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Significance of pathologic oxygen supply dependency in critically ill patients: comparison between measured and calculated methods

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Abstract. *Objective:* oxygen supply dependency at normal or high oxygen delivery rate has been increasingly proposed as a hallmark and a risk factor in critical illnesses. We hypothesized that as fas as an adequate oxygen delivery is provided, oxygen consumption, when determined by indirect calorimetry, is not dependent on oxygen delivery in critically ill patients whereas calculated oxygen consumption is associated with artefactual correlation of oxygen consumption and delivery.
Design: oxygen delivery, oxygen consumption and their relationship were analyzed prospectively. Metabolic data gained from both measured and calculated methods were obtained simultaneously before and after volume loading.
Setting: the study was completed in the intensive care unit as part of the management protocol of the patients.
Patients: 32 consecutive patients entered the study and were divided into 3 groups according to a clinical condition known to favour oxygen supply dependency: sepsis syndrome, adult respiratory distress syndrome and acute primary liver failure.
Intervention: the rise in oxygen delivery was obtained by colloid infusion (oxygen flux test) performed in hemodynamically and metabolically stable patients. All were mechanically ventilated. No change in therapy was allowed during the test.
Measurements and results: oxygen consumption was simultaneously evaluated by calculation (Fick Principle) and direct measurement using indirect calorimetry. Oxygen delivery was derived from the cardiac output (thermodilution) and arterial content of oxygen. Oxygen supply dependency was considered while observing an increase in oxygen delivery greater than 45 ml/min·m^2. Irrespective of patient's clinical diagnosis and outcome, measured oxygen uptake remained unaltered by volume infusion whereas both oxygen delivery and calculated oxygen consumption increased significantly. Arterial lactate level > 2 mmol/l and measured oxygen extraction ratio > 25% failed to identify oxygen supply dependency when measured data were considered.
Conclusion: analysis of oxygen uptake, when measured by indirect calorimetry, failed to substantiate oxygen supply dependency in the vast majority of the critically ill patients irrespective of diagnosis and outcome. Mathematical coupling of shared variables accounted for the correlation between oxygen delivery and calculated oxygen consumption.

Key words: Adult respiratory distress syndrome – Acute hepatic failure – Indirect calorimetry – Lactate – Multiple organ failure – Oxygen delivery, Oxygen uptake – Sepsis syndrome

Multiple organ failure (MOF) is a prominent cause of death in the critically-injured patient [1–3]. Sepsis [1, 3] and adult respiratory distress syndromes [2, 4] are the commonest conditions whose course is complicated by the emergence of MOF. Abnormalities of DO_2, VO_2 and their relationship have been postulated as one of the major mechanisms leading to MOF during critical illnesses such as sepsis syndrome, septic shock and ARDS [5–7]. In these latter conditions, imbalance between oxygen demand and delivery has been observed either by an inappropriately low DO_2 as a result of a decrease in cardiac output, hemoglobin concentration and arterial oxygen saturation or by an abnormality of tissue oxyten extraction in the setting of increased oxygen demand and normal or high oxygen delivery [5, 8]. These mechanisms were believed to underly cellular hypoxia, dysfunction and eventually death [5].

However, studies on DO_2/VO_2 relationship remain controversial. A pathologic supply dependency of oxygen uptake in which VO_2 varies directly with DO_2 over a wide range of oxygen supply even at normal or high delivery rates has been reported in sepsis syndrome and ARDS [5, 9–18]. Its features included increased oxygen demand and defective peripheral oxygen extraction with increased critical DO_2 and the accumulation of blood lactate as a marker or anaerobic metabolism and pathologic dependence [8]. Importantly this pathologic dependence as well

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as elevated blood lactate levels were believed to increase the mortality in sepsis syndrome and ARDS by reflecting occult cellular hypoxia [5]. Other investigators, who measured VO_2 by indirect calorimetry either in ARDS or sepsis syndrome, failed to reproduce this pathologic dependence [16, 19–21] and/or disputed its prognostic significance [20, 21]. These discrepancies could be explained by differences either in interventions used to alter DO_2 (oxygen "flux test"), or in the patient population with regard to diagnosis, delay before study and metabolic status. Most importantly in the vast majority of these studies [5, 9–18], VO_2 and DO_2 were calculated, which may explain the dependence of VO_2 on DO_2 by mathematical coupling of the shared variables between DO_2 and VO_2, i.e. cardiac output and arterial oxygen content [22, 23].

Owing to the potential widespread pathophysiologic, prognostic and therapeutic implications of VO_2 dependence on DO_2 in the critically-ill patients both variables were simultaneously and prospectively evaluated by calculation and direct measurement in 3 groups of patients with ARDS, sepsis syndrome and fulminant hepatic failure before and after volume loading. The endpoints of this prospective study were to investigate the influence of the technique used for the VO_2 evaluation (measurement or calculation) on the VO_2/DO_2 relationship and to evaluate the presence of pathologic supply dependance in these patients with regard to their clinical diagnosis and metabolic status, and its prognostic implications with regard to outcome.

Materials and methods

Patient population

Thirty-two consecutive critically-ill patients were included in the study (May 1989 to April 1991). These patients were divided for analysis into 3 groups according to their diagnosis at the time of the oxygen flux test. Multiple evaluations were undertaken in some patients during the acute phase of their clinical course, each result being considered as a separate datum. This strategy was justified by the important spontaneous and treatment-induced changes in hemodynamic and metabolic status in critical illness so that the difference between successive evaluations on a same patient may be as important as between different patients.

Inclusion criteria were a clinical diagnosis of sepsis syndrome, adult respiratory distress syndrome (ARDS) or acute hepatic failure (AHF), hemodynamic/metabolic stability before the oxygen flux test and a minimal increase of DO_2 of 45 ml/min·m^2 after volume loading. The latter figure was arbitrary selected in order to rely on effective oxygen flux tests to define the presence of oxygen supply dependency.

Group 1 included 14 patients (26 O_2 flux tests) with sepsis syndrome according to the criteria as defined by Bone et al. [23] whereas Group 2 included 13 patients (16 O_2 flux tests) with ARDS and Group 3 included 5 patients (10 O_2 flux tests) with AHF. Criteria for ARDS included: a) $PaO_2/FIO_2 < 19.95$ kPa (150 mmHg) with a positive end expiratory pressure applied of at least 5 cmH_2O; b) pulmonary wedge pressure $\leq$ 2.39 kPa (18 mmHg); c) widespread and recent pulmonary infiltrates; d) a compatible underlying disease and, e) no past history of pulmonary impairment. Criteria for AHF included: a) a total serum bilirubin $\geq$ 68.4 µmol/l; b) a prothrombin time $\leq$ 1.6 INR ($\leq$ 40%) and, c) the presence of severe encephalopathy (grade III-IV) within 2 weeks of appearance of first symptoms. All group 1 patients had either bacterial, fungal or viral infection that was confirmed by culture of blood, sputum, urine or a known site of infection. Primary diagnosis in the ARDS group included sepsis confirmed by culture (5 patients), hematological neoplasia (2 patients), acute necrotising pancreatitis (2 patients), graft versus host disease (1 patient), allogenic bone marrow transplantation (1 patient), fulminant hepatic failure (1 patient) and kidney/pancreas transplantation (1 patient). Causes of AHF were non-A non-B viral hepatitis (2 patients), infection with hepatitis-B virus (1 patient), paracetamol intoxication (1 patient) and acute alcoholic hepatitis (1 patient). As far as possible, care was taken to avoid any crossover between these 3 diagnostic patient groups: according to the criteria used to define sepsis syndrome and ARDS and with the standard evaluation techniques, no group 3 patient had ARDS or sepsis syndrome at the time of evaluation. Similarly, no patients with sepsis syndrome had ARDS or AHF at any time during the ICU stay. However, a septic focus and hepatic failure were documented respectively in 5 and 1 patients of the ARDS group.

The severity of disease was assessed at the time of evaluation by the Apache II score [25], the Goris score and the number of system organ failures [26]. The critical condition of these patients was reflected by the global and specific mortality rate. Table 1 summarized the details of the patient population.

Data collection

Dependence of VO_2 on DO_2 was evaluated by increasing DO_2 while observing a change in VO_2 following baseline determinations (oxygen flux test).

A total of 52 O_2 flux tests were selected on the basis of a minimal increase of DO_2 of 45 ml/min·m^2. O_2 flux test was carried out by volume loading. Intravenous infusion of packed-red cells and colloids (fresh frozen plasma or albumin 5%) was used in order to keep the arterial oxygen content as stable as possible. The volume infused ranged from 200 ml to 1085 ml (mean ± SEM: 607 ml ± 18) according to the clinical status of the patients. The mean duration of the infusion was 1.28 h ± 0.06. Before starting the infusion care was taken that the patients were in stable hemodynamic and metabolic conditions. Temperature, heart rate, arterial and right filling pressures, arterial oxygen and carbon dioxide tensions, and continuously measured VO_2 and VCO_2 were checked for stability by arterial blood gas analysis, indirect calorimetry and pulmonary artery catheterization for at least the last 2 h before the O_2 flux test. All patients were mechanically ventilated with a volume-cycled machine, a mean ± SEM FIO_2 of 0.4 ± 0.01 (range: 0.21–0.75) and positive end-expiratory pressure as clinically indicated. They were all sedated with a continuous infusion of an opiate (fentanyl, 100–300 µg/h) and benzodiazepine (midazolam: 2–3 mg/h). All patients required a continuous infusion of dopamine (median dose 6 µg/kg/min) to maintain hemodynamic stability. No change of therapy was allowed during the oxygen flux test and the preseding 2 h. On the day of the test all patients were administered no caloric substrates except for 50 to 100 g glucose/day.

Data analysis

All the data were obtained simultaneously at baseline and after volume infusion.

- Cardiac output (CO; l/min) was measured by the thermodilution technique (pulmonary artery catheter): each reported value was the mean of 3 successive measurements.

Table 1. Patient data at the time of evaluation (Oxygen flux-test)

	Group 1 [b]	Group 2 [b]	Group 3 [b]	Total
Patients (*n*)	14	13	5	32
O_2 Flux-Test (*n*)	26	16	10	52
Age (year) [a]	49 ± 4	55 ± 7	43 ± 5	51 ± 3
Sex (F/M)	5/9	3/10	2/3	10/22
Apache II score [a]	16.1 ± 1.4	20.2 ± 1.0	17.5 ± 1.4	18.0 ± 0.7
Goris score [a]	7.6 ± 0.5	7.8 ± 0.6	5.6 ± 0.6	7.4 ± 0.3
Organ failure (*n*) [a]	4.7 ± 0.2	4.6 ± 0.3	3.6 ± 0.4	4.5 ± 0.2
Mortality *n* (%)	7 (50%)	10 (77%)	2 (40%)	19 (59%)

[a] Results are expressed as mean ± SEM

[b] Group 1 refers to patients with sepsis, group 2 to patients with adult respiratory distress syndrome and group 3 to patients with acute primary liver failure (see text for discussion)

- Arterial and mixed venous O_2 saturation (SaO_2, SvO_2; %) were measured with a Radiometer OSM3 hemoximeter (Radiometer, Copenhagen, Denmark).
- Arterial and mixed venous partial pressure of oxygen (PaO_2, PvO_2; kPa) were measured using standard electrodes (Corning Instruments; Medfield, USA).
- Arterial and mixed venous O_2 content (CaO_2, CvO_2; ml/dl) were calculated from the following equation:
CaO_2 (CvO_2) = SaO_2 ($SvO_2 \times Hb \times 1.39 + 0.0031 \times PaO_2$ (PvO_2).
- The arterio-venous O_2 content difference (AVD; ml/dl) was:
$AVD = CaO_2 - CvO_2$
- Oxygen delivery (DO_2; ml/min) was calculated as follows:
$DO_2 = CO \times CaO_2 \times 10$
- Oxygen uptake (VO_2; ml/min) was measured and calculated. VO_2 was calculated (VO_2c) by the use of the Fick equation:
$VO_2c = CO \times AVD \times 10$

Measured VO_2 (VO_2m), VCO_2 and respiratory quotient (RQ) were obtained simultaneously from continuously performed gas exchange measurements by an automatic metabolic monitor (Deltatrac/Datex®) which has already been validated [27, 28]. Each reported value was the mean of 3 successive measurements obtained immediately after the 3 determinatious of CO, and during blood sampling. This metabolic monitor is based on the open gas circuit principle and consists of a paramagnetic oxygen-sensor, a CO_2 analyser using the infrared absorption technique and a flow meter. The use of the Haldane transformation gives the monitor the opportunity to measure only the expired gas flow, the inspired gas flow being deduced on the assumption that O_2 and CO_2 are the only 2 gases to be exchanged into the lung. Consequently, there is an increase in the VO_2m measurements errors at high FIO_2 levels [29]. This is minimized by the use of a differential paramagnetic oxygen sensor so that the results remain accurate until an FIO_2 level of 75% [28, 30]. The accuracy of VO_2m was regularly assessed by burning a known quantity of ethanol. The increase of VO_2m was considered significant if >6% [27, 28].

- Oxygen extraction ratio was derived from both the indirect (EO_2c) and direct (EO_2m) methods of VO_2 evaluation: $EO_2c = VO_2c/DO_2 = AVD/CaO_2$; $EO_2m = VO_2m/DO_2$.
- Arterial lactate level (normal value < 2 mmol/l) was measured in the arterial blood using an electrochemical method (Roche-Kontron; Basel, Switzerland).
- Values of VO_2m, VO_2c, VCO_2 and DO_2 were adjusted for the total body area (ml/min·m^2). Cardiac index (CI; l/min·m^2) was equal to CO/total body area.

Data were analyzed in the total population and in the 3 definite patient groups according to the following endpoints:

a. Comparison between calculated and measured VO_2 before and after volume loading and analysis of the subsequent DO_2/VO_2 relationship;

b. Evaluation of a pathologic relationship between DO_2 and VO_2 with respect to clinical diagnosis using measured VO_2 as a reference standard and considering as random error changes in $VO_2 \leq 6\%$ from baseline [28, 29];

c. Study of the potential prognostic significance of DO_2/VO_2 relationship with regard to patient's outcome by comparing metabolic data obtained before and after volume loading in patients who died and survived;

d. Assessment of the value of arterial lactate level (>2 mmol/l) and oxygen extraction ratio ($EO_2m > 25\%$) in identifying an oxygen debt by analyzing DO_2/VO_2 relationship with respect of these parameters.

Statistical analysis

Results were expressed as means ± SEM. Owing to uneven distribution of characteristics in some subgroups the Wilcoxon paired rank test was used to compare variables obtained before and after the oxygen flux test as well as to compare the individual changes in calculated VO_2 with that in measured VO_2.

Comparison of metabolic data obtained before and after volume loading between patients who died or survived were carried out using a two-way analysis of variance with adjustment for repeated measurements. Equality of the variance-covariance matrices for the two levels of outcome was assessed by the generalization of the Box's M test. For this purpose the arterial lactate variable needed a logarithmic transformation. The Pearson correlation coefficient was calculated between the rises in DO_2 and both changes in VO_2m and VO_2c respectively. We used the SPSS statistical package.

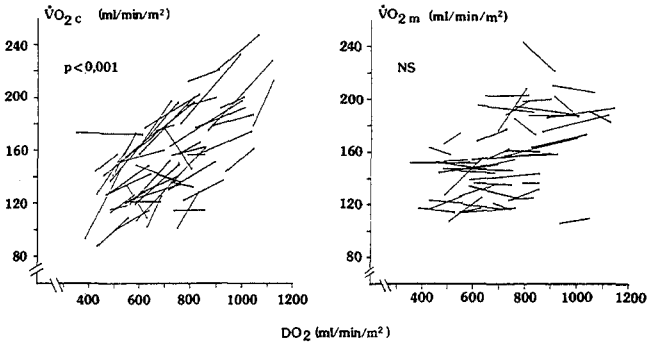

Fig. 1. VO_2 was either calculated (*left*) or measured (*right*) independently from DO_2 (indirect calorimetry) before and after volume loading. Baseline DO_2 was higher than 330 ml/min·m^2 in all the patiens. After completion of volume infusion, significant oxygen supply dependency could be demonstrated with calculated data whereas VO_2m did not change significantly in the patient population. (See text for further details). Abbreviations as in Table 2

Results

Oxygen supply dependency: comparison between measured and calculated VO_2

At the time of evaluation, baseline DO_2 exceeded 330 ml/min·m^2 in all the patients studied. At the end of the volume infusion period, DO_2 increased from 645 ± 22 ml/min·m^2 to 788 ± 23 ml/min·m^2 ($p < 0.001$) on account of a significant increase in cardiac output and to a lesser extent in arterial oxygen content. Similarly calculated VO_2 increased significantly (145 ± 4 ml/min·m^2 to 163 ± 5 ml/min·m^2, $p < 0.001$) whereas measured VO_2 did not change in the patient population (154 ± 4 ml/min·m^2 to 156 ± 4 ml/min·m^2, NS) (Fig. 1). Changes in EO_2m parallelled the ones in VO_2m and DO_2 whereas EO_2c decreased while VO_2c increased. The mean

Table 2. Effects of volume loading on haemodynamic and metabolic parameters in the patient population (n = 32; n tests = 52)

	Baseline	After	Δ	%
DO_2 (ml/min·m^2)	645 ± 22	788 ± 23	143 ± 8*	22.2
CI (ml/min·m^2)	4.373 ± 161	5.122 ± 162	749 ± 57*	17.1
CaO_2 (ml/dl)	14.9 ± 0.2	15.5 ± 0.2	0.6 ± 0.1*	4.0
VO_2m (ml/min·m^2)	154 ± 4	156 ± 4	2 ± 1	1.3
VO_2c (ml/min·m^2)	145 ± 4	163 ± 5	18 ± 2*	12.4
RQ	0.84 ± 0.01	0.84 ± 0.01	0	0
EO_2m (%)	25 ± 0.01	20 ± 0.01	−5 ± 0.004*	−20
EO_2c (%)	23 ± 0.01	21 ± 0.01	−2 ± 0.004*	−8.7
Lactate (mmol/l)	1.53 ± 0.17	1.47 ± 0.14	−0.06 ± 0.06	−3.9
SvO_2 (%)	71 ± 0.78	73 ± 0.62	2 ± 0.45*	2.8

Results are expressed as mean ± SEM

* denotes a p value of less than 0.001

CaO_2: arterial oxygen content; CI: cardiac index; DO_2: oxygen delivery; EO_2c: calculated oxygen extraction ratio; EO_2m: measured oxygen extraction ratio; RQ: respiratory quotient; SvO_2: mixed venous O_2 saturation; VO_2c: calculated oxygen consumption; VO_2m: measured oxygen consumption

arterial lactate level was within the normal range before evaluation and did not change significantly after completion of volume loading (1.53±0.17 to 1.47±0.14 mmol/l, NS). Respiratory quotient remained stable during the volume infusion. Changes in hemodynamic and metabolic data in the patient population during volume loading are outlined in Table 2.

In 8 patients/9 tests (17%) VO_2m increased by more than 6% after volume infusion. When compared to the whole population, this subgroup did not behave differently in terms of clinical diagnosis, outcome and arterial lactate level (Table 3).

Table 3. Clinical and metabolic data of the patients with O_2 supply dependency[a]

Patients (*n*)	8 (3Group 1, 2 Group 2; 3 Group 3)			
Mortality (*n*)	4			
Tests (*n*)	9			
	Baseline	After	Δ	(%)
DO_2 (ml/min·m²)	652±52	822±66	170±21*	26.1
VO_2m (ml/min·m²)	143±9	159±10	16±3*	11.2
VO_2c (ml/min·m²)	139±11	152±14	13±8	9.4
Lactate (mmol/l)	1.33±0.29	1.23±0.27	−0.1±0.03	−0.08
SvO_2 (%)	74±1.45	76±1.03	2±0.93	2.7

[a] O_2 supply dependency defined by an increase in VO_2>6%
Results are expressed as mean ±SEM
* denotes a *p* value of less than 0.01
Abbreviations as in Tables 1 and 2

Table 4. Effects of volume loading on haemodynamic and metabolic parameters: influence of clinical diagnosis

	Group 1	Group 2	Group 3
Patients (*n*)	14	13	5
Tests (*n*)	26	16	10
DO_2 (ml/min·m²)			
– Baseline	704±32	580±30	592±51
– After	850±33	719±28	738±57
– Δ (%)	146±11*** (21)	139±17*** (24)	146±23*** (25)
VO_2m (ml/min·m²)			
– Baseline	163±5	151±8	138±9
– After	164±5	153±8	142±8
– Δ (%)	1±2 (0.6)	2±3 (1.3)	4±3 (2.9)
VO_2c (ml/min·m²)			
– Baseline	157±5	140±7	124±11
– After	175±6	155±8	143±11
– Δ (%)	18±3*** (11.5)	15±5*** (10.7)	19±8* (15.3)
Lactate (mmol/l)			
– Baseline	1.24±1.3	1.97±0.44	1.57±0.35
– After	1.33±0.15	1.69±0.33	1.47±0.33
– Δ (%)	0.09±0.01 (7.3)	−0.28±0.15 (−14.2)	−0.10±0.14 (−6.4)
SvO_2 (%)			
– Baseline	71±0.80	69±1.91	74±1.15
– After	73±0.79	71±1.27	76±0.96
– Δ (%)	2±0.43*** (2.8)	2±1.11 (2.9)	2±1.07 (2.7)

Results are expressed as mean ±SEM
* $p<0.05$; ** $p<0.01$; *** $p<0.001$
Abbreviations as in Table 2

Oxygen supply dependency: VO_2c versus VO_2m with respect to clinical diagnosis (Table 4)

Classification of the patients according to their clinical diagnosis at the time of the test did not modify the previous analysis. After volume loading and irrespective to patient's condition (sepsis syndrome, ARDS or liver failure) DO_2 and VO_2c increased significantly whereas VO_2m remained unaltered (Fig. 2).

Oxygen supply dependency: impact on patient's outcome

Patients were further divided for analysis according to outcome (Table 5). DO_2, VO_2m and VO_2c were significantly greater and lactates conversely lower in survivors than in non-survivors, either before or after volume load-

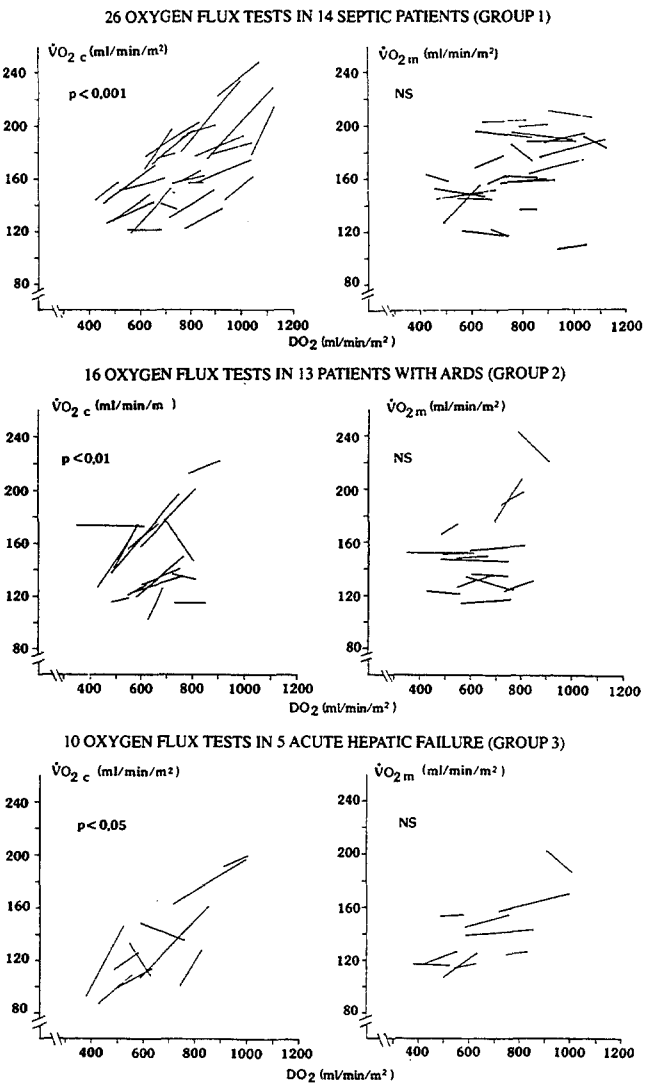

Fig. 2. Irrespective of the clinical diagnosis at the time of evaluation, i.e. sepsis (*top*), ARDS (*middle*) or acute liver failure (*bottom*), changes in VO_2m (*right*) were unaffected by volume infusion whereas calculated data (*left*) denoted a pathologic oxygen supply dependency. Abbreviations as in Table 1 and 2

ing. Changes in DO_2, VO_2c, VO_2m and arterial lactate levels failed to identify those who ultimately died (Table 5). Irrespective of patient's outcome VO_2m remained unaffected by volume loading (144 ± 6 to 147 ± 6 ml/min·m^2 in non-survivors vs 165 ± 6 to 167 ± 5 ml/min·m^2 in survivors) whereas both DO_2 and VO_2c increased significantly (Fig. 3).

Oxygen supply dependency: predictive value of arterial lactate level and oxygen extraction ratio

In order to assess the predictive value of arterial lactate level > 2 mmol/l and $EO_2m > 25\%$ in identifying an oxygen debt and oxygen supply dependency, DO_2/VO_2 relationship was analyzed with respect of these parameters at the time of evaluation. Of 32 patients 9 (28%) had blood lactates > 2 mmol/l. AHF was present in 6 of these patients and MOF in all of them. For both elevated and low arterial lactate levels dependence of VO_2 on DO_2 could only be demonstrated when VO_2c was considered (Table 6). The same held true for EO_2m (Table 6). On the contrary, whatever the value of EO_2m and arterial lactate, VO_2m failed to substantiate any supply dependency.

Discussion

With the advance in the intensive care management during the initial resuscitative period, MOF has become in recent years the major cause of prolonged intensive care unit stay, morbidity and mortality for the critically-ill patient [1–3]. Critical insults such as sepsis syndrome, ARDS and acute liver failure are known risk factors for the development of MOF [1–3]. Although the pathogenesis of MOF is still a matter of speculation one hypothesis is that during the resuscitative phase alterations in microcirculatory physiology and local activation of cellular elements secondary to the initial injury mediates inadequate microcirculatory flow, defective peripheral oxygen extraction and occult tissue hypoxia that preceed the transition to overt organ dysfunctions [6, 31, 32].

Several investigators have pointed out that abnormalities in the relationship between DO_2 and VO_2 could unmask this oxygen debt [5, 17]. Pathologic oxygen supply dependency in which VO_2 varies in the same direction with a change in DO_2, even during hyperdynamic conditions, has been increasingly reported to underly cellular hypoxia in sepsis syndrome and ARDS and was suggested to herald MOF and to predict patient's outcome [5]. Thus, this abnormal dependence of VO_2 on DO_2 above the normal critical level of oxygen supply and its correlatives, defective oxygen extraction ability and increased blood lactate levels should porten obvious pathophysiologic, prognostic and therapeutic implications.

In this prospective study, using directly measured VO_2 before and after volume loading to increase DO_2, we demonstrated that pathologic supply dependency was rather uncommon in 3 groups of patients whose clinical condition was believed to favour this dependence. In addition, neither measured oxygen extraction ratio nor arte-

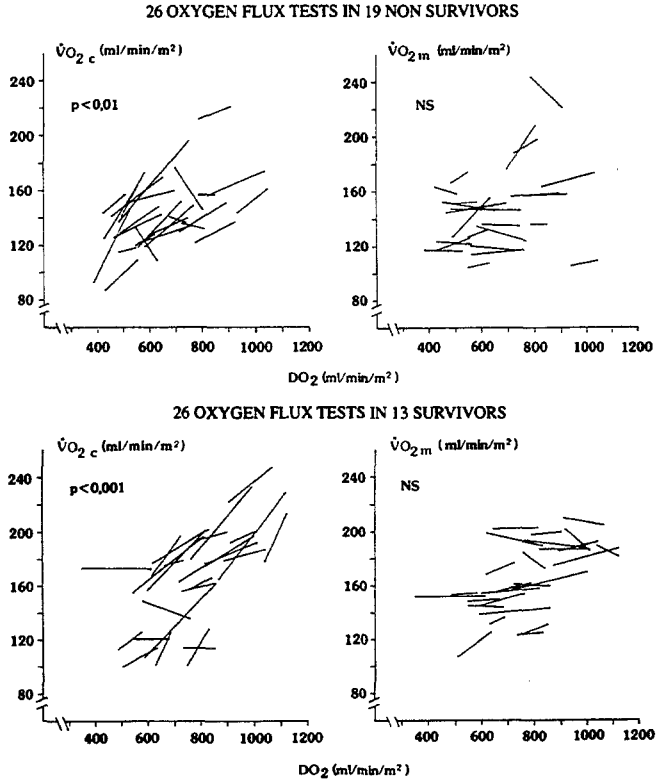

Fig. 3. Patient's outcome could not be predicted either by changes in VO_2c (*left*) or VO_2m (*right*) after volume loading. Either in non-survivors (top) or survivors (bottom) VO_2m remained unaltered whereas VO_2c increased with DO_2. Abbreviations as in Table 2

Table 5. Effects of volume loading on haemodynamic and metabolic parameters: impact on patient's outcome

	Non-survivors	Survivors
Patients (*n*)	19	13
Tests (*n*)	26	26
DO_2 (ml/min·m^2)		
– Baseline	594 ± 29	696 ± 31†
– After	728 ± 30	848 ± 31††
– Δ (%)	134 ± 10*** (23)	153 ± 13*** (22)
VO_2m (ml/min·m^2)		
– Baseline	144 ± 6	165 ± 6†
– After	147 ± 6	167 ± 5†
– Δ (%)	3 ± 2 (2)	2 ± 2 (1)
VO_2c (ml/min·m^2)		
– Baseline	135 ± 5	156 ± 6††
– After	150 ± 5	176 ± 8††
– Δ (%)	15 ± 4** (11)	20 ± 4*** (13)
Lactate (mmol/l)		
– Baseline	2.02 ± 0.29	1.05 ± 0.11††
– After	1.93 ± 0.24	1.01 ± 0.8††
– Δ (%)	-0.09 ± 0.11 (−5)	-0.04 ± 0.07 (−4)
SvO_2 (%)		
– Baseline	71 ± 0.94	71 ± 1.26
– After	73 ± 0.93	73 ± 0.82
– Δ (%)	2 ± 0.48*** (2.8)	2 ± 76* (2.8)

Results are expressed as mean ± SEM
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ when baseline data were compared with values obtained after volume infusion.
† $p < 0.05$; †† $p < 0.01$; ††† $p < 0.001$ when differences between survivors and non-survivors were considered.
Abbreviations as in Table 2

Table 6. Oxygen supply dependency: predictive value of arterial lactate level (mmol/l) and measured oxygen extraction ratio

	Lactate > 2	Lactate ≤ 2	$EO_2m > 25\%$	$EO_2m \leq 25\%$
Patients (*n*)	9	23	14	18
Tests (*n*)	10	42	21	31
DO_2 (ml/min·m²)				
– Baseline	586 ± 47	658 ± 28	524 ± 24	726 ± 24
– After	698 ± 49	809 ± 25	672 ± 25	867 ± 26
– Δ (%)	112 ± 11** (19)	151 ± 10*** (23)	148 ± 13*** (28)	141 ± 11*** (19)
VO_2m (ml/min·m²)				
– Baseline	142 ± 9	157 ± 5	157 ± 7	153 ± 6
– After	145 ± 8	159 ± 5	159 ± 6	155 ± 5
– Δ (%)	3 ± 4 (2)	2 ± 1 (1)	2 ± 2 (1)	2 ± 2 (1)
VO_2c (ml/min·m²)				
– Baseline	128 ± 8	149 ± 5	141 ± 6	148 ± 6
– After	141 ± 9	168 ± 5	163 ± 7	163 ± 7
– Δ (%)	13 ± 5* (10)	19 ± 3*** (13)	22 ± 4*** (16)	15 ± 4*** (10)
Lactate (mmol/l)				
– Baseline	3.51 ± 0.47	1.06 ± 0.06	1.63 ± 0.29	1.46 ± 0.20
– After	3.17 ± 0.32	1.06 ± 0.06	1.40 ± 0.21	1.52 ± 0.19
– Δ (%)	0.34 ± 0.28 (−10)	0 (0)	−0.23 ± 0.11* (−14)	0.06 ± 0.07 – (4)
SvO_2 (%)				
– Baseline	73 ± 1.22	71 ± 0.91	67 ± 1.33	73 ± 0.63
– After	75 ± 1.25	73 ± 0.69	70 ± 0.91	75 ± 0.55
– Δ (%)	2 ± 0.87* (2.7)	2 ± 0.52*** (2.8)	3 ± 0.96** (4.5)	2 ± 0.38*** (2.7)

Results are expressed as mean ± SEM
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$
Abbreviations as in Table 2

rial lactate level did predict delivery dependence of VO_2 at the time of evaluation. Hence patient's outcome was unrelated to the relationship of VO_2 to DO_2.

Several factors may account for the discrepancies between previous reports [5, 9–18] and this study. Differences in methods used to change DO_2 could affect the behavior of VO_2 due to the own drug-induced changes in metabolic rate and oxygen demand. This metabolic effect could account for a primary change in VO_2 and secondary compensatory change in DO_2 to match oxygen demand. Differences in patient population with respect to clinical diagnosis, hemodynamic status and microcirculatory condition at the time of evaluation are of paramount importance. Most studies on DO_2/VO_2 relationship have been conducted in patients with sepsis syndrome and ARDS [5, 9–21]. Since sepsis is a common cause and complication of ARDS these two conditions are closely associated [1, 2]. Whereas the effect of human sepsis on critical DO_2 is unknown, experimental animal models demonstrated that sepsis syndrome increased the critical DO_2 by increasing oxygen demand and by diminishing the ability of tissues to extract oxygen [33, 34]. Microembolisation, loss of autoregulation of microcirculatory blood flow and endothelial cells injury were mechanisms proposed to account for this extraction defect [31]. Therefore, inhomogeneous groups of patients, particularly in the ARDS population, might have critically influenced the relationship between DO_2 and VO_2 depending on the coexistence of sepsis, the magnitude of peripheral extraction defect and the actual oxygen demand. In addition, in the setting of a dysfunctional microcirculatory environment, which is a common condition in many of these patients, "normal" dependence of VO_2 on DO_2 could have relied on an inadequately treated hypodynamic state and truly supply-driven ischemia as a result of hypovolemia or myocardial dysfunction. Therefore, to overcome these potential confounding variables care was taken in this study to assess the presence of oxygen supply dependency in homogeneous groups of patients with regards to clinical diagnosis, to alter DO_2 by an identical intervention and to provide all the patients with an adequate cardiac output.

Finally, the method of VO_2 determination played a major role in the finding of oxygen supply dependency. The studies which addressed the issue of the dependence of VO_2 on DO_2 in sepsis syndrome and ARDS consistently demonstrated pathology supply dependency whenever VO_2 was calculated [5, 9–18]. In contrast, when oxygen uptake was measured directly, VO_2 was usually not correlated with DO_2 either in sepsis syndrome or ARDS [16, 19–21]. In this study VO_2 was systematically evaluated by calculation and direct measurement before and after volume loading. Whereas calculated data almost consistently led to pathologic supply dependency, the latter was supported by direct measurement of VO_2 in only 17% of the tests.

Unlike some previous studies in which supply dependence of VO_2 was assessed using calculated VO_2 [9, 11, 15, 35] neither EO_2m nor arterial lactate level did predict delivery dependence of VO_2 when measured oxygen consumption was considered. Similarly, Ronco et al. [21] reported that increased lactate did not predict dependence of measured VO_2 on DO_2 in patients with ARDS. Since blood lactate levels reflected the balance between peripheral production and hepatic elimination, elevation of blood lactate might not always be indicative of tissue hypoxia. In particular the 9 patients with arterial lactate > 2 mmol/l at the time of evaluation had severe liver dysfunction due to either primary hepatic failure or as part of MOF. So defective hepatic clearance rather than hypoxic driven-peripheral overproduction accounted for hyperlactacidemia in the subgroup. Further explanations for the lack of correlation between blood lactate and oxygen supply dependency include the inability of tissues to receive or use oxygen [36] and inactivation of pyruvate deshydrogenase which would increase both lactate and pyruvate in the same proportion without resorting to tissue hypoxia [8].

Although at the time of evaluation survivors had significantly greater DO_2 and VO_2m and lower blood lactate than non-survivors [37], unlike other investigators [5] we could not demonstrate any relation between patient's outcome and DO_2/VO_2 relationship. Oxygen flux test by volume loading did not reveal a supply dependency in the group of non-survivors. Nevertheless analysis of individual data on DO_2/VO_2 relationship enabled the selection of 8 patients in whom pathologic supply dependency could be demonstrated. This subgroup did not differ

from the whole population in terms of clinical diagnosis, outcome, baseline DO_2 and arterial lactate. So, plateau levels of VO_2m could be observed in the majority of the patients irrespective of clinical diagnosis, baseline lactate, EO_2m and outcome.

These data support that, provided a satisfactory DO_2 was ensured to the patient, pathologic oxygen supply dependency as assessed by directly measured VO_2 was uncommon in conditions which were suggested to favour this dependency and the emergence of MOF. Analysis of DO_2/VO_2 relationship based on calculated VO_2 was flawed by mathematical coupling of shared variables. Reliance on EO_2m and lactate level as a guide to assess tissue oxygenation and to tailor therapy and on DO_2/VO_2 relationship to predict patient's outcome may be misleading.

As global tissue hypoxia is absent in the majority of these patients, further studies are warranted in order to obtain information on potential organ system hypoxia as a culprit in the emergence of MOF.

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