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Indices of pulmonary oxygenation in pathological lung states: an investigation using high-fidelity, computational modelling

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Background. Existing indices of pulmonary oxygenation vary misleadingly with external factors such as inspired oxygen fraction ($F_{I_{O_2}}$), arterial carbon dioxide tension ($P_{a_{CO_2}}$), and haemoglobin (Hb). Previous work suggested that some indices may be acceptably useful in particular scenarios such as acute respiratory distress syndrome (ARDS) or where $F_{I_{O_2}} > 60\%$. However, it is not possible to identify such scenarios in most clinical contexts; therefore we aimed to examine the induced variability of existing indices in a population of patients with a variety of lung defects.

Methods. We configured nine virtual patients within the Nottingham Physiology Simulator, each with a unique pulmonary configuration but identical arterial blood gases at $F_{I_{O_2}}$ 30%, $P_{a_{CO_2}}$ 6.0 kPa and Hb 8.0 g dl^{-1}. Factors ($F_{I_{O_2}}$, P_{CO_2}, Hb) were varied independently and indices of oxygenation including calculated venous admixture (Q_s/Q_t), arterial oxygen tension ($P_{a_{O_2}}/F_{I_{O_2}}$), arterio-alveolar gas tension gradient ($PA-a_{O_2}$), and respiratory index ($PA-a_{O_2}/P_{a_{O_2}}$) were recorded.

Results. All indices varied with $F_{I_{O_2}}$, with greatest variation with lung defects having least true (absolute) shunt. Calculated Q_s/Q_t resisted induced variation best of all the indices, but varied by 30% of its mean value during $F_{I_{O_2}}$ variation. $P_{a_{O_2}}/F_{I_{O_2}}$ varied greatly, especially during variation in $F_{I_{O_2}}$ (up to 74% of its average value), and most markedly in defects with little true (absolute) shunt. $P_{a_{CO_2}}$ and Hb variation caused small, consistent changes in all indices that were similar between lung-states.

Conclusions. No existing index of oxygenation adequately describes the severity of gas exchange defect. Existing indices of oxygenation vary with disease severity, disease type, and external factors such as $F_{I_{O_2}}$. A novel and robust index is needed.

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Clinicians use indices of oxygenation to quantify severity of lung damage and monitor its progress with treatment. Such indices are used as surrogates to reflect the lung state and should be unaffected by factors such as inspired oxygen fraction ($F_{I_{O_2}}$), arterial carbon dioxide tension ($P_{a_{CO_2}}$), and haemoglobin concentration (Hb). Existing indices of oxygenation have been shown to vary with external factors, implying a change in the patient's lung state when there is none.[1 2] This can lead to inaccuracies when indices are used to define lung states [e.g. the use of $P_{a_{O_2}}/F_{I_{O_2}}$ (PF) ratio to define the acute respiratory distress syndrome (ARDS)] and can cause misinterpretation of the effect of treatment and the course of disease.[2 3] In the intensive care unit two patients with differing lung pathology (e.g. pulmonary emboli and acute asthma) may have a similar $P_{a_{O_2}}$ on differing $F_{I_{O_2}}$. Determining which patient has the worse lung state is difficult using current indices that are dependent upon $F_{I_{O_2}}$, $P_{a_{CO_2}}$, and Hb. If the $F_{I_{O_2}}$, $P_{a_{CO_2}}$, or Hb change the next day, determining improvement or deterioration in the lung state is difficult as the index may not reflect true change in lung state alone.

Previous work examining indices in modelled ARDS showed that a number of these indices may be acceptable to use in particular conditions. It has been suggested that

calculated shunt fraction ($\dot{Q}s/\dot{Q}t$) is acceptable when $F_{I_{O_2}}$ is between 0.4 and 0.6, but was unreliable when $F_{I_{O_2}}$ is larger than 0.6.[4] It has also been suggested that venous admixture ($\dot{Q}s/\dot{Q}t$) is the most accurate index to use in patients with ARDS (assuming substantial true shunt).[2] Calculation of $\dot{Q}s/\dot{Q}t$ requires invasive sampling of mixed venous blood from the pulmonary artery, and this adds risk for the patient.[5] Gowda and Klocke[1] concluded that $P_{a_{O_2}}/F_{I_{O_2}}$ is a useful estimate of gas exchange abnormality in all patients when the $F_{I_{O_2}}$ is more than 0.5 and $P_{a_{O_2}}$ is less than 13.3 kPa (a situation that necessitates the presence of a substantial true shunt).

It is likely that the variability of the current indices of oxygenation is dependent upon the ventilation–perfusion (VQ) configuration. Because it is impossible to identify the patient's VQ distribution by external examination and standard monitoring, the suggestions of previous authors described above may not be useful because the suggested reliability of indices may not hold true for lung states other than ARDS (e.g. pulmonary embolism and chronic obstructive pulmonary disease). To develop a new index, or to make the current indices broadly applicable, we must quantify the amplitude and pattern of variation of the current indices in a variety of lung states.

Investigating the behaviour of these indices in patients with lung damage is unethical and impractical. Thus, we planned to use a validated, sophisticated computational model (the Nottingham Physiology Simulator: NPS) to describe the variation of pulmonary indices with external factors in a population of patients with various VQ defects. The NPS has been validated for such use and has been used to examine the variation of indices of oxygenation with external physiological factors in a single-patient ARDS model.[6]

Methods

The Nottingham Physiology Simulator

The principles underlying the computational modelling in the NPS have been described previously.[7–10] The NPS has been validated in simulating the gas-exchange defect in ARDS.[6] The version of the NPS used in this investigation was NPS-270307; the source-code and a Windows® executable of this version of the NPS are available from the corresponding author.

Configuration of subjects

Nine 'virtual' subjects were created; they were identical in all respects (Table 1) except their lung state. Each subject had a unique gas-exchange defect, containing mismatch of ventilation and perfusion in addition to some true (absolute) shunt (see Appendix for definitions of terms). Each of the nine virtual subjects had a true (absolute) shunt fraction of 24, 26, 28, 30, 32, 34, 36, 38, or 40% of cardiac output (CO); VQ matching was configured by adjusting bronchiolar or pulmonary vascular resistances so that all of these subjects had identical arterial gas tensions when $F_{I_{O_2}}$=0.3. Thus, those subjects with greater true (absolute) shunt had less severe VQ mismatching, while those with less true (absolute) shunt had more significant VQ mismatching. The range of values for true (absolute) shunt (rather than total, calculated shunt; see Appendix) was chosen to be representative of the patient population of interest.

Table 1 Configuration of the virtual subjects used in this investigation

Weight	70 kg
Inspired gas	Warmed and humidified
Inspiratory flow pattern	Constant flow
Tidal volume	6 ml kg^{-1}
Respiratory rate	15 bpm
Positive end-expiratory pressure	0 cm H_2O
Inspiratory to expiratory ratio	1:2
Respiratory exchange ratio	0.8
Cardiac output	9.5 litre min^{-1}
Base excess	0 mmol $litre^{-1}$
True (absolute) shunt	24–40%

The bronchial and vascular resistances of the 100 alveolar units were used to configure VQ matching. For example, by increasing vascular resistance in a region of the lung, an area of relative deadspace can be created. The use of sliders in the NPS allows configuration of this complex model to create a set of nine subjects who *appear* identical when $F_{I_{O_2}}$ 0.3, $P_{a_{CO_2}}$ 6 kPa, and Hb 8 g dl^{-1}. The values provided in Table 2 allow the reader to configure the model for themselves to reproduce the VQ defects described.

Virtual patients with larger true (absolute) shunt fraction are described subsequently as 'true-shunt-rich' and those with smaller true (absolute) calculated shunt fraction as 'true-shunt-poor'.

Table 2 Configuration of the virtual patients; the true (absolute) shunt fraction is expressed as a percentage of cardiac output. The VQ defects may be configured by adjusting the bronchial and vascular resistances in the model. *The five values refer to the consecutive settings of the five sliders in the bronchial resistance box, in the NPS. †The five values refer to the consecutive settings of the five sliders in the vascular resistance box, in the NPS

True (absolute) shunt (%)	Bronchial resistance sliders*	Vascular resistance sliders†
24	900-1 864-30 1-50 1-80 1-100	1-1 1-20 1-50 1-80 8.4-100
26	900-1 778-30 1-50 1-80 1-100	1-1 1-20 1-50 1-80 7.8-100
28	900-1 702-30 1-50 1-80 1-100	1-1 1-20 1-50 1-80 6.8-100
30	900-1 620-30 1-50 1-80 1-100	1-1 1-20 1-50 1-80 6.3-100
32	900-1 529-30 1-50 1-80 1-100	1-1 1-20 1-50 1-80 5.3-100
34	900-1 441-30 1-50 1-80 1-100	1-1 1-20 1-50 1-80 4.4-100
36	900-1 1-46 1-50 1-80 1-100	1-1 1-20 1-50 1-80 4.8-100
38	900-1 1-34 1-50 1-80 1-100	1-1 1-20 1-50 1-80 7.3-100
40	400-1 1-20 1-50 1-80 1-100	1-1 1-20 1-50 1-80 16-100

Table 3 Maximal induced variation in each index, expressed as a percentage of the average value throughout variation of each factor, for each virtual patient

Varying factor	Index examined	True (absolute) shunt fraction								
		24%	26%	28%	30%	32%	34%	36%	38%	40%
$F_{I_{O_2}}$	Q_s/Q_t	30.2	25.6	22.9	18.2	14.6	11.4	8.0	4.6	2.0
	PF	73.9	72.4	66.0	57.8	45.5	25.5	32.8	40.8	48.7
	$P_A-a_{O_2}$	34.3	37.8	40.3	46.1	53.1	62.0	66.0	70.0	73.5
	RI	55.6	48.7	45.8	39.2	35.9	30.2	29.4	30.5	32.2
Pa_{CO_2}	Q_s/Q_t	2.5	3.9	4.1	3.9	4.0	3.7	3.0	1.9	0.6
	PF	9.5	9.6	9.3	9.5	9.4	9.5	10.0	10.9	12.2
	$P_A-a_{O_2}$	68.4	68.8	68.4	67.8	68.1	68.4	69.1	70.8	72.2
	RI	86.7	87.2	85.9	84.6	85.0	85.6	87.1	90.7	93.5
Hb	Q_s/Q_t	5.5	5.7	5.4	5.2	5.3	5.2	4.2	3.0	1.5
	PF	10.4	10.4	10.2	10.2	10.3	10.7	11.0	12.0	13.1
	$P_A-a_{O_2}$	19.3	17.5	16.6	18.1	18.3	19.0	20.0	21.8	23.3
	RI	26.5	24.2	23.2	24.3	24.3	24.7	26.5	28.2	30.6

Evaluation of indices of oxygenation

The following indices of oxygenation were investigated: arterial oxygen tension (Pa_{O_2}), alveolar oxygen tension ($P_{A_{O_2}}$), calculated venous admixture (Q_s/Q_t), PF ratio ($Pa_{O_2}/F_{I_{O_2}}$), arterio-alveolar gas tension gradient ($P_A-a_{O_2}$), and respiratory index ($P_A-a_{O_2}/Pa_{O_2}$), where $P_A-a_{O_2}$ denotes the difference between alveolar and arterial partial pressure of oxygen.

The $F_{I_{O_2}}$, Hb, and Pa_{CO_2} were varied in isolation while clamping the other variables at baseline values (Table 3). $F_{I_{O_2}}$ was varied between 30% and 100% in 10% increments, Hb between 8 g dl^{-1} and 15 g dl^{-1} in 1 g dl^{-1} increments, and Pa_{CO_2} between 4 kPa and 11 kPa in 1 kPa increments. Alveolar oxygen tension ($P_{A_{O_2}}$) was calculated using the alveolar gas equation. Once arterial gas partial pressures had reached equilibrium Pa_{O_2}, $P_{A_{O_2}}$, Q_s/Q_t, P/F, $P_A-a_{O_2}$ and $P_A-a_{O_2}/Pa_{O_2}$ were calculated.

The values of tidal volume, respiratory rate (RR), PEEP, inspiratory to expiratory (I:E) ratio, and CO were chosen to represent typical patients with lung pathology.[3 11] Hypoxic pulmonary vasoconstriction (HPV) and dynamic oxygen–haemoglobin association–dissociation were

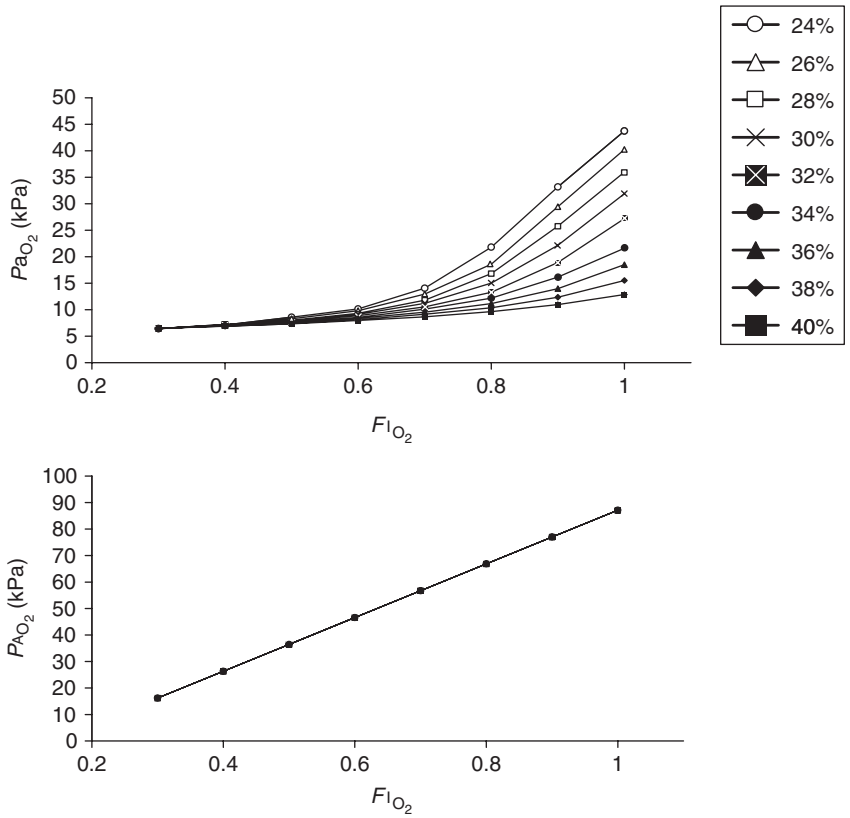

Fig 1 Variation of Pa_{O_2} and $P_{A_{O_2}}$ with $F_{I_{O_2}}$, while Pa_{CO_2} and Hb are kept constant. Percentage values in the figure key denote the true (absolute) shunt fraction.

enabled. Tidal volume (Vt) and RR were constant throughout the investigation (Table 1), in order to maintain a constant lung state. Respiratory exchange ratio was varied when manipulation of Pa_{CO_2} was required.

Results

The effect of $F_{I_{O_2}}$ upon Pa_{O_2} and $P_{A_{O_2}}$ while Pa_{CO_2} and Hb are kept constant is illustrated in Figure 1. Pa_{O_2} increased with $F_{I_{O_2}}$, the effect being modest for true-shunt-rich defects but large for true-shunt-poor defects. $P_{A_{O_2}}$ increased linearly with $F_{I_{O_2}}$, the effect being similar for all shunt defects.

Variations in Qs/Qt, $Pa_{O_2}/F_{I_{O_2}}$, $P_A-a_{O_2}$, and $P_A-a_{O_2}/Pa_{O_2}$ induced by changing $F_{I_{O_2}}$, Hb, and Pa_{CO_2} are presented in Figures 2–4, respectively. Maximal variation in each index in each virtual patient is presented in Table 3.

FI_{O_2} *variation*

Calculated, total Qs/Qt decreased linearly with increasing $F_{I_{O_2}}$. This decrease was largest in true-shunt-poor configurations (maximum 30% variation), while in true-shunt-rich configurations calculated Qs/Qt resisted $F_{I_{O_2}}$-induced variation fairly robustly (maximum 2% variation) (Fig. 2).

PF ratio varied nonlinearly with $F_{I_{O_2}}$ being smallest when $F_{I_{O_2}}$ was between 60% and 80%. PF ratio was more affected by $F_{I_{O_2}}$ variation in true-shunt-poor configurations. In true-shunt-poor configurations, PF ratio increased substantially at large $F_{I_{O_2}}$, while in true-shunt-rich configurations this was not observed.

Alveolar–arterial oxygen tension gradient $P_A-a_{O_2}$ increased linearly with $F_{I_{O_2}}$, up to a $F_{I_{O_2}}$ of 60%. When $F_{I_{O_2}}$ was 60–90% true-shunt-rich defects continued to increase linearly, whereas the true-shunt-poor defects reached a plateau with the maximum value attained when $F_{I_{O_2}}$ was 60%.

Respiratory index (RI: $P_A-a_{O_2}/Pa_{O_2}$) varied nonlinearly with $F_{I_{O_2}}$ being largest when $F_{I_{O_2}}$ was 60–90%. Respiratory index was relatively unaffected by changing $F_{I_{O_2}}$ at very large values ($F_{I_{O_2}}$ 70–90%) in the true-shunt-rich VQ configurations but was variable throughout the range of $F_{I_{O_2}}$ variation in true-shunt-poor VQ configurations.

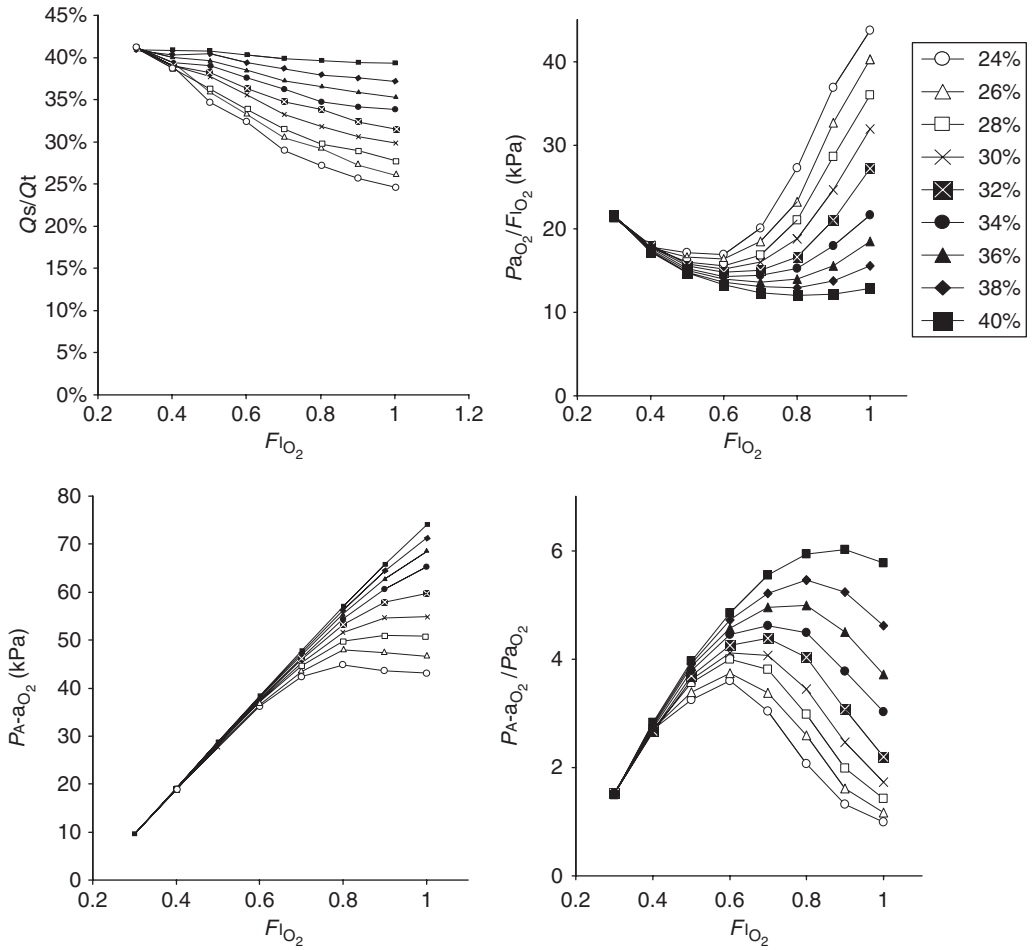

Fig 2 Variation in the indices of oxygenation (Qs/Qt, $Pa_{O_2}/F_{I_{O_2}}$, $P_A-a_{O_2}$, and $P_A-a_{O_2}/Pa_{O_2}$) with $F_{I_{O_2}}$, while Pa_{CO_2} and Hb are kept constant. Percentage values in the figure key denote the true shunt fraction.

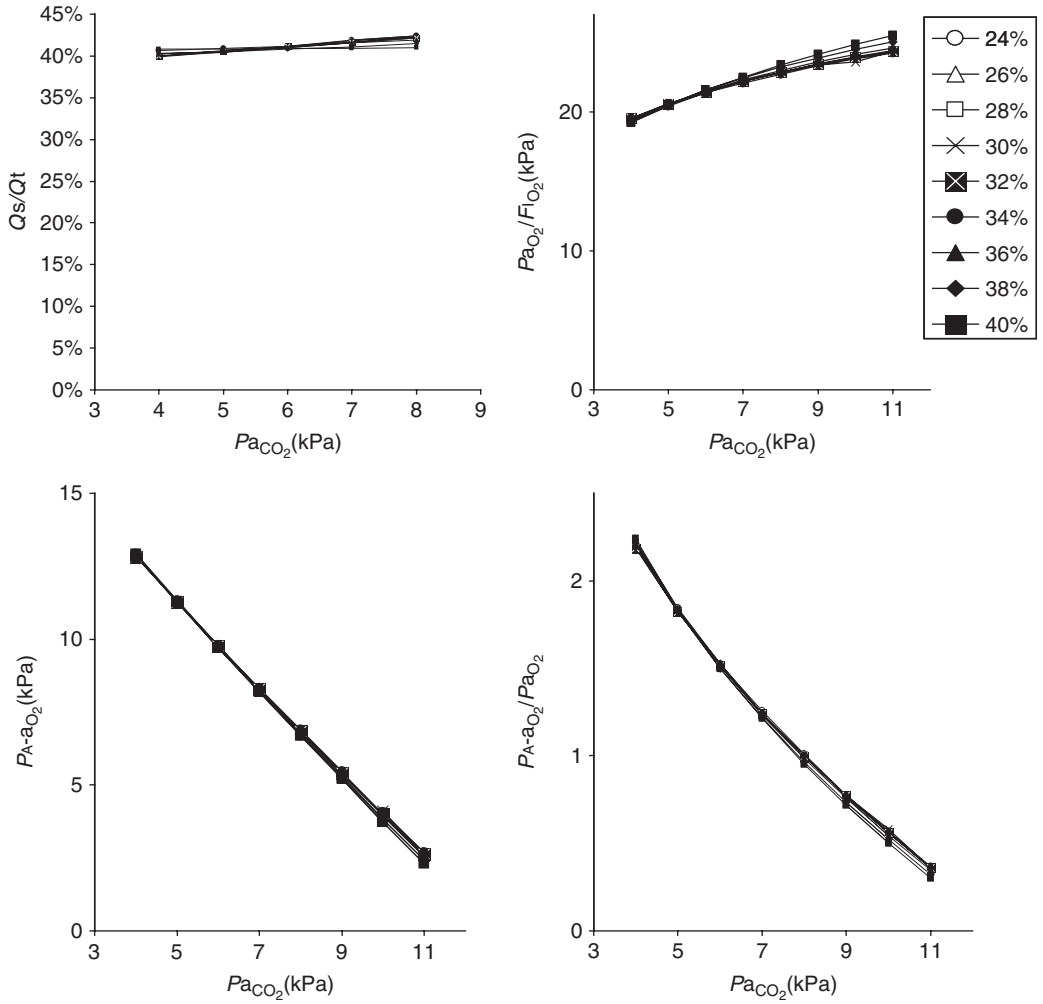

Fig 3 Variation in the indices of oxygenation (Qs/Qt, $Pa_{O_2}/F_{I_{O_2}}$, $P_A - a_{O_2}$, and $P_A - a_{O_2}/Pa_{O_2}$) with Pa_{CO_2}, while $F_{I_{O_2}}$ and Hb are kept constant. Percentage values in the figure key denote the true shunt fraction.

Pa_{CO_2} *variation*

Pa_{CO_2} variation caused minimal change in calculated shunt fraction. PF ratio increased linearly with Pa_{CO_2}, while $P_A - a_{O_2}$ and RI decreased linearly. True-shunt-rich and true-shunt-poor defects behaved similarly in response to variation in Pa_{CO_2} (Fig. 3).

Hb variation

Increasing Hb caused calculated shunt fraction and PF ratio to increase approximately linearly. $P_A - a_{O_2}$ decreased linearly with increasing Hb. Respiratory index was the index most affected by changes in Hb, decreasing linearly as the Hb increased. True-shunt-rich and true-shunt-poor defects behaved similarly in response to variation in Hb (Fig. 4).

Discussion

We have demonstrated that the currently used indices of pulmonary oxygenation are affected by external physiological factors, and that this induced variation is particularly marked during variation in $F_{I_{O_2}}$. We have also shown that the indices behave differently depending upon the subjects' pulmonary configuration. Generally, it may be concluded that true-shunt-rich defects are more robustly described by the current indices, while in the presence of true-shunt-poor defects there is marked inducible variation in the currently used indices.

Calculated shunt fraction appeared to be the most robust descriptor of oxygenation defect and this finding has been described several times previously;[2 12 13] however, calculated shunt fraction appears not to be a robust descriptor of lung state in true-shunt-poor lung configurations during variation in $F_{I_{O_2}}$. With the growing unwillingness to use pulmonary artery catheters in the critical care setting, pulmonary artery cannulation, with its attendant risks, seems not to be justified on the basis of calculating shunt fraction.[5]

Our findings agree with the conclusions of Gowda and Klocke[1] who asserted that PF ratio was robust when the $F_{I_{O_2}}$ was greater than 50% and Pa_{O_2} was less than 13.3 kPa

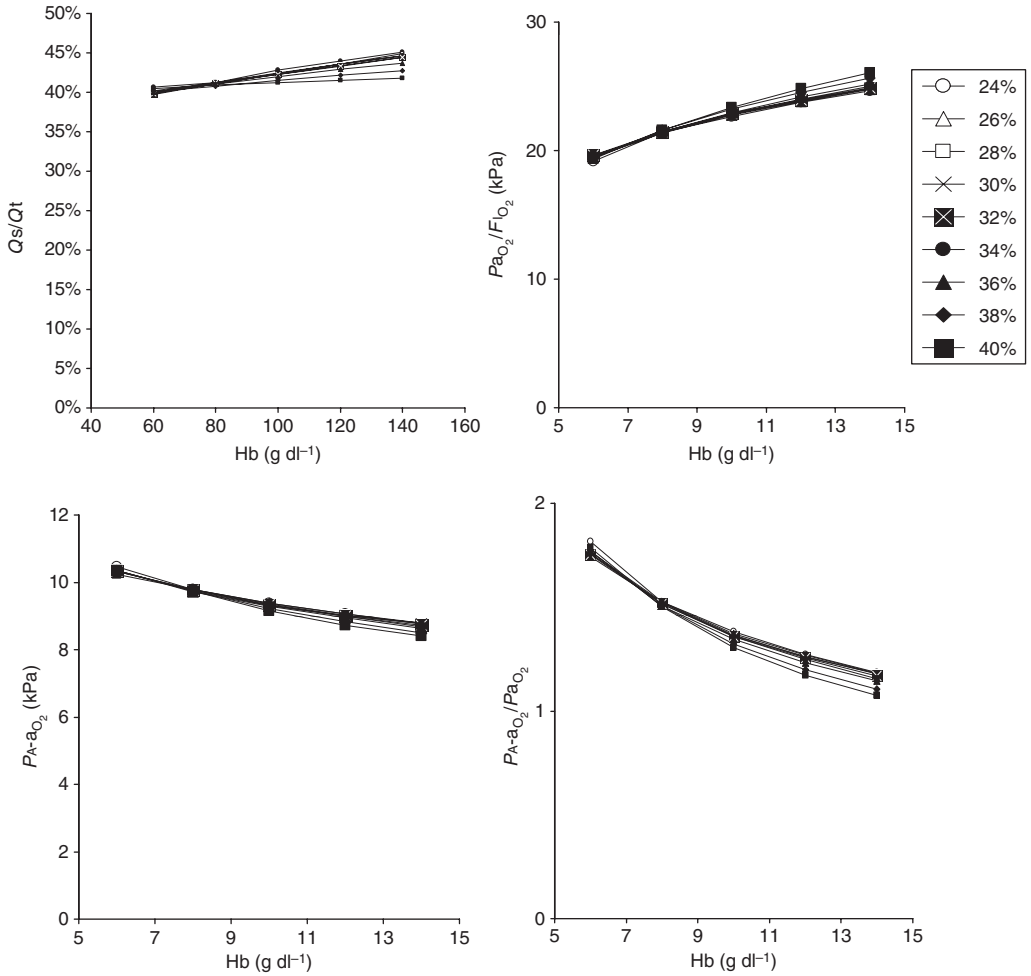

Fig 4 Variation in the indices of oxygenation (Qs/Qt, Pa_{O_2}/FI_{O_2}, $PA-a_{O_2}$, and $PA-a_{O_2}/Pa_{O_2}$) with Hb, while FI_{O_2} and Pa_{CO_2} are kept constant. Percentage values in the figure key denote the true shunt fraction.

(implying significant true shunt). While PF ratio resisted variation induced by varying FI_{O_2} in the presence of true-shunt-rich lung configuration, it varied substantially in true-shunt-poor configurations, even under the strict conditions specified. Thus, use of the PF ratio in a patient matching these conditions but whose lung state was relatively true-shunt-poor would result in misleading apparent variation in disease severity during manipulation of FI_{O_2}.

Very severely ill patients often experience true-shunt-rich defects (e.g. ARDS), but it may be seen that the virtual 'patients' used in this study appeared equally unwell when FI_{O_2} was 30%. This indicates the possibility of inappropriate use of the indices in a true-shunt-poor defect, with consequent misleading variation. Since we cannot identify the VQ distribution of a patient at the bedside, the indices we use to make diagnoses and to monitor disease progression and response to treatment must be equally applicable to true-shunt-rich and true-shunt-poor pulmonary defects. Furthermore, patients may move between true-shunt-poor and true-shunt-rich lung states during disease progression and treatment, and an index of oxygenation should remain applicable during ongoing treatment.

Our study has limitations. We have assumed in our calculations that the baseline pathology in the patients is not altered by the manipulation of FI_{O_2}, Hb, or Pa_{CO_2}. In reality, large increases in FI_{O_2} may cause atelectasis and large changes in Hb and Pa_{CO_2} may affect metabolic rate.[14 15] These factors have a potential effect, but one that we expect would not change our findings.

In conclusion, existing indices of pulmonary oxygenation behave differently in true-shunt-rich and true-shunt-poor pulmonary configurations and such configurations are not distinguishable at the bedside. Furthermore, there is no identifiable, reliable portion of any of the curves produced that would allow us to support previous recommendations that the PF ratio may be used within limited conditions. It is our contention that none of the existing indices is fit for purpose, and a new index is required that will effectively describe the critically ill patient's oxygenation defect in a variety of lung pathologies.

Funding

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Appendix

A definition of physiological terms used in the manuscript:

- True (absolute) shunt fraction: the fraction of CO not undergoing gas-exchange with the alveoli. The virtual subjects used in this investigation varied between 24% and 40% true (absolute) shunt, but had identical total (calculated) shunt fraction (see below).
- Total (calculated) shunt fraction: the fraction of CO as true (absolute) shunt that would produce the observed arterial and mixed venous gas tensions given the known $F_{I_{O_2}}$ in the absence of other ventilation–perfusion mismatch. The total (calculated) shunt fraction will usually be larger than the patient's true (absolute) shunt fraction because it incorporates degrees of 'partial' shunt, where perfused alveoli are inadequately ventilated.
- Ventilation–perfusion configuration: the NPS provides independently adjustable resistances in the pulmonary arterioles and bronchioles to control the distribution of pulmonary ventilation and perfusion. By setting the vascular and bronchiolar resistances to each of the 100 alveolar compartments a great variety of ventilation–perfusion permutations may be configured.

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