Purpose of review
A major cause of hypoxemia in anesthesia is ventilation-perfusion (V\textsubscript{A}/Q) mismatch. With more advanced surgery and an aging population, monitoring of V\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{A}/Q and also to relate V\textsubscript{A}/Q to inflammation. The recording of V\textsubscript{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\textsubscript{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\textsubscript{A}/Q ratio. Example V\textsubscript{A}/Q plots appear in Figures 1 and 2. One of the attractive features of using V\textsubscript{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\textsubscript{A}/Q = 1. In bronchospasm, parts of the lung have decreased ventilation and therefore operate at a lower V\textsubscript{A}/Q ratio, and parts of the lung are unaffected and operate at a nearly normal V\textsubscript{A}/Q ratio [1].

Although V\textsubscript{A}/Q abnormalities are often talked about in clinical management, there is currently no technique in routine clinical use for measuring V\textsubscript{A}/Q distributions. The gold standard method for measuring V\textsubscript{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\textsubscript{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\textsubscript{A}/Q distributions have also been applied to research questions specifically of interest in thoracic anesthesia and one-lung ventilation (OLV) [2].
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.

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.
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(How to use a new method to reduce the time required to measure \( V_A/Q \) distributions by this approach). 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 only 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 \( V_A/Q \). Yrén 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 a lesser 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 MMIMIS 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
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mRNA expression of endothelin receptor A (mediating vasoconstriction) and B (mediating vasodilatation 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-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 pneumoperitonaeum, 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.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

7. Online preprint The technique of separating shunt from low $V_{A}/Q$ by varying FiO$_2$ as done in the commercially available ‘automatic lung parameter estimator’ may be used also in more demanding clinical situations. However, a critical check of arterial oxygen tension throughout the study will be needed.
11. With the most recent advances and technical refinements, MRI with hyperpolarized 3 helium can produce moderate to high spatial resolution maps of alveolar PO$_2$ covering the entire lung. Heterogeneity in alveolar PO$_2$ was able to discriminate early, subtle changes in asymptomatic smokers versus nonsmokers.


In a model of acute cotton smoke inhalation injury in sheep, the authors assess regional V/Q imaging alongside regional imaging of inflammation. V/Q mismatch and markers of inflammation occurred early in injury and first appeared at approximately the same time. Of note, these early V/Q changes were subtle and would likely not be detected with approximations of V/Q abnormalities like venous admixture.


The study describes an experimental model setup which together with the functional electrical impedance tomography may enable future studies addressing optimal peroperative management in OLV with capnotherapy.


An interesting study showing that the abdominal insufflation of CO2 for protective reasons is also a prerequisite for favorable redistribution of lung blood flow away from collapsed lung. This is not achieved with air insufflation.


The study shows an expected mechanism of impaired oxygenation in morbidly obese patients, reasonably explained by airway closure because of reduced lung volume.


In this experimental study combinations of CPR and mechanical ventilation caused increase of high V/Q and showed an adverse effect of high oxygen concentration.


This is an advanced experimental study showing that the redistribution of lung blood flow in ventilated lung regions in acute lung injury by nitric oxide is caused primarily by vasoconstriction by endothelin in nonventilated lung. This is an explanation clearly different to what is generally assumed.


This is an impressive review of the relationship between ventilation/perfusion and gas exchange in the lung, analyzing basic concepts and relating them to clinical situations.


Critical review of V/Q matching during anesthesia.