

The Multiple Inert Gas Elimination Technique 50 years later: Lessons Learned

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ABSTRACT

The Multiple Inert Gas Elimination Technique (MIGET) was developed in the early 1970's to measure the way in which pulmonary ventilation ($\dot{V}A$) and blood flow (\dot{Q}) are distributed one to the other. It is based on the elimination of six foreign inert gases simultaneously infused intravenously, with computer analysis of their elimination pattern to deduce, qualitatively and quantitatively, the shape of the responsible $\dot{V}A/\dot{Q}$ distribution. After summarising MIGET's physiological basis, this article presents the key observations made using MIGET over many years in health and in three chronic lung diseases – chronic obstructive pulmonary disease (COPD), bronchial asthma and interstitial lung disease. While significantly advancing our understanding of the pathophysiology of these diseases, the findings have led to many still unanswered questions of clinical significance in each case. These questions are also presented and discussed. (BRN Rev. 2019;5(4):294-309)

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INTRODUCTION

This review centres on the Multiple Inert Gas Elimination Technique, known as MIGET¹. The objectives are to provide a brief technical overview, and then summarise some key discoveries made in health and disease using MIGET. The scope is limited to human studies, including health and three common chronic respiratory diseases – chronic obstructive pulmonary disease (COPD), bronchial asthma and interstitial pulmonary fibrosis. After presenting key observations, remaining unanswered questions are also identified. With more than 500 published English-language reports using MIGET, this review is necessarily incomplete, but a 2017 book¹ provides deeper understanding of MIGET theory and applications and cites all such articles that could then be found.

The MIGET was invented in the 1970's^{2,3} to assess a technically challenging unsolved pulmonary physiological problem: how to measure the distribution of alveolar ventilation ($\dot{V}A$) in relation to the distribution of pulmonary perfusion (\dot{Q}). More precisely, how to measure the distribution of the *ratio* of $\dot{V}A$ to \dot{Q} , a ratio designated $\dot{V}A/\dot{Q}$. It is a functional approach based on the simultaneous pulmonary exchange of several inert gases. It does not provide regional $\dot{V}A/\dot{Q}$ information, but rather the frequency distribution of $\dot{V}A/\dot{Q}$ ratios throughout the entire lung, in the same way that one might plot the frequency distribution of body weight in a large population of people.

The importance of the $\dot{V}A/\dot{Q}$ ratio and its distribution cannot be overstated: gas exchange depends on the $\dot{V}A/\dot{Q}$ ratio in every alveolus. It has been known for decades that if $\dot{V}A$ is

not well-matched to \dot{Q} , such that in some regions $\dot{V}A/\dot{Q}$ is low, while other regions possess a high $\dot{V}A/\dot{Q}$ ratio (i.e., when $\dot{V}A/\dot{Q}$ *inequality* is present), the ability of the lungs to exchange any gas, including oxygen (O_2) and carbon dioxide (CO_2), is compromised⁴⁻⁸. This results in arterial hypoxaemia (and, sometimes, hypercapnia) and reduction in the O_2 uptake (and CO_2 elimination) ability of the lungs. If the body is unable to restore O_2 uptake and CO_2 elimination to normal despite persisting $\dot{V}A/\dot{Q}$ inequality by a) increasing O_2 extraction in the tissues (and raising venous carbon dioxide partial pressure [PCO_2] in the venous blood coming from the tissues); and/or b) raising alveolar ventilation; and/or c) raising cardiac output, tissues may become hypoxic and hypercapnic to the point of organ failure and death.

MULTIPLE INERT GAS ELIMINATION TECHNIQUE (MIGET): BASIC PRINCIPLES

Exchange of all non-reactive gases (that is, gases that do not chemically react with cells or tissues, damaging them) by the lungs is governed by the simple principle of conservation of mass. This means that every molecule of a gas that is inhaled but does not leave in exhaled gas moves across the alveolar blood-gas barrier and into the blood to be transported to the tissues by perfusion.

This was recognised early in the 20th century, as illustrated by Rahn's and Fenn's 1955 "Graphical analysis of the respiratory gas exchange"⁵. These authors quantified the mass conservation principle by two simple equations. The first expressed gas uptake as the product of

alveolar ventilation and the inspired-mixed expired gas concentration difference. The second expressed gas uptake as the product of pulmonary blood flow and end-capillary to mixed venous concentration difference. Conservation of mass simply meant that both ways of expressing gas uptake must yield identical solutions for gas uptake.

While the concept is straightforward, solving the equations for O_2 and CO_2 is difficult because their binding curves in blood are both non-linear and interdependent. But when they are solved, they 1) show that the $\dot{V}A/\dot{Q}$ ratio is the principal determinant of alveolar PO_2 and PCO_2 ; and 2) define the value of the alveolar PO_2 which must exist for any given $\dot{V}A/\dot{Q}$ ratio. Local alveolar PO_2 thus reflects the local $\dot{V}A/\dot{Q}$ ratio.

Inert gases (gases that are chemically non-reactive, do not combine with haemoglobin [Hb] and are carried in blood only in physical solution) are also exchanged in a manner that obeys the same mass conservation principles. Their great advantage is that their “dissociation curves” are defined by a single parameter – their solubility in blood.

If one infuses a foreign inert gas (dissolved in saline or dextrose) into a peripheral vein, ensuring that inspired air does not contain that gas, the gas reaches the lungs, where some molecules diffuse across the blood:gas barrier to be eliminated by ventilation, while others remain in the capillary blood, to be circulated to the tissues by blood flow. For a poorly soluble gas (in a normal lung), most molecules will be eliminated by ventilation, and only a minority will remain in the blood and circulated to the tissues. However, for a

highly soluble gas, most molecules remain in the blood, and only a minority will be eliminated by ventilation. It is this property – solubility-dependence of gas exchange - on which MIGET is based. The elimination of each inert gas also depends on the distribution of $\dot{V}A/\dot{Q}$ ratios such that by measuring the elimination of a mixture of inert gases of different solubilities one can mathematically determine the $\dot{V}A/\dot{Q}$ distribution that gave rise to the measured elimination pattern.

The two-equation concept used by Rahn and Fenn⁵ applies to all gases, but for inert gases infused intravenously as above, the two equations and their solution are straightforward, and the result is as follows:

Equation 1:

$$\dot{V}gas = \dot{V}A \times FA = \dot{V}A \times k \times PA$$

Equation 2:

$$\begin{aligned} \dot{V}gas &= \dot{Q} \times [Cv - Cec] = \dot{Q} \times s \times [P\bar{v} - Pec] \\ &= \dot{Q} \times s \times [P\bar{v} - PA] \end{aligned}$$

The symbols require explanation: $\dot{V}gas$ in both equations is the number of molecules moving per unit time from capillary blood into alveolar gas; $\dot{V}A$ and \dot{Q} are alveolar ventilation and capillary perfusion respectively; FA and PA are alveolar (A) fractional concentrations (F) and partial pressures (P) of the inert gas; the constant k is the proportionality constant between F and P; $P\bar{v}$ and Pec are the mixed venous and end-capillary blood partial pressures of the inert gas, and furthermore, the explicit assumption is made (in equation 2) that $Pec = PA$ for any inert gas in every alveolus. This implies full diffusion equilibration, generally accepted as always occurring for inert gases. Finally, s is the solubility of the

inert gas such that $s \times P_{\bar{V}}$ represents the concentration of the inert gas in mixed venous blood while $s \times P_A$ is the concentration of the inert gas in end-capillary blood.

When the two expressions are equated (because mass conservation means \dot{V}_{gas} is the same when calculated from both equations), using the correct units, and terms are re-arranged, the result simplifies to this:

Equation 3:

$$P_A/P_{\bar{V}} = P_{\text{ec}}/P_{\bar{V}} = \lambda / [\lambda + \dot{V}_A/\dot{Q}]$$

Here, using proper units, solubility (s) now appears as the blood:gas partition coefficient, λ .

This simple equation has profound implications and is the essential basis of MIGET as shown by figures 1 and 2. Figure 1 plots, for a homogeneous lung with a \dot{V}_A/\dot{Q} ratio of 1.0, $P_{\text{ec}}/P_{\bar{V}}$, as a function of λ . In the figure, P_{ec} is replaced by P_A , the arterial inert gas partial pressure, which it equals when the lungs are homogeneous. A \dot{V}_A/\dot{Q} ratio of 1.0 is close to resting normal human values. The abscissa in figure 1 uses a logarithmic scale for λ , allowing a very wide range of values of λ , and the line shown is simply the visual expression of equation 3. The ratio $P_A/P_{\bar{V}}$, termed "retention", cannot be less than zero (completely eliminated from blood by ventilation) or greater than 1.0 (completely retained in the blood). Six gases are indicated, positioned at their known partition coefficient (λ) values. These are the six MIGET gases; note that they cover a very wide range of solubility such that virtually the entire range of retention is measurable.

Figure 2 shows how the four classical causes of arterial hypoxaemia (hypoventilation, shunt,

\dot{V}_A/\dot{Q} inequality and diffusion limitation⁹) individually affect the behaviour of equation 3, with the homogeneous curve drawn for comparison. *Hypoventilation* (top left) shifts the curve leftwards but does not change the shape since it simply means that \dot{V}_A in equation 3 is reduced from normal. *Shunt* (top right) produces a very different picture. By definition, a shunt is a region that is unventilated but still perfused (i.e., $\dot{V}_A/\dot{Q} = 0$) and thus undergoes no exchange of any gas. The blood in a shunt region therefore passes through the capillaries unchanged (from mixed venous) for all gases, and mixes in the left atrium with the blood from the rest of the lung. A shunt therefore simply compresses the curve upward and one can read the value of the shunt fraction from the left-hand asymptote of the curve. The asymptote of 0.5 indicates shunt is 50% of the cardiac output. *\dot{V}_A/\dot{Q} inequality* (lower left) changes the shape of curve. This is because of change integrating to summing the retention curves from different alveoli - each being "S" shaped and these span a range. On reaching the left atrium, the blood from these alveoli mixes in proportion to how much blood they receive, and when you calculate the result, it must be a curve with a shape different than normal, as shown. Finally, with *diffusion limitation* (lower right), the inert gas curve is unaffected. This is because all inert gases are much (~30 times) less vulnerable to diffusion limitation than is O_2 , such that limitation sufficient to affect inert gases would cause lethal hypoxaemia.

This figure indicates how the curves differ substantially among the four causes of hypoxaemia, which in turn means that measuring the retention values of the six gases, will enable separate identification of the four

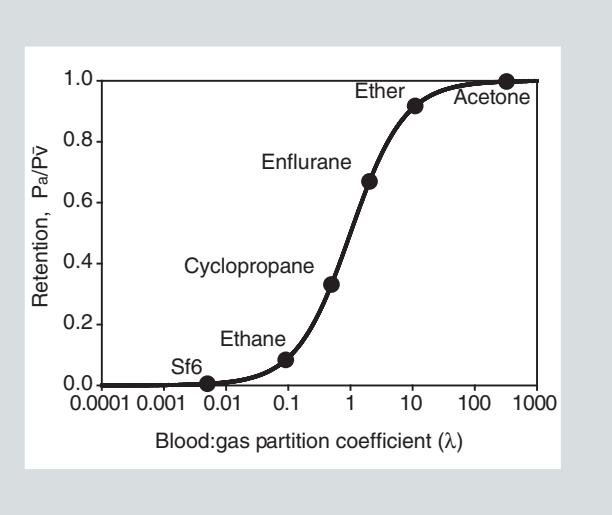


FIGURE 1. Shows the relationship between fractional inert gas retention (i.e., arterial/mixed venous partial pressure ratio) and blood:gas partition coefficient (λ) when the inert gas is infused intravenously in solution and undergoes partial elimination in the lungs. Retention increases smoothly with λ in accordance with equation 3. The positions of the six gases used in multiple inert gas elimination technique (MIGET) show that the entire retention range is captured by this combination of gases. Pa: systemic arterial partial pressure; Pv: pulmonary arterial partial pressure; SF6: Sulfur hexafluoride.

causes of hypoxaemia in any given patient, and moreover, singly or in combination. As described in Hopkins et al.¹, a computer algorithm has been written to calculate the shape, position, and moments of the $\dot{V}A/\dot{Q}$ frequency distribution, the size of any shunt and dead space, and the extent of diffusion limitation and (hypo/hyper) ventilation that must exist to fit the measured retention curve. This article now reviews these findings in health and three important lung diseases – COPD, asthma, and interstitial lung disease - chosen as interesting regarding mechanisms of abnormal gas exchange and remaining unanswered questions.

In each example shown below, the curves have been re-created by computer from original

hand-drawn figures in the sometimes decades-old original studies. This improves resolution and picture quality. Details will of course vary by patient, but the main features accurately reflect the original findings in each case.

NORMAL SUBJECTS

Normal young subjects have very little $\dot{V}A/\dot{Q}$ inequality¹⁰⁻¹⁶, as expected from knowing that arterial PO_2 is commonly close to that of a homogeneous lung. Figure 3 is typical of a seated, resting normal subject.

First, the frequency distribution shown in figure 3 needs explanation. Two curves are shown, one for ventilation and one for blood flow, with the abscissa, the $\dot{V}A/\dot{Q}$ ratio, plotted on a logarithmic scale from the lowest value (0.005) that MIGET can distinguish from shunt ($\dot{V}A/\dot{Q}$ of zero) to the highest value (100) that MIGET can separate from dead space ($\dot{V}A/\dot{Q}$ infinitely great)¹. Each curve shows how much ventilation and blood flow (ordinate) are directed to lung regions of any specified $\dot{V}A/\dot{Q}$ (abscissa) ratio across that range. At any given $\dot{V}A/\dot{Q}$ ratio, the values reflect all alveoli throughout the lung with that $\dot{V}A/\dot{Q}$ no matter whether they occupy a single location or are scattered across regions. The circles represent values at specific $\dot{V}A/\dot{Q}$ ratios equally spaced along the abscissa, based on a multi-compartment framework to convert the retention curves into $\dot{V}A/\dot{Q}$ distributions. The smooth line drawn through all of the circles is a mathematical fit to the circles, separately for each curve. Small potential irregularities in the curves are beyond the resolution of MIGET. While irregularities may exist,

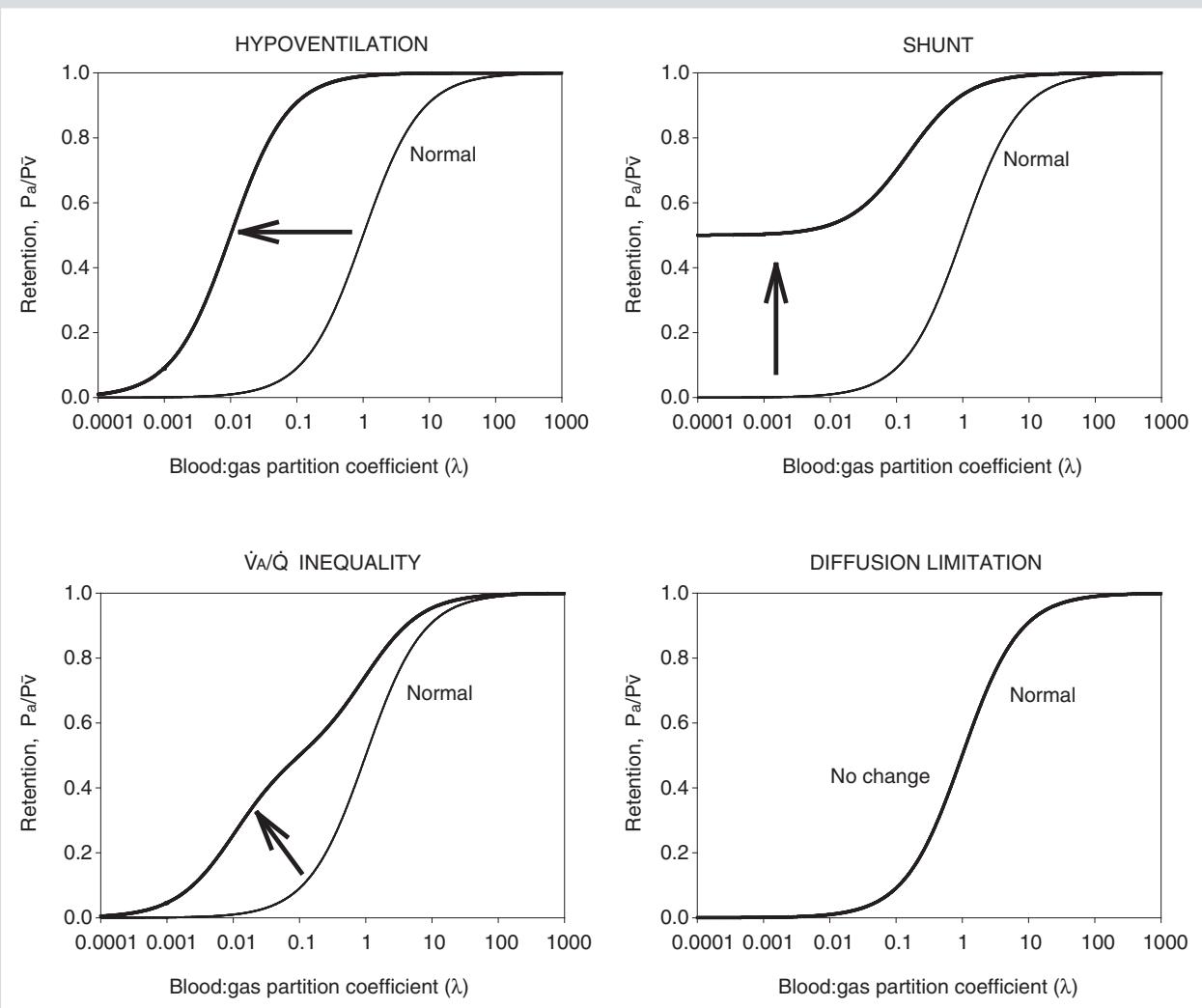


FIGURE 2. Shows how the four causes of arterial hypoxaemia individually affect the retention curve, with qualitative and quantitative differences allowing their clear identification by multiple inert gas elimination technique (MIGET), even when present in combination. Pa: systemic arterial partial pressure; Pv: pulmonary arterial partial pressure; Q: blood flow; Va: pulmonary ventilation.

this is unlikely, because there are ~500 million alveoli spread among ~100,000 gas exchange units (acini). With this number of units contributing to the curves, it is highly probable that the curves are indeed smooth, just as a frequency distribution of human body mass across 100,000 individuals would be smooth.

Both shunt perfusion and dead space ventilation are indicated, in this case zero and ~2.5 L/min respectively. In young normal subjects, shunt is not seen (airways are not obstructed and alveoli are not fluid-filled) but dead space is always present, essentially completely explained by the volume of the conducting airways between the mouth

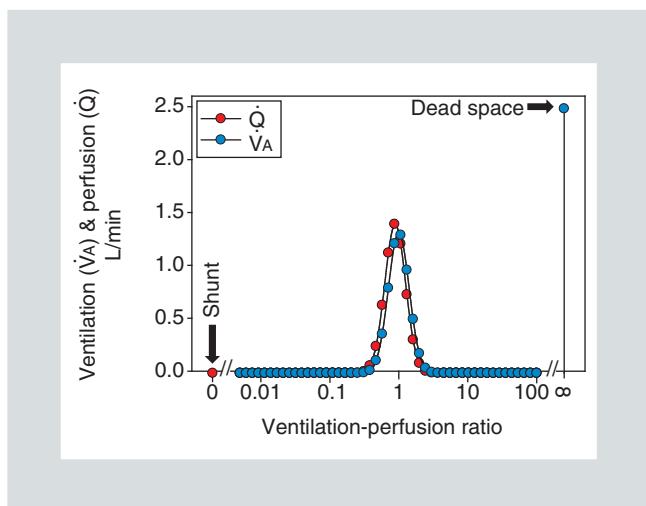


FIGURE 3. Shows a typical \dot{V}_A/\dot{Q} distribution in a seated young healthy subject. The distribution is narrow (confined to about one decade of \dot{V}_A/\dot{Q} ratios, with little dispersion) and does not contain areas of abnormally low or high \dot{V}_A/\dot{Q} ratio or shunt. \dot{Q} : blood flow; \dot{V}_A : pulmonary ventilation.

and the alveoli. Here, with a total ventilation of 8.3 L/min, the (normal) dead space ventilation comprises 2.5/8.3, or 30%, of the total. The \dot{V}_A/\dot{Q} curves are logarithmically normal (symmetrical on a log scale) about a mean \dot{V}_A/\dot{Q} ratio of about 1. This mean arises from total alveolar ventilation being numerically similar to cardiac output (5-6 L/min) such that their ratio is about 1.

In subsequent figures herein, dead space ventilation is not plotted, because the required ordinate scale would compress the remaining distribution. In general, dead space (i.e., unperfused lung as indicated by MIGET) is found to correspond to the volume of the conducting airways.

The degree of \dot{V}_A/\dot{Q} inequality is indicated by the width of the curves, quantified for each as the second moment about the mean

(conceptually equivalent to standard deviation). If the curves had no width (second moment zero) they would appear as a vertical line at the mean \dot{V}_A/\dot{Q} of the lung, indicating a homogeneous lung. This is never seen even in health, and figure 3 is typical of young normal subjects, with a second moment (which we term “LOG SD”) of about 0.4 (on a log scale). The most severe inequality, seen in acute lung injury, is about 2.5. As the figure shows, there are no regions with $\dot{V}_A/\dot{Q} < \sim 0.4$ and none with $\dot{V}_A/\dot{Q} > \sim 3$, its full width spanning only one decade of \dot{V}_A/\dot{Q} ratios.

An important interpretive point is that if alveoli are poorly ventilated but still perfused, the distribution will include areas of low \dot{V}_A/\dot{Q} ratio, raising LOG SD much more for blood flow (\dot{Q}) than ventilation (\dot{V}_A). The converse applies: poorly perfused but still ventilated alveoli will appear as areas of high \dot{V}_A/\dot{Q} ratio, with an elevated LOG SDV. This means that a high LOG SDQ implies airways dysfunction while a high LOG SDV means interference to perfusion.

The amount of inequality in figure 3 is minor and is consistent with the degree of inequality found by imaging methods¹⁷. It is explained by well-known gravitational and structural influences on regional ventilation and blood flow. Typically, alveolar PO_2 is ~100 mmHg, arterial PO_2 90-95 mmHg, and their difference is only 5-10 mmHg.

Both exercise and high altitude independently result in modestly greater \dot{V}_A/\dot{Q} inequality, with LOG SD increasing to about 0.5-0.6^{11,13-15}. This is unexpected because these conditions increase pulmonary artery pressure, reducing

the gravitational gradient in blood flow, thus improving $\dot{V}A/\dot{Q}$ distribution. While it is probable that under both conditions greater inequality is caused by increased interstitial fluid buildup, based on greater fluid movement out of the capillaries as pulmonary artery pressure rises, this has not been proven.

What MIGET has also shown is that normal subjects exercising at altitude develop arterial hypoxaemia beyond that seen at rest, due to both the above-mentioned increase in $\dot{V}A/\dot{Q}$ inequality and incomplete diffusion equilibration (i.e., red cells do not have enough exchange time for capillary PO_2 to reach alveolar values)^{12,15}. When blood flow is high, capillary transit time is reduced, and at altitude, the driving PO_2 gradient for diffusion is also reduced as PO_2 falls onto the steep part of the O_2 dissociation curve. Together, increased $\dot{V}A/\dot{Q}$ inequality and diffusion limitation reduce arterial PO_2 and O_2 availability, and hence, exercise capacity.

Breathing pure O_2 has been shown to create or increase shunt¹⁰, sometimes in combination with disappearance of low $\dot{V}A/\dot{Q}$ regions previously present while breathing air. This likely represents a combination of increased blood flow from release of hypoxic vasoconstriction and absorption atelectasis from absence of nitrogen (N_2) in the alveolar gas. Perfusion of low $\dot{V}A/\dot{Q}$ units can also increase from this release of vasoconstriction.

The key unsolved issue in normal subjects is the cause of greater $\dot{V}A/\dot{Q}$ inequality during exercise and at altitude. Precise lung imaging methods, although not yet well-enough developed, may be the best way forward.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Chronic obstructive pulmonary disease (COPD) results in often substantial $\dot{V}A/\dot{Q}$ inequality. Most MIGET studies in COPD were carried out in the 20th century¹⁸⁻³³. At the time, COPD was understood as both alveolar destruction (emphysema) and long-term airway inflammation (chronic bronchitis) in variable combination. Patients were accordingly classified as type A (dominant emphysema) and type B (dominant chronic bronchitis), while comorbidities such as obesity, hypertension, heart failure, diabetes and sleep apnoea were not emphasized. Emphysema alone was known to cause expiratory (but not inspiratory) airways obstruction through greater than normal dynamic airway compression and also to cause hyperinflation through loss of elastic recoil. Bronchitis was known to cause inspiratory and expiratory airways limitation through both thickened airway walls and luminal mucus (both reducing airway diameter). In some patients there may also be a contribution from airway smooth muscle contraction. Patients classified as mostly emphysematous typically suffer mild arterial hypoxaemia (PO_2 60-70 mmHg or more) and no hypercapnia. They often hyperventilate, reducing arterial PCO_2 to ~30-35 mmHg. Patients classified more as chronic bronchitic typically fail to hyperventilate, resulting in greater hypoxaemia and, often, chronic hypercapnia.

Given this understanding of COPD pathophysiology, it was predicted that MIGET would reveal areas of low $\dot{V}A/\dot{Q}$ ratios from reduced ventilation in obstructed regions, no matter whether emphysema or bronchitis was dominant, and that the main difference between

types A and B would be in their total ventilation. Furthermore, it was expected that there would be a range of regional airway obstruction severity from mild to severe, such that the \dot{V}_A/\dot{Q} curves would become broader than normal but not split into separate modes. Finally, knowing that diffusing capacity (for carbon monoxide) was usually reduced, it was expected that some of the arterial hypoxaemia would be due to alveolar-capillary diffusion limitation. These predictions were not borne out.

Figures 4A, B and C show that three major patterns of \dot{V}_A/\dot{Q} inequality in COPD were revealed by MIGET. The key findings were that:

- 1) The distributions were mostly bimodal or trimodal, not broad and unimodal.
- 2) There was always a population of alveoli within the normal range of \dot{V}_A/\dot{Q} ratios.
- 3) Distinctly different patterns were apparent as figure 4 shows. Thus, some patients had a population of very high \dot{V}_A/\dot{Q} alveoli, some had the converse – a population of very low \dot{V}_A/\dot{Q} alveoli – and some had both low and high \dot{V}_A/\dot{Q} regions.
- 4) Type A patients almost always had the pattern shown in figure 4A while type B patients could have any of the three patterns, but usually did show low \dot{V}_A/\dot{Q} regions.
- 5) Shunt was minimal, and often not measurable ($< 0.1\%$)
- 6) Alveolar-capillary diffusion limitation was never observed, even during exercise.

The probable explanation of distinct modality in the distributions is that the disease process is inherently very non-uniform, as imaging studies now reveal. Thus, some regions are affected much more than others, and some function normally for gas exchange. Emphysema is

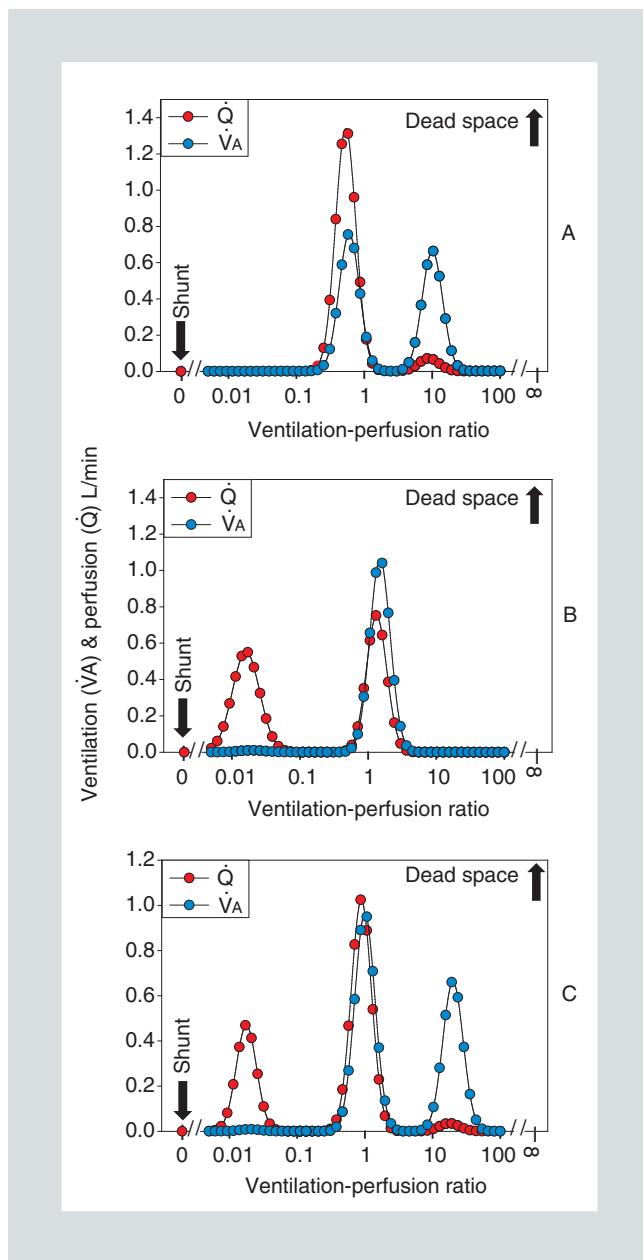


FIGURE 4. Shows the three principal patterns of \dot{V}_A/\dot{Q} inequality seen in patients with chronic obstructive pulmonary disease (COPD) Types A, B and C. As explained in the text, high \dot{V}_A/\dot{Q} regions likely represent areas of alveolar emphysema while low \dot{V}_A/\dot{Q} areas likely reflect reduced airway diameter from chronic inflammation.

known to be greater in non-dependent lung regions due to greater gravitational stress from the weight of the lung tissue beneath causing

alveolar wall strain. Conversely, bronchitis would be expected to affect lower lung regions more because they were better ventilated (prior to disease) due to both gravity and bronchial anatomy, delivering more tobacco-related inhaled inflammatory mediators.

The probable explanation of high $\dot{V}A/\dot{Q}$ areas is emphysematous destruction of alveolar wall capillaries greatly reducing – but not eliminating – blood flow in emphysematous regions which still receive some ventilation, thus resulting in elevated $\dot{V}A/\dot{Q}$ ratios. The greater dynamic compression from emphysema appears not to greatly reduce ventilation (inspiratory airflow is little affected) but rather to prolong the expiratory phase to prevent low $\dot{V}A/\dot{Q}$ ratios from developing. The probable explanation of low $\dot{V}A/\dot{Q}$ areas is indeed bronchitis reducing airway luminal area, increasing resistance and reducing local gas flow. While differences in total ventilation between Types A and B patients undoubtedly affect arterial PO_2 and PCO_2 , the blood gas values are mostly the result of the $\dot{V}A/\dot{Q}$ pattern observed, modulated by differences in ventilation.

Absence of shunt is common, and hard to explain when poorly ventilated regions possess a $\dot{V}A/\dot{Q}$ ratio in the 0.01-0.1 range, implying 90 to 99% reduction in ventilation. The question is what stabilises $\dot{V}A/\dot{Q}$ ratios at such minimal values, preventing total airway occlusion and a $\dot{V}A/\dot{Q}$ ratio of zero? An unproven hypothesis is that collateral ventilation develops, ventilating alveoli distal to fully obstructed airways, thus preventing atelectasis. Finally, reduced diffusing capacity is likely explained mostly by loss of capillaries in emphysematous regions. There is so little perfusion in these areas

that even if they were subject to diffusion limitation, this would minimally affect the mixed capillary blood reaching the left heart, especially as their $\dot{V}A/\dot{Q}$ ratios are putatively elevated, enhancing diffusive equilibration.

In this analysis, the focus has mostly been on the airways and associated obstructive processes, but the pulmonary circulation should not be forgotten. First, hypoxic pulmonary vasoconstriction (HPV) will act to reduce perfusion in the lowest $\dot{V}A/\dot{Q}$ regions because of their low local PO_2 . This automatically raises local $\dot{V}A/\dot{Q}$ and should improve the $\dot{V}A/\dot{Q}$ distribution overall. That HPV is present, yet of fairly minimal benefit to gas exchange, has been shown by MIGET studies comparing the distribution while breathing room air and added O_2 , or after giving pulmonary vasoactive drugs^{18,23,24,31-33}. Also, when $\dot{V}A/\dot{Q}$ inequality and spirometric changes are compared over the range of severity of COPD defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification³⁴ gas exchange abnormalities may precede measurable spirometric changes. Figure 5 shows MIGET data from 150 COPD patients. It plots $\dot{V}A/\dot{Q}$ inequality (LOG SDQ and LOG SDV) against forced expiratory volume in one second (FEV_1) (% predicted) for patients in the four GOLD grade. The error bars indicate 95% confidence limits. The findings are impressive: even at GOLD 1, when FEV_1 averages 87% of normal, $\dot{V}A/\dot{Q}$ inequality is very significant. The LOG SDQ is already abnormal (upper panel) while LOG SDV is on the upper limit of normal (lower panel). This likely means that the early changes in overall function occur in the parenchyma rather than the conducting airways and may involve not just the small airways, but also the pulmonary vasculature^{32,35,36}.

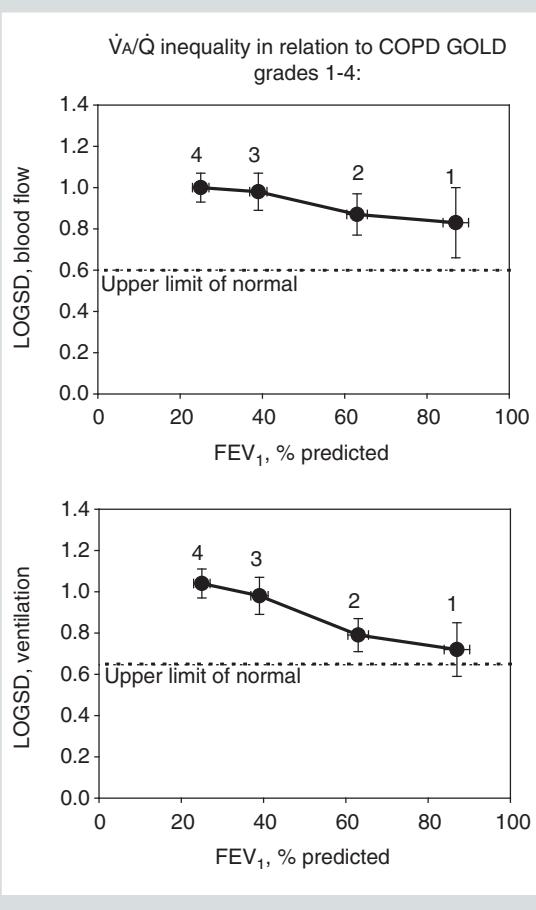


FIGURE 5. Shows the relationship between $\dot{V}A/\dot{Q}$ inequality and FEV_1 across the four GOLD stages of COPD severity. Note that substantial inequality is seen already in grade 1, while further worsening by GOLD grade is not dramatic. See text for further analysis.

COPD: chronic obstructive pulmonary disease; FEV_1 : forced expiratory volume in one second; GOLD: Global Initiative for Chronic Obstructive Lung Disease; \dot{Q} : blood flow; $\dot{V}A$: pulmonary ventilation.

Then, as spirometry deteriorates and patients move into higher GOLD grades, there is only modest further worsening of these indices of inequality. Noting that LOG SD values as high as 2.5 occur in acute lung injury, one must ask why $\dot{V}A/\dot{Q}$ inequality does not progress more severely with GOLD progression.

One hypothesis is that more severe COPD destroys lung tissue such that badly affected regions eventually lose both ventilation and blood flow, and thus become invisible to MIGET.

These “armchair” explanations of MIGET findings in COPD are however just that – thoughts generating hypotheses to be tested as applicable technology becomes available. Thus, research questions raised by MIGET include those raised above.

BRONCHIAL ASTHMA

Asthma is a disease cluster sharing the phenomenon of airways obstruction with COPD. However, unlike COPD, emphysema is not present. Rather, airways obstruction is due to: 1) increased airway smooth muscle contraction, mostly in response to inhaled particulate/chemical matter, 2) airway wall remodelling, with chronic inflammation reducing airway luminal area, and 3) luminal narrowing from mucus within the airway lumen. At least some of these factors can be partly reversed, such that asthma commonly presents temporal variability in airways obstruction, leading to the classical clinical history of asthma episodes interspersed with periods of remission.

As with COPD, phenotypic complexity has been increasingly recognised, however, most MIGET studies in asthma were done in the last part of the 20th century. Moreover, as pharmacotherapy has improved, the findings from past studies need to be confirmed or refuted in terms of applicability to the current era. What is now described therefore pertains

mostly to research performed in the 20th century and reflects what are considered to be the key findings noted then.

Figure 6 exemplifies a patient with essentially asymptomatic asthma and near-normal spirometry, where lack of symptoms would not predict much functional abnormality³⁷. However, MIGET shows substantial $\dot{V}A/\dot{Q}$ inequality, with a population of low $\dot{V}A/\dot{Q}$ regions making the distribution abnormal. Similar discordance between spirometry and $\dot{V}A/\dot{Q}$ inequality has been reported by others^{38,39}. However, it should be stressed that in patients with well-controlled and minimal asthma, the $\dot{V}A/\dot{Q}$ distribution has often been found to be normal. The low $\dot{V}A/\dot{Q}$ regions when present likely result from peripheral airway narrowing from a combination of bronchoconstriction, airway remodelling and mucus secretion.

That bronchodilator administration raises FEV_1 , but can (transiently) worsen – not improve – gas exchange³⁷ suggests that the low $\dot{V}A/\dot{Q}$ regions were due to mucus and/or airway remodelling more than to bronchoconstriction. It is probably explained by greater post-dilator perfusion of the low $\dot{V}A/\dot{Q}$ population from pharmacological reversal of pulmonary hypoxic vasoconstriction in those regions. The further implication is that while the normalization of FEV_1 suggests large airway dilatation, $\dot{V}A/\dot{Q}$ inequality reflects obstruction of smaller peripheral airways. More recent studies using agents to reduce bronchoconstriction or mucus production⁴⁰⁻⁴² showed some improvement in gas exchange.

This fits with studies using MIGET to examine $\dot{V}A/\dot{Q}$ inequality (in asymptomatic asthmatics

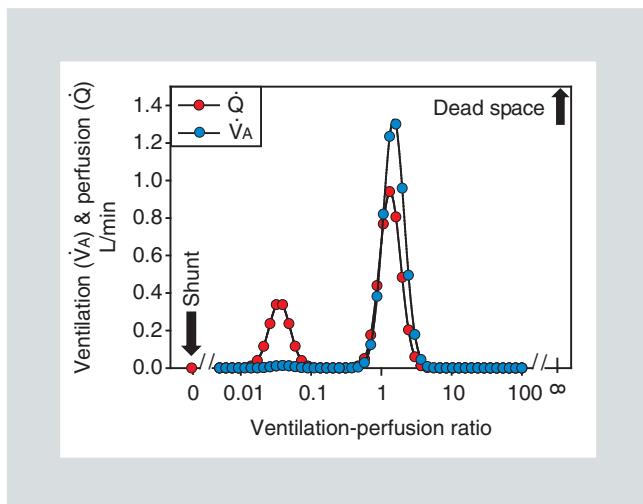


FIGURE 6. Shows $\dot{V}A/\dot{Q}$ inequality in an asymptomatic asthmatic, noting that many such patients may have a normal $\dot{V}A/\dot{Q}$ distribution. Of interest, a separate mode of low $\dot{V}A/\dot{Q}$ ratios is seen, without shunt. Unlike COPD, high $\dot{V}A/\dot{Q}$ areas are not seen. See text for further analysis.

with initially normal $\dot{V}A/\dot{Q}$ patterns) after bronchoprovocation with inhaled methacholine, mannitol, or platelet activating factor^{38,43-46}. As expected, these agents do acutely lead to substantial reduction in FEV_1 , but usually to only modest $\dot{V}A/\dot{Q}$ inequality. This suggests that acute, mostly large airway constriction is not the main factor in $\dot{V}A/\dot{Q}$ inequality, and adds to the sense that above factors (remodelling, mucus, constriction) in smaller peripheral airways is more important⁴⁷. However, this remains to be proven.

Another clinically important finding is that arterial PO_2 is often higher than expected for the extent of $\dot{V}A/\dot{Q}$ inequality, which means that arterial PO_2 underestimates $\dot{V}A/\dot{Q}$ inequality. The reason is a mildly elevated cardiac output which keeps mixed venous PO_2 higher than if cardiac output was normal. This in turn buffers what would otherwise be a greater fall in arterial PO_2 .

Ventilation-perfusion inequality has been assessed by MIGET weekly (for 9 weeks) in 26 patients with moderate, clinically stable, treated asthma (FEV₁/forced vital capacity [FVC] 79% predicted). Abnormal $\dot{V}A/\dot{Q}$ inequality was found in all patients in two or more weeks. Bimodal blood flow distributions containing low $\dot{V}A/\dot{Q}$ units were observed in 24 subjects, but was variable, seen in only one third of all measurements. About 75% of the total variance in $\dot{V}A/\dot{Q}$ inequality was due to intersubject differences, the remainder being due to changes over time within subjects⁴⁸.

As with COPD, shunting is rarely evident, again suggesting a role for collateral ventilation in avoidance of atelectasis. But unlike COPD, high $\dot{V}A/\dot{Q}$ regions are not seen, further supporting the hypothesis that high $\dot{V}A/\dot{Q}$ regions in COPD are the result of alveolar destruction, not commonly seen in asthma.

Research questions raised by MIGET studies in asthma include:

1. Confirming or refuting that $\dot{V}A/\dot{Q}$ inequality is commonly distributed bimodally, suggesting that airways are either unaffected or severely affected. There appears not to be a continuous range of $\dot{V}A/\dot{Q}$ inequality. This “all or none” behaviour may have important clinical implications, e.g., for targeted drug delivery. Further, whether the affected regions remain in the same locations, or rotate regionally over time, is unknown. Also, which generation(s) of airways are most important in creating $\dot{V}A/\dot{Q}$ inequality would be useful to know, again as inhaled drug parameters (particle size, flow rates) could be tailored to best reach the most affected generations.

2. Discovering how much of the $\dot{V}A/\dot{Q}$ inequality is related to each of the contributing factors – bronchoconstriction, remodelling and mucus – again for therapeutic reasons.
3. Elucidating the role of pulmonary vascular smooth muscle in $\dot{V}A/\dot{Q}$ inequality in asthma, because airway inflammation and smooth muscle contraction and inhaled corticosteroids and β -agonists bronchodilators effects are not likely limited to the airways.
4. Evaluating the importance of persistent $\dot{V}A/\dot{Q}$ inequality in essentially asymptomatic patients: should therapy target symptoms or pathophysiology?

INTERSTITIAL PULMONARY FIBROSIS

Figure 7 provides an example of a patient with advanced pulmonary fibrosis⁴⁹. Similar findings were reported by others⁵⁰⁻⁵². Not enough research exists to know if all forms of fibrosis lead to the same $\dot{V}A/\dot{Q}$ pattern as shown here, but the fundamental pathology of thickened, fibrotic alveolar walls suggests that patterns might be similar. There is a distinct difference between the pattern shown and that in COPD and asthma: regions of extremely low $\dot{V}A/\dot{Q}$ and unventilated regions ($\dot{V}A/\dot{Q}$ of zero, i.e., shunt) are usually seen⁵³. MIGET is at its limit of resolution here, and the quantitative separation of shunt from regions of very low $\dot{V}A/\dot{Q}$ is not precise. However, the combined perfusion of zero and low $\dot{V}A/\dot{Q}$ regions is robust, and substantial shunt and low $\dot{V}A/\dot{Q}$ regions must both be present in the example of figure 7. The existence of such regions is likely explained by

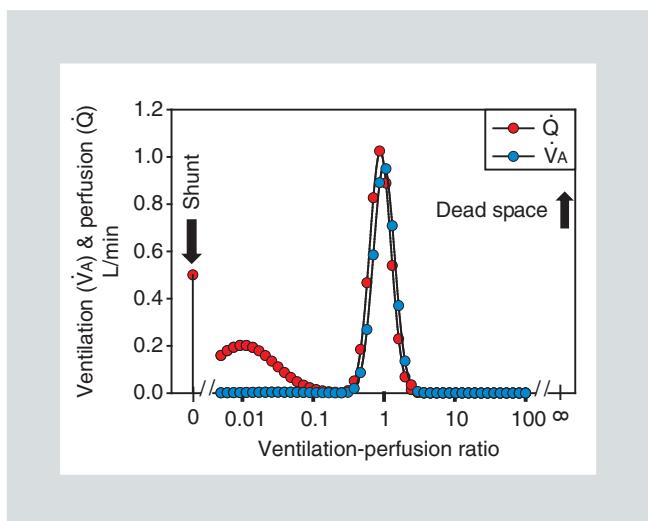


FIGURE 7. Shows the $\dot{V}A/\dot{Q}$ pattern in advanced interstitial lung disease. Thickened alveolar walls likely reduce local ventilation greatly and may prevent gas exchange altogether, resulting in some shunt. See text for further analysis.

severe regional reduction in lung compliance caused by fibrosis, reducing local ventilation.

In contrast to asthma and emphysema, resting arterial hypoxaemia is often severe, and can be explained by the $\dot{V}A/\dot{Q}$ pattern in the presence of an often subnormal cardiac output, lowering the mixed venous PO_2 . Thus, the physiological basis of the relationship between arterial PO_2 and cardiac output is the mirror image of that in asthma where cardiac output is often somewhat elevated. The high pulmonary vascular resistance from vascular destruction likely contributes to impaired right ventricular function and low cardiac output.

Hypoxaemia may be aggravated by alveolar-capillary diffusion limitation, even at rest⁵⁰. Fibrosis is the only chronic lung disease known to consistently show this, likely due to microvascular destruction reducing capillary wall surface area for diffusion combined

with the greatly thickened alveolar interstitium impairing diffusive movement between gas and blood. Shunt may reflect complete diffusion failure in especially severely fibrotic regions.

During exercise, $\dot{V}A/\dot{Q}$ inequality does not worsen yet arterial PO_2 almost always falls. Further reduction in mixed venous PO_2 (from resting) is partly responsible, while the other factor is the development, or worsening, of alveolar-capillary diffusion limitation as higher cardiac output must flow through a compromised pulmonary vasculature unable to respond normally by capillary distention/recruitment to buffer red cell transit time⁴⁹⁻⁵¹.

Research questions raised by MIGET in fibrosis would be more of physiological than clinical interest and revolve around confirming the above-described findings. However, as therapeutic advances are made, MIGET would be a valuable tool to assess functional improvement.

SUMMARY AND CONCLUSIONS

For almost half a century, measuring the $\dot{V}A/\dot{Q}$ distribution using MIGET in health and disease has provided enormous physiological and clinical insight into most pulmonary diseases. At the same time, it has raised many questions that still remain to be answered. The MIGET should be viewed as a unique and important method in an expanding toolbox of approaches for assessing lung structure and function in health and disease. While the most important observations with MIGET have now been made and reported (in over 500 research studies), the

future holds great promise for using MIGET in combination with emerging imaging methods and other complementary tools to better understand the underlying pathophysiology and thereby improve therapy.

DISCLOSURES

Dr. Wagner has nothing to disclose.

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