Why a Pulmonary Function Laboratory?

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A senior medical student recently posed this question with sincerity and, after an initial reluctance and temporary apnoea, I decided this should be answered in full.

It is customary for those of us who are current custodians of a store of knowledge to lean heavily on the official pronouncements of our elders, and this is what Melville Arnott (Lancet, January 2, 1960.1.1.) recently had to say about respiratory failure.

"For the past decade or so clinicians have been approaching the problems of cardiac and renal failure along physiological lines, thinking in terms of cardiac output, glomular filtration-rates, and so on. But they still seem curiously reluctant to use physiological lines of thought in the analysis and treatment of respiratory disease. We now have many comparatively simple and reasonably accurate methods of measuring respiratory function, and these generally sharpen clinical diagnosis. Yet many British teachers of medicine either ignore them altogether or refer to them as some sort of activity of backroom playboys and not the sort of thing for a practical doctor. The current clinical approach is still dominated by 'stony dullness' and 'dry sounds'. Perhaps all this is due to the innate conservatism of the Old World; but the fault is not solely that of the clinician. It is also that of the physiologist, because in some British medical schools the treatment of respiratory function (dysfunction really) is still frozen at the stage of 'lung statics'."

Again the President of the Royal College of Physicians, London, Sir Robert Platt, Bart., in an introductory remark to a book concerning Clinical Physiology states:

"The fascination of the Medicine of my time, which has made it so exciting to have witnessed the last 40 years, has been twofold: first, the rational understanding of the phenomena of disease in terms of physiology; and second, the therapeutic triumphs which although sometimes seeming to arise by chance were only possible on the new background of clinical science.

Interest was shifting from the procedures of experimental physiology to the more subtle experiments of nature as witnessed at the bedside, and in the pursuit of their clinical studies it is perhaps not going too far to say that the new physicians have in the last 20 years contributed as much or more to the study of physiology as have the physiologists to medicine."

The important implications of these remarks lie in the direction towards which they point, namely that field of observation which is the province of every doctor, the wards. The "backroom playboys" and the men in ivory towers are clearly being challenged. The wards provide a wealth of disordered physiology for which the carefully nursed apparatus of the ivory towers and of the catacombs of science may be quite inadequate. It is well to remember that it was the physicians who demanded better spirometers. The ordinary Benedict-Roth spirometer which has been a standard item of furniture of the physiological laboratory for 30 years failed dismally in the accurate assessment of maximum expiratory flow rates, because its moving parts had too high an inertia and a resonance frequency of about 0.5—1.0 cycle per second, instead of twice this for the satisfactory measurement of maximum voluntary ventilation or forced expiratory volume. Again the Hamilton manometer, cherished for decades had to yield, because of its low frequency responses, to the electro-manometer of the strain gauge or capacitance type as demanded particularly by the cardioligist engaged in measurement of pulmonary and peripheral resistance.

The photo-electric cell used for the estimates of oxy-haemoglobin percentages in blood samples has been an esoteric play thing in certain laboratories since 1932, but it needed the impetus of cardiac surgery to bring this instrument out of splendid isolation and harness it as a working tool to the needs of the cardiologist concerned with cardiac output and accurate shunt flow calculations. Many more examples can be quoted to emphasize the liberating influence of the demanding physician on such incarcerated instruments, and the real challenge in any University stems from the clinical mind no longer content with intuition and instinctive diagnostics.

For over 100 years have pathologists reigned supreme in the autopsy room as the final arbiter of clinical problems, and will, no doubt continue to do so, until the tedium of this gamemanship of physician versus pathologist gives way to greater precision in the understanding of disordered function as a result of established disease. In no field is this more urgent than in the disorders of the circulation, and of the lung.

The dawn of any new era is usually heralded by questioning the orthodox, and in the field of respiratory disease the overwhelming effect of the following question is still universally perceptable, namely; "Can clinical observation alone provide an adequate understanding of lung disease?"

Most conscientious physicians have been familiar with the dilemma of hypo-ventilation and received little comfort from the use of an oxygen-tent in the presence of cyanosis in patients with respiratory failure, particularly if the improvement in colour coincided with a sinister drop in the rate of respiration, the latter being frequently the only measurement taken in many hospitals catering for the disorders of the lung. Again the development of oedema and cardiac failure in a variety of dissimilar lung diseases has seriously worried physicians, and continues to do so since the laboratory has so far failed to offer even a remotely satisfactory explanation for its often sudden occurence. Without an adequate understanding of its genesis, therapy of cor plumonale is at best empirical and the use of digitalis very questionable.

HOW, THEN, CAN A RESPIRATORY FUNCTION LABORATORY AID THE EVERY DAY PROBLEMS OF THE WARD?

In essence, most pulmonary function tests are supplementary to careful clinical scrutiny, and render information in each patient of a facet in the overall mechanisms for, and cost of maintenance of normal arterian oxygen and carbon dioxide levels. No single pulmonary function test yields all the information necessary, and what is required is a combination of tests which selectively establish information concerning:

1. The mechanics of ventilation.

2. The effectiveness of this ventilation in terms of alveolar ventilation.

3. The size of the physiological dead space and the partial pressures of oxygen and carbon dioxide at alveolar level.

4. The diffusion of oxygen and carbon dioxide across the alveolar membrane.

5. The perfusion of the pulmonary capillaries in relation to the distribution of ventilation.

6. The arterial oxygen and carbon dioxide gas tensions and their effect on pH and milieu interieur.

THE MECHANICS OF VENTILATION

The efficiency of ventilation depends on the volumes of the lungs and dead space of the upper respiratory tract, and the efficiency of the thorax to act as bellows. The latter can be tested by analysing the forces and resistances concerned in breathing. The elastic restorative force is dependent on the degree of inflation (i.e. volume). This force increases gradually with the depth of inspiration, the energy stretching the "spring" being stored in the lung and thorax. It is usual to express this relationship of volume to the elastic force

as *compliance* or litres/cm H_2O pressure. It is obvious that this measurement can only be made when no actual air is flowing. The resistance caused by air flow and the viscous resistance within the tissues is expressed as the pressure difference between mouth pressure and that at alveolar level, and this is equal to about the square of the velocity of flow. The gradient between mouth and alveoli can now be measured by recording the oesophageal pressure, which equals the intrathoracic pressure. Thus by plotting the oesophageal pressure against the flow at the mouth, or the change in volume, it is possible to calculate *air flow resistance and compliance.* In normal subjects the air flow resistance is similar in inspiration and expiration during normal breathing. In chronic obstructive emphysema there is usually a gross difference in the resistance in the two phases of respiration, with a marked increase on expiration. In asthma, the resistance is increased during both phases.

Tests concerned with the mechanics of breathing are meaningless in the absence of knowledge of the overall ventilatory capacity. The simple determination of the vital capacity has largely been superseded by the measurement of the maximum voluntary ventilation (or maximum breathing capacity in the old terminology), and the single forced expiration test. The vital capacity still provides an overall idea of ventilatory impairment, but it fails to relate the volumes measured to time and the functional residual capacity. Clearly it is necessary to bear in mind the interdependence of most tests, particularly the vital capacity, on such factors as changes in air flow, tissue resistance, compliance of chest and lung, muscular work, and above all the size of the lung. The *maximum voluntary ventilation,* a test of the maximum volumes of air expired over a unit period of time (which in practice is 15 seconds and this is multiplied by four to obtain the minute volume figure), and the *timed forced expiration test,* (a measure of the volume of air that can be forcefully expired over periods of either .75, 1.0, 2.0 or 3.0 seconds), have excellent discriminatioi. The variability of these two tests in a normal individual is small. The two tests give similar and related information. The former suggests that the minute volume of respiration in any individual should be a fraction of the maximum voluntary ventilation. It is easy to see that in patients with emphysema or lung fibrosis the time needed for each breath and the volume delivered with each breath over 60 seconds will cause the breathing reserve to diminish and a state may soon be reached when a patient requires his maximum voluntary ventilation at rest.

The timed forced expiration test offers a short cut to the determination of the maximum voluntary ventilation inasmuch as the duration of this test determines the percentage of the vital capacity which can be delivered in that time. The time of .75 seconds, in normal individuals, is sufficient for the expiration of over 90% of the vital capacity. By determining the percentage of the vital capacity delivered it is easy to calculate the total time needed for the total vital capacity to be delivered. On multiplying this volume by the number of similar breaths a patient might be capable of in one minute, the maximum voluntary ventilation can be calculated from the single breath technique. The normal figure of about 100 litres for the mvv vary, of course, with age and sex, but are useful and fairly reproduceable.

Expiratory flow rates and the *timed vital capacity* are very useful tests particularly in the assessment of bronchodilator drugs. Similiarly the maximum voluntary ventilation or maximum breathing capacity depends on functioning lung tissue and airway resistance and the normal figure of 110 litres/min or more will be significantly reduced in the presence of much airway resistance. Clinically, dyspnoea becomes manifest at about 35% of the maximum voluntary ventilation. The breathing reserve can be calculated from the maximum voluntary ventilation-amount of ventilation used at rest/100, or

$$\frac{\text{MVV-RMV}}{\text{MVV}}$$

The value normally is about 95%. The *dyspnoea index*=%MVV used for resting ventilation or

$$\frac{\text{RMV}}{\text{MVV}\times 100}$$

Another useful manipulation is the establishment of the *air velocity index*, which is

$$\frac{\%\text{MVV}}{\%\text{VC}}$$

This is normally above 1.2 and when reduced to 0.8 it will point to air-trapping.

Alveolar Ventilation

The determination of the lung volumes is incomplete without the knowledge of the residual volume, which requires special techniques for its determination. The *residual volume* can be determined by means of the helium dilution closed circuit technique, or the open circuit nitrogen washout technique. The sum of vital capacity + residual volume=*total lung capacity* which in the normal is about 5.5 litres or more. The sum of the residual volume and the expiratory reserve capacity = *functional residual capacity*. An increase in residual volume invariably leads to an increase in tidal volume in order to maintain normal partial pressures of oxygen and carbon dioxide at alveolar level. An increase in tidal volume also requires the minute ventilation to be increased, and therefore increases the work of breathing. The effective minute ventilation, however, is only that volume of ventilation which enters the alveoli. Since the respiratory tract is composed of a conducting airway and the alveoli, the alveolar ventilation constitutes a fraction of the tidal minute ventilation, the remainder being dead space ventilation. The dead space consists of the anatomical conducting pathway, alveoli which are ventilated and not perfused with blood, and hyperventilated and poorly perfused alveoli. The sum of these spaces is known as the *physiological dead space*. It can be calculated from the Bohr equation which states that:

Dead space=

$$\frac{\text{tidal volume (alv. } pCO_2\text{-expired } pCO_2)}{\text{alv. } pCO_2}$$

Instead of avl. pCO_2,
the arterial pCO_2 is normally used.

The *total alveolar ventilation*=
minute ventilation—dead space ventilation, and this can be obtained from the CO_2 clearance formula, which states that V. alv.=

$$\frac{\text{volume } CO_2\%\times\text{BTPD}}{\text{arterial } pCO_2}$$

Clearly the measurement of alveolar ventilation is obligatory in all hypoventilation states associated with arterial CO_2 retention, particularly as CO_2 retention will occur whenever the alveolar ventilation falls below four litres per minute. A glance at the oxygen dissociation curve will show that at levels of three litres the arterial oxygen saturation will still be within the limits of the normal, while CO_2 retention is already fairly high.

In emphysema not only will the residual volume be increased but intrapulmonary gas distribution is often unequal. The nitrogen washout technique over seven minutes will show an increased index of intrapulmonary mixing, i.e., the alveolar nitrogen concentration will be above 2.5% after seven minutes of oxygen breathing.

Alveolar Oxygen and Carbon Dioxide Tensions.

The lungs at alveolar level behave like a gas chamber where the partial pressures of the respiratory gases are approximately constant. The partial pressure of oxygen is about 105 mm. Hg. and that of carbon dioxide is about 40 mm. Hg. For these tensions to remain at these levels it is necessary to have an effective alveolar ventilation of about four litres per minute and a physiological dead space of about the same as the anatomical dead space, provided that the patient breathes air. It is simple to see that alveolar hypoventilation and changes in residual volume or air distribution will not maintain such alveolar gas tensions. An approximate estimate of the alveolar oxygen and CO_2 tensions can be obtained from the arterial gas tensions, but these can never be the same as the alveolar gas tensions because the 1-2% venous admixture which takes place in the

left heart and pulmonary venous blood cannot be technieally obtained. The alveolar air equation does, however, give a fairly close approximation for *alveolar oxygen tension*. It states that

$$\text{alv. } pO_2 = \text{inspired } pO_2 - \frac{\text{art. } pCO_2}{RQ}$$

(RQ=respiratory quotient)

Diffusion of Oxygen and Carbon Dioxide across the Alveolar Membranes.

The above tests are vital in an understanding of the efficiency of ventilation, but they do little towards testing efficiency of gas exchange. While it is conceivable and very probable that impaired ventilation may influence perfusion of the corresponding lung lobes in instances of underventilated lung cysts or lobes, the measurements of simultaneous lobar capillary perfusion with those of ventilation are, as yet, very academic and not clinically very helpful. Nevertheless, it is known that even if there is a normal ventilation perfusion ratio the blood leaving the lungs may still be undersaturated, if the barrier to diffusion if gas from the alveoli to the haemoglobin in the capillaries is increased. There is no direct method of measuring the thickness of the alveolar walls or the surface area of the lung in life, but it is possible to measure the diffusing capacity of the lung as a whole. This is an important concept inasmuch as it constitutes the most fundamental step in the understanding of the lung function since the measurement of the vital capacity, and it is the cornerstone towards the evolution of a clinical appreciation that known disorders of the lungs cause primarily disorders of function, the most important being the loss of diffusing surface for the exchange of respiratory gases. The

$$\text{diffusing capacity for oxygen} = \frac{\text{mls. uptake of gas/minute}}{\text{the gradiant of partial pressure of the gas across the alveolar membrane..}}$$

Diffusion constitutes the random movement of gas molecules from a high to a low concentration. Apart from temperature and barometric pressure, diffusion is influenced by the thickness of a membrane and takes place in the direction of the pressure gradient. The *pulmonary diffusing capacity* is defined as milliliters of gas transferred per minute per 1 mm. Hg pressure gradient across the alveolar membrane. In practice small concentrations of carbon monoxide are used to determine the lung diffusing capacity. Haemoglobin has 210x the affinity of oxygen for carbon monoxide and the pulmonary diffusing capacity= 15 mls of CO/1 mm. Hg. This value multiplied by 1.23 will give the diffusing capacity for oxygen. The diffusing capacity increases on effort and in conditions associated with a high pulmonary blood flow, and falls considerably with the loss of lung substance and capillary bed. It is particularly low in severe emphysema.

The denominator of this important formula is expressed as the mean alveolar partial pressure-mean capillary partial pressure. The avidity with which carbon monoxide and oxygen are taken up by the haemoglobin results in the alveolar membrane being the principal limiting factor to the rate of uptake of the two gases. CO was first used for the calculation of diffusing capacity by Krogh in 1915 and very little original thought has been added to this brilliant concept subsequently. Since the partial pressure of CO in capillaries is zero, one merely needs to measure the alveolar mean CO partial pressure and then the amount of gas absorbed per unit time in order to obtain rapid estimates in man. The mean alveolar pressure can only be approximated from end tidal air samples and it is quite clear, therefore, that in the presence of impared intra-pulmonary mixing, as for instance, in emphysema, the residual volume should be known as well as the nitrogen washout time. Otherwise, the so-called end tidal air sample is, in fact, not such a sample and the concentration and tension of CO in that sample bears no relationship to that at alveolar level. Nevertheless, everyone is agreed that the present methods of measuring diffusing capacity have established gross reduction in diffusing surface in emphysema and that prognostication can be based on its reduction to critical levels. It is of interest that the

normal diffusing surface increases 75% above resting level with effort.

The Ventilation Perfusion Ratio.

Normally the cardiac output of about five litres is equally divided between both lungs so that about 2.5 litres of blood reach the pulmonary capillary bed of each lung. Similarly, the alveolar ventilation of four litres is equally divided. Thus the ideal ventilation perfusion ratio would be for each lung:

$$\frac{\text{Ventilation}=2\ \text{L/m}}{\text{Perfusion}=2.5\ \text{L/m}}=0.8$$

It follows that this ratio will be grossly altered should one pulmonary artery be occluded, unless the ventilation to the unaffected side is doubled, which would mean a total alveolar ventilation of 0.8 litres. The total cardiac output, of course, would have to be shunted to the normal side. To maintain this ratio at 0.8 and the arterial blood gases normal, the normal lung ventilation=4 L/min:
lung perfusion=5 L/min:
the abnormal lung ventilation=4 L/min:
lung perfusion=0 L/min:
therefore, total ventilation=8 L/min:

Arterial Oxygen and Carbon Dioxide Tensions and Blood pH.

Finally, the efficiency of the lungs to maintain normal pH of the blood, arterial oxygen saturation and CO_2 tensions, clearly depends on a combination of functions as determined by the foregoing tests as well as normal renal function and probably posterior pituitary and adrenal hormonal control. The central nervous system has additional and important influences on lung function, respiratory drive and probably also lung capillary permeability. Few of these influences can, as yet, be satisfactorily tested. Respiratory drive certainly depends on central control via the respiratory centre. This is sensitive to changes in blood pH, CO_2 tension, and anoxia. The latter is probably the most important remaining stimulus to breathing in patients with pulmonary insufficiency and CO_2 narcosis. Blood gas analysis, particularly pCO_2, pO_2, and pH of arterial blood are obligatory investigations in the rational management of patients in respiratory failure and have the same, if not greater, urgency in guiding therapy as have blood sugars in diabetic coma or blood urea in renal failure.

EDITOR'S NOTE:

The Journal is particularly proud to have been able to print the above paper. The activities of the Pulmonary Function Lab. as a teaching, research, and clinical investigation unit place a harsh limit on Dr. Cudkovicz's time.

At present, the laboratory maintains an active research program, which includes a classified project concerned with respiratory function in selected Naval men. Concurrently, the lab provides facilities for examination of clinical problems of cardiopulmonary nature, in order to further define proper diagnosis and treatment.

Included in the experience of first year students, will be their familiarization with and operation of the instrumentation of the lab. This program is allied with the series of lectures given by the Dept. of Physiology on pulmonary function. Further teaching is provided residents, internes and students of the various clinical departments. They are provided with an opportunity to follow up their patient's status by observing the patient performing the tests and by consultation with the laboratory medical staff concerning the interpretation of results.

The mechanical implementation is devised to measure directly and accurately those values mentioned in the above paper. There is, as of yet, no instrument capable of the interpretation of these values. Thus, even as fine a laboratory as this has not supplanted the necessity for an appreciation and understanding of pulmonary "physiopathological" phenomena.

Dr. Cudkovicz extends an invitation to all interested parties, to visit and inspect the Laboratory facilities.

R.B.L.