Contribution of multiple inert gas elimination technique to pulmonary medicine · 1

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Principles and information content of the multiple inert gas elimination technique

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The chief function of the lung is pulmonary gas exchange which requires adequate levels of ventilation and perfusion of the alveoli. The lung must match pulmonary oxygen uptake ($\dot{V}O_2$) and elimination of carbon dioxide ($\dot{V}CO_2$) to the whole body metabolic oxygen consumption and carbon dioxide production whatever the oxygen and carbon dioxide partial pressures in the arterial blood.

During the first half of this century[1,2] the heterogeneity of the ventilation-perfusion ($\dot{V}A/\dot{Q}$) ratios within the lung was identified as a factor causing hypoxaemia (table). However, the importance of $\dot{V}A/\dot{Q}$ inequality in producing hypercapnia in patients with some forms of lung disease has been pointed out only more recently.[3] At the end of the second world war a crucial step towards a better understanding of the physiology of pulmonary gas exchange was the development of the three compartment model of the lung almost simultaneously by Fenn *et al*[4] and Riley and Cournand.[5] The graphical analysis of this representation of the lung[5] (fig 1) provided the conceptual basis for the traditional interpretation of arterial blood gas measurements in the clinical setting – that is, venous admixture, physiological dead space. The progress in the mathematical description of the behaviour of oxygen and carbon dioxide in the blood[6–8] facilitated substantial contributions to the numerical analysis of pulmonary gas exchange.[9] These studies showed that traditional variables derived from physiological gases (Pa_{O_2}, Pa_{CO_2}, alveolar–arterial P_{O_2} difference ($A–aP_{O_2}$), venous admixture, and physiological dead space) are sensitive to $\dot{V}A/\dot{Q}$ mismatch, but they also vary with changes in total lung indices such as minute ventilation, cardiac output, and inspired P_{O_2}. This behaviour can lead to misinterpretations in the clinical setting. In the mid 1960s Farhi[10] demonstrated the quantitative relation of the blood-gas partition coefficient (λ) of a gas – the $\dot{V}A/\dot{Q}$ ratio – and the capacity of an alveolar unit to exchange that gas. Using the principles laid down by the work of Farhi,[10] and extending the application of inert gas elimination by adding more gases, the multiple inert gas elimination technique (MIGET)[11–13] was developed in the mid 1970s. This technique provides more information concerning the role of the $\dot{V}A/\dot{Q}$ relations on pulmonary gas exchange than previously available. It overcomes some important drawbacks of other methods such as the topographical radioactive tracer based techniques (ventilation-perfusion scans) which have limited resolution and thus underestimate the degree of $\dot{V}A/\dot{Q}$ inequality. Approaches[14] similar to MIGET but using different inspired oxygen fractions (F_{IO_2}) rather than different inert gases as the forcing function erroneously assumed no effect of F_{IO_2} on $\dot{V}A/\dot{Q}$ inequality.

The MIGET, in addition to its ability to estimate $\dot{V}A/\dot{Q}$ distributions in real lungs, provides information on other pulmonary factors

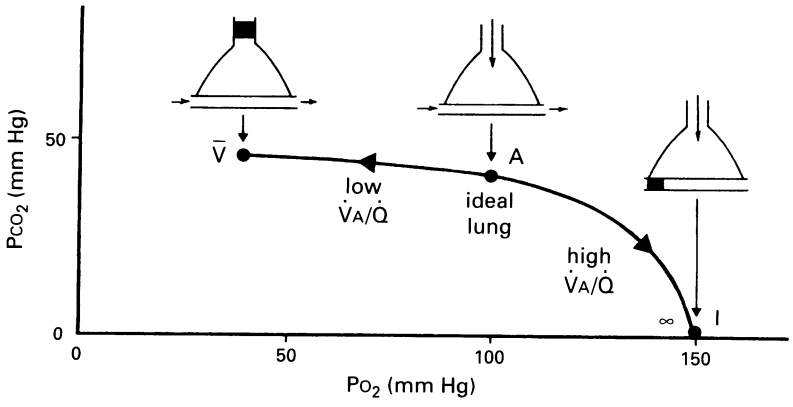

Figure 1 The three compartment lung: Riley's oxygen–carbon dioxide diagram.[5] *The lung is represented by three units on the basis of the arterial and the expired partial pressures of oxygen and carbon dioxide. One type of unit (dead space, I) is unperfused so its $\dot{V}A/\dot{Q}$ ratio is infinity. The P_{O_2} and P_{CO_2} is then equivalent to those of the inspired gas mixture. A second type of unit ($\bar{V}$) is unventilated so its $\dot{V}A/\dot{Q}$ ratio is zero and its P_{O_2} and P_{CO_2} are equivalent to those of mixed venous blood. Finally, a third type of unit (ideal, A) presents balanced ventilation and perfusion rates ($\dot{V}A/\dot{Q}$ ratio = 1).*

Factors determining arterial hypoxaemia

Intrapulmonary	*Extrapulmonary*
Main factors:	
$\dot{V}A/\dot{Q}$ mismatching	↓ Minute ventilation
Shunt	↓ Cardiac output
Alveolar-end capillary	↓ Inspired P_{O_2}
O_2 diffusion limitation	↑ O_2 uptake
Secondary factors:	
	↓ P_{50}
	↓ Hb concentration
	↑ pH

$\dot{V}A/\dot{Q}$ = ventilation-perfusion; Hb = haemoglobin; P_{50} = P_{O_2} that corresponds to 50% oxyhaemoglobin saturation.

causing hypoxaemia (table) and also allows a numerical analysis of the influence of extrapulmonary factors on arterial PO_2, as described below.

During the past 15 years a great deal of work has been done on the theoretical basis of the MIGET (to define its limits), different modalities of the technique have been developed, and a substantial amount of clinical research has been produced by several groups around the world. This introductory article to the series on the contribution of MIGET to pulmonary medicine aims to report the essentials of the technique, namely: (1) principles of measurement, (2) information content, (3) limitations, and (4) some practical details of the different modalities of the method. The mathematical complexities of the technique will be omitted as they are available elsewhere to the interested reader.[11-13] Finally, we will analyse the contribution of the MIGET to the understanding of the physiology of the normal lung and its behaviour in stress situations such as exercise and altitude.

Physiological basis and assumptions

The MIGET constitutes a conceptual and technical development of the historical work carried out by Kety,[15] Farhi,[10] and others[16] analysing the relations between inert gas exchange in the lungs, the $\dot{V}_A/\dot{Q}$ ratio distribution, and the solubilities of the gases used. These authors established the following basic equation for a single lung unit. This equation expresses mass balance during steady state elimination of the gas such as that which occurs during intravenous infusion of a dissolved gas in solution:

$$Pc'P_A = Pv \cdot \lambda/(\lambda + \dot{V}_A/\dot{Q}) \qquad \text{(equation 1)}$$

This indicates that both end capillary (Pc') and alveolar (P_A) partial pressures of an inert gas (assumed to be equal in a single lung unit[17]) depend on the partial pressure of this gas in the venous side of the capillary (Pv) and the expression in the right hand side of the equation, which includes the solubility of the gas (λ), expressed as the partition coefficient, and the $\dot{V}_A/\dot{Q}$ ratio of the lung unit. Equation 1 can be rearranged as follows:

$$Pc'/Pv = P_A/Pv = \lambda/(\lambda + \dot{V}_A/\dot{Q}) \qquad \text{(equation 2)}$$

The Pc'/Pv ratio indicates the retention (R) of the gas in the blood while the P_A/Pv ratio express its excretion (E) to the ambient air. Thus, equation 2 can be expressed in the following way:

$$R = E = \lambda/(\lambda + \dot{V}_A/\dot{Q}) \qquad \text{(equation 3)}$$

According to this mathematical expression, the retention and the excretion of an inert gas depend only on the solubility of the gas and the $\dot{V}_A/\dot{Q}$ ratio of the lung unit. The MIGET uses simultaneous venous infusion of six inert gases in trace concentrations (SF_6, ethane, cyclopropane, enflurane, diethyl ether, and acetone) covering a broad spectrum of partition coefficients from 0·005 (SF_6) to 300 (acetone) to characterise the distribution of the $\dot{V}_A/\dot{Q}$ ratios within the whole lung. Equation 3, describing the events in a single lung unit, can be applied to each lung unit and the results summed to represent total lung gas exchange:

$$R = Pa/P\bar{v} = \sum_{n=1}^{n=j} \dot{Q}_J \cdot [\lambda/(\lambda + \dot{V}_A/\dot{Q})] \qquad \text{(equation 4)}$$

$$E = P_E/P\bar{v} = \sum_{n=1}^{n=j} \dot{V}_{AJ} \cdot [\lambda/(\lambda + \dot{V}_A/\dot{Q})] \qquad \text{(equation 5)}$$

Here, $\dot{Q}_J$ and $\dot{V}_{AJ}$ represent, respectively, the fractional perfusion and ventilation of each of the N lung units present in the lung ($\sum_{n=1}^{n=j} \dot{Q}_J = \sum_{n=1}^{n=j} \dot{V}_{AJ} = 1$). For each inert gas the retentions are calculated as the ratio between arterial partial pressure and mixed venous partial pressure ($R = Pa/P\bar{v}$) and the excretions as the ratio between mixed expired partial pressure and mixed venous partial pressure ($E = P_E/P\bar{v}$). By using a multicompartmental approach with enforced smoothing, the retentions of the six inert gases allow the estimation of a continuous distribution of the pulmonary blood flow against $\dot{V}_A/\dot{Q}$ ratios on a logarithmic scale (fig 2). Similarly, the excretions of the six inert

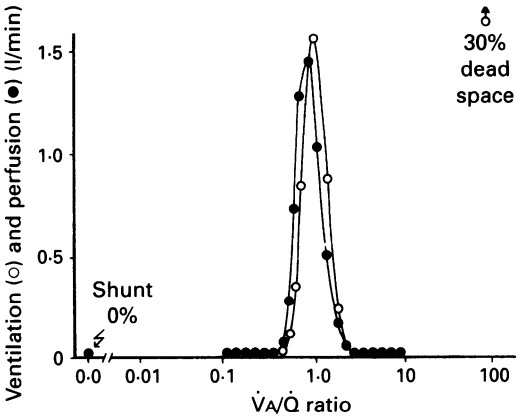

Figure 2 Ventilation-perfusion distributions. Ventilation (○) and perfusion (●) are plotted against ventilation-perfusion ($\dot{V}_A/\dot{Q}$) ratio on a logarithmic scale in a resting young healthy subject breathing room air. Both ventilation and blood flow curves are centered (first moment) around a $\dot{V}_A/\dot{Q}$ ratio of 1 and they are narrow (second moment). No perfusion to low $\dot{V}_A/\dot{Q}$ units ($\dot{V}_A/\dot{Q}$ ratios < 0·1) nor ventilation to high $\dot{V}_A/\dot{Q}$ areas ($\dot{V}_A/\dot{Q}$ ratios > 10) are observed. Note also the absence of shunt. Each individual data point represents a particular amount of blood flow (●) or alveolar ventilation (○) to the corresponding pulmonary compartment ($\dot{V}_A/\dot{Q}$ ratio). Total cardiac output corresponds to the sum of the 50 blood flow points and total alveolar ventilation is the sum of the 50 ventilation points.

gases provide an estimation of the distribution of the alveolar ventilation against $\dot{V}A/\dot{Q}$ ratios. Because equations 4 and 5 have the term $[\lambda/(\lambda+\dot{V}A/\dot{Q})]$ in common, the blood flow and the ventilation distributions are mathematically interdependent, reflecting the same distribution of the $\dot{V}A/\dot{Q}$ ratios seen from opposite sides of the blood-gas barrier (fig 3). The expression enforced smoothing, in the mathematical sense, requires compartments with similar $\dot{V}A/\dot{Q}$ ratios to have similar perfusion. In summary, the key variables for recovering $\dot{V}A/\dot{Q}$ distributions from real lungs, either in normal subjects or in patients with lung disease, are the $P\bar{v}$, Pa, and PE of the six inert gases, their corresponding partition coefficients, and $\dot{V}E$. In the presence of pulmonary and systemic arterial catheters, cardiac output is computed using steady state mass balance equations as explained below. The MIGET contains a number of assumptions that can be grouped into three different categories:

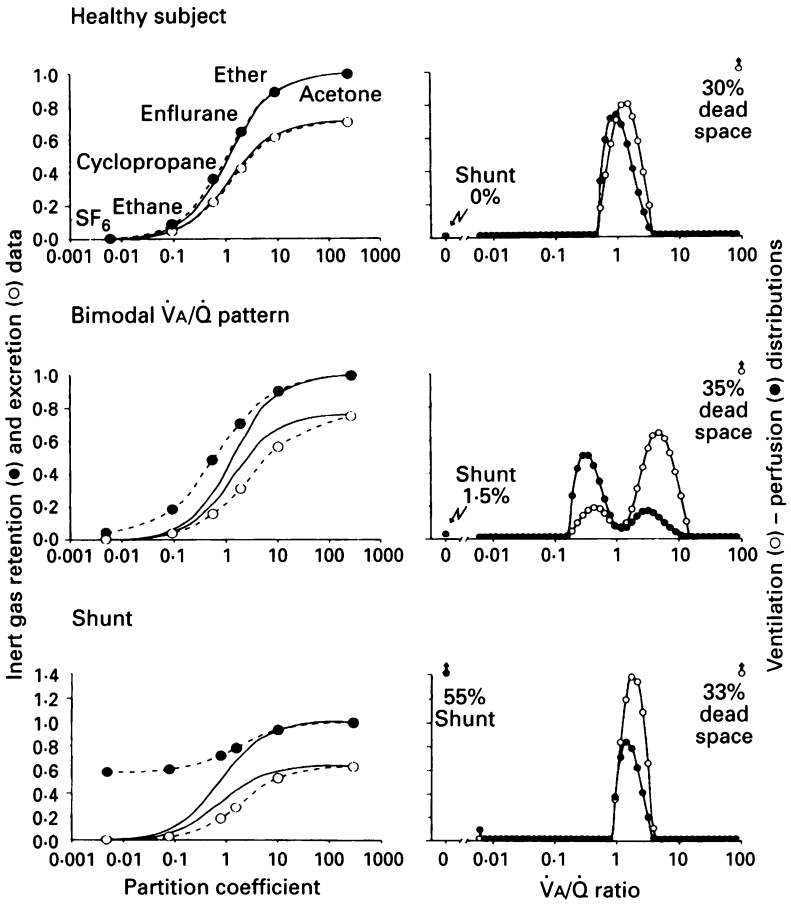

Figure 3 Inert gas retention and excretion data versus ventilation-perfusion distributions. Retentions ($Pa/P\bar{v}$) and excretions ($PE/P\bar{v}$) for the six inert gases are plotted against their blood-gas partition coefficient (solubility) (left panels) for three different types of ventilation-perfusion ($\dot{V}A/\dot{Q}$) distributions shown in the corresponding right panels. From top to bottom: normal lung; bimodal both ventilation and perfusion distributions (some patients with chronic obstructive pulmonary disease); and increased shunt (adult respiratory distress syndrome). In the retention-excretion plots continuous lines indicate the normal retention and excretion curves of the uppermost panel while the discontinuous lines represent the best fit to the measured data (dots). Notice that increased perfusion to units with low $\dot{V}A/\dot{Q}$ ratios (low $\dot{V}A/\dot{Q}$ areas) is essentially indicated by the increase in the retentions of the more insoluble gases except SF_6, while the decrease in the excretions of the more soluble gases except acetone indicate increased ventilation to units with high $\dot{V}A/\dot{Q}$ ratios (high $\dot{V}A/\dot{Q}$ areas). Retention of SF_6 and excretion of acetone are essentially the markers of the amount of shunt (%$\dot{Q}T$ to $\dot{V}A/\dot{Q}$ ratios $<0{\cdot}005$) and dead space (%$\dot{V}A$ to $\dot{V}A/\dot{Q}$ ratios >100), respectively.

STEADY STATE CONDITIONS

The technique requires the existence of steady state conditions in all $\dot{V}A/\dot{Q}$ units, as defined by mass balance between the amount of gas exchanged between the pulmonary capillary blood and the alveoli, and that exchanged between the alveoli and the atmosphere. This is required for validity of equations 1–5. This means that R and E must be constant during the period of measurement within a given experimental condition, though it is not necessary for absolute partial inert gas pressures to be constant.

CHARACTERISTICS OF THE INERT GASES

The gases must show a linear relation between partial pressure and concentration in blood (they must obey Henry's law). It is also assumed that diffusion equilibration occurs between alveolar gas and end capillary blood for each inert gas.

THE LUNG MODEL

The lung is considered to consist of a number of homogeneous compartments arranged in parallel, each with constant and continuous ventilation and perfusion. The mathematical model assumes that the distribution of ventilation and perfusion have regular contours and do not present sudden irregularities. Further important assumptions are smoothing (described earlier) and non-negativity of perfusion.

A substantial amount of research has been done to test the principal assumptions and constraints of the MIGET.[13 18–22] All are acceptable provided that the technique is used properly, but must be kept in mind when results are interpreted.

Information content and limitations

The principal objective in using the MIGET is to estimate the distribution of ventilation-perfusion ratios. However, a number of additional pieces of information become available from inert gas data, and all are now summarised.

$\dot{V}A/\dot{Q}$ DISTRIBUTION

This most fundamental outcome of the MIGET consists of a quantitative picture of the presence or absence of functional lung units of particular $\dot{V}A/\dot{Q}$ ratio. When such units are identified as present, the amount of blood flow associated with units of each identified $\dot{V}A/\dot{Q}$ ratio is computed. The result is conveniently presented graphically as in fig 2. The abscissa is the $\dot{V}A/\dot{Q}$ ratio, most conveniently plotted on a logarithmic scale. The range of partition coefficients of the six gases (from 0·005 for SF_6 to 300 for acetone) allows for a similar range of $\dot{V}A/\dot{Q}$ ratios to be identified. Thus, the lowest $\dot{V}A/\dot{Q}$ resolved from zero is 0·005 and the highest (that cannot be differentiated from infinitely great) is 100·0. Between these limits of resolution any arbitrary number of functional units can be chosen, equally log spaced along the x axis.

Traditionally 50 "compartments" are used in all. The ordinate consists of both ventilation ($\dot{V}A$) and blood flow ($\dot{Q}$) for each compartment, and the graph is then the frequency distribution of ventilation and blood flow as a function of the $\dot{V}A/\dot{Q}$ ratio.

This graphical representation is useful in giving a general overview of the distribution. It identifies domains of interest along the $\dot{V}A/\dot{Q}$ axis (below normal, normal, and above normal $\dot{V}A/\dot{Q}$ ratio), and suggests patterns of distribution as unimodal, bimodal, or trimodal (from six gases it is mathematically impossible to resolve more than three modes).

The graphical representation does not in itself quantify the degree of inequality. To do this we, and others, have developed a series of convenient parameters of the distributions of both ventilation and blood flow. One is the first moment of the distribution (on a log scale) which is simply the mean abscissa value, or mean $\dot{V}A/\dot{Q}$ ratio, of each curve. More informative are the second moments of the distributions about their respective means on a log scale, and the square roots of these moments have been called log SDQ and log SDv for blood flow ($\dot{Q}$) and ventilation ($\dot{V}$) curves respectively. The letters "SD" refer to standard deviation, which is applicable only if the entire distribution is logarithmically normal. In other cases (skewed or multimodal curves) there is nothing wrong with the parameter, but it is no longer strictly reflective of the standard deviation. These parameters then quantify the amount of $\dot{V}A/\dot{Q}$ inhomogeneity. This semantic issue should not limit applicability of the parameter which is broad and well suited to comparing distributions – for example, before and after interventions. Useful additional parameters are the fractions of total ventilation and blood flow within arbitrarily defined ranges of $\dot{V}A/\dot{Q}$ ratio. Since the distribution in normal young subjects is completely contained within the two decade range between $\dot{V}A/\dot{Q}=0{\cdot}1$ and $\dot{V}A/\dot{Q}=10{\cdot}0$, a conservative parameter of low $\dot{V}A/\dot{Q}$ abnormalities is the total (fractional) blood flow in units whose $\dot{V}A/\dot{Q}$ ratio is $<0{\cdot}1$. The corresponding parameter for abnormal high $\dot{V}A/\dot{Q}$ regions is total (fractional) ventilation of units having $\dot{V}A/\dot{Q}$ ratios $>10{\cdot}0$. Still other parameters include (when more than one $\dot{V}A/\dot{Q}$ mode is present) the fractional ventilation and blood flow of each mode, shunt (blood flow in units of $\dot{V}A/\dot{Q}$ ratio $<0{\cdot}005$), and dead space (ventilation in units of $\dot{V}A/\dot{Q}$ ratio >100) (see below).

Parameters can also be derived directly from the retention and excretion data themselves rather than from the associated computed distribution. Hlastala *et al*[23] have used the areas between the retention and excretion curves as quantitative indices, and Gale *et al*[24] have used related parameters such as the root mean square value (over the six gases) of retention minus excretion. This parameter is in effect an average alveolar–arterial difference for the inert gases.

Rather than argue which set of parameters is best, we prefer to use those parameters which best address the physiological question posed in the particular case, and frequently many, if not all, of the above are used.

SHUNT AND DEAD SPACE

The principal strength of the MIGET is the ability to identify the presence of lung units over a broad range of $\dot{V}A/\dot{Q}$ ratios, and the above describes information available over the $\dot{V}A/\dot{Q}$ ratio range 0·005–100. Outside this range all perfusion in areas of very low ($<0{\cdot}005$) or zero $\dot{V}A/\dot{Q}$ (shunt or unventilated lung units) is combined into a single parameter referred to as the shunt. Similarly, all ventilation in units of $\dot{V}A/\dot{Q}>100$ including unperfused lung ($\dot{V}A/\dot{Q}$ infinitely high) is referred to as dead space. Shunt, when present, can be due to perfusion of unventilated or extremely poorly ventilated lung regions or to direct vascular communications such as atrial septal defects with reverse (right to left) flow, or rarely to arteriovenous channels in the lung. As one of the standard 50 "compartments" used in the computed program of the MIGET shunt is directly estimated, as is flow to all other lung units. The distinguishing feature of shunt for the purposes of gas exchange is complete retention of all inert gases in the blood flowing through such regions. Post-pulmonary shunt (through bronchial or thebesian circulations) is *not* detected by the MIGET.

In a corresponding manner the dead space value returned by the computer algorithm reflects anatomical (conducting airway) dead space, together with any external instrumental dead space and also that part of alveolar ventilation that reaches alveoli which are, for any reason, completely unperfused (or which have a $\dot{V}A/\dot{Q}$ ratio of >100).

It is not possible from MIGET data alone to further subdivide either shunt or dead space into its potential components.

DIFFUSION LIMITATION OF GAS EXCHANGE

The $\dot{V}A/\dot{Q}$ distribution, shunt, and dead space are parameters based on convective gas and blood flow through the lung, and the MIGET algorithm is based on a theory that expressly assumes that all diffusive processes affecting pulmonary gas movement are sufficiently rapid not to affect gas exchange. That the MIGET algorithm can so often adequately fit experimental data in the face of these assumptions suggests that under most conditions the assumptions are reasonable. Two forms of diffusion limitation are recognised as being theoretically possible, however; (1) that associated with diffusion of gases between alveolar gas and capillary blood, and (2) that associated with diffusive mixing of inspired gas with resident alveolar gas.

The former problem, when it occurs, impairs oxygen exchange much earlier than inert gas exchange; the inert gases are in fact essentially invulnerable to this form of diffusion limitation.[25–27] Consequently, under such conditions, application of MIGET will still estimate the $\dot{V}A/\dot{Q}$ distribution despite oxygen diffusion limitation; however, oxygen exchange will be affected not only by $\dot{V}A/\dot{Q}$ inequality but also by diffusion limitation. When the MIGET algorithm uses the derived $\dot{V}A/\dot{Q}$ distribution to estimate the amount of hypoxaemia that $\dot{V}A/\dot{Q}$

inequality should produce,[25–27] the value of the expected arterial Po_2 will be too high (when compared with the measured arterial Po_2) because of the depression of actual arterial Po_2 by diffusion limitation. Thus, if the expected arterial Po_2 exceeds the measured value by more than experimental error, the presence of oxygen diffusion limitation is inferred. If one assumes a uniform distribution of lung oxygen diffusing capacity to blood flow, it is then possible to compute the oxygen diffusing capacity that would reconcile the measured and expected arterial Po_2 values.[28] This is a useful tool when characterising impaired oxygen diffusive equilibration in the lung. Two other phenomena may also cause a similar difference between expected and actual arterial Po_2 values. Firstly, significant pulmonary tissue oxygen utilisation which is hypothesised to occur, for example, in pneumonia would result in a lower arterial Po_2 than the non-metabolised inert gases would predict. This has, however, not been found.[29] Secondly, post-pulmonary shunts via the bronchial and/or thebesian circulations may depress actual arterial Po_2 but not affect inert gas exchange, thus also resulting in a higher expected Pao_2. It can be difficult to exclude this phenomenon when expected Pao_2 exceeds the measured value, but the good agreement between expected and measured values almost always seen at rest suggests that such shunts are generally undetectable. During normoxic heavy exercise expected Pao_2 often exceeds the measured value, suggesting diffusion limitation for oxygen, but the relative importance of diffusion limitation and post-pulmonary shunt are not definitively ascertainable. However, logic favours diffusion limitation for two reasons: (1) the expected to measured difference becomes greater in hypoxia, and (2) the calculated post-pulmonary shunt would (especially in hypoxia) have to exceed 10% of the cardiac output, an unreasonable value.

Impaired *gas phase* diffusive mixing can also be identified by MIGET. Here the factor that separates vulnerability of different gases to this phenomenon is the gas molecular weight. Hence oxygen (MW = 32) is relatively invulnerable to this problem compared with the gases SF_6 (MW = 146) and enflurane (MW = 180) used in the MIGET. The other gases used in MIGET have molecular weights ranging from 30 (ethane) to 74 (ether). Consequently, if molecular weight is an important determinant of inert gas exchange it would affect each of the six gases differently and thus prevent the MIGET algorithm from fitting the measured inert gas data accurately. This is because the algorithm accounts for the solubility of each gas but ignores molecular weight. One would therefore expect a poor fit to the data by the algorithm and, in particular, directional errors in fitting the data that reflected the molecular weight for each gas. Thus high molecular weight gases would be retained in the blood to a greater degree, and low molecular weight gases to a lesser degree, than would be expected from solubility alone. In normal animals and subjects such evidence for gas phase diffusive limitation is difficult to obtain, but many years ago Truog *et al*[30] saw this in the anaesthetised rat. More recently we have seen this to a minor degree in exercising pneumonectomised fox hounds.[31] It should be kept in perspective, however. Such gas phase diffusive limitation appears to account for no more than a 1–2 mm Hg drop in arterial Po_2, whereas $\dot{V}_A/\dot{Q}$ mismatch and/or oxygen diffusion limitation across the blood gas barrier often produces severe hypoxaemia.

MODEL ADEQUACY

The preceding argument indicated that gas phase diffusive limitation would produce a poor fit to the inert gas data by the MIGET algorithm, and this would be reflected by a high residual sum of squares (between the data themselves and the least squares best fit to these data produced by the algorithm). However, it was pointed out that the errors for individual gases would systematically follow their molecular weight.

Another possibility exists to explain a potential poor fit of the model to experimental data – that is, a high residual sum of squares (RSS) due to random measurement errors. By establishing the measurement accuracy of MIGET we can estimate the variance of inert gas data and thus compute the expected distribution of RSS due to normal measurement errors. Data sets producing RSS values systematically greater than expected point to a discrepancy between the basic physiological model described above and lungs under current study. Thus, if gas exchange is not adequately described by the conventional steady state equations, either the assumptions have been violated – that is, the subject is not in a steady state as required – or the lung is for some reason not exchanging gas in concordance with the model used. A good example of the latter is reported by Powell,[32 33] who applied the MIGET to avian lungs. Using the standard MIGET algorithm the RSS were clearly not compatible with expectations; they were several fold higher. Measurements made with the same personnel and equipment at the same time, but in canine lungs, did not produce abnormal RSS values. When the MIGET algorithm was changed to reflect the different gas exchange process of avian versus mammalian lungs – that is, by modelling cross-current rather than alveolar gas exchange[33] – the RSS reverted to normal for the same data.

MEASUREMENT OF CARDIAC OUTPUT

Steady state mass balance equations are the basis of the MIGET. Thus, since the inert gases are infused intravenously rather than inhaled they are absent from inspired gas, much like carbon dioxide. Consequently inert gas output measured by expired gas analysis (total ventilation times gas concentration) equals that computed as the product of the difference between the pulmonary arterial and systemic arterial inert gas concentrations and cardiac output.

In the presence of pulmonary and systemic

arterial catheters it is thus a straightforward matter to compute cardiac output. In fact, each gas gives an essentially independent estimate of cardiac output, and thus a robust average value of this variable can be determined. In computing this average, however, it is important to properly weigh the contribution of each gas in accordance with conventional error propagation theory.[13]

INFLUENCE OF EXTRAPULMONARY FACTORS ON GAS EXCHANGE

It is well known that arterial P_{O_2} is determined by a combination of intrapulmonary and extrapulmonary factors (table). The intrapulmonary factors include (1) the degree of $\dot{V}_A/\dot{Q}$ mismatch, shunt and dead space, and (2) diffusion limitation if present. The extrapulmonary factors of primary importance are: (1) F_{IO_2}, (2) total ventilation, (3) cardiac output, and (4) $\dot{V}_{O_2}$ (metabolic rate).

As described above in the section on diffusion limitation, it is possible to predict the arterial P_{O_2} expected from the measured $\dot{V}_A/\dot{Q}$ inequality and the particular combination of extrapulmonary factors that existed at the time of measurement. The MIGET algorithm, however, allows the observer to change any or all of the extrapulmonary factors, and then to recompute the expected value of arterial P_{O_2}. In addition to the four primary extrapulmonary variables (table) secondary variables such as haemoglobin concentration, haemoglobin P_{50}, body temperature, and blood acid-base status can also be changed singly or in any combination.

Such flexibility is useful in understanding not only expected effects of therapeutic interventions, but also in separately determining the quantitative role of each extrapulmonary factor when they change between two conditions of MIGET measurement. For example, if a vasodilator was given to a patient with high pulmonary artery pressure cardiac output may well increase, while at the same time the $\dot{V}_A/\dot{Q}$ distribution may change for the worse. Arterial P_{O_2} will reflect the integrated effect of these changes. It is a simple matter to execute the MIGET algorithm (a) with the data obtained before giving the drug, (b) using the post-drug inert gas data with the predrug cardiac output, and (c) using all post-drug data to study the individual influences on arterial P_{O_2} of each factor. It is similarly possible to use the algorithm to separately assess, for example, the effect of shunt versus that of $\dot{V}_A/\dot{Q}$ inequality on arterial P_{O_2}.

Practical considerations

The original technique (fig 4) was described using inert gas levels determined from three different sites: mixed venous blood ($P\bar{v}$), arterial blood (Pa), and mixed expired gas (P_E). This modality uses direct measurements of all the variables involved in the estimation of the $\dot{V}_A/\dot{Q}$ distribution (equation 3) and provides a measurement of cardiac output as described earlier. However, it requires the placement of a catheter in the pulmonary artery. When such a catheter is not used a modality of the MIGET without mixed venous sampling[24] can be used with similar accuracy. In this instance cardiac output needs to be directly obtained (using indocyanine green or perhaps one of the non-invasive techniques). Since all the necessary variables except $P\bar{v}$ are now measured, $P\bar{v}$ can be computed from mass balance:

$$\dot{Q}_T.\lambda.P\bar{v} = \dot{Q}_T.\lambda.Pa + \dot{V}_E.P_E \quad \text{(equation 6)}$$

$$P\bar{v} = Pa + (\dot{V}_E.P_E/\lambda.\dot{Q}_T) \quad \text{(equation 7)}$$

This modality of the technique is also able to

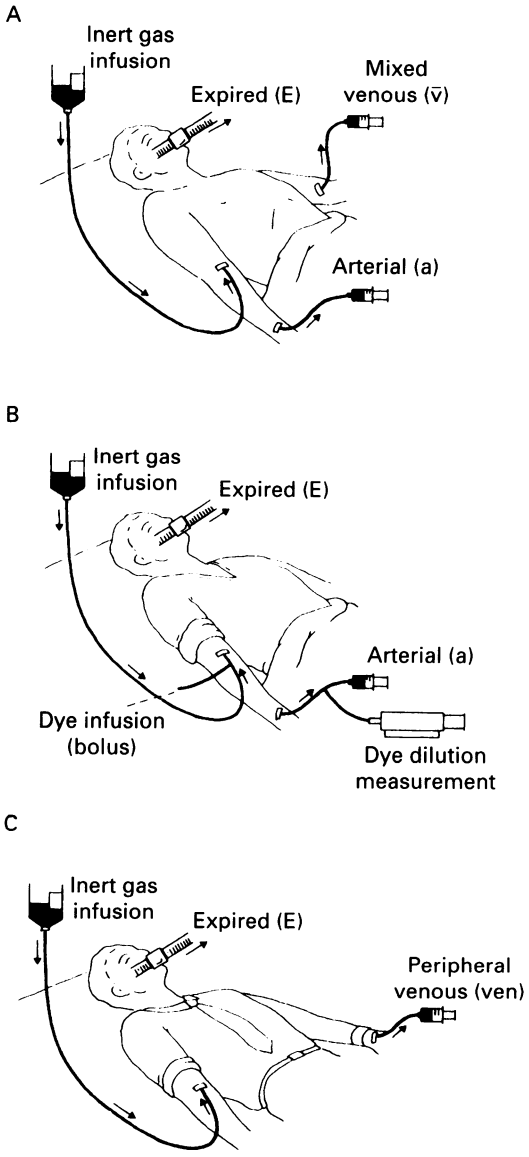

Figure 4 Different modalities of the MIGET. (A) Original description of the technique with arterial (Pa), mixed expired (P_E) and mixed venous ($P\bar{v}$) samplings. In (B) only arterial (Pa) and mixed expired (P_E) samplings are required. Cardiac output ($\dot{Q}_T$) is then measured by green dye and mixed venous partial pressures ($P\bar{v}$) of the six inert gases are estimated by mass balance. It does not require the placement of a catheter in the pulmonary artery. In (C) only peripheral venous (Pven) and mixed expired (P_E) samplings are done. This modality (see text) is useful when serial measurements in the same subject are planned.

estimate the predicted arterial P_{O_2} according to the $\dot{V}_A/\dot{Q}$ distributions and to test for alveolar-end capillary oxygen diffusion limitation[27] if measurements of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ are obtained simultaneously since equations analogous to (6) and (7) can then be applied to calculate $P\bar{v}_{O_2}$ and $P\bar{v}_{CO_2}$.

Finally, a third modality of the MIGET[34] requiring only mixed expiratory and peripheral venous sampling is also available. This is obtained from a distally oriented 20-gauge cannula inserted into a peripheral vein (usually in the forearm opposite to the side of the infusion of the inert gas solution). Because inert gases are not metabolised in the tissues of the hand, and after some 90 minutes of inert gas infusion in a resting position, virtual equilibration between blood and tissues is achieved and the peripheral venous blood reflects the inert gas concentrations of the inflowing arterial blood. In this condition partial pressures of the inert gases in the peripheral vein (Pven) have been shown to be 95% of Pa (Pa=Pven/0·95) and reproducible enough to permit substitution of peripheral venous for arterial sampling. However, since $\dot{Q}_T$ is not directly measured there is still an unknown in equation 7. Cardiac output can be estimated within a reasonable range on the basis of relatively simple non-invasive procedures such as Doppler echocardiography. By numerical analysis it has been shown that the log SDQ and log SDv are mostly insensitive to the uncertainty of the estimation of cardiac output. It must be pointed out, however, that this approach without arterial sampling is not useful for estimating the first moment of the distributions, the amount of shunt and dead space, nor the percentage of perfusion or ventilation at a given range of $\dot{V}_A/\dot{Q}$ ratios. By contrast, this less invasive approach of the MIGET is particularly useful in those situations wherein the main focus of interest is the shape and the dispersion of the $\dot{V}_A/\dot{Q}$ distributions, and arterial catheterisation needs to be avoided because repeated measurements over time are planned. The results of this modality have been validated by two different studies in patients with asthma using repeated measurements almost daily or weekly.[35 36]

EXPERIMENTAL DETAILS AND DATA PROCESSING

The ability to obtain accurate information using the MIGET requires careful and detailed technical aspects. The different steps of the data collection described below must be followed carefully to maintain the experimental error within the tolerable limits and to preserve the steady state.

Preparation of the inert gas solution for sterile infusion

A mixture of the six inert gases is equilibrated with 1 litre of either normal saline or 5% dextrose. A tank of gas containing approximately 20% SF_6, 20% cyclopropane, and 60% ethane is connected to the plastic bag with the solvent by using sterile intravenous tubing with a 0·22 μm Millipore filter inserted. Gas from the tank is then pumped into the bag until the latter is somewhat distended. The bag is vigorously shaken for approximately one minute and the gas in the bag is then vented to the atmosphere. This cycle should be repeated once to reach full equilibration between the saline or dextrose and the tank gas mixture. Next, 0·7 ml liquid diethyl ether/l saline is transferred into the bag, followed by the addition of 7 ml liquid acetone/l, and finally, 3 ml liquid enflurane/l. The bag is then gently inverted several times to facilitate the distribution of the last three gases into the liquid phase. Each of these steps must be done using sterile disposable material and following the necessary precautions to preserve sterility.

Infusion of the inert gas solution

The solution is infused into a peripheral superficial vein of the forearm by means of a roller pump directly from the bag in which it was prepared. A fresh 0·22 μm Millipore filter is inserted into the line to preserve sterility. A constant and smooth rate of infusion of 3 ml/min is used in subjects studied at rest. To achieve a steady state a period of about 30 minutes with the infusion running is usually required before any sampling is carried out.

Sampling procedure

After ensuring quiet breathing and stable minute ventilation of the subject (often tidal volume, respiratory rate, end tidal F_{O_2} and F_{CO_2}, ECG, and $\dot{V}_{O_2}$ are all monitored on line) arterial (4–8 ml) and mixed venous (4–8 ml) samples are drawn simultaneously using heparinised barrel matched ungreased glass syringes. The entire sample is collected by slow steady withdrawal over several respiratory cycles lasting about 30 seconds. For the collection of (duplicate) 15 ml samples of mixed expired gas we use matched barrel/plunger glass syringes. A one way low resistance valve is connected through a large bore heated plastic tube to a mixing box containing a long coiled copper tube 10 cm in diameter and 70 cm in length, which is kept heated several degrees above body temperature. This allows adequate mixing of the expiratory gases without significant loss of soluble inert gases in condensate and produces a lag time that must be allowed for in the sampling procedure. It is advantageous to take duplicate sets of samples in each experimental condition. It is also important to take duplicate control samples of the mixed expired gas and pulmonary and systemic arterial blood before the infusion of the inert gases to exclude spurious signals that could confound the analysis of later samples. The control blood samples are later reused for (duplicate) measurement of the solubilities of the inert gases.

Measurements of inert gas concentrations

Before the study the syringes to be used for blood sampling must be weighed both before and after heparinisation. The heparin used should be tested in order to avoid those brands that contain acetone.[37] The mixed expired

samples can be directly injected into the gas chromatograph to measure inert gas concentrations. For the blood samples we proceed in the following way. Each syringe is weighed a third time, after blood sampling, in order to measure the volume of blood (calculated as weight divided by density). Density is measured later from pooled samples. Approximately 10 ml of nitrogen is transferred into each syringe for equilibration of inert gases between blood and the nitrogen phase. This procedure is carried out in a shaking water bath at body temperature for approximately 40 minutes. The combined volume of the nitrogen and blood is then measured at body temperature and the gas above the blood is anaerobically transferred to a dry syringe to be measured in the gas chromatograph. The peak of the least soluble gas, SF_6, is measured by an electron capture detector (ECD) while the remaining five gases (all hydrocarbons) are measured by a flame ionisation detector (FID). The characteristics of the set-up of the gas chromatograph for the MIGET and the quality control procedures have been detailed elsewhere.[11 38] The chromatographic peaks so measured from the gas phase after the equilibration procedure are not equal to Pa and $P\bar{v}$ of each inert gas. These partial pressures must therefore be calculated using standard mass balance formulae[11] that take into account (1) height or area of the chromatographic peaks (fig 5), (2) partition coefficients of each inert gas, and (3) volumes of heparin, blood, and gas in the syringe during the equilibration procedure. Technicalities of the sample processing and the measurement of solubilities are described elsewhere.[11 38] It is important to note that the coefficient of variation of the entire procedure for measuring gases in blood should not exceed 3% for the five more soluble inert gases at physiological levels (generally determined from 10 samples of a common pool). For SF_6 the coefficient of variation is invariably greater and a value of 5–6% is reasonable.

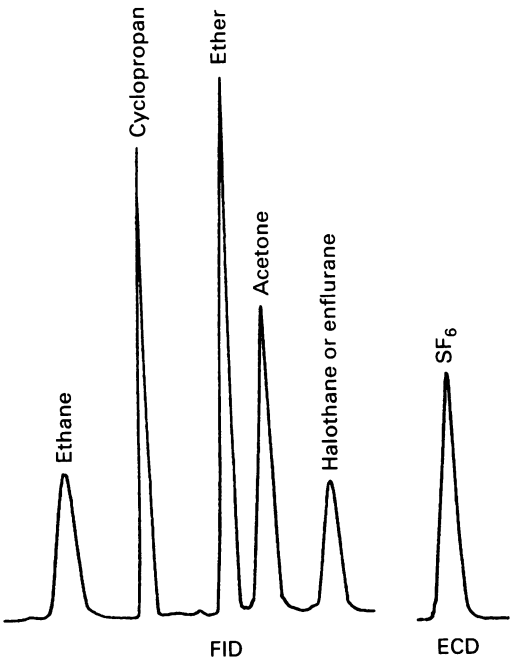

Figure 5 Gas chromatogram obtained from a mixed venous blood sample. Chromatographic measurements are done after the equilibration of the blood sample (blood phase) with a similar volume of nitrogen (gas phase), as explained in the text. The peak of each inert gas is identified in the figure. FID = flame ionisation detector; ECD = electron capture detector.

Recovering the $\dot{V}_A/\dot{Q}$ distributions

The data obtained during the inert gas elimination studies – namely R ($Pa/P\bar{v}$ ratio) and E ($P_E/P\bar{v}$ ratio) for each of the six inert gases and their partition coefficients – are fed into a computer program that estimates the distribution of $\dot{V}_A/\dot{Q}$ ratios consistent with that quantitative pattern of gas tension ratios. The program estimates the variance of the retention of each inert gas and adjusts the numerical contribution (weight) of that gas according to the corresponding error of measurement. Two complementary mathematical approaches can be used to examine the $\dot{V}_A/\dot{Q}$ distributions associated with each set of six inert gas data. One is the least square best fit regression analysis (LSBF) with enforced smoothing and the other is the linear programming method (LP). The purpose of the LP is to provide an absolute upper bound of the family of distributions compatible with the measured data allowing for both the experimental errors and the underdetermined nature of the problem (the gas exchange behaviour of approximately 10^5 lung units is examined using only six sets of data). This approach has been useful for evaluating the limits of the MIGET[13 21 22] but it is cumbersome and time consuming. By contrast, the LSBF with enforced smoothing is a useful way for day by day calculations in the clinical setting.[39] The residual sum of squares (RSS) is, as mentioned earlier, a quantitative estimation of the overall experimental error in the procedure. The analysis of the frequency distribution of the RSS from many measurements carried out in a particular laboratory constitutes a precise way to evaluate adequacy of the data. The χ^2 distribution for six degrees of freedom to assess the frequency occurrence of RSS gives a value of 5·3 for $p = 0{\cdot}5$, 10·6 for $p = 0{\cdot}1$, and 16·8 for $p = 0{\cdot}01$. In other words, 50% of data sets should have RSS $< 5{\cdot}3$, 90% of RSS should be less than 10·6, and 99% less than 16·8. The range of the second moment (log SDQ and log SDV) is from 0·30 in healthy young subjects (see below) to about 2·5 in extreme lung disease. The overall intrasubject coefficient of variation for log SDQ and log SDV is 6% if the mean of duplicate measurements is used.[40]

Results in normal subjects

AT REST BREATHING ROOM AIR

The characteristic $\dot{V}_A/\dot{Q}$ distribution in normal seated young subjects (< 30 years) consists of narrow perfusion and ventilation curves centered around a $\dot{V}_A/\dot{Q}$ ratio of one (fig 2). Mean values for the second moment of the distribution (log SDQ and log SDV) range from 0·35 to 0·43.[26] The upper 95% confidence limit for log SDQ is 0·60, and for log SDV is 0·65.[24 28 41 42] No (or virtually no) perfusion to $\dot{V}_A/\dot{Q}$ ratios

$<0{\cdot}005$ (shunt) is present.[26] Likewise, the amount of ventilation to $\dot{V}A/\dot{Q}$ ratios >100 (including instrumental, anatomical, and physiological dead space) is approximately 30%. As fig 2 illustrates, no perfusion to lung units with $\dot{V}A/\dot{Q}$ ratios $<0{\cdot}1$ (low $\dot{V}A/\dot{Q}$) is observed; similarly ventilation to lung units with $\dot{V}A/\dot{Q}$ ratios >10 (high $\dot{V}A/\dot{Q}$) is not present. Age related changes in the second moment (increased heterogeneity with aging) is expected,[26 43] similar to the decline in Pa_{O_2}. However, the $\dot{V}A/\dot{Q}$ distributions of older healthy subjects remain to be determined.

AT REST BREATHING 100% OXYGEN

After 30 minutes of breathing 100% oxygen[26] no changes in $\dot{V}A/\dot{Q}$ mismatch have been shown in young subjects. The only variations observed in this condition were a moderate shift of the $\dot{V}A/\dot{Q}$ distributions to the right as a result of the increase in the overall $\dot{V}A/\dot{Q}$ ratio of the lung associated with increased ventilation, and the presence of a very small amount of shunt (0·5% of cardiac output). By contrast, overt increase in $\dot{V}A/\dot{Q}$ inequality was observed in a very small study of older subjects (aged 39–60 years) during 100% oxygen breathing. Increase in both low $\dot{V}A/\dot{Q}$ areas (%$\dot{Q}T$ to $\dot{V}A/\dot{Q}$ ratios $<0{\cdot}1$) and in the amount of shunt were detected. The development of reabsorption atelectasis after denitrogenation of lung units with critically low $\dot{V}A/\dot{Q}$ ratios, as predicted by Briscoe *et al*,[44] has been the mechanism invoked for the development of shunt during 100% oxygen breathing. Likewise, the release of hypoxic pulmonary vasoconstriction in this condition would explain the increase in the blood flow of lung units with low $\dot{V}A/\dot{Q}$ ratios. The changes in the perfusion distribution (log SDQ) during 100% oxygen breathing have been used as a way of testing the reactivity of the pulmonary vascular tone in different situations.[25 45]

EXERCISE

During submaximal exercise the dispersion of the $\dot{V}A/\dot{Q}$ distributions does not change[24 28 41] but the $\dot{V}A/\dot{Q}$ ratios at the mean of both ventilation and perfusion distributions substantially increases due to the higher overall $\dot{V}A/\dot{Q}$ ratio.[46] The efficiency of the lung as an oxygen and carbon dioxide exchanger therefore improves in this condition. However, hypoxaemia (or increase in $A\text{–}aPo_2$) may occur in athletes during heavy exercise at sea level.[47] The MIGET has been used to analyse the physiological mechanisms behind this phenomenon. It has been shown that the increase in the $A\text{–}aPo_2$ in exercise is due, in part, to $\dot{V}A/\dot{Q}$ mismatching,[24 28 41] but it is mostly explained by alveolar-end capillary oxygen diffusion limitation.[27 28 42] The technique has indicated that pulmonary oxygen diffusing capacity during heavy exercise in man is high, but still somewhat lower than that previously estimated by morphometric measurements.[48]

Abnormalities of pulmonary gas exchange during exercise in healthy subjects are clearly accentuated if exercise is carried out during hypoxia produced either by breathing a low inspired oxygen fraction[42] or simulating altitude in a hypobaric chamber.[24 27 28 49] The increase in log SDQ during exercise is not associated with altered spirometry, but shows a significant correlation with the increase in mean pulmonary artery pressure. On the other hand, $\dot{V}A/\dot{Q}$ mismatching in exercise is reversed during acute altitude exposure by breathing 100% oxygen.[24] During chronic extreme altitude exposure the development of units with very low or zero $\dot{V}A/\dot{Q}$ ratios (shunt) is a common feature.[49] Ventilation-perfusion mismatch occurring with exercise at altitude appears, in part, to be determined by the rate of ascent as opposed to the altitude reached.[49 50] It has been hypothesised that the development of some degree of pulmonary oedema[28 49] might explain the deterioration in pulmonary gas exchange during heavy exercise, but no direct evidence has yet been obtained. Alternative explanations for the $\dot{V}A/\dot{Q}$ mismatching such as airway obstruction (due to exercise-induced or hypocapnia-induced bronchoconstriction) or non-uniform hypoxic vasoconstriction are not consistent with the described findings.

Summary

This introductory review summarises four different aspects of the multiple inert gas elimination technique (MIGET). Firstly, the historical background that facilitated, in the mid 1970s, the development of the MIGET as a tool to obtain more information about the entire spectrum of $\dot{V}A/\dot{Q}$ distribution in the lung by measuring the exchange of six gases of different solubility in trace concentrations. Its principle is based on the observation that the retention (or excretion) of any gas is dependent on the solubility (λ) of that gas and the $\dot{V}A/\dot{Q}$ distribution. A second major aspect is the analysis of the information content and limitations of the technique. During the last 15 years a substantial amount of clinical research using the MIGET has been generated by several groups around the world. The technique has been shown to be adequate in understanding the mechanisms of hypoxaemia in different forms of pulmonary disease and the effects of therapeutic interventions, but also in separately determining the quantitative role of each extrapulmonary factor on systemic arterial Po_2 when they change between two conditions of MIGET measurement. This information will be extensively reviewed in the forthcoming articles of this series. Next, the different modalities of the MIGET, practical considerations involved in the measurements and the guidelines for quality control have been indicated. Finally, a section has been devoted to the analysis of available data in healthy subjects under different conditions. The lack of systematic information on the $\dot{V}A/\dot{Q}$ distributions of older healthy subjects is emphasised, since it will be required to fully understand the changes brought about by diseases that affect the older population.

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