Model-driven gas exchange monitoring in the critically ill

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Abstract
Understanding pulmonary gas exchange performance is a dynamic process which, depending on clinical context, exhibits different levels of complexity. Global tools such as tension-based indexes yield clinically crucial information under very specific conditions. Yet, accurate mechanistic insight can only originate in model-based tools. One-parameter models such as shunt or dead space are well established in clinical practice whilst two or three-parameter models have just been advanced and their role is yet to be delineated. Although the latter provide superior accuracy, this comes at the cost of increased complexity and possibly the need for invasive data sets. Modelling gas exchange enables a quantitative and physiologically-driven management of patients with lung failure. Assumptions are inherent to each tool and can clinically mislead if not accounted for. Thorough understanding of their subjacent theoretical construct is a prerequisite for their judicious use. This manuscript aims to describe current gas exchange monitoring tools, with special reference to their mathematical framework and constituent pitfalls. A unifying perspective on their clinical role is proposed.

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Impaired respiratory function is common amongst critically ill patients; hence, insightful monitoring of gas exchange is paramount as it may translate into precise and objective therapeutic management.

Blood-gas relationships may be ascertained with a wide array of methods able to yield both qualitative and quantitative information, depending on clinical context. Outside the intensive care unit, clinicians may exhibit a “lumped” approach, such as merely reading system outputs (e.g. PaO₂, SpO₂ or SaO₂) or their interrelation to system input (e.g. PaO₂/FI O₂). Although this may suffice when facing simple clinical scenarios, its limits often push intensivists to favour mechanistic information derived from a system model approach. Shunt and dead space calculations are examples of classical one-parameter system models to address blood gas data, described as early as 1950 [1, 2]. These are well entrenched in current practice and capable of guiding an individualized hemodynamic and ventilator support; an interesting perspective on their use came from authors investigating their ability to monitor the membrane lung [3].

Recently, two-parameter models have emerged as a more extensive method to identify and follow disturbances of pulmonary gas transfer. They dichotomize the oxygenation problem into shunt and a non-shunt compartment which is assigned to either diffusion limitation (Rdiff), alveolar dead space (Vdalv) or ventilation-perfusion (V/Q) mismatch. Although superior as to performance to fit data when FI O₂ is varied, they have yet to become routine clinical practice tools.

All models come with caveats which are to be acknowledged in order to avoid seriously consequential pitfalls. Correct interpretation and bedside implementation of model-derived data warrants understanding of their underlying mathematical construct and its inherent assumptions.

BASIC PRINCIPLES
This section aims to restate only those basic principles needed to allow a better understanding of the categorization and comparison of current tools to monitor pulmonary gas transfer.
Following a ubiquitous physiological principle such as mass conservation, a quantitative formulation of the ratio of alveolar ventilation to alveolar perfusion can be reached as previously described by Rahn and Riley [1, 2]:

\[ VA/Q = \frac{(CcO_2 - CvO_2)}{(FiO_2 - FAO_2)} \text{ (equation 1)} \]

where VA is alveolar ventilation; Q is total blood flow; Cc and Cv are pulmonary end-capillary and arterial blood concentrations; Fi and FA represent inspired and alveolar gas fractions; for simplicity, the Haldane transformation is neglected.

Diffusion, as stated by Fick, can be written as:

\[ VO_2 = DLO_2 \cdot (PAO_2 - PcO_2) \text{ (equation 2)} \]

where DLO2 is total diffusion capacity of O2, PA is alveolar pressure and Pc is pulmonary end-capillary blood concentration.

After converting fractions to pressures (FAO2 = PAO2 / (PB – PH2O) where PB is the barometric pressure and PH2O is water vapour pressure) and by combining equation 1 with 2, this gives:

\[ VA/Q = \frac{(CcO_2 - CvO_2)}{(FiO_2 - \frac{(VO_2 / DLO_2 + PcO_2)}{(PB - PH2O)})} \text{ (equation 3)} \]

Equation 3 attests that main pulmonary factors modulating blood gas tensions (PcO2) are the range of V/Q ratios and the quality of the lung capillary barrier (DLO2). Extrapulmonary determinants represent another category subsumed in equation 3; total ventilation, haemoglobin (Hb), the composition of inspired gas and mixed venous blood, which in fact mirrors cardiac output and oxygen uptake, are the most relevant in daily practice [4]. Secondary extrapulmonary factors relate to the oxygen (ODC) and carbon dioxide (CO2DC) dissociating curves. Both categories can move in perfectly opposite directions such that lumped parameters like PaO2 or PaO2/FiO2 can be both inaccurate and misleading. Depending on the clinical context and chosen therapeutic strategy, it may become crucial to discern between the two types of factors (principle 1).

Although its position as a gold standard has been questioned, the multiple inert gases elimination technique (MIGET) remains the reference tool to describe pulmonary factors [5]. It allows diffusion impairment to be discarded as a common cause of hypoxemia leaving only the full V/Q spectrum to account for gas exchange disturbances in the critically ill population [6]. Thus, from a lung perspective, hypoxaemia and hypercapnia are best explained by shunt, dead space and V/Q mismatch, all parts of a continuum. Partitioning the contribution of each mechanism would define the most comprehensive tool (principle 2).

**TENSION-BASED PARAMETERS**

Tension-based indexes are first-order monitoring tools. Although they make useful adjuncts to any scoring system, they are essentially devoid of mechanistic insight and fail to meet the above-stated principles. Under special circumstances (see below), they may allow mechanistic information to be qualitatively deduced.

1. **ALVEOLAR-ARTERIAL PO2 (A-aPO2)**

   The simplified alveolar gas equation corrects alveolar gas tensions for respiratory quotient and corresponding arterial tensions and serves to compute A-aPO2:

   \[ PAO_2 = PO_2 - PACO_2 / R \text{ (equation 4)} \]

   where PO2 is the O2 pressure in the inspiratory gas, PACO2 is the alveolar CO2 pressure and R is the respiratory quotient. For simplicity, it is often assumed that PACO2 is close to arterial CO2 tension (PaCO2) but coexistent shunt invalidates this approximation [7].

   A-aPO2 was originally devised to distinguish hypoventilation-related hypoxemia from that elicited by a V/Q inequality or a diffusion limitation [8]. It was later shown to be fallible exactly under these circumstances; given that hypercapnia varies inversely with A-aPO2, a concomitant V/Q mismatch would tend to normalize this index and remain unaccounted for [9]. Meaningful yet qualitative information can be derived when FiO2 is varied; with increasing FiO2, A-aPO2 is expected to rise proportionately if shunt is prevalent whereas it will describe an inverted V shape if V/Q inequalities prevail [10].

2. **PAO2/FiO2**

   PaO2/FiO2 ratio is possibly the most popular tension-based tool to characterize gas exchange performance and a very strong predictor of mortality in the acute respiratory distress syndrome (ARDS). Its use is expected to extend outside critical care areas as arterial blood sampling is no longer obligatory for its determination. For peripheral oxygen saturations (SpO2) lying on the bend of the ODC, nonlinear computation of PaO2/FiO2 from SpO2/FiO2 [11] or mathematical conversion of venous oxygen tensions (PvO2) to arterial values (PaO2) [12] can circumvent the need to directly measure PaO2.

   The amount of nonaerated lung can be tracked by the natural logarithm of PaO2/FiO2 obtained during pure oxygen ventilation [13]. Bedside estimation of end-expiratory lung volume (EELV) [14], or the delivered volume after a recruitment manoeuvre [15], are complementary methods to weigh the “baby lung” and launch a protective ventilation strategy.
Limitations of the $\text{PaO}_2/\text{FiO}_2$ ratio mainly stem from its nonlinear behaviour when $\text{FiO}_2$ is varied. This relationship is actively and unpredictably modulated by the same intrapulmonary and extrapulmonary factors stated above, so that with fixed V/Q alterations an infinite number of $\text{PaO}_2/\text{FiO}_2$ ratios becomes possible. A comprehensive mathematical formulation based on established gas transfer relations (see equation 7) has been derived [16] and simplifies to:

$$f(\text{FiO}_2) = \frac{\text{PaO}_2}{\text{FiO}_2} = \text{PaO}_2$$ (equation 5)

where $f(\text{FiO}_2)$ comprises six physiological coefficients: $\text{PB}$, $\text{PaCO}_2$, $\text{R}$, $\text{Hb}$, $S$ (shunt ratio), $\text{AVD}$ (arterio-venous difference in oxygen content).

This translates the poor capacity of this index to specifically capture the magnitude of alveolo-capillary damage. Clinically, it is highly consequential as disease misclassification may ensue and cause treatment plans to neglect the true subjacent pathology [17].

MODEL-BASED GAS EXCHANGE MONITORING

Gas exchange models merely approximate the real physiological picture. The ultimate test of model accuracy is its capacity to predict output (e.g. $\text{SaO}_2$, $\text{SpO}_2$, or expired fraction of $\text{O}_2 – \text{FeO}_2$) from a given input (e.g. $\text{FiO}_2$) (principle 3). This also turns out to be a good measure of its comprehensiveness in that a tool obeying principle 2 cannot but satisfy principle 3.

Classical one-parameter models (physiological dead space, venous admixture/shunt) and research tools such as the multicompartmental MIGET are based on forward modelling theory whereby a system structure is assumed and behaviour is predicted. Monoparametrical models often fail to see inside the “black box” and provide a poor fit to measured data. On the contrary, MIGET meets all three enunciated principles and shows the best fit although complexity itself disqualifies it as a routine clinical procedure.

An inverse modelling approach, whereby the least complicated but essential system structure is inferred from input-output linkages, indicates that the minimum number of parameters needed to appropriately depict gas exchange is two [18]. Models revolving around two parameters, although far from encapsulating all details of gas transfer, provide the next best fit to patient data after MIGET.

A detailed mathematical description is beyond our scope and can be found elsewhere [19]; instead, best clinical use of available models will be emphasized with special reference to their theoretical framework.

A.ONE-PARAMETER MODELS OF GAS EXCHANGE

In its simplest form, the oxygenation problem can be ascribed to a single cause: shunt, dead space, V/Q mismatch or diffusion limitation. Each model only satisfies principle 1. Of these, the first two are most clinically relevant and represent second-order monitoring tools.

1. SHUNT/VENOUS ADMIXTURE

Venous admixture may be thought of as the “alveolar dead space” of blood. It represents the deviation of arterial blood gas tensions towards mixed venous blood gas composition from that of an “ideal” alveolar blood-air interface which is defined by: 1) a local $R$ equal to the respiratory quotient of the whole lung; and 2) a normal diffusion capacity (see Fig. 1) [20]. This “ideal” capillary–arterial gap is the result of alveoli with V/Q ratios less than “ideal” (lying at the left side of “X” in Fig. 1) and also includes true shunt (V/Q = 0). As theoretically predicted, when present, diffusion problems augment the gap as well.

A conceptual model consists of two alveolar compartments of which one provides “ideal” gas exchange and the other completely lacks ventilation (see Fig. 2). After writing mass balance equations for blood flow and oxygen content, the classical shunt equation of Berggren can be readily arrived at:

$$\text{Shunt ratio } (S) = \frac{(\text{CcO}_2 – \text{CaO}_2)/(\text{CcO}_2 – \text{ CvO}_2)}{S/(1-S)}$$ (equation 6)

Resolution of the term $\text{C CO}_2$ requires the use of equation 4 and an ODC equation [21] to arrive at the corresponding pulmonary end-capillary saturation. Although computation of the denominator requires the use of a pulmonary artery catheter, this could be obviated by rewriting equation 6 and assuming a fixed AVD value (i.e. 4.3 mL dl$^{-1}$) [20]. This approach is sensitive to cardiac output oscillations.

$$S/(1-S) = (\text{CcO}_2 – \text{CaO}_2)/\text{AVD}$$ (equation 7)
With increasing FiO₂, V/Q inequalities wane and equation 6 will approximate true shunt. Any pure oxygen-related atelectasis may be successfully negated, or at least minimized, if sufficient positive end-expiratory pressure is already applied [22]. Measurement of shunt during 100% oxygen predicts the amount of nonaerated lung and becomes a useful bedside method to track recruitment/derecruitment episodes [13].

Computation of shunt is the most cited technique to characterize native and membrane lungs of patients on extracorporeal membrane oxygenation (ECMO) [3]. It has been successfully implemented in a mathematical model of oxygenation during veno-venous ECMO which can be accessed online (www.ecmomodel.unimi.it) to help start up a preemptive therapeutic strategy [23].

2. DEAD SPACE

Similar to venous blood eluding gas exchange, air leaving non-perfused territories can be thought of as a “shunt”. Regardless of whether it originates in conducting airways (VDana) or in alveoli (VDalv), dead space causes the composition of mixed alveolar air to diverge from that of an “ideal” compartment towards that of the inspired air (see Fig. 1).

Quantification of any dead space volume (VD) can be reduced to a two compartment model analysis: a ventilated but non-perfused compartment and one capable of gas exchange (W) (see Fig. 3). Mass balance relationships can be combined to obtain the following generalized formulation:

\[
\frac{(PW-PE)}{(PW-PI)} = \frac{VD}{VD + VW}
\]  
(equation 8)

where any tracer gas is characterized by: PW as the partial pressure inside compartment W; PE as the partial pressure in the mixed expired air flowing from both compartments; PI as the partial pressure in inspired air; VW is the volume of compartment W; and VD is the volume of the non-perfused compartment (V/Q = ∞). The absolute principle of this is that PW must only reflect the gas within W and cannot account for the gas within the dead space (V/Q = ∞) (principle 4).
For the particular case of VDana and CO₂ as a tracer gas, equation 8 becomes:

\[(PAmCO₂ - PECO₂)/PAmCO₂ = VDana/VT \quad (equation \, 9)\]

where PAmCO₂ is the mean CO₂ pressure of mixed alveolar air (approximated by end-tidal CO₂ (PETCO₂) if time-constants are perfectly homogeneous across the lung) and PECO₂ is CO₂ pressure of mixed expired air which can be derived from a volumetric capnogram (Vcap) or classically measured with a Douglas bag; VT is tidal volume.

Being ascribed to Bohr, equation 9 conveys one very important message: mean CO₂ pressure of all ventilated alveoli can only determine anatomical VD. Indeed, equation 9 was originally conceived to derive PAmCO₂ based on known VDana which had been measured on cadaver airways [24].

When compartment W is taken to represent an alveolar sector with “ideal” characteristics, equation 8 translates to the classical physiological dead space (VDphys) computation:

\[(PAiCO₂ - PECO₂)/PAiCO₂ = VDphys/VT \quad (equation \, 10)\]

where PAiCO₂ is the alveolar CO₂ tension of an “ideal” territory as already defined. VDphys will include not only anatomical dead space and true alveolar dead space (V/Q = ∞) but also territories with V/Q values higher than “ideal” (lying at the right side of “X” in Fig. 1). Most confusion stems from defining PAiCO₂ as this will establish the V/Q range of what actually constitutes dead space.

Approximation of PAiCO₂ with PaCO₂ as originally suggested by Riley, is referred to as Enghoff’s physiological dead space (VDe).

\[(PaCO₂ - PECO₂)/PaCO₂ = VDe/VT \quad (equation \, 11)\]

This is the favoured method to assess wasted ventilation and has recently been applied to artificial lungs as well [3]. Coexistent shunt, especially when larger than 40%, will erroneously elevate VDe [25]. This may turn out to be clinically useful when an inclusive index of lung state is called for as in prediction of mortality [26]. Dynamic monitoring of VDe detects lung collapse [27] and indicates the best positive end expiratory pressure (PEEP) [28] or the optimum inspiratory flow pattern [29]. On the contrary, a single value may not allow a differentiated ventilator strategy, as it may indicate both atelectasis and overdistention [30], each triggering a totally opposite action. Correction for shunt seems justified and has been achieved by several authors, with the most direct method provided by Kuwabara et al. [31]. As oxygen content is simplistically equated to oxygen pressures, the following results from equation 6:

\[PcCO₂ = PvCO₂ - [PvCO₂ - PaCO₂/(1-S)] \quad (equation \, 12)\]

Concordant with Riley’s model, PcCO₂ is taken to represent PAiCO₂ and thus equation 10 is combined with 12 to yield a corrected VDphys.

Carbon dioxide kinetics will probably play an increasing role as a routine clinical decision tool with the advent of respiratory monitors capable of continuously tracking Vcap. With PaCO₂ superimposed on a CO₂-VT plot, the graphical determination of VDe becomes possible and reproduces equation 11 [32]. The most common way to derive VDana is according to Fowler’s equal area method which is, in fact, a geometrical representation of equation 9. In order to standardize Vcap, a mathematical function was recently applied to the raw CO₂ waveform, allowing a more robust measurement of VDana and other curve specifics [33]. The same author group foregrounded the use of a mean alveolar CO₂ pressure (PABohrCO₂) to calculate “true” alveolar dead space (VDBohr), uncontaminated by shunt effects [30]. It was commented that this approach merely equates to equation 9 [34]: using the mean of “all” alveoli as a substitute for PW (see equation 8) will undoubtedly encapsulate units with high V/Q ratios (e.g. V/Q = ∞) and therefore principle 4 is violated — VDalv/VDphys just cannot be inferred, only VDana can. This contrasts with the proven ability of VDBohr to actually track VDalv in a cardiac surgery patient [34], or detect overdistention during a PEEP trial [35]. To clarify this discrepancy, it is useful to consider the proposed determination of the “airway-alveolar” interface which is different from Fowler’s method. As the authors clearly show, under most circumstances, Fowler’s method will underestimate the VDana calculated by their method [33]. The net result is that PABohrCO₂ will lie at the right side of PAmCO₂, which is closer to a virtual PAiCO₂ (i.e. PaCO₂ according to Riley). Conveniently, this means that, under most circumstances, PABohrCO₂ will not be the “true mean” as it fails to represent all alveoli and VDBohr will then be able to capture VDalv.

Measured together, VDe and VDBohr cover the entire continuum of V/Q ratios, provide complementary data and can act in concert to enable a lung-protective ventilatory strategy.

Lastly, the information obtained from Vcap could extend beyond the assessment of CO₂ volumes. Waveform morphology distorts specifically with alveolar recruitment and reflects acinar gas mixing and perfusion [36, 37]. The translatability of these findings into clinical practice is yet awaited.

B. TWO-PARAMETER MODELS OF GAS EXCHANGE

These are third-order tools to monitor pulmonary gas exchange as they meet both principles 1 and 3. Their conceptualization originates in Riley’s work (see Fig. 1) [20]. Between ideal capillary and arterial blood, two virtual oxygen gaps can be delineated: one caused by “pure” shunt (distance between AR and C) and a second represented by...
the difference between ideal capillary and mixed capillary blood ($\Delta P O_2$ is distance from X to C). The latter could be attributed to either Rdiff, V/Q mismatch (any V/Q > 0) or a mixture of these but, with Rdiff cast off as a common cause of hypoxemia in the critically ill (see above), $\Delta P O_2$ can be entirely attributed to the V/Q state.

Shunt and $\Delta P O_2$ are embedded in plots of $P iO_2$ versus $SpO_2$ such that, after adjustment for their effect and correction for alveolar air (equation 4), complete identity between ODC and the $P iO_2$ – $SpO_2$ diagram is mathematically demonstrable [38]. An increasing shunt will produce a specific downward shift of the original ODC whereas $\Delta P O_2$ relates to a rightward displacement of the curve (see Fig. 4); ultimately, a unique $P iO_2$ – $SpO_2$ plot inclosing all synchronous gas exchange abnormalities is ready to be deciphered.

The first mathematical formulation of these models was generated by Sapsford and Jones. Simplistically, it can be restated as:

$$f(PiO_2) = f(PiO_2) = SaO_2$$ (equation 13)

where $f(PiO_2)$ comprises two unknowns (shunt and $\Delta P O_2$) and several physiological coefficients of which haemoglobin and cardiac output result in the largest sensitivity. Correct identification of system parameters requires at least two $PiO_2$/SaO$_2$ data sets which should range over the maximal downward curvature of the $P iO_2$ – $SpO_2$ plot to ensure optimum model fit (i.e. close to SaO$_2$/SpO$_2$ of 96%) [40]. The implicit assumption hereof is that multiple F$O_2$ steps will not alter lung physiology; this may be valid only as long as an upper limit of 0.8 is respected [41].

A refinement came from Kjaergaard et al. [19] who advanced a three-compartment, two-parameter model (see Fig. 5). Data sets belong to a plot of F$O_2$ versus $SpO_2$. A fixed perfusion split ($f_2 = 0.9$) is assigned to the non-shunted blood serving two alveolar compartments ventilated according to a variable fraction (fA$_2$) which indirectly becomes a measure of V/Q heterogeneity. Optimum gas exchange is simulated at zero shunt and fA$_2$ equal to 0.9 ($\Delta P O_2 = 0kPa$).

Figure 4. Effects of increasing shunt or reducing ventilation — perfusion (V/Q) ratio on a plot of $P iO_2$ versus $SpO_2$. The dashed line identifies the oxygen dissociation curve (reproduced with permission from Rowe et al. [39]).
Critical illness offers a diverse array of challenges, ranging from a simple dichotomous decision of whether to turn prone an ARDS patient to a dynamic, quantitative assessment of lung state following a change in ventilator settings. Physicians will face situations which call for a pragmatic and undifferentiated approach devised to set out a timely therapeutic plan. The necessity for a low tidal volume strategy should rely on the clinical context and elementary tools such as the PaO₂/FiO₂ ratio. Likewise, Enghoff’s VD may serve as a very strong predictor of mortality in ARDS patients and this is probably due to its global nature resulting from the failure to separate shunt from dead space. An accurate split-view of these two mechanisms may turn out to be advantageous when an informed open lung strategy is considered. The solution thereof is a combination of VD BOHR and the computation of equation 6 during a short episode of pure oxygen ventilation. Alternatively, discriminating between shunt and V/Q imbalance with third-order monitoring tools may generate an even more inclusive and reproducible picture, one closer to patient physiology and remarkably accurate when set against MIGET.

Thus, it appears that appropriateness in context may be the correct descriptor of the ideal tool. If weighed carefully, clinical settings will advise one of the right balance between the information yield and the complexity of a test. An optimum, but often different monitoring method will then ensue within each clinical scenario. To answer the question above, any tool may be ideal but only when used in the right context.

### CONCLUSION
Model-based quantification of pulmonary gas exchange merely approximates the complexity of real physiological processes. If limits inherent to their underlying mathematical construct are thoroughly acknowledged, these tools enable rational, uniform and physiologically-oriented clinical decision making. Optimum use rests in each clinician’s ability to tune the right model to the appropriate context and patient in a timely fashion.

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