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REVIEW

Clinical relevance of ventilation-perfusion inequality determined by inert gas elimination

R. Rodriguez-Roisin, P.D. Wagner

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ABSTRACT: The first part of this review deals with the basic mechanisms and factors determining hypoxaemia and hypercapnia and the different approaches used in clinical practice and in clinical research to assess the presence of ventilation-perfusion mismatching, shunt and diffusion limitation for oxygen, and more specifically the multiple inert gas elimination technique (MIGET), in pulmonary medicine. The second part reviews three different respiratory disorders where the complex interplay between intrapulmonary and extrapulmonary factors regulating oxygen are essentially interpreted through the results afforded by the MIGET over the last decade. The gas exchange response to bronchodilators in bronchial asthma, an airway disease, and then the major determinants governing abnormal gas exchange in acute pulmonary embolism, a pulmonary vascular disorder, and during haemodialysis, a respiratory entity of extrapulmonary origin, are successively explored in the light of the inert gas method.

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Depts of Medicine, Servei de Pneumologia, Hospital Clinic, Facultat de Medicina, Universitat de Barcelona, Barcelona, Spain, and Section of Physiology, School of Medicine, University of California at San Diego, La Jolla, California, USA.

Correspondence: R. Rodriguez-Roisin, Servei de Pneumologia, Hospital Clinic, Villarroel 170, 08036-Barcelona, Spain.

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Hypoxaemia and hypercapnia in respiratory disease

Most respiratory diseases, both acute and chronic, have multiple physical effects upon the lungs. Mechanical properties are particularly affected by the obstructive and restrictive disease states such as chronic obstructive lung disease (COPD), bronchial asthma, and interstitial pulmonary fibrosis. These, and other diseases, also affect other components of the lung such as the circulation and the blood:gas barrier. Thus, pulmonary vascular obstruction and destruction and/or obliteration of pulmonary blood vessels in COPD, asthma, and pulmonary fibrosis affect both bloodflow and its distribution within the lung. As a result, most lung diseases alter the distribution of ventilation, of bloodflow, or of both, and lead to abnormalities in pulmonary gas exchange.

Alveolar hypoventilation, shunt, diffusion limitation for oxygen and ventilation-perfusion ($\dot{V}_A/\dot{Q}$) inequality are the four classical physiological mechanisms by which such structural and functional changes due to lung disease alter gas exchange. Table 1 lists the most common kinds of acute and chronic respiratory disorders that affect pulmonary gas exchange and show which of these mechanisms are most important in each disease state. This table also indicates typical arterial blood gas values in these diseases. While all four causes of hypoxaemia can be important on different occasions, it is uncommon for shunt or O_2 diffusion limitation in the lung to lead to an increase in arterial carbon dioxide tension ($Paco_2$). With hypoventilation, hypercapnia will always be present, while with $\dot{V}_A/\dot{Q}$ inequality, hypercapnia may or may not be present [1], depending upon the underlying individual ventilatory conditions. As shown in table 1, the most common, and quantitatively the most significant, factor contributing to abnormal gas exchange is altered $\dot{V}_A/\dot{Q}$ relationships. Table 2 illustrates those intrapulmonary factors that contribute to hypoxaemia as well as those extrapulmonary factors that, either directly or indirectly (through their effect on mixed venous oxygen tension ($P\bar{v}o_2$)), can also affect arterial oxygen tension (Pao_2). Total alveolar ventilation is considered here an extrapulmonary factor because it is primarily the result of tidal volume (less series dead space–dead space common to more than one $\dot{V}_A/\dot{Q}$ unit) and frequency, which are set by extrapulmonary breathing control mechanisms. Not shown in table 2 is the basis for how extrapulmonary factors (other than ventilation and inspired Po_2) may contribute to hypoxaemia. This is the level of mixed venous Po_2 ($P\bar{v}o_2$), a well-known concept, yet often overlooked in clinical settings. A decreased $P\bar{v}o_2$ is the final common pathway by which the extrapulmonary factors other than inspired Po_2 and ventilation lead to arterial hypoxaemia. Thus, mixed venous hypoxaemia may result from a low cardiac output, an increased O_2 uptake or a decreased blood O_2 content due to several factors (altered haemoglobin concentration, temperature, P_{50}, pH). In the presence of intrapulmonary

Table 1. – Mechanisms of altered gas exchange in common pulmonary diseases

Disease	Typical Pa_{O_2}	Typical Pa_{CO_2}	$\dot{V}_A/\dot{Q}$ inequality	Shunt	Hypo-ventilation	O_2 diffusion limitation
COPD Type A	70	35	Yes	No	No	No
COPD Type B	50	50	Yes	No	Yes	No
Asthma	65	35	Yes	No	No	No
Interstitial Fibrosis	60	35	Yes	Yes	No	Yes
Pneumonia	50	30	Yes	Yes	No	No
ARDS	40	30	Yes	Yes	No	No
Pulmonary Embolism	70	30	Yes	No*	No	No

COPD: Chronic obstructive pulmonary disease, types A and B according to Burrows' classification; ARDS: adult respiratory distress syndrome; *: only at a late stage; Pa_{O_2}: arterial oxygen tension; Pa_{CO_2}: arterial carbon dioxide tension; $\dot{V}_A/\dot{Q}$: ventilation-perfusion distribution; values are given in mmHg, breathing room air.

abnormalities of gas exchange, $P\bar{v}_{O_2}$ can have a surprisingly large effect on the resultant Pa_{O_2}. For example, Pa_{O_2} in bronchial asthma often exceeds that of diffuse pulmonary fibrosis, yet at the same time the amount of $\dot{V}_A/\dot{Q}$ mismatching may be more severe in asthma. This is explained by the higher cardiac output, hence $P\bar{v}_{O_2}$, usually seen in asthma [2, 3].

The most important clinical intrapulmonary factors determining Pa_{O_2} are shunt and $\dot{V}_A/\dot{Q}$ mismatching. Among the extrapulmonary ones, inspired O_2 fraction, total alveolar ventilation, cardiac output and O_2 consumption are viewed as the most influential. Alternatively, Pa_{CO_2} may also be determined by extrapulmonary factors, due to changes in CO_2 production, alveolar ventilation, or in acid-base status.

Table 2. – Intrapulmonary and extrapulmonary factors that contribute to hypoxaemia

Intrapulmonary	Extrapulmonary	
$\dot{V}_A/\dot{Q}$ Inequality	Reduced:	Total ventilation
Shunt		Cardiac output
O_2 Diffusion		Inspired P_{O_2}
Limitation		Haemoglobin concentration
		P_{50} of O_2 dissociation curve
	Increased:	O_2 consumption
		pH

$\dot{V}_A/\dot{Q}$: ventilation-perfusion ; P_{O_2}: oxygen tension.

It should be apparent from table 1 that the most prominent of the pathophysiology of gas exchange in pulmonary disease is abnormal $\dot{V}_A/\dot{Q}$ relationships. A rational approach to therapy and to understanding of the underlying pathogenetic mechanisms, therefore, requires the ability to quantify $\dot{V}_A/\dot{Q}$ relationships in the lung.

Traditional approaches for measuring $\dot{V}_A/\dot{Q}$ inequality

Topographical radioactive tracer-based approaches, namely ventilation-perfusion scans, have long been (and are still) available to the clinician and serve extremely useful functions in specific clinical situations such as suspected pulmonary embolism. However, when used in patients with generalized lung disease, such as COPD or asthma, the results often grossly underestimate the degree of ventilation/bloodflow mismatching actually present. This is easily demonstrated by the failure to account for the observed hypoxaemia on the basis of the $\dot{V}_A/\dot{Q}$ inequality measured by such external radioactive methods. The degree of $\dot{V}_A/\dot{Q}$ abnormality measured by topographic techniques is, thus, much less than that actually present within the lung. The limited spatial resolution of external counting devices leads to underestimation of the intra-regional $\dot{V}_A/\dot{Q}$ mismatching by the isotopic methods, although this is improving nowadays with technical advances in equipment. The signal is not strictly proportional to bloodflow or alveolar ventilation, but also reflects the distribution of the lung volume. Moreover, this can be the cause of an underestimation of the inter-regional $\dot{V}_A/\dot{Q}$ mismatch. In the absence of direct measurements of cardiac output and ventilation, isotopic approaches only give relative $\dot{V}_A/\dot{Q}$ distribution because the global $\dot{V}_A/\dot{Q}$ relationship is assumed to be equal to one. This approximation also leads to underestimation of the global $\dot{V}_A/\dot{Q}$ inequality.

Unfortunately, use of the respiratory gases O_2 and CO_2 as tools for assessing $\dot{V}_A/\dot{Q}$ mismatching, leads sometimes to unsatisfactory results that can be difficult to interpret. There are several reasons for this. The classical indices that are based upon the physiologic gases, such as venous admixture (breathing room air) or shunt (upon breathing oxygen) ($\dot{Q}_S/\dot{Q}_T$), physiological dead space ($\dot{V}_D/\dot{V}_T$) and alveolar-arterial O_2 partial pressure differences ($P_{(A-a)O_2}$), are all "as if" indicators of the degree of heterogeneity. Venous admixture represents poorly oxygenated blood which passes through the lung. It is

that shunt which alone would explain all of the observed hypoxaemia. Similarly, physiological dead space, another common parameter utilized to describe inefficiency of gas exchange, is that dead space which alone would explain the differences between arterial and mixed expired P_{CO_2}. It is composed of anatomical (airway) dead space and alveolar (effective) dead space resulting from $\dot{V}_A/\dot{Q}$ heterogeneity. Neither venous admixture nor physiological dead space can separate $\dot{V}_A/\dot{Q}$ inequality from true intrapulmonary shunt in the case of $\dot{Q}_S/\dot{Q}_T$, nor changes in $\dot{V}_A/\dot{Q}$ abnormalities from changes in airway dead space in the case of $\dot{V}_D/\dot{V}_T$. They are "lumped parameter" estimates based upon simple two-compartment models of the lung [4]. Thus they are difficult to interpret in terms of actual respiratory pathophysiology. In addition, these terms are highly dependent upon the inflowing mixed venous blood:gas composition. Generally, assumptions must be made about mixed venous blood, and unless they can be independently verified by direct pulmonary arterial catheterization, not always done in the clinical setting, the magnitude of the indices calculated can be considerably in error, particularly when following one patient over time. Finally, each of these indices is sensitive to global variables such as total alveolar ventilation, total cardiac output, and inspired O_2 fraction. When any of these three parameters is altered, and this often happens in the critical care setting especially, changes in the indices will occur even if the actual amount of intrapulmonary abnormality remains completely unaltered [4]. This adds another layer of confusion upon any interpretative scheme of these indices [5]. Thus quantitation of the degree of $\dot{V}_A/\dot{Q}$ mismatching has been a constant goal ever since the initial three-compartment analysis developed almost simultaneously by FENN *et al.* [6] and RILEY and COURNAND [7] in the mid-1940's. Consequently, some alternative means for assessing ventilation/bloodflow inequality that does not depend upon the respiratory gases is needed.

The multiple inert gas elimination technique

Background and rationale

In 1951, KETY [8] published a remarkable review which consisted mainly of a kinetic analysis of inert gas exchange in the lungs and peripheral tissues. Using mass balance equations under steady state conditions, it was shown how the elimination or uptake of an inert gas in a homogeneous area of lung is a function of only two variables, namely the blood:gas partition coefficient of the gas and the ventilation-perfusion ratio of the lung unit. Subsequently, in the 1960's, FARHI [9] considerably extended this theory to show how inert gases could be used to estimate $\dot{V}_A/\dot{Q}$ inequality quantitatively. However, his analysis was limited to two-compartment models, much like the traditional approaches of the three-compartment analysis [6, 7] based upon physiologic gases alluded to above.

Some fifteen years ago, one of us began to explore the potential for extending FARHI's approach [9] by using a larger number of inert gases, and developed the so-called multiple inert gas elimination technique (MIGET), as a means of obtaining even more information about the distribution of $\dot{V}_A/\dot{Q}$ relationships. It became evident that fairly complex distributions of $\dot{V}_A/\dot{Q}$ ratios could be measured with as few as six inert gases [10]. Using mass balance equations, the fractional elimination of inert gases of widely differing solubility undergoing steady state elimination from several theoretical lung models containing different degrees of $\dot{V}_A/\dot{Q}$ mismatch was calculated. Algorithms were devised which would take the calculated elimination data, and by using a smoothing constraint [11] produce a $\dot{V}_A/\dot{Q}$ ratio distribution compatible with the particular set of data in the presence of experimental error. It was found that with six gases it was possible to relatively accurately recover $\dot{V}_A/\dot{Q}$ distributions containing up to three separate populations of lung units, even in the presence of realistic levels of noise.

It soon became apparent that not only could the arterial partial pressures of the eliminated gases be used in this manner to reconstruct the pulmonary perfusion distribution, but in a very symmetrical way, the mixed expired partial pressures could be used to calculate the distribution of ventilation. Ultimately, arterial and mixed expired data were combined in order to produce an internally consistent combined distribution of ventilation and bloodflow [11]. Figure 1 illustrates the principles of the technique showing, for four different types of $\dot{V}_A/\dot{Q}$ ratio distribution, the corresponding relationships between inert gas elimination and solubility during steady state gas exchange. From this figure, striking changes in the inert gas elimination data are observed with significant alterations in the $\dot{V}_A/Q$ distribution pattern. Figure 1 is drawn based only on the steady state equations for gas exchange as defined by KETY [8] and FARHI [9], such that within any homogeneous area ("compartment") of the lung, endcapillary (Pc') and alveolar (P_A) partial pressures (assumed equal) are given by the following equation:

$$P_{c'} = P_A = P\bar{v} \cdot \frac{\lambda}{\lambda + \dot{V}_A/\dot{Q}} \qquad \text{(equation 1)}$$

where λ corresponds to the partition coefficient.

Applying this equation, compartment by compartment, to the $\dot{V}_A/\dot{Q}$ distributions on the right side of figure 1 for gases of different solubility yields (upon perfusion-weighted summation of compartmental terms) the corresponding arterial inert gas retention ($P_a/P\bar{v}$) data shown in the lefthand panels.

Over the last ten years, considerable effort has been expended in determining the information content of this approach. A least squares approach to recovering the distribution from inert gas data was devised [11] as well as several linear programming techniques for exploring the bounds on distributions compatible with a given set of inert gas elimination data [12, 13]. Methods for dealing with random error have also been devised, and the analytical technology for making the inert gas measurements has undergone continual evolution and improvement [14, 15].

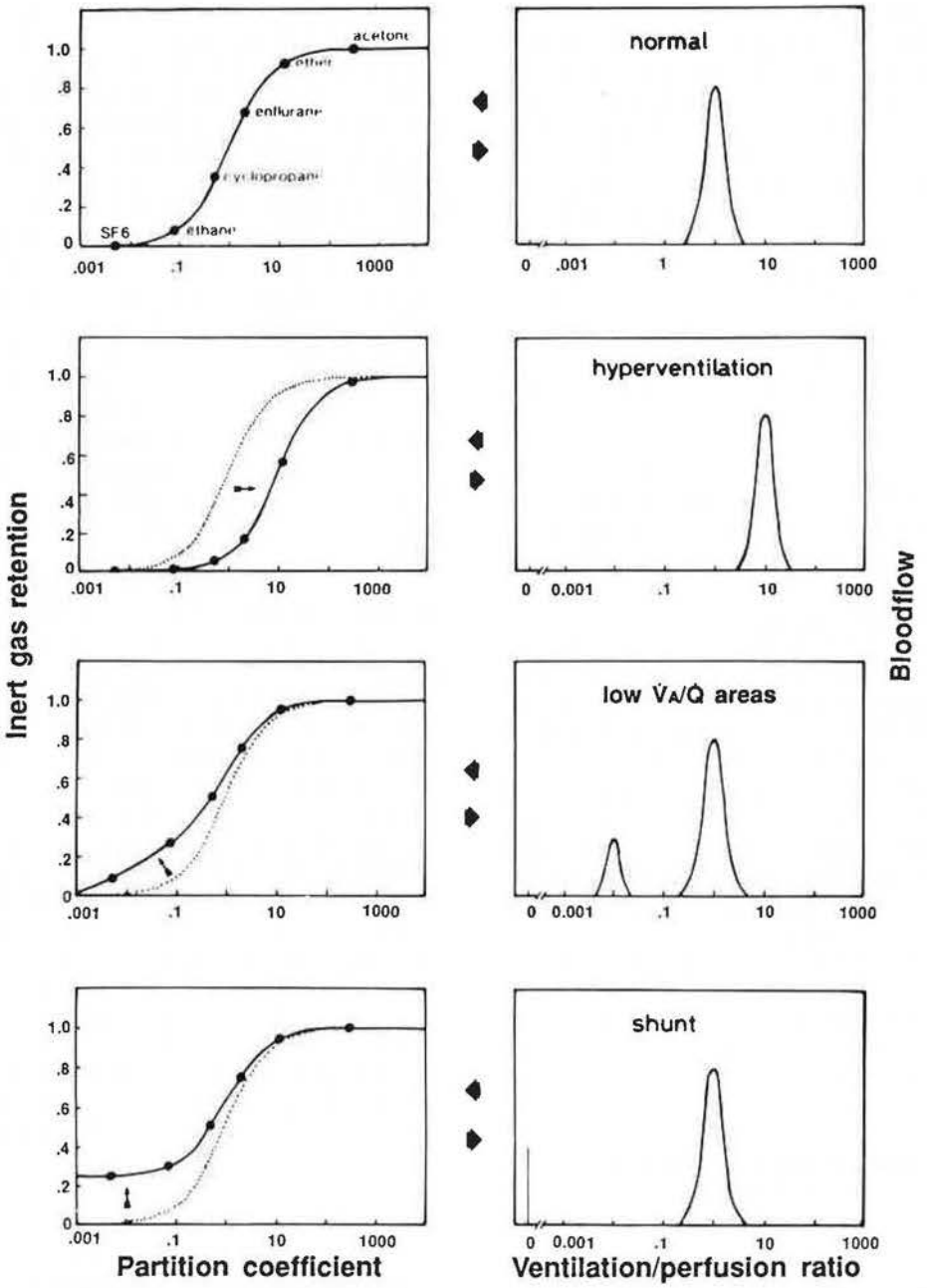


Fig.1. – Retention (arterial/mixed venous concentration ratio) of 6 inert gases plotted against their blood:gas partition coefficient (left panels) for four different ventilation-perfuson ($\dot{V}_A/\dot{Q}$) distributions shown in the righthand panels. The dotted lines on the retention plot indicate the normal retention curve of the uppermost panel, and the arrows highlight the nature of the change in shape or position of the retention curve caused by the particular distribution shown on the right. Notice that large alterations in retention data are produced by these distributions and, in particular, how distributions with low $\dot{V}_A/\dot{Q}$ areas and shunt lead to quite different retention-partition coefficient curves.

Procedure

The experimental requirements for the method are relatively simple. A mixture of the six gases is dissolved either in saline or dextrose which is then infused intravenously into a peripheral vein at a rate of about 3 ml·min^{-1} (for a resting human being). After allowing some 30 min or so for the inert gases to achieve a steady state within the lungs, the inert gas concentrations are measured during quiet breathing in mixed expired gas, arterial blood, and pulmonary arterial blood. Minute ventilation is measured together with the partition coefficients of the six gases in the patient's blood. If pulmonary arterial samples cannot be obtained, mixed venous inert gas levels can be calculated by mass balance from arterial and mixed expired levels and cardiac output, minute ventilation and partition coefficients, as described below. These data can be used in addition to compute cardiac output by mass balance for each gas in the mixture

and a mean cardiac output can be obtained. Inert gas concentrations are measured by gas chromatography after extraction of gases from blood in gas-tight syringes [13]. The results can be expressed in a number of different ways. A pictorial representation of a multi-compartment $\dot{V}_A/Q$ distribution that fits the data can be drawn (fig. 2). Total values of bloodflow and ventilation in defined regions of the $\dot{V}_A/\dot{Q}$ spectrum can be given, moments of the recovered distribution can be calculated (only the first and second moments are routinely used), and arterial-alveolar differences for the inert gases can also be calculated and used as indirect estimates of the degree of $\dot{V}_A/Q$ mismatch. The second moment of the distribution on a logarithmic scale, *i.e.* its dispersion, can be determined experimentally with a coefficient of variation of between 8–9% for a single measurement. In the usual scheme, duplicate measurements are made, and this reduces that coefficient of variation by the square root of two to approximately 6% [16].

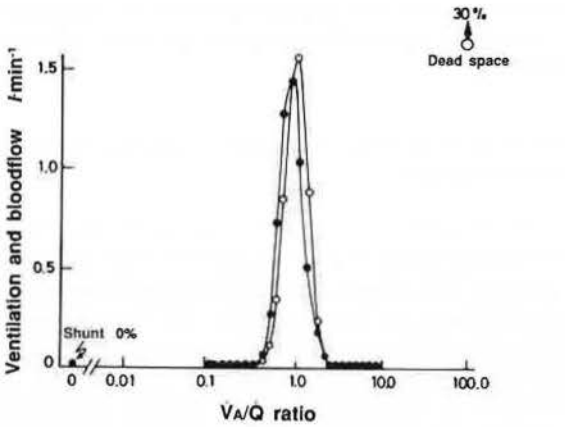


Fig. 2. – Example of the distribution of ventilation (o) and bloodflow (•) against ventilation-perfusion ($\dot{V}_A/\dot{Q}$) ratio on a log scale in a resting young individual, breathing room air. Note that both distributions are symmetrical, are appropriately positioned about a $\dot{V}_A/\dot{Q}$ ratio of 1.0 (1st moment); and there is little dispersion (narrowness) on each curve (2nd moment) without low $\dot{V}_A/\dot{Q}$ or high $\dot{V}_A/\dot{Q}$ areas. Note also the absence of shunt. Each individual data point represents a particular amount of bloodflow or alveolar ventilation. Total cardiac bloodflow corresponds to the sum of all bloodflow points just as total alveolar ventilation is the sum of all ventilation points.

While the original technique requires estimates of inert gas concentrations in three sites: mixed expired gas, arterial blood, and pulmonary arterial blood, it is possible to use the method without having to directly sample from all three sites. Thus, an alternative method employs direct measurement of mixed expired gas and arterial blood inert gas concentrations, but utilizes measured values of cardiac output to calculate by mass balance the corresponding mixed venous concentrations. This has been shown to give results as good as the approach in which pulmonary arterial blood is directly sampled. The method can be used in situations where an indwelling pulmonary catheter is not indicated or may not be placed. The use of a venous line to inject indocyanine green for measurement of cardiac output has also been successfully applied in several clinical settings [17, 18].

A second alternative allows one to avoid even arterial blood sampling. In this approach, the inert gases are infused in solution into the peripheral vein of one arm, and blood is sampled from a peripheral vein of the opposite arm at the same time as making expired gas measurements [19]. This technique, by avoiding both pulmonary arterial and systemic arterial catheterization, is ideally suited for repetitive measurements over extended periods of time (for instance, in patients with bronchial asthma where questions arise about variability of ventilation/bloodflow mismatching during the course of treatment). This approach, however, is restricted to situations of long-term (at least 90 min) steady state conditions and cannot follow rapid changes in function that might occur over the time course of a few minutes. The rationale behind this approach is that the inert gases are not metabolized in the tissues of the hand, therefore, after a period of equilibration, the peripheral venous blood will have the same concentrations of each inert gas as will the inflowing arterial blood. This approach has recently been validated by comparing it with the more invasive one of using arterial blood in different series of asthmatics followed weekly [20].

Resolution and advantages of the MIGET

The technique allows one, for the first time, to obtain a close approximation to the functional distribution of $\dot{V}_A/\dot{Q}$ ratios within the lung. It is, however, a technically demanding approach and requires considerable theoretical knowledge for its proper interpretation and utilization. Its particular strengths include the tracer nature of the approach, such that the method itself does not alter the physiology of gas exchange in the lung (the inert gas levels are of the order of a few ppm). This should be contrasted with techniques in which inspired oxygen concentration is manipulated in order to gain insight into $\dot{V}_A/\dot{Q}$ relationships. Here there is every reason to believe that increasing inspired P_{O_2} will either release hypoxic pulmonary vasoconstriction, or cause absorption atelectasis, or both [21, 22], and thereby change the very $\dot{V}_A/\dot{Q}$ distribution that is being measured. Second, by administering all six gases simultaneously, an internally consistent picture is obtained. Using techniques of sequential administration of different oxygen concentrations, changes could occur over time that would confound the issues. Most importantly, the results are not intrinsically affected by the same variables that will alter venous admixture or physiological dead space parameters even if the underlying $\dot{V}_A/\dot{Q}$ distribution is not altered (factors such as changes in cardiac output or total alveolar ventilation). Thus, under any given set of conditions, the appropriate $\dot{V}_A/\dot{Q}$ distribution is obtained. Finally, while two- and three-compartment approaches to quantifying $\dot{V}_A/\dot{Q}$ inequality are at best poorly able to separate low $\dot{V}_A/\dot{Q}$ areas (poorly ventilated lung) from shunt ($\dot{V}_A/Q=0$) on the one hand, and high $\dot{V}_A/\dot{Q}$ areas (poorly perfused lung) from dead space ($\dot{V}_A/\dot{Q}$=infinity) on the other, the MIGET is, by its nature, better able to achieve this function than any other former approach.

The reason for this is straightforward and resides in the utilization of several gases of different but appropriate solubilities. Consequently, the quantitative relationships between the gases is an important component that allows the resolution amongst units of different $\dot{V}A/\dot{Q}$ ratios.

Nevertheless, some aspects of pulmonary gas exchange cannot be assessed by the MIGET. For instance, the inert gas method cannot separate the effects of parallel *versus* series VA/Q heterogeneity if series inequality is present. In other words, the inert gas method can be analysed on the basis of a parallel model even if series inequality is present, but that series inequality is not identifiable by this approach [23]. Re-inspiration of gas from series dead space may result in the underestimation of measured dead space and a slight alteration in the $\dot{V}A/\dot{Q}$ distribution in the middle range [24]. Acetone is the most soluble of the gases used, and an accurate measurement of the excretion of acetone (by avoiding condensation of water vapour through the expired circuit and also the contaminant effects of some brands of heparin on blood [25]) is necessary to distinguish between dead space ventilation from ventilation to lung units with high $\dot{V}A/\dot{Q}$ ratios.

The inert gas elimination technique can assist not only in the delineation of $\dot{V}A/\dot{Q}$ mismatching and shunt providing a quantitative estimate of these phenomena, but is also a useful tool in addressing the potential presence of alveolar to endcapillary diffusion limitation for oxygen. As shown previously (and assumed in equation 1), inert gases equilibrate across the lung extremely rapidly [26]. Thus, within the first few hundredths of a second of the red cells' exposure to alveolar gas in its transit through the lung capillary, there is partial pressure equilibration of all inert gases between alveolar gas and blood. Oxygen, however, requires an order of magnitude longer to achieve essential equilibration, approximately 0.2–0.3 s in normal conditions [27]. Under such conditions, neither oxygen nor the inert gases are diffusion-limited in the lung because capillary transit time is of the order of 0.75 s. However, in the presence of pathology and/or during exercise, particularly under hypoxic conditions, oxygen may not reach equilibrium between alveolar gas and endcapillary blood in a single transit. This can therefore generate alveolar-arterial Po_2 differences and hypoxaemia. Because the inert gases equilibrate so much more quickly than oxygen, their exchange is still not diffusion limited. It is possible therefore to quantitatively compute the arterial Po_2 that would be expected (predicted) to occur from the amount of $\dot{V}A/\dot{Q}$ mismatch detected by the inert gas technique. When this is done, it can be compared to the actual Pao_2 measured in the subject. If these agree statistically, one can conclude that diffusion limitation is not occurring for oxygen. Under certain conditions, however, diffusion limitation for oxygen may be present, and then one would expect more hypoxaemia than can be explained by the inert gas elimination data. This has been found to occur in normal subjects heavily exercising, especially when breathing hypoxic gas mixtures [28, 29] and also in patients with restrictive lung diseases both at rest [30] and during exercise breathing room air [2, 30]. It otherwise appears to be an undetectable component of pulmonary gas exchange, both in health and disease.

Clinical examples of the information available from MIGET

In the text below we will review three different examples of clinical respiratory problems, where the complex interactions of intrapulmonary and extrapulmonary factors regulating O_2 and CO_2 are specifically assessed on the basis of the results afforded by the MIGET. In the first condition, we will discuss the issue of the gas exchange response to bronchodilators in bronchial asthma, a disease affecting primarily the airways. In the second example, we will deal with a pulmonary vascular disease, acute pulmonary embolism, and the interplay of the different mechanisms governing abnormal gas exchange. Finally, in the last condition, the major determinants of hypoxaemia that develops during haemodialysis, a respiratory disorder of extrapulmonary origin, are explored by means of the results given by the MIGET.

Bronchial asthma and gas exchange response to bronchodilators

In 1978, WAGNER *et al.* [3] measured $\dot{V}A/\dot{Q}$ inequality by means of the MIGET in patients with asymptomatic asthma. All except one showed clearly bimodal $\dot{V}A/\dot{Q}$ distributions but no shunt (fig. 3). The presence of a bimodal distribution of VA/Q ratios was compatible with the presumed pathophysiology of gas exchange abnormalities in bronchial asthma, namely airway narrowing caused by generalized bronchoconstriction coupled with mucus plugging and/or bronchial wall oedema. Such airways obstruction produces low $\dot{V}A/\dot{Q}$ areas that are well perfused but not sufficiently ventilated. The absence of shunt was thought to be due to the efficiency of collateral ventilation which is considered an important mechanism maintaining alveolar ventilation beyond obstructed airways. A finding of considerable interest was that VA/Q mismatch can be present despite a nearly normal Pao_2 and $Paco_2$. This finding, as discussed above, exemplifies how the degree of arterial hypoxaemia caused by a given amount of $\dot{V}A/\dot{Q}$ abnormality depends considerably on other factors, such as cardiac output, which in turn increases the $P\bar{v}o_2$. The increased cardiac output was related to the anxiety of the experimental study, and possibly to some residual bronchodilating effects from earlier regular treatment.

Another conspicuous finding of this study was the presence of a transient deterioration in both $\dot{V}A/\dot{Q}$ relationships and Pao_2, together with a return to normal in maximal airflow rates (FEV_1 and forced expiratory flow between 25–75% of forced vital capacity ($FEF_{25-75\%}$)) after nebulized isoproterenol (fig. 3). It was concluded that the major factor contributing to this further worsening of $\dot{V}A/\dot{Q}$ relationships was an increase in cardiac output. Release of hypoxic pulmonary

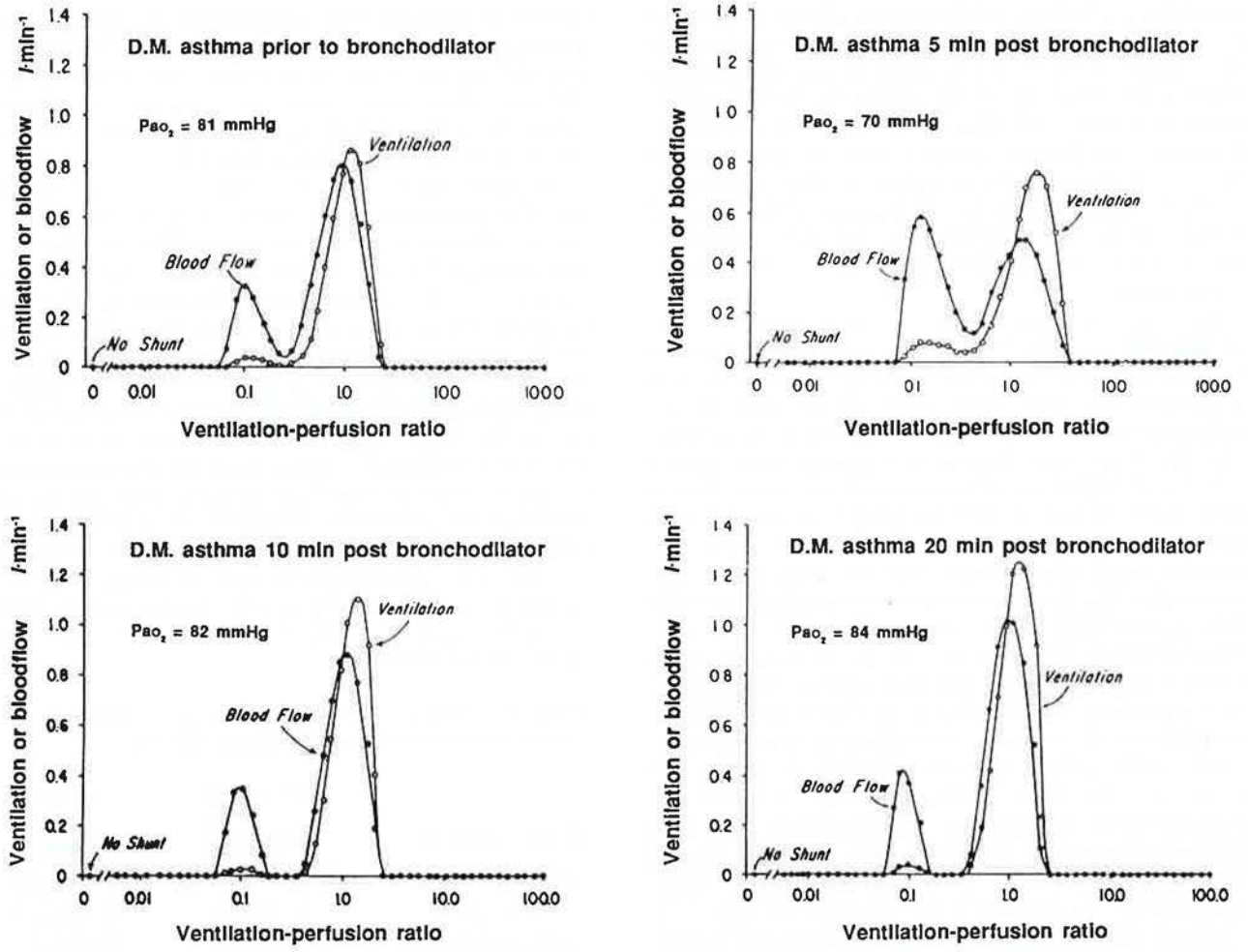


Fig. 3. – Representative sequence of ventilation-perfusion ($\dot{V}A/\dot{Q}$) distributions in an asthmatic patient taken from the study of WAGNER *et al.* [3]. At baseline, notice the bimodal bloodflow distribution (averaging approximately 20% of the cardiac output) but no shunt in the face of a normal arterial oxygen tension (Pa_{O_2}). Five minutes after isoproterenol, the low $\dot{V}A/\dot{Q}$ areas contained twice as much pulmonary perfusion as before the drug was given and Pa_{O_2} fell 11 mmHg. By 10 and 20 min after bronchodilator, the distributions of ventilation and bloodflow were not essentially different from pre-bronchodilatation results and Pa_{O_2} values were within normal limits. (Reprinted with permission of the American Review of Respiratory Disease).

vasoconstriction was not thought as important because the fraction of bloodflow to low $\dot{V}A/\dot{Q}$ ratio units did not increase after 100% O_2 breathing in four of these patients, as it did after isoproterenol. Unfortunately, it is not possible, from these data, to differentiate the separate roles of active vasodilatation reducing the pulmonary vascular tone and increased cardiac output in producing augmented fractional bloodflow to low $\dot{V}A/\dot{Q}$ ratio areas. Indeed, data from CORTE and YOUNG [31] and also from our own group [32, 33] have shown subsequently that patients with asthma, particularly those with the most severe exacerbation of the disease, elicit a considerable hypoxic vascular response breathing 100% O_2.

The increased perfusion of low $\dot{V}A/\dot{Q}$ areas associated with bronchodilator inhalation at 5 min in figure 3 raises an interesting problem of interpretation. What the data of this panel clearly say is that a greater fraction of the cardiac output is perfusing areas of the lung with an abnormally low $\dot{V}A/\dot{Q}$ ratio. Theoretically, three separate mechanisms could singly, or in combination, account for this. First, due to an increase in total perfusion and/or selective reversal of hypoxic vasoconstriction, existing low $\dot{V}A/\dot{Q}$ areas could have their perfusion increased. The second possibility is that new areas of low $\dot{V}A/\dot{Q}$ ratio could have been created simply by overperfusion without reduction in ventilation. The third possibility is that new areas of low VA/Q ratio could be created through reduction in ventilation of areas in the lung. From the strict mathematical standpoint, data such as those illustrated in figure 3 cannot distinguish amongst these three possibilities. Common sense, however, would suggest that when a bronchodilator is given, and at the same time flow rates at the mouth are shown to improve, local reduction in ventilation is an unlikely candidate for the changes shown in the figure. In addition, to produce areas whose VA/Q ratio is of the order of 0.05 (one 20th of normal) through overperfusion, it would require a 20-fold increase in local bloodflow. While mathematically feasible, this would not seem physiologically likely. The

remaining mechanism (of those listed above) is increased perfusion of areas which are already poorly ventilated. In the example of figure 3, this would be consistent with an approximate doubling of the perfusion of these areas, which is a more reasonable possibility. Thus, while no definitive mechanistic analysis can be given for the effect of bronchodilators (or indeed of other manoeuvres in other clinical conditions), an analysis of the observed changes using both common sense and logic would lead one to reject what appear to be quite unreasonable explanations.

Since HALMAGYI and COTES [34] draw attention to the finding that patients with COPD may develop arterial hypoxaemia after administration of epinephrine and aminophylline, there have been similar observations following the effects of various bronchodilating drugs [35, 36]. Since then there were numerous other studies [37–39] of "paradoxical hypoxaemia" occurring shortly after administration of bronchodilators to patients with asthma, in spite of improvement in airflow rates. The changes noted often varied with the drug given. The observation that the administration of bronchodilators may alter gas exchange despite its beneficial effect on bronchoconstriction has been one of the most provocative findings in patients with bronchial asthma. Furthermore, the observation in asthmatics of lack of improvement in distributions of alveolar ventilation and pulmonary perfusion while airflow rates are returning to normal has raised an interesting debate. Because non-selective beta-adrenergic agonists (*i.e.*, isoproterenol) have been thought to produce a deleterious effect on Pa_{O_2} through their well-known beta cardiovascular effects (more specifically pulmonary vasodilatation secondary to increased cardiac output), it was suggested that a more specifically $beta_2$-agonist (for instance, salbutamol), which may not provoke such increase in cardiac output, could be associated with a greater fall in Pa_{O_2} if it caused the same increase in $\dot{V}_A/\dot{Q}$ mismatching.

Interestingly, other studies of the effects of bronchodilators on $\dot{V}_A/\dot{Q}$ mismatching have yielded different results. Young asymptomatic asthmatics challenged with aerosolized antigen [40] showed that $\dot{V}_A/\dot{Q}$ inequality rapidly and completely reverted toward normal levels following the administration of metaproterenol. Later, YOUNG *et al.* [41] reported in patients in whom asthma was induced by exercise that $\dot{V}_A/\dot{Q}$ mismatch improved and cardiac output rose, several minutes after inhalation of salbutamol. In 1985, HEDLIN *et al.* [42] documented that salbutamol improved the $\dot{V}_A/\dot{Q}$ distribution and restored the blood gases to normal in all but one of a group of asthmatic children following histamine challenge. It was not clear from their data, though, that $\dot{V}_A/\dot{Q}$ impairment was greater than that expected in this situation after exercise or challenge was discontinued or whether these changes were statistically significant, thus making their data difficult to interpret. Subsequently, BALLESTER *et al.* [33] have shown that, during intravenous salbutamol (4 $\mu g \cdot min^{-1}$ for 1 h) in patients with acute severe asthma, there is development of further $\dot{V}_A/\dot{Q}$ inequality along with a substantial rise in cardiac output with the outcome of an unaltered Pa_{O_2}; there is likewise an increase in O_2 consumption. In contrast, in a similar group of acute asthmatic patients $\dot{V}_A/\dot{Q}$ distributions did not deteriorate 15 min after inhaled salbutamol (300 μg) while there were no changes in cardiac output, O_2 consumption, or Pa_{O_2}. Yet, both forms of administration of salbutamol significantly improved FEV_1 to the same degree without changes in minute ventilation. The differences in the effects on $\dot{V}_A/\dot{Q}$ abnormalities of salbutamol (which are summarized in table 3), administered by two different routes, may well be explained by the relevant associated cardiovascular and metabolic effects (basically, increases in cardiac output and O_2 consumption, respectively) which can reasonably be related to the greater plasma levels of salbutamol presumably achieved during the intravenous administration of the drug. Again, from these data there is not sufficient information to differentiate between an increase in cardiac output provoking an increase in the amount of dispersion of pulmonary bloodflow, or a reduction in pulmonary vascular tone. Even more recently, our group [43] has also demonstrated a lack of change in $\dot{V}_A/\dot{Q}$ mismatch in patients with severe chronic asthma who did show a significant improvement in FEV_1 after 300 μg of inhaled salbutamol.

Table 3. – Gas exchange response to intravenous and inhaled salbutamol in acute severe asthma

	Intravenous	Inhaled
Minute Ventilation	Unchanged	Unchanged
Cardiac Output	Increased	Unchanged
O_2 Consumption	Increased	Unchanged
$\dot{V}_A/\dot{Q}$ Inequality	Increased	Unchanged
Pa_{O_2}	Unchanged	Unchanged

$\dot{V}_A/\dot{Q}$: ventilation-perfusion distribution; Pa_{O_2}: arterial oxygen tension.

Formerly, similar results were fairly well reproduced by us [44] in an experimental model of canine "asthma" (challenged with inhaled methacholine), which was followed by aerosolized epinephrine, isoproterenol and salbutamol. Following isoproterenol, since minute ventilation remained unchanged, increased cardiac output together with decreased pulmonary vascular resistance worsened $\dot{V}_A/\dot{Q}$ mismatch (intrapulmonary factor). The resulting deleterious effect on Pa_{O_2}, thus, was counterbalanced by the improvement in Pv_{O_2} due to increased cardiac output (extrapulmonary factor). After epinephrine and salbutamol, a similar bronchodilator effect was associated with only slight deterioration in $\dot{V}_A/\dot{Q}$ relationships. The effects of the former drug on $\dot{V}_A/\dot{Q}$ distributions, Pa_{O_2}, cardiac output, heart rate, and pulmonary vascular resistance were less and of shorter duration than those of isoproterenol. In contrast, salbutamol resulted in changes similar to but more persistent than those caused by epinephrine. These results essentially showed that the gas exchange responses to three different bronchodilators in this model of bronchoconstriction are closely related to the expected

pharmacologic effects (alpha, $beta_1$, and $beta_2$) of these drugs. Moreover, they also confirmed that Pao_2 changes *per se* may not necessarily reflect changes in $\dot{V}A/\dot{Q}$ inequality because increased cardiac output may prevent increased $\dot{V}A/\dot{Q}$ mismatch from resulting in a decreased Pao_2. It is of note that nebulized epinephrine (1 mg) has been shown to be as effective as salbutamol in patients with acute asthma without associated adverse effects [45], using conventional techniques.

Worsening or lack of improvement in $\dot{V}A/\dot{Q}$ mismatch after spirometric variables in both experimental and human asthma conditions have returned to normal suggest that the gas exchange abnormalities are related to mucus plugging and/or bronchial wall oedema in the peripheral, small airways, rather than to reversible bronchoconstriction in larger airways. Indeed, this hypothesis has been subsequently strengthened by ROCA *et al.* [46] in patients with acute severe asthma requiring hospitalization on admission and during recovery, such that spirometric variables and $\dot{V}A/\dot{Q}$ inequality indicate distinct pathophysiologic phenomena with quite different time courses of recovery in this clinical condition. According to this concept, maximal airflow rates predominantly reflect bronchoconstriction in large, central airways, whereas $\dot{V}A/\dot{Q}$ maldistribution is more related to the events that operate in the lung's "quiet zone" [47]. Very recently, this hypothesis has been reinforced by FERRER *et al.* [48] who demonstrated that patients with acute asthma who are discharged from the emergency room following a severe attack show that both the time course and the improvement of spirometric variables and $\dot{V}A/\dot{Q}$ mismatch data are paralleled as opposed to those who are hospitalized, whose results are not.

It becomes evident that worsening of hypoxaemia by bronchodilators may be a side-effect of the treatment of patients with asthma. A small decrease in Pao_2 in a patient without pre-existing moderate to severe hypoxaemia is unlikely to have any clinical significance; in contrast, a similar decrease in a patient with pre-existing severe hypoxaemia might be potentially life-threatening. However, one can certainly not withhold bronchodilators in patients with asthma because of their transient (and sometimes unpredictable) deleterious effect on Pao_2.

In summary, taking all of these studies together, several implications that may have clinical relevance for the care of patients with asthma can be inferred. First, considerable $\dot{V}A/\dot{Q}$ inequality may be present in the face of little arterial hypoxaemia, because of the usually elevated cardiac output preserving $P\bar{v}o_2$. Second, increased hypoxaemia may well occur following use of adrenergic bronchodilators owing to an increase in the amount of $\dot{V}A/\dot{Q}$ mismatching. Third, inhaled salbutamol seems to be an efficient and safe therapeutic approach, unlike other inhaled non-selective beta-adrenergic agents, because of the lack of deleterious effect on $\dot{V}A/\dot{Q}$ mismatch for the same degree of bronchodilatation. Cardiac output changes, therefore, become important in governing overall gas exchange abnormalities in bronchial asthma, particularly during the intravenous administration of the most beta-selective adrenergic bronchodilating drugs or after any of the inhaled non-selective ones.

Mechanisms of arterial hypoxaemia in pulmonary embolism

The potential causes for hypoxaemia in acute pulmonary embolism are several and different explanations have been postulated [49, 50]. First, $\dot{V}A/\dot{Q}$ mismatching may be a possible factor in the arterial hypoxaemia. This can happen by mechanical redistribution of pulmonary bloodflow away from obstructed vascular areas. There can also be $\dot{V}A/Q$ inequality due to resolving areas of pulmonary infarction, atelectasis, or oedema that remain perfused but poorly, or not ventilated at all, because of alveolar wall stiffness and/or alveolar space filling secondary to fluid oedema or cellular debris. Another possibility may be related to the development of humorally-induced bronchomotor changes, causing pneumoconstriction, and hence VA/Q mismatching. Second, and in addition to VA/Q mismatch, there may be shunting of blood through non-ventilated alveoli caused either by atelectasis owing to pulmonary surfactant loss or alveolar flooding by pulmonary oedema. However, fully developed pulmonary oedema in pulmonary embolism is rarely if ever seen in man. Another possibility of intrapulmonary shunting is the opening of direct pulmonary arteriovenous channels provoked by high pulmonary artery pressure, including the reopening of the foramen ovale. Thirdly, there have been suggestions of diffusion limitation for O_2, caused by either a reduced red cell transit time or the development of interstitial oedema, that might result in an increased diffusional pathway for O_2 between the lumen of the alveoli and the red cell.

The MIGET has only recently been used in patients with acute pulmonary embolism, and only a few patients have been studied. D'ALONZO *et al.* [51] was the first to study 2 patients with acute, massive pulmonary embolism. Both individuals showed a considerable increase in the $P(A\text{-}a)O_2$ and also substantial $\dot{V}A/\dot{Q}$ inequality, the measurements being made one and eight days following the acute episode, respectively (fig. 4). The increased $\dot{V}A/\dot{Q}$ inequality was due entirely to the presence of high VA/Q areas, namely an increase in the percentage of ventilation diverted to high VA/Q regions consistent with the underlying pulmonary vascular obstruction. Although no low $\dot{V}A/\dot{Q}$ areas were shown, both patients had a considerable amount of shunt (20% and 38% of cardiac output, respectively), not evident on chest radiographs, as well as ventilation of totally unperfused lung units (dead space). The increased $P(A\text{-}a)O_2$ was explained mostly by the large shunt present and $\dot{V}A/\dot{Q}$ mismatching had a smaller contribution to the hypoxaemia of these two patients. Diffusion limitation to O_2 was not found to be a mechanism of abnormal gas exchange in these cases.

Two years later, MANIER *et al.* [49] pointed out that the decrease in $P\bar{v}O_2$ constitutes the major determinant of hypoxaemia in acute pulmonary embolism, and is enhanced by the associated $\dot{V}A/\dot{Q}$ inequality. The latter was noted to be a moderate amount of bloodflow distributed in low $\dot{V}A/\dot{Q}$ ratio units, and also shunt (mean 9% of cardiac output). The amount of ventilation in high VA/Q areas was considerable (mean 54%).

Interestingly, 13% of the increased $P(A\text{-}a)O_2$ was explained by an O_2 diffusional limitation component. However, a major breakthrough in our understanding of the underlying gas exchange abnormalities in patients with pulmonary embolism has come from HUET *et al.* [50] who documented 7 patients with severe, acute pulmonary embolism. These authors emphasized the role of a low $P\bar{v}O_2$ in the presence of either $\dot{V}A/\dot{Q}$ mismatch or shunt which contributed to hypoxaemia in these patients. Similarly, as in the report of D'ALONZO *et al.* [51], both $\dot{V}A/Q$ inequality and shunt were evident.

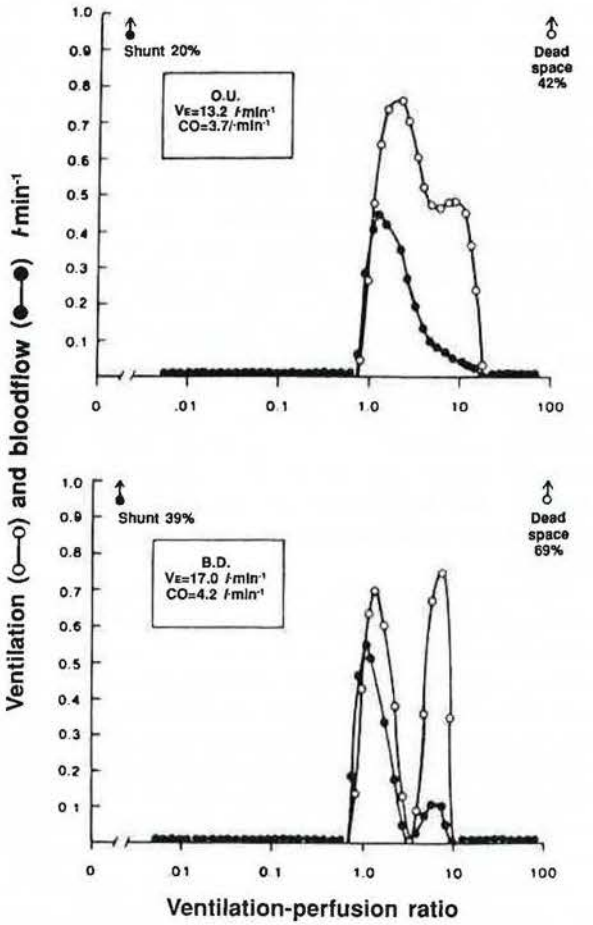


Fig. 4. – Ventilation-perfusion distributions recovered by D'ALONZO *et al.* [50] in 2 patients (O.U. and B.D.) with acute pulmonary embolism showing considerable ventilation-perfusion ($\dot{V}A/Q$) inequality and substantial amounts of shunt and of dead space. Note that $\dot{V}A/Q$ mismatch was characterized by the presence of high $\dot{V}A/Q$ areas (*i.e.*, increased ventilation in high $\dot{V}A/Q$ ratio units) (see text for further explanation). CO: cardiac output; VE: minute ventilation rate. (Reprinted with permission of the American Review of Respiratory Disease.

However, the important observation was the time courses of $\dot{V}A/\dot{Q}$ abnormalities and both the clinical and radiographic findings. In this regard, $\dot{V}A/\dot{Q}$ mismatching accounted for most of the hypoxaemia in the 2 patients assessed early after embolism (*i.e.*, less than 48 h after the acute episode), whose chest X-rays were normal. In the other 5, in contrast, whose assessment was done between 84–216 h after the occurrence of pulmonary embolism, moderate to large amounts of shunt (range 3–17% of cardiac output) were shown, along with radiological evidence of atelectasis or alveolar filling, and these shunts accounted for most of the hypoxaemia. It would be interesting, however, to confirm these data by assessing sequentially the evolution of $\dot{V}A/\dot{Q}$ abnormalities in a larger series of patients with pulmonary embolism. In all the patients, ventilation to unperfused areas (dead space) was markedly increased (mean 52% of ventilation).

In summary, based on these few studies it seems that, first, both shunt and $\dot{V}A/Q$ mismatching are major consequences of severe, acute pulmonary embolism. Ventilation-perfusion inequality includes the presence of both low and high $\dot{V}A/\dot{Q}$ areas. Second, shunt seems to be more important in the subacute stages of the disease whereas part of the $\dot{V}A/\dot{Q}$ mismatch, more specifically bloodflow perfusing lung units with low $\dot{V}A/\dot{Q}$ ratios, plays a major role during the early phases as important factors modulating hypoxaemia. Third, mixed venous Po_2 is a major factor, in the presence of either shunt and $\dot{V}A/\dot{Q}$ mismatch, contributing to the low values of Pao_2. Fourth, diffusion limitation for O_2 is hardly altered such that there is little consistent evidence to support a significant contribution of this factor for determining hypoxaemia in pulmonary embolism.

Mechanisms of abnormal gas exchange in haemodialysis

Diffusion impairment [52, 53], hypopnoea (alveolar hypoventilation without associated hypercapnia) accompanied by a decrease in the respiratory exchange ratio (RQ) [54–59], and $\dot{V}A/\dot{Q}$ inequality [60–62] have all been implicated as mechanisms underlying the development of arterial hypoxaemia during haemodialysis. However, it is essentially impossible to agree on which factors are most important by using conventional gas exchange techniques such that the question remained unanswered for some time. Accordingly, we used the MIGET [63] in a group of patients with chronic renal failure before, during, and after regular haemodialysis to more critically assess the mechanisms of hypoxaemia by directly measuring the $\dot{V}A/\dot{Q}$ distribution. As did others [64], we found a significant fall in Pao_2 during the procedure. Concomitantly, there were significant decreases in minute ventilation, alveolar ventilation, CO_2 elimination throughout the lungs, and RQ since pulmonary O_2 consumption remained unchanged. As a result, alveolar Po_2 fell, essentially by as much as Pao_2, such that $P(A\text{-}a)O_2$ was unchanged. Cardiac output also dropped significantly and there was a significant reduction in the percentage of bloodflow to nonventilated (shunt) or poorly ventilated low $\dot{V}A/Q$ ratio units during haemodialysis (which alone would have raised Pao_2) (fig. 5). Distributions of $\dot{V}A/Q$ ratios were moderately abnormal before dialysis, including both low $\dot{V}A/\dot{Q}$ areas and high $\dot{V}A/\dot{Q}$ areas (almost all of this was due to dead space). Therefore, if anything, $\dot{V}A/\dot{Q}$ mismatching improved as Pao_2 decreased. The most likely cause of this finding is a decrease in extravascular lung water due to haemodialysis [65], although it may well also be the result of the simultaneous fall in cardiac

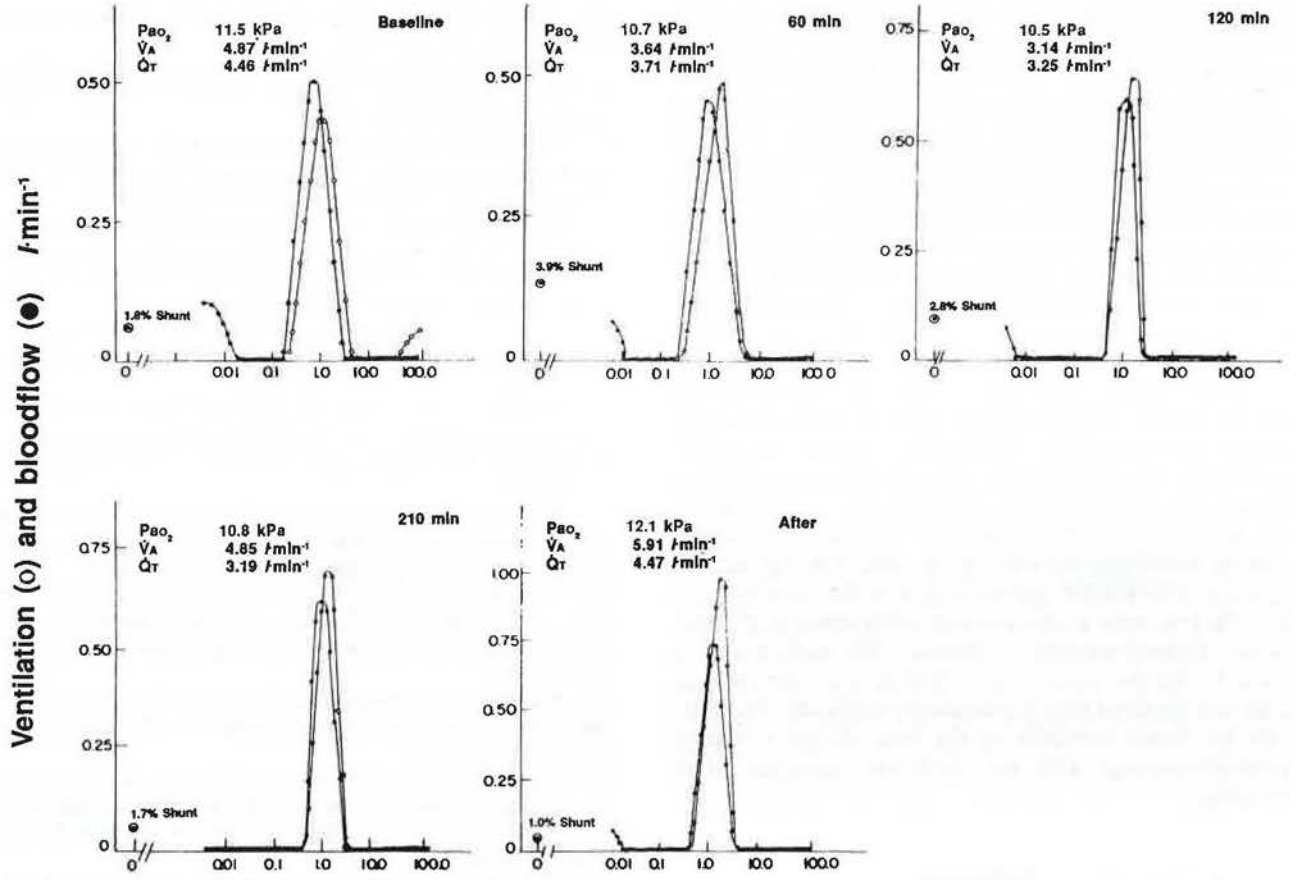


Fig. 5. – Representative serial ventilation-perfusion ($\dot{V}_A/\dot{Q}$) distributions of one patient with chronic renal failure in the study of ROMALDINI *et al.* [59]. There is a progressive improvement in low V_A/Q areas (from 11.4% of bloodflow before haemodialysis to 8.6, 5.5, and 1.7% at 60, 120, and 210 min during haemodialysis, respectively); arterial oxygen tension (Pao_2) also decreased as did alveolar ventilation (V_A) and cardiac output (Q_T). After haemodialysis, all but low $\dot{V}_A/\dot{Q}$ areas (with only 4.3% of Q_T) of the variables returned toward baseline values. (Reprinted with permission of the American Review of Respiratory Disease

output. The finding that perfusion of low $\dot{V}_A/\dot{Q}$ areas did increase again as soon as dialysis was discontinued, suggests that some of the $\dot{V}_A/\dot{Q}$ improvement was related to the transiently decreased cardiac output. Because this increase was not toward pre-dialysis values, our data therefore suggest an effect of both decreased cardiac output and possible reduction in extravascular lung water acting to improve V_A/Q mismatching. Similar results, also using the MIGET, have been shown in a canine model of dialysis [66].

The question arises as to whether the relationship between cardiac output and nonventilated (shunt) or poorly ventilated areas is just another manifestation of the well-known, but poorly understood, positive association between shunt and cardiac output [67, 68] or whether haemodialysis actually reduces $\dot{V}_A/\dot{Q}$ maldistribution. We suggest that both of these mechanisms coexist and operate to explain our findings.

The hypothesis of a role for O_2 diffusion limitation as an additional mechanism for arterial hypoxaemia seems less likely. It was demonstrated that the combined effect of reduced alveolar ventilation, cardiac output, and $\dot{V}_A/\dot{Q}$ mismatch was sufficient to account for all of the observed hypoxaemia. Another argument, leucocyte microaggregation in the pulmonary capillary network during haemodialysis [53, 60–62], with subsequent rapid red cell transit in the rest of opened capillaries, was unlikely since we found that patients dialyzed with polyacrylonitrile, as opposed to those done with cuprophan, membranes decreased their Pao_2 just as much despite the absence of leucopenia. Alternatively, obstruction of capillaries by leucocyte microaggregation should increase, if anything, the ventilation in high $\dot{V}_A/\dot{Q}$ areas, a finding not shown in our study [63]. Finally, the percentage reduction in carbon monoxide diffusing capacity (DLCO) shown previously by other investigators [53, 61] would not be sufficient to explain the observed falls in Pao_2.

Summary and conclusions

This review has shown the extent of information available from the MIGET, such that: 1) an estimate of the pattern of ventilation and perfusion is obtained from which; 2) numerical parameters describing the quantitative abnormalities can be readily calculated; 3) the presence of diffusion limitation of pulmonary oxygen transport can be inferred; and 4) the alveolar-arterial Po_2 difference can be partitioned into components due to shunt, $\dot{V}_A/\dot{Q}$ inequality and alveolar-endcapillary diffusion limitation for oxygen; finally, 5) changes over time in arterial oxygenation can be apportioned into intrapulmonary and extrapulmonary factors to improve

our understanding of the physiological basis of these changes, especially critical when many of the determinants of Pao_2 may be changing at the same time.

In spite of a few limitations [23–25] the multiple inert gas elimination technique has proven to be a useful method in the analysis of pulmonary gas exchange. Yet, it is sometimes regarded as a formidable research tool not generally well-suited to clinical application. At the present time, the technique is limited by the time elapsed for the gas extraction to process the blood samples and, also, the time for manual conversion of chromatographic data to digital data for the computer. This may well be overcome in the future by using new technology, such as rapid extraction from blood and continuous on-line measurements [69] with direct links between chromatograph and computer. Meanwhile, studies using the peripheral venous approach, such as those recently done in patients with different clinical forms of asthma [20, 46, 48], have clearly demonstrated that the conclusion of clinical nonsuitability need not be true. The use of inert gases to characterize gas exchange in the lung has thus provided us with a new level of understanding of respiratory pathophysiology in disease. The method can be used to follow clinical and therapeutic interventions and as a research tool in pulmonary medicine. Possibilities for future research in the field of gas exchange pathophysiology with this technique continue to be exciting.

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Signification clinique des inégalités de ventilation-perfusion déterminées par élimination des gaz inertes. R. Rodriguez-Roisin, P. Wagner.

RÉSUMÉ: La première partie de cette revue concerne les mécanismes de base et les facteurs déterminants de l'hypoxémie et de l'hypercapnie, ainsi que les différentes approches utilisées en practique clinique et dans la recherche clinique, pour déterminer la présence d'une mauvaise congruence de la ventilation et de la perfusion, celle de shunts et des limitations

de la diffusion pour l'oxygène, en particulier par la méthode d'élimination de gaz inertes multiples (MIGET), en médecine pulmonaire. La seconde partie passe en revue trois maladies respiratoires différentes, où l'interrelation complexe entre les facteurs intrapulmonaires et extrapulmonaires réglant l'oxygène peut être interprétée essentiellement par les résultats obtenus au cours de la dernière décennie par la technique MIGET. Sont explorés successivement grâce à la méthode des gaz inertes, la réponse des échanges gazeux après administration de bronchodilatateurs dans l'asthme bronchique - une maladie des voies aériennes, les déterminants majeurs des anomalies des échanges gazeux dans l'embolie pulmonaire aiguë - une maladie vasculaire pulmonaire, et enfin les mêmes anomalies au cours de l'hémodialyse - une entité respiratoire d'origine extrapulmonaire.
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