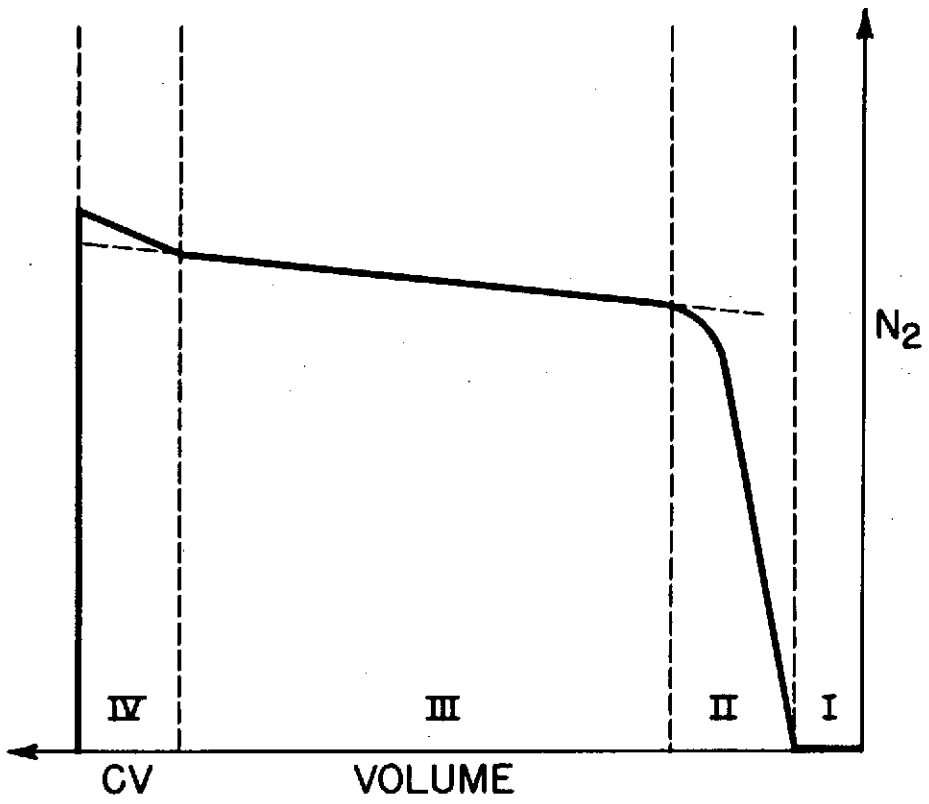

Fig. 1. The closing volume test. N_2 concentration (ordinate) is plotted against volume (abscissa) during complete expiration after a single vital capacity inspiration with 100% O_2. Phases I - IV are explained in the text.

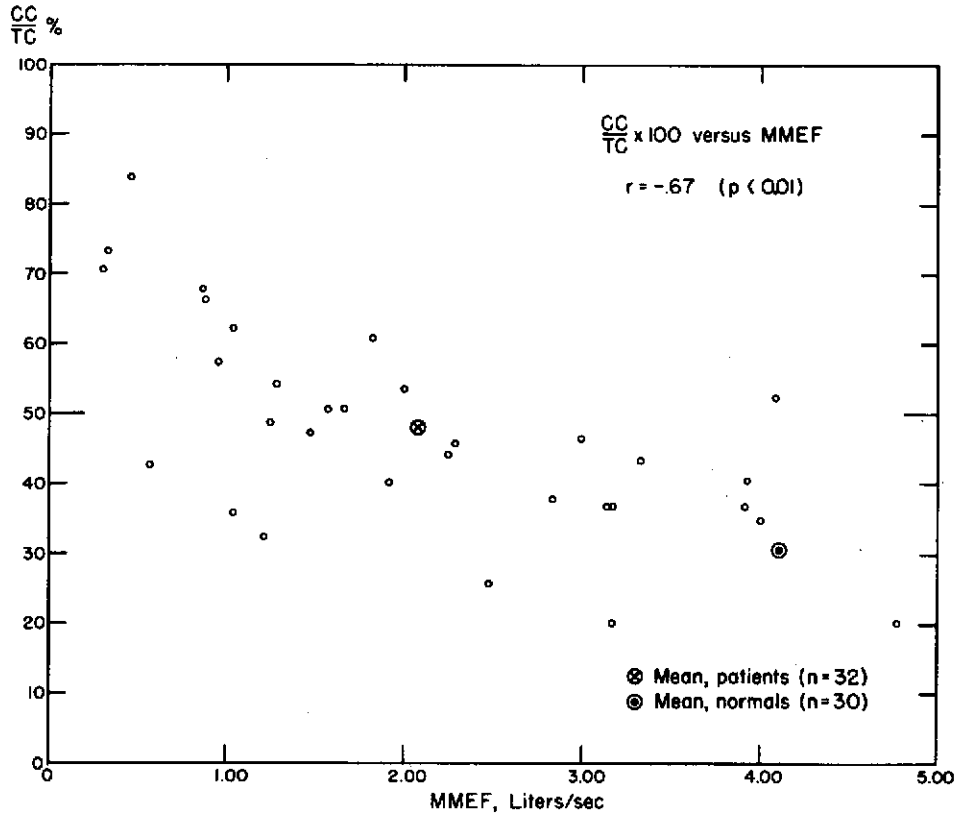

Fig. 2. Closing capacity (CC = RV + CV) in % TC is plotted against MMEF from the maximal flow-volume loop for 32 patients (o) with the mean value (⊗). The mean for 30 normals (⊙) is included.

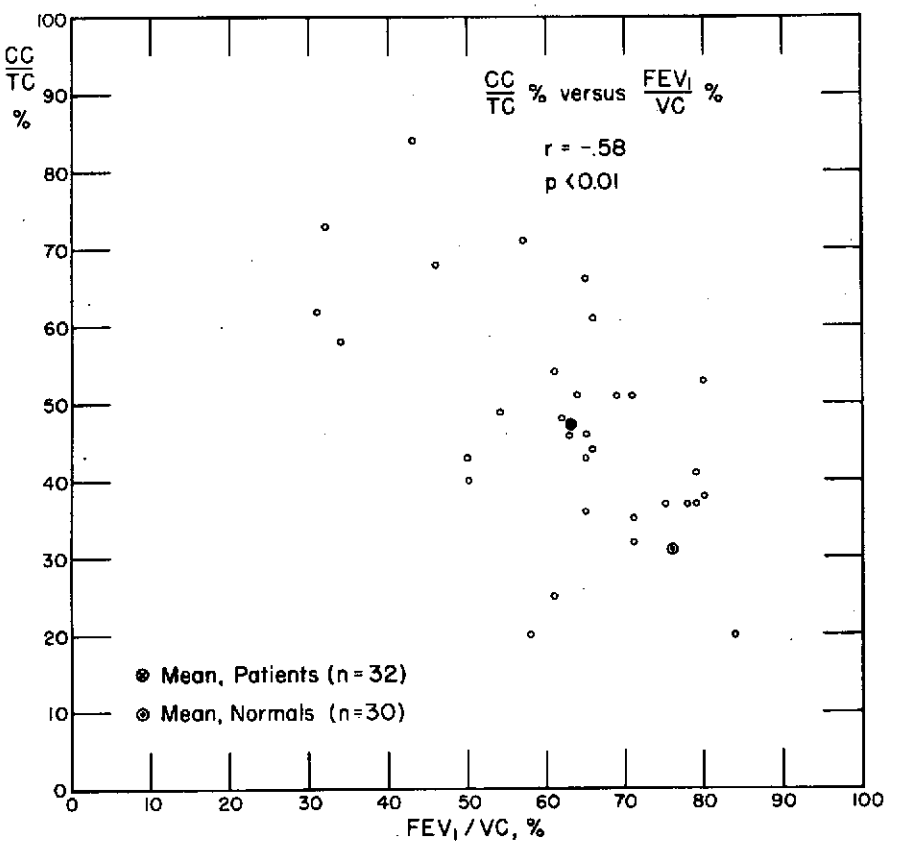

Fig. 3. Closing capacity in % TC is plotted against FEV_1 in % TC for 32 patients (o) with the mean value (⊗). The mean value for 30 normals (⊙) included.

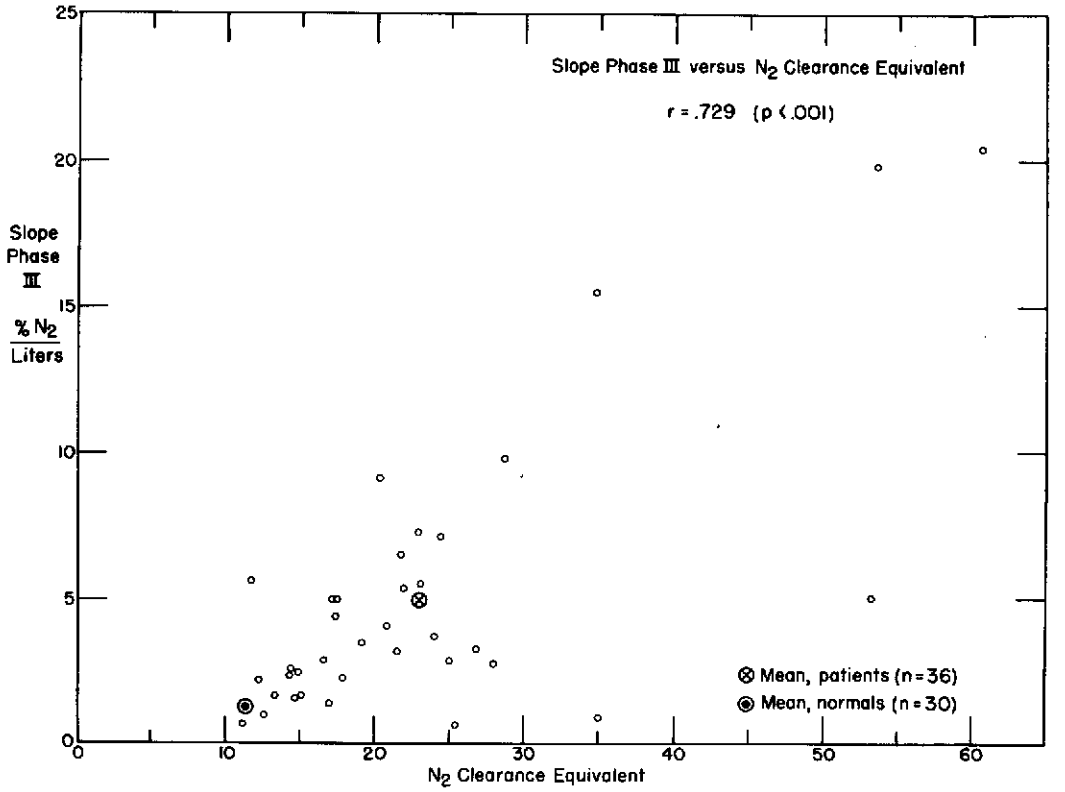

Fig. 4. The slope of Phase III is plotted against the nitrogen clearance equivalent for 36 patients (o) with the mean value (⊗). The mean for 30 normal subjects is also indicated (◉).

TABLE I. Closing Volumes and Capacities: Normals

Male	Age	CV Liters	VC Liters	$\frac{CV}{VC}$%	RV Liters	CC Liters	$\frac{CC}{TC}$%	FRC Liters	$\frac{CC}{FRC}$%	Diagn.	Smoking
1	14	0.20	3.08	6.5%	0.70	0.90	23.8%	1.71	52.6		--
2	15	0.28	4.05	4.6%	1.09	1.37	26.7%	2.36	58.1		--
3	16	--	4.76	--	1.65	--	--	3.93			--
4	19	0.78	5.46	14.4%	2.08	2.86	37.9%	3.87	73.9		+
5	28	0.61	4.49	13.6%	0.82	1.43	26.9%	2.02	70.8		--
6	29	0.56	6.15	9.1%	1.21	1.77	24.0%	3.83	46.2		--
7	32	0.59	5.85	10.1%	0.99	1.58	23.1%	3.23	48.9		--
8	33	0.92	5.89	15.7%	1.35	2.27	31.4%	3.38	67.2		+
9	34	0.58	5.96	9.8%	1.23	1.81	25.2%	2.52	71.8		--
10	34	0.42	5.95	7.0%	1.23	1.65	23.0%	3.21	51.4		+
11	36	0.32	3.40	9.5%	0.81	1.13	26.8%	2.02	55.9		--
12	38	0.48	4.90	10.0%	1.56	2.02	31.6%	3.44	58.7		--
13	38	0.54	5.89	9.1%	1.68	2.22	29.3%	3.12	71.2		--
14	41	0.88	4.94	17.8%	1.46	2.34	36.6%	2.84	82.4		+
15	42	0.11	5.43	2.1%	1.49	1.60	23.1%	2.83	56.5		--
16	43	0.67	4.77	13.8%	1.61	2.28	35.7%	3.24	70.3		--
17	45	0.46	4.90	9.4%	1.07	1.53	25.6%	2.78	55.0		--
18	45	1.10	4.13	26.7%	1.58	2.68	46.9%	3.73	71.8		+
19	46	0.83	4.22	19.6%	1.64	2.47	42.2%	2.98	82.9		--
20	46	0.64	4.95	12.8%	1.23	1.87	30.3%	3.02	61.9		--
21	48	0.51	5.34	9.5%	1.10	1.61	25.0%	3.30	48.8		--
22	55	0.47	5.9	9.0%	1.65	2.12	31.0%	2.83	74.9		--
23	57	0.10	4.16	2.4%	1.28	1.38	25.4%	2.50	55.2		--
24	57	0.52	4.46	11.6%	3.21	3.73	48.6%	4.74	78.7		++

Table I continued

Female	Age	CV Liters	VC Liters	$\frac{CV}{VC}$%	RV Liters	CC Liters	$\frac{CC}{TC}$%	FRC Liters	$\frac{CC}{FRC}$%	Diagn.	Smoking
25	9	0.09	1.96	4.4%	0.40	0.49	20.8%	1.31	37.4		--
26	11	0.12	1.98	6.0%	0.62	0.74	28.5%	1.10	67.3		--
27	13	--	1.80	--	0.53	--	--	1.36	--		--
28	19	--	4.22	--	1.27	--	--	2.85	--		--
29	27	0.24	4.03	6.1%	0.69	0.93	19.7%	2.02	46.0		--
30	27	0.11	3.81	2.8%	1.53	1.64	30.7%	3.13	52.4		--
31	30	--	2.89	--	1.18	--	--	2.08	--		--
32	41	0.65	3.34	19.3%	0.95	1.60	37.2%	2.37	67.5		+
33	42	0.73	3.83	18.8%	1.89	2.62	45.8%	3.54	74.0		++
34	60	0.48	2.90	16.7%	1.26	1.74	41.8%	2.18	79.8		++

CV: Closing Volume
VC: Vital Capacity
RV: Residual Volume
CC: Closing Capacity = CV + RV
TC: Total Capacity
FRC: Functional Residual Capacity
Smoking: + indicates number of packs per day.

TABLE II. Mixing Functions and Airflow Characteristics: Normals

Males	Age	Slope Ph. III %/Liter	N_2 Cl. Equiv.	MMEF L/sec.	FEV_1 Liters	$\frac{FEV_1}{VC}$%	Diagn.	Smoking
1	14	0.9	10.4	3.57	2.07	63%	--	--
2	15	1.2	11.5	6.00	3.71	84%	--	--
3	16	0.8	10.8	3.85	4.45	85%	--	--
4	19	3.0	9.6	5.00	4.10	75%	--	+
5	28	1.4	10.9	4.70	3.85	82%	--	--
6	29	0.5	11.4	2.64	3.78	62%	--	--
7	32	0.6	9.4	6.00	4.63	78%	--	--
8	33	1.0	13.3	4.50	4.05	68%	--	+
9	34	0.6	12.5	6.67	4.80	81%	--	--
10	34	0.5	10.3	4.52	4.45	75%	--	+
11	36	0.8	9.6	5.36	2.79	80%	--	--
12	38	0.8	10.3	3.91	3.38	70%	--	--
13	38	0.6	10.2	2.63	3.46	69%	--	--
14	41	1.3	15.5	4.43	3.98	76%	--	+
15	42	0.3	9.5	4.08	3.91	70%	--	--
16	43	1.8	14.6	2.67	3.19	66%	--	--
17	45	0.6	11.4	5.30	3.95	77%	--	--
18	45	2.1	11.8	3.29	3.48	75%	--	+++
19	46	1.8	13.3	2.43	2.69	58%	--	--
20	46	1.1	10.8	3.78	3.92	78%	--	--
21	48	0.6	11.9	6.83	4.23	79%	--	--
22	55	0.8	11.6	4.00	3.71	74%	--	--
23	57	0.8	11.0	5.25	3.73	83%	--	--
24	57	2.1	16.3	4.29	3.36	70%	--	++

Table II continued

Females	Age	Slope Ph. III %/Liter	N_2 Cl. Equiv.	MMEF L/sec.	FEV_1 Liters	$\frac{FEV_1}{VC}\%$	Diagn.	Smoking
25	9	1.9	10.3	2.17	1.93	83%	--	--
26	11	1.5	9.4	1.92	1.73	80%	--	--
27	13	2.9	10.2	1.92	1.73	74%	--	--
28	19	1.3	10.7	4.29	3.88	92%	--	--
29	27	1.3	10.2	4.00	3.41	84%	--	--
30	27	1.6	9.7	5.13	3.61	92%	--	--
31	30	0.8	11.1	3.28	1.93	73%	--	--
32	41	1.7	11.2	3.58	2.75	78%	--	+
33	42	1.7	14.0	2.83	2.95	70%	--	++
34	60	1.2	14.6	3.48	2.16	70%	--	++

Slope Ph. III: Slope of phase III on N_2 curve in % N_2/Liter of VC
N_2 Cl. Equiv: N_2 Clearance Equivalent, the ventilation with O_2 required to clear one liter of FRC of N_2 by washout
MMEF: Maximal Mid-Expiratory Flow
FEV_1: Forced Expired Volume in 1 sec.

TABLE III. Closing Volumes and Capacities: Patients

Males	Age	CV Liters	VC Liters	$\frac{CV}{VC}$%	RV Liters	CC Liters	$\frac{CC}{TC}$%	FRC Liters	$\frac{CC}{FRC}$%	Diagn.	Smoking
35	9	1.08	1.47	73.1	0.93	2.01	83.8	1.45	139.0	C.F.	--
36	12	0.54	1.93	28.6	0.90	1.44	50.9	2.33	61.8	C.F.	--
37	13	0.22	2.17	10.1	0.87	1.09	35.9	1.46	74.7	Asth.	--
38	14	0.39	2.00	19.5	1.26	1.65	50.6	2.02	81.7	C.F.	--
39	16	0.39	6.25	6.0	1.58	1.97	25.2	3.47	56.8	Asth.	--
40	18	--	2.77	--	3.07	--	--	3.50	--	C.F.	--
41	19	0.63	3.98	15.8	1.62	2.25	40.2	3.24	69.4	B.E.	++
42	20	0.06	3.85	1.6	0.89	0.95	20.0	2.24	42.4	Br.	--
43	22	0.11	4.57	2.4	1.02	1.13	20.2	2.33	48.5	Asth.	++
44	25	0.85	4.86	17.4	1.47	2.32	36.7	3.71	62.5	Asth.	+++
45	39	0.74	4.39	17.0	1.21	1.95	34.8	2.18	89.4	Br.	--
46	41	0.70	3.67	18.9	1.35	2.05	40.8	2.88	71.2	Congest. H.F.	--
47	44	1.91	5.98	31.8	3.52	5.43	57.5	6.08	89.3	B.E.	--
48	46	0.75	4.20	17.8	2.01	2.76	44.4	3.36	82.1	Asth.	+
49	55	0.22	2.38	9.1	1.08	1.32	37.6	2.35	56.2	Fibr.	--
50	56	0.58	4.10	14.1	2.77	3.35	48.8	3.64	92.0	Br.	++
51	57	1.24	3.66	33.8	2.71	3.95	62.0	4.78	82.6	Asb.	+
52	57	0.79	3.88	20.3	1.81	2.60	45.7	3.83	67.9	Asth.	+
53	57	1.01	4.91	20.7	1.98	2.99	43.4	4.27	70.0	Asth.	--
54	58	1.46	5.92	24.8	2.40	3.86	46.4	4.29	90.0	Asth.	+
55	59	1.40	3.89	35.9	3.52	4.92	66.4	4.04	122	B.E.	+++
56	60	0.86	3.58	23.9	2.24	3.10	53.3	3.01	103	Br.	+
57	63	1.02	3.16	32.3	4.87	5.89	73.4	5.60	105	Emp.	+

Table III continued

Males	Age	CV Liters	VC Liters	$\frac{CV}{VC}$ %	RV Liters	CC Liters	$\frac{CC}{TC}$ %	FRC Liters	$\frac{CC}{FRC}$ %	Diagn.	Smoking
58	64	2.32	4.53	51.3	3.02	5.34	70.7	4.37	122.0	Fibr.	(++)
59	68	0.70	3.48	20.4	2.51	3.21	53.6	3.51	91.0	Asth.	--
Females	**Age**	**CV Liters**	**VC Liters**	$\frac{CV}{VC}$ %	**RV Liters**	**CC Liters**	$\frac{CC}{TC}$ %	**FRC Liters**	$\frac{CC}{FRC}$ %	**Diagn.**	**Smoking**
60	12	0.26	2.24	11.8	0.69	0.95	32.4	1.53	62.0	B.E.	--
61	17	--	2.54	--	0.72	--	--	1.54	--	Asth. B.E.	--
62	37	0.59	3.33	18.0	1.44	2.03	36.8	3.18	63.8	H.S.	+
63	40	0.74	2.76	27.0	2.40	3.14	60.8	3.48	90.2	Pneum.	+
64	41	0.09	3.09	3.0	1.65	1.74	36.7	2.87	60.6	B.E.	+
65	53	0.20	2.29	8.8	1.35	1.55	42.6	2.05	75.6	old Tb.	--
66	57	0.48	1.45	32.8	1.85	2.33	70.6	2.21	105.0	Tb. Emp.	+
67	58	1.14	2.82	40.8	2.36	3.50	67.6	3.38	103.5	Asth.	+
68	62	0.41	1.84	22.2	1.14	1.55	51.9	1.73	89.6	Br.	--
69	63	0.57	2.85	20.0	1.95	2.52	52.5	2.48	101.6	Restr.	+
70	64	0.43	2.35	18.5	1.31	1.74	47.5	1.69	102.9	Obstr.	--

Abbreviations for diagnoses:

Asb: Asbestosis
Asth: Asthma
BE: Bronchiectases
Br: Bronchitis
CF: Cystic Fibrosis
Congest. H.F.: Congestive heart failure
Emp: Emphysema
Fibr: Fibrosis
HS: After heart surgery
Obstr: Airway obstruction
Pneum: Pneumonia
Restr: Restrictive defect

Other abbreviations: See foornote Table I

TABLE IV. Mixing Functions and Airflow Characteristics: Patients

Males	Age	Slope Ph. III	N_2 Cl. Equiv.	MMEF	FEV_1	$\frac{FEV_1}{VC}\%$	Diagn.	Smoking
35	9	3.2	26.9	0.46	0.65	43%	C.F.	--
36	12	9.7	28.7	1.57	1.65	71%	C.F.	--
37	13	2.8	25.1	1.04	1.65	65%	Asth.	--
38	14	15.4	34.8	1.67	1.63	64%	C.F.	--
39	16	0.6	25.5	2.48	3.37	61%	Asth.	--
40	18	20.4	60.6	0.42	0.74	33%	C.F.	--
41	19	5.0	53.3	1.92	1.93	50%	B.E.	++
42	20	0.9	35.1	3.17	2.26	58%	Br.	--
43	22	0.6	11.3	4.78	3.85	84%	Asth.	++
44	25	1.6	13.4	3.91	4.13	78%	Asth.	+++
45	39	2.7	28.1	4.00	3.13	71%	Br.	--
46	41	2.1	12.4	3.92	3.24	79%	Congest. H.F.	--
47	44	2.8	16.8	0.96	1.86	34%	B.E.	--
48	46	2.5	14.5	2.25	2.71	66%	Asth.	+
49	55	5.3	22.1	2.83	2.10	80%	Fibr.	--
50	56	2.4	15.0	1.25	2.11	54%	Br.	++
51	57	4.9	17.3	1.04	1.10	31%	Asb.	+
52	57	4.9	17.6	2.29	2.68	63%	Asth.	+
53	57	1.5	14.8	3.33	3.26	65%	Asth.	--
54	58	1.6	15.2	3.00	3.95	65%	Asth.	+
55	59	2.3	14.2	0.88	2.14	65%	B.E.	+++
56	60	4.3	17.5	--	1.76	65%	Br.	+
57	63	7.2	23.0	0.33	0.78	32%	Emp.	+

Table IV continued

Males	Age	Slope Ph. III	N_2 Cl. Equiv.	MMEF	FEV_1	$\frac{FEV_1}{VC}$%	Diagn.	Smoking
58	64	1.3	17.1	--	2.84	66%	Fibr.	(+++)
59	68	3.1	21.6	2.00	1.94	61%	Asth.	--
Females	**Age**	**Slope Ph. III**	**N_2 Cl. Equiv.**	**MMEF**	**FEV_1**	**$\frac{FEV_1}{VC}$%**	**Diagn.**	**Smoking**
60	12	3.4	19.3	1.22	1.66	71%	B.E.	--
61	17	4.0	20.9	3.00	2.32	86%	Asth. B.E.	--
62	37	0.9	12.7	3.13	2.78	79%	H.S.	+
63	40	9.0	20.4	1.82	1.98	66%	Pneum.	+
64	41	3.6	24.1	3.17	2.40	75%	B.E.	+
65	53	7.0	24.5	0.57	1.13	50%	old Tb.	--
66	57	19.8	53.5	0.30	0.70	57%	Tb. Emp.	+
67	58	5.5	11.8	0.85	1.26	46%	Asth.	+
68	62	5.4	23.2	1.29	1.39	69%	Br.	--
69	63	2.2	18.0	4.08	2.14	80%	Restr.	+
70	64	6.4	21.9	1.48	1.53	62%	Obstr.	--

Abbreviations: See Tables II and III.

TABLE V. Analysis of Discriminating Power of Selected P.F. Tests between Smokers and Non-Smokers

	ALL			SMOKERS			NON-SMOKERS			DIFFERENCE: SMOKERS & NON-SMOKERS				
ITEM	M	SD	cv	M	SD	cv	M	SD	cv	M	SED	t	p	
CV (Liters)	0.500	.231	46%	0.720	0.225	31%	0.410	0.234	57%	+0.310	0.09	3.45	<.01	S
CV/VC%	10.9	4.14	38%	16.4	5.5	33%	8.6	3.6	42%	+7.8	1.67	4.67	<.001	HS
CC/TC%	30.8	6.04	20%	38.8	8.2	21%	27.4	5.1	19%	+11.4	2.45	4.65	<.001	HS
CC/FRC%	63.0	10.8	17%	71.9	9.3	13%	59.2	11.4	19%	+12.7	4.33	2.93	<.01	S
Slope Ph. III	1.23	0.63	51%	1.62	0.73	45%	1.09	0.59	54%	+0.53	0.24	2.18	<.05	BS
N_2 Cl. Equiv.	11.5	1.53	13%	13.0	2.35	18%	10.9	1.23	11%	+2.1	0.62	3.39	<.01	S
MMEF (L/sec.)	4.07	1.26	31%	3.99	0.72	18%	4.10	1.45	35%	-0.104	0.51	0.205	>.8	NS
$MEF_{25\%VC}$	1.64	.61	37%	1.40	.24	17%	1.73	.74	43%	-.33	.268	1.22	>.2	NS
$FEV_1/VC\%$	75.7	7.4	10%	73.0	3.5	5%	77	8.8	11%	-4.0	3.24	1.08	<.10	NS
DL_{CO} % pred.	112	27	24%	89	15	17%	120	41	34%	-31	16	1.94	.1>p>.05	NS
Age	34	--	--	41	--	--	32	--	--	9	--	--	--	--

M: Mean
SD: Standard deviation
cv: Coefficient of variation
SED: Standard error of difference
t: Mean difference/SED

p: p-value in Fisher's tables
S: Significant
HS: Highly significant
BS: Barely significant
NS: Not significant

TABLE VI

Individual Reproducibility of CV

	Subject No. 11 (36 y)		Subject No. 22 (55 y)	
#	CV		CV	
1	.193		.590	
2	.229		.721	
3	.273		.737	
4	.278		.432	
5	.097		.283	
6	.235		.493	
7	.270		.518	
8	.164		.617	
9	.113		.530	
10	.253		.493	
11	.121		.556	
12	.207		.594	
13	.243		.551	
14	.218		.423	
15	.159		.615	
16	.200		.435	
17	.174		.431	
18	.206		.532	
19	.238		.657	
20	.104		.597	
21	.152		.340	
	Mean .197	CV/VC: 5.8%	Mean .531	CV/VC: 9.0%
	Range .097-.278		Range .283-.617	
	S.D. .05	1.6%	S.D. .112	1.9%
	c.v. 28%		c.v. 21%	

PART III

TOTAL BODY VOLUME ESTIMATED BY STEREOPHOTOGRAMMETRY AND BY HYDROSTATIC WEIGHING

ABSTRACT

Water displacement or hydrostatic weighing is most commonly used for determining body volume (V_b) to estimate density (mass: volume) and therefrom gross body composition (H_2O method). This is not applicable to operations in space and a stereophotogrammetric method for V_b has been applied to astronauts (stereo method). A comparative study was performed by measuring V_b consecutively with both methods on 10 healthy male subjects. There was a very high correlation between the two methods ($r = .996$, $p < .001$). However the stereo method gave consistently higher results than the H_2O procedure and the difference was statistically highly significant ($p < .005$). It is assumed that the systematic overestimation is due to the inability of the stereo method to discern hidden concavities of the body contour, e.g. at the armpits and the groin. The feasibility of correcting future stereo measurements using a regression of H_2O versus stereo data from this study is considered. Further validation on a large number of subjects is recommended.

TOTAL BODY VOLUME ESTIMATED BY STEREOPHOTOGRAMMETRY AND BY HYDROSTATIC WEIGHING

Precise knowledge of total body volume is essential for estimating gross body composition in terms of fat content and fat-free weight from body density (D).

$$D = \frac{\text{Mass}}{\text{Volume}} \qquad (1)$$

Until recently body volume has been determined either by the helium dilution method (7) or by weighing the subject under water with corrections for gas contained in the lungs and airways, and estimating the volume of water displaced by the body (1). The helium dilution method is accurate, but requires complex equipment and has not been widely used. The hydrostatic procedure is relatively simple and convenient to perform on healthy subjects but is unsuitable for children and seriously ill patients and it is certainly not applicable for operations in space in the absence of gravity. The technique of stereophotogrammetry first applied by Pierson (6) for use in anthropometry has been greatly refined and improved by Herron and his associated (2) in its application to the human body.

The following preliminary report presents a comparison between determinations of total body volume by stereophotogrammetry (stereo) and by the method of under water weighing (H_2O) in their application to the estimation of body density (equation 1) and composition.

Methods and Procedures

Measurements were made consecutively with both methods on ten healthy male volunteers between 8 - 9 in the morning in the fasting state. In two of subjects the stereo and H_2O measurements were made two days apart, but their body weight had not changed more than 100 g. The biostereometric photography of the subjects was performed with a four-camera system with

strobe projector on loan for this study from Dr. R. Herron similar to that employed on the astronauts of the SKY-LAB program (8). The photographer had been trained in the procedure in Dr. Herron's laboratory where the photographs were analyzed and processed.

For the hydrostatic weighing the subject is seated in a light metal chair suspended from a dynamometer balance (Chatillon 31154) of 15 kg capacity in a stainless steel tank filled with water that is maintained at 34°C. The chair is lowered by block and tackle so that the subject is immersed up to his chin. Immediately before putting his head under water the subject is required to take five deep breaths fairly rapidly, followed by a maximal inspiration. Then a mouthpiece is offered to him by an attendant and he exhales approximately 2/3 of his vital capacity, previously marked on the recording drum, into a spirometer. At this point the operator calls "halt", the mouthpiece is withdrawn and the subject submerges his head without further loss or intake of air (nose clip) for 10-15 sec until the reading is taken on the balance. The entire procedure is practiced before entering the tank and the subject is directed not to press his lungs while submerged to minimize the reduction in lung volume. Three consecutive measurements are performed and the corresponding readings of submerged weight and exhaled gas volumes are noted together with the water temperature. The exhaled gas volume is corrected to BTPS conditions and subtracted from the subjects total lung capacity previously measured in the pulmonary function laboratory by a N_2 washout method (4) to obtain the residual volume in the lungs on submerging.

Body volume and density are calculated by the following equations:

$$V_b = \frac{Ma - (Mw + RV \cdot Dw)}{Dw} \qquad (2)$$

$$D_b = \frac{Ma \cdot Dw}{Ma - (Mw + V_R \cdot Dw)} \qquad (3)$$

where V_b: body volume, Ma: weight in air, Mw: weight under water, RV: residual lung volume, Dw: density of water at tank temperature and D_b: body density. The variation between three measurments of V_b taken in this manner is less than 0.20 liters (approximately 0.3% V_b). The average of three measurements was taken for each subject.

In order to insure that the gas volume in the subjects lungs during the stereophotography was as close as possible to the RV during the underwater weighing, the subject took a maximal inspiration and exhaled slowly to the same volume marked on the spirometer before holding his breath for the photograph.

Results

Table 1 shows the results for body density (column 2) and net body volume (column 3) by the H_2O method. Net body volume is the gross volume less the lung gas volume (column 4) and is used to estimate D by equation 3. Since the stereo method gives gross body volume, the lung gas volume (column 4) must be added to the net volume (column 3) by the H_2O method in order to compare the two directly (column 5 and 6).

Without exception the values with the stereo method were higher than with the H_2O procedure. Using a paired comparison, in which the individual differences were analyzed, the mean difference (2.191 liters) was statistically highly significant ($p < .0005$), but the standard error of the mean difference was relatively small (SEM: .273 liters).

The linear regression of the values obtained with the H_2O method (y) and the stereo method (x) is plotted in Fig. 1 with the identity line. The correlation coefficient was quite high:

$$r = .996$$

The regression equation was:

$$y = 1.008x - 2.791$$

$$SDy \text{ at } \bar{x} = 0.914 \text{ liter}$$

The individual points were all close to the regression line (Fig. 1).

Discussion

The high correlation coefficient and the tight fit of the data around the regression line for the two methods implies that both procedures have a high degree of precision. However, the highly significant difference between the mean values raises the question: which of the two methods is more accurate in estimating the true body volume. A strong argument in favor of the H_2O method is that the values obtained for body density give results more compatible with those to be found in the literature from direct determinations on body tissues for animals (5) and man (3).

The mean density (D) for the 10 subjects by the H_2O method was 1.064 (Table 1 column 2) and with the stereo method 1.030. According to the equation proposed by Keys and Brozek (3) for the fat fraction of the body (Ff)

$$Ff = \frac{4.201}{D_b} - 3.813$$

the mean D from the H_2O method gives a fat fraction of 13.5%, which is in good agreement with the mean value of 13.9% reported by the same authors for a larger number of subjects in the same age category. Making the same calculation with the mean D from the stereo method results in a fat fraction of 26.6% indicating considerable obesity. Not one of our subjects was grossly overweight. Therefore it appears justified to assume that the results of the H_2O method are closer to the true value.

In view of the consistency and precision of the stereo method and the fact that the discrepancy with the H_2O method is apparently not due to a random error but to a strictly systematic one, it might be feasible to utilize the regression established from our data to adjust stereo values obtained in future studies to correspond to values that would be found by the H_2O method. With this in mind we have transformed the stereo data from Table 1, column 6 to the adjusted body volume by equation 4. The individual results are shown in Table 1, column 9 and are plotted in Fig. 2. All points are now closely clustered around the identity line and the mean values differ by only 0.016 liters and the average for body density is identical (Table 1, column 2 and 11). Obviously the validity of this type of manipulation of the stereo data will have to be tested on a much larger number of paired measurements on subjects of different body types before it can be accepted with confidence.

The systematic overestimation of body volume by the stereo method can be most readily explained by the inherent inability of the photographic technique to describe certain hidden concavities of the body contour accurately. This applies in particular to the armpits, the groin and the buttocks. However, if it can be shown that this source of error is sufficiently consistent to be amenable to a correction, as proposed here, the stereo method would be acceptable as a rapid, convenient and accurate method for estimating body volume.

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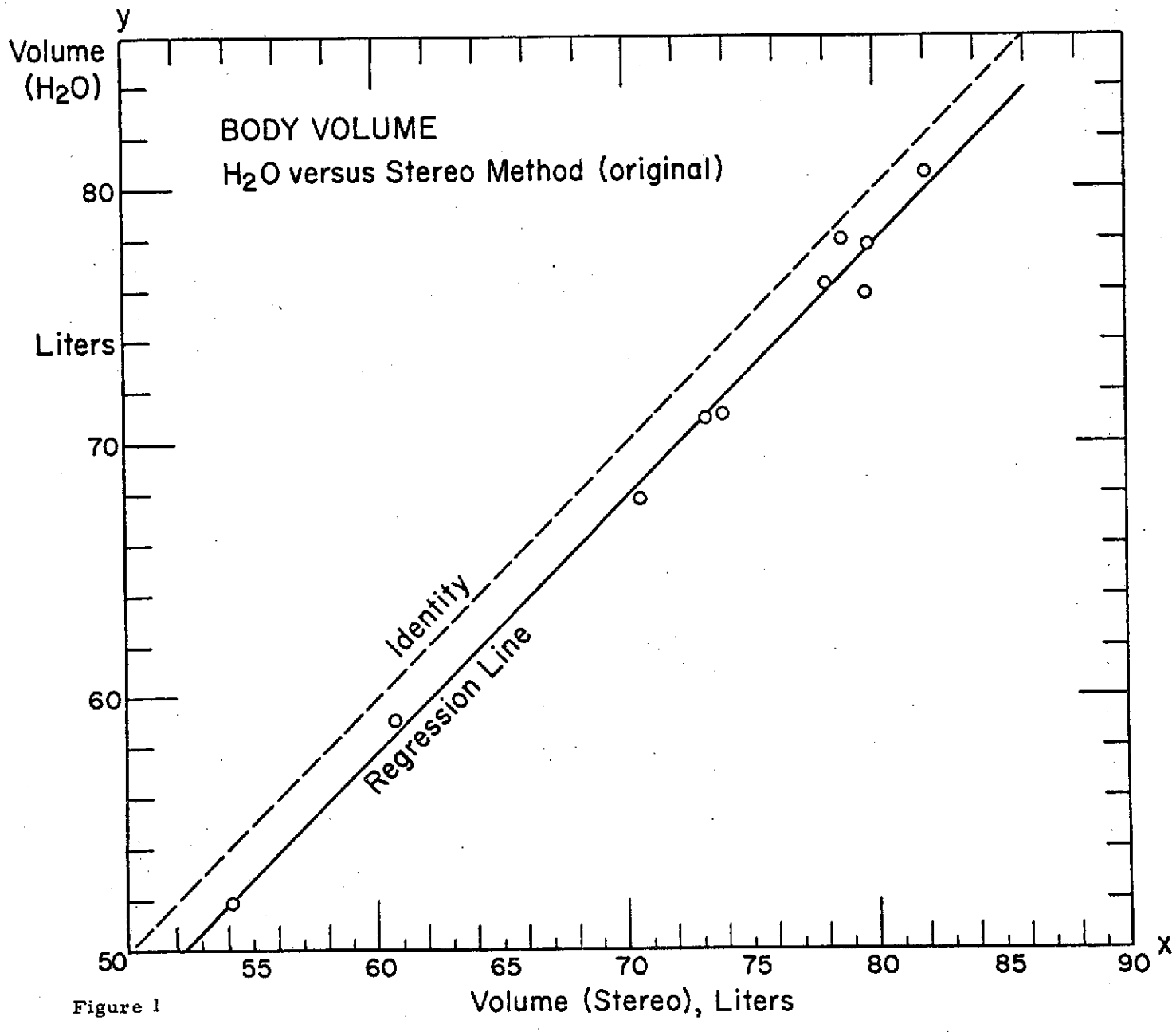
y
Volume
(H_2O)
BODY VOLUME
H_2O versus Stereo Method (original)
80
Liters
70
60
50
Identity
Regression Line
55
60
65
70
75
80
85
90
X
Volume (Stereo), Liters

Figure 1

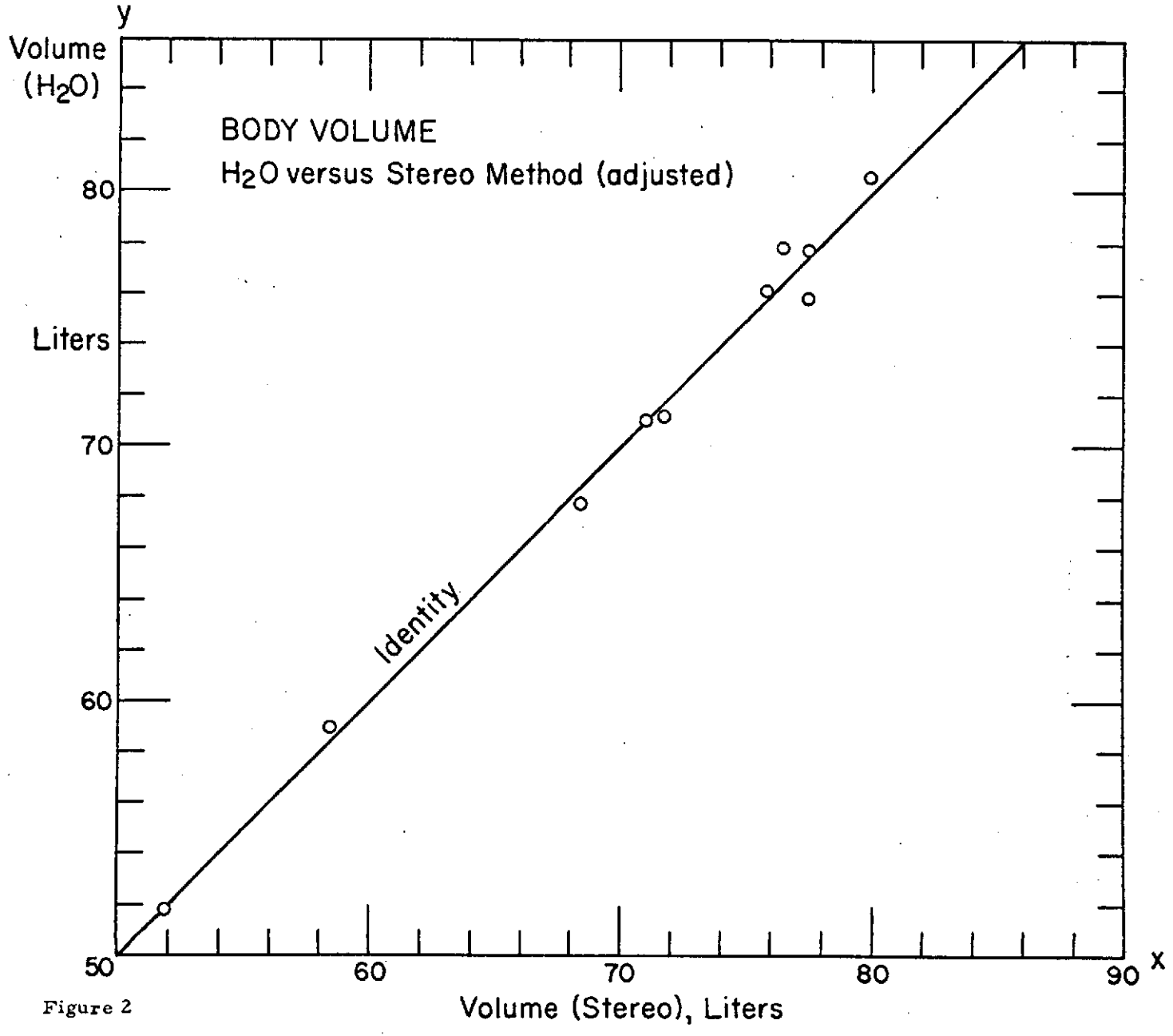
y
Volume
(H_2O)
BODY VOLUME
H_2O versus Stereo Method (adjusted)
80
Liters
70
60
Identity
50
60
70
80
90
x
Volume (Stereo), Liters

Figure 2

Table 1

	Hydrostatic Weighing					Stereophotogrammetry					
						Original			Adjusted		
	1	2	3	4	5	6	7	8	9	10	11
Subj. Nr.	Mass kg.	D	Vol. net	Vol. Lung	Vol. gross	Vol. gross	Vol. net	D	Vol. gross	Vol. net	D
1	60.40	1.087	55.566	3.458	59.024	60.728	57.270	1.055	58.423	54.962	1.099
2	77.35	1.042	74.232	3.716	77.948	78.729	75.013	1.031	76.568	72.854	1.062
3	77.05	1.054	73.102	3.137	76.239	78.073	74.936	1.028	75.907	72.773	1.059
4	71.70	1.069	67.072	4.172	71.199	73.953	69.826	1.027	71.954	67.623	1.060
5	78.65	1.042	75.480	5.233	80.713	82.085	76.852	1.023	79.951	74.717	1.053
6	79.65	1.068	74.579	3.169	77.748	79.776	76.607	1.040	77.623	74.451	1.070
7	71.55	1.034	69.197	1.798	70.995	73.296	71.498	1.001	71.091	69.292	1.033
8	68.40	1.085	63.041	4.721	67.762	70.590	65.869	1.038	68.364	63.639	1.075
9	53.55	1.068	50.140	1.665	51.802	54.221	52.556	1.019	51.864	50.195	1.067
10	78.10	1.090	71.651	4.238	75.889	79.783	75.545	1.034	77.630	73.392	1.064
Mean	71.64	1.064	67.406	3.526	70.932	73.123	69.597	1.030	70.916	67.390	1.064

Net Volume is gross volume less lung volume. $D=\frac{\text{Mass}}{\text{Net Volume}}$

All volumes are in Liters.