Intensive Care Med (1996) 22: 277–285

ORIGINAL

P. Jolliet
J. B. Thorens
L. Nicod
C. Pichard
U. Kyle
J. C. Chevrolet

Relationship between pulmonary oxygen consumption, lung inflammation, and calculated venous admixture in patients with acute lung injury

Received: 21 November 1994
Accepted: 6 October 1995

P. Jolliet (✉) · J.B. Thorens
J.C. Chevrolet
Medical ICU, University Hospital, Geneva, Switzerland

L. Nicod
Division of Pneumology, University Hospital, Geneva, Switzerland

C. Pichard · U. Kyle
Division of Gastroenterology and Nutrition, University Hospital, 1211 Geneva 14, Switzerland

Abstract *Objective:* To determine in patients with acute lung injury whether increased pulmonary oxygen consumption (VO_{2pulm}), computed as the difference between oxygen consumption measured by indirect calorimetry (VO_{2meas}) and calculated by the reverse Fick method (VO_{2Fick}), would: (1) correlate with the degree of lung inflammation assessed by bronchoalveolar lavage (BAL); (2) lead to an overestimation of calculated venous admixture (Q_{va}/Q_t).
Design: Prospective study.
Setting: University hospital, medical intensive care unit.
Intervention: None.
Measurements and results: In nine mechanically ventilated patients with acute lung injury (Apache II 12 ± 5, lung injury score 2 ± 0.6, mean ± SD), whole-body VO_2 (VO_{2wb}) was determined simultaneously by indirect calorimetry and the reverse Fick technique, after which BAL was immediately performed. VO_{2meas} was significantly higher than VO_{2Fick} (128 ± 24 and 102 ± 18 ml/min per m^2, respectively, $p < 0.001$). Median VO_{2pulm} was 25.3 ml/min per m^2 (range 1.98–51.5), thus representing 19 ± 11% of VO_{2wb}. Total BAL cellularity was increased in all patients (median 47, range 24–200 $\times 10^4$/ml), as was the total polymorphonuclear (PMN) count (median 78 range 5–93 $\times 10^4$/ml). Macrophage counts were in the normal range. There were raised BAL levels of interleukin-6 (IL-6) (median 945, range 23–1800 ng/ml) and elastase (median 391, range 5–949 ng/ml). Median protein levels were 270 μg/ml (range 50–505). There was no correlation between VO_{2pulm} and BAL cellularity, PMNs, elastase, IL-6, or protein. Q_{va}/Q_t was 31.7 ± 8%. Q_{va}/Q_t, corrected for the presence of VO_{2pulm}, (Q_{va}/Q_{tcorr}), was 30.3 ± 8% ($p < 0.01$ vs Q_{va}/Q_t), a 4.2% overestimation due to VO_{2pulm}. There was no correlation between Q_{va}/Q_t or Q_{va}/Q_{tcorr} and VO_{2pulm}.
Conclusions: In mechanically ventilated patients with acute lung injury, VO_{2pulm} was increased and led to a 19% underestimation of VO_{2wb} determined by the reverse Fick method, as well as to a 4.2% overestimation of calculated Q_{va}/Q_t. Lung

inflammatory activity was increased, as assessed by BAL cellularity, IL-6 and elastase levels. However, there was no correlation between VO_{2pulm} and the intensity of pulmonary inflammation.

Key words Acute lung injury · Pulmonary oxygen consumption · DO_2/VO_2 relationship · Venous admixture · IL-6 · Elastase

Introduction

In normal humans, O_2 consumption by the lungs (VO_{2pulm}), which can be estimated by the difference between whole-body O_2 consumption (VO_{2wb}) measured by indirect calorimetry and calculated by the reverse Fick method [1], represents approximately 1–4% of a subject's VO_{2wb} [2]. In a canine model of experimental pneumococcal pneumonia, Light demonstrated that VO_{2pulm} was increased to 13–15% of VO_{2wb}, which he hypothesized resulted from the presence in the lungs of large numbers of oxygen-consuming inflammatory cells [1]. This entailed an underestimation of VO_{2wb} determined by the reverse Fick method, and an overestimation of the calculated venous admixture (Q_{va}/Q_t) unless a correction was introduced in the classic Q_{va}/Q_t equation [1]. Several studies performed in human subjects, mostly patients in the intensive care unit (ICU), have illustrated the concept that a raised VO_{2pulm} could occur in the presence of pulmonary inflammatory states [3–13]. However, the issues of which cells, and in what number, are responsible for VO_{2pulm}, as well as that of the impact of a raised VO_{2pulm} on Q_{va}/Q_t determination have so far not been addressed and are the basis for the present study. We reasoned that, in ICU patients with acute lung injury, recruitment of activated inflammatory cells (mostly polymorphonuclear cells (PMNs) and macrophages) to the lungs must occur and that the combination of increased cellularity and degree of activation should raise VO_{2pulm}. We further hypothesized that there should be a correlation between the magnitude of VO_{2pulm} and the degree of inflammatory activity in the lung, as assessed by bronchoalveolar lavage cellularity, protein, interleukin-6 (IL-6), and elastase levels. Finally, we assessed the impact of an increased VO_{2pulm} on the determination of Q_{va}/Q_t, and the need to correct the classic equation.

Materials and methods

Patients

All eligible patients admitted to the medical ICU during a 12-month period were studied. Patients were included if they were intubated and mechanically ventilated with fractional inspired oxygen (FIO_2) of ≤ 0.6 for non-cardiogenic respiratory failure (cardiac index ≥ 3 l/min per m^2, pulmonary artery occlusion pressure ≤ 18 mmHg), presented localized or diffuse infiltrates on chest X-ray, and had pulmonary and peripheral artery catheters in place. The FIO_2 limit was set at 0.6 due to the considerable variability in measured O_2 consumption with the equipment used with a higher FIO_2. Lung injury (LIS) was assessed by a score described by Murray et al. [14]. Systemic inflammatory response syndrome (SIRS) was defined according to criteria established by a recent consensus conference [15] as the presence of two or more of the following: (a) a body temperature $> 38°$ or $< 36\,°C$; (b) a heart rate of > 90 beats/min; (c) tachypnea, as manifested by a respiratory rate of > 20 breaths/min or hyperventilation indicated by a $PaCO_2 < 4.3$ kPa; (d) an alteration of the white blood cell (WBC) count of $> 12\,000$ cells/mm^3 or the presence of $> 10\%$ immature neutrophils ("bands"). Sepsis was defined as SIRS in response to infection with a pathogen identified by cultures from blood, tracheal aspirates, or bronchoalveolar lavage (BAL) [15]. Community-acquired pneumonia or aspiration pneumonia was diagnosed according to widely accepted criteria [16]. Pneumonia occurring during mechanical ventilation was diagnosed on the basis of a clinical pulmonary infection score (CPIS) taking into account temperature, WBC count, volume and aspect of tracheal secretions, PaO_2/FIO_2, chest X-ray, and cultures from tracheal aspirates, previously validated in a study from our institution [17].

The study was approved by the Ethics Committee of our institution, and informed consent was obtained from next of kin.

Protocol

Patients were studied as soon as possible after inclusion criteria were met. Sedation was maintained by a continuous intravenous infusion of midazolam. When required by the patients' clinical condition, muscle paralysis was achieved by intermittent bolus injections of pancuronium bromide. All patients were ventilated in the controlled mode (Evita respirator, Dräger Werk AG, Lübeck, Germany) with FIO_2 and positive end-expiratory pressure (PEEP) titrated to maintain an arterial oxygen saturation (SaO_2) $\geq 90\%$ prior to the beginning of the protocol. Subsequently, no changes in FIO_2 or PEEP were made, and SaO_2 was continuously monitored by pulse oximetry (N-200 pulse oximeter, Nellcor, Hayward, Calif.). All sedative and inotropic drug infusion rates were maintained constant, and tracheal suctioning and nursing care withheld throughout the procedure. The mean systemic arterial pressure (MAP) was continuously monitored via an indwelling arterial catheter. The procedure was discontinued if there was a decline in SaO_2 to $< 90\%$ or MAP to < 60 mmHg, which required ventilator or inotropic drug modification, or if tracheal suctioning or nursing was required.

Measurements and calculations

Oxygen consumption and venous admixture

Measured oxygen consumption (VO_{2meas}) was obtained by indirect calorimetry (Deltatrac Metabolic Monitor, Datex Instrumentarium,

Helsinki, Finland). Briefly, this apparatus measures oxygen and carbon dioxide concentrations in inspired and expired gas and calculates oxygen consumption (VO_2) and CO_2 production (VCO_2) for 1 min [18]. Its accuracy, sensitivity, and reproductibility have been validated [18]. The device was calibrated before and after each procedure with a gas mixture containing 95% O_2 and 5% CO_2. The Deltatrac was then connected to the respirator circuit. Stable conditions were determined by a $\leq 5\%$ variability in minute-by-minute indirect calorimetry VO_2 determinations, performed over 30 min. If those conditions were met, the last five measurements were used to determine VO_{2meas}. Calculated oxygen consumption (VO_{2Fick}) was determined during the last 5 min of indirect calorimetry by the reverse Fick method:

VO_{2Fick} (ml/min/m^2) = cardiac index (CI) $\times$ (CaO_2–CvO_2) $\times$ 10 where CaO_2 = arterial oxygen content (ml/100 ml) = {[hemoglobin (g/100 ml) $\times$ 1.31 $\times$ arterial oxygen saturation (SaO_2)] + 0.003 $\times$ arterial O_2 partial pressure (PaO_2)}, and CvO_2 = mixed venous oxygen content (ml/100 ml) = {[hemoglobin (g/100 ml) $\times$ 1.31 $\times$ mixed venous saturation (SvO_2)] + 0.003 $\times$ venous O_2 partial pressure (PvO_2)}. The value of 1.31 was chosen as it is the true value that should be used for determining the amount of O_2 combined with hemoglobin, as demonstrated by Gregory [19]. Blood gas tensions and hemoglobin saturation were determined by an ABL 520 (Radiometer, Copenhagen, Denmark) blood gas analyzer, which measures saturation by spectrophotometry. The variability in the measurements of hemoglobin and SaO_2 had been previously determined by ten repeated measurements in ten patients and shown to be 2.5% for hemoglobin and 0.2% for SaO_2.

Pulmonary O_2 consumption was calculated as the difference between measured and Fick oxygen consumptions: $VO_{2pulm} = VO_{2meas} - VO_{2Fick}$.

Oxygen delivery (DO_2) was computed as DO_2 (ml/min/m^2) = CI $\times$ CaO_2 $\times$ 10.

Venous admixture (Q_{va}/Q_t) was calculated as $Q_{va}/Q_t = (Cc'O_2 - CaO_2)/(Cc'O_2 - CvO_2)$, where $Cc'O_2$ represents the calculated O_2 content of end-capillary blood: $Cc'O_2$ = {[hemoglobin (g/100 ml) $\times$ 1.31 $\times$ 1.0] + 0.003 $\times$ PcO_2}. PcO_2, capillary O_2 partial pressure, is assumed to be equal to the alveolar O_2 partial pressure (PAO_2), calculated from the simplified alveolar gas equation [20]. Calculated venous admixture corrected for VO_{2pulm} was computed, according to Light, as: $Q_{va}/Q_{tcorr} = [Cc'O_2 - CaO_2 - (VO_{2pulm}/Q_t)]/[Cc'O_2 - CvO_2]$ [1].

Cardiac output (Qc) was measured by the thermodilution technique, using 10 ml iced dextrose 5% in water. The injections were repeated five times. The highest and lowest values were discarded, and Qc was reported as the mean of the three remaining values.

BAL

BAL was performed immediately after VO_2 determinations, through a flexible fiberoptic bronchoscope (Olympus BF type 1T20B), using 4 $\times$ 50 ml aliquots (total 200 ml) of sterile saline solution at 37 °C [21]. BAL was performed in a subsegment of either the lobe with the infiltrate, in case of unilobar X-ray infiltrate, or in the lobe with the most marked infiltrate in the case of plurilobar infiltrates. The fluid was processed for cell counts, bacteriological analysis, and measurement of IL-6, elastase, and protein content. Specimens were isolated for Gram-staining and culture. A hemocytometer was used to determine the total cell count. The percentage and type of cells were identified with a Wright–Giemsa stained cytocentrifuge preparation. Results were expressed as cell/ml BAL fluid recovered and compared to published results for normal subjects [22]. IL-6 was measured by an enzyme amplified sensitivity immunoassay (EASIA) technique (Medgenix Diagnostics, Fleurus, Belgium). Elastase-α1-proteinase inhibitor complexes were measured by an enzyme-linked immunosorbent assay (ELISA) technique (Diagnostica Merck, Darmstadt, Germany) [23]. Protein content was determined by a protein-dye binding technique [24].

Other assays

Peripheral WBCs and serum lactate were obtained up to 4 h before the beginning of the protocol.

Statistics

Mean VO_2 determined by both methods and Q_{va}/Q_t and Q_{va}/Q_{tcorr} were compared by a paired *t*-test. Correlations between BAL cellularity and mediator and protein levels, as well as between VO_{2pulm} and calculated venous admixture, were assessed by the Pearson product-moment or the Spearman rank correlation coefficients, depending on the parametric or non-parametric nature of the data. Statistical significance for all tests was set at $p < 0.05$.

Results

A total of 11 patients were entered in the study. Two patients were excluded because of technical problems during data collection (hemodynamic instability, change in FIO_2 or inotropic drugs, nursing, disconnection between the calorimeter and the ventilator) and could not be studied again. No problems arose during BAL requiring the procedure to be discontinued. The diagnoses, main clinical characteristics, duration of mechanical ventilation prior to the measurement protocol, and outcome for the remaining 9 patients are summarized in Table 1.

Oxygen transport and consumption

The coefficient of variation (mean ± SD) for the 30 min of indirect calorimetry was 4.9 ± 2.2% and for cardiac output 4 ± 1.9%. The median DO_2 was 532 ml/min per m^2 (range 356–876). VO_{2meas} and VO_{2Fick} were 128 ± 24 and 102 ± 18 ml/min per m^2, respectively ($p < 0.001$). As Table 2 shows, all individual values of VO_{2meas} were higher than those of VO_{2Fick}. The median VO_{2pulm} was 25.3 ml/min per m^2 (range 1.98–51.5), thus representing 19 ± 11% of VO_{2wb}.

Calculated venous admixture

Q_{va}/Q_t and Q_{va}/Q_{tcorr} (mean ± SD) were 31.7 ± 8 and 30.3 ± 8%, respectively ($p < 0.01$, paired *t*-test). The overestimation of Q_{va}/Q_t due to VO_{2pulm} was 4.2%.

Table 1 Clinical and laboratory characteristics of the patients (*AMI* acute myocardial infarction, *ARDS* adult respiratory distress syndrome, *COPD* chronic obstructive pulmonary disease, *Days MV* number of days elapsed on mechanical ventilation when the measurements were performed, *Dp* dopamine, *Db* dobutamine, *NE* norepinephrine, *SIRS* systemic inflammatory response syndrome, *WBC* white blood cells in peripheral blood, *s* survived, *d* died)

Patient No.	Diagnosis	Sex	Age (years)	Apache II score	Lung injury score	Days MV	Temp. (°C)	Lactate (mmol/l)	WBC/mm^3	Inotropic drugs (μg/kg per min)	Outcome
1	COPD, SIRS	F	74	22	1	4	35.0	2.9	8200	Dp 3, Db 30, NE 0.2	s
2	Acute eosinophilic pneumonia	F	63	10	2.8	9	36.5	1.8	22900	Dp 3, Db 30	s
3	Sepsis (*Proteus mirabilis*)	M	69	8	2.5	2	37.0	5.3	11800	Dp 3	s
4	Dermatomyositis, aspiration pneumonia	M	78	18	2.5	1	35.5	6.7	12200	Dp 3, NE 0.1	d
5	Multilobar pneumonia (*Streptococcus pneumoniae*)	F	38	12	2	1	38.5	3.2	7000	Dp 12	s
6	Mesenteric ischemia, SIRS	M	78	12	2	4	38.4	3.0	9000	Dp 2.5, NE 0.08	d
7	Sepsis (*Staphylococcus aureus*), ARDS	F	19	6	2.5	11	38.1	1.4	15100	Dp 3	s
8	Peritonitis (*Candida albicans*)	F	79	13	2.3	11	36.5	1.5	16300	Dp 3	d
9	AMI, pneumonia	F	73	17	0.7	2	36.3	1.2	28400	Dp 3, Db 20	d
Mean			63	13	2	5	36.8	3			
(± SD)			(20)	(5)	(0.7)	(4.1)	(1.2)	(1.8)			

There was no correlation between Q_{va}/Q_t and Q_{va}/Q_{tcorr} and VO_{2pulm} or the LIS. Individual values for oxygen consumption and calculated venous admixture are shown in Table 2.

BAL results

Individual BAL results are given in Table 3. A mean (±SD) of 91.5(±30) ml of BAL fluid was recovered (46% of instilled fluid). Total cellularity was increased in all patients (median 47×10^4/ml, range 24–200), as were the percentage and total counts of PMNs (median 78, range 5–93, median 24.2×10^4/ml, range 1–186, respectively). Macrophage percentages varied widely (median 18%, range 7–89) and total counts were mostly within the normal range (median 19.1×10^4/ml, range 4–35). IL-6, elastase, and protein measurements were not available for two patients (1 and 7) for technical reasons. Median IL-6 and elastase levels for the remaining seven patients were 945 and 391 ng/ml, respectively, with wide ranges (IL-6: 23–1800; elastase: 5–949). Median protein levels were 270 μg/ml (range 60–505).

Relationship between VO_{2pulm} and BAL cellularity and mediators

There was no correlation between VO_{2pulm} and BAL cellularity ($r = 0.27$), PMNs ($r = 0.29$) or macrophages ($r = 0.14$), nor was a correlation found between VO_{2pulm} and elastase ($r = 0.10$), IL-6 ($r = 0.28$), or protein ($r = 0.16$).

In addition, no correlation was found between VO_{2pulm} and plasma lactate levels, peripheral WBC counts, body temperature, chest X-ray, FIO_2, hemodynamic parameters, or mortality.

Discussion

The results of this study confirm that, in a small group of nine ICU patients with acute lung injury from various causes, VO_{2pulm} was present, as it should be, and was increased, representing a mean of 19% of VO_{2wb}. Thus, VO_{2pulm} led to a mean 19% underestimation of VO_{2wb} determined by the reverse Fick method and to a minimal (4.2%), although significant overestimation of Q_{va}/Q_t. BAL analysis indicated increased total cellularity, PMN count, and levels of elastase, IL-6, and protein. However, no correlation was found between the level of inflammation and the magnitude of VO_{2pulm}. These results raise a number of issues.

Table 2 Oxygen consumption and venous admixture (VO_{2meas} oxygen consumption determined by indirect calorimetry, VO_{2Fick} oxygen consumption determined by the reverse Fick method, VO_{2pulm} pulmonary oxygen consumption, Q_{va}/Q_t calculated venous admixture, Q_{va}/Q_{tcorr} calculated venous admixture, corrected for VO_{2pulm})

Patient No.	VO_{2meas} (ml/min/m^2)	VO_{2Fick} (ml/min/m^2)	VO_{2pulm} (ml/min/m^2)	Q_{va}/Q_t (%)	Q_{va}/Q_{tcorr} (%)
1	116	97	19	21	19.7
2	118	85	33	35.3	33.2
3	146	120	26	25.7	24.3
4	96	90	6	36.6	36.3
5	147	95	52	41.5	38.9
6	163	125	38	35.2	33.6
7	152	133	19	35.8	35.1
8	114	80	34	38.5	36.4
9	99	97	2	15.4	15.3
Mean	128	102	25	31.7	30.3
($\pm$ SD)	(24)	(18)	(16)	(8.8)	(8)

Limitations and methodological weaknesses

Potential methodological weaknesses might have interfered with the validity of our results. First, the value of VO_{2pulm} could result from measurement variability [25]. Indeed, published results indicate that the range of error in determining VO_2 by the reverse Fick method lies between 7 and 12% [26], and at 5% for indirect calorimetry [18]. The validation tests in this study indicated a variability of 2.5 and 0.2% for hemoglobin and SaO_2, respectively. Thus, a potential error of 2.7%, for both arterial and mixed venous blood, and thus of 5.4% for the calculated arteriovenous O_2 content difference must be considered. The added 4% variability in cardiac output measurement places the total variability of VO_{2Fick} at approximately 10%. The coefficient of variation for indirect calorimetry was 4.9%. Thus, a value for VO_{2pulm} of up to 15% of VO_{2wb} could result from the variability of the methods used, in the absence of any *significant* VO_{2pulm}. This seems unlikely in our patients for two reasons. First, a value of VO_{2pulm} of 19% was found, higher than could be accounted for by the 15% variability outlined above; second, VO_{2meas} was higher than VO_{2Fick} in all patients, as can be seen from the individual data in Fig. 2. VO_{2Fick} would be expected to be higher than VO_{2meas} in some patients if variability was the sole explanation. Second, patient instability during the procedure could have altered the results. This also seems improbable, for three reasons (a) the criteria for insuring a stable baseline before measurements began, described in the materials and methods section, were stringent and were always met in our patients. (b) as stated above, VO_{2meas} was higher than VO_{2Fick} in all patients. (c) the 4.9% variability in indirect calorimetry is low [18] and reasonably rules out any major instability during measurements.

Third, iced isotonic dextrose was used to determine cardiac output. A recent study, comparing the use of iced or room-temperature injectate, showed that iced injectate results in a significant bias between VO_{2meas} and VO_{2Fick}, indicating the presence of VO_{2pulm}, whereas the latter does not [27]. However, that study was performed in patients after cardiopulmonary bypass, and does not address the issue of which approach best reflects the pathophysiological reality in patients with inflammatory activity in the lungs, such as ours.

The fourth point relates to methodological problems with BAL or measurements of inflammatory mediators. BAL was always performed by the same operator, an experienced pulmonologist. No problems arose during the procedure. The return of fluid was only 46%, less than the usual $\geq 60\%$ return in non-intubated patients [22], but is consistent with that published in a recent study in mechanically ventilated patients with ARDS [28]. Cell population and inflammatory mediator levels were determined with validated techniques.

Fifth, limitations could stem from the heterogeneity of the diagnoses in our patients (Table 1). VO_{2pulm} has been observed in both homogeneous and heterogeneous patient populations, as discussed below. However, our study is the first to attempt to establish its correlation with BAL inflammatory parameters, and, as discussed below, such a correlation could only be present in certain disease states, such as pneumonia [1]. Sixth, the restriction to patients requiring an $FIO_2 \leq 0.6$ could have hidden a possible relationship between these variables occurring at a higher FIO_2, i.e., with more severe lung injury. This hypothesis cannot be excluded, although there are no data available to substantiate it. Finally, the small number of patients in this study could be insufficient to demonstrate any significant relationship.

Table 3 Bronchoalveolar lavage results

Patient No.	Total cells ($\times 10^4$/ml)	Viability (%)	PMN (%)	PMN ($\times 10^4$/ml)	Macrophages (%)	Macrophages ($\times 10^4$/ml)	Lymphocytes (%)	Eosinophils (%)	IL-6 (ng/ml)	Elastase (ng/ml)	Protein (mg/ml)
1	31	93	78	24	14	4	8	0	–	–	–
2	40	95	13	5	20	8	13	51	122	23.3	170
3	200	99	93	186	7	14	0	0	1749	391	445
4	58	98	84	49	7	4	9	0.5	945	450	385
5	135	95	78	105	18	24	3	0	1800	949	505
6	27	96	5	1	89	24	5	0	47	14	60
7	47	94	15	7	75	35	4	6	–	–	–
8	24	95	14	3	84	20	2	0	23	4.6	160
9	113	96	80	90	17	19	3	0	1784	528	170
Range	(24–200)	(93–98)	(5–93)	(1–186)	(7–89)	(4–35.2)	(0–13)	(0–51)	(23–1800)	(14–949)	(60–505)

Relation to other published series

Given these methodological limitations, the next issue is whether the magnitude of VO_{2pulm} found in our patients relates to the data from patients published so far. Several human studies have confirmed that when the lungs are infected or inflammed, VO_{2pulm} could increase to levels above those found in normal subjects [3–13]. Pertinent information from these studies is summarized in Table 4. As the table shows, the range of VO_{2pulm} varies considerably, from 15 to 89 ml/min/m^2, and from 8 to 40% of VO_{2wb}, the highest values being reported by Becq et al. [12] in patients with bacterial pneumonia. Even though the available data do not allow precise comparison between the patients from these series and those in the present study, the mean $VO_{2\,pulm}$ of 19% in our patients is within the range for these studies.

Possible determinants of $VO_{2\,pulm}$

In his canine model of pneumococcal pneumonia, Light hypothesized [1] that the pneumonia was due to the presence of large numbers of O_2-consuming inflammatory cells, such as PMNs and macrophages, in the diseased lobes [29]. Indeed, many experimental studies have shown that PMNs and macrophages show a rapid and quantitatively important increase in O_2 consumption while destroying pathogenic material, termed the "respiratory burst" [30–35]. Our patients had an increased total cellularity and number of PMNs in BAL fluid, which were correlated with the levels of IL-6 and protein. There was also a fairly strong association with elastase, even though it was not significant, probably due to the small number of samples. A raised PMN count is usually found in infectious and in many pulmonary inflammatory processes [29], while elastase is considered a marker of such cell activation [31]. Increased levels of elastase in BAL fluid have been documented both in patients at risk of developing and in patients with overt adult respiratory distress syndrome [36]. The source of elastase production in this condition has been shown to be PMNs [37]. An objection could be made that, as plasma elastase was not measured in our study, the elastase found in our patients' BAL fluid may have exuded from the plasma. However, a recent study has shown that 99.7% of elastase recovered in BAL fluid had an intrapulmonary origin [38]. Nonetheless, there was no direct proof that the PMNs were undergoing active O_2-consuming processes at the time of BAL in our patients, since neither chemiluminescence nor H_2O_2 production, parameters

Table 4 Estimates of pulmonary O_2 consumption in human subjects reported in the literature (*NR* not reported, *ARF* acute respiratory failure, *CPB* cardiopulmonary bypass, *CMV* controlled mechanical ventilation, *SIMV* mechanical ventilation in synchronized intermittent mandatory ventilation, *SB* spontaneous breathing, VO_{2pulm} pulmonary O_2 consumption, % of VO_{2wb} pulmonary O_2 consumption expressed as % of whole-body VO_2 determined by indirect calorimetry

Study	Patient characteristics	Patients intubated	No. of patients/ measurements	Apache II (mean)	FIO_2 (mean)	VO_{2pulm} (mean or median)	% of VO_{2wb} (mean)
Fritts et al. (1961) [3]	Tuberculosis	No	6/16	–	0.21	NR	12
Fritts et al. (1963) [4]	Normal controls	No	18/18	–	0.21	NR	0.7
	Tuberculosis	No	21/21	–	0.21	NR	9.5
	Bronchogenic carcinoma	No	9/9	–	0.21	NR	11.6
Levinson et al. (1987) [5]	ARF from various causes	Yes	29/39	NR	0.4	46 ml/min	16
Takala et al. (1989) [6]	Post-CPB (a) during CMV	Yes	20/20	NR	0.4	49 ml/min	16
	(b) during SIMV	Yes	5/10		0.4	76 ml/min	22
	(c) during SB	No	8/8		NR	78 ml/min	24
Chopin et al. (1990) [7]	Sepsis	Yes	12/60	22	≤ 0.5	15 ml/min per m^2	10
Smithies et al. (1991) [8]	ARF from various causes	Yes	8/20	18	NR	36 ml/min	13
Bizouarn et al. (1992) [9]	Post-CPB	Yes	10/50	NR	NR	34 ml/min	22
Myburgh et al. (1992) [10]	ARF from various causes	Yes	20/33	29	NR	24 ml/min	8
Smithies et al. (1992) [11]	"Sepsis syndrome" criteria	Yes	26/106	NR	NR	47 ml/min per m^2	27
Becq et al. (1992) [12]	ARF from: (a) bacterial pneumonia	Yes	8/32	NR	≤ 0.5	89 ml/min per m^2	40
	(b) various causes	Yes	8/32			38 ml/min per m^2	22
Oudemans-van Straaten et al. (1993) [13]	(a) Before CPB	Yes	10/10	NR	0.4	35 ml/min per m^2	32
	(b) After CPB	Yes				38 ml/min per m^2	27
Chiolero et al. (1994) [27]	Post-CPB	Yes	10/30	NR	≤ 0.5	18 ml/min per m^2 [a]	13[a]

[a] *Using iced injectate*

which are usually accompanied by an increase in the O_2 consumption of these cells [30], were performed. However, the increase in elastase, its short half-life, and the fact that its release is known to be often synchronous with the PMNs oxidative burst could provide indirect evidence that the PMNs were activated and consuming O_2 [29–31]. The effect of IL-6 is more difficult to interpret, since it can be produced by numerous cell types and thus probably represents a general marker of an acute phase response [39].

The macrophage count was within normal limits in our patients, and thus trying to interpret the lack of correlation between that count and $VO_{2\,pulm}$ would be highly speculative. However, a marker of macrophage activation might have identified patients with normal counts but activated macrophages. Indeed, in an animal model of endotoxin-induced lung injury, alveolar macrophages were not increased in number but produced increased amounts of hydrogen peroxide and greater peaks in chemiluminescence than controls [40]. In any case, whether PMNs or macrophages are considered, any correlation between these more specific markers of activation and VO_{2pulm} remains to be determined.

Perhaps the most important point is the extent to which the BAL fluid reflects the state of both lungs. In substance, the difference between the two methods of determining VO_{2wb} corresponds to the total O_2 consumption of both lungs, whereas BAL samples only about 3% of the total number of alveoli [21]. Furthermore, the subsegment was chosen in the region with the most severe infiltrate, as shown on X-ray. Thus, PMNs and macrophages harvested from BAL fluid might be highly active, whereas cells from the rest of the lung could be quiescent or only slightly activated. In this case, cells and mediators would be increased, but VO_{2pulm} low. Conversely, in the case of diffuse infiltrates, the cells in BAL fluid could have largely exhausted their potential for activation, or not yet have migrated and become active, while in other regions they might be numerous and highly activated. Cells and mediators in BAL would therefore be low, but VO_{2pulm} would be high. Interestingly, the only patient with increased VO_{2pulm}, and PMNs, elastase, and IL-6 in BAL had acute multilobar pneumococcal pneumonia (Patient 5). Thus, if there is a relationship between VO_{2pulm} and the level of inflammation, it might not be apparent unless an index of the latter reflects both lungs.

Finally, BAL only accesses the alveolar compartment. It is possible that increased O_2 consumption in the lungs could result from the activity of cells located in the interstitial compartment. The cells might be

PMNs, macrophages, or fibroblasts, as their numbers are increased in some forms of acute lung injury. There are, however, no data to substantiate this hypothesis at the present time.

Impact of VO_{2pulm} on Q_{va}/Q_t determination

In his study, Light hypothesized that as the classic equation for calculating Q_{va}/Q_t does not take VO_{2pulm} into account, an increased VO_{2pulm} would result in an overestimation of blood flow to shunting or low-perfusion lung units [1]. Our study confirms this, but the degree of this overestimation was very small (4.2%), albeit significant. Our results further confirm those of Myburgh et al. [10], who found no correlation between the magnitude of VO_{2pulm} and Q_{va}/Q_t. There is no obvious explanation for this lack of correlation, especially since there is a risk of spurious correlation, as the terms CaO_2 and CvO_2 are contained in both Q_{va}/Q_t and VO_{2Fick}, (see the equations in the materials and methods section). If all other parameters are kept constant and either CaO_2 or CvO_2 changed, Q_{va}/Q_t and VO_{2pulm} will vary in the same direction.

Clinical relevance of our findings

Two aspects of our findings should be outlined. The first pertains to the relationship between DO_2 and VO_2 in critically ill patients. There has been much debate in recent years over the optimal method of determining VO_{2wb}, especially in the evaluation of what has been termed the "pathological supply dependency" of VO_2 in conditions such as sepsis and the adult respiratory distress syndrome [41,42]. Indeed, there is a risk of establishing a spurious correlation between DO_2 and VO_2 when VO_{2wb} is determined by the reverse Fick method, due to mathematical coupling resulting from shared variables [43]. There is now an emerging consensus that VO_{2wb} should be measured by indirect calorimetry to avoid this pitfall [42]. Our results, as well as those of the studies cited in Table 4, further confirm that VO_{2meas} and VO_{2Fick} are not equivalent and that using VO_{2Fick} leads to an underestimation of VO_{2wb}. Thus, indirect calorimetry should be preferred to determine VO_{2wb} in ICU patients.

The second point is whether an increased VO_{2pulm} has any prognostic or therapeutic value. One possibility would be that increased FIO_2 could fuel O_2 consumption by lung phagocytes and potentiate lung damage through the generation of reactive O_2 species [44]. However, we found no correlation between FIO_2 and VO_{2pulm}. Nor was there any correlation between the level of VO_{2pulm} and indices of lung injury or mortality. Thus, at present, the clinical significance of an increased VO_{2pulm} is unclear except for its consequences on VO_{2wb} determinations and, possibly, Q_{va}/Q_t determinations.

In conclusion, increased VO_{2pulm} in intubated ICU patients with acute lung injury led to an underestimation of whole-body O_2 consumption when using the reverse Fick method. Concomitantly, VO_{2pulm} led to a slight overestimation of calculated venous admixture. BAL showed increased levels of PMNs, elastase, and IL-6, indicating heightened inflammatory activity. There was, however, no correlation between the magnitude of VO_{2pulm} and any of the cellular or humoral parameters of inflammatory activity. This probably reflects the fact that BAL samples one subsegment, whereas VO_{2pulm} reflects the activity of both lungs. Alternatively, other parameters of PMN activation might better reflect O_2 consumption by these cells. Whether other parenchymal cells, undetected by BAL, could participate in VO_{2pulm}, and whether a raised VO_{2pulm} has any prognostic or therapeutic value remains to be determined.

Acknowledgement The present study was conducted with the financial support of Drägerwerk AG, Lübeck, Germany.

References

1. Light R (1988) Intrapulmonary oxygen consumption in experimental pneumococcal pneumonia. J Appl Physiol 64: 2490–2495
2. Nunn JF (1993) Non-respiratory functions of the lung. In: Nunn J (ed) Applied respiratory physiology. Butterworth, London Boston, pp 306–317
3. Fritts HW, Richards DW, Cournand A (1961) Oxygen consumption of tissues in the human lung. Science 133: 1070–1072
4. Fritts HW, Strauss B, Wichern W, Cournand A (1963) Utilization of oxygen in the lungs of patients with diffuse, non-obstructive pulmonary disease. Trans Assoc Am Physicians 76: 302–311
5. Levinson MR, Groeger JS, Miodownik S, Ray C, Brennan MF (1987) Indirect calorimetry in the mechanically ventilated patient. Crit Care Med 15: 144–147
6. Takala J, Keinänen O, Väisänen P, Kari A (1989) Measurement of gas exchange in intensive care: laboratory and clinical validation of a new device. Crit Care Med 17: 1041–1047
7. Chopin C, Mehdaoui H, Boniface B, Mangalaboyi J, Chambrin MC, Lestavel P, Rimé A, Fourrier F (1990) Transport, consommation et extraction de l'oxygène au cours des états septiques graves. Rean Soins Intensive Med Urg 6: 147–153

8. Smithies MN, Royston B, Makita K, Konieczko K, Nunn JF (1991) Comparison of oxygen consumption measurements: indirect calorimetry versus the reversed Fick method. Crit Care Med 19: 1401–1406
9. Bizouarn P, Soulard D, Blanloeil Y, Guillet A, Goarin Y (1992) Oxygen consumption after cardiac surgery – a comparison between calculation by Fick's principle and measurement by indirect calorimetry. Intensive Care Med 18: 206–209
10. Myburgh JA, Webb RK, Worthley LI (1992) Ventilation/perfusion indices do not correlate with the difference between oxygen consumption measured by the Fick principle and metabolic monitoring systems in critically ill patients. Crit Care Med 20: 479–482
11. Smithies MN, Bihari DJ (1992) Problems with oxygen consumption in the ICU. Intensive Care Med 18: S41
12. Becq MC, Mangalaboyi J, Chopin C, Chambrin MC, Rime A, Mehdaoui H, Lestavel P, Fourrier F (1992) The difference between the oxygen consumption estimated by Fick and expired gas methods increases in pneumonia. Intensive Care Med 18: S41
13. Oudemans-van Straaten HM, Scheffer GJ, Eysman L, Wildevur CRH (1993) Oxygen consumption after cardiopulmonary bypass – implications of different measuring methods. Intensive Care Med 19: 105–110
14. Murray JF, Matthay MA, Luce JM, Flick MR (1988) An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 138: 720–723
15. ACCP/SCCM (1992) American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 20: 864–874
16. Reynolds HY (1985) Introduction to pneumonia. In: Wyngaarden J, Smith L (eds) Cecil textbook of medicine. Saunders, Philadelphia London, Toronto, pp 1494–1498
17. Pugin J, Auckenthaler R, Mili N, Janssens JP, Lew D, Suter PM (1991) Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. Am Rev Respir Dis 143: 1121–1129
18. Ronco JJ, Phang PT (1991) Validation of an indirect calorimeter to measure oxygen consumption in critically ill patients. J Crit Care 6: 36–41
19. Gregory IC (1974) The oxygen and carbon monoxide capacities of foetal and adult blood. J Physiol 236: 625–632
20. Nunn JF (1993) Distribution of pulmonary ventilation and blood flow. In: Nunn J (ed) Applied respiratory physiology. Butterworth-Heinemann, London Boston, pp 156–197
21. Reynolds HY (1987) State of the art: bronchoalveolar lavage. Am Rev Respir Dis 135: 250–263
22. Merchant RK, Schwartz DA, Helmers RA, Dayton CS, Hunninghake GW (1992) Bronchoalveolar lavage cellularity. The distribution in normal volunteers. Am Rev Respir Dis 146: 448–453
23. Suter S, Schaad UB, Roux-Lombard P, Girardin E, Grau G, Dayer JM (1989) Relation between tumor necrosis factor-alpha and granulocyte elastase-alpha 1-proteinase inhibitor complexes in the plasma of patients with cystic fibrosis. Am Rev Respir Dis 140: 1640–1644
24. Bradford M (1976) A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein dye binding. Anal Biochem 72: 248–254
25. Takala J, Ruokonen E (1993) Assessment of systemic and regional oxygen delivery and consumption. In: Vincent J (ed) Yearbook of intensive care and emergency medicine. Springer, Berlin Heidelberg New York, pp 413–421
26. Russell JA, Wiggs BR (1990) Oxygen kinetics: pitfalls in clinical research revisited. J Crit Care 5: 213–217
27. Chiolero R, Mavrocordatos P, Bracco D, Schutz Y, Cayeux C, Revelly JP (1994) O_2 consumption by the Fick method. Am J Respir Crit Care Med 149: 1118–1122
28. Steinberg KP, Mitchell DR, Maunder RJ, Milberg JA, Whitcomb ME, Hudson LD (1993) Safety of bronchoalveolar lavage in patients with adult respiratory distress syndrome. Am Rev Respir Dis 148: 556–561
29. Sibille Y, Reynolds HY (1990) Macrophages and polymorphonuclear neutrophils in lung defense and injury. Am Rev Respir Dis 141: 471–501
30. Babior B (1978) Oxygen-dependent microbial killing by phagocytes. N Engl J Med 298: 659–668; 721–725
31. Weiss SJ (1989) Tissue destruction by neutrophils. N Engl J Med 320: 365–376
32. Malech HL, Gallin JI (1987) Neutrophils in human disease. N Engl J Med 317: 687–694
33. Johnston RB (1988) Monocytes and macrophages. N Engl J Med 318: 747–752
34. Stähelin H, Suter E, Karnovsky ML (1956) Studies on the interaction between phagocytes and tubercle bacilli. I. Observations on the metabolism of guinea pig leucocytes and the influence of phagocytes. J Exp Med 104: 121–136
35. Stähelin H, Karnovsky ML, Suter E (1957) Studies on the interaction between phagocytes and tubercle bacilli. III. Some metabolic effects in guinea pigs associated with infection with tubercle bacilli. J Exp Med 105: 265–277
36. Suter PM, Suter S, Girardin E, Roux-Lombard P, Grau GE, Dayer JM (1992) High bronchoalveolar levels of tumor necrosis factor and its inhibitors, interleukin-1, interferon, elastase, in patients with adult respiratory syndrome after trauma, shock, or sepsis. Am Rev Respir Dis 145: 1016–1022
37. Lee CT, Fein AM, Lippmann M, Holtzman H, Kimbel P, Weinbaum G (1981) Elastolytic activity in pulmonary lavage fluid from patients with adult respiratory distress syndrome. N Engl J Med 304: 192–196
38. Lengas A, Poletti V, Pacifico L, di Domizio C, Patelli M, Spiga L (1994) Acute lung inflammation: neutrophil elastase versus neutrophils in the bronchoalveolar lavage – neutrophil elastase reflects better inflammatory activity. Intensive Care Med 20: 354–359
39. Le J, Vilcek J (1989) Interleukin 6: a multifunctional cytokine regulating immune reactions and the acute phase protein response. Lab Invest 61: 588–602
40. Jacobs RF, Keil DP, Balk RA (1986) Alveolar macrophage function in a canine model of endotoxin-induced lung injury. Am Rev Respir Dis 134: 745–751
41. Dantzker DR, Foresman B, Gutierrez G (1991) Oxygen supply and utilization relationships. A reevaluation. Am Rev Respir Dis 143: 675–679
42. Smithies M, Bihari DJ (1993) Delivery dependent oxygen consumption: asking the wrong questions and not getting any answers. Crit Care Med 21: 1622–1626
43. Archie JP (1980) Mathematic coupling of data. A common source of error. Ann Surg 193: 296–303
44. Brigham KL (1986) Role of free radicals in lung injury. Chest 89: 859–863
45. Jones KP, Reynolds SP, Capper SJ, Kalinka S, Edwards JH, Davies DH (1991) Measurement of interleukin-6 in bronchoalveolar lavage fluid by radioimmunoassay: differences between patients with interstitial lung disease and control subjects. Clin Exp Immunol 83: 30–34
46. De Benedetti E, Nicod L, Reber G, Vifian C, de Moerloose P (1992) Procoagulant and fibrinolytic activities in bronchoalveolar fluid of HIV-positive and HIV-negative patients. Eur Respir J 5: 411–417