Net and Gross Lung Failure Among Patients Sent for Pulmonary Function Testing

R. HOLLOWAY, M.D., S. CHETTY (6TH-YEAR MEDICAL STUDENT) AND P. MOODLEY (5TH-YEAR MEDICAL STUDENT), University of Natal and Respiratory Unit, King Edward VIII Hospital, Durban

SUMMARY

In investigating whether a useful purpose could be served by classifying patients thought to have lung failure into those with a wide alveolar to arterial oxygen gradient (net lung failure), and those with underventilation (gross lung failure), the blood gases of 107 consecutive patients sent for lung function were measured.

It was found that the presence of a widened alveolar to arterial oxygen gradient was the commonest disturbance (86% patients), whereas alveolar hypoventilation was found in less than 15% of the patients (15%).

After a widened alveolar to arterial oxygen gradient, the next most common disturbance was hyperventilation (found in 42% of patients).

It is concluded that this classification might be useful since it directs attention to the underlying disturbance. It is also concluded that laying undue stress on hypoventilation is misleading for hyperventilation and a widened alveolar to arterial oxygen gradient are more commonly encountered.


A basis for understanding lung mechanics was already laid at the beginning of this century. By the end of the first world war gas exchange was all but completely investigated and the principles of acid-base metabolism were understood. Electrodes for the measurement of blood gases appeared shortly after the Second World War and when 15 years later radio-isotopes made their debut into pulmonary physiology, regional ventilation came under investigation.

As a result of all this the modern pulmonary function laboratory can accurately measure most of the variables which need to be known for an understanding of normal and disturbed lung function. Indeed, more information is available on the working of the lung than perhaps any other organ.

Yet the student faced with what he imagines must be lung disease is frustrated. There seem to be no rules on how to use this information in the quest for a diagnosis. Unsure of what he must measure he is not enlightened when, having made a decision, he is presented with the results expressing unfamiliar concepts in unusual units.

We feel that no attempt has been made to guide the student through the maze of information which wells up out of the laboratory. Simplification, when it is attempted, is rarely directed toward simplification of the search for a diagnosis but rather toward making the tests themselves easier to understand.

In an attempt to do something about this, we decided to measure the blood gases of patients sent for pulmonary function and investigate whether these could form the basis for understanding underlying disturbances.

We consulted the literature for evidence that others had considered this approach rational, and found that Fishman and Senior have used just such an approach. They pointed out that lung failure can be examined in terms of derangements of blood gases and coined the term 'net respiratory failure' to designate one disturbance.

Using this approach we have classified patients according to whether they have disturbances of alveolar ventilation and whether they have abnormal alveolar to arterial oxygen gradients. We have also been able to examine the incidence of the various types of blood gas disturbances. The results suggest that the most common disturbances have not received the most attention.

MATERIAL AND METHODS

Subjects

The blood gases of 107 consecutive patients referred for lung function were studied. Patients were grouped according to disease. Sixty-six per cent (73 patients) were suffering from chronic non-specific lung disease, 9% from asthma (reversible airways disease with remissions during which there was a normal FEV); but in some instances abnormal alveolar to arterial oxygen gradients—see below), 5% from lung fibrosis (diagnosed by X-ray and pulmonary function tests) and the remaining 20% from a variety of conditions such as air-trapping, bronchiolitis, pneumonia, cardiomyopathy, allergy, polycythaemia, tuberculosis, lung emboli and bronchiectasis.

Because the patients with chronic non-specific lung disease constituted the majority group, they have been considered separately. Where possible they have been classified into group A, B or X. Information was available to permit this in 44 of the 73 who had chronic non-specific lung disease. Of these 28 were type X (mixed), 3 type B (mainly bronchitis), and 13 type A (mainly emphysema).

Methods of Investigation

Arterial blood was collected from either the femoral or the brachial artery. In most instances femoral artery blood was collected in a heparinized small vein set (Baxter R35).
These blood samples were analysed immediately. Tests performed on the polythene tube of the scalp-vein set showed it to be impervious to both oxygen and carbon dioxide over the minutes between sampling and analysis (we discontinued tests after 2 hours). When brachial-artery blood was used, indwelling catheters were employed and the blood taken into heparinized syringes.

Carbon dioxide tension was measured in 2 laboratories controlled by one of us (R.H.), a Radiometer carbon dioxide electrode was used in the one and in the other carbon dioxide was measured by the interpolation method. The carbon dioxide electrode was calibrated by means of gases whose carbon dioxide tensions were known.

In both laboratories oxygen tension was measured by means of Radiometer electrodes. These were standardized using thermostat water ($P_{O_2} 21\% \times PB = 47\, \text{mmHg}$) and a solution whose $P_{O_2}$ was taken to be zero (saturated sodium sulphite in 0.01M borax). The electrodes were calibrated before each measurement. About 4 times weekly, blood was tonometered with gases of known oxygen tension and the electrode checked by comparing the measured $P_{O_2}$ with the $P_{O_2}$ of the gas. In this way it was possible to establish that the difference was $1.1 \pm 2.2\, \text{mmHg}$.

**RESULTS**

The results of blood gas measurements on the 107 consecutive patients appear in Table I. They have been divided into 3 groups according to their $P_{acO_2}$. The first group, called 'hyperventilators' had an arterial $P_{acO_2}$ of less than 35 mmHg. The 'normoventilators' were those whose $P_{acO_2}$ lay between 35 - 45 mmHg, and the minority, whose $P_{acO_2}$ lay above 45 mmHg, have been called 'hypoventilators'.

Also contained in Table I are the mean forced expiratory volumes expressed as a percentage of the vital capacity (FEV$_1$/VC).

While there was no significant difference between the FEV$_1$/VC of the hyperventilators and the normoventilators, the mean FEV$_1$/VC of the hypoventilators was significantly below that of the other 2 groups indicating that as a group they had a higher $P_{acO_2}$ and greater airways obstruction. They also had significantly greater desaturation of their arterial blood. This was in part due to their high $P_{acO_2}$ but a widened alveolar to arterial oxygen gradient also contributed.

There was no statistically significant difference between the mean $P_{acO_2}$ of the hyper- and normoventilators but the hyperventilators had a significantly ($P < 0.01$) greater alveolar to arterial oxygen gradient.

The findings among the patients with chronic non-specific lung disease are given in Table II. It can be seen that they are similar. There were, if anything, fewer hypoventilators (7%). In this subgroup, as in the larger group, there is surprising similarity between the arterial oxygen tension of the hyper- and normoventilators.

**DISCUSSION**

There are 3 types of lung failure. The first arises out of disturbed gas flow 'ventilation failure'. The second follows disturbance of blood flow 'perfusion failure', and the third failure of the lungs to match ventilation and perfusion or 'ventilation - perfusion' failure.

Ventilation failure is gross lung failure and the other 2 together constitute net lung failure. Net and gross lung failure can be distinguished by examination of the blood gases.

**Differentiation Between Net and Gross Failure**

A high alveolar carbon dioxide tension indicates ventilation failure or gross lung failure, while an arterial oxygen...
Diagnosing Gross Lung Failure

Gross lung failure is said to be present when alveolar carbon dioxide tension exceeds the upper limit of normal (45 mmHg). For most purposes, certainly for all clinical purposes the reasonable assumption can be made that alveolar and arterial carbon dioxide tensions are the same.

The normal arterial carbon dioxide pressure lies between 35 - 45 mmHg and an arterial (alveolar) carbon dioxide of more than 45 mmHg indicates the presence of gross lung failure.

Diagnosing Net Lung Failure

The calculation of alveolar oxygen tension: While breathing air, the maximum alveolar oxygen tension (no carbon dioxide present) would be 150 mmHg at sea level.*

With a normal respiratory gas-exchange ratio of 0.85, 12 molecules of carbon dioxide replace every 10 molecules of oxygen removed from alveolar gas. Knowing this and the inspired oxygen pressure together with the arterial (alveolar) carbon dioxide pressure, it is possible to calculate the alveolar oxygen as follows:

\[ \text{P\text{AO}}_2 = 150 - 1.2 \times \text{P\text{CO}}_2 \]

where \( \text{P\text{AO}}_2 \) = alveolar oxygen tension
\( \text{P\text{CO}}_2 \) = arterial (alveolar) carbon dioxide tension.

Calculating the alveolar to arterial oxygen gradient: Once the alveolar oxygen tension has been calculated it is possible to compute the alveolar to arterial oxygen gradient by subtraction. The arterial oxygen tension is measured (blood gas analysis) and the alveolar oxygen tension found by difference.

Example

Arterial carbon dioxide measured 40 mmHg
Therefore alveolar oxygen (equation 1) 102 mmHg
Arterial oxygen tension measured 92 mmHg
Therefore alveolar to arterial oxygen gradient 10 mmHg

The alveolar to arterial oxygen gradient found in the example is the normal. Quite unlike carbon dioxide (where there is no gradient) oxygen in the arterial blood is at a lower pressure than in the alveolar gas. Delicate mechanisms must operate to bring the arterial oxygen anywhere near alveolar and, as has been seen, even in the normal, the best that is achieved is an alveolar to arterial oxygen gradient of 10 mmHg. In our laboratory we accept up to 15 mmHg as normal.

It is when these mechanisms fail that net lung failure is diagnosed. Net lung failure is defined as an elevated alveolar to arterial oxygen gradient.

Our aim during this study was to see whether examination of the blood gases in this way could be of value in assessing lung disorders. The blood gases taken individually indicate whether a subject is underventilating (a high \( \text{P\text{CO}}_2 \)) and if there is arterial hypoxaemia (a low \( \text{P\text{AO}}_2 \)).

Hypoxaemia of a magnitude greater than that accounted for in terms of underventilation and carbon dioxide displacing oxygen from alveoli (net lung failure) can be diagnosed by examination of the 2 gases together.

Once the presence of underventilation has been established, measures designed to improve ventilation can be instituted, and if an elevated alveolar to arterial oxygen gradient is found, attention can be directed toward discovering which of the 4 possible causes is operating:

1. Ventilation perfusion imbalance.
2. A right to left shunt.
3. A diffusion defect.
4. Cardiac failure where very desaturated mixed venous blood passes through a normal shunt.

Expressed in terms of net and gross lung failure the findings of this study indicate that while gross lung failure was present among 15% of the patients studied (the hyperventilators), net lung failure was far more common, occurring in all groups.

While this approach leads the investigator, even the uninitiated, toward a diagnosis which has meaning in terms of deranged function, it shows what we believe to be defects in knowledge and ideas concerning treatment.

LUNG FAILURE WITH HYPOVENTILATION

Books have been written on the treatment of gross respiratory failure and the student reading almost any standard text cannot but gain the impression that underventilation, if not the commonest form of lung failure, is found very frequently.

In this study we were surprised to note that only 15% of the patients seen in the laboratory were underventilating. We thought that perhaps patients with alveolar hypventilation were so ill that they were not sent to the laboratory, and therefore examined 752 consecutive blood gas analyses (performed in our laboratory) from the whole hospital (some 2,000 beds). Out of 752 blood samples 67 (8.9%) had a \( \text{P\text{CO}}_2 \) of more than 45 mmHg, a proportion very like that found in blood samples from laboratory patients.

Even this does not prove that underventilation is uncommon among patients with lung disease (for the blood gas service is offered to all, a host of other acid-base disturbances will have been investigated and may have swamped the patients with lung disease, but it lends weight to the suggestion that the student who expects to frequently find a high arterial carbon dioxide tension (alveolar hypventilation) is likely to be surprised. We took this further by examining another group of patients. These were children with severe laryngotracheobronchitis (croup) being studied in another division of the Respiratory Unit.

A preliminary investigation showed that even though all the patients studied had upper airways obstruction (ribs recession and stridor) only 19% (6 out of 31) had a high \( \text{P\text{CO}}_2 \). Since then more patients have been seen and further subdivided into those who on clinical grounds
were judged to be in the severest group. Among them there are more underventilators but the proportion is still only 46% (6 out of 13).  

We have concluded that underventilation is not as common as the wealth of information on what to do about it implies.

**LUNG FAILURE WITH A WIDE ALVEOLAR TO ARTERIAL OXYGEN GRADIENT**

By far the most common form of lung failure was net failure (found among 92 out of the 107 patients). This was found not only among the underventilators but among patients who were ventilating normally and those with alveolar hyperventilation. Indeed the severest forms of net lung failure (the widest alveolar to arterial oxygen gradients) were found among patients with alveolar hyperventilation.

The alveolar to arterial oxygen gradient has received considerable attention and the interested student has no difficulty in discovering how hypoxaemia associated with a wide gradient comes about. However, advice on how to reduce the gradient comes mainly from special works devoted to the treatment of congenital shunts, cardiac failure and diffusion defects—the underlying causes. Attempts have been made to improve the ventilation perfusion (V/Q) matching within the lung, but to date the majority of them have involved disturbances encountered during intermittent positive pressure ventilation. The student faced with a patient with a V/Q defect as part of his disease finds little help on how to treat him.

An interesting possibility has come as a by-product of the current controversy concerning bronchodilators and their effect on arterial blood gases. In common with others, workers from this laboratory have found that inhaled isoprotol aerosols produce significant arterial hypoxaemia. This probably occurs when the drug deranges matching of blood vessel tone (controlling blood flow) with bronchial tone (controlling gas flow) producing a fall in V/Q. However, when small doses are given intravenously or when phenylephrine (a vasoconstrictor) is added to isoprotol this fall in arterial oxygen is prevented. Indeed, instead of there being a fall, in some patients the reverse occurs.

Possibly current interest in lung pharmacology will clarify the situation and drugs with regional (V/Q) activity may become available.

**LUNG FAILURE WITH HYPERVENTILATION**

We have asked ourselves why so little attention is devoted to hyperventilation among patients with lung disease. Although a disturbed alveolar to arterial oxygen gradient was the most common disturbance encountered in this study (86% of the patients) alveolar hyperventilation was the next most common finding, being present in 42% of the patients.

The disinterest cannot be because the patients who were hyperventilating were not sick. Some of the most disabled patients in this study were hyperventilating and the same was found in the other study, referred to above, where the blood gases of children with laryngotracheo-bronchitis were examined. There, 2 out of 7 patients who died were hyperventilators.

There are a great many conditions associated with hyperventilation. These vary from intoxications (alcohol, paraldehyde, salicylates, 2,4-dinitrophenol) metabolic disorders (hypothyroidism, cirrhosis of the liver, beri-beri) and disturbances of temperature (pyrexia and cooling) to central nervous conditions (brain stem lesions, intracranial haemorrhage, encephalitis) and diseases of the lung producing fibrosis or hypoxia.

Although it is not possible to exclude all of these causes among the patients presented here, many of them are unlikely. Perhaps the most reasonable explanation is that the patients who were hyperventilating had chronic hypoxaemia. Acute hypoxia does not produce hyperventilation until alveolar oxygen reaches 65 mmHg and since there is an alveolar to arterial oxygen gradient even in the normal this presumably means that no hyperventilation occurs with arterial oxygen tensions of above 55 mmHg. But the same is not true of chronic hypoxia. Here the threshold arterial oxygen tension may be much higher probably because central chemoreceptors sensitive to cerebrospinal fluid pH, block the effects of acute but not of chronic oxygen deprivation.

However, hypoxaemia is unlikely to have been the cause for hyperventilation in all of the patients. There was, for example, no difference between the mean PaO2 of those hyperventilating and those ventilating normally, and some chronic hyperventilators (as evidenced by a negative base excess and normal pH with low PaCO2) had arterial oxygen tensions well above 80 mmHg (in one instance 110 mmHg). It could be reasoned that these patients would have been hypoxaemic had they not been hyperventilating, but some of the group patients mentioned above continued to hyperventilate even when they were given pure oxygen to breathe; in them at least hypoxia alone fails to explain the hyperventilation.

In other studies done in this laboratory the ability of normal subjects to improve arterial oxygenation by hyperventilation was investigated. It was found that although alveolar oxygen tensions could be elevated the same was not true of the arterial oxygen. With hyperventilation there occurred a simultaneous increase in the alveolar to arterial oxygen gradient so that in the normals, for example, when alveolar oxygen rose by 26 SD 9.99 mmHg the arterial oxygen remained unchanged.

Observations such as the above have prompted us to search for other possible causes for hyperventilation. One interesting possibility is suggested by the link between hyperventilation and disturbances of cardiac output. It has been suggested that there is a direct proportionality between cardiac output and PaCO2. Work done in this laboratory shows that while this may be so, the relation is not a simple one. Although cardiac output and PaCO2 bore a straight line relationship in normals (PaCO2 = 0.62 cardiac output (litres) + 36.6 : r = 0.51 : P < 0.001 : n = 110), this was not true in patients recovered from
pulmonary tuberculosis\textsuperscript{a} who were also hyperventilating. In them the relationship had shifted so that for a given P\textsubscript{a}CO\textsubscript{2} they had a higher cardiac output (P\textsubscript{a}CO\textsubscript{2} = 0.99 cardiac output (litres)) + 22 : r = 0.54 p less than 0.001 : n = 86.

It is possible that among the hyperventilators found in this series there were patients whose arterial carbon dioxide tension was low in association with a relatively low cardiac output.

Burrows and his colleagues\textsuperscript{a} have pointed out that patients suffering from chronic non-specific lung disease type A (mostly emphysema) have a P\textsubscript{a}CO\textsubscript{2} lower than that predicted on the basis of FE\textsubscript{V}.

Out of the group of 44 chronic non-specific lung disease patients presented here, 22 had arterial tensions lower than 35 mmHg and a further 5 were hyperventilating with respect to their FE\textsubscript{V}. (P\textsubscript{a}CO\textsubscript{2} less than that predicted on the basis of the formula of Burrows et al.: P\textsubscript{a}CO\textsubscript{2} = 11.5/FE\textsubscript{V} + 30.7).

Patients with emphysema are said to have lower cardiac outputs than those with bronchitis.\textsuperscript{a} If the relation between P\textsubscript{a}CO\textsubscript{2} and Q is the same in them as among the group of normals whose equation is presented above, then a low P\textsubscript{a}CO\textsubscript{2} is to be expected in association with low cardiac outputs.

Whatever the cause for hyperventilation the facts are that in this study a high proportion of patients sent for pulmonary function testing were hyperventilating often in association with net lung failure.

We should like to thank the technical and clerical staff of the Respiratory Unit; Professor E. B. Adams in whose department this work was done, for guidance; and the Medical Superintendent of King Edward VIII Hospital for facilities. This work was supported in part by the South African Medical Research Council and in part by the Wellcome Trust.

---

**REFERENCES**


---

**The Role of the Medical Adviser in the Pharmaceutical Industry in South Africa**

B. S. DE WET, M.B., CH.B., Assistant Medical Adviser, Roche Products (Pty) Ltd, Isando, Transvaal

**SUMMARY**

The position of the medical adviser to the pharmaceutical industry is emerging as a new and challenging specialty. His judgement and skills, which influence the industry’s research and marketing decisions, may affect the very nature of the practice of medicine.

*Date received: 16 August 1971.*