CR-134210

DEPARTMENT OF PHYSIOLOGY

LOVELACE FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH

ALBUQUERQUE, NEW MEXICO 87108

(NASA-CR-134210) SPECIALIZED PHYSIOLOGICAL STUDIES IN SUPPORT OF MANNED SPACE FLIGHT Annual Research Report, 3 Jan. - 31 Dec. (Lovelace Foundation for Medical Education and) 46 p HC $5.50 CSCL 06S

N74-18750

G3/04

Unclas

32542

RESEARCH REPORT ON:

SPECIALIZED PHYSIOLOGICAL STUDIES IN SUPPORT OF MANNED SPACE FLIGHT

TO: THE NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

LYNDON B. JOHNSON SPACE CENTER, HOUSTON, TEXAS

CONTRACT: NAS 9-12572

FEBRUARY 1974

46

Annual Research Report

To: NASA L.B. Johnson Space Center
Biomedical Research Office
Houston, Texas 77058

Contract: NAS9-12572 Monitor: E.L. Michel (DB)

Report Period: January 3, 1973 - December 31, 1973

CONTENTS

Prepared by U.C. Luft with contributions by J. Loeppky, L.G. Myhre, and N. Tuttle.

PART I

CIRCULATORY AND RESPIRATORY TRANSIENTS DURING AND AFTER ORTHOSTASIS AND THE EFFECTS OF β-ADRENERGIC BLOCKADE

Orthostatic stress when applied to man by passive head-up tilt or simulated by lower body negative pressure produces marked changes in cardiovascular functions. The most consistent of these are a rise in heart rate and narrowing of the pulse pressure associated with a decline in stroke volume and cardiac output (2). Vasovagal syncope, occasionally seen in healthy active individuals in orthostasis, occurs more frequently after cardiovascular deconditioning by space flight or prolonged bed rest (15) and tests of this nature have been useful in evaluating the condition of astronauts during and after space operations. Most of the effects of orthostasis are apparently mediated via the autonomic nervous system and many of the alterations can be accounted for by increased sympathetic activity in response to cardiovascular reflexes. Sympathetic responses can be manipulated by certain drugs which block the β-adrenergic receptors and thus attenuate the rise in heart rate usually resulting from sympathetic stimulation of the sino-atrial node (7). These agents reduce the chronotropic cardiac effect of the catecholamines released by the nerve endings as well as those released from the adrenal medulla (23). This offers an opportunity to assess the role played by sympathetic activity in the cardiorespiratory response to orthostatic stress by administering a β-adrenergic blocking agent before a tilt-table test and comparing the results with those obtained on the same subjects without premedication.

The majority of previous studies on orthostasis dealing with changes in cardiac output (2, 24, 26) have employed invasive procedures, which in themselves can significantly affect autonomic responses and tolerance to orthostatic stress (21). In this study a non-invasive method, the single-breath procedure described by Kim, Farhi, and Rahn (11), was used to estimate mixed venous P_{CO_2} and cardiac output. This method permitted us to perform serial determinations at short intervals before, during, and after orthostasis and thus to focus attention on the rapid

transients occurring during the first few minutes in the erect posture and after return to recumbency as well as on the relatively steady states attained after stabilization of compensatory changes. The single-breath method has recently been validated against simultaneous measurements by the direct Fick procedure in this laboratory (NAS 9-12572 Rep. 1973) and has been used for the pre- and post-flight evaluation of astronauts in the SKY-LAB program (4).

Methods and Procedures:

Six male volunteers were the subjects. They were all in good health ranging from 29 to 62 years of age; mean age was 39. During the experiments they breathed through a unidirectional valve (Lloyd-Collins) for the collection of expired air in Douglas bags. Gas analyses were performed with a respiratory mass-spectrometer (SRI-MEDSPECT MS8) which was calibrated before and after each run with gas mixtures analyzed by the Scholander method. O_2 and CO_2 concentrations were recorded continuously from a sampling capillary, placed midstream approximately one inch from the subject's mouth in the valve orifice, leading to the mass-spectrometer. The response time of the instrument was 90% of a step change in 90 milliseconds at a sampling rate of 4 ml/sec. The outputs for O_2 and CO_2 from the mass-spectrometer were connected to two different recorders in parallel. A visicorder (Honeywell-1508A) provided a breath-by-breath record on a time base, while the prolonged expirations for the single-breath cardiac outputs were plotted with a Bryans 22000 X-Y recorder on a calibrated O_2 - CO_2 diagram. Heart rates were derived from the ECG using chest electrodes. Blood pressure was taken every minute automatically from a cuff on the left arm (AIResearch-BPMS) and recorded separately (Honeywell-708C). When in the upright position, the subjects placed their left arm on an elevated arm rest at approximately heart level to minimize venous congestion. The tilt table was a modified x-ray table with footboard covered with a foam rubber matress. Changes in posture from supine to 60° or vice versa took 15 sec.

All experiments were performed in the afternoon at least one hour after a light lunch. Each subject performed the test twice on different days without medication (controls) and once two hours after ingesting 40 mg of

propranolol hydrochloride (Inderal). The subjects rested for 10 minutes in the supine posture on the table before the initial measurements. Baseline measurements involving two separate collections of expired air and three single-breath maneuvers (SB) were made during 6 minutes preceding tilt. Immediately after reaching the 60° tilted posture measurements were made in the first three minutes. These were repeated during the 11-13th minute and the 21-23rd minute whereupon the subject was returned to the supine position. Again measurements were made during the first three minutes and repeated during the 11-13th minute. The exact timing of the bag collections and SB recordings can be seen from the protocol in Tables I and II. Where several SB records were taken during the same bag collection period, the same value for O_2 uptake was used for each of them (equation 2). SB records taken between bag collections were related to the mean oxygen consumption calculated from the preceding and the following collection. Oxygen uptake ($\dot{V}_{O_2}$), CO_2 output ($\dot{V}_{CO_2}$) and respiratory exchange ratio (RER) were calculated by the open circuit method, whereby the inspired volume ($\dot{V}_I$) was derived by the Haldane transformation. End-tidal CO_2 concentrations were taken to represent alveolar levels and were converted to $P_{A_{CO_2}}$ to calculate alveolar ventilation ($\dot{V}_A$):

$$\dot{V}_A = \frac{\dot{V}_{CO_2}}{P_{A_{CO_2}}} \; 863 \qquad (1)$$

The cardiac output ($\dot{Q}_{SB}$) was calculated using the equation proposed by Kim et al. (11).

$$\dot{Q}_{SB} = \frac{\dot{V}_{O_2}\,(R - .32)}{4.7(P\bar{v}_{CO_2} - Pa_{CO_2})} \qquad (2)$$

$\dot{V}_{O_2}$ and RER were calculated from the mixed expired air. Pa_{CO_2} and $P\bar{v}_{CO_2}$ were derived from the plot of the SB maneuver on the O_2/CO_2 diagram by the three point "moving spline" method with the help of a computer program. In view of the small systematic difference that was found between the SB method and the direct Fick procedure (NAS 9-12572 Rep. 1973), all $\dot{Q}_{SB}$ values in this study were adjusted by the regression established in the comparative study.

$$\dot{Q} = 1.18 \times \dot{Q}_{SB} + 0.553 \quad (3)$$

The pairs of data for all measurements in the two control tests on each subject were averaged for the comparison with the results after propranolol. A paired comparison was also made between the $\dot{Q}$ values obtained in the two control series. The mean coefficient of variation was 15.5%, which reflects not only the repeatability of the SB method but also day-to-day variations within the subjects.

Results:

Circulation

The effects of the changes in posture on the circulatory system with and without β-adrenergic blockade are summarized with mean values for all subjects in Table I and Figure 1, with the individual data in Tables III - VIII.

At supine rest heart rate was on the average 13 beats lower with propranolol (P) than in the controls (C). During the first three minutes at 60^{o} heart rate increased in both groups and then stabilized for the remainder of the upright period. However, while the controls (C) showed a rise of 15 bpm the P group increased heart rate only half as much. As a result the P group maintained a heart rate 20 beats lower than the controls during orthostasis. On return to the supine posture heart rate fell abruptly in both groups to a level below the pre-tilt baseline returning toward the latter in the following 10 minutes.

Cardiac output did not change much in the C group during the first 3 minutes at 60^{o}, but with P it dropped markedly during the first minute and was significantly lower than in C ($p < .05$) at this point. During the second and third minute however, $\dot{Q}$ temporarily rose again with P approaching the level of the last minute before tilt. By the sixth minute $\dot{Q}$ had dropped further in all tests but more so in group P (23%) than in C (13%). While $\dot{Q}$ continued to fall gradually in group C for the remainder of the upright phase the reverse was observed with P where $\dot{Q}$ increased steadily during the last 10 minutes of orthostasis and surpassed the C group by 0.5 L/min at the end of the period. On return to recumbency $\dot{Q}$ dropped temporarily

during the first minute with P while C increased slightly. By the third minute $\dot{Q}$ overshot the pre-tilt level in both groups and gradually returned to it in the following 10 minutes.

Since HR remained stable in both groups after the third minute upright, the difference in behavior of $\dot{Q}$ between the two groups was entirely due to differences in stroke volume (V_s) during the latter part of orthostasis (Fig. 1). At the end of this phase V_s was 47% larger with P than in C, and this was statistically significant ($p < .05$). On returning to the supine posture V_s increased immediately by a significant amount ($p < .05$) in the C group, but did not start to rise until the second minute in the tests with P. Similarly V_s reached its peak for the C group in the second minute and one minute later with P.

The arterio-venous O_2 difference ($a\text{-}\bar{v}D_{O_2}$) dropped temporarily during the first 3 minutes at 60° more abruptly in the C group than with P, but increased up to 6 minutes in all experiments. During the remainder of the tilt $a\text{-}\bar{v}D_{O_2}$ in the group with P dropped below C, as would be expected from the inverse changes in $\dot{Q}$. In the first minute after tilt back to supine it increased immediately by more than one-third of its value in the preceding minute at 60° in both groups, but returned close to the initial pre-tilt level in the following two minutes.

Pulse pressure (PP) was consistently lower with P than in group C in the first supine period and dropped by about the same amount in both groups during the first minute at 60°. While it levelled off in the C group in the second minute, it continued to fall with P. However, in the third minute PP increased in all six subjects with P, so that the mean was actually higher than in C at this time. By the sixth minute PP was again lower with P and continued at the same level to the end of orthostasis. On return to the supine posture PP did not rise as much with P as in the others so that the difference between the two was about as great as in the pre-tilt supine period.

Respiration

Mean values for ventilation ($\dot{V}_I$), oxygen uptake ($\dot{V}_{O_2}$), respiratory exchange ratio (RER), alveolar CO_2 pressure ($P_{A_{CO_2}}$), and the alveolar

fraction of total ventilation ($\dot{V}_A/\dot{V}_E$) are summarized in Table II for two measurements supine before tilting, at the beginning, middle, and end of orthostatic stress, and two periods after return to the supine position. The data on each individual are to be found at the bottom of Tables III-VIII.

On the average $\dot{V}_{O_2}$ was slightly lower than the controls in all tests with P, regardless of time and posture, with the exception of the last three minutes at 60° (note: one subject was missing at this point). There was a statistically significant drop in $\dot{V}_{O_2}$ in all tests on transition to the upright posture (15% for group P and 10% for C) and a greater rise in $\dot{V}_{O_2}$ on return to supine after orthostasis (15% for P and 34% for C), but this was statistically significant in the controls only ($p < .05$).

Ventilation increased significantly ($p < .05$) on assuming the upright position in spite of the decline in $\dot{V}_{O_2}$. At the same time the RER increased above unity and $P_{A_{CO_2}}$ dropped in both groups. All of these changes were statistically significant. The measurements after 11-13 and 21-23 minutes of orthostasis show that while $\dot{V}_I$ had reverted close to the initial supine level and RER was even lower than initially, $P_{A_{CO_2}}$ remained considerably below the preceding supine values. Alveolar ventilation assumed a slightly higher fraction of total ventilation ($\dot{V}_A/\dot{V}_E$) at times where the latter increased, but the change was significant only in group C on return to the supine posture. At the same time $P_{A_{CO_2}}$ increased again close to the initial supine values.

Discussion:

Control Series

The alterations in cardiovascular function in response to changes in posture observed in the control series of this study are generally in agreement with those reported in numerous previous investigations. It is generally accepted (6, 13) that the drastic increase in hydrostatic pressure in the blood vessels of the dependent part of the body on changing from the supine to the upright posture leads to passive vasodilatation in those areas with a corresponding shift of blood volume out of the thorax, thus jeopardizing central blood volume. At the same time the drop in hydrostatic pressure in the cephalad vessels reduces the baroreceptor drive in the

carotid sinus thus triggering adrenergic sympathetic activity which in turn stimulates cardiac function and peripheral vascular resistance.

The procedure employed here permitted us to follow these dynamic responses on a minute-by-minute basis. Thus the marked fall in pulse pressure on tilt to 60° was observed simultaneously with a rise in heart rate in the first minute. At that time no change in cardiac output nor stroke volume was seen in the control series. This would suggest that the tachycardia is initiated by direct action of the change in hydrostatic pressure on the baroreceptors rather than curtailment of blood flow at this time. Nevertheless, heart rate continued to increase during the second and third minutes at which time $\dot{Q}$ and V_S started to fall. It is also noteworthy that HR stayed remarkably constant throughout the following 20 min at 60° while V_S and $\dot{Q}$ dropped considerably during this period in the controls. The latter may reflect a continuing loss of central blood volume not only due to intravascular pooling in the lower extremities (19) but also to loss of plasma fluid by extravasation (25). In contrast to our findings of a gradual decline in $\dot{Q}$ throughout orthostasis in the controls, Segel et al. (18) using N_2O and a body-plethysmograph reported no further changes in $\dot{Q}$ over 20 minutes of 90° tilt after a drastic fall in pulmonary blood flow during the first few minutes (2 subjects).

The constancy of HR during the latter part of orthostasis was unexpected in view of Sjöstrand's observation that pulse frequency varies inversely with thoracic blood volume and the diastolic volume of the heart (19). However, this relationship certainly does apply to the changes observed on return from the erect to the supine posture where HR dropped immediately to values below the initial supine period. This coincided with a rise in stroke volume and pulse pressure reflecting a surge of blood into the thorax. According to Bainbridge (1) distention of the great veins and right auricle by increased filling pressure usually elicits cardiac acceleration. Recent investigations on conscious (10) as well as anesthetized (12) dogs using artificial volume loading indicate that this is due either to inhibition of the parasympathetic system or direct stimulation of atrial mechanoreceptors; none of these experiments were associated with changes in posture. In the present study, as in many others, the increase in central blood volume on returning to recumbency was invariably followed

immediately by marked slowing of the heart rate with a significant increase in stroke volume and pulse pressure. One must assume that on tilting from the upright to the supine posture the sudden rise in hydrostatic pressure generates a strong depressor reflex from the carotid sinus which overrules the accelerating drive usually caused by an influx of blood to the chest. In spite of the sharp drop in heart rate, cardiac output increased substantially for a brief period after return to supine because of the even greater increase in stroke volume.

The sudden increase in $a\text{-}\bar{v}D_{O2}$ in the first minute of recovery from orthostasis also points to the fact that the major part of the pooled blood with low oxygen content is returned to the central circulation at this time. $\dot{Q}$, V_s, and HR all returned to their initial supine levels well within 10 minutes recovery. This is in contrast with the results of Tuckman and Shillingford (24), who reported that $\dot{Q}$ (dye-dilution method) did not return to baseline within 25 min of recovery from a similar tilt.

The significant increase in $\dot{V}_I$ during the first three minutes after tilting apparently represents true hyperventilation, since it occurs while $\dot{V}_{O2}$ is reduced and RER is greater than 1.0. This phenomenon usually subsided after a few minutes with exception of those instances where syncope was imminent (e.g., Table V). The origin of this orthostatic hyperventilation that has been reported by many others is uncertain, but it is conceivable that it is initiated by afferent impulses from the arterial baroreceptors (9). Another possible cause is the reduction in cerebral blood flow associated with an increase in P_{CO2} in the brain (16) stimulating the central chemoreceptors. In view of the immediate increase in $\dot{V}_I$ on tilting, the reflex mechanism might appear more plausible than the humoral one. On the other hand, the fact that $P_{A_{CO2}}$ was maintained at a lower level throughout orthostasis might well be explained by the greater arterio-venous P_{CO2} difference in the brain due to reduced cerebral blood flow (6) which calls for a lower arterial P_{CO2} to maintain the same CO_2 level at the central chemoreceptors. $\dot{V}_I$ was actually about the same as in the pre-tilt controls in the latter part of orthostasis in keeping with the lower CO_2 output. The drop in $P_{A_{CO2}}$ of 4-5 mm Hg seen in our subjects is of the same order as reported by others (3, 16). Bjurstedt et al. (3) measured

both alveolar and arterial P_{CO_2} and found that the difference between the two increases on transition from supine to erect posture, so that the reduction in P_{CO_2} is only half as great in the arterial blood as in the alveolar gas. This is attributable to changes in the distribution of ventilation and blood flow in the lungs.

In the first three minutes after return to the supine position $\dot{V}_I$ again increased above the pre-tilt supine values. This time it was concomitant with a significant rise in $\dot{V}_{O_2}$ in the control group and RER did not increase, thus denoting true hyperpnea, not hyperventilation.

It stands to reason that neither the drop in $\dot{V}_{O_2}$ at the beginning of orthostasis nor its rise immediately after return to recumbency reflect actual alterations in metabolic rate but rather the depletion and repletion of O_2 stores in the body, which are associated with a non-metabolic decrease or increase in $\dot{V}_{O_2}$, respectively. The reduction of $\dot{V}_{O_2}$ during the first three minutes in the upright position with a slightly reduced $a\text{-}\bar{v}D_{O_2}$ and little change in $\dot{Q}$ can be explained by a redistribution of cardiac output with a smaller contribution from the vasculature of the lower extremities where blood flow is sluggish and O_2 extraction is greater, and a larger contribution from the remainder of the body. At this point part of the metabolic O_2 requirements is being taken from the O_2 stores of the blood and does not show up in the measured $\dot{V}_{O_2}$. On the other hand, the increase in $\dot{V}_I$ at this time would tend to increase O_2 stores in the lungs and the arterial blood, but this effect is very small. Incidentally, the increase in FRC coincident with tilting to 60° would also add to the oxygen store in the lungs. But this took place before the measurement of $\dot{V}_{O_2}$ was started.

The tilt back to supine was followed by a marked increase in $\dot{V}_{O_2}$ for the first few minutes, this time signifying the replenishment of O_2 stores as pooled blood with low O_2 content was returned to the central volume. The latter is clearly evident from the transient peak in the $a\text{-}\bar{v}D_{O_2}$ while $\dot{Q}$ is rising rapidly. Direct measurements of O_2 content in blood from the femoral artery and vein by Reeves et al. (17) revealed that the difference between the two was 12.3 vol% in the upright (70°) as compared to 4.1 vol% in the supine position at rest. Rahn and Ament (16) have made similar observations on $\dot{V}_{O_2}$ during orthostasis and recovery. They claim

that the increase in $\dot{V}_{O_2}$ on return to recumbency was greater in their experiments than could be accounted for by blood pooling alone and suggest that a true O_2 debt may be incurred during orthostasis. Taking into account not only the reduced cardiac output, as Rahn and Ament (16) did, but also the much lower O_2 content of pooled blood during orthostasis (17), we believe that the excess O_2 uptake observed after return to supine posture can be adequately explained as replenishment of O_2 stores without invoking a metabolic oxygen debt. The only evidence we could find that might speak in favor of a lactacid rather than an alactacid O_2 debt is an insignificant decrease in standard bicarbonate (mean -0.6 mM/L) after 8-10 min of orthostasis reported by Bjurstedt et al. (3).

Effects of Propranolol

Some of the cardiovascular responses to changes in posture were notably altered by propranolol. While the heart rate (HR) was significantly reduced with P during the first supine period attesting to an attenuation of β-adrenergic activity, both experimental and control groups responded to the upright tilt with an increase in heart rate reaching a plateau after three minutes. However, with P the increment was not nearly as great. If the response in HR were mediated entirely by the β-adrenergic receptors, no change would be expected after tilting. The fact that a limited response was forthcoming suggests that a reduction in parasympathetic tone as well as sympathetic activation participates in the tachycardia of orthostasis. Using unanesthetized dogs to observe ventricular function with selective autonomic denervation, Stone et al. (22) found that β-blocked animals could increase their HR by reducing parasympathetic activity. Indeed Pickering et al. (14), who studied reflex bradycardia in relation to blood pressure, came to the conclusion that reflex changes in HR following alterations in blood pressure are predominantly parasympathetic.

The hemodynamic adjustments to the upright position were apparently not as smooth in the P group as in the controls (Fig. 1), possibly due to the limited HR. $\dot{Q}$ and V_s dropped immediately and $\dot{Q}$ was significantly ($p < .01$) lower than in the controls in the first minute. During the next two minutes, however, there was a transitory recovery of $\dot{Q}$ and V_s with a coincident rebound in PP. This initial instability in the group with

β-blockade was overcome by the 6th minute upright and from then on to the end of the period striking differences emerged between the two groups. While $\dot{Q}$ and V_s gradually declined after the third minute upright in group C, there was a marked increase in these functions in the P group, so that at 16 and 21 minutes V_s was significantly larger than in the controls and $\dot{Q}$ had returned to the level observed supine before the tilt. No remarkable changes in HR and PP occurred in either group during this time. Such an improvement in cardiac function can be explained only by an increase in venous return in spite of continuing orthostatic stress. To what extent venoconstriction may have contributed to this remains speculative. There is remarkably little evidence for active constriction of capacity vessels in orthostasis to be found in the literature (6), but to our knowledge venous reactivity to gravity has not been investigated after β-adrenergic blockade. In any event this observation attests to the greater importance of an adequate venous reservoir than the rise in heart rate during extended orthostasis. A corollary to this can be found in the work of Weissler et al. (26), who demonstrated in man that sudden tachycardia produced by atropine fails to elicit an increase in $\dot{Q}$ in the upright posture, while it invariably does so in supine position where the venous reservoir is not limited.

After return to the supine posture from 60° the group with P responded as promptly as the controls with bradycardia and an increase in PP. However, while $\dot{Q}$ and V_s increased during the first minute in the controls, there was a slight drop in $\dot{Q}$ and no change in V_s with P until the second minute and the increase was not as great. Whether the lag in cardiac function was due to the disturbance of autonomic control by the β-blockade or the reflux of blood previously pooled in the lower extremities was not as great as in the controls is open to conjecture. One observation in favor of the latter was a much smaller excess in $\dot{V}_{O_2}$ in the first three minutes after tilt-down with P. Using the figures in the last line of Table II as true metabolic rate the P group took up 210 ml more O_2 in the first three minutes to replenish O_2 stores while the controls required 297 ml for the same period. This can be taken as indirect evidence that less blood was sequestered in the periphery during the latter part of the tilt in the group with β-adrenergic blockade than in the controls.

Finally, attention is drawn to an observation not directly related to the topic of this study. With few exceptions $\dot{V}_{O_2}$ was consistently lower regardless of posture after ingestion of propranolol (average 6%) and the RER was regularly higher. This has been reported by others (20) who have invoked a general metabolic effect of propranolol, besides reducing myocardial metabolism, with greater utilization of carbohydrates.

Orthostatic Tolerance

Three of the six subjects experienced some nausea, dizziness, and anxiety once or twice during the latter part of orthostasis. In only one of them had the protocol to be abbreviated by returning him to the supine position, once in a control test after 18 min at 60° and the second time with propranolol at 16 min. The second subject also felt dizzy at the end of one control run and with propranolol. The third one was adversely affected only with propranolol. The number of incidents is too small to draw any conclusions as to whether or not β-adrenergic blockade reduces orthostatic tolerance. But it is not unreasonable to speculate that the incidence of vasovagal symptoms would have been higher if the relative bradycardia induced by the drug had not been more than compensated for by a significant increase in stroke volume after 10 minutes of orthostasis, thus maintaining an adequate circulation.

APPENDIX - PART I

Critique of Procedures:

A critical appraisal of the single-breath method (11) was presented in a previous report from this laboratory (NAS 9-12572 Rep. 1973) with suggested adjustments to approximate values obtained by the direct Fick procedure. The following discussion deals with the question: What kind of information can be obtained from a procedure based on the Fick principle under the experimental conditions described in the preceding paper? Any estimate of pulmonary blood flow ($\dot{Q}$) using the Fick equation based on samples not taken under rigorous steady state conditions cannot be accepted without certain reservations. One of the premises of the concept is that O_2 uptake as measured from the respired air at the mouth is exactly equal to that taking place on the average in the tissues. This implies that O_2 stores in the lungs, in the blood, and in the tissue (myoglobin) are not in a transient state, but at an equilibrium. On a theoretical basis Hamilton (8) postulated that in order to insure optimal conditions a given steady state must be maintained for 10-15 minutes before measurements are taken. On the other hand, direct measurements on mixed venous blood performed sequentially during the first 5 minutes of heavy exercise reported by Donald et al. (5) have shown the O_2 content drops rapidly but stabilizes already after 1-1/2 min. In the light of these findings it would appear that the measurements made at supine rest before tilting to 60°, all those obtained after 6 minutes in orthostasis, and the final measurements at 6 and 11 minutes after return to the supine posture would meet the requirements of a steady state, whereas the values derived from measurements during the three minutes immediately following changes in posture do not because rapid alterations in hemodynamics are taking place. The following remarks will deal with these two phases only.

The circulatory data in Table I and Figure 1 for the three minutes after tilt up and tilt down are based on an SB maneuver at the beginning of each minute for $a\text{-}\bar{v}D_{O_2}$, while expired air was being collected continuously and the average $\dot{V}_{O_2}$ over the three minutes was used with

a-$\bar{v}D_{O_2}$ from each SB to estimate $\dot{Q}$ and V_s for each minute. While the values for a-$\bar{v}D_{O_2}$ are probably valid for the time at which each SB maneuver was performed, the data for $\dot{Q}$ and V_s must be distorted because $\dot{V}_{O_2}$ was not constant but was changing due to shifts in blood O_2 stores during these periods (16).

In order to differentiate the transients in $\dot{V}_{O_2}$ immediately after change in posture an additional series of experiments was performed where expired air was measured and analyzed for three consecutive one-minute periods before and after tilt up and tilt down using a Tissot (120 liter) instead of averaging three minutes in a Douglas bag as in the first series. The protocol was exactly the same as previously, only that orthostasis was maintained for 10 minutes only instead of 23 minutes. No single-breath maneuvers were performed in this series to avoid any disturbance of spontaneous respiration and O_2 stores in the lungs. Four subjects who had also participated in the main experimental series were available for the additional tests.

Results and Comments:

The results of the additional tests are given in Table IX for each subject with the mean values below. Looking at $\dot{V}_{O_2}$ each minute after tilting up there is a 21% drop in the first minute continuing through the second minute with a slight rise in the third. Assuming that metabolic rate continued at the same level as prior to tilt, a total of 159 ml, less O_2 was taken up during the first three minutes at 60° and was presumably procured from O_2 stores in the body (16). During the first minute after return to the supine posture $\dot{V}_{O_2}$ nearly doubled, falling again during the second and approaching the pre-tilt baseline in the third minute. The additive excess O_2 uptake during these three minutes was 198 ml and this represents O_2 restorage. The fact that the excess $\dot{V}_{O_2}$ after tilt down was greater than the O_2 deficit measured in the three minutes after tilt up can be explained by a small additional deficit that was not measured during the remaining 7 minutes at 60°. This is compatible with the gradual decline in cardiac output observed after the third minute in the control group of the main series (Fig. 1, Table I).

The shifts in O_2 stores with posture were associated with coincident, inverse changes in CO_2 stores. On return to supine position CO_2 output (Table IX, below) was considerably greater than supine before tilt. However, the excess $\dot{V}_{CO_2}$ in the first minute supine (69 ml) was much less than the coincident excess $\dot{V}_{O_2}$ (154 ml). The expected storage of CO_2 during orthostasis must have been partly offset by the observed hyperventilation.

In Table X the A columns show mean values for $\dot{V}_{O_2}$, $a\text{-}\bar{v}D_{O_2}$, and $\dot{Q}$ obtained in the previous study on the four subjects who participated in the additional tests for comparison with B, the values measured in the latter. The difference is that in A $\dot{V}_{O_2}$ was measured cumulatively over three minutes after tilt up and tilt down, whereas in B it was measured for each minute separately. The average values for the same three minutes ($\overline{B}$) were within 10% of those in A so that one can assume that the response of the subjects was practically identical on both occasions. Therefore it appeared justified to estimate $\dot{Q}$ for Series B using the values for $a\text{-}\bar{v}D_{O_2}$ obtained in Series A for each of the three minutes erect and supine. At 60° the adjustment of $\dot{Q}$ in B does not make much difference, as $\dot{Q}_A$ is within 10% of $\dot{Q}_B$ and the conclusion based on the former may be valid. However, on tilting back to supine $\dot{Q}_A$ was evidently underestimated during the first minute, because $\dot{V}_{O_2}$ was actually much higher at that time than the three minute average ($\dot{V}_{O_2}$ $\overline{B}$) used to calculate it. In the third minute, on the other hand, $\dot{Q}_A$ was overestimated as $\dot{V}_{O_2}$ had dropped considerably by this time. These results strongly suggest that the peaks in $\dot{Q}$ and V_s on return to supine as shown in Fig. 1 and Table I in the second minute were actually attained already in the first minute.

REFERENCES

1. Bainbridge, F.A. The influence of venous filling upon the rate of the heart. J. Physiol. (London) 50:65, 1915.

2. Bevegård, S., A. Holmgren, and B. Jonsson. The effect of body position on the circulation at rest and during exercise, with special reference to the influence on the stroke volume. Acta Physiol. Scand. 49:279-298, 1960.

3. Bjürstedt, H.v., C.M. Hesser, G. Liljestrand, and G. Matell. Effects of posture on alveolar-arterial CO_2 and O_2 differences and on alveolar deadspace in man. Acta Physiol. Scand. 54:65-82, 1962.

4. Buderer, M.C., J.A. Rummel, C.F. Sawin, and D.G. Mauldin. Use of the single-breath method of estimating cardiac output during exercise-stress testing. Aerospace Med. 44(7):756-760, 1973.

5. Donald, K.W., J.M. Bishop, G. Cumming, and O.L. Wade. The effect of exercise on cardiac output and circulatory dynamics of normal subjects. Clin. Sci. 14:37-73, 1955.

6. Gauer, O.H. and H.L. Thron. Postural changes in the circulation, pp. 2409-2439. In: W.F. Hamilton (ed.) The Handbook of Physiology, Vol. III Circulation. American Physiological Society, Washington, D.C. 1965.

7. Grollman, A. and E.F. Grollman. Pharmacology and Therapeutics (7th ed.). Lea and Febiger, Philadelphia, pp. 311-313, 1970.

8. Hamilton, W.F. Measurement of the cardiac output, Chapter 17. In: W.F. Hamilton (ed.) The Handbook of Physiology, Vol. I Circulation. American Physiological Society, Washington, D.C. 1962.

9. Heymans, C. and E. Neil. Reflexogenic Areas of the Cardiovascular System. London, Churchill, 1956.

10. Horwitz, L.D. and V.S. Bishop. Effect of acute volume loading on heart rate in the conscious dog. Circ. Res. 30:316-321, 1972.

11. Kim, T.S., H. Rahn, and L.E. Farhi. Estimation of true venous and arterial P_{CO_2} by gas analysis of a single breath. J. Appl. Physiol. 21(4):1338-1344, 1966.

12. Linden, R.J. Function of nerves of the heart. Cardiovascular Research 6:605-626, 1972.

13. McCally, M. (ed.) Hypodynamics and Hypogravics. Academic Press, New York, 1968.

14. Pickering, T.G., B. Gribbin, E. Strange Petersen, D.J.C. Cunningham, and P. Sleight. Effects of autonomic blockade on the baroreflex in man at rest and during exercise. Circ. Research 30:177-185, 1972.

15. Piemme, T.E. The clinical spectrum of postural hypotension, pp. 181-186. In: M. McCally (ed.) Hypodynamics and Hypogravics. Academic Press, New York, 1968.

16. Rahn, H. and R. Ament. The effects of posture upon the gas exchange and alveolar gas composition. WADC-TR-55-357. Wright Air Development Center, Dayton Ohio, 1955.

17. Reeves, J.T., R. F. Grover, S. Gilbert Blount, Jr., and G.F. Filley. Cardiac output response to standing and treadmill walking. J. Appl. Physiol. 16(2):283-288, 1961.

18. Segel, N., R. Dougherty, and M.A. Sackner. Effects of tilting on pulmonary capillary blood flow in man. J. Appl. Physiol. 35: 244-249, 1973.

19. Sjöstrand, T. Volume and distribution of blood and their significance in regulating the circulation. Physiol. Rev. 33:202-228, 1953.

20. Sowton, E. and J. Hamer. Hemodynamic changes after beta adrenergic blockade. Am. J. Cardiology 18:317-320, 1966.

21. Stevens, P.M. Cardiovascular dynamics during orthostasis and the influence of intravascular instrumentation. Amer. J. Cardiol. 17: 211-218, 1966.

22. Stone, H.L., V.S. Bishop, and E.Dong, Jr. Ventricular function in cardiac-denervated and cardiac-sympathectomized conscious dogs. Circ. Research 20:587-593, 1967.

23. Taylor, S.H. and P.A. Majid. Comparison of tests of adrenergic beta-receptor blockade in man and their application to a comparison of the beta-blocking potency of propranolol and oxyprenolol. Postgraduate Med. J. Nov. Suppl.:57-60, 1970.

24. Tuckman, J. and J. Shillingford. Effect of different degrees of tilt on cardiac output, heart rate, and blood pressure in normal man. Brit. Heart J. 28:32-39, 1966.

25. Waterfield, R.L. The effects of posture on circulating blood volume. J. Physiol. (London) 72:110-120, 1931.

26. Weissler, A.M., J.J. Leonard, and J.V. Warren. Effects of posture and atropine on the cardiac output. J. Clin. Invest. 36: 1656-1662, 1957.

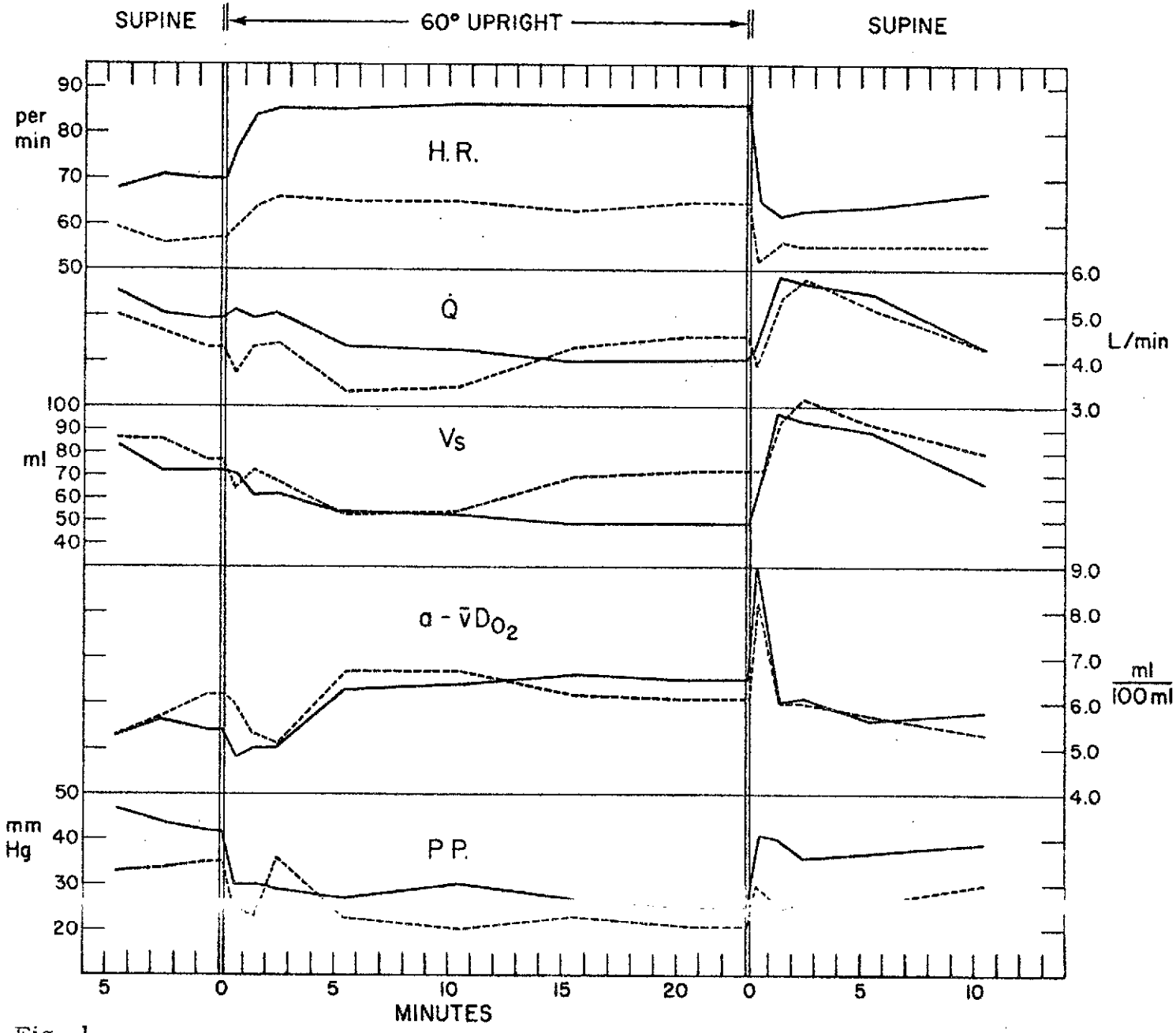
SUPINE
60° UPRIGHT
SUPINE
per min
H.R.
Q̇
L/min
ml
Vs
a - v̄D$_{O_2}$
ml / 100 ml
mm Hg
P P.
MINUTES

Fig. 1

Table I. Summary of Circulatory Data

Posture	Min.	HR b/m C	HR b/m P	$\dot{Q}$ liters/min C	$\dot{Q}$ liters/min P	V_s ml C	V_s ml P	a-$\bar{v}D_{O_2}$ ml/100 ml C	a-$\bar{v}D_{O_2}$ ml/100 ml P	PP mm Hg C	PP mm Hg P
	1	68 *	59	5.51	5.05	83	87	5.3	5.3	47	33
1. Supine	3	71 *	56	5.03	4.69	72	86	5.6	5.7	44	34
	5	70 *	57	4.94	4.30	72	75	5.4	6.2	42 *	35
										*	
	1	76 *	60	5.11 *	3.71	70	64	4.8 *	6.0	30	25
	2	84 *	64	4.91	4.31	61	72	5.0	5.3	30	23
60°	3	85 *	66	5.03	4.38	62	67	5.0	5.1	29	36
Upright	6	85 *	65	4.31	3.36	54	53	6.3	6.7	27	23
	11	86 *	65	4.20	3.45	52	54	6.4	6.7	30	20
	16	86 *	63	4.06	4.25	49 *	69	6.6	6.2	27	23
	21	86 *	65	4.06	4.55	49 *	72	6.5	6.1	25	21
		*	*			*			*	*	
	1	65 *	52	4.31	3.84	67	72	9.0	8.2	41 *	29
	2	62 *	56	5.89	5.39	97	94	6.0	6.1	40 *	25
2. Supine	3	63 *	55	5.72	5.76	94	103	6.1	6.0	36	26
	6	64 *	55	5.49	5.12	89	92	5.6	5.7	37 *	26
	11	67	55	4.29	4.31	66 *	79	5.8	5.3	39 *	30

Columns: C = Controls, P = Propranolol. Propranolol: n = 6 except 21 min. upright and $\dot{Q}$, V_s, and a-$\bar{v}D_{O_2}$ during first min. supine after tilt where n = 5.

Statistically significant differences on changes in posture or between C and P are indicated as * $p < 0.05$ or * $p < 0.01$.

Table II. Summary of Respiratory Data

Posture	Min	$\dot{V}_I$ L/min C	$\dot{V}_I$ L/min P	$\dot{V}_{O_2}$ L/min C	$\dot{V}_{O_2}$ L/min P	RER C	RER P	$P_{A_{CO_2}}$ mm Hg C	$P_{A_{CO_2}}$ mm Hg P	$\dot{V}_A / \dot{V}_E$ C	$\dot{V}_A / \dot{V}_E$ P
1. Supine	1 - 2	8.81	8.48	.280	.257	.92	.98	34.8	35.7	.74	.73
	5 - 6	8.06	7.93	.263	.254	.90	.92	34.7	35.3	.73	.74
		*	*	*	*	*	*	*	*		
60° Upright	1 - 3	9.68	9.06	.238	.217	1.04	1.06	29.6	29.6	.75	.75
	11-13	8.17	8.19	.254	.230	.81	.85	31.3	30.7	.70	.70
	21-23	8.16	9.34	.250	.257	.81 *	.88	31.1	30.4	.70	.71
				*				*		*	
2. Supine	1 - 3	9.49	9.57	.335	.296	.82 *	.89	34.1	33.1	.75	.74
	11-13	7.44	7.18	.236	.226	.85	.87	33.6	33.8	.71	.71

C = Controls, P = Propranolol. Propranolol: n=6 except 21-23 min. upright where n = 5. Statistically significant differences after changes in posture or between C and P are indicated by * $p < 0.05$ or * $p < 0.01$.

Table III. Subject FB

Circulatory Data

Posture	Min	HR C	HR P	$\dot{Q}$ C	$\dot{Q}$ P	V_s C	V_s P	a-$\bar{v}D_{O_2}$ C	a-$\bar{v}D_{O_2}$ P	PP C	PP P
1. Supine	1	62	48	5.53	3.39	91	71	5.7	6.8	50	35
	3	69	48	5.01	3.13	73	65	5.7	7.5	45	33
	5	65	53	5.23	3.41	80	64	5.2	7.1	42	39
60° Upright	1	70	50	4.00	2.80	58	56	6.6	7.0	36	26
	2	72	49	4.47	4.45	64	91	6.0	4.4	42	30
	3	72	52	3.64	2.97	50	57	7.4	6.6	37	35
	6	77	55	3.82	2.77	51	50	7.1	8.1	34	34
	11	78	58	3.36	2.92	44	50	8.0	8.6	38	37
	16	77	55	3.23	3.27	44	59	8.2	7.4	37	35
	21	84	59	3.04	2.94	36	50	8.8	7.8	48	31
2. Supine	1	66	53	4.97	2.89	76	55	7.3	9.9	54	32
	2	62	54	5.98	3.83	96	71	6.1	7.5	47	32
	3	62	52	5.38	4.98	88	96	6.8	5.7	37	26
	6	64	46	4.46	3.59	71	78	6.8	6.7	42	31
	11	69	49	3.85	3.47	56	71	6.6	5.7	47	31

Respiratory Data

Posture	Min	$\dot{V}_I$ C	$\dot{V}_I$ P	$\dot{V}_{O_2}$ C	$\dot{V}_{O_2}$ P	RER C	RER P	P_{ACO_2} C	P_{ACO_2} P	$\dot{V}_A/\dot{V}_E$ C	$\dot{V}_A/\dot{V}_E$ P
1. Supine	1-2	8.18	6.56	.296	.229	.84	.92	36.7	37.4	.72	.75
	5-6	6.76	6.70	.270	.242	.79	.93	37.2	36.8	.74	.79
60° Upright	1-3	7.82	6.52	.262	.197	.86	.91	33.7	32.7	.75	.73
	11-13	6.91	6.60	.267	.252	.72	.73	35.2	35.1	.70	.70
	21-23	6.90	5.87	.257	.230	.73	.75	34.6	35.8	.69	.72
2. Supine	1-3	8.56	6.08	.354	.286	.77	.76	36.5	39.2	.77	.80
	11-13	6.06	4.97	.250	.198	.75	.80	36.1	38.1	.75	.73

C = Controls (means of two tests)
P = Propranolol

Table IV. Subject WC

Circulatory Data

Posture	Min	HR C	HR P	$\dot{Q}$ C	$\dot{Q}$ P	V_s C	V_s P	a-$\bar{v}D_{O_2}$ C	a-$\bar{v}D_{O_2}$ P	PP C	PP P
1. Supine	1	78	66	7.31	7.74	93	117	4.7	3.6	39	21
	3	81	64	7.38	5.06	91	79	4.3	5.6	41	36
	5	79	66	5.31	6.43	67	97	5.6	4.5	37	32
60° Upright	1	75	67	5.86	5.18	79	77	4.7	4.8	21	20
	2	86	73	5.86	4.33	68	59	4.8	5.8	25	23
	3	86	74	6.77	4.47	80	60	4.1	5.6	25	26
	6	84	69	6.78	3.81	82	55	4.4	5.9	21	27
	11	86	71	6.09	3.42	72	48	5.0	5.9	31	23
	16	88	71	5.77	6.61	65	93	5.2	3.8	29	20
	21	91	72	5.29	5.86	59	81	5.7	5.0	30	16
2. Supine	1	81	62	7.57	6.25	94	101	5.6	6.0	30	33
	2	73	66	8.71	10.80	120	164	4.7	3.5	28	25
	3	72	66	7.62	12.36	106	187	5.6	3.0	25	30
	6	74	63	8.30	9.79	114	155	4.1	3.2	29	21
	11	78	66	6.16	6.21	79	94	4.5	4.1	34	31

Respiratory Data

Posture	Min	$\dot{V}_I$ C	$\dot{V}_I$ P	$\dot{V}_{O_2}$ C	$\dot{V}_{O_2}$ P	RER C	RER P	$P_{A_{CO_2}}$ C	$P_{A_{CO_2}}$ P	$\dot{V}_A/\dot{V}_E$ C	$\dot{V}_A/\dot{V}_E$ P
1. Supine	1-2	11.27	9.85	.329	.280	1.00	1.04	34.7	33.8	.73	.75
	5-6	9.43	9.37	.296	.289	.92	.91	34.5	33.4	.73	.73
60° Upright	1-3	13.28	11.70	.275	.249	1.15	1.15	27.9	27.7	.73	.76
	11-13	9.05	6.55	.292	.203	.78	.81	32.6	33.0	.68	.66
	21-23	9.42	9.49	.302	.293	.79	.84	32.7	31.4	.68	.71
2. Supine	1-3	13.20	13.80	.406	.375	.91	.98	32.8	29.6	.74	.77
	11-13	9.55	9.64	.267	.257	.90	.93	31.6	30.5	.69	.70

C = Controls (means of two tests)
P = Propranolol

Table V. Subject JL

Circulatory Data

Posture	Min	HR C	HR P	$\dot{Q}$ C	$\dot{Q}$ P	V_s C	V_s P	a-$\bar{v}D_{O_2}$ C	a-$\bar{v}D_{O_2}$ P	PP C	PP P
1. Supine	1	68	55	6.43	4.97	95	90	4.7	5.2	66	24
	3	69	45	5.26	4.31	77	96	5.7	6.0	54	27
	5	68	52	5.82	4.01	86	77	5.0	6.5	39	29
60° Upright	1	89	55	4.94	3.66	57	67	4.7	6.3	44	13
	2	92	59	4.93	3.01	55	51	4.8	7.6	30	11
	3	97	58	4.48	4.51	47	78	5.2	5.1	10	40
	6	97	66	3.42	3.34	35	51	7.5	7.7	22	18
	11	100	64	4.00	3.42	41	53	6.9	8.4	30	8
	16	95	47	3.84	3.68	41	78	7.3	7.8	29	12
	21	97	--	3.46	--	36	--	8.3	--	8	--
2. Supine	1	55	42	3.40	4.13	65	98	10.4	6.8	42	19
	2	52	52	6.58	4.02	127	77	5.5	7.0	34	17
	3	54	50	6.01	3.30	113	66	6.0	8.5	32	16
	6	58	46	5.28	3.60	92	78	5.8	7.0	33	14
	11	59	45	4.19	3.31	71	74	6.1	6.7	33	20

Respiratory Data

Posture	Min	$\dot{V}_I$ C	$\dot{V}_I$ P	$\dot{V}_{O_2}$ C	$\dot{V}_{O_2}$ P	RER C	RER P	$P_{A_{CO_2}}$ C	$P_{A_{CO_2}}$ P	$\dot{V}_A/\dot{V}_E$ C	$\dot{V}_A/\dot{V}_E$ P
1. Supine	1-2	9.78	8.96	.301	.259	.95	1.00	34.0	35.6	.74	.70
	5-6	8.99	7.86	.292	.259	.89	.88	34.7	36.5	.72	.69
60° Upright	1-3	10.01	9.57	.233	.230	1.09	1.09	28.6	29.2	.77	.77
	11-13	9.66	13.79	.274	.286	.83	1.00	29.2	22.5	.70	.80
	21-23	9.80	--	.286	--	.81	--	29.5	--	.70	--
2. Supine	1-3	10.22	9.57	.354	.282	.84	.87	33.9	31.1	.75	.72
	11-13	7.70	6.33	.254	.252	.81	.77	34.7	35.7	.68	.66

C = Controls (means of two tests except at 60°, 21 min.)
P = Propranolol

Table VI. Subject UL

Circulatory Data

Posture	Min	HR C	HR P	$\dot{Q}$ C	$\dot{Q}$ P	V_s C	V_s P	a-$\bar{v}D_{O_2}$ C	a-$\bar{v}D_{O_2}$ P	PP C	PP P
1. Supine	1	83	67	4.48	4.92	54	73	6.4	6.6	38	29
	3	86	67	4.15	4.10	49	61	6.5	7.4	41	43
	5	85	66	4.15	3.94	49	60	5.9	7.1	41	38
60° Upright	1	97	72	5.76	3.99	60	55	4.0	6.1	12	28
	2	101	76	3.99	3.98	40	52	5.8	6.1	14	14
	3	103	76	4.36	6.31	42	83	5.3	3.9	22	30
	6	98	72	2.64	3.62	27	50	9.2	6.9	15	15
	11	101	75	3.18	3.48	32	46	8.0	7.3	15	15
	16	101	76	3.10	3.17	31	42	7.9	8.1	22	27
	21	99	76	3.51	3.30	36	43	6.8	7.9	11	14
2. Supine	1	75	62	2.00	2.84	27	46	13.6	11.1	34	30
	2	73	66	3.53	4.23	48	64	7.8	7.5	42	24
	3	75	63	3.77	4.06	51	64	7.3	7.8	40	19
	6	77	70	3.52	3.74	46	53	7.5	7.5	38	26
	11	82	64	3.14	4.20	39	66	7.4	5.7	45	34

Respiratory Data

Posture	Min	$\dot{V}_I$ C	$\dot{V}_I$ P	$\dot{V}_{O_2}$ C	$\dot{V}_{O_2}$ P	RER C	RER P	$P_{A_{CO_2}}$ C	$P_{A_{CO_2}}$ P	$\dot{V}_A/\dot{V}_E$ C	$\dot{V}_A/\dot{V}_E$ P
1. Supine	1-2	9.66	10.99	.283	.326	.82	.90	28.7	32.1	.73	.72
	5-6	8.42	9.58	.246	.278	.79	.88	28.6	31.9	.70	.70
60° Upright	1-3	10.31	10.73	.231	.244	.94	1.00	24.2	26.1	.75	.75
	11-13	9.76	9.83	.254	.254	.79	.87	25.9	28.1	.69	.69
	21-23	9.20	9.97	.233	.261	.79	.85	25.4	28.0	.69	.69
2. Supine	1-3	8.47	10.51	.271	.316	.75	.86	29.4	30.9	.71	.73
	11-13	8.38	8.89	.232	.241	.79	.90	28.0	29.1	.68	.73

C = Controls (means of two tests)
P = Propranolol

Table VII. Subject LM

Circulatory Data

Posture	Min	HR C	HR P	$\dot{Q}$ C	$\dot{Q}$ P	V_s C	V_s P	a-$\bar{v}D_{O_2}$ C	a-$\bar{v}D_{O_2}$ P	PP C	PP P
1. Supine	1	53	49	5.47	5.40	103	110	5.1	4.6	47	50
	3	56	48	4.67	6.42	84	134	6.0	3.9	51	34
	5	60	47	4.75	3.41	79	73	5.9	7.4	58	42
60° Upright	1	54	46	5.42	4.19	102	91	4.7	5.5	37	27
	2	64	51	5.63	6.72	88	132	4.5	3.5	42	26
	3	63	55	6.03	4.49	96	82	4.2	5.2	52	32
	6	64	51	5.05	3.48	79	68	5.0	6.4	39	9
	11	59	51	4.66	4.22	80	83	5.5	5.1	44	15
	16	67	57	4.63	4.85	70	85	5.7	5.2	28	22
	21	62	54	4.64	6.72	75	124	5.8	4.3	27	24
2. Supine	1	56	43	5.09	--	91	--	8.5	--	55	40
	2	58	47	6.01	4.09	105	87	6.4	7.0	58	32
	3	56	45	6.31	4.23	113	94	6.1	6.7	58	36
	6	54	49	6.40	4.28	121	87	5.0	5.9	58	39
	11	55	45	4.62	4.00	84	89	5.4	5.5	47	36

Respiratory Data

Posture	Min	$\dot{V}_I$ C	$\dot{V}_I$ P	$\dot{V}_{O_2}$ C	$\dot{V}_{O_2}$ P	RER C	RER P	P_{ACO_2} C	P_{ACO_2} P	$\dot{V}_A/\dot{V}_E$ C	$\dot{V}_A/\dot{V}_E$ P
1. Supine	1-2	7.40	7.99	.279	.248	.92	1.08	39.2	38.4	.77	.75
	5-6	7.93	6.29	.278	.253	.98	.89	38.8	40.1	.77	.78
60° Upright	1-3	8.05	7.94	.249	.232	1.02	1.09	35.5	35.6	.76	.77
	11-13	6.51	5.94	.255	.216	.80	.85	36.0	35.8	.76	.75
	21-23	8.21	10.01	.264	.290	.88	.98	32.4	33.3	.76	.74
2. Supine	1-3	8.91	7.23	.381	.285	.79	.84	37.7	37.8	.78	.76
	11-13	6.75	5.56	.245	.221	.90	.88	37.4	39.2	.76	.78

C = Controls (means of two tests)
P = Propranolol

Table VIII. Subject SR

Circulatory Data

Posture	Min	HR C	HR P	$\dot{Q}$ C	$\dot{Q}$ P	V_s C	V_s P	a-$\bar{v}D_{O_2}$ C	a-$\bar{v}D_{O_2}$ P	PP C	PP P
1. Supine	1	64	67	3.83	3.87	61	58	5.0	5.2	40	39
	3	62	63	3.69	5.11	60	81	5.3	3.9	31	32
	5	63	60	4.36	4.62	70	77	4.5	4.4	33	31
60° Upright	1	72	67	4.70	2.42	66	36	3.8	6.2	27	38
	2	87	73	4.59	3.34	53	46	4.0	4.5	28	31
	3	91	80	4.88	3.54	54	44	3.6	4.2	30	51
	6	88	77	4.14	3.15	47	41	4.4	5.0	31	32
	11	92	73	3.90	3.26	43	45	4.7	5.1	24	19
	16	89	71	3.78	3.93	42	55	5.1	4.8	16	23
	21	95	65	3.82	3.94	41	61	5.3	5.4	10	18
2. Supine	1	59	50	2.81	3.09	48	62	8.8	7.4	33	17
	2	54	52	4.51	5.37	84	103	5.5	4.3	30	22
	3	57	51	5.23	5.60	92	110	4.7	4.1	25	29
	6	57	55	4.97	5.69	87	103	4.3	3.7	24	22
	11	57	61	3.80	4.68	67	77	4.5	4.0	28	27

Respiratory Data

Posture	Min	$\dot{V}_I$ C	$\dot{V}_I$ P	$\dot{V}_{O_2}$ C	$\dot{V}_{O_2}$ P	RER C	RER P	$P_{A_{CO_2}}$ C	$P_{A_{CO_2}}$ P	$\dot{V}_A/\dot{V}_E$ C	$\dot{V}_A/\dot{V}_E$ P
1. Supine	1-2	6.57	6.52	.192	.201	1.01	.94	35.2	36.9	.72	.68
	5-6	6.82	7.76	.193	.201	1.01	1.05	34.4	32.8	.72	.72
60° Upright	1-3	8.62	7.90	.176	.149	1.16	1.13	27.9	26.4	.73	.70
	11-13	7.15	6.45	.181	.167	.91	.81	29.1	29.7	.69	.62
	21-23	7.06	11.35	.195	.212	.87	.97	30.6	23.3	.69	.67
2. Supine	1-3	7.59	10.25	.246	.229	.87	1.03	34.2	30.2	.72	.66
	11-13	6.21	7.67	.169	.187	.96	.96	33.7	30.1	.67	.67

C = Controls (means of two tests)
P = Propranolol

Table IX. Additional Tests

Subject	Items	Supine 1 Minutes 1	Supine 1 Minutes 2	Supine 1 Minutes 3	60° Minutes 1	60° Minutes 2	60° Minutes 3	Supine 2 Minutes 1	Supine 2 Minutes 2	Supine 2 Minutes 3
JL	$\dot{V}_I$	6.11	5.64	6.55	6.97	7.39	7.34	9.21	8.20	7.49
	$\dot{V}_{O2}$	.241	.239	.290	.199	.238	.207	.376	.335	.304
	$\dot{V}_{CO2}$	.207	.189	.224	.194	.211	.179	.260	.259	.236
	RER	.86	.79	.77	.97	.89	.86	.69	.77	.78
LM	$\dot{V}_I$	6.97	8.29	8.08	7.89	5.91	8.29	10.31	7.08	7.00
	$\dot{V}_{O2}$	.277	.315	.333	.275	.217	.331	.518	.294	.324
	$\dot{V}_{CO2}$	.276	.318	.329	.290	.217	.308	.410	.269	.283
	RER	1.00	1.01	.99	1.05	1.00	.93	.79	.91	.87
UL	$\dot{V}_I$	10.11	10.26	9.54	8.98	9.91	9.50	13.42	10.93	9.11
	$\dot{V}_{O2}$	.334	.340	.332	.206	.246	.272	.561	.369	.297
	$\dot{V}_{CO2}$	.284	.276	.262	.194	.213	.224	.394	.295	.234
	RER	.85	.81	.79	.94	.87	.82	.70	.80	.79
SR	$\dot{V}_I$	6.93	7.05	5.63	11.51	8.31	8.91	7.22	5.28	6.04
	$\dot{V}_{O2}$	.212	.206	.198	.196	.131	.156	.264	.231	.232
	$\dot{V}_{CO2}$	.212	.200	.176	.283	.172	.184	.197	.161	.175
	RER	1.00	.97	.89	1.44	1.31	1.18	.75	.70	.75
Means	$\dot{V}_I$	7.53	7.81	7.45	8.84	7.88	8.51	10.04	7.87	7.41
	$\dot{V}_{O2}$	.266	.275	.288	.219	.208	.242	.430	.307	.289
	$\dot{V}_{CO2}$	.245	.246	.248	.240	.203	.224	.315	.246	.232
	RER	.93	.90	.86	1.10	1.02	.95	.73	.80	.80

Table X.

		$\dot{V}_{O_2}$ L/min			$a\text{-}\bar{v}D_{O_2}$ ml/100 ml	$\dot{Q}$ L/min	
	Min	A	B	$\bar{B}$	A	A	B
Supine 1	1-3	.259	.276		5.5	4.71	5.02
60°	1	.222	.219	.223	4.3	5.16	5.09
	2		.208		4.8	4.63	4.33
	3		.242		4.6	4.83	5.26
	4-10	--	--	--	--	--	--
Supine 2	1	.313	.430	.342	10.3	3.04	4.17
	2		.307		6.3	4.97	4.87
	3		.289		6.0	5.22	4.82

Group A: Data from 4 subjects in main series
Group B: Additional tests on the same four subjects
$\bar{B}$: Mean values over 3 minutes on Group B
$\dot{Q}$ for Group B is calculated using $a\text{-}\bar{v}L_{O_2}$ from Series A.

PART II

THE DETERMINATION OF TOTAL BODY WATER BY AN ETHANOL DILUTION METHOD

The physiological significance of changes in body weight, be it in health or disease, can be properly assessed only with knowledge of total body water content (TBW). Disturbances in fluid balance are common in many pathological states, such as renal and cardiac diseases or endocrine disorders. In healthy individuals the total amount and distribution of body fluids can be markedly altered by thermal stress, strenuous exercise, or water immersion. The orthostatic intolerance of astronauts returning to earth after extended space operations has been associated with weight loss and a reduction in plasma fluid volume.

So far clinical methods for measuring TBW have been limited to the use of antipyrine (9) and its derivatives, which involve injections and repeated blood sampling, or the injection or ingestion of hydrogen isotopes, deuterium (8) or tritium (3). Neither of these can be repeated at frequent intervals because of potential toxicity or residual radioactivity.

In view of the need for a convenient, preferably non-invasive method for measuring TBW, we have explored the feasibility of using an ethanol dilution method first proposed by Grüner (1) in 1957. The exquisite solubility of ethanol in water and its good permeability in body tissue would make the ethanol dilution method most attractive if a precise and rapid method were available to measure it.

Recently the need for convenient, non-invasive methods for measuring alcohol for forensic purposes in wide scale traffic accident control programs has expedited the development of several devices which permit an accurate estimate of blood alcohol levels from samples of expired air.

The following provides a preliminary report on the results of a current study using the ethanol (ETH.) dilution method in comparison with simultaneous tritium (HTO) dilution studies for the estimation of total body water (TBW) in normal subjects.

Concurrent determinations of body density in our subjects provided an opportunity to relate TBW not only to gross body weight (Wt) but also to fat free mass (FFM) and thus establish correlations which can be useful in assessing the nutritional status and physical condition of an individual.

Methods and Procedures:

The general principle for all dilution methods for TBW is that if a given amount (I) of a water soluble indicator is injected or ingested, TBW can be calculated if its concentration c in body fluids is measured after complete equilibration.

$$TBW = \frac{I}{c} \qquad (1)$$

After ingestion of ethanol its concentration in the bloodstream increases up to a peak (see Fig. 1) as it is absorbed and distributed in the body. Thereafter it declines gradually over the next few hours as it is metabolized or excreted by the lungs and kidneys. If a series of determinations is made at intervals after equilibration and the concentrations are plotted against time to define the slope of decay, one can establish the concentration c_0 that would have existed if complete mixing and equilibration had taken place instantaneously after ingestion by projecting the slope to the zero intercept in time.

This can be done graphically (Fig. 1) or with the following equation.

$$c_0 = \frac{\Sigma t \cdot \Sigma(t \cdot c) - \Sigma c \cdot \Sigma t^2}{(\Sigma t)^2 - n\Sigma t^2} \qquad (2)$$

where t is the sampling time after ingestion, c the concentration in each sample, and n the number of samples.

Ethanol was measured on expired air samples exhaled directly into an ALCO-ANALYZER (Luckey Laboratories), which is a specially designed gas chromatograph. The instrument is calibrated with a special breath simulator from which air equilibrated with prepared ethanol solutions at 34C is introduced into the analyzer simulating desired ethanol concentrations in the blood.

Simultaneous measurements of TBW were made using tritium by the procedure described by Logsdon et al. (4). The subjects presented themselves for the test at 8 a.m. having refrained from food and drink for 8 hours. They were weighed to the nearest 100 g and then received a potion containing 0.5 g ethanol per kg body weight diluted in 150 ml of iced water with a small amount of Daquiri Mix (powder) to make it more palatable. In addition they drank 250 μc of tritium in 10 ml of water, all subjects receiving the same dose. The solutions were consumed in the course of 15 minutes. Ninety minutes after starting the drink the first breath samples were taken. During the intervening period a calibration curve for the ALCO-ANALYZER was established with 0.02, 0.04, and 0.06% ethanol by the simulator. The breath analyses were repeated after 120, 150, 180, and 210 minutes. At each of those intervals the subject exhaled into the machine three times about 4 minutes apart to allow the chromatograph to return to zero. The deflections of the three measurements were averaged and plotted against the mean time. Immediately after each sampling period the calibration of the analyzer was checked by introducing the ethanol concentration closest to the preceding measurement from the simulator, i.e., 0.06% for 90', 0.04 for 120 and 150', and 0.02% for 180 and 210'. This permitted corrections for any slight changes in sensitivity during the test period. A second complete calibration was performed after the test with fresh calibrating solutions to account for any loss of ethanol by evaporation. Shortly after three hours a venous blood sample was taken for tritium determination.

Mostly on the same day or within a few days of the TBW measurement body density was determined on each subject by the immersion technique (5) and fat fraction and fat free mass (FFM) calculated according to Keys and Brožek (2). The 10 subjects who volunteered for the test were a random sample of members of this institution ranging in age from 28 to 63 years (mean 38). As it happened, 5 of these men (Group A) were active middle- and long-distance runners who engaged in a fairly regular exercise program. The other 5 (Group B) were not particularly active physically, but nevertheless in good health.

Results and Comments:

All results are contained in Table I for each subject individually with mean values for all 10 below. Mean values for Groups A and B are also shown separately.

In the comparison between the ethanol (ETH.) and the tritium (HTO) method for TBW satisfactory agreement was found. The difference between the means for TBW (liters) was 0.6 liters or 1.4%. With two exceptions the individual differences were within 3% and the scatter was random, indicating that there was no systematic difference. The correlation coefficient between TBW (ETH.) and (HTO) was $r = .830$ and this was statistically significant ($p < .01$). Individual values for TBW as a fraction of body weight (Wt) ranged from .506 to .720 with a mean value of .603.

Table I has been arranged in descending order of the individual's body water fraction (TBW/Wt), and it is readily apparent that the latter varies directly with the fat free mass as a fraction of gross weight (FFM/Wt). Because fatty tissue contains relatively little water, TBW is always found to correlate much better with FFM than with Wt, and for this reason TBW has sometimes been used as a means to estimate FFM indirectly. The correlation between TBW and FFM for our subjects is shown in Fig. 2. The correlation coefficient $r = .864$ is statistically significant and FFM could be predicted from TBW by the regression:

$$FFM = 1.449TBW - 1.362 \qquad (3)$$

On the average, mean body weight was the same in Groups A (runners) and B (non-runners), but FFM was much higher in A than in B, because B had about 10% more fat than A. This is also clearly reflected in the difference in TBW/Wt between the two groups, .647 for A and .559 for B, and this was statistically significant ($p < .01$).

The body water fraction of Group B using ETH. is in good agreement with mean values found by other investigators (6) for an average population of men in the same age range. On the other hand, the values

for TBW/Wt in our Group A are very similar to those reported by Novak et al. (7) on different categories of trained athletes. For instance in baseball players the body water fraction was .628 on the average and in track men .705. The difference between athletes and non-athletes is not surprising since the major part of FFM is muscle tissue with a high water content. The relationship between FFM/Wt and TBW/Wt for the 10 subjects in our study is plotted in Fig. 3. In this manner a clear separation is obtained between the "runners" and "non-runners."

Conclusions:

The results of this preliminary study with the ethanol dilution method for total body water demonstrate that they are comparable to those obtained with other accepted methods. Obvious advantages of the method are its harmless and non-invasive nature and the fact that it could be repeated at intervals of less than 6 hours if necessary, thus making it useful for studies of rapid changes in body hydration such as heat stress or pathological conditions involving de- or hyperhydration. Further refinements of the method are in progress which involve greater sensitivity of the analyzer in order to reduce the necessary initial dose of ethanol. The amount used in this study (0.5 g/kg), although not inebriating, was sufficient to cause light headedness and headaches in some of the subjects, particularly since it was taken on an empty stomach. If sufficient measuring points to establish the decay curve could be obtained with a dose of 0.3 g/kg ethanol, undesirable side effects would be avoided.

REFERENCES

1. Grüner, O. Bestimmung des Körperwassergehaltes mit Hilfe von Alkohol. Klin. Wschr. 35:347-351, 1957.

2. Keys, A. and J. Brožek. Body fat in adult man. Physiol. Rev. 33:245-325, 1953.

3. Langham, W.H., W.J. Eversole, F.N. Hayes, and T.T. Trujillo. Assay of tritium activity in body fluids with use of a liquid scintillation system. J. Lab. Clin. Med. 47:819-825, 1956.

4. Logsdon, D.F., J.F. Green, and J.W. Harper. Reproducibility of repeated total body water measurements with tritium. SAM Technical Report 69-36, USAF School of Aerospace Medicine, Brooks Air Force Base, Texas. July 1969.

5. Luft, U.C. and T.P.K. Lim. Modified procedure for the determination of body volume by hydrostatic weighing, p. 107. In: Techniques for Measuring Body Composition. National Academy of Sciences, National Research Council, Washington, D.C., 1961.

6. Moore, F.D., K.H. Olesen, J.D. McMurrey, H.V. Parker, M.R. Ball, and C.M. Boyden. The Body Cell Mass. W.B. Saunders Co., Philadelphia, 1963, p. 532.

7. Novak, L.P., R.E. Hyatt, and J.F. Alexander. Body composition and physiologic function of athletes. JAMA 205:140-146, 1968.

8. Schloerb, P.R., B.J. Friis-Hansen, J.S. Edelman, A.K. Solomon, and F.D. Moore. The measurement of total body water in the human subject by Deuterium Oxide dilution. J. Clin. Invest. 29:1296-1310, 1950.

9. Soberman, R.J., B.B. Brodie, B.B. Levy, J. Axelrod, V. Hollander, and J.M. Steele. Use of antipyrine in measurement of total body water in man. J. Biol. Chem. 179:31-42, 1949.

Table I

	No.	Subj.	Wt kg	FFM kg	FFM / Wt	(ETH.) TBW L	(HTO) TBW L	(ETH.) TBW / Wt	(HTO) TBW / Wt	(ETH.) TBW / FFM	(HTO) TBW / FFM
	1.	FB	60.4	57.3	.949	43.5	42.2	.720	.699	.759	.736
	2.	JL	71.7	63.3	.883	47.8	45.2	.667	.630	.755	.714
A	3.	AP	68.4	64.4	.942	42.7	40.7	.624	.595	.663	.632
	4.	LM	80.8	70.8	.876	49.8	52.8	.616	.653	.703	.746
	5.	DG	79.1	70.2	.887	48.0	45.8	.607	.579	.684	.652
	Mean	1-5	72.1	65.2	.907	46.4	45.3	.647	.631	.713	.696
	6.	BJ	77.1	63.7	.826	45.2	46.6	.586	.604	.710	.732
	7.	GA	64.2	53.4	.832	37.5	38.3	.584	.597	.702	.717
B	8.	UL	78.7	61.4	.780	45.9	45.7	.583	.581	.748	.744
	9.	YK	67.9	55.9	.823	36.5	42.8	.538	.630	.653	.766
	10.	AO	71.6	53.7	.750	36.2	38.4	.506	.536	.674	.715
	Mean	6-10	71.9	57.6	.802	40.3	42.4	.559	.590	.697	.735
	Mean	1-10	72.0	61.4	.855	43.3	43.9	.603	.610	.705	.715

Wt: weight, FFM: fat free mass, TBW: total body water, ETH.: ethanol method, HTO: tritium method, A: runners, B: non-runners.

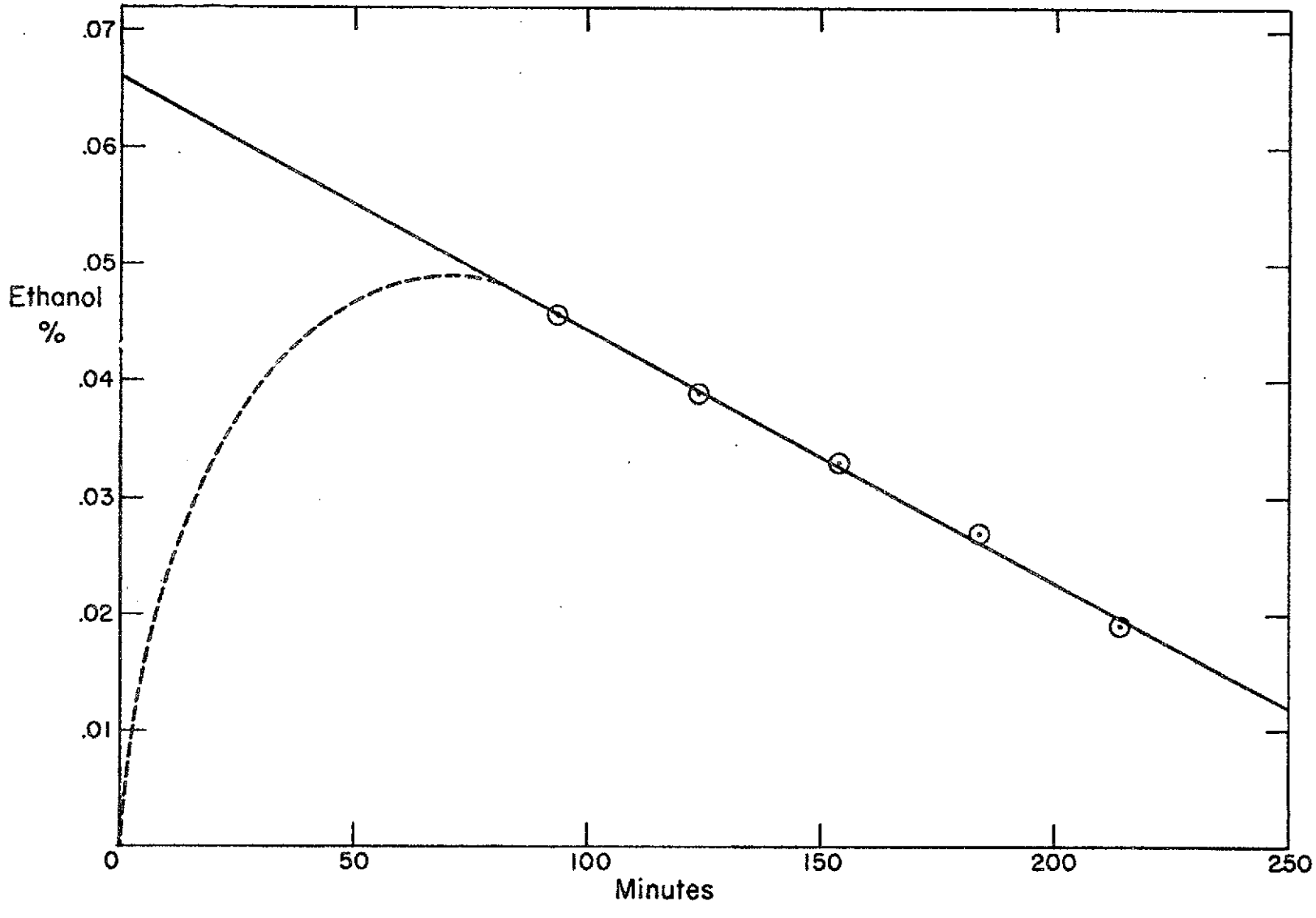

Fig. 1. Ethanol decay curve from breath analyses after ingestion of 0.5 g/kg ethanol at time 0. Each point is mean of three breaths. Solid line: regression of points extrapolated to 0 time to obtain c_0.

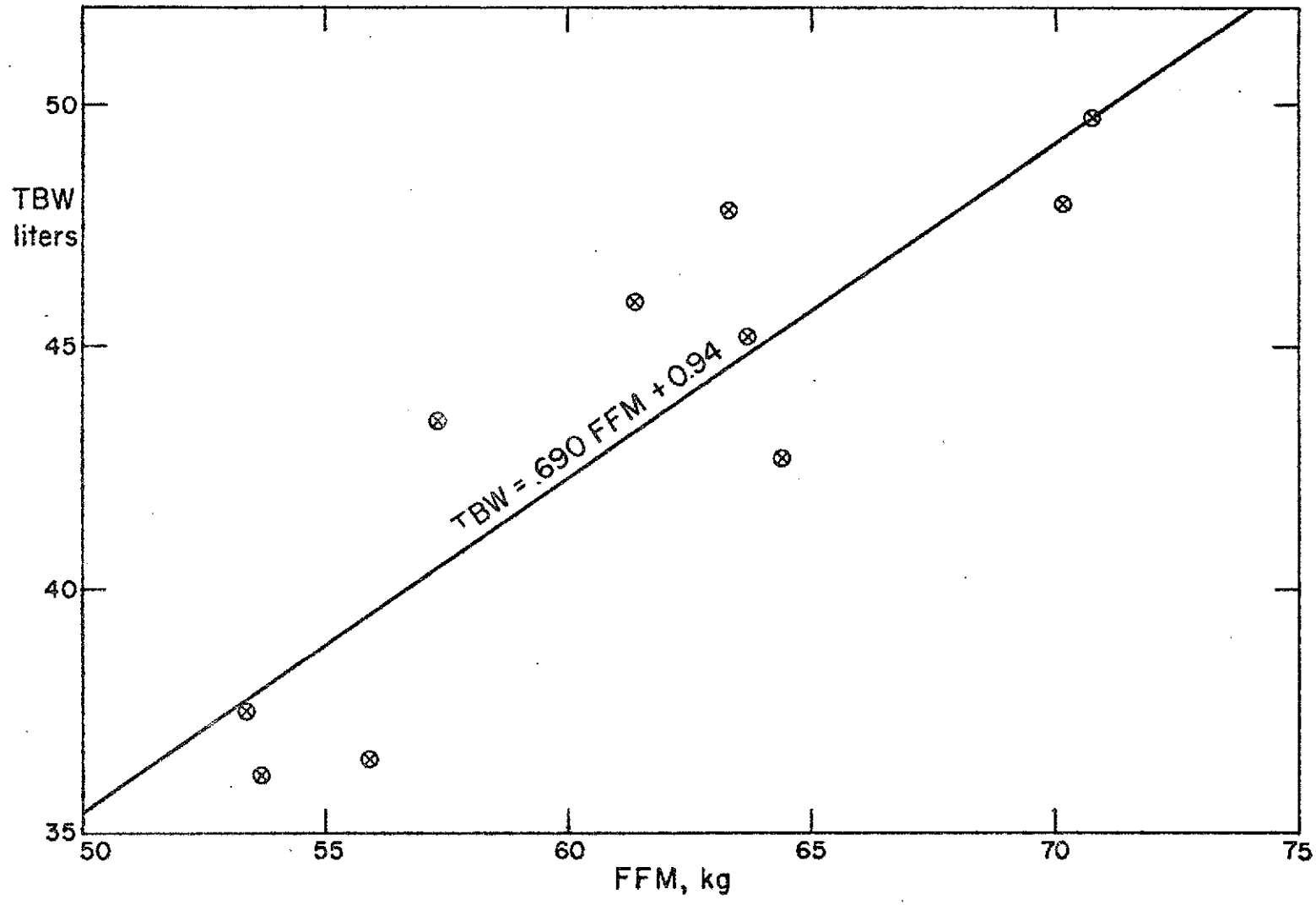

Fig. 2. Relationship between total body water (TBW) with the ethanol method and fat free mass (FFM). ($r = .864$, $p < .01$)

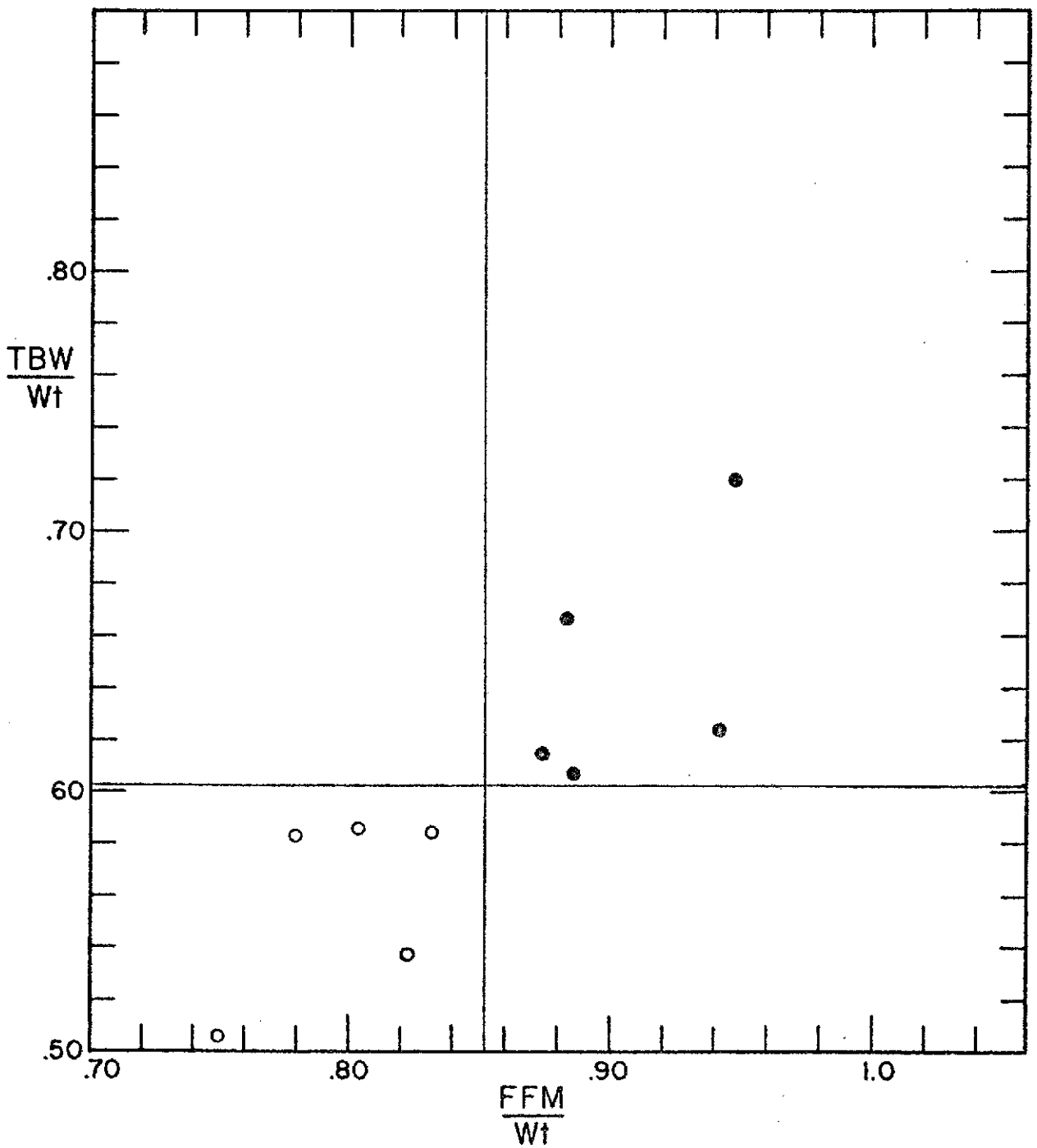

Fig. 3. Relationship between body water fraction with the ethanol method and fat free fraction. Filled circles: runners; open circles: non-runners. The cross indicates the mean values for all subjects.

PART III

INCREASED TOTAL RESPIRATORY CONDUCTANCE BREATHING 100% O_2 (FORCED OSCILLATION METHOD)

Nadel and Widdicombe (5) reported that the inhalation of an hypoxic gas mixture (10-15% O_2 in N_2) produces constriction of the upper and lower airways in anesthetized experimental animals and provided evidence that this was caused by stimulation of the carotid sinus chemoreceptors and that the motor pathways of this reflex were probably located in the vagus nerve. Observations by Astin and Penman (1) on patients with arterial hypoxemia due to chronic obstructive lung disease, whose airway resistance dropped by an average 20% after breathing 30% oxygen for 20 minutes, appear to confirm the existence of a bronchomotor reflex induced by arterial hypoxemia in man. No change in flow resistance was observed when 30% oxygen was administered to non-hypoxic controls. Indirect evidence for an attenuation of bronchomotor tone with relatively small increments in arterial P_{O_2} has accumulated in our laboratory (Albuquerque, 5400 ft.) in studies on the distribution of ventilation and blood flow in the lungs of chronic hypoxemia pulmonary patients. After breathing a gas mixture of 25.5% O_2 for 10-15 minutes, which raised the arterial P_{O_2} by an average 10 mm Hg, it was found that ventilation was more uniformly distributed than previously, breathing air (4). The improvement in ventilation was tentively attributed to increased airway conductance. Similar observations have been reported by Howard and Penman (2) after administering 30% oxygen to hypoxic pulmonary patients at or near sea level.

Little attention has been given to the possibility of changes in airway conductance that may occur with different concentrations of oxygen in the cabin atmosphere of space vehicles, apart from the changes in gas density (3). An instrument developed in this laboratory (NAS 9-7009 Rep. 1970) which measures total respiratory conductance by the forced oscillation method with a constant volume pump appeared to be most suitable for investigating respiratory mechanics while breathing air and oxygen in view of the possible implications for future manned space operations as well as for clinical situations.

Methods and Procedures:

The equipment used was identical to that described previously (NAS 9-7009, Feb. 1970 and NAS 9-12572, Feb. 1973). The forced oscillations are generated by a constant volume pump with adjustable stroke volume (15-45 ml) and frequency (2-17 cps) and applied to the subject's mouth. A constant bias flow (0.5 L/sec) of air or oxygen is drawn through the system permitting the subject to breathe normally during the test.

The subjects breathed through the mouthpiece quietly for 2-3 minutes. The frequency of the pump was then adjusted to the resonant frequency of the subject's respiratory system by closing the flow/pressure loop on the oscilloscope as an indication that there was no phase difference between them. At the same time pressure and flow were recorded against time on a Visicorder (Honeywell) oscillograph to measure the frequency at resonance. Total respiratory conductance (TRC) was determined from the angle of the closed flow/pressure loop on the oscilloscope as well as from the oscillograph record by dividing the flow amplitude by the pressure amplitude at resonance ($\Delta\dot{V}/\Delta P$ = TRC in ml x sec^{-1} x $cm\,H_2O^{-1}$).

Measurements were made on 12 subjects. Eight of these had no history of pulmonary disease and were within normal limits on routine pulmonary function tests. Four of the subjects were patients suffering from chronic obstructive lung disease by clinical diagnosis and pulmonary function tests.

After recording TRC breathing air on each subject, 100% O_2 was substituted for air in the bias flow while the subject continued to breathe through the system. In the normal subjects 6 minutes were allowed to insure complete nitrogen washout and in the patients 10 minutes. Then the measurements were repeated.

Results and Comments:

The values obtained for TRC on 12 subjects while breathing air and 100% oxygen, as measured by the forced oscillation method, are

presented in Table I. Since there was no apparent difference between the healthy subjects (nos. 1-8) and the pulmonary patients (nos. 9-12), the data from all 12 were combined for statistical analysis. Nine out of 12 showed an increase in TRC and 3 no change. The mean increase in TRC was only 11%, nevertheless it was statistically significant. These results cannot be explained on the basis of physical differences between air and oxygen, because the latter has both a slightly higher density and viscosity than the former, which would tend to reduce apparent airway conductance rather than increase it. Our observation that normal subjects respond to increased oxygen pressure in the inspirate with an improvement in airflow is in contrast to the findings of Astin et al. (1) mentioned earlier, that individuals who were not hypoxic (mean Pa_{O_2} 99 mm Hg) did not show any change in airway resistance measured by whole body plethysmography when breathing 30% O_2, while their patients (mean Pa_{O_2} = 70 mm Hg) did.

No measurements of arterial P_{O_2} were done on the patients nor the healthy subjects in the present study. However, since the average Pa_{O_2} in Albuquerque, according to statistics from this laboratory is 73 mm Hg, it is conceivable that all 12 of our subjects were under some chemoreceptor stimulation from the carotid sinus and therefore responded to increased oxygen pressure with improved airway conductance as the patients of Astin et al. did near sea level. Witzleb et al. (6) have shown that the action potentials recorded from the carotid sinus nerve usually increase in frequency whenever Pa_{O_2} drops below 100 mm Hg and that this regularly appears at 80 mm Hg. This might explain why the response in TRC was present in most of our subjects, even if they had no respiratory impairment.

These preliminary results on the effects of oxygen on bronchomotor tone are encouraging in as much as the method is capable of revealing even subtle changes in respiratory mechanics. Further studies are indicated on a larger number of subjects breathing hypoxic mixtures (10-15%) as well as slightly hyperoxic gas (25-30%) with continuous monitoring of alveolar (end-tidal) P_{O_2} and P_{CO_2} in an attempt to establish the P_{O_2} threshhold for the bronchomotor response.

REFERENCES

1. Astin, T.W. and R.W.B. Penman. Airway obstruction due to hypoxemia in patients with chronic lung disease. Amer. Rev. Resp. Dis. 95:567-575, 1967.

2. Howard, P. and R.W.B. Penman. The effect of breathing 30% oxygen on pulmonary ventilation-perfusion inequality in normal subjects and patients with chronic lung disease. Clin. Sci. 32: 127-137, 1967.

3. Mead, J. Respiratory mechanics, chapter 4. In: Physiology in the Space Environment, Vol. II Respiration. Publication 1485B, NAS-NRC, Washington, D.C. 1967.

4. Mostyn, E.M. and U.C. Luft. Alveolar and arterial gases in pulmonary patients living at 5300 ft. on breathing oxygen equivalent to sea level. (abstr.) Chest 62:372, 1972.

5. Nadel, J.A. and J.G. Widdicombe. Effect of changes in blood gas tensions and carotid sinus pressure on tracheal volume and total lung resistance to airflow. J. Physiol. (London) 163:13-33, 1962.

6. Witzleb, E., H. Bartels, H. Budde, and M. Mochizuki. Der Einfluss des arteriellen O_2 Druckes auf die chemoreceptorischen Aktionspotentiale im Carotissinusnerven. Pflüg. Arch. ges Physiol. 261:211-218, 1955

Table I. Total Respiratory Conductance (liter·sec^{-1}·cm H_2O^{-1})

No.	Subj.	Air	100% O_2	Difference O_2-Air
1.	UL	.720	.788	+.068
2.	GA	.466	.544	+.078
3.	TM	.554	.569	+.015
4.	NC	.708	.842	+.134
5.	DK	.752	.858	+.106
6.	JL	.521	.654	+.133
7.	WD	.628	.785	+.157
8.	DA	.666	.666	0
9.	FH	.551	.616	+.065
10.	BL	.493	.493	0
11.	FM	.820	.898	+.078
12.	DMc	.820	.820	0
Mean		.642	.711	+.069

This difference between the means is statistically significant ($p < .01$).