Ventilation/perfusion distributions revisited

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Purpose of review
A major cause of hypoxemia in anesthesia is ventilation-perfusion (V_A/Q) mismatch. With more advanced surgery and an aging population, monitoring of V_A/Q is of increasing importance.

Recent findings
The classic multiple inert gas elimination technique has been simplified with a new approach based on mass spectrometry. V_A/Q distributions can also be measured, at the bedside, by varying inspired oxygen concentration. MRI, 3-dimensional single photon emission computed tomography, positron emission tomography, and electrical impedance tomography enable imaging of perfusion and ventilation, and in some of the techniques also the distribution of inflammation. One-lung ventilation with thoracoscopy and capnothorax require careful monitoring of V_A/Q, made possible bedside by electrical impedance tomography. Carbon dioxide, but not air, for pneumoperitoneum enhances shift of perfusion to ventilated regions. Ventilatory support during cardiopulmonary resuscitation causes less V_A/Q mismatch when inspired oxygen concentrations are lower. Mechanisms of redistribution of lung blood flow by inhaled nitric oxide include endothelin-mediated vasoconstriction in collapsed lung regions.

Summary
Methods are continuously developing to simplify measurement of V_A/Q and also to relate V_A/Q to inflammation. The recording of V_A/Q has helped to explain important aspects of gas exchange in thoracic anesthesiology and in intensive care medicine.

Keywords
arterial oxygenation, one-lung ventilation, shunt, V/Q mismatch, ventilation/perfusion ratio

INTRODUCTION

Alveolar ventilation/perfusion (V_A/Q, sometimes abbreviated as 'V/Q') ratio distributions are plots of the total amounts of ventilation and total amounts of perfusion that are supplying each collection of lung units operating at a specific V_A/Q ratio. Example V_A/Q plots appear in Figures 1 and 2. One of the attractive features of using V_A/Q ratio distributions to quantify pulmonary gas exchange is that the plots are quite intuitive and easy to interpret. For example, consider the obvious differences between Figure 1, depicting a lung with normal and efficient gas exchange, and Figure 2, depicting bronchospasm. In the normal lung, close matching of ventilation and perfusion is reflected in a single narrow mode, centered close to $V_A/Q = 1$. In bronchospasm, parts of the lung have decreased ventilation and therefore operate at a lower V_A/Q ratio, and parts of the lung are unaffected and operate at a nearly normal V_A/Q ratio [1].

Although V_A/Q abnormalities are often talked about in clinical management, there is currently no technique in routine clinical use for measuring V_A/Q distributions. The gold standard method for measuring V_A/Q distributions, the multiple inert gas elimination technique (MIGET), was developed as a research method and has never been adopted in routine clinical care of patients (see Wagner 2008, [1], for an excellent review of MIGET). In research studies, however, MIGET and some more recent methods developed to measure V_A/Q ratio distributions (some discussed below) have been applied to many questions of general interest in anesthetic management, for example, mechanisms of formation of atelectasis. V_A/Q distributions have also been applied to research questions specifically of interest in thoracic anesthesia and one-lung ventilation (OLV) [2].

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KEY POINTS

- V/Q measurements and V/Q imaging clarify the mechanisms of arterial hypoxemia.
- New methods, including imaging techniques, have been developed to facilitate measurements of V/Q distributions.
- Results from recent experimental and clinical studies help to explain effects on oxygenation of resuscitation, pneumoperitoneum, capnothorax, hyperoxia, and inhaled vasodilators.

RECENT DEVELOPMENTS IN MEASURING VENTILATION/PERFUSION DISTRIBUTIONS

MIGET was developed in the early 1970s and continues to be used by a handful of specialized laboratories (for example Rivas *et al.* 2015, discussed below). From the 1970s to the turn of the century, MIGET was not only the gold standard method for measuring V_A/Q distributions; it was the only viable method for measuring V_A/Q distributions. In the last 10–15 years, several new approaches to measuring V_A/Q distributions have been developed, opening the possibility of many more research studies on questions of interest in thoracic anesthesia and other areas. The first part of this review focuses on recent developments from the last few years.

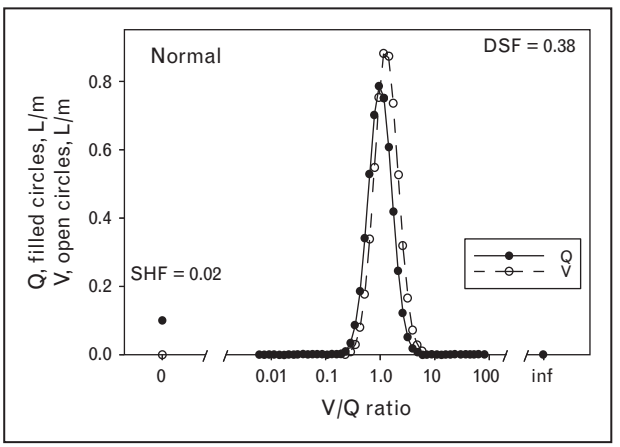

FIGURE 1. A normal V_A/Q distribution. Efficient gas exchange requires minimal shunt (shunt fraction shown is 2%), deadspace limited to the anatomic deadspace (deadspace fraction shown is 38% and typically on these plots is off scale), and close matching of ventilation and perfusion. V_A/Q matching is reflected by a single narrow mode for both V and Q distributions, and close overlap of these modes. Perfusion = filled circles, solid line; ventilation = open circles, dashed line. V_A/Q, ventilation-perfusion.

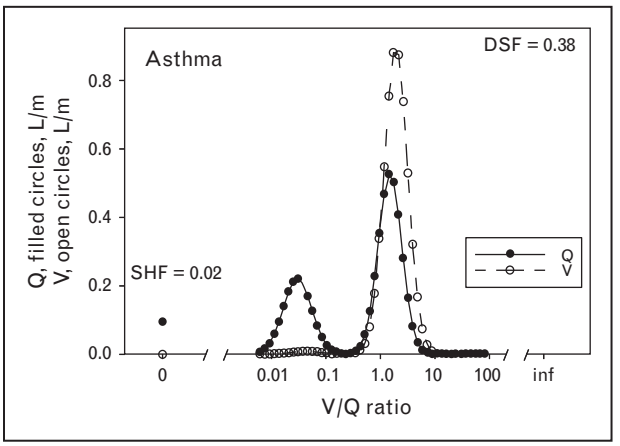

FIGURE 2. A V_A/Q distribution characteristic of the findings in asthma. Bronchoconstriction is typically heterogeneous, affecting some parts of the lung but not others. In affected areas, V is lowered, thus lowering the local V_A/Q ratio. The result is a bimodal V_A/Q distribution with the constricted regions represented by a low V_A/Q mode, and the normal lung regions represented by a more normal V_A/Q mode. This bimodal distribution affects efficiency of gas exchange primarily for oxygen, but also for carbon dioxide. The mechanism for arterial hypoxemia is the low V_A/Q mode and only rarely in asthma is hypoxemia caused by shunt. Same format as Fig. 1. Shunt fraction is again 2%, deadspace fraction is again offscale at 38%. V_A/Q, ventilation-perfusion.

GAS EXCHANGE METHODS FOR VENTILATION/PERFUSION DISTRIBUTIONS

The conventional MIGET is technically demanding and difficult to master, and has only been used by a handful of laboratories in the last 40 years. Kretzschmar *et al.* [3] compared a new simplified method for measuring V_A/Q distributions, called MIGET by micropore membrane inlet mass spectrometry (MMIMS), with conventional MIGET, which uses gas chromatography for sample analysis. Their study showed the new method provides accuracy at least equal to conventional MIGET, but with smaller blood sample requirements and much more rapid sample analysis.

An alternative approach to using inert gas infusions to measure V_A/Q distributions is to assess the changes in arterial oxygenation as FIO_2 is varied. Although the concept actually predated MIGET, recent developments have advanced this concept to systems that are being tested in research studies. Thomsen, Rees, and coworkers recently summarized some of the history and design issues in the development of a commercially available system to automatically vary FIO_2 and calculate V_A/Q distributions, the automatic lung parameter estimator

(ALPE) [4]. This same group also recently assessed new methods to reduce the time required to measure V_A/Q distributions by this approach [5]. As the variation in FIO_2 is a cornerstone in the ALPE one may ask whether a temporarily low FIO_2 can impose any risk to the patient. The technique was therefore tested in patients undergoing coronary bypass graft surgery [6▪]. Lowering inspired O_2 to 17% for a few minutes increased pulmonary artery mean pressure by 4 mmHg and lowered oxygen saturation by 7% from initial 99% and PaO_2 from around 15 kPa to 7 kPa. Values returned rapidly to initial levels on discontinuation of the low inspired O_2. The authors concluded that the technique can be used also under more critical conditions. However, the authors of this review want to emphasize that a critical check of arterial oxygen tension throughout the study will be needed.

IMAGING METHODS FOR VENTILATION/PERFUSION DISTRIBUTIONS

Imaging methods to quantify V_A/Q distributions seek to measure V_A/Q in each anatomic region of the lung quantitatively and with high spatial resolution. Most imaging methods do not have potential for bedside monitoring [with the exception of electrical impedance tomography (EIT)]. They provide only a snapshot of V_A/Q distributions rather than repeated measurements, and they tend to be expensive. All imaging methods, however, have the advantage over gas exchange methods of telling us not only that there are V_A/Q abnormalities, but the additional important information of where these abnormalities are distributed in the lungs. Additionally, most imaging methods provide not just the local V_A/Q ratio, but also independent assessments of the distributions of V and Q and therefore the respective role of each in V_A/Q abnormalities. These methods therefore have great potential to provide new insights into questions relevant to thoracic anesthesia. The challenges, however, are formidable. Quantitative images of perfusion distribution and ventilation distribution with high spatial resolution have been difficult to obtain and validate. Then, in most methods, these separate regional images of V and Q must be mapped to the same regions of the lung at high spatial resolution, a challenge referred to as coregistration. Coregistration is especially difficult in the lung because of the large tissue deformations that result from normal breathing.

The group at San Diego recently reported an MRI method that combines perfusion imaging based on arterial spin tag labeling, with ventilation imaging based on washin kinetics of oxygen. This new method has a major advantage over some other MRI methods in that no expensive hyperpolarized gas for contrast is required. They recently used this method to demonstrate changes in V_A/Q distributions in normal humans in the prone versus supine posture [7].

Regional V_A/Q ratios can also be calculated from MRI measurements of regional alveolar PO_2 (measured from oxygen dependent spin decay of hyperpolarized 3 helium) combined with mixed venous blood gas measurements [8]. Alternatively, much of the same information content can be obtained directly from the alveolar PO_2 measurements [9]. Hamedani *et al.* [10▪] have reported recently on developments and refinements in high resolution imaging of alveolar PO_2 and demonstrated a high sensitivity to the early subtle changes in asymptomatic smokers.

Advances in 3-dimensional single photon emission computed tomography imaging have demonstrated great promise in providing detailed maps of regional V_A/Q. Nyrén *et al.* [11] recently reported use of SPECT to assess the effects of prone versus supine posture, in normal humans, on V distribution, Q distribution, and the V_A/Q distribution. They also assessed the effects of inhaled anesthetic administration on these distributions during spontaneous breathing [12]. More recently, similar methods have been applied to assess bronchopulmonary dysplasia [13] and in a mouse model of cigarette exposure [14].

Some of the most validated advances in V_A/Q imaging in the last 15 years have been the positron emission tomography (PET) methods developed by Venegas and coworkers in Boston [15]. Most recently, Musch *et al.* [16▪▪] combined their PET methods for imaging V, Q, and V_A/Q, with PET methods for imaging regional inflammation in the lung, and examined early changes in an animal model of smoke inhalation injury.

EIT is a noninvasive bedside imaging method with great potential for bedside monitoring of changes in V_A/Q distributions. Featuring high temporal resolution but limited spatial resolution, the method is well suited for measuring regional ventilation, and recent developments have included the use of hypertonic saline washin-washout kinetics for regional perfusion [17].

Microsphere methods require harvest of the lungs for analysis and are limited exclusively to studies in animal models. The high spatial resolution, independent maps of V and Q have provided many insights into mechanisms of V_A/Q heterogeneity over the last 15–20 years, most recently in examining V_A/Q heterogeneity within and between anatomically defined lung units in rats [18].

RECENT APPLICATIONS OF VENTILATION/PERFUSION DISTRIBUTIONS IN ANESTHESIA AND THORACIC ANESTHESIA

OLV is an important method to facilitate thoracic surgery [19,20]. Analogous to the development of laparoscopy to reduce surgical trauma, thoracoscopy has also evolved but it requires an optimized exposure of the surgical field and this can be achieved by insufflation of carbon dioxide into the pleural cavity, so-called capnothorax [21,22]. However, the technique may entail respiratory and hemodynamic impairments that require careful monitoring. EIT for the detection of real time dynamic changes in pulmonary ventilation and perfusion distributions was therefore tested in a piglet model [23▪]. As expected, ventilation was almost eliminated in the collapsed lung during OLV and perfusion was also decreased but to alesser extent. This caused a V_A/Q mismatch, contributing to a major extent to the impaired oxygenation.

Insights into the relatively mild V_A/Q mismatch with capnothorax are provided by a recent study of laparoscopy. The increased abdominal pressure during laparoscopic surgery by the inflation of abdominal gas, pneumoperitoneum, pushes the diaphragm cranially and causes atelectasis. However, shunt is not increased and oxygenation of blood is maintained [24,25]. For safety reasons, CO_2 is used for the insufflation. Whether abdominal CO_2 has an effect on lung perfusion and its distribution, remains an issue. This was tested in an experimental study in piglets, using air instead of CO_2 [26▪▪]. CO_2-pneumoperitoneum caused a shift of blood flow away from dependent, atelectatic to ventilated regions as studied by SPECT. Air-pneumoperitoneum caused smaller shift and CO_2-pneumoperitoneum together with the vasodilator sodium nitroprusside caused an even lesser shift in lung blood flow. Oxygenation decreased in parallel with decreased redistribution of blood flow. Thus, CO_2 but not air shifted blood flow toward better ventilated areas, proposedly by increased hypoxic pulmonary vasoconstriction.

Bariatric surgery to reduce weight in morbidly obese patients causes a persisting reduction of BMI and has become widely used [27,28]. Obesity is associated with reduced functional residual capacity (FRC) and widened alveolar–arterial oxygen differences [29]. However, effects of obesity and bariatric surgery on V_A/Q distributions were, until recently, unknown. For this reason morbidly obese patients were investigated before bariatric surgery and 1 year after surgery [30▪], and V_A/Q distributions were measured with conventional MIGET. Before bariatric surgery the subjects had reduced PaO_2 (76 mmHg) caused by a small amount of shunt (4%) together with a broad unimodal blood flow dispersion (logSDQ 0.8). During oxygen breathing shunt increased two-fold in parallel with reduction of perfusion of low V_A/Q units suggesting reabsorption atelectasis. After bariatric surgery pulmonary gas exchange abnormalities were decreased. The findings of moderate shunt and V_A/Q imbalance in morbid obesity is reasonably explained by airway closure because of reduced lung volume with a return toward normal with weight loss.

The optimum combination of cardiopulmonary resuscitation (CPR) and ventilatory support and whether to ventilate with 100% oxygen or lower concentrations remain controversial issues [31–33]. In an experimental study on anesthetized pigs, V_A/Q distributions measured with MIGET by MMIMS were studied at different fractions of inspired oxygen (1.0, 0.7, 0.21) during CPR after inducing ventricular fibrillation [34▪]. CPR caused a significant shift from normal V_A/Q to the high V_A/Q range. Using EIT a shift of ventilation from dorsal to ventral regions was seen and the pulmonary shunt increased considerably during CPR with the largest shunt with 100% oxygen ventilation. Thus a major finding was an adverse effect of high oxygen concentration.

An additional potentially detrimental effect of breathing enriched oxygen concentrations was suggested by the study of Li *et al.* [35▪]. In healthy, young volunteers, increased FIO_2 was associated with increased V_A/Q mismatch, with increasing perfusion of dorsal lung regions as assessed by EIT. This suggested pulmonary vasodilation even at small increases in FIO_2.

Another aspect of V_A/Q distributions relevant to thoracic anesthesia is the effect of inhaled nitric oxide (INO) on oxygenation of blood. The general opinion is that INO improves oxygenation in patients with acute respiratory failure by selective vasodilation in ventilated lung [36,37]. Thus blood flow redistribution from nonventilated lung regions to the ventilated ones is achieved. Although this appears reasonable, one may ask how vasodilation in the pulmonary vessels that lowers the pulmonary artery pressure can cause a redistribution of blood flow upward from dependent collapsed lung regions to nondependent ventilated regions [38]. This is the distribution of pathology in severe lung injury [39]. In a study in endotoxemic piglets, another mechanism behind the redistribution was proposed [40▪▪]. The hypothesis was that INO may also cause vasoconstriction via endothelin (ET-1) in atelectatic lung regions. INO almost doubled the ratio between

mRNA expression of endothelin receptor A (mediating vasoconstriction) and B (mediating vasodilation and clearance of ET-1) in atelectatic lung regions. Moreover, INO caused a shift in blood flow away from atelectatic lung regions in the endotoxemic piglets as assessed by SPECT, but not during ET-receptor antagonism (Tezosentan). These findings suggest that vasoconstriction by endothelin in non-ventilated regions may be a major cause of redistributed lung blood flow during NO breathing.

Finally, a couple of reviews have analyzed mechanisms and consequences of V_A/Q disturbances. Petersson and Glenny [41▪▪] provide an overview of the relationship between ventilation/perfusion ratios and gas exchange in the lung. The authors discuss five causes of hypoxemia: hypoventilation, low inspired oxygen tension, diffusion limitation, low V_A/Q regions, and shunt. Hypoventilation and low V_A/Q regions also impair CO_2 removal but their effects on $PaCO_2$ are modified by CO_2-triggered hyperventilation. The effect of V_A/Q mismatch can be approximately estimated using calculation of $PA\text{-}aO_2$, venous admixture, and dead space ventilation. In another review, the effects of general anesthesia on V_A/Q are discussed [42▪]. Resting lung volume (FRC) is reduced, promoting airway closure and absorption atelectasis. The former causes low V_A/Q and the latter shunt. Together these two physiological disturbances account for three-quarters of the impairment of oxygenation during regular and uneventful anesthesia. General anesthetics blunt hypoxic pulmonary vasoconstriction, but to a limited degree, and this has a very minor effect on gas exchange if there is a normal V_A/Q match. Preventing the fall in FRC by continuous positive airway pressure or positive end-expiratory pressure, opening up collapsed alveoli by recruitment maneuvers and using moderate inspired O_2 are measures to keep lung units open and to ensure acceptable V_A/Q matching and gas exchange. When designing a 'protective ventilation' strategy during anesthesia, a good understanding of lung physiology may be helpful.

CONCLUSION

Hypoxemia is a recurrent problem during thoracic surgeries as well as in other anesthetic settings and a major cause is V_A/Q mismatch. Techniques to assess V_A/Q based on gas uptake and elimination as well as imaging techniques continue to be refined. More advanced anesthesia and surgical techniques, for example, OLV with capnothorax, stress the need of V_A/Q monitoring. Our understanding of V_A/Q mismatch (and mechanisms behind redistribution of lung blood flow) during pneumoperitoneum, capnothorax, resuscitation, obesity, and inhaled vasodilators, has increased significantly in the last several years. These advances have been enabled by old and new tools for assessing V_A/Q ratio distributions.

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Conflicts of interest

J.E.B. is president and owner of Oscillogy LLC, the company that manufactures the MIGET by MMIMS system.

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