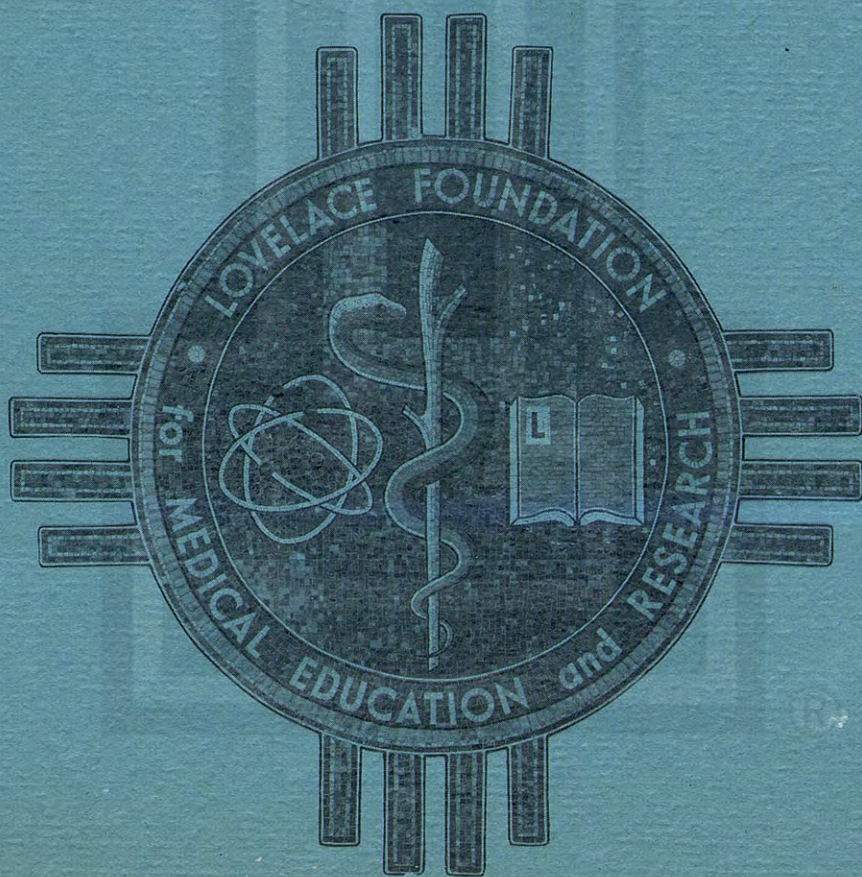
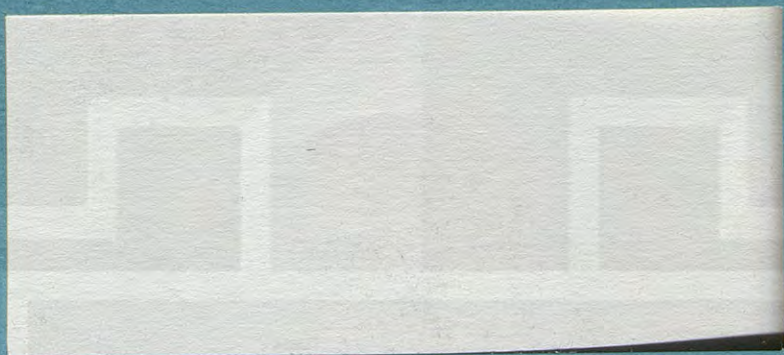




Biomedical Techniques for Use In
Manned Space Laboratories

Part II

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RESPIRATORY SYSTEM

It is a truism, but at the same time a basic point of reference, to recall that the function of the respiratory system is to accomplish the exchange of gases between the blood and the ambient atmosphere. In some aspects, at least, the respiratory system must be examined in association with the pulmonary circulation. The basic respiratory unit is the alveolus, which for proper function must receive a suitable supply of gas and blood. To maintain proper gas exchange the quality and quantity of ventilation must be adequate; relative uniformity of mixing of gas in relation to flow of pulmonary capillary blood must be present; alveolar capillary membrane permeability must be normal; and shunting of venous blood around functional alveolar - capillary units must be minimal. A breakdown in any of these areas will result in impairment of gas exchange, leading to hypoxia and hypercarbia. In addition, there must be satisfactory gas transport between the lung and the other body tissues.

This basic understanding leads to a requirement for anatomical-physiological considerations involving static lung volumes and capacities, the mechanics and dynamics of breathing, the components involved in alveolar gas exchange, and the attributes of blood gas transport.

Static Lung Volumes and Capacities

Measurement of static lung volumes and capacities provides the anatomical basis for physiological consideration of other aspects of pulmonary function, and, particularly if trends in change can be observed, may provide an indication of physiological dysfunction, or pathological disorder.

The standard definitions accepted by respiratory physiologists are as follows: (Pappenheimer, et al., 1950)⁸⁶

Volumes

There are four primary and distinct volumes:

1. Tidal volume (TV): the volume of gas inspired and expired during each respiratory cycle.
2. Inspiratory reserve volume (IRV): the maximal amount of gas that can be inspired from the end-inspiratory position.
3. Expiratory reserve volume (ERV): the maximal volume of gas that can be expired from the end-expiratory level.
4. Residual volume (RV): the volume of gas remaining in the lungs at the end of a maximal expiration.

Capacities

There are four capacities, each of which is the sum of two or more volumes:

1. Total lung capacity (TLC): the amount of gas contained in the lung at the end of a maximal inspiration.
2. Vital capacity (VC): the maximal volume of gas that can be expelled from the lungs by forceful effort following a maximal inspiration.
3. Inspiratory capacity (IC): the maximal volume of gas that can be inspired from the resting expiratory level.
4. Functional residual capacity (FRC): the volume of gas remaining in the lung at the resting expiratory level. The end-expiratory baseline used here is that established by Christie (1932)¹⁶, in contrast with the mid-capacity level that has also been used. The various subdivisions of volume and capacity are illustrated in figure 1, (Pace 1965⁸⁵).

Traditionally it has been the practice to measure lung volumes and capacities by the use of water-filled spirometers such as the Benedict-Roth, or in some circumstances, the Tissot. For those volumes that can be measured by direct methods (*i.e.*, excluding residual volume), the subject breathes into and out of the spirometer through a system of valves to establish tidal volume. A deep inspiration is made and expired to resting level for the measurement of inspiratory volume; a full expiration is subsequently made to obtain expiratory reserve volume. Measurement of residual volume is made in another manner which will be discussed later. It is obvious, however, that

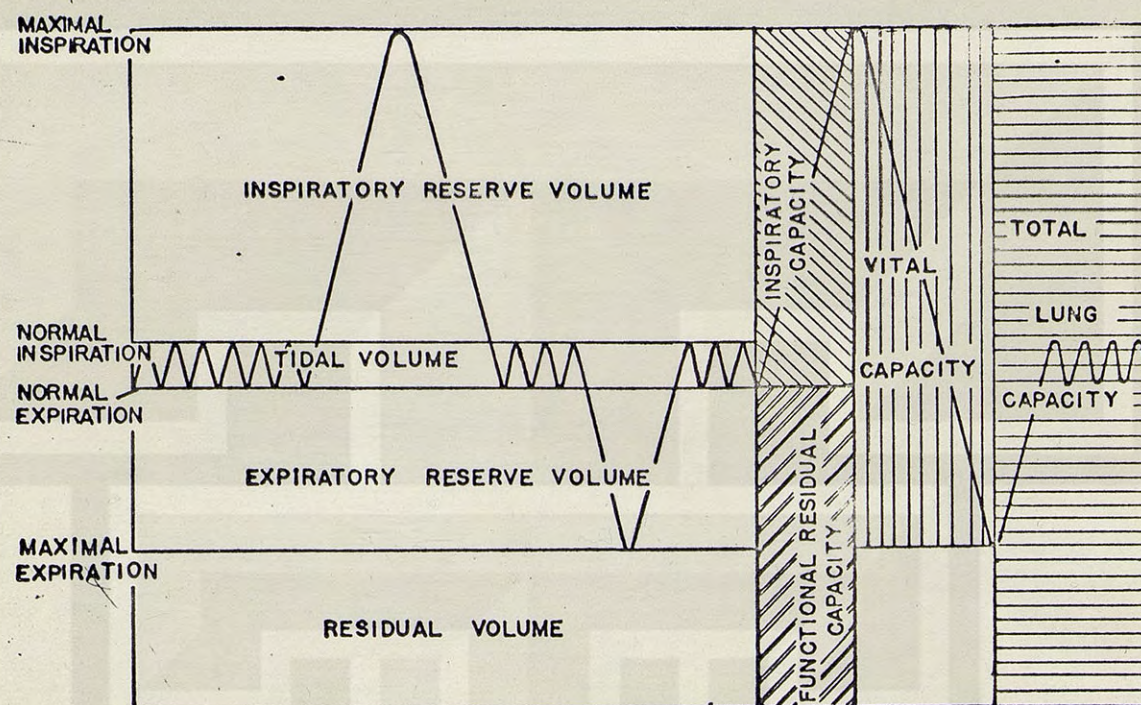


Figure 1. Lung volumes and capacities. Relationship of various subdivisions of lung volume.

Source: Pace (1965)⁸⁵.

the water-filled spirometer has no place in a weightless environment. Consequently, other techniques for these measures must be considered.

Dry spirometry

Several spirometers have been designed which use a gas bellows without a water seal. Notable among these are the Vitalor made by the McKesson Appliance Co., Toledo, Ohio (McKesson and Edwards, 1961)⁷⁷ and the Pulmonor made by the Jones Medical Instrument Co., Chicago, Illinois (Vance, 1963)¹²⁶, each of which is relatively portable and suitable for general survey purposes.

One that has received considerable laboratory attention is the Wedge spirometer, manufactured by Med-Science Electronics, Inc., St. Louis, Missouri. For measurement of volume changes during quiet breathing, a flat response up to 4 cycles per second is adequate (Bernstein and Mendel, 1951)¹³, although for rapid volume changes such as those found during maximum voluntary ventilation, devices that respond accurately up to several times that frequency (e.g., 26 cps) are required (McCall et al., 1957)⁷⁵. The Wedge spirometer is stated to have excellent response characteristics (Mead and Milic-Emilie, 1964)⁷¹. With a large surface area and low inertia, it has a high dynamic response, and provides signals proportional to both volume and flow, which can be led off, if required, to a fast-response X-Y recorder, or oscilloscope. Although somewhat large and bulky it could serve a very useful purpose in a space laboratory, if actual spirometry were considered advisable.

The Servo-spirometer, which is also made by Med-Science Electronics, has been suggested for use in space laboratories (North American Aviation, Inc., 1963)⁸². The servo-spirometer operates on a mechanism such that when a subject breathes into a cylinder containing a piston, the resulting pressure change activates an electric motor which moves the piston in a direction to compensate automatically for the pressure change. Thus, the pressure in the cylinder remains constant and the movement of the piston is a measure of the volumes and flows of the subject's breathing. There is no doubt that this system would be of value in a space laboratory, but since it is more complex, bulkier and heavier (approximately 70 lbs. and 2 cubic

feet), and provides little additional information, it is doubtful if it would possess any significant advantages over the less complex and less bulky Wedge spirometer.

Respirometers

Various types of special purpose respirometers have been devised, such as the Ventube (J. H. Emerson Co., Cambridge, Mass.), and the Wright Respirometer (C. E. Smith, Arlington, Mass.), which are portable and accurate for clinical purposes (Warring, 1965)¹⁰⁵, and are suitable for survey purposes. It is doubtful, however, if they have the flexibility and accuracy required for laboratory use.

The Proper spirometer, discussed by Pace (1965)⁸⁵ is a device which works on the rotameter principle, and when properly used is reputed to deliver values comparable to those obtained with the Benedict-Roth. It is, however, open to error, and lacks the flexibility required for laboratory work.

Bag methods

The Douglas bag, or special polyethylene bags made for the purpose, can, of course, be used for collection of respiratory samples for measurement of lung volumes. Their advantage, however, is nullified by the requirement for a gas meter or spirometer to measure the sample. For very short missions, however, where few samples are required, the storage of such bags for subsequent measurement might be feasible.

Pneumotachography

The pneumotachograph was originally developed by Fleisch in 1925³³. Basically it consists of a tube containing a linear flow resistance along with a device for recording the pressure difference across the resistance while gas is flowing through the tube. It follows the principle of Poiseuille's Law, which states that if flow is laminar, the pressure drop along a tube of uniform cross section is linearly related to the flow.

Various components have been used to provide the linear resistance. The original device developed by Fleisch (1925)³³ used parallel tubes and was bulky;

Lilly (1950)⁶¹ utilized a fine mesh screen; while Fry and his associates (1957)⁴⁰ at the National Heart Institute employed in one meter a system of vertical plates, and, in another, concentric cylinders. The last named group conducted a comparative study of three different types of pneumotachograph in terms of dead space, linearity, stability of calibration, impedance to respiratory flow, and dynamic accuracy. All demonstrated an acceptable linearity and accuracy of dynamic response (up to 34 cps); the meter with concentric cylinders, made by National Instrument Laboratories, Inc., Riverdale, Md., had the smallest dead space (41 ml), but lost its calibration after 15 minutes of use; the screen meter, made by Technitrol Engineering Co., Philadelphia, Pa., had the highest dead space (310 ml) but maintained good calibration; the model with parallel vertical plates, made by National Instrument Laboratories, had an intermediate dead space (85 ml), and also maintained its calibration. One of the factors affecting calibration is the deposit of moisture on the resistance element. In the case of the parallel plate device, moisture is encouraged to drain off the plates by gravitation. Since the gravitational factor will not apply in the weightless state, it may be necessary to prevent the moisture from forming. This has already been approached in the design of screen mesh flowmeters in which an electric current is applied to the screen to increase the temperature (Silverman and Whittenberger, 1950)⁹⁸.

Another form of pneumotachograph measures gas flow in terms of loss of heat from a thermally sensitive resistive device. Heated thermistors are incorporated in a bridge circuit. Heat loss during passage of a gas is determined by the geometry of the device and its components, the number of gas molecules contacting the element, their specific heat, and the temperature differential. The output can be calibrated in terms of volume flow, approximately proportional to the absolute pressure of the gas. The calibration, however, differs for different types of gas, oxygen, nitrogen, water vapor and carbon dioxide. For expired gas measures the calibration has to be based upon expected average concentrations of the different gases. The response time, however, is short, with a time constant of 0.1 seconds, and the overall accuracy is reputed to be within $\pm 2\%$. Devices of this nature

are made by Technology, Inc., Dayton, Ohio, and by Spacelabs, Inc., Van Nuys, California.

The pneumotachograph, of course, provides a measure of flow. Planimetry of the flow curve, however, gives a measure of volume, or alternatively, application of integrating electronic circuitry can provide a direct readout of volume on the flow trace. The latter is currently being done with success in Luft's laboratory at the Lovelace Foundation, and several integrating systems are commercially available (Electronics for Medicine, Sanborn).

The Flow-volume Loop

As a further modification, flow information from the pneumotachograph can be combined with volume information from a spirometer (or integrating pneumotachograph) to form a flow volume (VF) loop, as originally employed by Hyatt and his associates (1958)⁵⁰. The loop is obtained by imposing the volume signal and the flow signal on to the X and Y axes respectively, of an oscilloscope, or fast response X-Y recorder. A record is made of the loop during a forced maximum inspiratory and forced maximum expiratory maneuver. A resting tidal loop is subsequently registered on the same record, and lung volumes and capacities measured as shown in figure 2. A calibration device is incorporated into the oscilloscope or X-Y plotter to indicate the deflection occurring for flows of 1 liter per second and volumes of 1 liter. Bartlett (1961)⁷ utilized this technique to investigate the possibilities of pulmonary function evaluation in space flight. He obtained his volume signals from a Wedge spirometer, or servo-spirometer during his ground studies, but pointed out that for space flight conditions the integrated signal of a pneumotachograph would provide a suitable input.

Other applications of the flow volume loop will be discussed in connection with measures to evaluate the mechanics of breathing.

Residual Volume, Functional Residual Capacity and Total Lung Capacity

For measurement of most lung volumes and subsequent calculation of most lung capacities, simple spirometry or flowmeter techniques suffice. For measurement of the residual volume, however, on which calculation of functional

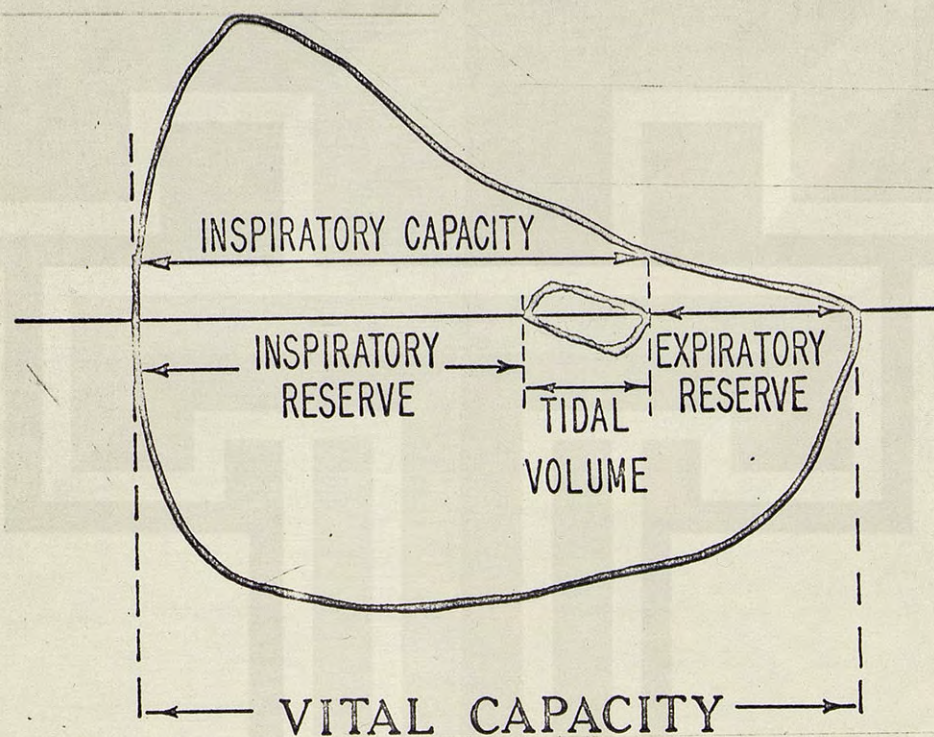


Figure 2. Resting V-V loop superinposed on maximum loop showing use of the loops for obtaining volume values for subdivisions of lung air.

Source: Bartlett et al. (1962)⁸.

residual capacity and total lung capacity depends, a more elaborate approach is required. In fact, under the conditions of an orbiting space laboratory it may not be practicable to make more than an estimate. It might be noted, however, that the postural changes which have been observed in these lung volumes are at least to some extent gravity dependent, and hence changes could be expected in the weightless state.

Two of the most common standard methods of measurement involve either equilibration of a known gas between the lung and an exterior connected circuit, or use of a whole-body plethysmograph. The equilibration systems use either an open-circuit technique or a closed circuit technique.

Open Circuit Technique. (Darling et al. 1940)^{25, 26}

The open circuit technique is based on determining the amount of N_2 in the air-containing lungs at a pre-determined resting level of respiration, and subsequently calculating the volume of air represented by the N_2 , knowing that air comprises 80% N_2 . In an artificial atmosphere of different composition than air, the appropriate nitrogen fraction would be employed. Allowances are made for N_2 concurrently excreted by the body tissues, and for impurities in the oxygen inspired. The technique is achieved by having the patient inspire "pure" oxygen and expire into a large nitrogen-free spirometer. In young healthy subjects the alveolar N_2 is washed out to 1% in about four minutes, but where air trapping or poor ventilation exists the wash-out process may take longer. Seven minutes is generally considered a suitable period, although continuous monitoring will indicate when equilibrium has been reached.

The volume of expired gas in the spirometer is measured, along with its nitrogen concentration. If the volume collected and measured began at the moment of complete expiration, the resulting calculation gives a measure of the residual volume. If it began at full inspiration, the total lung capacity is measured, and if it began at the resting respiratory level, the functional residual capacity is measured.

With respect to feasibility of the technique for space use, nitrogen concentration can readily be measured by a nitrogen meter. Assuming the availability of both oxygen and nitrogen, the major limitation of this method in orbiting

conditions lies in the requirement for a large spirometer (commonly a Tissot type) or gas collecting device of perhaps 50-100 liters capacity, plus the complex plumbing. It is possible that gas could be collected in polythene bags and subsequently measured by a gas meter, but the bulk and weight of a gas meter are prohibitive. As an alternative, volume could be measured by expiration through an integrating pneumotachograph.

Closed Circuit Techniques

Oxygen-Nitrogen: In the early closed circuit technique developed by Christie (1932)¹⁶ the subject rebreathed into a closed circuit which included a spirometer containing oxygen. On attaining equilibrium (or, in about 7 minutes) the nitrogen concentration in the spirometer was measured and the functional residual capacity calculated, allowing for tissue nitrogen eliminated, and impurities in the oxygen. The methods, however, led to errors arising from a) changing composition of the inspired gas mixture, b) difficulties in calculation of O_2 consumption from the spirometer, and c) magnification of errors due to small net change in nitrogen concentration (Cournand et al., 1940)²³. Modification led to filling the whole circuit with oxygen and utilizing a blower to ensure mixing (cited in Fowler, 1950)³⁵. The resulting equipment is bulky and complex. Bearing in mind, however, that the errors in the original Christie technique, are more marked in subjects with respiratory disease and that the astronauts are fit, healthy young men, it might be feasible to utilize the original Christie technique with a Wedge spirometer, a nitrogen meter, and a polarographic or other type oxygen sensor which could be available for other purposes, assuming an oxygen-nitrogen atmosphere. The resulting measure would not be as accurate as might be achieved by other means but it would provide a useful comparative reading. In a helium-oxygen atmosphere, the same technique could be used, monitoring helium instead of nitrogen.

Helium Method: To overcome some of the difficulties associated with the Christie technique, McMichael (1939)⁷⁸, in addition to maintaining constant spirometer volume by adding oxygen and using a pump to ensure mixing, used first hydrogen and then helium as an indicator gas. In an oxygen-nitrogen atmosphere, the concentration of helium in the lungs is normally zero. If a

known volume of helium (e.g., 10%) is added to a closed circuit of known external volume and equilibration of the helium achieved between the lungs and the external circuit, the resulting concentration of helium in the spirometer, or bellows, of the circuit is the same as in the lung. From the bellows volume and helium concentration, the functional residual capacity can be calculated. Helium concentration can be continuously monitored by thermal conductivity methods or by a mass spectrometer.

From the point of view of use in space, the equipment again is bulky and complex. In addition, in an oxygen-nitrogen atmosphere a source of helium would be required, while in an oxygen-helium atmosphere the technique would not be applicable.

Plethysmographic Method: The whole-body plethysmograph was developed as a valuable technique by Dubois and his colleagues (1956)³⁰ at the University of Pennsylvania. The principle is based on an application of Boyle's law, by which pressure changes are related to volume changes, provided the temperature remains constant. In practice, the subject sits within a 600 liter airtight box, breathing ambient air through a mouthpiece. To ensure constant temperature conditions, the box is vented periodically to the room outside by means of a solenoid-operated valve until equilibrium is attained. At a given time in the respiratory cycle (e.g., end-expiration), the mouthpiece is occluded by an electrically operated shutter. The subject is instructed to pant against this obstruction. At end-expiration the alveolar pressure is equal to atmospheric pressure because there is no gas flow. After occlusion, the thorax enlarges with inspiration, decompressing the thoracic gas and creating a new volume and a new alveolar pressure. This new pressure is sensed by a gauge at the mouth behind the occluding shutter, mouth pressure being considered equal to alveolar pressure under conditions of no flow with the glottis open. Enlargement of the thorax compresses the air around the patient; the pressure change was originally recorded by a sensitive capacitance gauge in the plethysmograph. An unbonded strain gauge is now commonly used. The signal from the mouth pressure is recorded on the vertical axis of an oscillograph and thoracic volume change on the horizontal axis. Panting permits registration of a representative trace from which a slope can be measured:

By Boyle's Law: $PV = (P + \Delta P)(V + \Delta V)$

Knowing P (atmospheric pressure less water vapor pressure), $\Delta P / \Delta V$ (slope of the trace) and disregarding the absolute magnitude of ΔP which is very small compared to P , the equation can be solved for V , the thoracic gas volume, taking into account calibration factors of the plethysmograph. To account for adiabatic compression of gas in the box during panting, a volume of air equivalent to the panting volume is cycled in and out of the box at the panting rate.

With this system, fast and accurate measurements can be made of thoracic gas volumes, which include those volumes not in free communication with the airway. Consequently, this system also measures the volume of trapped gas and "slow space" gas not normally measured by open or closed circuit techniques.

While it is obviously a method of choice for ground laboratory measurement its application to space laboratories seems unlikely at this time. Its usefulness for other measures, however, such as airway resistance, pulmonary non-elastic tissue resistance, and pulmonary capillary blood flow, suggest that some consideration should be given to the system.

It is understood that Vorwald of Wayne State is developing a form of "electric field" whole-body plethysmograph, in which the subject, inside a Faraday cage, is exposed to a continuous electrostatic field. Movement of the chest in respiration causes perturbations of the field which can be sensed, amplified, and recorded. The technique, when developed, shows promise for space use.

Electrical Impedance Plethysmography

The human thorax can be regarded as an electrical volume conductor. As discussed in connection with Cardiac Output, the resistivity (ρ) of a homogeneous conducting material, expressed in ohm-centimeters, is related to its resistance (R) by the following equation:

$$(1) \quad R = \rho L / A$$

where L = length in cm., and A the cross-sectional area in cm^2 . For a cylindrical conductor the equation, as previously noted, can be written as:

(2)

$$V = \rho L^2 / R$$

where V = volume.

In segmental plethysmography, in which the volume changes are attributable to changes in blood flow, the specific resistivity of the blood, namely 150 ohm-centimeters, can be substituted for ρ . In dealing with lung volumes, however, this factor cannot be applied, since change in volume is not related primarily to blood flow. Allison and his associates (1964)¹ have shown theoretically, and by empirical experiment, that the resistivity of the thorax as an electrical volume conductor can be represented by the product of the base resistance and the length between the electrodes determining that base resistance. In other words, the thorax as an electrical volume conductor could be represented as a homogenous cube with a side of a given length. The specific resistivity of such a cube can be measured as the product of the resistance along one side and the length of that side, provided that with enlargement of the cube the ratio of the length to the cross-sectional area remains unitary. Thus, with a fixed length of side, the specific resistivity of a cube is represented by the resistance along that side, and changes in resistance bear a linear relationship to changes in electrical conducting volume, provided that the length between the detecting electrodes remains constant.

(3)

$$\text{Thus: } \frac{\Delta R}{R_o} = \frac{\Delta V}{V_o}$$

where R_o and V_o represent the base resistance and initial electrical volume. The initial electrical volume for a given base resistance is represented by a cube of side equal to the distance between the detecting electrodes.

Comparison with spirometer readings showed in their studies that with the upper detecting electrodes across the shoulders, and the lower at the level of the 12th rib dorsally, and a distance of 30 cm between them, representing a volume of 27,000 ml, measurable changes in resistance could be interpreted as changes in volume. Thus, for example, if the initial resistance were measured at 10 ohms between the detecting electrodes, a change in resistance of 1 ohm with a breathing maneuver would represent a change in vol-

ume of 2700 ml. Similarly a change in resistance of 1.8% was equivalent to an average tidal of volume of 500 ml.

Using this principle, Allison et al. (1964)¹ found an error, in comparison with spirometer readings, of 7% or less. At high inspiratory, and forced expiratory volumes, there was less accurate agreement between impedance changes and spirometer volumes. The spirometer values were higher than the impedance changes, perhaps because of changes in cross-sectional area are no longer unitary with respect to the fixed length.

As previously noted in the discussion on cardiac output, electrical impedance systems are sensitive to subject movement, and, particularly where quantitative measures are being made, require the subject to be at rest. Caranna and his associates (1964)¹⁴ at MacDonnell Aircraft, St. Louis, however, have reported a 2-electrode system with which they can measure tidal volume and lung capacities with minimal distortion regardless of body position, and even during bicycle ergometer exercise. Their tracings, however, do not reflect the changes associated with cardiac action reported by Allison, and by Kubicek's group (See Cardiac Output). Their system requires initial calibration of the subject's trace with a spirometer. It would seem advisable that if an electrical impedance system is going to be used on the chest that it should be sufficiently flexible for both respiratory and cardiac measurements.

The impedance system can provide usefully accurate measures for the determination of tidal volume, vital capacity, inspiratory reserve volume, and expiratory reserve volume. Allison (1966, personal communication) is currently completing work on use of the technique for the determination of functional residual capacity. By pre-calibration on the ground, it may be possible to obtain an index referable to functional residual capacity which could be applied to impedance measures made in orbit.

Other Methods

Various techniques have been developed for the measurement of respiration rate, and chest motions associated with respiration. These, in the main, have employed devices such as thermistors or thermocouples

at the mouth to record changes in temperature with respiration, strain gauges attached to straps around the chest, or Whitney-type mercury-tube transducers fixed round the chest. Rates from these devices can be electronically processed, integrated, and calibrated in terms of volume to provide a reading of tidal volume, but the accuracy of the result is open to question.

Some interesting modifications of these techniques have been reported. Krobath and Reed (1964)⁵⁴ report a device consisting of an elastic rubber cone mask which fits over the nose and mouth and contains a transducer assembly. In the circular opening of the mask are placed three aluminized mylar leaves which move with respiration. A radio frequency signal of 25vRMS at 200 kc is applied to the leaves. Receiving plates are mounted in front of and behind the leaves. Deflection of the leaves modulates the signal received. The resulting signal is processed to register volume of air flow. In addition, the fluctuating air temperature is also recorded and calibrated in terms of air flow, while change in water vapor content is recorded by a system based upon the electrical conductivity of sodium chloride crystals, which depends upon their moisture content. The dead space of the assembly is only 25 ml. It is not known how well the device performs in comparison with other systems.

Another device, reported by Montoya and Henke (1964)⁷⁴ from the Martin Company in Denver, takes cognizance of the fact the restrictive bands around the chest may alter the pattern of breathing. To overcome this artifact they developed a system which utilizes two strain gauges, one mounted on each of two flexible plastic tubes and held in place against the chest by a snugly fitted elastic chest band. One tube is mounted vertically over a pectoral muscle and one over a corresponding scapula. Movement of the chest deforms the elastic tubes and is recorded by the strain gauges. Methods of measurement involving chest movement are satisfactory for respiratory rate registration, but when used for the estimation of volumes they fail to take into account the contribution of diaphragmatic movement and abdominal breathing.

Recommendations

For the measurement of lung volumes and capacities in orbital conditions there would seem to be three major approaches. The technique combining the greatest simplicity, scope, and reliability would appear to be the use of the integrating pneumotachograph with display on an oscilloscope or X-Y plotter. Considerable validation of the method, however, is still required on the ground, and even more so under weightless conditions. In the latter case in particular, experimentation is desirable to develop a method to reduce possible interference occurring from the accumulation of water vapor. Should actual spirometry be required, and it is difficult to see any advantage of spirometry in routine use, a bellows-type Wedge spirometer with X-Y display would seem to be suitable. It is probable that the size of the existing equipment can be reduced still further without great loss in reliability. Electrical impedance pneumography also deserves consideration, particularly as a back-up, for example, for the pneumotachograph, and for prolonged intermittent or continuous traces. The essential simplicity of the instrumentation and minimal subject violation assist in outweighing the disadvantages that might accrue from motion sensitivity.

The whole-body plethysmograph, however, cannot be summarily dismissed, simply because of its bulk. There is little doubt that this device provides the most accurate, reliable, and comprehensive measurement system for lung volumes and capacities and for other aspects of respiratory investigation. While its use for routine respiratory measurement in a space laboratory could not be reasonably justified, a portion of a spacecraft could be modified for such use in a special purpose mission if the need became manifest. In a large manned orbiting laboratory it would seem possible, for example, that an airlock could be modified for this purpose.

The problem of measurement of residual volume and functional residual capacity remains difficult, largely because of the bulk and plumbing complexity of the necessary apparatus. In an oxygen-nitrogen atmosphere, perhaps the most feasible, if not the most accurate, method would be a closed circuit method using a Wedge spirometer or integrating pneumotachograph, and analyzers

for oxygen and nitrogen. In an oxygen-helium atmosphere, the helium could be similarly analyzed. Closed circuit methods employing helium or hydrogen as indicators in an oxygen-nitrogen atmosphere do not lend themselves to space cabin use because of the requirement for a source of helium. There is a possibility, however, as noted earlier, that an index of functional residual capacity, or residual volume, may be obtained by the technique of electrical impedance plethysmography, although further validation is required before final recommendation can be made.

MECHANICS AND DYNAMICS OF BREATHING

Measurements of lung volume, although valuable for baseline information, provide minimal information on the mechanics and dynamics of breathing. In the weightless state, and particularly in the presence of artificial atmospheres and perhaps even contaminated atmospheres, changes might be expected, and it would seem advisable to undertake measures indicating the nature and trend of any change. Measurements involve overall assessments of mechanical function, pressure, and volume, to determine the compliance, and airway and tissue resistances. Some of the techniques can be applied with little problem. Some are demanding in equipment and subject cooperation.

Flow-volume Relationships

The measurement of dynamic lung volumes provides an overall assessment of the efficiency of the mechanical function of the pulmonary system and involves the relationship between air flow and changing lung volume.

Hyatt (1965)⁵¹ in his review, notes that essentially two types of measures are made, although numerous names and techniques have been applied to subdivisions of the measures. One measure involves aspects of the forced vital capacity (FVC) maneuver, and the other arises from the maximum breathing capacity (MBC) test.

In the FVC maneuver the subject exhales as rapidly and completely as possible after a maximum inspiration. It has been shown (Fry and Hyatt, 1960³⁹; Hyatt, Schilder, and Fry, 1958⁵⁰) that at lung levels near total lung capacity there is no physiologically defined limit to respiratory flow and consequently maximal flow is related to maximal effort. At volumes below two-thirds of vital capacity, however, maximal flow values decrease with the level of lung inflation, and increased effort actually reduces flow slightly, because of increased constriction of the conducting airways from the increased transpulmonary pressure. There are no fixed maxima on inspiratory flow, and it again would appear to be effort dependent.

From these findings it may be inferred that firstly, maximal expiratory flows are a function of lung inflation, and consequently that volumes at which flows are measured must be specified; secondly, flow-volume relations over the lower two-thirds of vital capacity are not prone to subjective variability and hence are readily reproducible.

These considerations have led, both empirically and on theoretical analysis, to various methods of quantifying the FVC maneuver, as illustrated in Table 1, which is modified by Hyatt (1965)⁵¹ from the work of Gandevia and Hugh-Jones (1957)⁴⁴. Traditionally the FVC maneuver is performed by having the subject breath into a fast-recording spirometer, which produces a volume-time trace of the forced expiration, from which various timed volumes and flow rates can be extracted. The disadvantages of spirometers for use in space conditions have already been discussed. The same maneuver, however, can be recorded with an integrating pneumotachograph. Hyatt (1965)⁵¹ points out that the flow versus volume plot provides even more useful information than the flow versus time, and observes that, if necessary, the former can readily be converted into the latter by numerical and graphic manipulation, or by electronic means. The integrating pneumotachograph, which is primarily a flow meter, provides the necessary information for the plot when the volume signal is placed on the X-axis of an oscilloscope or X-Y plotter, and the flow signal on the Y-axis. The resulting trace is illustrated in figure 3 (Hyatt, 1965)⁵¹. This figure also indicates the method of deriving a volume-time trace from a volume-flow trace by taking small increments of volume (e.g., 0.2 liters), determining a flow rate for each increment, calculating the time, and transferring it to the time-plot. The figure further illustrates the positioning of different measures on the trace, as will be discussed.

The measures listed in Table 1 which can be derived from this trace include timed volumes, mean maximal flow rates; maximal flow rates at a given point in expiration, and peak flow rates. The absolute volume of the forced vital capacity has also been used as a measure.

Table 1. Proposed Nomenclature

	Description	Recommended Term	Abbreviation	Some Previous Terms
1	Maximal volume measured on expiration after the deepest inspiration	Vital capacity	VC	
2	Maximal volume measured on inspiration after a full expiration	Inspiratory vital capacity	IVC	
3	Spirogram of a forced, complete inspiration or expiration	Forced inspiratory/expiratory spirogram	FIS/FES	Fast inspiratory/expiratory vital spirogram; expirogram
4	Volume of gas exhaled over a given time interval during a complete forced expiration	Forced expiratory volume, qualified by time interval used in sec	FEV _T	Timed vital capacity; fast expiratory capacity; forced expiratory volume; capacity usable on effort (Fr. CPUE); maximum expiratory volume (Fr. VEMS)
5	Volume of gas expired after full inspiration, expiration being as rapid and complete as possible (i.e., forced)	Forced vital capacity	FVC	Timed vital capacity; fast vital capacity; fast maximum expiratory capacity; forced expiratory vital capacity
6	FEV _T expressed as % of VC or FVC*	Percentage expired qualified by time interval used in sec	FEV _T %	Timed vital capacity; timed expiratory capacity; optimal frequency (Fr.)
7	Peak expiratory flow (liters/min or liters/sec) measured by various instruments	Peak expiratory flow qualified by name of instrument used	PEF	
8	Volume of air exhaled over a specified volume range of the FES divided by the time to exhale this volume, expressed as liters/min or liters/sec	Mean maximal expiratory flow qualified by volume range in liters or as % of the FES		
9	Examples: A. Volume between 0.2 and 1.2 liters of the FES/time B. Volume between 25 and 75% of the FES/time C. Volume between 50 and 75% of the FES/time	Mean maximal expiratory flow, .2-1.2 liters	MMEF _{.2-1.2L}	Maximal expiratory flow rate (MEFR) (15)
		Mean maximal expiratory flow, 25-75% of FES	MMEF _{25-75%}	Maximal midexpiratory flow (MMF) (61)
		Mean maximal expiratory flow, 50-75% of FES	MMEF _{50-75%}	Expiratory rate during third quarter of a maximal forced expiration (E ₅₀₋₇₅) (35)
9	Maximal expiratory flow at a specific volume during a complete forced expiration, expressed in liters/min or liters/sec†	Maximal expiratory flow qualified by the volume at which measured, expressed as % of the FVC exhaled		
	Examples: A. Flow at point when 25% of FVC exhaled	Maximal expiratory flow, 25% of FVC	MEF _{25%}	
	B. Flow at point when 50% of FVC exhaled	Maximal expiratory flow, 50% of FVC	MEF _{50%}	
	C. Flow at point when 75% of FVC exhaled	Maximal expiratory flow, 75% of FVC	MEF _{75%}	

* The method of measuring the vital capacity should be indicated by use of VC or FVC in the denominator. Thus, $FEV_{1\%} = \frac{FEV_1}{VC} \% \text{ or } \frac{FEV_1}{FVC} \%$.

† Such values can be read directly from a flow-versus-volume plot of an FVC maneuver.

Note: Should one want to quantify a forced, complete inspiration, this could be designated by substituting "I" for "E" in items 4, 6, 8 and 9. Item 5 in this case would be designated forced inspiratory vital capacity or FIVC.

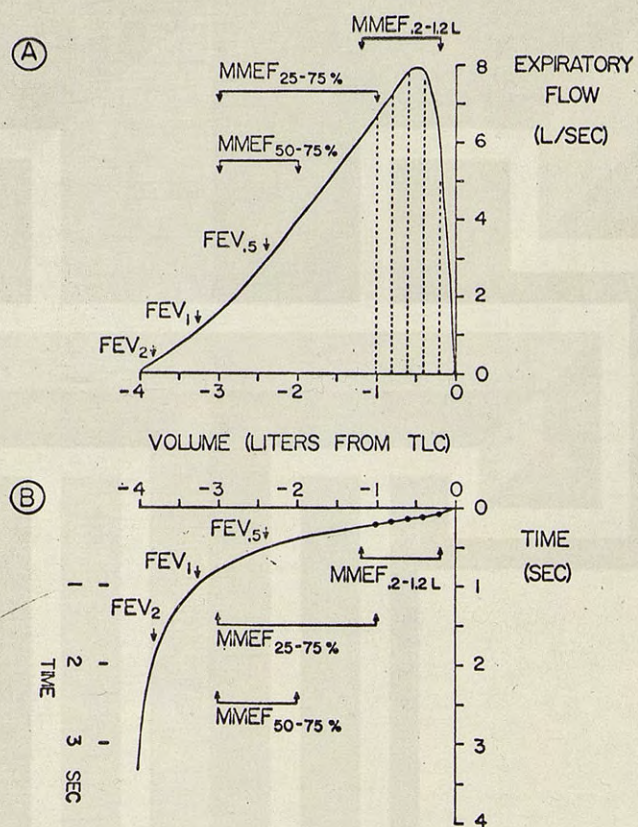


Figure 3. A: FV plot of an FVC maneuver from a normal subject.
B: the derived volume-time trace of the same breath.

Source: Hyatt (1965)⁵¹.

Timed Volumes

Timed volumes refer to the volumes of gas expired during various increments of time. Essentially, timed volumes obtained from a spirometer are a substitute for flow measures. Utilizing the slope of the spirometry curve over a given time or volume range, an average flow for that range can be obtained. Various times have been used, from 0.43 to 3.2 seconds, although common durations are 0.5, 1, and 2 seconds. These points are noted in figure 3. Since volumes measured from the start of expiration include considerable variation in flow, from zero to peak, and since, as noted above, the first third of expiration is effort dependent, it is probably better to select a starting point after the beginning of expiration, and measure a given volume therefrom. Selection for this purpose has included the range from 0.2 to 1.2 liters, but perhaps it would be still better to measure over the range from 25% to 75% of the volume, or even 50% to 75%, where the flow is more readily reproducible. Timed volumes are most easily obtained from a volume-time trace, but can be derived from the pneumotachograph volume-flow trace either manually or after electronic processing. Special automatic spirometers are available for timed volume measures, such as those used by Gaensler (1951)⁴², Wright and Gilford (1959)¹¹², and others. It is also possible to exhale through a wide-bore valve into a collecting bag and time the exhalation with a stopwatch. The special purpose spirometers, however, are unsuitable for space use, and the bag collection method is obviously open to great error and provides no continuous record.

To reduce variations associated with age, size, and sex, the results of timed forced expiratory volumes may be expressed as a per cent of the vital capacity or forced vital capacity, although in interpretation it must be borne in mind that both the numerator and denominator can be proportionately reduced and present an apparently normal index.

Maximal Flow Rates

Maximal flow rates, which may refer either to mean maximal flows over a range of volume, or to maximal flow rates at a given level of volume, can be read directly off the volume-flow trace. Some ranges are illustrated in

figure 3. Common ranges for measurement of a mean are from 0.2 to 1.2 liters, or perhaps preferably from 25% to 75%, or 50% to 75%, of the expiratory volume. Suggested points of measurement for maximal flow are at the 25%, 50%, and 75% levels of expiratory volume. Hyatt (1965)⁵¹ quotes a personal observation of Lloyd and Wright, who found in a small group of normals that measurement of maximal expiratory flow at a volume of 1 liter above residual volume was not so useful as that taken at 50% of expiratory volume, and suggests accordingly that maximal expiratory flow measurements near mid-vital capacity may be superior to those made at very low volume.

Peak Flow Rate

Peak flow rate can also be measured from the volume-flow trace. Peak flow rate, however, is inherently dependent on the subject's effort, and on the level of the initial lung volume. Consequently, measures must be made after a maximal inspiration. Several instruments have been devised for use in peak flow measurements as a screening test. Notable among these are the Wright flow meter and the Puffmeter.

The Wright flow meter (Wright and McKesson, 1959)¹¹³ has received wide acceptance as a screening device. Air entering the meter displaces a rotary vane against a spiral spring which progressively uncovers an orifice according to the extent of displacement of the vane. The deflection of the vane, modified by the tension of the spring, is proportional to the air flow. An exterior pointer attached to the vane registers the flow rate on a dial. The instrument can be held in the hand and weighs about 2 lbs. After full inspiration, measures are made by exhaling forcibly into the device. Comparisons with peak flows measured by a pneumotachograph have showed good agreement (Wright and McKesson, 1959)¹¹³. Lloyd and Wright (1965)⁶⁴ also undertook an evaluation of this meter but found it overestimated by about 10% between flows of 200 to 500 liters per minute as compared with a pneumotachograph. There is little doubt that it is a valuable instrument for screening purposes, but its use in space would seem unnecessary if other apparatus such as an integrating pneumotachograph were available.

The same consideration would apply to the Puffmeter (Goldsmith, 1958)⁴⁶

The Puffmeter is a form of rugged, portable pneumotachograph in which the resistance is made from a porous, vitrified, cup-shaped, grinding wheel. An attached pressure gauge is calibrated in terms of air flow rate. Goldsmith found a high correlation (0.992) between values found with the Puffmeter and with a standard screen pneumotachograph. The instrument has been extensively used in screening tests in detection of persons with pulmonary air flow obstruction.

Maximum Breathing Capacity

The maximum breathing capacity (MBC) is the maximum volume of gas that can be breathed in a given time (usually standardized per minute). The maximum voluntary ventilation (MVV) is the maximum volume that can be breathed by voluntary effort. In the normal healthy cooperative subject the two should be identical. The MBC is commonly recorded on a spirometer for 10-30 seconds, but special high frequency response, fast recording spirometers are necessary for accurate results (Bernstein and Mendel, 1951¹³, Wells et al., 1959¹⁰⁶, and others) and are unsuitable for space use.

The test can also be undertaken by breathing through a low resistance valve (e.g., a Rudolph valve) into a Douglas bag, or similar collecting device, and subsequently measuring the gas delivered in a given time. The disadvantage of Douglas bag collections has been discussed.

Useful measures, however, can be made from the flow-volume loop. Bartlett and his colleagues (1963)⁹ observed that when an MVV loop is superimposed on a flow-volume loop it follows the maximum envelope during the major portion of a breath half-cycle until it breaks away abruptly, transects the zero velocity abscissa, and rejoins the maximum envelope for another half-cycle. Because of this relationship, they simulated an MVV loop by erecting perpendiculars at each end of several assumed tidal volumes, and calculated the time for moving each assumed tidal volume on the basis that the time equals the square of the volume divided by the area. Optimum placement of the tidal volume is found by determining from a family of curves derived from the flow-volume plot the optimum limit of inspiration for a given

breathing frequency. The predicted MVV by this method compares favorably with the predicted MVV obtained by spirometer. Bartlett suggests that the predicted MVV might well be used as an index instead of the measured MVV.

Still another technique for measuring the MBC was devised by Warring and Siemsen (1957)¹⁰⁴ using an instrument, the Ventube, based on the Venturi principle. The Ventube is a cylinder with an internal diameter which becomes progressively smaller from each end towards the middle. A single side-arm at the throat is connected to a balloon filled with a known volume of air. On rapid breathing through the tube, air is aspirated from the balloon in quantity proportional to the volume of air passing through the tube. In practice the balloon is filled with about 500 cc of air by way of a 100 cc syringe, the tubing clamped, and then fitted to the Ventube side-arm. The clamp is opened and an MBC maneuver carried out for 15 seconds. The tube is again clamped and the volume of air remaining in the balloon is measured in a standard manner by the 100 cc syringe. The volume of aspirated air is calculated, and the breathing volume which it represents is obtained from conversion tables. Good agreement has been found between results obtained by this method and by other methods, such as the use of a Douglas bag and Rudolph or Collins valve, or by spirometer.

Although it is obviously a valuable and simple technique, again it is doubtful if the additional equipment is desirable in a space laboratory.

Volume Displacement Plethysmography

Volume displacement plethysmography has been used for the evaluation of flow volume relationships (Mead 1960)⁶⁹. The volume displacement plethysmograph, in contrast with the pressure-sensing plethysmograph, is used to measure volume change in breathing by way of an attached exterior Krogh spirometer which follows the motion of the chest cage. Flows can be obtained by electronic differentiation of the volume signal or from a pneumotachograph in the breathing circuit. The bulk and complexity of the apparatus, however, make it an unnecessary luxury for space laboratory conditions.

Pressure-volume Relationships

The muscular force of inspiration is required to overcome the elastic recoil of the lungs and thorax, the frictional resistance that arises during tissue movement of the lung and thorax, and the frictional resistance of the conducting airways. The elasticity of tissues of the lungs and thorax is demonstrable in terms of the relationship between pressure and volume, measured under static conditions in the form of compliance. Compliance is the change in volume per unit change in pressure (L/cmH₂O). By Hooke's Law, the relation between volume and pressure, or stretch and force, is dependent on the change in volume or distance. The slope of the line of relationship between the two is a measure of the compliance.

Measurement of pulmonary compliance ideally requires a measure of the transpulmonary pressure, *i. e.*, the pressure differential between the intrapleural space and the mouth. Under most circumstances this is an impracticable measurement, and intraesophageal pressure is used instead.

Various methods of obtaining esophageal pressure measurements have been discussed by Mead et al., (1955)⁷⁰, all based upon the passage of a small-bore rubber catheter through the nose into the esophagus. Sealed to the esophageal end of the catheter is a thin walled rubber balloon. The system is filled with air, and the reflected pressure changes within the balloon are observed by an inductance type manometer. Another modification utilizes an open-ended catheter. In this case, the catheter and the recording system are filled with water and the pressure changes recorded by a capacitance manometer. It is necessary for the system to be responsive to frequency components up to about 10 cps.

Different sizes of balloon have been used, varying from about 3 cm long by 1 cm in diameter (Mead and Whittenberger, 1953)⁷² to 18 cm long by 1 cm in diameter (Fry et al., 1952)⁴¹. Mead et al., (1953)⁷² showed that, overall, the long-balloon possessed advantages over the short-balloon, and over water-filled catheters. In any event, a water filled system would be unsuitable for space use.

Still another system utilizes a miniature pressure transducer mounted

directly on the tip of the catheter, as has been suggested by Gauer and Gienapp (1950)⁴⁵ and used by Lim and Luft (1959)⁶³. Concurrent volume measurements can be made from a spirometer or an integrating pneumotachometer.

Although pulmonary compliance is a static measure representing the elastic recoil of the lungs, in practice it is measured in either static or dynamic conditions. In the normal subject static and dynamic compliance should be nearly identical. In the static measurement the subject inspires a measured volume and holds his breath with the glottis open for a pressure measurement, repeating the procedure for several different volumes. A pressure volume curve is constructed from the measures, with the average compliance of the lungs being read as the slope of the curve. The slope is usually constant over the range used, although not so at extremes of the vital capacity.

Compliance measurements can also be made by the use of an interrupter technique (Fry et al. 1954)³⁸ whereby an electronically operated shutter interrupts the air flow at various lung volumes during respiration. At the moment of no flow, the transpulmonary pressure rapidly reaches a steady state, which is recorded on the manometer in relation to the lung volume at that time.

An alternative method of making dynamic measures was propounded by Neergard and Wirz, (1927)⁸⁰, and is based on the fact that at the moment between the beginning of expiration and end of inspiration there is no flow, and consequently, no pressure against flow resistance. Thus, transpulmonary pressure at that time represents pressure against the elastic recoil of the lungs.

With suitable techniques of obtaining continuous pressure and volume, compliance is most readily measured from a pressure-volume trace on an oscilloscope or X-Y plotter as the slope of the line joining the points of zero air flow.

In clinical conditions where the linearity of the relationship may be modified by the non-elastic resistance of the airflow the effect of the latter

can be removed electronically from the pressure signal by "bucking" the pressure signal with an electric signal proportional to airflow (Marshall, 1965)⁶⁷.

Interpretation of compliance values must take into account the lung volumes at which the compliance is measured. It is common to relate it to the FRC. Compliance measures show a postural change along with the FRC. Both compliance and FRC are reduced in changing from the erect to the supine position. The relationship between them, however, remains unaltered (Lim and Luft, 1959)⁶³. The FRC in turn is dependent on the size of the lung and on the balance between the retraction of the lung and the expansion of the chest wall. Marshall and Widdicombe (1961)⁶⁸ point out that compliance measurements made during normal tidal volume, but at lung volumes considerably above or below FRC, may give low values because of the effects of stress relaxation. They consequently recommend that measures be made on breaths inspired from the FRC.

It is apparent that under space laboratory conditions the major limiting feature in compliance measurement lies in the subject violation imposed by the requirement to swallow an esophageal catheter inserted through the nose. While the procedure is neither hazardous, nor even unduly uncomfortable, it does seem formidable to the inexperienced subject. There is, however, no less complex way by which a measure can be obtained representative of transpulmonary pressure. Consequently, if it is considered necessary to make compliance measures, (and because of the changes that can be expected with weightlessness it would seem advisable), experienced subjects and investigators will be necessary. Experience, of course, will be gained through the necessity of establishing pre-flight baseline values.

It would seem that the technique combining the least bulk and complexity with the greatest reliability would involve the continuous recording of respiration volume by way of an integrating pneumotachograph, and concurrent registration of intraesophageal pressure from a pressure transducer mounted on a catheter tip, and subsequent display of the respective values on an oscilloscope or X-Y plotter.

The compliance of individual lungs can be measured during broncho-

spirometry. The latter, however, would appear to be an unnecessary imposition for space laboratory conditions, unless under exceptional circumstances.

Compliance of Lung-thoracic Cage System

Measurements of compliance of the lung-thoracic cage system require a measurement of transthoracic pressure. The most satisfactory method to obtain a measure of this pressure is the use of a body respirator in an unconscious or paralyzed subject, a technique obviously not practicable in a manned space laboratory.

The relaxation method of Rahn et al. (1946)⁸⁹ has also been used. In this technique, after inspiration of a given volume of air, the subject closes his nose and mouth, opens his glottis, and relaxes his chest muscles. Trans-thoracic pressure is measured by a nasal tube in the nostril. Repetition at different volumes produces a relaxation pressure curve. Consistency in results is difficult to achieve, however, and a trained and experienced subject is required to complete the maneuver satisfactorily.

Pressure-flow Relationships

There are two components of non-elastic resistance, one related to airway resistance and the other to pulmonary and thoracic tissue, or viscous, resistance. Airway resistance is represented by the alveolar pressure divided by the flow rate at that pressure.

The relationship between pressure and flow can be expressed in quadratic form:

$$P = K_1 \dot{V} + K_2 \dot{V}^2$$

where K_1 and K_2 are constants representing an association with laminar flow and turbulent flow respectively. Thus, the relationship is non-linear, and although curves can be obtained describing the relationship at different flow rates, resistance measured at 0.5 liters per second is taken as being a representative measure of resistance during normal breathing (Marshall, (1965)⁶⁷).

For actual measurement under dynamic conditions, values relating to the flow rate at the mouth and the transairway pressure are required. The latter is the pressure difference between the alveoli and the mouth. The whole body pressure-sensitive plethysmograph, along with a heated pneumotachograph (Dubois et al. 1956)²⁹ provides the most direct measurement. The subject, inside the plethysmograph, breathes through a pneumotachograph and an interrupter valve. The flow meter is heated to prevent condensation of water vapor, and consequently breath volume is limited to the capacity of the flow meter system (about 300 ml). The subject therefore pants. Panting, however, serves to magnify volume displacements during variations of alveolar pressure, and minimize other interfering factors associated with changes of temperature, water vapor pressure, and varying exchange of CO_2 and O_2 in the lung.

On inspiration, alveolar pressure is reduced, thereby increasing alveolar volume. The change in volume is reflected as a change in pressure by the sensitive plethysmograph manometer. Changes in airflow are plotted simultaneously against plethysmographic pressure changes, which are proportional to alveolar pressure changes. Immediately subsequent, the interrupter is closed and a plot obtained of mouth pressure (alveolar pressure) and plethysmograph pressure. This provides a calibration of alveolar pressure in terms of plethysmograph pressure. Airway resistance can then be calculated from the respective alveolar pressures and flows.

Problems associated with whole-body plethysmography in orbital conditions have already been discussed. If such a device can be made available, however, it would provide an invaluable method of determining airway resistance measures. The volume displacement whole-body plethysmograph has also been used for the purpose (Jaeger and Otis, 1964)⁵².

In a review of the subject of non-elastic resistance, Marshall (1965)⁶⁷ discusses other means of obtaining measures, in the absence of a plethysmograph, using continuous pressure and flow tracings from a pneumotachograph with a pressure read-out. At a given rate of flow (e.g., 0.5 liters per second) the non-elastic resistance can be calculated by subtracting from the total pressure difference at that rate the component exerted against elastic

resistance. The latter can be obtained from a concomitant measure of compliance. Non - elastic resistance calculated in this manner includes elements of pulmonary and thoracic tissue resistance.

Still another method utilizes the information from pressure-volume traces, whereby two points of similar lung volume are selected, one on inspiration and the other on expiration, and the pressure differential occurring between these two points is obtained from a concurrent pressure trace. The flow rate at these two points is determined from the slope of the volume trace, and the non-elastic resistance is found by dividing the pressure differential by the sum of the flow rates at the two points.

Perhaps the most elegant system, using electronic processing of the signals, was developed by Mead and Whittenberger (1953)⁷². The flow signal from a pneumotachograph is placed on the Y-axis of an oscilloscope or X-Y plotter, and the intraesophageal pressure on the X-axis. Assuming that the pressure exerted against elastic resistance is proportional to the volume inspired, a signal proportional to the volume inspired is also applied to the X-axis in the opposite vector to that of the pressure signal. This volume signal is so adjusted as to close the pressure-flow loop and form a more or less straight line. With the loop closed, the pressure recorded at the beginning and end of inspiration (zero airflow) is the same. The slope of the line provides a measure of non-elastic resistance. The "quality" of the line is improved by panting, although under these circumstances the resistance is lowered.

Methods of measurement of non-elastic resistance utilizing a shutter to interrupt the airflow in a pneumotachometer were developed by Neergard and Wirz (1927)⁸¹ in conjunction with their compliance measures, on the principle that when airflow is stopped the pressure equalizes rapidly between the alveoli and the mouth proximal to the shutter. Although the pressure so measured at the mouth includes conversion of some of the kinetic energy of the lungs and chest wall into pressure, the resulting measure provides a good approximation of alveolar pressure. By making several measures during a respiratory cycle, the non-elastic resistance can be derived from the ratio of pressure to flow. This method, however, is not widely accepted.

Clements and Elam (1955)¹⁸ modified the method for continuous reading by devising a rotary airflow interrupter with a motor-driven chopper and pressure gauges. In an evaluation of the instrument, however, Lloyd and Wright (1963)⁶⁴ found considerable variation in results, both in consecutive measures, and in comparison with whole body plethysmography.

Pulmonary viscous resistance does not lend itself to independent measurement. A value, however, can be obtained by measuring total non-elastic resistance, e.g., as obtained from pressure and flow measures, and subtracting from that the airway resistance as obtained by the whole body plethysmograph.

For orbital space laboratory conditions, then, it would seem that the most reliable information on pressure-flow relationships, airway and pulmonary resistance would be forthcoming from a whole-body pressure sensitive plethysmograph. Valuable information, however, can be obtained from less bulky and cumbersome devices. If measures of intraesophageal pressure are going to be made for compliance studies it would be appropriate to combine the compliance measures with pressure and flow studies, using the subtraction method of Mead and Whittenberger (1953)⁷² previously discussed. If, however, measures of esophageal pressure are considered inadvisable (and there does not appear to be good reason to consider them as such with experienced persons) then good indications of non-elastic resistance can still be obtained from flow and volume curves, or by a repetitive interrupter method as described.

At the same time, consideration should again be given to the development of a suitable whole-body plethysmograph for use on special missions.

Work of Breathing

Work in the physical sense is the product of force and distance, or pressure and volume. Thus, $W = \int P dV$

In the respiratory system work is involved in overcoming elastic

resistance, airway resistance, and in moving the lungs and thoracic cage. Thus, the work involved in overcoming elastic recoil of the lungs, airway resistance, and non-elastic pulmonary resistance, can be calculated from a trace of transpulmonary pressure against volume, as the area bounded by the inspiratory curve and the ordinate, when volume is placed on the ordinate. The area bounded by the ordinate and the diagonal joining the points of beginning and end inspiration represents the work of overcoming elastic recoil; the remainder represents the additional work of moving non-elastic tissue and overcoming airway resistance.

The work of moving the thoracic cage does not lend itself to measurement in orbital space laboratory conditions. In respiratory paralysis, deep anesthesia, or neuromuscular block of the respiratory muscles, when ventilation is maintained by a body respirator, the work can be calculated from simultaneous measurements of transthoracic pressure, *i. e.*, the pressure differential between the mouth and the inside of the respirator with inspiration, and the volume of gas moved during inspiration.

The O_2 consumption during different levels of exercise also provides an index of work performed. The O_2 consumed, of course, includes both that required in doing external work and in increased respiratory work. This measure can be obtained in several ways using a waterless spirometer or Douglas bag, but in accordance with earlier discussion, the use of the integrating pneumotachograph would appear the most satisfactory. In this situation, one flow meter would be required to measure the volume of inspired gas over a given period of exercise while another, through appropriate valving, would measure the expired gas. The volume of inspired O_2 would be calculated from the partial pressure of O_2 in the inspired air. The O_2 concentration in the expired air would be derived from the output of a rapid response O_2 sensor. The difference between the inspired and expired O_2 , of course represents the O_2 consumption. Kissen and McGuire (1966)⁵³ have recently presented instrumentation to achieve this end.

Spirometric and Douglas bag methods would necessitate collection of the gas and subsequent analysis by other methods such as by mass spectrometry or gas chromatography.

RESPIRATORY GAS ANALYSIS

It is apparent that traditional methods of respiratory gas analysis employing the Scholander or Haldane type of apparatus will not be applicable in space conditions, dependent as they are on manipulation of fluid levels. It is, thus, necessary to consider other methods of measurement of the volume and partial pressure of respiratory gases, including in particular, oxygen, carbon dioxide, nitrogen, and perhaps helium.

The study undertaken by Beckman Instruments, Inc., on behalf of the U. S. Air Force includes valuable information in this field, particularly with respect to the development and uses of spaceborne gas chromatography and mass spectrometry. Another very helpful general review, without particular application to space use, is by Severinghaus (1960)⁹³.

One of the most useful devices for this purpose is the mass spectrometer. Essentially there are three types of mass spectrometers, the magnetic analyzers (Consolidated Systems Corporation), the time-of-flight mass spectrometer (Bendix) and the coincidence mass spectrometer (Garrett AiResearch). A mass spectrometer has also been developed and flown operationally in the X-15 by the NASA Flight Research Center at Edwards. In each case the sample is first ionized by a stream of electrons in an ionization chamber. In the magnetic analyzer, the resulting beam is tightly collimated and passed through an applied magnetic field, which causes the ions to bend out of their original linear path. Dependent on the change to mass ratio, the ion path is curved to a greater or less degree, and provides separation of the ions which are collected and counted on specific collector plates.

In the time-of-flight mass spectrometer, the ions are exposed to a pulsed radio frequency source, which imparts kinetic energy to them proportional to their molecular weight. They are then accelerated towards a detector, and since the velocity derived from the kinetic energy is dependent on the mass, the lighter ions reach the detector earlier than the heavier. The time of flight provides a measure proportional to mass.

In the coincidence spectrometer, which is another form of time-of-flight spectrometer, when the molecule is ionized, the secondary electron which is split off is collected on an electron collector placed very close to the ion source. The positive ion passes in the opposite direction to an ion collector, a relatively much greater distance away. The difference in time between detection of the electron and detection of the ion is the time-of-flight of the ion, from which mass can be derived.

In each case, appropriate electronics and recorders provide a trace of the mass spectrum of the sample as a function of the mass number. Components of a sample can be identified by comparison of the spectra with known traces, or, for monitoring of specific components, corresponding mass peaks can be selected and used, for example, in breath by breath analysis to provide a continuous output proportional to the concentration of the specific components.

The mass spectrometer has a wide range of diagnostic versatility. In addition to its usefulness in monitoring toxic contamination of the cabin atmosphere, for which it might well be employed, and for other biochemical studies, it can be used as a fast response system for inhaled and exhaled oxygen, for exhaled carbon dioxide, and for nitrogen. All three gases, and for that matter, helium, can be monitored from a single sample introduced via a capillary tube into the ionization chamber. Although all three types of devices are under 15 lbs. in weight further miniaturization and development is recognized before any could be incorporated into a space vehicle.

The gas chromatograph is another device which would have application to the analysis of respiratory gases. A prototype spaceborne gas chromatograph has been developed by Beckman Instruments, Inc., while other interested companies include Melpar Incorporated, and the Perkin Elmer Company. The principle depends on introducing a sample for analysis into a closed system containing an inactive carrier gas, normally helium, which carries the sample through pre-selected capillary columns containing either solid absorbents or liquid partitioning agents. The passage of the sample components is selectively retarded by the affinity of the components for the material in the columns. The components are separated according to their retention time. On elution from the end of the column they are passed to a sensitive detection system and identified.

A common form of detector is a thermal conductivity cell. An ionization detector of the breakdown voltage type has been used. Several studies have been undertaken for the analysis of respiratory gases. Dressler et al. (1960)²⁸ used a Beckman system with a thermal conductivity cell detector for the analysis of oxygen and carbon dioxide with an accuracy of 0.1 volume per cent for the former and 0.8 for the latter, as compared to values obtained with a micro Scholander technique (.03 volume per cent).

Rapid response infrared carbon dioxide sensors have been devised, some of which are too large for consideration in spacecraft systems. Miniaturized carbon dioxide analyzers designed for atmospheric monitoring of spacecraft have been developed by Perkin Elmer and by Beckman. Their action depends on a highly specific absorption by carbon dioxide of light in the infrared band at 4.28μ . The instrument is made selective by utilizing two filters, one transmitting the carbon dioxide absorption band and one an adjacent band. In the absence of carbon dioxide, the difference between the two transmissions, as measured on a detecting cell, is nulled out by a variable third filter. Introduction of carbon dioxide into the beam increases the absorption in one filter. A signal is created proportional to the partial pressure of carbon dioxide in the sample. This type of atmospheric monitor does not appear to have been used for respiratory gas analyses but it could be modified for the purpose if required.

The nitrogen meter, marketed under the trade name of Nitralyzer by Med-Science Electronics, was originally developed by Lilly and his colleagues in 1943⁶², and has received wide acceptance and some modifications. The device is essentially an emission spectrograph. The sample is admitted into a partially evacuated sample chamber, electrically excited between the anode and cathode, and caused to emit radiation. The radiation discharge is filtered by passage through a filter specific for the wavelength emitted by ionized nitrogen, and thereafter detected by a photocell. The intensity is proportional, although not in a directly linear manner, to the content of nitrogen present. The meter is calibrated by samples of known nitrogen content. The current equipment is probably susceptible to further miniaturization and specialized development for space use.

Specialized oxygen meters have also been developed, notable among them being the paramagnetic oxygen analyzer originally developed by Pauling and currently marketed by Beckman. Its action depends on the fact that oxygen intensifies a magnetic field and will increase the displacement of any diamagnetic material from the field. In this device nitrogen is contained within a glass dumbbell suspended on a quartz thread within an unsymmetrical magnetic field. In the presence of oxygen, the dumbbell rotates out of the field. The force required to return the dumbbell to a null balance point has a linear relationship to the pO_2 of the sample and can provide a measure of the pO_2 .

The thermal conductivity meter (Cambridge Instrument Co., N. Y.) has a particular application to the measurement of helium, which, among the respiratory gases and contaminants, has an unusually high thermal conductivity. It has also been used for measurement of carbon dioxide, which has a distinctly lower thermal conductivity than oxygen. The instrument, although used previously for other forms of physico-chemical analysis, was first employed for respiratory gas analysis by McMichael (1939)⁷⁸ who utilized it for hydrogen analysis in determining lung volumes. It was later used by Meneely and Kaltreider (1949)⁷³ for helium determinations. The method depends on creating an imbalance in two arms of a Wheatstone bridge exposed to the cooling effect of the sample, the other two arms being sealed. The imbalance is read on a galvanometer. Response time of the Cambridge instrument is relatively slow (20 secs to several minutes) and it is not suitable for breath by breath analysis. In Meneely's work the accuracy was comparable with that obtained by manometric techniques.

An acoustic gas analyses based on the changes that occur in the velocity of sound in different gases was described by Faulconer and Ridley (1950)³¹ on the basis of work previously done in the Mayo Clinic. Quantification depends on measurement of the delay in transmission of pulses, or the phase shift of sound, in the ultrasonic frequencies. The instrument (National Instrument Laboratories) has a very high sensitivity (0.004% for oxygen and 0.0008% for carbon dioxide) but is complex and requires concentrated attention and skill in operation. It is doubtful if the extreme sensitivity is an overweening

advantage for space use.

From the above discussion it is apparent that many methods are available, and feasible, for respiratory gas analysis in orbital space conditions, dependent on volume, skill, and experimental requirements. There is no doubt that the mass spectrometry is the most versatile technique, and also lends itself to other atmospheric and biochemical analysis. It is not intended here, however, to select any one technique or instrumentation system as being superior to another. A comprehensive trade-off study is required, taking into account all potential uses of such instrumentation, as related to the specific mission, specific vehicle, crew size, available skills, etc., before any particular instrumentation system could be selected. In any event, the system, or systems, selected, will require further specific development related to the requirements for which they will be used and the craft and conditions in which they will be employed.

ALVEOLAR GAS EXCHANGE

In consideration of methods for determining the adequacy of alveolar gas exchange in a space vehicle, it becomes increasingly necessary to bear in mind the reason for those measurements. The reason is not primarily to elucidate some of the more esoteric mechanisms in respiratory physiology, but to determine any changes, or trends towards change, that may occur by reason of, or in association with, exposure to an uncommon environment. This requirement should be met by the simplest clinical laboratory testing compatible with acquisition of the desired results. In some cases, even this may not be very feasible.

Satisfactory alveolar gas exchange depends upon adequate alveolar ventilation, uniformity of gas distribution and blood flow, and unimpaired gas diffusion.

Alveolar Ventilation

Minute ventilation is the volume of air or gas entering the respiratory passages each minute. Alveolar minute ventilation is the volume of fresh air entering the alveoli each minute. Effective alveolar ventilation is the fraction of the total ventilation which comes in contact with well-perfused alveoli. The elements making up alveolar minute ventilation ($\dot{V}_A$) are the tidal volume (TV), the anatomic dead space (V_D) and the respiratory frequency (f). Thus:

$$\dot{V}_A = (TV - V_D) \times f \quad (1)$$

The anatomic dead space is the volume of the conducting airway which does not take part in gas exchange. Measurements of respiratory frequency and tidal volume have already been discussed. Measurements of the anatomic dead space in an oxygen-nitrogen environment is commonly made by the single breath oxygen technique of Fowler (1948)³⁴. In this procedure, expired nitrogen concentration is continuously recorded by a nitrogen meter, along with volume flow rate, after a single breath of pure oxygen. The expired nitrogen concentration remains effectively zero until the dead space volume has been expired, at which point it theoretically rises in a square

front to a plateau representative of alveolar nitrogen concentration. Because of mixing between dead space and alveolar space, a square front is not in fact formed, but by visual examination of the trace an equilibrium point can be determined indicating the position where a theoretical square front would lie. The dead space volume is the volume of air expired from the beginning of expiration to the time of occurrence of the theoretical square front.

It is apparent that this technique would not be feasible in a pure oxygen environment. With other mixed gas environments, such as oxygen-helium, or oxygen-neon, presumably the concentration of the diluent gas could be monitored similarly to provide the same information. Techniques with ambient gases other than air would require validation, however, before they could be recommended.

Instead of graphic analysis of the trace, the volume of the dead space can be derived from Bohr's equation, as follows, utilizing the symbology recommended by the American Physiological Society (Pappenheimer et al. 1950)⁸⁶:

$$V_D = \frac{[FA_{N_2} - FE_{N_2}]}{[FA_{N_2} - FI_{N_2}]} VE \quad (2)$$

At the end of the single oxygen breath, FI_{N_2} is zero, and the question becomes:

$$V_D = \frac{[FA_{N_2} - FE_{N_2}]}{FA_{N_2}} VE \quad (3)$$

FA_{N_2} is obtained from the nitrogen meter; VE is obtained from an integrating pneumotachograph, while FE_{N_2} is obtained by dividing the area under the nitrogen curve for a given expiration by the duration of that expiration.

Dead space varies with age, sex, extent of lung distension, posture, disease, and the sequelae of surgical interference, but mean values are shown in the following table.

Table 2

ANATOMIC DEAD SPACE (ml)
IN HEALTHY SUBJECTS
(mean value)

Young women (semirecumbent)	104
Young men (semirecumbent)	156
Young men (supine)	115
Young men (during maximal expiration)	110
Young men (during maximal inspiration)	230
Older men (semirecumbent)	180

Source: Comroe (1965)¹⁹

Commonly a mean value of 150 ml is used as a representative figure for young healthy men, although Radford (1964)⁸⁸ points out that the dead space volume of an adult in ml is approximated by his ideal weight in pounds.

Of more significance than the anatomic dead space is the physiological dead space, although in the normal healthy adult the two should be identical. The physiologic dead space includes the anatomic dead space and the portion of the alveolar ventilation, which, because of uneven relationships between pulmonary blood flow and functioning alveoli, is ineffective in arterializing venous blood.

The physiologic dead space can be calculated by applying Bohr's equation to measures of expired carbon dioxide, which is eliminated only where functioning alveoli are adequately supplied with pulmonary blood flow, thus:

$$V_D = \frac{[F_{A_{CO_2}} - F_{E_{CO_2}}] VE}{F_{A_{CO_2}}} \quad (4)$$

Although the measure can be readily quantified by infrared sensor, glass electrode, mass spectrometer, or gas chromatograph, the fraction of alveolar CO_2 is a difficult measure to obtain, since it is difficult to determine at what point in the respiratory cycle the measure should be made; but if there is no significant alveolar dead space ventilation or venous-to-arterial shunts the equation can be restated in terms of partial pressures, with the alveolar P_{CO_2} represented by the arterial P_{CO_2} , thus:

$$V_D = \frac{[P_{a_{CO_2}} - P_{E_{CO_2}}] VE}{P_{a_{CO_2}}} \quad (5)$$

Use of this equation, however, requires a sample of arterial blood, and determination of the carbon dioxide tension within that sample. The taking of arterial samples under orbital conditions cannot of course be considered lightly. The problems of sampling and determination of gas tensions will be considered later.

Utilizing the same principle, namely, that expired carbon dioxide must be derived from mixed venous blood in association with functioning alveoli, the effective alveolar ventilation can be calculated directly from measurements of expired carbon dioxide.

Thus:

$$\dot{V}_{\text{CO}_2} = F_{\text{A}_{\text{CO}_2}} \dot{V}_{\text{A}} \quad (6)$$

rearranging,

$$\dot{V}_{\text{A}} = \frac{\dot{V}_{\text{E}_{\text{CO}_2}}}{F_{\text{A}_{\text{CO}_2}}} \quad (7)$$

Again, however, a representative alveolar sample is required and results may vary according to the type of sample. With appropriate conversions, and assuming normal ventilation/perfusion relationships, the carbon dioxide tension of arterial blood can be used instead of an alveolar measurement. Correcting for conversion, where required, from STPD to BTPS, and from fractional concentration to partial pressure, equation (7) becomes:

$$\text{VA(ml)} = \frac{\dot{V}_{\text{E}_{\text{CO}_2} \text{ (ml)}} \times 0.863}{P_{\text{a}_{\text{CO}_2}}} \quad (8)$$

Summarizing the requirements for determination of alveolar ventilation in an orbiting spacecraft, it is apparent that dead space volume is the critically difficult measure. Under most circumstances in the normal healthy adult an assumed value can be used. For orbital space conditions, however, it will be necessary to establish first whether any change in dead space occurs as a result of weightlessness. Since dead space volume varies with posture, such a hypothesis would seem reasonable. The most feasible method to obtain the measure in an oxygen - nitrogen environment would seem to be the single oxygen breath technique, using a nitrogen meter and integrating pneumotachograph. In a pure oxygen environment that technique would not apply, but physiological dead space could be estimated from carbon dioxide elimination measurements.

While results obtained utilizing arterial blood samples are considered to provide a more accurate representation of alveolar ventilation and dead space, the traumatization of the subject is not considered justifiable for the purpose. At the same time, consideration could be given to the use of capillary blood samples and estimation of P_{CO_2} by glass electrode techniques. This will be considered later.

If no change is found in dead space volume associated with orbital conditions, further space-borne measures of dead space would be unnecessary. Representative values from tables such as Table (2), or values obtained from pre-flight ground studies, could be employed and alveolar ventilation calculated from total ventilation and frequency.

Uniformity of Alveolar Ventilation

In a review of the intrapulmonary distribution of inspired gas, Fowler (1952)³⁶ cites the work of different authors to show that even in the normal healthy person gas is not evenly distributed to all alveoli. Some are hyper-ventilated and some are hypoventilated. In the orbiting space vehicle the picture might be still further modified by redistribution associated with loss of hydrostatic pressure head in the lung, or perhaps by patchy atelectasis associated with a high oxygen pressure.

Traditionally, clinicians have obtained a qualitative impression of ventilation distribution in the lungs by use of the stethoscope, and most certainly the trained ear can detect relative differences with remarkable sensitivity. In addition, with the use of standardized x-ray procedures, changes in relative radiolucency are also interpreted as representing changes in ventilation distribution. However, while the skilled use of a stethoscope would be strongly recommended to provide an indication of ventilation distribution, it is doubtful if the foreseeable state of the art in space-borne radiography would justify a primary recommendation of the latter for that purpose. If radiological equipment is deemed advisable for other purposes, however, its use for standardized chest x-rays could provide useful corroboration of other findings.

Various forms of physiological testing have been used to determine the occurrence and extent of uneven gas distribution, (Bates and Christie, 1950¹¹; Comroe and Fowler, 1951²¹; Gournand et al., 1941²⁴; Darling et al., 1940²⁵; Krogh and Lindhard, 1917⁵⁶), in addition to consideration of radiological translucency, but certainly one of the simplest is the single oxygen breath test of Fowler (1948)³⁴ already described in connection with measurement of dead space volume.

The extension of this test is predicated on the fact that the "plateau" formed on the trace representing the alveolar nitrogen concentration is not in fact horizontal but, in the normal adult, after expiration of the first 750 ml, shows a slow increase in concentration up to 1.5% during expiration of the next 500 ml. Where unevenness of distribution on inspiration is more marked, and where rates of gas flow on expiration are unequal, it may show an increase in concentration up to as much as 16%. The test thus provides a semi-quantitative measure of ventilation distribution, in addition to an estimate of dead space.

Some other techniques are based on the washout of nitrogen which occurs when oxygen is breathed continuously for a specified duration. The simplest technique involves the breathing of oxygen for 7 minutes followed by a forced expiratory sample. With normally even distribution, nitrogen will be washed out evenly during the oxygen breathing, and the final sample will contain less than 2.5% nitrogen.

As a more complex alternative, nitrogen elimination can be continuously monitored, breath by breath, and a curve derived showing the exponential fall in nitrogen concentration (Fowler et al. 1952)³⁷. Plotting of the data on semi-log paper, along with a plot of the theoretical elimination rate, allows analysis of the data to provide a measure of slow and fast clearance.

When there is uneven ventilation, although the inequality may be distributed throughout the alveoli, the nitrogen clearance is manifested as though there were a poorly ventilated portion with slow washout and a well ventilated portion with fast washout, each of which can be represented by a straight line on semi-log graph paper. The extent of the unevenness is indicated by the amount of deviation of the actual values from a true line.

The techniques described require the presence of a two-gas atmosphere. In the presence of air, or oxygen-nitrogen, measures are made from a nitrogen analyzer. In oxygen-helium, or oxygen-neon, presumably the same principles would apply, but validation of the techniques would be required. The techniques of course would be inapplicable to an oxygen atmosphere.

In the latter case, if deemed advisable, and in fact in other atmospheres, as well, use could be made of the closed-circuit helium technique devised by Bates and Christie (1950)¹¹. In this technique, akin to that used in closed-circuit helium measurement of residual capacity, a known volume of foreign gas such as helium is added to a closed circuit system and its dilution by alveolar gas is monitored by, for example, a mass spectrometer. The resulting curve of concentration versus number of breaths provides an index of uniformity of distribution. As was noted in discussion of residual capacity measures, the necessary equipment is bulky and complex, and although the method would be applicable to pure oxygen atmospheres as well as oxygen-nitrogen atmospheres, a source of helium would be required. The method could not be used in an oxygen-helium atmosphere, although if necessary, nitrogen could be used for a tracer in this situation.

Thus, to determine the uniformity of ventilation distribution, it would seem that the stethoscope in skilled hands, and perhaps chest radiography, would provide useful qualitative information. More definitive, but relatively simple testing would involve the single breath oxygen technique with continuous monitoring of nitrogen (or the other diluent gas in two-gas atmosphere), to be carried out in conjunction with determination of dead space. There is no doubt that more complex techniques would provide still more definitive information, but their added complexity under difficult circumstances makes their justification dubious. In a pure oxygen atmosphere the use of a closed circuit method with an added foreign gas would be mandatory, but again the complexity makes justification of the operation difficult.

Uniformity of Capillary Blood Flow

Clinicians have realized since the 19th century, or before, that pulmonary capillary blood flow is not uniformly distributed, and that its distribution is probably affected by the gravitational vector (Orth, 1887⁸⁴, cited by West, 1963¹⁰⁷). As a result, flow under terrestrial conditions is greater in the lower lobes in the standing position. It would seem reasonable to hypothesize that this relationship will change under the weightless conditions of space. It most certainly becomes more marked under conditions of applied sustained acceleration (Barr, 1962⁶; Wood et al., 1963¹¹¹; and others). In addition, distribution can be still further affected by pathology and disease.

As a result, various combinations of normal and abnormal alveolar gas distribution, and normal and abnormal pulmonary capillary blood flow, can arise. These in turn can produce various degrees of local hypoxemia which result effectively in various degrees of venous-to-arterial shunt. The normal relationship in healthy man, the ventilation/perfusion ratio, is expressed as:

$$\frac{VA}{Q_c} = 0.8 \quad (9)$$

Gross alterations in ventilation or perfusion will alter the ratio unless the individual alterations are such as to compensate for each other. Should the ventilation and perfusion of an alveolus, or group of alveoli, be such that mixed venous blood flows by unventilated alveoli, an absolute shunt will exist. The extent of this absolute shunt can be estimated by measuring arterial blood oxygen during the inhalation of oxygen. If the shunt is great enough, the arterial blood oxygen will not be increased, despite the inhalation of oxygen, since the latter does not gain access to the shunted blood. The question of arterial blood sampling will be considered later. It is very doubtful, however, if the above procedure would provide information of value in orbital space conditions.

Acquisition of more definitive information on the extent of venous-arterial shunts, to include both absolute shunts and expressions of low ventilation/perfusion ratio, rightly belongs in the ground-based cardiopulmonary laboratory,

and could not be reasonably considered for routine use in an orbiting space laboratory. It is conceivable that a special experiment might be set up with specially trained experimenter and subject. The procedure depends on the fact that the amount of oxygen in arterial blood is made up of the oxygen in oxygenated blood plus the oxygen in partly, or fully, shunted blood.

Thus:

$$CaO_2 \dot{Q} = CcO_2 \dot{Q}_c + C\bar{v}O_2 \dot{Q}_s \quad (10)$$

where CaO_2 = arterial oxygen concentration
 $\dot{Q}$ = total blood flow
 CcO_2 = pulmonary capillary oxygen concentration
 $\dot{Q}_c$ = blood flow through capillaries
 $C\bar{v}O_2$ = mixed venous oxygen concentration
 $\dot{Q}_s$ = blood flow through shunt

Now $\dot{Q}_c = \dot{Q} - \dot{Q}_s \quad (11)$

Therefore $CaO_2 \dot{Q} = CcO_2 (\dot{Q} - \dot{Q}_s) + C\bar{v}O_2 \dot{Q}_s \quad (12)$

Rearranging $\frac{\dot{Q}_s}{\dot{Q}} = \frac{CcO_2 - CaO_2}{CcO_2 - C\bar{v}O_2} \quad (13)$

Thus, the extent of the shunt can be measured in terms of the total pulmonary blood flow, or cardiac output. The technique, however, calls for measurement of cardiac output, arterial oxygen concentration, mixed venous oxygen concentration, and an estimate by the procedure of Lilienthal et al., (1946)⁵⁹ of the oxygen concentration of end-pulmonary capillary blood.

Still other methods of determining ventilation distribution and blood flow have involved the use of inspired radioactive materials and radioactive injectates. Hugh-Jones and his colleagues (Dollery et al., 1961²⁷; West et al., 1961¹⁰⁸) have used radioactive oxygen-15 in studies of regional blood flow; Bates and his associates (Ball et al., 1962⁵) have used radioactive xenon, both inspired as an insoluble material and injected as a soluble compound whence it is eliminated in the lung; and Markason and his colleagues (1962)⁶⁶ have used radioactive krypton for the purpose. The complexity of

instrumentation and techniques render the procedures unacceptable, however, as well as the fact that the half-life of oxygen-15 is two minutes, that of krypton-85 is $4\frac{1}{2}$ days, and that of xenon-133 is $7\frac{1}{2}$ days.

While these procedures are not feasible for space use in the foreseeable future, useful qualitative information can be readily obtained from the single breath carbon dioxide expiration test, (Comroe et al., 1962)²⁰. Since expired carbon dioxide comes from alveoli with a significant capillary blood flow, continuous rapid analysis of a single expiration by, for example, an infrared analyzer, will give qualitative information on ventilation perfusion relationships provided that ventilation is asynchronous, *i. e.*, if the early portion of the expired breath comes from well ventilated regions and the later portion from poorly ventilated regions. Disregarding again the first 750 ml of expiration, which may contain gas from the anatomic dead space, continuous rapid response analysis is made of the remainder. If the concentration of carbon dioxide is only slightly greater at the end of the analysis than the beginning (allowing for continued elimination of carbon dioxide) the V/Q ratio can be considered similar in both the poorly and well ventilated regions. If ventilation is uneven but matched by uneven perfusion, the concentration of carbon dioxide will be the same throughout expiration. If the last portion of analyzed gas shows a considerably higher concentration than the first, then the first part must come from a region with an increased ratio and the last portion from a region with decreased ratio.

Thus, while much investigation remains to be done in space as well as on the ground, the only potentially feasible method of investigating ventilation perfusion relationships at this time would seem to be the analysis of expired carbon dioxide, perhaps backed up by chest radiography.

Diffusion Capacity

The diffusion capacity defines the ability of gases to pass between the alveoli and the hemoglobin through the alveolar-capillary membranes and the intervening materials. As with measures of ventilation-perfusion ratio,

measurement of diffusion capacity cannot be considered routine in orbital space laboratories, and, except perhaps for a special experiment with special equipment, skilled investigator, and trained subject or subjects, it is probably not feasible in the foreseeable future.

Determination calls for a measure of the flow of gas across the tissues as related to the pressure differential dictating that flow. The measure, for accurate representation, requires the use of gases with an affinity for hemoglobin such that their diffusion capacity is not falsely influenced by varying capillary blood flow. The gases used are carbon monoxide and oxygen.

Several techniques have been described for the use of carbon monoxide in this manner since the original work of the Kroghs in 1910, and the techniques, although complex, have been refined into various standard forms. It would be a pointless exercise to describe them in detail since any procedure selected for special orbital experiment would depend on the experimenter. A rebreathing technique has been described by Krouhoffer (1954)⁵⁷ using radio-tagged carbon monoxide; a steady-state breathing technique which requires a measure of arterial P_{CO_2} for the computation of alveolar carbon monoxide tension is described by Filley and his colleagues (1954)³²; another steady-state technique entails calculation of alveolar P_{CO} from inspired and expired carbon monoxide concentrations, using an assumed dead space volume (Bates et al., 1954)¹⁰; still another method requires inhalation of a single breath of low concentration carbon monoxide in helium, oxygen, and nitrogen, followed by breath holding and subsequent calculation of mean alveolar P_{CO} from Krogh's exponential equation describing take-up of alveolar carbon monoxide (Ogilvie et al. 1957)⁸³.

Smith and Hamilton (1962)¹⁰⁰ described a carbon monoxide method using a gas chromatograph for measurement purposes, and neon as the inert gas added for the purpose of measuring the initial alveolar CO concentration. Although they collected their samples in balloon bags and then expelled them into a tonometer over mercury, it is probable that more direct sampling systems could be designed. This same group (Hamilton and Smith, 1965)⁴⁸ have also fashioned a slide-rule for application of the Krogh formula for D_{CO}

which provides an accuracy well within clinical requirements, and allows completion of the calculations in one to two minutes.

It is emphasized, however, that in addition to the complexity of the equipment and techniques, and in some cases the requirement for arterial sampling, the procedures in all cases require the use of a toxic gas which will be released into the closed system of a spacecraft atmosphere and may also leak from storage. Consequently they cannot be lightly recommended.

The use of oxygen, on the other hand, is physiological and safe. Determination of diffusing capacity with oxygen, however, is grossly complicated by several factors. Firstly, pulmonary capillaries already contain a significant partial pressure of oxygen (the more so in a pure oxygen environment) which cannot be neglected in determining the driving pressure; secondly, the capillary P_{O_2} undergoes change along the course of the capillary; and thirdly, the extent of O_2 dissociation from hemoglobin is not related to P_{O_2} in a linear fashion (i. e., the oxygen dissociation curve is S-shaped). These factors dictate the necessity for a complex integration procedure and measurement of arterial and mixed venous P_{O_2} at a high (21%) and low (12-14%) level of oxygen breathing to determine mean capillary P_{O_2} and the extent of venous admixture. In addition, the procedure requires measures of oxygen consumption and calculation of PA_{O_2} from measures of inspired oxygen and expired carbon dioxide tension. The technique is detailed by Lilienthal et al. (1946)⁶⁰. Principles and procedures for diffusion estimations are also outlined in reviews by Comroe (1965)¹⁹ and Comroe et al., (1962)²⁰.

Thus, in reiteration, it is considered that measurement of diffusion capacity, although possible under special circumstances and after specific examination, cannot be regarded as feasible for routine determination in an orbiting space laboratory in the foreseeable future.

BLOOD GAS AND pH

The effectiveness of gas exchange in the respiratory system is reflected in the gas concentration and tension in the blood. Thus, it becomes necessary to consider techniques for the determination of the content and partial pressure of oxygen and carbon dioxide in mixed venous and arterial blood, both as confirmatory measures, and to assist in the determination of other respiratory parameters. In addition, since these values are in part determined by the hydrogen ion concentration, it is also necessary to consider measures of pH.

Mixed venous blood, representative of venous blood from all parts of the body, is accessible only in the right side of the heart, and since mixed venous sampling requires intracardiac catheterization it cannot be considered acceptable for use in a space laboratory, except under very special circumstances.

In several test procedures, however, it becomes of critical importance to obtain representative samples of arterial blood. Normally, these are obtained by the use of a heparinized arterial needle and cannula inserted into the brachial artery. Insertion of the needle and collection of samples is a skilled procedure which may cause considerable discomfort to the subject. Thus, while its use might be considered under special circumstances, using willing scientist astronauts as subjects, it could not reasonably be considered for routine use.

Attention, however, has been directed towards the use of "arterialized" capillary blood as a substitute for arterial blood. On the assumption that capillaries at the arterial end of the capillary bed will be at a higher pressure and consequently bleed more freely, and will be representative of arterial blood gas, studies have been undertaken on capillary blood from the preheated ear lobe. Several of these have shown an acceptable correlation between the values for capillary blood and those for arterial blood determinations of pH, P_{CO_2} , CO_2 content, and oxygen saturation (Lilienthal and Riley, 1944⁵⁸, 1946⁵⁹; Singer et al. 1955⁹⁹; Andersen et al., 1960², 1962³; Gambino, 1961⁴³). As an alternative, blood from a hand vein after 10 minutes immersion at 45° C has been found to be a suitable substitute (Severinghaus, 1965⁹⁶).

One of the major problems, and one that is perhaps insoluble in a high oxygen environment, is the collection of capillary samples under anaerobic conditions. Shock and Hastings (1934)⁹⁷ collected their samples under oil, but this technique was found to be unsatisfactory, since, among other reasons, the oil absorbs carbon dioxide.

Lilienthal and Riley (1944)⁵⁸ developed a method of collecting ear lobe blood in a small rubber cup attached to a tuberculin syringe under "virtual anaerobic conditions" which they showed were satisfactory for the purpose. Sanz (1957)⁹⁰ has made direct measurements of pH with a pH electrode on the ear. Astrup's group (Andersen et al., 1960)² have collected their samples in capillary tubes, containing a dried heparin fluoride mixture, which are then placed in a specially designed apparatus for the determination of pH and calculation of P_{CO_2} . The quantities of blood obtained by this last technique are extremely small (about $25 \mu l$). To obtain larger quantities, suitable for the necessary determinations, it would seem that some technique akin to that of Lilienthal and Riley is required. The collection in the weightless state, however, is complicated by the fact that although blood will flow from the capillaries because of capillary pressure, it will not fall into a collecting cup; also, as previously noted, in a high oxygen environment the capillary blood flowing from the ear will be exposed, at least for several seconds, to a high partial pressure of oxygen. It would seem useful to develop a vacuum device to fit on the ear lobe, by which capillary blood could be sucked into a collecting syringe without undue exposure to the atmosphere. With such a device, even under weightlessness and in a high oxygen environment, capillary blood could be readily obtained and used as a substitute for arterial blood.

For actual blood gas analysis, investigators have traditionally relied on manometric methods such as those of Van Slyke, whereby the pressure of gas evolved from a sample of blood is measured following the addition of reagents in a closed system, and the volume of gas responsible for that pressure is calculated with reference to the gas laws. In the case of oxygen, percent saturation is determined by measuring similarly the content of a fully saturated sample and calculating the percent saturation. The system, however, requires the manipulation of a mercury column to adjust the pressure and consequently is gravity dependent. The Roughton-Scholander bubble technique (Scholander

and Roughton, 1943)⁹¹ is likewise unsuitable because of the unpredictable behavior of a bubble in the weightless state.

A measure of oxygen saturation can, however, be obtained by spectrophotometric techniques. The absorption of light by hemoglobin in a hemolysed sample of blood shows a relationship described by Beer's Law, which indicates that, with the incident light intensity constant, the oxygen saturation at a given concentration of hemoglobin is a logarithmic function of the intensity of light transmitted through the solution. The extinction coefficients of oxyhemoglobin and reduced hemoglobin are different, and the difference is exaggerated by measuring the optical density at two different wavelengths, one providing maximum difference and one zero difference.

Spectrophotometric methods for determination of blood oxygen saturation using the Beckman DU spectrophotometer have been described by Nahas (1951)⁷⁹, among others, and also by Holling et al., (1955)⁴⁹, who compared the technique with Haldane and Van Slyke methods and found that above 60% oxygen saturation there was no significant difference among the three methods. A micro method, with collection of capillary blood in glass capillary tubes has been described by Auckland (1962)⁴. The blood is hemolysed by freezing, subsequently thawed, sucked into a capillary cuvette and its optical density measured by spectrophotometer at two wavelengths.

Oximetry can be regarded as a form of spectrophotometry for the specific purpose of determining oxygen saturation. Light may be either transmitted through the specimen or reflected from it. In reflection oximetry, non-hemolysed blood is used, and, in fact, the oximeter can be applied over the skin. The wavelength of light (generally between 650 and 700 m μ) is chosen so as to give a maximum difference between the extinction coefficients of oxyhemoglobin and reduced hemoglobin. While the techniques are most applicable to the direct sampling of blood flowing through a cuvette, close correlations can be obtained with results derived from an oximeter applied to the heated ear lobe. The work of Wood in this field is well known (Wood and Geraci, 1949)¹¹⁰ and the value and disadvantages of ear oximetry have been previously discussed in considering determination of cardiac output. A review of the techniques of oximetry is also made by Comroe and Wood (1950)²².

Although the content of blood gases cannot be readily determined by standard methods in space conditions, it is probable that either a gas chromatograph or a mass spectrometer, or both, will be available in the spacecraft for atmospheric monitoring purposes. To use these systems for measurement of content or tension, however, requires that the gases first be evolved into some form of tonometer or cuvette. The separation of liquid and gas phases under these circumstances might well provide problems. Suitable reagents for the purpose would be saponin, with potassium ferricyanide, along with lactic acid if elution of carbon dioxide is desired. Thereafter, gases could be introduced into either of the devices either automatically or as a manual sample. In the field of gas chromatography, several systems for blood gas determination have been described, such as those of Chambliss and Nouse (1961)¹⁵, Lukas and Ayers (1961)⁶⁵, Thomas (1963)¹⁰², and Wilson et al., (1961)¹⁰⁹, but very much less information is available on the use of the mass spectrometer for blood gas work. In any event, for use in space, if it were considered necessary, techniques and equipment would have to be developed compatible with the space borne systems.

In addition to mass spectrometry and gas chromatography, several special methods are available for the measurement of oxygen tension. These have primarily been used for monitoring oxygen in a gas mixture. Although some of those used for monitoring gas mixtures are unsuitable for biological fluids, the polarographic oxygen electrode has an application for measurement of oxygen tension in blood. The principle of its operation depends on the fact that an inert metal electrode (platinum, gold, silver, etc.) negatively charged to 0.4 to 0.7 volts in an electrolyte solution will give electrons to dissolved oxygen, reducing it to H_2O_2 or OH^- . The current passing into the solution from the electrode is directly related to the availability of oxygen. Clark (1956)¹⁷ modified the original device by a system in which a thin membrane between the sample and the cathode allowed only oxygen molecules to pass, and prevented contamination of the cathode and electrolyte. The Beckman/Spinco model, which demonstrates refinements over the original Clark model has received wide acceptance.

This electrode consists of a platinum wire cathode sealed in glass, with its tip exposed, and a silver/silver chloride anode. Cathode and anode are immersed in electrolyte which is sealed in by a thin membrane of polypropylene or Teflon. The latter permits faster reaction but is less stable in use. It is also sensitive to CO_2 . 90% response time with the former is in the range of 3-7 seconds. A micro electrode is also available from Beckman/Spinco mounted in an 18-gauge arterial needle for intra-arterial use. The electrodes are temperature sensitive and measures have to be made in a water bath at body temperature of 37°C . Calibration is necessary before use to determine scaling. This is accomplished by exposing the electrode to 0% oxygen and 20% oxygen (atmospheric) in a diluent gas.

The original Clark electrode had a point diameter of about 2 mm. It was sensitive to pressure and also required that the fluid be stirred or agitated in some manner to avoid formation of a stagnant layer immediately surrounding the electrode. This problem has been overcome by using as the cathode a fine platinum wire of diameter 0.001 inch.

The Beckman/Spinco model is mounted in a stainless steel cuvette and fitted in a water bath with appropriate ports. Lucite is unsuitable as a mounting since it absorbs oxygen. It is used in conjunction with a signal processor and readout system, Beckman Model 160 Physiological Gas Analyzer. A minimum sample volume of 0.3 ml is required. Further developments of the Beckman electrode are expected, including a model with stability of calibration for at least 30 days. The original Clark electrode with stirring device in a cuvette and water bath is available from the Yellow Springs Instrument Company.

Electrode systems are also applicable to the measurement of hydrogen ion concentration in blood. The principle of measurement by pH electrode depends on the development of an electromotive force between one electrode and another reference electrode when both are immersed in a test solution and linked by a potassium salt solution bridge.

The original "hydrogen electrode", which was unstable and subject to chemical "poisoning", gave way to the glass electrodes developed by McInnes

and his colleagues (1933)⁷⁶ which have undergone considerable refinement since. In this type of electrode a special glass (commercial 015 glass) is blown to form a small bulb which is connected to the end of a tube of ordinary glass. Within the tube, a silver/silver chloride electrode is sealed in a buffered KCl solution. Incorporated into the assembly is a reference electrode which consists of a calomel half-cell connected to the unknown solution by a KCl salt bridge. When dipped into a test solution the special glass electrode allows the passage of hydrogen ions only from the solution. An external current measures the change in potential between the outside and inside of the glass membrane. The glass electrode has a very high output impedance, and the amplifier for the potential difference requires a correspondingly high input impedance (10^{11} ohms). The resistance of the glass membrane is also very temperature sensitive, doubling for each 7°C decrease in temperature. Consequently, the system has to be operated at a closely controlled temperature, normally 37°C . Before use, the electrode is calibrated against a buffer solution of known pH.

A continuous flow of electrolyte is required at the electrolyte junction. While this can be gravity driven in terrestrial conditions, some other form of drive is required for weightless conditions. The Beckman Micro Blood pH electrode (Beckman Instruments) includes a pressurizing system for this purpose. It has been designed for spaceborne use, and includes a modular water bath and an expandable sample chamber which maintains a sampling chamber volume equal to the sample volume, thus eliminating bubbles.

Radiometer of Copenhagen market an ultramicro precision system based on the design of Sanz (1957)⁹⁰. In this system the glass electrode is a capillary tube surrounded by a buffer solution at constant pH in a water bath. The sample is sucked into the capillary tube, directly from the arterialized capillary. The tube and reference calomel electrode are then dipped into a KCl salt bridge solution and the potential difference is read from an appropriate pH meter. The system, however, is somewhat fragile, and would not be too suitable for space use.

The system developed by Astrup's group (Andersen et al., 1960)² and

marketed by Radiometer, is also based on the work of Sanz, but the design complexities have been ruggedized, partially automated, and formed into a convenient hand held device, which, with accessories, can be used for determining P_{CO_2} and standard bicarbonate as well as pH.

Severinghaus (1965)⁹⁵ and his group have recently developed a small pH meter consisting of an electrode and liquid junction. Blood is sucked into the capillary and passes the liquid junction in the course of its travel. Movement of the liquid in the current system is gravity dependent but could readily be pressurized by syringe or some similar device. The system is not yet commercially available but will be marketed by Radiometer in the near future. It would seem to have considerable application to space use.

The carbon dioxide electrode, originally described by Stow (1957)¹⁰¹ and developed by Severinghaus and Bradley (1958)⁹² utilizes the principle of the pH electrode. A small volume of mildly buffered bicarbonate is held against the end of the glass pH electrode by a membrane of, for example, Teflon, held in place by a butyl "O"-ring. A spacer separates the membrane from the electrode. When the electrode is placed in a solution such as blood, the membrane serves to isolate the electrode from the sample and other sources of contamination, but allows the equilibration of carbon dioxide between the sample and the bicarbonate. Passage of CO_2 is registered on the electrode as a direct logarithmic function of the P_{CO_2} of the sample. The system is calibrated before use against a known concentration of carbon dioxide. The reference electrode is 0.1 M KCl calomel, making a liquid junction with the glass electrode. The KEL-F reference electrode is superior to some of the earlier electrodes made of nylon.

The original electrode utilized a saturated cellophane spacer between the membrane and the glass electrode which caused a slow response time and some deviation from linearity at low carbon dioxide tensions. Better response was found with a separation made of fibers of glass wool, or powdered glass wool, to the extent that response time is better than with no separation at all, indicating some catalytic action (Severinghaus, 1962)⁹⁴.

Various membranes have been used to contain the bicarbonate, including

Teflon, silicone, natural rubber, polyethylene, and cellophane, but although other membranes, such as Silastic, may provide a faster response than Teflon, the speed is achieved at a sacrifice of durability. A 1 ml Teflon membrane at 37° C requires 1 minute to reach 95% of final CO₂ equilibrium. Faster response can be achieved by employing a more permeable membrane or reducing the thickness of the bicarbonate layer, but this reduces the operating life between recharge cycles. If kept moist the operating life may be several months.

The carbon dioxide electrode determines the CO₂ tension of only the unassociated molecules of carbon dioxide. Consequently, it cannot be readily used for measuring CO₂ content.

Andersen et al. (1960)² have used the Astrup pH electrode for determination of P_{CO₂} in capillary blood, using a special apparatus for equilibrating blood with carbon dioxide at known tension. They measure the pH of the unknown sample, equilibrate the sample with carbon dioxide at one, or two, known tensions and re-measure the pH, from which the original tension can be calculated.

Carbon dioxide electrodes are available from the National Welding Company, which has an electrode with a cuvette volume of 50 μ liters, and incorporates a reference electrode within the thermostated portion. Another is manufactured by Instrumentation Laboratories of Boston, also with a 50 μ liters cuvette. Severinghaus-type electrodes are also made by Instrumentation Associates, Inc., and Beckman.

Readout for electrodes is made by electrometer or pH meter with sensitivity such as to discriminate 60 μ V or 0.001 pH units. Several instruments are available, specially designed to accept all three electrodes. Instrumentation Laboratories (Boston) sells two meters with plug-in adaptors for standard electrodes. In addition, it markets a very reliable system incorporating electrodes, controlled temperature water baths, readout meter, etc. Although this system has not been designed for space use it could be so adapted.

The Beckman/Spinco Model 160 Physiological Gas analyzer has been

incorporated into a closed system with modular temperature controlled water baths, continuous flow sampling, non-gravity dependent liquid junction for the pH reference electrode, readout, and switchbox.

Medical Research Specialties, San Francisco, sells a water bath containing the Beckman macro-electrode, the National Welding CO₂ electrode, and a Radiometer capillary pH electrode suitable for continuous flow or spot sample measurement. The bath also contains a stainless steel cup for equilibrating solutions with known gas tensions. It is not a closed system, however, and would be impracticable in space use.

Epsco Medical Instruments Division incorporates a 12-foot tape readout system with the Yellow Springs Instrument Company thermostated water bath containing the original Clark electrode, a National Welding Company CO₂ electrode and a pH electrode. Again, however, this system has not been designed for space use.

Several other pH meters and recorders are available which have not however, been incorporated into gas analysis systems.

To summarize the requirements for blood oxygen, carbon dioxide, and pH measurement, it is reiterated that intracardiac and even intra-arterial sampling cannot be reasonably considered for space laboratory use. Thus, peripheral venous and "arterialized" capillary blood must be substituted. Techniques for sampling the latter in weightlessness and a high oxygen environment require development. For measurement of oxygen saturation ear oximetry would seem to provide a relatively simple and reasonably reliable system, unless a spectrophotometer is available for other purposes, in which case its use would provide greater accuracy.

A gas chromatograph or mass spectrometer, if available, could provide information on blood oxygen and carbon dioxide content, and by equilibrating samples in 100% O₂ and remeasuring, could provide a measure of saturation. Techniques for introducing gases from the blood into these devices under space conditions require further development.

For routine measurement of gas tensions and pH, the gas and pH electrodes provide a favorable approach. It is far from clear which manufacturer provides the best electrode or the best system, or even

whether an integrated modular system should be favored under individual components. A trade-off study examining experimental effectiveness and operational suitability would assist the comparison.

CONCLUSIONS

In summarizing the conclusions, it is emphasized that the foregoing analysis is the result of a theoretical study. Any recommendations made are those that suggest themselves as being the most hopeful, but require comprehensive testing for feasibility and effectiveness within the simulated, or in some cases the actual, environment of an orbiting space laboratory. Recommendations are included in each section of the text, but it is appropriate to re-summarize them here.

For measurement of most lung volumes and capacities, the use of an integrating pneumotachograph with display on an X-Y plotter would seem to be the most feasible approach, with electrical impedance pneumography as a back-up, and for prolonged intermittent or continuous traces. The requirement for actual spirometry seems doubtful, but, if necessary, the Wedge spirometer with X-Y display would be suitable.

Measurement of residual volume and functional residual capacity presents considerable difficulty because of bulk and plumbing complexity of apparatus. If necessary, however, in an oxygen-nitrogen atmosphere, the measure could be achieved by the closed-circuit method of Christie (1932)¹⁶, with suitable oxygen and nitrogen analyzers. In an oxygen-helium atmosphere analysis of helium would be necessary. There is also some possibility, as noted, of using electrical impedance methods to obtain an index of functional residual capacity which could be applied to a previous measure made on the ground.

For measures of the mechanics and dynamics of breathing, the integrating pneumotachograph is again valuable for determining volume and flow, using the flow-volume loop for determination of its various attributes, including timed volumes, mean maximal flow rates, specific flow rates, and peak flow rates. Determination of maximum breathing capacity provides some difficulty. Although special devices can be used for the purpose, it is very doubtful if their use would be justified. Useful information on MBC (or MVV) can be obtained from the flow-volume loop, using the technique of

Bartlett et al. (1963)⁹ to calculate a predicted MVV which could be used in place of an actual measured MVV.

Determination of pressure-volume relationships (static and dynamic compliance) introduces another major problem, namely, the requirement to obtain a measure of intra-esophageal pressure. This requires passage of an intra-esophageal catheter, which, while offering little discomfort to the trained cooperative physiological subject, will no doubt discourage the uninitiated. It is considered, however, that on special occasions, with willing scientist-astronauts, the measure could be implemented without undue difficulty, using a miniaturized pressure transducer mounted on a catheter tip, and displaying pressure and related volume on an X-Y plot. The same measures can be used for determination of the work of breathing. Measurement of compliance of the lung-thoracic cage system does not seem feasible in the space environment.

The same difficulty on obtaining pressure measurement applies to the determination of pressure-flow relationships. However, if measures of intra-esophageal pressure are made for compliance studies, it would be appropriate to undertake pressure and flow studies during the same experiment, using the electronic subtraction method of Mead and Whittenberger (1953)⁷², described in the text. Alternatively, although with less assurance of reliability, the technique of interrupting the airflow through a pneumotachograph (Neergard and Wirz, 1927⁸¹; Clements and Elam, 1955¹⁸) could be employed to derive some indication of the extent of pulmonary non-elastic resistance. Pulmonary viscous resistance is not amenable to direct measurement, but can be derived by subtraction of airway resistance from total pulmonary resistance. The only method of obtaining airway resistance, however, is by whole-body plethysmography.

At this point, it seems advisable to put in a plea for a space-borne whole-body plethysmograph. As noted in the text, such a device would serve many useful purposes in respiratory measurement, including the determination of lung volumes, airway resistance, and pulmonary capillary blood flow. In addition, as will be shown in another section, it can be used for determining body volume. Because of the need to have an external rigid box, neither the

space-suit nor a flexible bag-type device would be suitable. It is possible, however, that a portion of the spacecraft, normally used for other purposes, could be modified for use, when required, as a whole-body plethysmograph. In a large manned laboratory, which in all likelihood will contain an airlock, the latter would seem to offer possibilities for this purpose. It is not suggested that a whole-body plethysmograph be carried on all missions. It is possible, however, that a mission might be flown in which interest could be concentrated on the respiratory system, in which case a whole-body plethysmograph would be a valuable addition to the laboratory armamentaria. The recent development of Vorwald in electric field whole-body plethysmography might also be borne in mind.

For measurement of oxygen consumption, both as an index of work performed and for use in other calculations, the integrating pneumotachograph can again be employed, along with an oxygen pressure sensing device. Kissen and McGuire (1966)⁵³ have demonstrated the feasibility of this approach, although their instrumentation could undergo considerable development before being qualified for space use.

With respect to respiratory gas analysis, it is apparent that traditional methods employing the Scholander or Haldane apparatus are not feasible in the weightless state. Numerous other methods, including mass spectrometry, spectrophotometry, and gas chromatography are possible for general use, depending largely on their availability for other purposes, while in addition, specific systems are available for measurement of carbon dioxide, nitrogen, oxygen, and helium. While mass spectrometry is the most versatile technique, and could be employed for atmospheric and biochemical analysis in addition to respiratory gas analysis, it is not reasonable at this time to recommend any particular measurement system or systems, as being the most suitable for selection. All that can be said at this time is that methods of respiratory gas analysis can be readily developed for use in an orbiting space laboratory, and will be required for such measures. A comprehensive trade-off study is needed, taking into account all potential uses of such instrumentation, with particular reference to the purpose and type of given missions, the type of vehicle and its environmental control system, the size of crew, their tasks and their available skills, before any particular

instrumentation system could be selected. It is very probable, however, that at least some physiological instrument may duplicate, and act as back-up for, environmental control instrumentation. In addition, the system or systems, selected in most, if not all, cases will require further development for space qualification and integration into a space system.

Assuming suitable instrumentation, measurement of alveolar ventilation from respiratory gas depends upon accurate measurements of dead space volume. The most feasible technique to obtain this measure in a two-gas atmosphere would seem to be the single oxygen breath technique, using an appropriate diluent gas measure, such as a nitrogen analyzer in the case of nitrogen, and an integrating pneumotachograph. To determine effective ventilation, which is physiologically more significant, or in a pure oxygen environment, the principle of equation (8) could be employed, by which effective alveolar ventilation is calculated from measures of expired carbon dioxide (from, for example, an infrared CO₂ meter) and arterial P_{CO₂}. The latter, as has been noted can be obtained by the use of a glass electrode on a capillary blood sample.

Several techniques are in use to determine the uniformity of distribution of alveolar ventilation. As noted in the text, however, the complexity of the more definitive techniques renders them unsuitable for orbital laboratory use. It is considered that the stethoscope, in skilled hands, perhaps backed up by chest radiography, would provide useful qualitative information. More definitive, but still relatively simple, testing would involve examination of the trace of diluent gas concentration to determine the rate and magnitude of increase in concentration during expiration, as described in the text.

Measures to determine uniformity of capillary blood flow, ventilation perfusion ratios, and diffusion capacity, present formidable difficulties in the orbiting manned space laboratory. Although several potential techniques are discussed, it is concluded that unless the information is specifically sought on a special mission with a skilled investigator and trained subject, the experimentation required belongs in the ground-based cardiopulmonary laboratory. Some ancillary qualitative information on capillary blood flow, however, can be obtained by continuous analysis of carbon dioxide in expired

air, using the technique of Comroe et al., (1962)²⁰, in which it is assumed that expired carbon dioxide comes from alveoli with a significant capillary blood flow and that the early portion of the breath comes from well ventilated regions and the later portions, from poorly ventilated. The assumption is considered valid if the ventilation is asynchronous as determined by the single breath oxygen test. Thus, a qualitative impression can be obtained, based on the concentration of carbon dioxide in different portions of the expired air.

There would, however, appear to be no feasible methods for routine determination of diffusion capacity. Methods involving carbon monoxide are considered unwise because of the danger of contamination, while those using oxygen require measures of arterial and mixed venous P_{O_2} as well as exposure to hypoxia. The measure of mixed venous P_{O_2} , which requires cardiac catheterization, is considered unwise under the circumstances, while the technique and procedures in general are extremely complex.

Measurement of arterial oxygen, carbon dioxide, and pH raises problems of a different nature. Arterial puncture, while only mildly hazardous, is uncomfortable and not considered appropriate for routine use on astronauts. With trained willing subjects it would be a feasible procedure. For regular use, however, sampling of arterialized capillary blood is considered to be an effective and simpler substitute, although suitable sampling techniques will need to be developed, particularly for use in a high oxygen partial pressure atmosphere. The traditional methods of blood gas analysis are, of course, inapplicable in the weightless state. For oxygen and carbon dioxide analysis numerous other methods are available. These include spectrophotometry, oximetry (for oxygen), mass spectrometry, gas chromatography, and the use of specially designed electrode samplers, some of which have been miniaturized and developed into combined systems appropriate for space use. Electrodes for pH measurement are also available.

For measurement of oxygen saturation, ear oximetry would seem to be the simplest and most reliable procedure, although its accuracy and reliability are not accepted by all. There is no doubt that spectrophotometry would provide still greater accuracy. For measurement of blood oxygen and carbon dioxide content, a gas chromatograph or mass spectrometer

would seem to be the most useful, particularly if already available for other purposes. After suitable equilibration of samples with 100% oxygen, values could also be derived for oxygen saturation. Techniques would have to be developed, however, for introducing gases from the blood into these devices in the weightless state. For routine measurement of gas tension and pH, the gas and pH electrodes provide a favorable approach. As with respiratory gas analysis, however, it is far from clear which manufacturer provides the most suitable electrode or the most appropriate system. Again, a trade-off study is desirable, which would take into account the suitability, reliability, compatibility with other systems, and the versatility of the respective instrumentation systems, as well as the operational constraints of power, weight, and volume, and the requirements for integration into the total space system.

In conclusion, it is apparent that with relatively minor development of existing equipment, useful information on many aspects of respiratory physiology could be obtained with relatively little difficulty within the confines of an orbiting space laboratory. If necessary, those areas considered here to be unsuitable for examination in orbital conditions could also be investigated under special circumstances. It is again emphasized, however, that any recommendations made are based on theoretical considerations and require validation under simulated, and preferably actual, conditions before acceptance.

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