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 far 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·m². 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 DO2, VO2 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 DO2 as a result of a decrease in cardiac output, hemoglobin concentration and arterial oxygen saturation or by an abnormality of tissue oxygen 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 DO2/VO2 relationship remain controversial. A pathologic supply dependency of oxygen uptake in which VO2 varies directly with DO2 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 DO2 and the accumulation of blood lactate as a marker of anaerobic metabolism and pathologic dependence [8]. Importantly this pathologic dependence as well...
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 VO2 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 DO2 (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], VO2 and DO2 were calculated, which may explain the dependence of VO2 on DO2 by mathematical coupling of the shared variables between DO2 and VO2, i.e. cardiac output and arterial oxygen content [22, 23].

Owing to the potential widespread pathophysiologic, prognostic and therapeutic implications of VO2 dependence on DO2 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 VO2 evaluation (measurement or calculation) on the VO2/DO2 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 the 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 DO2 of 45 ml/min·m² 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 O2 flux tests) with sepsis syndrome according to the criteria as defined by Bone et al. [23] whereas Group 2 included 15 patients (16 O2 flux tests) with ARDS and Group 3 included 5 patients (10 O2 flux tests) with AHF. Criteria for ARDS included: a) PaO2/FIO2 < 199.5 kPa (150 mmHg) with a positive end expiratory pressure applied of at least 5 cmH2O; b) pulmonary wedge pressure ≤ 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 ≥ 68.4 μmol/l; b) a prothrombin time ≤ 1.6 INR (≤ 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 necroizing pancreatitis (2 patients), graft versus host disease (1 patient), allogetic 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 AHF, acute ARDS and AHF in 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 VO2 on DO2 was evaluated by increasing DO2 while observing a change in VO2 following baseline determinations (oxygen flux test).

A total of 52 O2 flux tests were selected on the basis of a minimal increase of DO2 of 45 ml/min·m². O2 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 patient were in stable hemodynamic and metabolic conditions. Temperature, heart rate, arterial and right filling pressures, arterial oxygen and carbon dioxide tensions, and continuously measured VO2 and VCO2 were checked for stability by arterial blood gas analysis, indirect calorimetry and pulmonary artery catheterization for at least the last 2 h before the O2 flux test. All patients were mechanically ventilated with a volume-cycled machine, a mean ± SEM FIO2 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 preceding 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   | Patients (n) | O2 Flux Test (n) | Age (year) | Sex (F/M) | Apache II score | Goris score | Organ failure (n) | Mortality (n) |
|---------|--------------|-----------------|------------|-----------|----------------|-------------|------------------|--------------|
| Group 1 | 14           | 16              | 49 ± 4     | 5/9       | 16.1 ± 1.4     | 7.6 ± 0.5   | 4.7 ± 0.2        | 7 (50%)      |
| Group 2 | 13           | 16              | 55 ± 7     | 3/10      | 20.2 ± 1.0     | 7.8 ± 0.6   | 4.6 ± 0.3        | 10 (77%)     |
| Group 3 | 5            | 10              | 43 ± 5     | 2/3       | 17.5 ± 1.4     | 5.6 ± 0.6   | 3.6 ± 0.4        | 2 (40%)      |
| Total   | 32           | 52              | 52 ± 3     | 102/22    | 18.0 ± 0.7     | 7.4 ± 0.3   | 4.5 ± 0.2        | 19 (59%)     |

* 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 O₂ saturation (SaO₂, SvO₂ %) were measured with a Radiometer OSM3 hemoximeter (Radiometer, Copenhagen, Denmark).

Arterial and mixed venous partial pressure of oxygen (PaO₂, PvO₂; kPa) were measured using standard electrodes (Corning Instruments; Medfield, USA).

Arterial and mixed venous O₂ content (CaO₂, CvO₂; ml/dl) were calculated from the following equation:

\[
CaO₂ (CvO₂) = SaO₂ (SvO₂ × Hb × 1.39 + 0.0031 × PaO₂ (PvO₂).
\]

The arterio-venous O₂ content difference (AVD; ml/dl) was:

\[
AVD = CaO₂ - CvO₂
\]

Oxygen delivery (DO₂; ml/min) was calculated and measured. VO₂ was calculated (VO₂c) by the use of the Fick equation:

\[
VO₂c = CO × AVD \times 10
\]

Measured VO₂ (VO₂m), VCO₂ 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 determinations of CO₂ and during blood sampling. This metabolic monitor is based on the open gas circuit principle and consists of a paramagnetic oxygen-sensor, a CO₂ 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 O₂ and CO₂ are the only 2 gases to be exchanged into the lung. Consequently, there is an increase in the VO₂m measurements errors at high FIO₂ levels [29]. This is minimized by the use of a differential paramagnetic oxygen sensor so that the results remain accurate until an FIO₂ level of 75% [28, 30]. The accuracy of VO₂m was regularly assessed by burning a known quantity of ethanol. The increase of VO₂m was considered significant if > 6% [27, 28].

Oxygen extraction ratio was derived from both the indirect (EO₂c) and direct (EO₂m) methods of VO₂ evaluation:

\[
EO₂c = VO₂c / DO₂
\]

Arterial lactate level (normal value < 2 mmol/l) was measured in the arterio-venous blood using an electrochemical method (Roche-Kontron; Basel, Switzerland).

Values of VO₂m, VO₂c, VCO₂ and DO₂ were adjusted for the total body area (ml/min·m²). Cardiac index (CI; l/min·m²) 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 VO₂ before and after volume loading and analysis of the subsequent DO₂/VO₂ relationship;

b. Evaluation of a pathologic relationship between DO₂ and VO₂ with respect to clinical diagnosis using measured VO₂ as a reference standard and considering as random error changes in VO₂ < 60% from baseline [28, 29];

c. Study of the potential prognostic significance of DO₂/VO₂ 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 (> 2.2 mmol/l) and oxygen extraction ratio (EO₂m > 25%) in identifying an oxygen debt by analyzing DO₂/VO₂ 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 VO₂ with that in measured VO₂.

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 DO₂ and both changes in VO₂m and VO₂c respectively. We used the SPSS statistical package.

Results

Oxygen supply dependency: comparison between measured and calculated VO₂

At the time of evaluation, baseline DO₂ exceeded 330 ml/min·m² in all the patients studied. At the end of the volume infusion period, DO₂ increased from 645 ± 22 ml/min·m² to 788 ± 23 ml/min·m² (p < 0.001) on account of a significant increase in cardiac output and to a lesser extent in arterial oxygen content. Similarly calculated VO₂ increased significantly (145 ± 4 ml/min·m² to 163 ± 5 ml/min·m², p < 0.001) whereas measured VO₂ did not change significantly in the patient population (154 ± 4 ml/min·m² to 156 ± 4 ml/min·m², NS) (Fig. 1). Changes in EO₂m paralleled the ones in VO₂m and DO₂ whereas EO₂c decreased while VO₂c 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     | %  |
|------------------|-------------------|------------------|-------|----|
| DO₂ (ml/min·m²)  | 645 ± 22          | 788 ± 23         | 143 ± 8* | 22.2 |
| CI (ml/min·m²)   | 4.373 ± 161       | 5.122 ± 162      | 749 ± 57* | 17.1 |
| CaO₂ (ml/dl)     | 14.9 ± 0.2        | 15.5 ± 0.2       | 0.6 ± 0.1* | 4.0 |
| VO₂m (ml/min·m²)| 154 ± 4           | 156 ± 4          | 2 ± 1  | 1.3 |
| VO₂c (ml/min·m²)| 145 ± 4           | 163 ± 5          | 18 ± 2* | 12.4 |
| RQ               | 0.84 ± 0.01       | 0.84 ± 0.01      | 0     | 0   |
| EO₂m (%)         | 25 ± 0.01         | 20 ± 0.01        | -5 ± 0.004* | -20 |
| EO₂c (%)         | 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 |
| SvO₂ (%)         | 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

CaO₂: arterial oxygen content; CI: cardiac index; DO₂: oxygen delivery; EO₂c: calculated oxygen extraction ratio; EO₂m: measured oxygen extraction ratio; RQ: respiratory quotient; SvO₂: mixed venous O₂ saturation; VO₂c: calculated oxygen consumption; VO₂m: 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%) VO2m 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).

Oxygen supply dependency: VO2c versus VO2m 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) DO2 and VO2c increased significantly whereas VO2m remained unaltered (Fig. 2).

Oxygen supply dependency: impact on patient’s outcome

Patients were further divided for analysis according to outcome (Table 5). DO2, VO2m and VO2c were significantly greater and lactates conversely lower in survivors than in non-survivors, either before or after volume loading.

Table 3. Clinical and metabolic data of the patients with O2 supply dependency

| Patients (n) | 8 (3 Group 1, 2 Group 2; 3 Group 3) |
| Mortality (n) | 4 |
| Tests (n) | 9 |

|Baseline | After | Δ (%) |
|DO2 (ml/min·m²) | 652 ± 52 | 822 ± 66 | 170 ± 21* | 26.1 |
|VO2m (ml/min·m²) | 143 ± 9 | 159 ± 10 | 16 ± 3* | 11.2 |
|VO2c (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 |
|SvO2 (%) | 74 ± 1.45 | 76 ± 1.03 | 2 ± 0.93 | 2.7 |

* O2 supply dependency defined by an increase in VO2 > 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 hemodynamic and metabolic parameters: influence of clinical diagnosis

| Group 1 | Group 2 | Group 3 |
|-----------------|-----------------|-----------------|
| Patients (n) | 14 | 13 | 5 |
| Tests (n) | 26 | 16 | 10 |
| DO2 (ml/min·m²) | | | |
| – Baseline | 704 ± 32 | 580 ± 30 | 592 ± 51 |
| – After | 850 ± 33 | 719 ± 28 | 738 ± 57 |
| – Δ (%) | 146 ± 11 *** | 139 ± 17 *** | 146 ± 23 *** |
| | (21) | (24) | (25) |
| VO2m (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) |
| VO2c (ml/min·m²) | | | |
| – Baseline | 157 ± 5 | 140 ± 7 | 124 ± 11 |
| – After | 175 ± 6 | 155 ± 8 | 143 ± 11 |
| – Δ (%) | 18 ± 3 *** | 15 ± 5 *** | 19 ± 8 * |
| | (11.5) | (10.7) | (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 | -0.28 ± 0.15 | -0.10 ± 0.14 |
| | (7.3) | (-14.2) | (-6.4) |
| SvO2 (%) | | | |
| – 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 ± 1.11 | 2 ± 1.07 |
| | (2.8) | (2.9) | (2.7) |

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

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 VO2m (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 ($144\pm6$ to $147\pm6$ ml/min·m$^2$ in non-survivors vs $165\pm6$ to $167\pm5$ 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 preced 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 cor-

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-

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**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†   |
| - $\Delta$ (%)  | 134±10*** (23)| 153±13*** (22) |
| $VO_2m$ (ml/min·m$^2$) |            |           |
| - Baseline       | 144±6         | 165±6†    |
| - After          | 147±6         | 167±5†    |
| - $\Delta$ (%)  | 3±2 (2)       | 2±2 (1)   |
| $VO_2C$ (ml/min·m$^2$) |        |           |
| - Baseline       | 135±5         | 156±6†‡   |
| - After          | 150±5         | 176±8†‡   |
| - $\Delta$ (%)  | 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±0.08† |
| - $\Delta$ (%)  | −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   |
| - $\Delta$ (%)  | 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

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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.
particularly in the ARDS population, might have critical importance. Most studies
between previous reports [5, 9-18] and this study. Differences in patient population with respect to
mechanisms proposed to account for this extraction de-
Microembolisation, loss of autoregulation of microcir-
sepsis on critical DO2 is unknown, experimental animal
ary compensatory change in DO2 to match oxygen de-
metabolic rate and oxygen demand. This metabolic effect
behavior of VO2 due to the own drug-induced changes in

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

| Lactate > 2 | Lactate ≤ 2 | EO2m > 25% | EO2m ≤ 25% |
|-------------|-------------|------------|------------|
| Patients (n) | 9           | 23         | 14         | 18         |
| Tests (n)    | 10          | 42         | 21         | 31         |

DO2 (ml/min·m²)

- Baseline 586 ± 47
- After 698 ± 49
- Δ (%) 112 ± 11** 151 ± 10*** 148 ± 13*** 141 ± 11***

VO2m (ml/min·m²)

- Baseline 142 ± 9
- After 145 ± 8
- Δ (%) 3 ± 2 (2) 2 ± 1 (1) 2 ± 2 (1) 2 ± 2 (1)

VO2c (ml/min·m²)

- Baseline 128 ± 8
- After 141 ± 9
- Δ (%) 13 ± 5* 19 ± 3*** 22 ± 4*** 15 ± 4***

Lactate (mmol/l)

- Baseline 3.5 ± 0.47
- After 3.17 ± 0.32
- Δ (%) 0.34 ± 0.28

SvO₂ (%)

- Baseline 73 ± 1.22
- After 75 ± 1.25
- Δ (%) 2 ± 0.87*

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

Several factors may account for the discrepancies be-
tween previous reports [5, 9-18] and this study. Differences in methods used to change DO2 could affect the behavior of VO2 due to the own drug-induced changes in metabolic rate and oxygen demand. This metabolic effect could account for a primary change in VO2 and secondary compensatory change in DO2 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 DO2/VO2 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 DO2 is unknown, experimental animal models demonstrated that sepsis syndrome increased the critical DO2 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 critical-
ly influenced the relationship between DO2 and VO2 de-
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 condi-
tion in many of these patients, “normal” dependence of VO2 on DO2 could have relied on an inadequately treat-
ed hypodynamic state and truly supply-driven ischemia as a result of hypovolemia or myocardial dysfunction. Therefore, to overcome these potential confounding vari-
ables 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 DO2 by an identical intervention and to provide all the patients with an adequate cardiac output.

Finally, the method of VO2 determination played a major role in the finding of oxygen supply dependency. The studies which addressed the issue of the dependence of VO2 on DO2 in sepsis syndrome and ARDS consistently demonstrated pathology supply dependency whenever VO2 was calculated [5, 9–18]. In contrast, when ox-

iary production and hepatic elimination, elevation of
blood lactate might not always be indicative of tissue hypoxia. In particular the 9 patients with arterial lac-
tate > 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 oxy-
gen 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 tis-
sue hypoxia [8].

Although at the time of evaluation survivors had sig-
nificantly greater DO2 and VO2m and lower blood lac-
tate than non-survivors [37], unlike other investigators [5] we could not demonstrate any relation between patient’s outcome and DO2/VO2 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 DO2/VO2 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 DO2 and arterial lactate. So, plateau levels of VO2m could be observed in the majority of the patients irrespective of clinical diagnosis, baseline lactate, EO2m and outcome.

These data support that, provided a satisfactory DO2 was ensured to the patient, pathologic oxygen supply dependency as assessed by directly measured VO2 was uncommon in conditions which were suggested to favour this dependency and the emergence of MOF. Analysis of DO2/VO2 relationship based on calculated VO2 was flawed by mathematical coupling of shared variables. Reliance on EO2m and lactate level as a guide to assess tissue oxygenation and to tailor therapy and on DO2/VO2 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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