OXYGEN UPTAKE, ENERGY EXPENDITURE AND OXYGEN SUPPLY DEPENDENCY

physical, physiological and clinical aspects

ZUURSTOFOPNAME, ENERGIEVERBRUIK EN HET VERBAND TUSSEN ZUURSTOFOPNAME EN ZUURSTOFAANBOD

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CONTENTS

Chapter 1

INTRODUCTION

1.1 Aerobic energy metabolism

In living organisms a constant expenditure of energy is required for the maintenance of body functions. Energy is expended for the maintenance of chemical and electrical gradients across cellular membranes and for the synthesis of macromolecules (proteins, glycogen, triglycerides). The energy expenditure required to maintain cellular integrity and function is called basal metabolism, and is determined by the amount of metabolically active body mass. Additional energy above basal energy expenditure is expended in mental and physical activity and in the process of digestion and absorption of ingested foodstuffs. The basal metabolism of patients with burns, fever, fractures, major trauma or after surgery is increased (4,35,43,44).

The energy requirement of man is met by the chemical energy content of carbohydrates, fat and protein. In aerobic energy metabolism these fuels are oxidized, whereby oxygen is consumed and carbon dioxide is produced. For the maintenance of energy supply by aerobic energy metabolism the organism is therefore dependent on the supply of calories and the supply of oxygen from the environment.

Healthy humans have fuelstores in the form of glycogen, fat and protein, so that caloric intake less than caloric expenditure can be tolerated for longer periods. In patients both underfeeding and overfeeding have adverse effects (2,3,19,29,45,53,54). On the basis of these findings it has been advocated to replace a patient's caloric expenditure with an equal caloric supply (2), which requires assessment of an individual patient's energy expenditure by methods described in section 1.2.

In contrast to the ample calorie-stores, the body's oxygen store is small, and only adequate for oxygen demand during several minutes. To maintain aerobic metabolism a continuous oxygen supply and uptake from the environment is required.

Under physiologic conditions, oxygen supply and oxygen extraction from blood are regulated to adapt oxygen uptake to oxygen demand. When oxygen supply is decreased, e.g. due to heart or lung failure, or inability of the blood to carry sufficient oxygen, oxygen extraction increases and maintains oxygen uptake. However, as oxygen supply decreases further, a critical level of oxygen supply will be reached where oxygen extraction can no longer increase in proportion to the reduced oxygen supply, and oxygen uptake will decrease (9). In critically ill patients it has been described that oxygen uptake is limited by oxygen supply, above the normal critical oxygen supply level (5,6,13,22,26,33,34,37). It is assumed that this indicates inadequate tissue oxygenation and is related to multiple systems organ failure and mortality in critically ill patients (6,22,33).

To detect inadequate tissue oxygenation and evaluate the effect of therapy to increase oxygen supply, analysis of the relationship between oxygen uptake and oxygen supply in critically ill patients has been recommended (6,59). The methods to determine oxygen uptake are described in section 1.2.

1.2 Assessment of energy metabolism

An individual subject's caloric requirement may be determined either by estimation on the basis of an empiric formula or by measurement with direct or indirect calorimetry.

Empiric formulae to predict energy expenditure usually have been derived from measurements of energy expenditure in healthy subjects. A widely used predictive equation is the Harris-Benedict formula which uses body weight, height, sex and age to estimate body mass (25):

Energy expenditure = 66 + 13.8W + 5.0H - 6.8A (males)
Energy expenditure = 665 + 9.7W + 1.8H - 4.7A (females)

Energy expenditure in kcal/day, W = weight (kg), H = height (cm) and A = age (yr)

Empiric formulae have been reported to be inaccurate for prediction of energy expenditure in patients (17,24,38,39,42,43, 46,51) and healthy controls (1,11,17). Therefore, the routine measurement of energy expenditure has been advocated (17,31).

Energy expenditure can be measured by direct or indirect calorimetry. In direct calorimetry the heat loss from the body is measured. During direct calorimetry the measured subject must remain in an airtight chamber, which limits the clinical use of this technique. The heat released from the body arises mainly from oxidative processes, and the energy equivalent (in kcal) of one litre oxygen consumption is known (23). In indirect calorimetry energy expenditure is calculated from oxygen uptake and carbon dioxide production (61):

Energy expenditure (kcal/day) = 3.9 $\dot{V}O_2$ + 1.1 $\dot{V}CO_2$ - 2.17 N

$\dot{V}O_2$ = oxygen uptake and $\dot{V}CO_2$ = carbon dioxide output (both in l/day, STPD), and N = urea nitrogen production (gram/day).

In this thesis the nitrogen correction (-2.17 N) was omitted, which avoids the need for 24-h urine collection to determine urea nitrogen production, at the cost of an error of less than 2% (64). Head et al. compared energy expenditure determined by direct and indirect calorimetry in spontaneously breathing patients and found a mean difference between the two methods of less than 1% (27). Webb et al. found agreement within 3% in subjects in "energy balance" (60).

Indirect calorimetry depends on measurement of oxygen uptake and/or carbon dioxide production. Oxygen uptake can be calculated using the Fick equation for oxygen, or measured by respiratory gas analysis. Using the Fick equation, oxygen uptake is calculated as the product of cardiac output and arteriovenous oxygen content difference:

$$\dot{V}O_2 = CO \times (C_aO_2 - C\bar{v}O_2)$$

$\dot{V}O_2$ = oxygen uptake (ml/min)
CO = cardiac output (l/min)
C_aO_2 = arterial blood oxygen content (ml/l)
$C\bar{v}O_2$ = mixed venous blood oxygen content (ml/l)

The determination of mixed venous oxygen content and cardiac output require the use of a pulmonary artery catheter. These catheters may cause serious complications, such as pneumothorax, arrhythmias or sepsis. The relative error in the arteriovenous oxygen content difference can be large when the arteriovenous oxygen content difference is small. In combination with the measurement error of cardiac output during mechanical ventilation, the error in $\dot{V}O_2$ calculated by the Fick method may be considerable.

The second method to determine $\dot{V}O_2$ is respiratory gas analysis. Measurement of the oxygen concentration in inspired gas and the oxygen and carbon dioxide concentrations in expired gas, as well as measurement (or calculation) of the respiratory minute volume, allows calculation of $\dot{V}O_2$ and $\dot{V}CO_2$. In steady-state conditions a small difference in oxygen uptake measured by respirometry and calculated by the Fick method might be expected, due to oxygen consumption by the lungs, estimated as 1 to 4% of total body oxygen uptake (49). Under carefully controlled laboratory conditions, close agreement between the two methods was found in mechanically ventilated pigs (30). In patients steady-state conditions may not be met, and oxygen uptake determined by respirometry is reported to be consistently higher (up to 25%) than oxygen uptake calculated by the Fick method (21,41,56). In another study in patients a close correlation without a systematic difference between the two methods was found (10).

In the studies in chapters 3 to 5 of this thesis $\dot{V}O_2$ and $\dot{V}CO_2$ were determined by respiratory gas analysis with a metabolic monitor designed specifically for use in mechanically ventilated patients. The metabolic monitor consists of an oxygen analyzer, a carbon dioxide analyzer and a flow meter. The accuracy of the measurement of $\dot{V}O_2$, $\dot{V}CO_2$ and RQ by the metabolic monitor was previously determined with laboratory tests simulating the conditions, flows and gas exchange that may be expected in critically ill patients. To simulate oxygen exchange nitrogen was injected by a Brooks mass flow system. Tests were repeated while using PEEP ventilation and a humidifier. There was a maximal error in $\dot{V}O_2$ measurement of 3% of the minute values (14).

In the study described in chapter 2 a commercially available metabolic monitor (Deltatrac™, Datex/Instrumentarium, Helsinki, Finland) was used to measure $\dot{V}O_2$ and $\dot{V}CO_2$ in spontaneously breathing subjects (47). Using the previously described method to simulate $\dot{V}O_2$ and $\dot{V}CO_2$, the accuracy of $\dot{V}O_2$ and $\dot{V}CO_2$ measurement by a prototype of the Deltatrac™ metabolic monitor in the setup for measurement in spontaneously breathing subjects was within 1.1%. This is better than the accuracy of 3% in $\dot{V}CO_2$ and 4% in $\dot{V}O_2$ measurement reported by Takala et al. (56). In chapter 6 the Deltatrac™ metabolic monitor prototype was used to measure $\dot{V}O_2$ in mechanically ventilated pigs. Using the previously described methods, the accuracy of $\dot{V}O_2$ measurement by the Deltatrac™ metabolic monitor was found to be less than 2% during mechanical ventilation with an inspiratory oxygen concentration of 40% and positive end-expiratory pressure (PEEP) up to 20 cm H_2O.

Respiratory gas analysis to assess oxygen uptake is sensitive to errors due to exchange of gaseous anesthetics, leakage of expired gas, inaccurate calibration of gas analyzers and fluctuating inspiratory oxygen concentration (8). At high inspiratory oxygen concentration the sensitivity of the Haldane algorithm to sensor errors increases (57), therefore in studies in this thesis measurements were only performed when F_IO_2 was 60% or less. If the above-mentioned conditions are excluded, respiratory gas analysis provides an accurate, non-invasive method to assess oxygen uptake continuously.

Carbon dioxide production may be assessed just as oxygen uptake, by respiratory gas analysis or calculation by the Fick method. For long-term studies the doubly labelled water ($^2H_2{}^{18}O$) method can also be used to calculate carbon dioxide production from the difference between turnover rates of oxygen-18 and deuterium. Energy expenditure can be calculated from the carbon dioxide production, after the respiratory quotient ($RQ=\dot{V}CO_2/\dot{V}O_2$) over the measurement period has been estimated. The difference between energy expenditure determined with respiratory gas analysis and the doubly labelled water method was found to be within 10% in humans (52) and animals (48).

1.3 Outline of the thesis

In the first part of this thesis, the assessment of aerobic energy metabolism as a means to guide caloric supply to spontaneously breathing and mechanically ventilated subjects is studied (chapters 2 and 3). In the second part of this thesis the relation between aerobic energy metabolism and oxygen supply is investigated (chapters 4 to 6).

Caloric supply

In clinical practice energy expenditure is usually measured during short periods and the results are extrapolated to a 24-hour period (11,17,25,32,36,42).

To eliminate the influence of physical activity, nutrition and circadian rhythm on the assessment of energy expenditure, measurements must be performed under standard conditions. However, these conditions are usually not maintained, in order to minimize patient discomfort and optimize use of measurement equipment (17,32,36). The variability of energy expenditure measured under non-standard conditions was assessed, and energy expenditures measured under standard and non-standard conditions were compared in healthy controls and hospitalized patients (chapter 2).

In contrast to spontaneously breathing patients, energy expenditure of mechanically ventilated patients can be measured continuously without discomfort to the patient. Continuous 24-hour measurements have demonstrated that in critically ill patients energy expenditure may vary considerably during the day due to variations in physical activity, anxiety, pain, body temperature, nutrition, medication and circadian rhythm (12,16,18,40,50,58,62,63). These factors may vary considerably on subsequent days and energy expenditure can be expected to vary accordingly. To decide whether energy expenditure measured on a single day can predict the caloric demands of a patient for a longer period, the day-to-day variability of energy expenditure and its relation to clinical condition were investigated in critically ill, mechanically ventilated patients (chapter 3).

Oxygen supply

If oxygen uptake were limited by oxygen supply, as is reported in critically ill patients (5,6,13,22,26,33,34,37), determination of energy expenditure from oxygen uptake (indirect calorimetry) would not be a valid method to assess energy requirements. The reported limitation of oxygen uptake by oxygen supply was investigated in chapters 4 and 5.

In studies reporting that oxygen uptake is limited by oxygen supply in critically ill patients, oxygen uptake was calculated by an indirect method using the Fick equation for oxygen (section 1.2). In this calculation of oxygen uptake, two variables are used that also occur in the calculation of oxygen supply (product of cardiac output and arterial blood oxygen content). The measurement errors in the shared variables cardiac output and arterial blood oxygen content introduce a mathematic coupling of oxygen uptake and supply (15). The hypothesis that this mathematic coupling may cause an artifact in the study of the relationship between oxygen uptake and oxygen supply was investigated in postoperative and septic patients (chapter 4).

The relationship between oxygen uptake and oxygen supply in critically ill patients was investigated using independent methods to assess oxygen uptake and supply, avoiding mathematic coupling (chapter 5).

Multiple organ failure and mortality in critically ill patients have been related to limitation of oxygen uptake by inadequate oxygen extraction (6).

In critically ill patients vasodilation with prostaglandin E_1 (PGE_1) increases oxygen supply and oxygen uptake (7,55), and has been reported to reduce mortality (28), although the latter finding was not confirmed in other studies (7). In contrast to the reported beneficial effects of the vasodilator PGE_1, peripheral vasodilation has been associated with lactic acidemia (due to anaerobic metabolism) and mortality (20). To investigate whether the minimal oxygen supply required to maintain oxygen uptake and aerobic metabolism is altered by the vasodilator PGE_1, oxygen uptake, oxygen supply and lactate were measured during graded reduction of oxygen supply in anesthetized pigs (chapter 6).

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Chapter 2

ASSESSMENT OF ENERGY EXPENDITURE BY INDIRECT CALORIMETRY IN HEALTHY SUBJECTS AND PATIENTS WITH LIVER CIRRHOSIS

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Introduction

Energy expenditure (EE) of an individual patient can be estimated with an empiric formula, such as the Harris-Benedict equation (1), or measured via direct or indirect calorimetry. Empiric formulae derived from measurements of EE in healthy subjects have been reported to be inaccurate for prediction in individual patients (2-7) and healthy controls (7-9). In clinical practice, underfeeding or overfeeding may have detrimental effects on a patient's condition (10,11), therefore, to allow adaptation of caloric supply to caloric expenditure, the routine measurement of EE in patients has been advocated (7,12). In clinical research indirect calorimetry is used to study the influence of nutrition on EE (13,14) and the change of EE due to disease (15-19).

Measurement conditions during indirect calorimetry limit the patient's freedom of movement and/or cause discomfort, so these measurements are usually performed during short periods and the results are extrapolated to a 24-hour period (3,6,7,9,15-20). Measurements need to be standardized to eliminate the influence of physical activity, nutrition and circadian rhythm on the assessment of EE, and to obtain basal energy expenditure (BEE). This is EE after 12 hours sleep, an overnight fast, in supine position and in a thermoneutral environment (21). For practical reasons, more often "resting" conditions are used. Resting energy expenditure (REE) is defined as EE, with the subject lying in bed at rest, more than 2 hours after the last meal (22). In this way patient discomfort is minimized and the use of metabolic equipment is optimised (7,15,17).

The timing of resting measurements during the day and in relation to food intake may be important, and may be different in healthy controls and patients with disease affecting energy metabolism. Cirrhotic patients develop the catabolic state of starvation more rapidly than normal humans (23), while protein turnover is increased (24).

In this study the variability of resting energy expenditure was assessed, and predicted and measured resting energy expenditure were compared to measured basal energy expenditure in healthy controls and in hospitalized patients with liver cirrhosis.

Methods

Subjects

Metabolic measurements were performed in two groups of subjects. The first group consisted of 50 healthy controls, in five age categories (10-19, 20-29, 30-39, 40-49, 50-59 years) each category containing five male and five female subjects. The mean age was 35±13 years, body weight was 72±14 kg and height 177±9 cm. The second group consisted of 10 hospitalized patients with biopsy-proven liver cirrhosis (clinical data presented in table 1). The mean age in this group was 48±14 years, body weight was 63±21 kg and height 167±9 cm.

Table 1. Clinical data of 10 patients with liver cirrhosis

Nr	Sex	Age	W	H	Diagnosis	Asc	C
1	F	69	59	162	Primary biliary cirrhosis	+	C
2	F	55	58	157	Chronic active hepatitis	-	A
3	M	22	45	164	Chronic active hepatitis	+	C
4	M	41	52	174	Chronic hepatitis B	+	C
5	M	58	84	176	Alcoholic cirrhosis	+	C
6	F	56	63	168	Chronic active hepatitis	+	B
7	M	34	65	175	Alcoholic cirrhosis	-	A
8	M	58	111	179	Alcoholic cirrhosis	+	C
9	F	44	41	154	Alcoholic cirrhosis	-	A
10	F	47	48	158	Primary biliary cirrhosis	-	A

Age in years, W (weight) in kg, H (height) in cm, Asc indicates presence (+) or absence (-) of ascites, C is Child Classification of severity of liver disease.

Measurements

Energy expenditure (EE) was determined by indirect calorimetry. Through a transparent canopy placed over the head of the subject, a constant air flow ($\dot{V}$) of 55 l/min takes the expired gas to a Deltatrac™ metabolic monitor (Datex/Instrumentarium, Helsinki, Finland) described previously (25). The monitor measures the inspiratory oxygen concentration (F_IO_2) and the difference between inspiratory (F_IO_2) and expiratory (F_EO_2) oxygen concentration with a paramagnetic differential oxygen sensor. The expiratory carbon dioxide concentration (F_ECO_2) is measured continuously with an infrared sensor.

The inspiratory CO_2 level of the room air (F_ICO_2) is measured every two minutes. Prior to measurements the sensors are calibrated with a gas mixture of known composition. Carbon dioxide output ($\dot{V}CO_2 = \dot{V}.F_ECO_2$, in ml/min) as well as oxygen uptake ($\dot{V}O_2 = \dot{V}/[1-F_IO_2].(F_IO_2-F_EO_2-F_IO_2.[F_ECO_2-F_ICO_2])$ ml/min) are calculated each minute and converted to standard temperature and pressure dry gas (STPD) condition. Energy expenditure was calculated with the abbreviated Weir formula (26):

$EE = 1.44 \times ((3.9 \times \dot{V}O_2) + (1.1 \times \dot{V}CO_2))$, EE in kcal/day

The minute values of $F_IO_2-F_EO_2$, $F_ECO_2-F_ICO_2$, $\dot{V}O_2$, $\dot{V}CO_2$, RQ ($=\dot{V}CO_2/\dot{V}O_2$) and EE were sent to a printer and to a microcomputer for later analysis. The accuracy of $\dot{V}O_2$ and $\dot{V}CO_2$ measurement by the Deltatrac™ metabolic monitor was determined by a previously described method using N_2 and CO_2 injections to simulate $\dot{V}O_2$ and $\dot{V}CO_2$, and remained within 1.1% (27). Takala et al. found a mean error of 3% in $\dot{V}CO_2$ and 4% in $\dot{V}O_2$ measurements (28).

Energy expenditure (in kcal/d) was also estimated with the Harris-Benedict formula (1):

Male HBEE = 66 + 13.8 x W + 5.0 x H - 6.8 x A
Female HBEE = 655 + 9.7 x W + 1.8 x H - 4.7 x A

where W is weight (kg), H is height (cm) and A is age (years).

Protocol

All subjects were studied according to the same protocol, which consisted of two consecutive measurement days. Subjects with an odd trial number were studied under basal conditions on the first day, and under resting conditions on the second day. Subjects with an even number were studied in reverse order. On the first measurement day sex, age, body weight and height were recorded. On the "resting" day subjects were studied in supine position three times: between 08:30 and 10:00 hours (1-2 hours after breakfast), between 11:30 and 13:00 hours (before lunch), and finally between 16:30 and 18:00 hours (before dinner) to determine resting energy expenditure (REE1, REE2 and REE3 resp.). On the "basal" day subjects fasted overnight for at least 8 hours prior to the measurement and were studied after a 30 minute rest in supine position to assess the basal energy expenditure (BEE). Resting as well as basal measurements consisted of gas exchange measurements during 30 minutes. This study was conducted in accordance with the principles for human experimentation as defined in the Declaration of Helsinki.

Data analysis

To establish the time required to stabilize the measurement of metabolic gas exchange, the 30 minute recording period was subdivided into six 5-minute recording periods. The mean EE and RQ during these 5-minute recording periods were compared using analysis of variance (ANOVA). The same technique was used to compare REE1, REE2, REE3 and calculated HBEE to BEE. Results are expressed as mean±SD. A p-level of 0.05 was considered significant.

Results

Steady-state in metabolic gas exchange

The mean energy expenditure of healthy controls under basal and under resting conditions during 5-minute recording periods is depicted in Fig. 1A. During the first 5 min, BEE was 12±9.7% higher than in the remaining 25 min of the recording ($p<0.001$), and RQ was slightly lower than in the remaining period (0.81±0.09 vs 0.84±0.07, $p<0.001$). EE during the first 5 min of REE1, REE2 and REE3 was resp 27±14%, 28±13% and 31±14% higher than during the last 25 min of the recordings. In the second 5-min recording period REE1 was 5.1±5.3% ($p<0.05$), REE2 5.2±5.1% ($p<0.005$) and REE3 6.0±3.8% ($p<0.005$) higher than in the remaining 20 min periods.

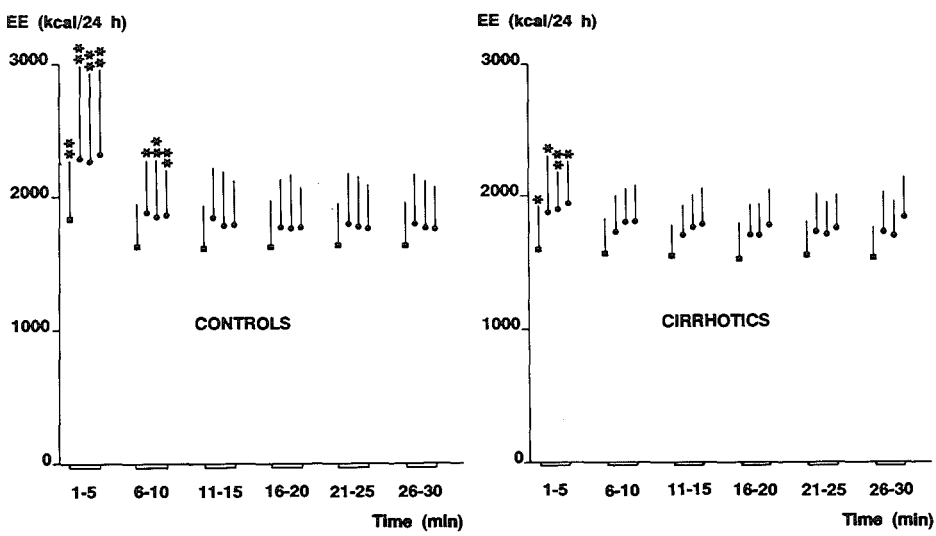

Figure 1. Basal (BEE; squares) and resting (REE1, REE2, REE3; dots) energy expenditure (EE) in controls and cirrhotics during 30-min study periods, divided in six 5-min periods. Stars indicate significance level of difference with EE in the remaining 5-min periods (* $p<0.05$, ** $p<0.01$).

Respiratory quotient during the first resting measurement (RQ1) decreased from 0.91±0.12 in the first 5-min period to 0.87±0.08 in the final period ($p<0.001$), RQ2 decreased from 0.88±0.12 to 0.84±0.08 ($p<0.001$) and RQ3 from 0.90±0.11 to 0.82±0.07 ($p<0.001$). After the third 5-min recording the RQ difference between 5-min periods was not statistically significant any more.

In cirrhotic patients BEE during the first 5 min was 5.4±2.9% ($p<0.05$) higher than in the remaining 25 min of the recording period (Fig. 1B), RQ did not change and averaged 0.80±0.07 in the total 30-min recording. Only in the first 5-min recording REE was higher than in the rest of the recording (REE1 8.1±7.2% ($p<0.05$), REE2 9.2±5.4% ($p<0.001$) and REE3 9.3±4.3% ($p<0.05$)). Respiratory quotient increased during the resting measurements, but only in the second and the third measurement the increase was statistically significant from the first to the final 5 min period (RQ2 from 0.84±0.10 to 0.88±0.09, RQ3 from 0.86±0.10 to 0.90±0.11, both $p<0.05$). Since in both groups energy expenditure did not change in time any more after the first 10 min of a 30-min recording, we used the last 20 min of recordings to compare REE and BEE.

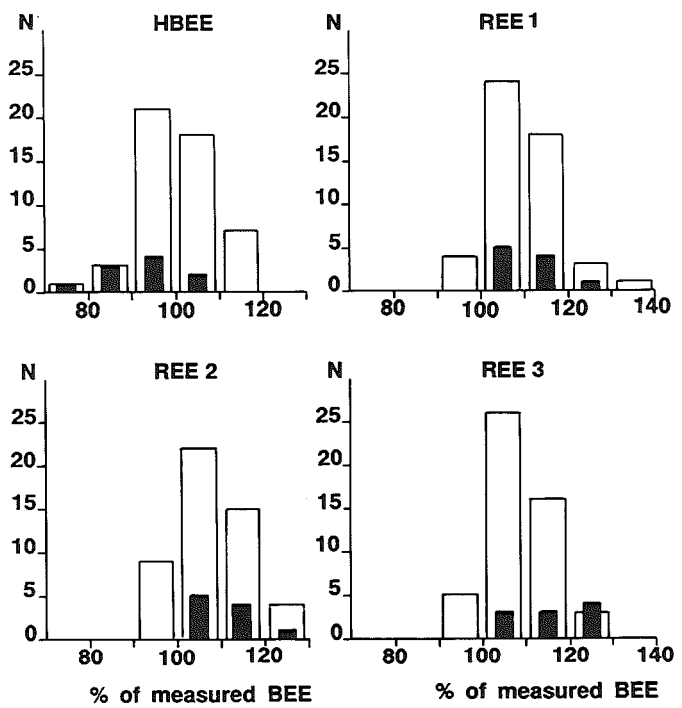

Figure 2. Frequency distribution of individual differences between measured (BEE) and predicted basal energy expenditure (HBEE) (top left figure) and between resting energy expenditure (REE1, REE2, REE3) and measured BEE. Open bars represent data of 50 healthy controls, closed bars represent 10 cirrhotic patients.

Comparison of HBEE, BEE and REE

Energy expenditure calculated with the Harris-Benedict equation (HBEE), basal (BEE) and resting energy expenditure (REE) are summarized in table 2. In healthy controls the group mean HBEE correctly predicted the group mean BEE. In only 11 controls (11/50 = 22%) the difference between HBEE and BEE was larger than 10% of BEE (Fig. 2). The resting measurements however were 110±8% (REE1), resp 108±8% (REE2), resp 108±6% (REE3) of the BEE (all $p<0.05$).

Table 2. Energy expenditure (in kcal/day) of healthy controls and cirrhotic patients calculated by the Harris-Benedict equation (HBEE) and measured under basal (BEE) and resting conditions in the morning (REE1), at noon (REE2) and in the afternoon (REE3). The statistical significance of differences between HBEE and BEE and between REE and BEE is indicated.

	CONTROLS			CIRRHOTICS		
	EE	%BEE	p	EE	%BEE	p
BEE	1645±315	(100)		1530±235	(100)	
HBEE	1635±270	(100±8)	0.86	1419±303	(93±10)	0.06
REE1	1808±365	(110±8)	0.05	1714±267	(112±6)	0.05
REE2	1782±384	(108±8)	0.05	1715±238	(112±6)	0.05
REE3	1775±316	(108±6)	0.05	1779±275	(116±7)	0.05

In cirrhotic patients the group mean HBEE was 93±10% of the mean BEE, the difference was not significant ($p=0.06$). The HBEE expressed as a percentage of BEE ranged from 74 to 108%. The resting measurements were 112±6% (REE1), resp 112±6% (REE2), resp 116±7% (REE3) of the mean BEE (all $p<0.05$). In cirrhotics, predicted BEE (HBEE) as percentage of measured BEE was lower than in controls ($p<0.01$) (Table 2).

In neither the controls nor in cirrhotic patients there was a statistically significant difference between the results of the three resting measurements. The mean coefficient of variation for resting measurements in controls was 5±3%, with a range of 0.8 to 10%. In cirrhotics the coefficient of variation was 5±2%, with a range of 2.4 to 8.8%.

Discussion

In nutritional therapy indirect calorimetry is usually performed under resting conditions during a short period and the result is extrapolated to a 24-hour period (3,4,6,9,15-20,29). Poor reproducibility of single REE estimates in healthy controls has been ascribed to adaptation of subjects to the calorimetry equipment (30). Indeed, in the present study the initial 5 to 10 minute values of EE were higher than in the remainder of the recording period. In resting measurements in controls this may have been due to hyperventilation, as indicated by a higher RQ in the initial measurement minutes. However, RQ increased during basal recordings in controls, whereas in cirrhotics RQ increased during resting recordings and did not change during basal recordings. The higher EE values at the onset of recordings were not due to a lower proportion of expired gas in the gas mixture entering the metabolic monitor, because this would result in underestimation of actual carbon dioxide output and oxygen uptake.

After deletion of the first 10 minutes of each 30-minute recording period, the variation coefficient between three successive resting measurements was 5% in both controls (range 0.8 to 10%) and in cirrhotics (range 2.4 to 8.8%). This is higher than the variation coefficient of duplicate REE determinations in healthy controls during continuous fasting (1.3%) or continuous feeding (2.8%) reported by Zurlo et al. (31), or in healthy controls and patients (1 to 2%) reported by Feurer et al. (32). The duration of measurements in these studies and our study was comparable, so the higher REE variation coefficient in our study may have been due to food intake at different intervals prior to resting measurements, the fact that we measured at three different hours of the day, and that subjects did not rest for 30 minutes prior to measurements. Because in individual subjects the variation coefficient was low, and no systematic difference between the three resting measurements was found, it might be concluded that the time of the day for REE measurements is unimportant. The variation coefficient reported in the literature of 4% in resting versus 2.4% in basal energy expenditure measurements on consecutive days (3,33) may indicate that there is little increase in variability when measurements are performed under resting rather than basal conditions.

Resting energy expenditure was higher than basal energy expenditure measured at the same time of day, by 10±8% in controls and by 12±6% in cirrhotics. REE is higher than BEE, because the former includes EE associated with food intake. The magnitude of the BEE-REE difference in this study is equal to the 10% reported by Elwyn et al. (22), although in our study subjects did not rest for 30 minutes prior to resting measurements.

This may indicate that resting prior to resting measurements is not necessary if the initial 10 minutes of recordings are deleted. However, in patients and controls in the present study BEE and REE were determined on consecutive days, so a small day-to-day variation of BEE and REE (reportedly 2.4 and 4% resp) (3,33) is included in our observations.

In clinical nutrition it might be preferable to measure EE under resting rather than basal conditions, because it more closely approximates 24-hour EE, which is the amount of calories that nutrition should supply. Measured REE may however differ considerably from 24-hour EE. The latter also includes EE associated with physical activity, which reportedly ranges from 138 to 685 kcal/day (33) or 10 to 19% of 24-hour EE (34) in persons confined to a small metabolic chamber.

In the present study the Harris-Benedict equation correctly predicted the group mean BEE of healthy controls. However, in individual subjects predicted EE was up to 21% lower than measured EE. In cirrhotic patients the largest error was 26% below measured EE and the group mean BEE was underestimated by 7%, although this was not statistically significant. Underestimation by the Harris-Benedict equation (HBEE) of BEE in cirrhotics might theoretically be explained by hypermetabolism due to increased protein turnover associated with liver cirrhosis (24,29,35). Owen et al. however showed, that although cirrhotic patients sooner reach a catabolic state of starvation than healthy controls, this is not associated with higher energy requirements (23). In cirrhotic patients with ascites, body weight would overestimate metabolically active body mass, so BEE in these patients would be overestimated by the HBEE (17). Basal energy expenditure of hospitalized patients may be decreased due to reduced physical activity (36), which could also lead to overestimation of BEE by the Harris-Benedict equation.

Conclusions

Resting energy expenditure can be reproducibly measured by indirect calorimetry with a ventilated hood system if the initial 10 minute values are deleted. The Harris-Benedict equation accurately predicts the mean basal energy expenditure in healthy controls, but individual predictions may be erroneous in both controls and patients with liver cirrhosis. Basal and resting energy expenditure differ considerably in controls as well as in cirrhotic patients, so conditions under which measurements are performed should be standardized.

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Chapter 3

DAY-TO-DAY VARIABILITY OF ENERGY EXPENDITURE IN CRITICALLY ILL SURGICAL PATIENTS

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Introduction

After major surgery or severe trauma patients frequently require a period of intensive care. When complications occur a prolonged stay at the intensive care unit (ICU) may ensue. To improve the general condition of these patients nutritional support is usually provided. Instead of standard nutritional support both its composition and dosage can be adapted to the specific metabolism of a patient. One aspect of the specific metabolism is an individual patient's total energy expenditure (TEE), which can be replenished by an equal caloric supply (1).

Underfeeding has been associated with decreased resistance to infection (2) and delayed wound healing (3). On the other hand, energy supply in excess of actual energy expenditure will cause fat synthesis and deposition, which has no beneficial effect (4) and may lead to hepatic dysfunction (5,6), hyperglycemia (7) or respiratory distress (8). Adequate caloric supply requires knowledge of an individual patient's TEE, obtained from either measurement or estimation of TEE (1).

Several factors are reported to influence TEE: motor activity (9), discomfort (10), pain (10), body temperature (11), nutrition (7,12), medication (13,14) and circadian rhythm (15). Since these factors may change considerably during the day and on subsequent days, TEE can be expected to vary accordingly. The variability of TEE during the day has been investigated previously in critically ill, mechanically ventilated patients (11,16-18). Little is known however about the day-to-day variability of TEE (19) and the factors associated with it.

If day-to-day variability is small during the patient's stay in the ICU, measurement of TEE on a single day can provide sufficient information on the caloric demands of a patient for a longer period. This would eliminate the need for daily determinations of TEE. If day-to-day variability of TEE is large, TEE should be measured daily or TEE measured on a single day should be corrected for changes in clinical condition on subsequent days. To determine whether total energy expenditure (TEE) on a single day reliably estimates TEE on subsequent days of a patient's stay at the ICU, the day-to-day variability of (TEE) and its relation to clinical condition were studied.

Methods

Mechanically ventilated patients on a surgical ICU were admitted to the study when it was expected that mechanical ventilation needed to be continued during at least two days. Patients with either air-leakage (from endotracheal cuff or thoracic drain), active bleeding, dialysis or F_IO_2 greater than 60% were excluded from the study. The measurements were stopped when it was decided to start weaning a patient from the ventilator or if any of the above mentioned exclusion criteria became applicable. Since one measurement setup was available, only one patient could be measured at a time. Measurements were stopped if after at least two days of measurements in one patient, another patient complied with the inclusion criteria. According to this protocol 60 patients were included in the study. The patient data are summarized in table 1. On average the first day of the study period (day 1) represented the sixth day after admission to the ICU. Severity of disease was assessed on each measurement day by means of the Simplified Acute Physiology Score (SAPS) (21). Contribution of the neurologic function to the SAPS was omitted, because the Glasgow coma score was not determined. Instead the average score of the other 13 variables was used.

Table 1. Clinical data (mean±SD) of 60 critically ill patients

Male/female	48/12	
Age (range)	53±17	(17-83) years
Interval day 1 - day of ICU admission	6±6	(0-26) days
SAPS on day 1	13±4	(5-23)
Mortality on ICU	17	(28%)
Trauma	14	(23%)
Infection	48	(80%)
Postoperative	28	(47%)
ARDS	12	(20%)
Nutrition on day 1		
Enteral	27	(45%)
Parenteral	23	(38%)
Parenteral and enteral	2	(3%)
5% Glucose	8	(13%)

Measurements

Total energy expenditure was determined by indirect calorimetry: oxygen uptake ($\dot{V}O_2$) and carbon dioxide output ($\dot{V}CO_2$) were measured continuously with an automated metabolic monitor, which was designed specifically for use in mechanically ventilated patients. The metabolic monitor consists of an oxygen analyzer, a carbon dioxide analyzer and a flow meter. Validation studies of the apparatus have shown a maximal error in $\dot{V}O_2$ and $\dot{V}CO_2$ measurement of 3% of the minute values (22). $\dot{V}O_2$, $\dot{V}_E$ and respiratory quotient ($\dot{V}CO_2/\dot{V}O_2$) are available on the bedside and were sent to a remote computer (DEC PDP 11/73) for later analysis. Artifacts caused by disconnection from the ventilator (e.g. for bronchopulmonary toilet) were suppressed by a computer algorithm (23). $\dot{V}O_2$ and $\dot{V}CO_2$ were used to calculate TEE with the abbreviated Weir formula (24):

TEE (in kcal/day) = 3.9 $\dot{V}O_2$ + 1.1 $\dot{V}CO_2$, $\dot{V}O_2$ and $\dot{V}CO_2$ in l/day

Rectal temperature was measured either continuously with a rectal temperature probe or once every hour with a mercury thermometer. The mean body temperature was calculated as the mean value of the hourly temperature values during the measurement period. Patients were in a supine position, nude and covered by one or two linen sheets. Mean ambient (room) temperature was kept at 22 °C. In all patients measurements of TEE were performed on at least two and at most on seven consecutive days. The duration of the measurement on each day ranged from 4 to 24 hours.

Data Analysis

Analysis of variance of TEE was performed with SAPS, body temperature, measurement day and patient number as explanatory variables. In order to calculate a correction factor for variables that influence day-to-day variability of TEE, the following linear regression model was used:

$TEE_n - TEE_{n-1} = k \times (F_n - F_{n-1}) \times TEE_{n-1}$
TEE_n, TEE_{n-1}: total energy expenditure on days n and n-1,
F_n, F_{n-1}: values of explanatory variable on days n and n-1,

The correction factor k was used to correct TEE_1 for changes in body temperature or SAPS by adding k x 100% to obtain an estimation of TEE_2..TEE_7. Relative errors in TEE estimation were calculated as the absolute percentual difference (APD) between the actual and estimated TEE:

APD = (|(estimated TEE - actual TEE)|/ actual TEE) x 100%

To investigate whether the classical correction (24) for elevated body temperature improves the estimation of TEE_2..TEE_7 from TEE_1, we added 13% per °C temperature difference to TEE_1 to obtain an estimation of TEE_2..TEE_7. In the same way as before the relative error in the TEE estimation (APD) was calculated.

The results of TEE estimation by the three models were evaluated by comparison of the errors, using Student's t test for paired observations. A p-level of 0.05 was considered significant.

Results

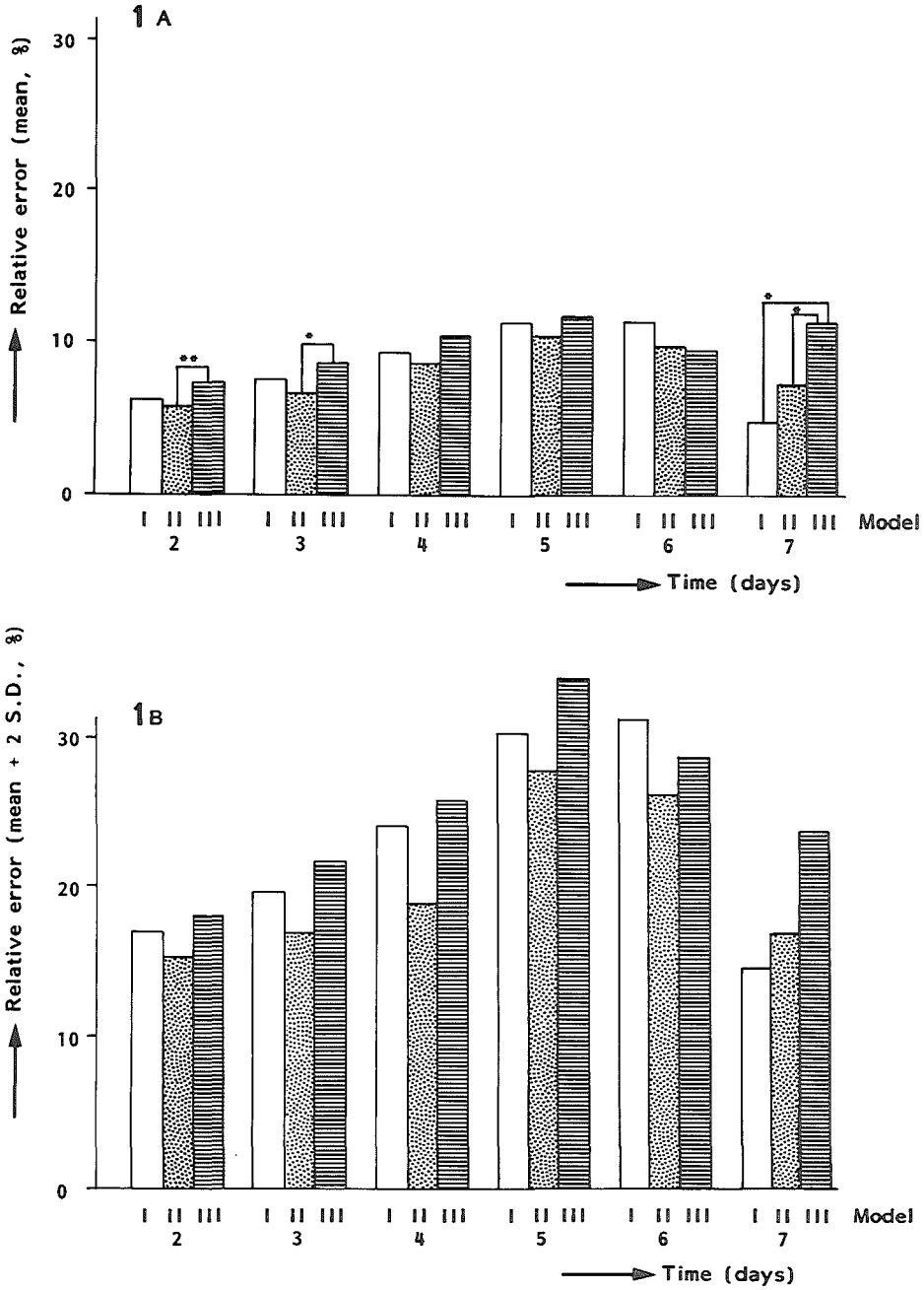
The results of TEE measurements are presented in table 2. On day 1 TEE was 2198±413 kcal/day (mean±SD, N=60), while on day 2 TEE appeared to be 2163±421 kcal/day (mean±SD, N=60). In the subgroup of 44 patients, measurements were also made on a third day, this resulted in a mean TEE of 2229±430 kcal/day on that day. In 26 patients TEE was measured on four subsequent days, in 16 patients on five days, in 11 patients on 6 days and in 6 patients on seven days.

Using analysis of variance it was found that the day-to-day variability of TEE depended on body temperature ($p<0.0001$), but not on measurement day ($p=0.544$) or SAPS ($p=0.368$). The relationship between TEE and temperature was analyzed by linear regression. An optimal correction factor of 6% per °C was found ($p<0.0001$).

Table 2. Day-to-day variability of TEE (in kcal/day, mean±SD) in critically ill surgical patients

N = 60		44	26	16	11	6
Day	TEE	TEE	TEE	TEE	TEE	TEE
1	2198±413	2232±431	2234±483	2260±484	2134±450	2148±443
2	2163±421	2215±443	2260±518	2296±518	2131±490	2165±509
3		2229±430	2312±485	2375±519	2232±502	2286±544
4			2269±396	2314±408	2214±432	2286±483
5				2309±400	2197±436	2260±494
6					2211±441	2333±502
7						2277±515

TEE on days 2 to 7 was estimated by means of three models: TEE_1 (model I), TEE_1 plus 6% (model II) or plus 13% (model III) per °C temperature difference. The accuracy of these models was evaluated with mean errors and mean+2SD errors. The latter indicates the error below which 95% of the estimations are found. Fig. 1A shows that the mean errors resulting from estimation of TEE on days 2 to 7 with 6% per °C are lower than the mean errors of the models I and III on days 2, 3, 4 and 5. In Fig. 1B the mean plus 2 x the standard deviation is depicted. On days 2 to 6 correction for body temperature with 6% per °C resulted in a smaller 95% confidentiality interval than that of the other two models.



Figures 1A and 1B. Mean (1A) and mean+2SD (1B) of the relative TEE estimation errors on days to 2 to 7. Errors when using no temperature correction (open bars), temperature correction with 6% per °C (dotted bars) and 13% per °C (striped bars) temperature difference are shown. * $p<0.05$, ** $p<0.005$

Discussion

As both under- and overfeeding may have detrimental effects on the clinical condition of critically ill patients, it is advocated to adapt caloric supply to an individual patient's TEE (1). With the now available metabolic monitors, TEE can be accurately measured in mechanically ventilated patients (9,11,16,22,26,27,30,31). Studies in mechanically ventilated, critically ill patients using continuous indirect calorimetry have shown that fluctuations in TEE can be caused by changes in clinical condition and in ICU therapy. Although therapeutic interventions occur throughout the day (11,16), and the induced TEE fluctuations can be large, they usually are short-lived (11) and probably contribute little to the mean daily TEE (18,28). In a previous study we have shown that despite these fluctuations short recording periods of TEE provide a fairly accurate estimation of 24 hour TEE: instead of a continuous 24 hour measurement, two 15 minute measurements of TEE performed at sufficient intervals after therapeutic interventions can be used to estimate a patient's daily TEE (29).

In the present study it was investigated whether measurement of TEE in a patient on a single day provides adequate accuracy in the determination of the caloric supply during a prolonged stay at the ICU. Secondly it was assessed if day-to-day variability is of any importance when the mean TEE of groups of patients is compared, e.g. septic vs not septic. We studied the day-to-day variability by continuous measurements of TEE by indirect calorimetry. It appeared that the mean TEE in the whole group of mechanically ventilated patients in this study was similar on the seven days of the study period. It can therefore be concluded that in the comparison of the mean TEE of groups of patients the effect of the day-to-day variability of TEE is of no importance. In the individual patient however day-to-day variability may be considerable. This is in agreement with the result of the study by Weissman et al. (19), who found a mean variability (defined as (highest daily REE - lowest daily REE) / lowest daily REE) of 15% in a 3 to 5 day period. Resting energy expenditure (REE) was defined as the energy expenditure of the patient lying motionless with eyes open, and responsive to surrounding events.

A considerable day-to-day variability of TEE implies that when the measurement of TEE on one day is used to estimate TEE on subsequent days large errors may be introduced. As we found that day-to-day variability of TEE depends on variations in body temperature, we tried to improve the accuracy of TEE estimation in individual patients by means of a correction for body temperature. First a correction factor of 13% per °C (based on the work of Dubois (19)) was used. This did not improve the accuracy of TEE estimation.

Then we analyzed the relationship between energy expenditure and body temperature in our group of patients by linear regression. This yielded an optimal correction factor of 6% per °C temperature difference. This deviates considerably from the 13% temperature correction per °C found by Dubois (20). The deviation could be partly explained by the fact that large temperature differences together with TEE variations caused by other factors in some of our patients, result in an underestimation of the influence of body temperature. The study by Dubois was performed in patients with high fever, and the influence of other factors on TEE may have been more important. However, in a subgroup of our study patients with a day-to-day variation in body temperature of more than 1 °C, the same temperature correction factor of 6% per °C was found. We did not account for the variation of sedation, muscle relaxation or changes in nutritional support regimen. Although these factors may influence day-to-day variability of TEE more than body temperature, their influence on TEE is not easily quantified. Temperature correction with our calculated factor reduced the error in the estimation of TEE, and has the advantage that it is easily applied, since body temperature is routinely measured in the ICU. Even after correcting TEE for temperature variation between subsequent days, errors of up to 25% of the actual TEE were found. Therefore when this estimation of TEE is used for the determination of the caloric supply for several days, under- or overfeeding may still occur.

Whether under- or overfeeding with 25% of actual TEE is acceptable or not remains debatable. Quebbeman et al. (4) state that an error of 20% is acceptable in the determination of caloric supply. This however only holds true when TEE is determined each day. When the measured TEE on one day is used to guide nutritional support during a week, a cumulative negative or positive energy balance may result. Bartlett et al. (30) found a direct correlation between cumulative caloric balance and mortality rate in critically ill surgical patients, but pointed out rightly, that from this association no inference regarding cause and effect can be made. To which extent under- or overfeeding will influence mortality and morbidity in critically ill patients is yet uncertain, since ethical reasons prevent a controlled prospective study where patients are deliberately under- or overfed during their ICU stay.

In conclusion, if a balance between caloric supply and demand is intended, it is advisable to adapt the caloric supply to the result of daily measurement of TEE by either continuous or intermittent indirect calorimetry.

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Chapter 4

OXYGEN DELIVERY AND OXYGEN UPTAKE IN POSTOPERATIVE AND SEPTIC PATIENTS

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Introduction

Under physiologic conditions oxygen uptake ($\dot{V}O_2$) of the human body is determined by the metabolic rate and not limited by oxygen delivery ($\dot{D}O_2$, defined as the product of cardiac output and oxygen content of arterial blood) above a critical $\dot{D}O_2$ level of approximately 300 ml/min/m² (1). Tissues are able to augment the extraction of oxygen from blood, when the relative increase in oxygen demand exceeds the relative increase in oxygen supply (2). Only below the critical $\dot{D}O_2$ level a decrease of $\dot{D}O_2$ leads to a decrease of $\dot{V}O_2$, which means that $\dot{V}O_2$ depends on $\dot{D}O_2$, instead of only on metabolic rate. This phenomenon is called physiologic oxygen supply dependency (Fig. 1).

Based on observations that there is a close relationship between changes in $\dot{D}O_2$ and $\dot{V}O_2$ over a wider than normal $\dot{D}O_2$ range in patients with ARDS (3-6), sepsis (7-9), chronic congestive heart failure (10), acute liver failure (11) or after cardiopulmonary bypass operation (12), it has been concluded that in these disease states $\dot{V}O_2$ is limited by $\dot{D}O_2$. The dependency of $\dot{V}O_2$ on $\dot{D}O_2$ above the normal critical $\dot{D}O_2$ level has been called pathologic oxygen supply dependency (Fig. 1).

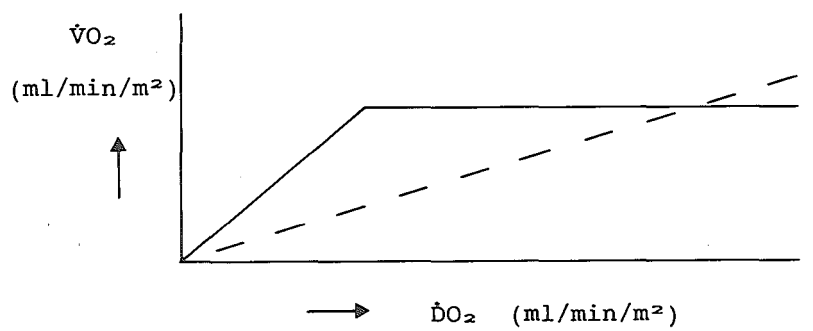


Figure 1. Relationship between $\dot{V}O_2$ and $\dot{D}O_2$ under physiologic (solid line) and pathologic (dashed line) conditions.

In previous studies reporting oxygen supply dependency (3-12), $\dot{V}O_2$ was calculated by the Fick equation as the product of cardiac output (CO) and arteriovenous oxygen content difference. As $\dot{D}O_2$ is calculated as the product of CO and oxygen content of arterial blood (C_aO_2), CO and C_aO_2 are used in the calculation of both $\dot{V}O_2$ and $\dot{D}O_2$, whereby a mathematic coupling of $\dot{V}O_2$ and $\dot{D}O_2$ is introduced. Archie has shown that this may result in a high correlation between $\dot{V}O_2$ and $\dot{D}O_2$, even when no functional relationship between these variables exists (13). Annat et al. measured $\dot{V}O_2$ by respirometry independently from $\dot{D}O_2$ in ARDS patients and concluded that in patients with normal arterial blood lactate levels no oxygen supply dependency occurred (14).

To investigate whether the previously reported pathologic oxygen supply dependency in postoperative and septic patients is an artifact due to mathematic coupling of data by shared variables, $\dot{V}O_2$ was calculated by the Fick method ($c\dot{V}O_2$) as well as measured by respirometry ($m\dot{V}O_2$), and the $c\dot{V}O_2$-$\dot{D}O_2$ relationship and $m\dot{V}O_2$-$\dot{D}O_2$ relationship were compared.

Methods

Patients

Two groups of mechanically ventilated patients, for clinical reasons monitored with a flow-directed pulmonary artery catheter and arterial catheter, were admitted to the study. Group I consisted of 13 patients immediately after a major abdominal operation. Serial measurements in these patients were started on their arrival at the Intensive Care Unit (ICU). Group II consisted of 7 septic patients, the diagnosis confirmed by at least two of the following criteria: 1) identified site(s) of infection, or 2) positive cultures of blood or fluid from the primary site(s), 3) fever (body temperature >38 °C), and 4) leukocytosis (white blood cell count >10,000/mm^3).

Patients were ventilated (Siemens Servo Ventilator) with tidal volumes between 10-15 ml/min/kg body weight. Patients with any of the following conditions were excluded from the study: 1) air leakage (from either endotracheal cuff or thoracic drain), 2) active bleeding, 3) dialysis, 4) inspired oxygen fraction greater than 60%, 5) insufficient observations (<6 measurements).

Measurement protocol

The study in each patient consisted of eight serial determinations of both oxygen delivery and oxygen uptake at 30 min intervals. Oxygen delivery ($\dot{D}O_2$) was calculated as the product of cardiac index (thermodilution) and oxygen content of arterial blood. Two different methods were used to determine oxygen uptake ($\dot{V}O_2$): 1) measurement ($m\dot{V}O_2$) by respirometry, independently from $\dot{D}O_2$, 2) calculation ($c\dot{V}O_2$) of the product of cardiac index and arteriovenous oxygen content difference.

Each of the eight serial determinations of $\dot{D}O_2$ and $\dot{V}O_2$ started with simultaneous arterial and mixed venous (pulmonary artery) blood sampling, immediately followed by measurement of cardiac output (CO). When a patient had bronchopulmonary toilet, or if any adjustment to the mechanical ventilator settings was made, measurements were postponed and resumed after a 15 min stabilization period. Arterial and mixed venous oxygen tensions (PO_2, mm Hg) were measured directly (Radiometer ABL 3, Copenhagen, Denmark), as were arterial and mixed venous oxyhemoglobin saturation (SO_2, Radiometer OSM 2). Haemoglobin concentration (Hb, g/dl) was determined at the first and last measurement (cyan method, Coulter Counter S+IV). Cardiac index was determined by thermodilution using a cardiac output computer (Mennen Horizon 2000). Ten ml 5% dextrose at room temperature was injected during 2 seconds with a pneumatic injector. The results of three end-expiratory injections were averaged. In three patients two injections at one half the respiratory cycle duration apart were averaged (15). Body temperature was recorded from the pulmonary artery catheter thermistor (blood temperature).

Measured $\dot{V}O_2$ was obtained from continuously performed gas exchange measurements by an automatic metabolic monitor designed specifically for use in mechanically ventilated patients (16). The metabolic monitor consists of an oxygen analyzer, a carbon dioxide analyzer and a flow meter. The accuracy of the measurement of $\dot{V}O_2$, $\dot{V}CO_2$ and RQ by the metabolic monitor was determined with laboratory tests simulating the conditions, flows and gas exchange that may be expected in critically ill patients. To simulate oxygen exchange nitrogen was injected by means of a Brooks mass flow system. Tests were repeated with positive end-expiratory pressure ventilation and a humidifier. A maximal error in $\dot{V}O_2$ measurement of 3% of the minute values was found (16).

To compare severity of disease in different patients, the Simplified Acute Physiology Score (SAPS, ref 17) was assessed in each patient. During the study all routine therapeutic interventions were applied as deemed appropriate by the intensive care physician. All procedures followed were in accordance with the Helsinki Declaration.

Calculations

Oxygen delivery (ml/min/m²) was calculated as $\dot{D}O_2 = CI \times C_aO_2 \times 10$, and cardiac index (l/min/m²) as CI = CO / BSA. Body surface area (in m²) was calculated from height and weight: $BSA = Weight^{0.425} \times Height^{0.725} \times 0.007184$, weight in kg, height in cm. Arterial and mixed venous blood oxygen content (C_aO_2, $C_{\bar{v}}O_2$, ml/dl) were calculated using the formula: oxygen content = $(1.39 \times Hb \times SO_2) + 0.0031 \times PO_2$. Calculated $\dot{V}O_2$ (ml/min/m²) was obtained from the Fick equation: $c\dot{V}O_2 = CI \times (C_aO_2 - C_{\bar{v}}O_2) \times 10$. Measured $\dot{V}O_2$ (ml/min/m²) was normalized for BSA by division of measured $\dot{V}O_2$ by BSA. Oxygen extraction ratio (OER) was calculated as $m\dot{V}O_2 / \dot{D}O_2$.

An estimate of the measurement variation in $c\dot{V}O_2$ and $\dot{D}O_2$ was obtained from the variation in three successive CO measurements and by estimation of oxygen content measurement variation. The latter estimation was based on repeated measurements of both oxygen saturation and haemoglobin concentration.

With the metabolic monitor $\dot{V}O_2$ is measured continuously and each minute the average value of $\dot{V}O_2$, $\dot{V}CO_2$, RQ and $\dot{V}_E$ is sent to a computer. Starting at the onset of arterial blood gas sampling the first 10 consecutive minute values of measured $\dot{V}O_2$ were averaged. Measurement variation was calculated as the standard error of the mean.

Data analysis

The relationship between $\dot{D}O_2$ and $m\dot{V}O_2$ and between $\dot{D}O_2$ and $c\dot{V}O_2$ was analyzed graphically and using linear (least-squares) regression analysis (F-statistic). Oxygen supply dependency was defined as a significant linear relationship ($p<0.05$) between $\dot{V}O_2$ and $\dot{D}O_2$. A method described by Stratton et al. (18) was used to calculate the contribution of mathematic coupling to the correlation coefficient and the slope of the regression line between $c\dot{V}O_2$ and $\dot{D}O_2$ (see addendum).

Table 1A. Clinical characteristics of 13 postoperative patients.

Pat	Sex	Age	Operation
1	F	87	Aortic bifurcation prosthesis
2*	F	51	Removal of bifurcation prosthesis, axillofemoral bypass
3	M	78	Aortic bifurcation prosthesis
4	F	40	Revascularisation of superior mesenteric and right renal artery
5	M	68	Aortic bifurcation prosthesis
6	M	48	Aortic bifurcation prosthesis
7	F	74	Aortic bifurcation prosthesis
8*	M	61	Aortic bifurcation prosthesis
9	M	61	Aortic bifurcation prosthesis
10	M	64	Aortic bifurcation prosthesis
11*	F	62	Splenectomy for ruptured spleen
12	M	64	Aortic bifurcation prosthesis for ruptured aneurysm of abdominal aorta
13	M	51	Aortic bifurcation prosthesis

* Patient with significant correlation between $\dot{D}O_2$ and $m\dot{V}O_2$

Table 1B. Clinical characteristics of 7 septic patients.

Pat	Sex	Age	Diagnosis	Positive cultures obtained from:§
14	M	64	Peritonitis	Abdomen (3), neck (3) thorax (3), blood (2)
15	M	82	Urosepsis	Blood and urine (0,1)
16	F	45	Peritonitis, abscess	Blood (1)
17*	M	40	Urosepsis, liver cirrhosis	Urine (0)
18	F	66	Peritonitis after sigmoid perforation	-
19	F	70	Multiple abscesses	Urine (1)
20	F	76	Wound infection	Blood (0), urine (1) wound (1), blood (3)

* Patient with significant relation between $\dot{D}O_2$ and $m\dot{V}O_2$
§ Between brackets: number of days prior to measurement

Results

Patient characteristics of both groups are shown in tables 1A and 1B. Patients were ventilated with inspired oxygen fractions between 30% and 60%. Eighteen patients were ventilated with intermittent positive pressure, two were ventilated with continuous positive pressure of 4 and 8 cm H_2O.
SAPS in group I ranged from 8 to 28 (median 12) and from 12 to 20 in group II (median 15). ICU survival in group I was 92%, in group II 57%.

The median $m\dot{V}O_2$ in group I was 143 ml/min/m² (range 70 to 322 ml/min/m²), median $c\dot{V}O_2$ was 130 ml/min/m² (range 51 to 279 ml/min/m²), and $\dot{D}O_2$ ranged from 225 to 948 ml/min/m² (median 397 ml/min/m²). In group II the median $m\dot{V}O_2$ was 167 ml/min/m² (range 99 to 228 ml/min/m²), median $c\dot{V}O_2$ was 154 ml/min/m² (range 56 to 270 ml/min/m²), and $\dot{D}O_2$ ranged from 237 to 1238 ml/min/m² (median 582 ml/min/m²). The estimated measurement variation in $\dot{D}O_2$ was 6.3%. The measurement variation in $c\dot{V}O_2$ was 16% and in $m\dot{V}O_2$ 1.5%. Individual correlation coefficients between $c\dot{V}O_2$ and $m\dot{V}O_2$ ranged from 0.000 to 0.839. When data of all patients were combined, $m\dot{V}O_2$ and $c\dot{V}O_2$ were significantly correlated ($R=0.757$, $p<0.0001$).

In the present study four possible results concerning the $\dot{V}O_2$-$\dot{D}O_2$ relationship in an individual patient could be found: a) a significant correlation between $m\dot{V}O_2$ and $\dot{D}O_2$, and between $c\dot{V}O_2$ and $\dot{D}O_2$, b) a significant relation between $m\dot{V}O_2$ and $\dot{D}O_2$, but not between $c\dot{V}O_2$ and $\dot{D}O_2$, or vice versa (c), or d) no relation between either $m\dot{V}O_2$ and $\dot{D}O_2$ or $c\dot{V}O_2$ and $\dot{D}O_2$. The number of patients in each of these categories is summarized in table 2.

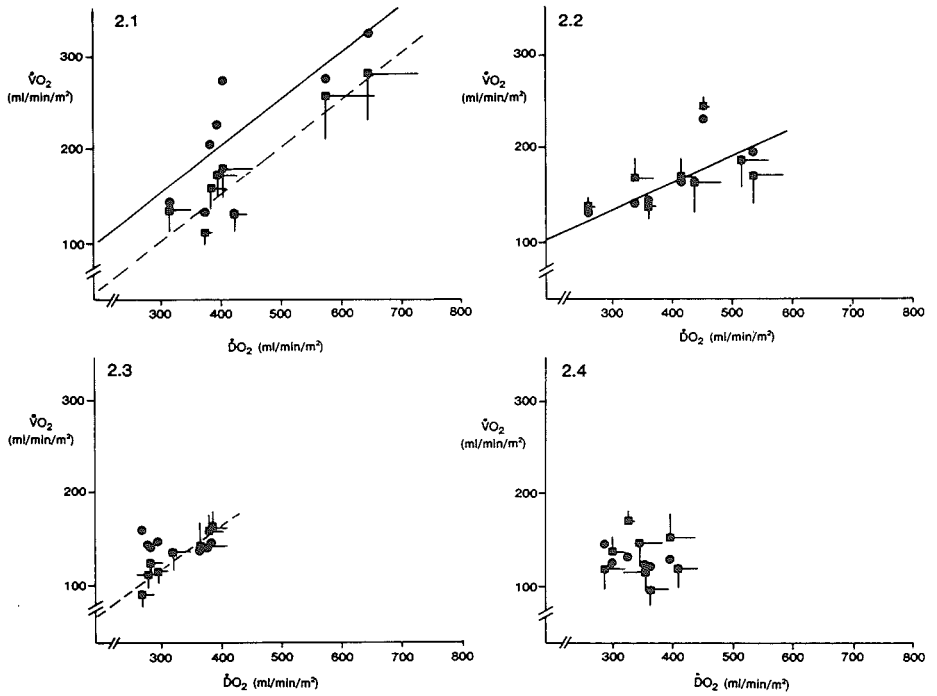
Table 2. Occurrence of oxygen supply dependency (OSD) in postoperative and septic patients when $\dot{V}O_2$ is measured by respirometry ($m\dot{V}O_2$) or calculated by the Fick method ($c\dot{V}O_2$).

		Postoperative			Septic		
		$c\dot{V}O_2$			$c\dot{V}O_2$		
		OSD	no OSD	Total	OSD	no OSD	Total
$m\dot{V}O_2$	OSD	2	1	3	0	1	1
	no OSD	5	5	10	3	3	6
	Total	7	6	13	3	4	7

The two different methods of $\dot{V}O_2$ determination lead to opposing conclusions on the existence of pathologic oxygen supply dependency in six postoperative and in four septic patients.

Serial measurements of $\dot{V}O_2$ and $\dot{D}O_2$ in four typical individual patients are shown in Fig. 2. In each figure $m\dot{V}O_2$ and $c\dot{V}O_2$ are plotted against $\dot{D}O_2$. Fig. 2.1 shows the results from patient 8: both $m\dot{V}O_2$ and $c\dot{V}O_2$ increase with increasing $\dot{D}O_2$. A linear correlation between $m\dot{V}O_2$ and $\dot{D}O_2$ is found (R^2=0.589, $p<0.05$, regression line y=0.50x-9), as well as between $c\dot{V}O_2$ and $\dot{D}O_2$ (R^2=0.848, $p<0.002$, regression line y=0.50x-41). The $\dot{D}O_2$ in this patient was well above the normal critical $\dot{D}O_2$, therefore pathologic oxygen supply dependency seemed to exist in this patient, according to both $m\dot{V}O_2$ and $c\dot{V}O_2$. The median oxygen extraction ratio (OER) was 0.47 (range 0.31 to 0.67). In patient 2 (Fig. 2.2) there was a significant relation between $m\dot{V}O_2$ and $\dot{D}O_2$ (R^2=0.607, $p<0.05$, y=0.28x+54), but not between $c\dot{V}O_2$ and $\dot{D}O_2$. In this patient the results of calculation and measurement of $\dot{V}O_2$ lead to opposing conclusions on the existence of oxygen supply dependency. The median OER was 0.39 (range 0.36 to 0.51). In patient 6 (Fig. 2.3), $m\dot{V}O_2$ is independent of $\dot{D}O_2$, while $c\dot{V}O_2$ shows a linear correlation with $\dot{D}O_2$ (R^2=0.870, $p<0.001$, y=0.47x-21). The median OER was 0.46 (range 0.37 to 0.60). In this patient, as in patient 2, the different methods for determination of $\dot{V}O_2$ lead to opposing conclusions. In patient 7 (Fig. 2.4) no apparent relationship between either $m\dot{V}O_2$ and $\dot{D}O_2$ or $c\dot{V}O_2$ and $\dot{D}O_2$ was found, so the two methods for determination of $\dot{V}O_2$ lead to the same conclusion: no oxygen supply dependency. The OER ranged from 0.29 to 0.50 (median 0.34).

In several patients body temperature increased during the study period; in patients with linearly related $m\dot{V}O_2$ and $\dot{D}O_2$ the median increase was 4.9 °C, in patients with unrelated $m\dot{V}O_2$ and $\dot{D}O_2$ the median increase was 1.5 °C.



Figures 2.1 to 2.4. Typical examples of $\dot{V}O_2$-$\dot{D}O_2$ relationship in individual patients. $\dot{V}O_2$ was measured by respirometry ($m\dot{V}O_2$, ●) as well as calculated by the Fick method ($c\dot{V}O_2$, ■). Vertical bars indicate estimated measurement variation (SD) in $c\dot{V}O_2$, horizontal bars indicate $\dot{D}O_2$ variation. Solid line is regression line depicting relationship between $m\dot{V}O_2$ and $\dot{D}O_2$, dashed line is regression line for $c\dot{V}O_2$ and $\dot{D}O_2$.

Discussion

Pathologic dependency of oxygen uptake ($\dot{V}O_2$) on oxygen delivery ($\dot{D}O_2$) has been reported in patients with ARDS, sepsis, chronic congestive heart failure, acute liver failure or after cardiopulmonary bypass operation (3-12). We investigated the influence of an artifact due to calculation of $\dot{V}O_2$ from cardiac output and arteriovenous oxygen content difference in a group of postoperative and septic patients. In each patient $\dot{V}O_2$ was calculated by the Fick method ($c\dot{V}O_2$) as well as measured by respirometry ($m\dot{V}O_2$). In 10 patients $c\dot{V}O_2$ was significantly correlated with $\dot{D}O_2$, but in only 2 of these $m\dot{V}O_2$ also correlated with $\dot{D}O_2$. In 2 other patients there was a significant correlation between $m\dot{V}O_2$ and $\dot{D}O_2$, but not between $c\dot{V}O_2$ and $\dot{D}O_2$. Apparently, the two different methods to determine $\dot{V}O_2$ may lead to opposing conclusions on whether or not $\dot{V}O_2$ and $\dot{D}O_2$ are related in an individual patient.

We hypothesized that the conclusions on the $\dot{V}O_2$-$\dot{D}O_2$ relationship based on $c\dot{V}O_2$ may be erroneous, partly because of mathematic coupling of $c\dot{V}O_2$ and $\dot{D}O_2$. Mathematic coupling of $c\dot{V}O_2$ and $\dot{D}O_2$ is introduced by the use of arterial oxygen content and cardiac output in both the calculation of $\dot{D}O_2$ and $c\dot{V}O_2$. Mathematic coupling of $c\dot{V}O_2$ and $\dot{D}O_2$ may produce a correlation between these variables, or it may obscure an existing correlation (13), and its influence is stronger when the measurement error in $c\dot{V}O_2$ and $\dot{D}O_2$ is larger. We determined the measurement error in $c\dot{V}O_2$ to be 16%. From the plot of the difference between paired values $m\dot{V}O_2$ and $c\dot{V}O_2$ against $m\dot{V}O_2$ (Fig. 3) it appears that differences are spread equally over the range of observed $m\dot{V}O_2$ values. This suggests a large random error in $c\dot{V}O_2$ (the $m\dot{V}O_2$ is the "gold standard").

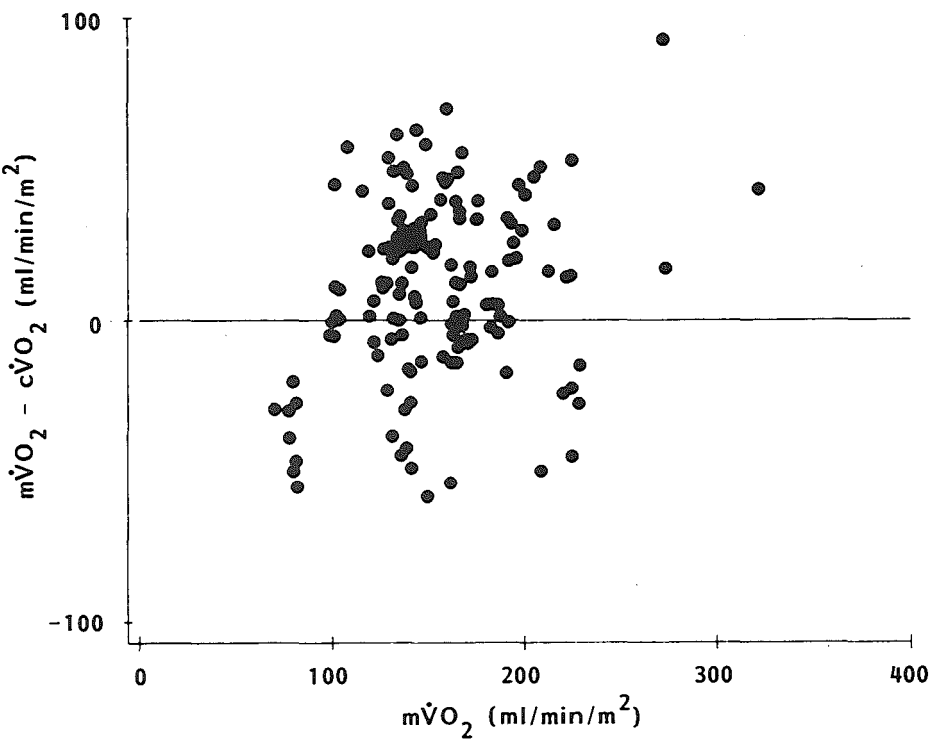


Figure 3. Plot of the difference between $\dot{V}O_2$ measured by respirometry ($m\dot{V}O_2$) and $\dot{V}O_2$ calculated by the Fick method ($c\dot{V}O_2$) versus $m\dot{V}O_2$ in 20 critically ill patients.

To demonstrate the influence of mathematic coupling in a patient with significantly correlated $c\dot{V}O_2$ and $\dot{D}O_2$, but unrelated $m\dot{V}O_2$ and $\dot{D}O_2$ (patient nr. 6), we calculated the contribution of mathematic coupling to the correlation coefficient and slope of the regression line between $c\dot{V}O_2$ and $\dot{D}O_2$. It appeared that the main part of the correlation between $c\dot{V}O_2$ and $\dot{D}O_2$, as well as of the slope of the regression line is attributable to mathematic coupling of $c\dot{V}O_2$ and $\dot{D}O_2$ (see addendum). This shows that $c\dot{V}O_2$ may be unsuitable for the investigation of the $\dot{V}O_2$-$\dot{D}O_2$ relationship, because of mathematic coupling.

In several studies the relationship between $\dot{V}O_2$ and $\dot{D}O_2$ in ARDS or septic patients has been compared to that in control patients (3,4,9,19,20). A higher correlation coefficient between $\dot{V}O_2$ and $\dot{D}O_2$ in the ARDS group than in the control group has been suggested to prove that mathematic coupling is irrelevant in the analysis of the relationship between $c\dot{V}O_2$ and $\dot{D}O_2$ (21,22). However, since the measurement variation in cardiac output determined by thermodilution has been shown to depend on the mode of ventilation (23,24), the contribution of mathematic coupling to the relationship between $c\dot{V}O_2$ and $\dot{D}O_2$ in the ARDS/sepsis group may be larger, when in this group more patients are mechanically ventilated than in the control group. This results in a higher correlation coefficient between $\dot{V}O_2$ and $\dot{D}O_2$, which is interpreted as more oxygen supply dependency in the ARDS/sepsis group.

In the present study, a significant correlation between $c\dot{V}O_2$ and $m\dot{V}O_2$ data (pooled from all patients) was found, as previously reported by Chappell (25). Several studies used this indirect evidence as justification to study the $\dot{V}O_2$-$\dot{D}O_2$ relationship by determining $c\dot{V}O_2$ instead of $m\dot{V}O_2$ (4,10,21,22,25). However, a significant correlation coefficient between pooled $m\dot{V}O_2$ and $c\dot{V}O_2$ data is insufficient evidence. The error in using $c\dot{V}O_2$ occurs, because the measurement variation in cardiac output and arterial blood oxygen content is present in both $c\dot{V}O_2$ and $\dot{D}O_2$.

Mathematic coupling of $\dot{D}O_2$ and $c\dot{V}O_2$ may partly explain why studies using $c\dot{V}O_2$ report pathologic oxygen supply dependency in ARDS patients (3-6), whereas a study using $m\dot{V}O_2$ reports lack of relationship between $\dot{V}O_2$ and $\dot{D}O_2$ in ARDS patients (14). Also, in the present study 10 out of 13 postoperative and 6 out of 7 septic patients showed no apparent relationship between $m\dot{V}O_2$ and $\dot{D}O_2$, in contrast to the result of other studies (7-9,19,20,26). Several other factors (besides mathematic coupling) may explain these conflicting results. Firstly, patients in our study may not have been as severely ill as those in other studies, and therefore not "ill enough" to develop pathologic oxygen supply dependency. The high SAPS score in both patient groups and the high mortality rate in the septic patients in our study seem to plead against this. Secondly, the $\dot{D}O_2$ in some of our patients could have been too high to be able to detect pathologic oxygen supply dependency. This seems unlikely as the $\dot{D}O_2$ range in our study is comparable to that of studies reporting pathologic oxygen supply dependency. Thirdly, the $\dot{D}O_2$ range in some patients may have been too narrow to disclose simultaneous $\dot{V}O_2$ variations.

A linear relationship between $m\dot{V}O_2$ and $\dot{D}O_2$ above the normal critical $\dot{D}O_2$ level was found in four patients (three out of 13 postoperative, one out of 7 septic). The $\dot{V}O_2$-$\dot{D}O_2$ relationship in these patients may either represent pathologic oxygen supply dependency or physiologic coupling of $\dot{V}O_2$ and $\dot{D}O_2$ by metabolic rate, because in these patients body temperature increased between 2.3 and 5.1 °C during the study period. Additional observations on postoperative and septic patients are needed to clarify this issue.

In summary, we have shown that mathematic coupling of $\dot{D}O_2$ and $\dot{V}O_2$ calculated by the Fick method may lead to erroneous conclusions concerning the $\dot{V}O_2$-$\dot{D}O_2$ relationship in postoperative and septic patients. This may partly explain the controversy on whether or not pathologic oxygen supply dependency exists.

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Addendum

Calculation of the contribution of mathematic coupling to the regression and correlation coefficient between $c\dot{V}O_2$ and $\dot{D}O_2$ in patient 6 (Fig. 2.3)

Measurement data

Nr.	$m\dot{V}O_2$	$c\dot{V}O_2$	$\dot{D}O_2$	CO	C_aO_2	$C_{\bar{v}}O_2$
1	135	135	318	4.1	147	84
2	137	141	363	4.8	143	87
3	143	113	277	3.7	142	84
4	160	90	268	3.6	141	94
5	141	158	378	5.0	143	83
6	141	124	281	3.8	140	78
7	146	160	383	5.2	139	81
8	146	114	294	3.9	142	87
mean	144	129	320	4.3	142	85
SD	8	24	48	0.6	2	5

Abbreviations: Nr. = number of measurement set; other abbreviations as in the main text.

To investigate whether there is a significant relationship between $\dot{V}O_2$ and $\dot{D}O_2$ linear regression analysis is performed. The following regression line is found: $c\dot{V}O_2=0.47x\dot{D}O_2-21$. The correlation coefficient between $c\dot{V}O_2$ and $\dot{D}O_2$ is 0.93. There is no significant relationship between $m\dot{V}O_2$ and $\dot{D}O_2$. A method described by Stratton et al. (18) is used to calculate the contribution of mathematic coupling to the correlation coefficient and the slope of the regression line between $c\dot{V}O_2$ and $\dot{D}O_2$.

The slope of the measurement errors (β_e) is 0.40 (equation 19), whereas the slope of the regression line is 0.47. The largest part of the slope can thus be attributed to measurement error. The measurement variation in $\dot{D}O_2$ is too large relative to the actual $\dot{D}O_2$ variation to allow a correction of the slope for mathematic coupling. The correlation of the measurement errors (σ_e) is 0.91 (equation 25), whereas with linear regression a correlation coefficient between $c\dot{V}O_2$ and $\dot{D}O_2$ of 0.93 is found. As with the slope, the largest part of the correlation coefficient is due to mathematic coupling. Because the measurement variation of $c\dot{V}O_2$ is too large relative to the actual $\dot{V}O_2$ variation, the corrected (true) correlation coefficient between $c\dot{V}O_2$ and $\dot{D}O_2$ cannot be calculated.

Using eight measurements of $\dot{D}O_2$ and $\dot{V}O_2$ in an individual patient, the actual $\dot{D}O_2$ variation should be at least 2000 ml/min/m² to be able to correct for mathematic coupling. When only spontaneous and routine ICU therapy-induced $\dot{D}O_2$ variations (±500 ml/min/m²) are available (as in the present study), at least 20 measurements of $c\dot{V}O_2$ and $\dot{D}O_2$ ought to be performed, after which a correction for mathematical coupling could be applied.

Chapter 5

INDEPENDENT OXYGEN UPTAKE AND OXYGEN DELIVERY IN SEPTIC AND POSTOPERATIVE PATIENTS

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Introduction

Sepsis remains a frequent complication in surgical patients, despite measures to prevent infection. Especially patients with septic shock have a high mortality. Although during the hyperdynamic phase of sepsis oxygen delivery ($\dot{D}O_2$ = cardiac output x arterial blood oxygen content) is increased, it has been found that oxygen uptake ($\dot{V}O_2$) changes linearly with $\dot{D}O_2$ (1-7). The close relationship between $\dot{V}O_2$ and $\dot{D}O_2$ has been termed pathologic supply dependency of oxygen uptake, because it occurs at $\dot{D}O_2$ levels where $\dot{V}O_2$ is independent of $\dot{D}O_2$ in non-septic patients. Pathologic oxygen supply dependency may indicate inadequate tissue oxygenation (oxygen debt) (6).

In studies reporting pathologic oxygen supply dependency, $\dot{V}O_2$ was calculated by the Fick method (1-7). Previously, we have shown that the interdependence of calculated $\dot{V}O_2$ and $\dot{D}O_2$ due to shared variables may lead to erroneous conclusions on the $\dot{V}O_2$-$\dot{D}O_2$ relationship (8,9). This must be avoided when the $\dot{V}O_2$-$\dot{D}O_2$ relationship is used to investigate the presence of oxygen debt, and the result is related to therapy, clinical condition and prognosis of an individual patient (2,3,5-7). To investigate whether pathologic oxygen supply dependency exists in septic patients and whether it is related to clinical condition and outcome, we assessed $\dot{V}O_2$ and $\dot{D}O_2$ by independent methods.

Although pathologic oxygen supply dependency was originally thought to occur only in patients with ARDS or sepsis (10), or only in septic patients with elevated lactate concentration (2,3), this phenomenon has also been demonstrated in patients without ARDS or sepsis, such as postoperative patients and patients with congestive heart failure, pulmonary hypertension or chronic obstructive pulmonary disease (11-16). To investigate the $\dot{V}O_2$-$\dot{D}O_2$ relationship in patients without sepsis, independent measurements of $\dot{V}O_2$ and $\dot{D}O_2$ were also performed in postoperative patients.

Methods

Patients

Patients were admitted to the study if (for clinical reasons) they had a pulmonary artery catheter and arterial catheter. Only mechanically ventilated patients (Siemens Servo Ventilator) were studied, because our instrumentation for $\dot{V}O_2$ measurement can only be used in mechanically ventilated patients (17). At high F_IO_2 the accuracy of the $\dot{V}O_2$ determination by this method decreases, so we excluded patients with F_IO_2>60%. Patients with gas leakage from endotracheal cuff or thoracic drain, or active bleeding were excluded to avoid errors in $\dot{V}O_2$ measurement.

For the sepsis group were selected patients with established or suspected sepsis. The diagnosis sepsis had to be confirmed by at least two of the following criteria: 1) identified site(s) of infection, 2) positive cultures of blood or fluid from the primary site(s), 3) fever (body temperature >38 °C), 4) leukocytosis (white blood cell count >10,000/mm^3). Patients after major abdominal surgery were selected for the postoperative group. Measurements in these patients were performed after their arrival at the Intensive Care Unit.

Table 1A. Clinical characteristics of 16 septic patients

Pat	Sex	Age	Diagnosis	Positive cult. from:*
1	M	64	Peritonitis	Abdomen (-3), thorax (-3), blood (-2,0) neck fistula (-3),
2	F	45	Peritonitis, abscess	Blood (-1)
3	M	82	Urosepsis	Blood (0,-1), urine(0,-1)
4	F	70	(Sub)hepatic abscesses	Urine (-1)
5	F	76	Wound infection	Blood (0), urine (-1) wound (-1), blood (-3)
6	F	66	Peritonitis after sigmoid perforation	-
7	M	54	Mesenterial thrombosis	Blood (0), abdomen (-1,+1)
8	M	58	Pneumonia	Sputum (-1)
9	M	62	Pancreatitis	Wound (+2)
10	M	56	Circulatory and respiratory failure after liver transplantation	-
11	M	46	Pancreatitis	Wound (-1,0)
12	M	56	Pancreatitis	Wound (-2)
13	M	73	Pneumonia	Sputum (-1,+1)
14	M	49	Abdominal wall abscess	-
15	M	45	Pneumonia	Blood (-1), ascites (-1,0)
16	M	75	Mediastinitis after oesophageal perforation	-

* Between brackets: number of days prior to (-) or after (+) measurement day

Table 1B. Clinical characteristics of 14 postoperative patients

Pat	Sex	Age	Operation
17	M	68	Aortic bifurcation prosthesis
18	M	48	Aortic bifurcation prosthesis
19	M	64	Aortic bifurcation prosthesis, after ruptured aneurysm of abdominal aorta
20	M	51	Aortic bifurcation prosthesis
21	M	77	Cholecystectomy, complicated by acute respiratory failure
22	M	69	Radical prostatectomy
23	M	80	Aortic bifurcation prosthesis, after ruptured aneurysm of abdominal aorta
24	M	74	Aortic bifurcation prosthesis, after ruptured aneurysm of abdominal aorta
25	M	70	Aortic bifurcation prosthesis
26	M	84	Aortic bifurcation prosthesis
27	M	62	Oesophagus resection and colon interposition
28	M	57	Crawford operation
29	F	68	Crawford operation
30	M	75	Aortic bifurcation prosthesis

Measurement protocol

The study in each patient consisted of eight serial determinations of both oxygen delivery ($\dot{D}O_2$) and oxygen uptake ($\dot{V}O_2$) at 30 min intervals. Each of the serial determinations of $\dot{D}O_2$ and $\dot{V}O_2$ started with arterial blood sampling, immediately followed by measurement of cardiac output. When a patient had bronchopulmonary toilet, or if any adjustment to the mechanical ventilator settings was made, measurements were postponed and resumed after a 15 minute stabilization period. When during the study body temperature changed with more than 1 °C compared with the first measurement, or when less than six measurements had been obtained the patient was excluded from the study. During the study all routine therapeutic interventions were applied as deemed appropriate by the intensive care physician.

Arterial oxygen tensions (P_aO_2, kPa) were measured directly (Radiometer ABL 3, Copenhagen, Denmark), as was arterial haemoglobin saturation (S_aO_2, Radiometer OSM 2). At the first measurement an arterial blood sample was obtained for determination of haemoglobin concentration (Hb, in mmol/l, cyan method, Coulter Counter S+IV) and lactate concentration (normal value <1.80 mmol/l, lactate dehydrogenase, Analytical Chemistry Analyzer, Dupont). A cardiac output computer (Mennen Horizon 2000) was used to determine cardiac output by thermodilution. Body temperature was recorded from the pulmonary artery catheter thermistor.

Oxygen uptake was obtained from continuously performed gas exchange measurements by an automatic metabolic monitor designed specifically for use in mechanically ventilated patients. The metabolic monitor consists of an oxygen analyzer, a carbon dioxide analyzer and a flow meter. The accuracy of the measurement of $\dot{V}O_2$ by the metabolic monitor was determined with laboratory tests simulating the conditions, flows and gas exchange that may be expected in critically ill patients. A maximal error in $\dot{V}O_2$ measurement of 3% of the minute values was found (17).

Calculations

Arterial blood oxygen content (C_aO_2, ml/dl) was calculated from: $C_aO_2=(2.24xHbxS_aO_2)+(0.02xP_aO_2)$. Oxygen delivery was calculated as $\dot{D}O_2=CIxC_aO_2x10$ in ml/min/m², cardiac index CI=CO/BSA (l/min/m²). Body surface area (BSA) was calculated from height and weight using a standard formula.

With the metabolic monitor $\dot{V}O_2$ is measured continuously and each minute the average minute values of $\dot{V}O_2$, $\dot{V}CO_2$, RQ and $\dot{V}_E$ are sent to a remote computer. Starting at the onset of arterial blood gas sampling the first 10 consecutive minute values of measured $\dot{V}O_2$ were averaged, and normalized for body surface area.

Statistical analysis

In each patient the relationship between $\dot{V}O_2$ and $\dot{D}O_2$ was analyzed using linear (least-squares) regression analysis (F-statistic) according to $\dot{V}O_2 = b \times \dot{D}O2 + a$. The group weighted mean and standard deviation (SD) of the regression coefficient (b) were calculated, in order to reduce the influence of measurements with large standard deviations of b on the group mean b. The following formulae were used:

weighted mean of b: $\Sigma(b/SD^2)/\Sigma(1/SD^2)$,

weighted standard deviation of b: $\sqrt{(1/\Sigma(1/SD^2))}$.

The mean regression coefficient in the septic and postoperative group were compared using Student's t test. Haemodynamic and metabolic parameters of septic and postoperative patients were compared using Student's t test. A p-value smaller than 0.05 was considered significant. Values are reported as mean±SD.

Results

Patient characteristics of both groups are shown in tables 1A and 1B. The postoperative group included patients recovering after elective surgery, as well as patients who underwent emergency surgery for ruptured aneurysm of the abdominal aorta. Patients were ventilated with inspired oxygen fractions between 30% and 60%. Twenty-four patients were ventilated with intermittent positive pressure, six were ventilated with continuous positive pressure of 4 to 10 cm H_2O.

The Simplified Acute Physiology Score (SAPS, ref 18) was 13±6 (range 8 to 28) in postoperative and 15±4 (range 7 to 20) in septic patients. Severity of sepsis score (ref 19) was 17±5 (range 9-24) and multiple organ failure (MOF) score (ref 20) was 7±3 (range 2-9). The intensive care mortality rate in the septic group was 63%, in the postoperative group 14%.

Haemodynamic and metabolic parameters, as well as the doses of inotropic and vasoactive medication used in both patient groups are presented in table 2. Septic patients had higher heart rate, cardiac index, oxygen delivery, and oxygen uptake than postoperative patients. Mean arterial blood pressure was lower in septic patients than in postoperative patients, although the difference was not statistically significant (p=0.06). During the measurements three patients (two septic, one postoperative) had haemodynamic shock, as defined by systolic arterial blood pressure below 90 mm Hg.

Table 2. Haemodynamic and metabolic parameters in septic and postoperative patients (mean±SD, range). See abbreviations section for explanation of abbreviations.

	Septic patients (N=16)		Postoperative patients (N=14)	
HR (/min)	125±19	(93-163)	96±19	(69-141)
CI (l/min/m²)	4.7±1.4	(2.4-6.7)	3.1±0.8	(2.0-4.1)
MAP (mm Hg)	75±14	(60-102)	86±17	(64-116)
PCWP (mm Hg)	14±6	(5-23)	11±6	(3-21)
P_aO_2 (kPa)	11±3	(7-19)	12±3	(8-19)
S_aO_2 (%)	95±3	(88-98)	97±2	(93-99)
C_aO_2 (ml/dl)	13.4±2.4	(9.5-18.2)	15.2±2.5	(10.6-18.5)
$\dot{D}O_2$ (ml/min/m²)	633±209	(265-1011)	481±160	(253-761)
$\dot{V}O_2$ (ml/min/m²)	164±31	(101-220)	136±19	(103-165)
OER	0.28±0.08	(0.16-0.45)	0.31±0.10	(0.20-0.46)
ABL (mmol/l)	2.90±1.60	(0.94-6.14)	2.97±2.38	(0.78-9.73)
Temp (°C)	37.6±1.4	(35.7-40.9)	36.7±1.4	(32.7-38.3)
Inotropic and vasoactive medication doses (in µg/kg/min)				
Dopamine	11±9	(N=11)	6±3	(N=5)
Dobutamine	6±2	(N=2)	5±3	(N=4)
Norepinephrine	0.04±0.02	(N=3)	-	
Nipride	-		0.17±0.08	(N=3)

The intra-individual $\dot{D}O_2$ variation during the study period ((highest $\dot{D}O_2$-lowest $\dot{D}O_2$)/mean $\dot{D}O_2$x100%) was 26±9% (range 13-47%) in septic and 30±9% (range 17-53%) in postoperative patients. These variations were due to therapeutic interventions such as fluid loading and changes in inotropic or vasoactive medication. Body temperature variation (highest-lowest) during the study ranged from 0.1 to 0.8 °C (mean±SD 0.3±0.2) in postoperative and from 0 to 0.9 °C (mean±SD 0.4±0.3) in septic patients.

Individual regression coefficients (slopes) ranged from -0.10 to 0.08 in septic patients, and were different from zero in two out of 16 septic patients (b=0.05 and b=0.08, both $p<0.05$) (table 3). One of these patients had an increased arterial blood lactate level (3.94 mmol/l) and died 7 days after the measurement day, but the other patient had a normal lactate level and survived. In postoperative patients b ranged from -0.07 to 0.09. A statistically significant regression coefficient (b=0.09, $p<0.01$) was found in one postoperative patient, who had a lactate level of 4.50 mmol/l and died 37 days after the measurement day. The weighted mean regression coefficient in the septic group was lower than in the postoperative group (0.02±0.01 vs 0.04±0.01, $p<0.001$). In both groups the weighted mean regression coefficient was significantly different from zero ($p<0.001$).

Table 3. Regression coefficients (b±SE, standard error) of the $\dot{V}O_2$-$\dot{D}O_2$ regression line ($\dot{V}O_2$ = b x $\dot{D}O_2$ + a) in septic and postoperative patients. SURV = Survival (ICU): + = survivor, - = non-survivor, (* $p<0.05$, ** $p<0.01$).

Septic patients (N=16)					Postoperative patients (N=14)				
Nr	b ± SE	ABL	SAPS	SURV	Nr	b ± SE	ABL	SAPS	SURV
1	-0.05±0.03	1.14	12	+	17	0.08±0.04	-	9	+
2	-0.01±0.06	2.03	19	-	18	-0.07±0.06	2.27	8	+
3	0.01±0.03	5.20	19	+	19	0.05±0.10	9.73	28	-
4	0.00±0.03	1.99	19	-	20	-0.06±0.05	2.08	8	+
5	-0.01±0.05	1.49	15	+	21	0.03±0.10	0.78	14	+
6	0.04±0.05	6.14	20	-	22	0.00±0.04	1.44	16	+
7	0.06±0.04	4.51	19	-	23	0.09±0.02**	4.50	11	-
8	0.00±0.05	2.59	15	-	24	-0.03±0.07	1.98	19	+
9	0.00±0.04	1.57	15	-	25	0.04±0.02	1.44	8	+
10	0.08±0.03*	3.94	11	-	26	0.08±0.03	2.65	10	+
11	-0.02±0.06	2.65	11	+	27	-0.02±0.05	1.65	15	+
12	0.03±0.03	3.01	14	-	28	0.07±0.03	4.68	8	+
13	0.01±0.02	0.94	16	-	29	0.02±0.04	3.92	15	+
14	0.00±0.03	2.45	17	+	30	0.02±0.02	1.43	17	+
15	-0.10±0.06	5.09	7	-					
16	0.05±0.02*	1.72	10	+					

Discussion

In the present study on septic and postoperative patients no dependency of $\dot{V}O_2$ on $\dot{D}O_2$ was found. The relation of pathologic oxygen supply dependency to the severity of circulatory failure, multiple organ failure and mortality of septic patients, that has been previously reported by others (1-7), could not be confirmed. The contrast between our results and those of other investigators may be explained by differences in patients studied and by different methods to assess $\dot{V}O_2$.

To allow comparison of our results with those of other studies we used the same inclusion criteria for the sepsis group as others (4-6). The sepsis severity score, simplified acute physiology score, multiple organ failure score and mortality rate indicate that the severity of sepsis in patients in our study was similar to that in studies by others (1-7). The $\dot{D}O_2$ of septic patients in our study was equal to that in some studies that did find pathologic oxygen supply dependency (2,3,5), although some studies report considerably lower $\dot{D}O_2$s than we do (1,4,6). Haupt et al. demonstrated that pathologic oxygen supply dependency existed only in septic patients with signs of circulatory failure who had an increased arterial blood lactate level (indicating oxygen debt), but not in patients with normal lactate (2,3). A similar finding was described by Astiz et al. (1). In our study the arterial blood lactate concentration was increased in 11 (out of 16) septic patients, with an average lactate level of 3.6 mmol/l, which is slightly lower than the average lactate concentrations of 3.8 to 8.0 mmol/l reported by others who found pathologic oxygen supply dependency (1-4), and may indicate that patients in our study had less severe impairment of tissue perfusion prior or during measurements. On the other hand, the mean arterial blood pressure of septic patients in our study was equal to or lower than that in several studies by others (1-3,5,6), which may indicate that circulatory failure at the time of measurements was comparable to that in other studies. Circulatory failure in the patient group studied by Kaufman et al. (4) was more severe than in our group, where only two out of 16 septic patients were in shock at the time of study. However, the identical criteria to diagnose sepsis and the similar $\dot{D}O_2$ range, arterial blood pressure and arterial blood lactate concentration as in several other studies (1-3,5,6) make it unlikely that a difference in the clinical condition of patients studied can fully explain why we observed no pathologic oxygen supply dependency, whereas other studies did.

A more likely explanation for the lack of pathologic oxygen supply dependency in our patients is that we assessed $\dot{V}O_2$ and $\dot{D}O_2$ by independent methods, while in studies by others reporting pathologic oxygen supply dependency, $\dot{V}O_2$ was calculated by the Fick method. If $\dot{V}O_2$ is calculated by the Fick method, $\dot{V}O_2$ and $\dot{D}O_2$ share cardiac output and arterial blood oxygen content as common components.

This may result in a spurious $\dot{V}O_2$-$\dot{D}O_2$ dependency or overestimation of actual $\dot{V}O_2$-$\dot{D}O_2$ dependency because of mathematic coupling of $\dot{V}O_2$ and $\dot{D}O_2$ (8,9,21,22). Although the contribution of $\dot{V}O_2$-$\dot{D}O_2$ coupling to the finding of oxygen supply dependency has been disputed (23,24), we demonstrated that mathematic coupling of $\dot{V}O_2$ and $\dot{D}O_2$ may indeed result in an apparent pathologic oxygen supply dependency (8). Mathematic coupling may explain why investigators who used the Fick method to determine $\dot{V}O_2$ reported pathologic oxygen supply dependency in patients with ARDS (10,25-28), congestive heart failure (12,16), or pulmonary hypertension (13), whereas (sometimes the same) investigators when using independent methods to determine $\dot{V}O_2$ and $\dot{D}O_2$ found no pathologic oxygen supply dependency in these patients (ARDS: (29,30), congestive heart failure: (31), pulmonary hypertension: (31)).

In our study the $\dot{V}O_2$-$\dot{D}O_2$ regression line had an average positive slope of 0.02 in the septic group and 0.04 in the postoperative group. This slight positive slope of the $\dot{V}O_2$-$\dot{D}O_2$ line in the supply-independent zone has been previously reported in experimental studies (32,33) and in septic patients (34), and might reflect delivery-dependent oxygen demand of the kidney and the heart. Any alteration in metabolic rate and oxygen demand during $\dot{V}O_2$-$\dot{D}O_2$ measurements may result in simultaneous changes of $\dot{V}O_2$ and $\dot{D}O_2$ and thus suggest a causal relationship between the two variables. A true dependency of $\dot{V}O_2$ on $\dot{D}O_2$ can not be excluded, so the analysis of the $\dot{V}O_2$-$\dot{D}O_2$ relationship does not provide reliable information on the presence of "oxygen debt".

The fact that we found no close relationship between $\dot{V}O_2$ and $\dot{D}O_2$ in a group of septic patients with multiple organ failure, increased lactate concentration and high mortality rate may indicate that septic patients in stable haemodynamic condition no longer have an "oxygen debt", or that "oxygen debt" is not detected by analysis of the $\dot{V}O_2$-$\dot{D}O_2$ relationship. On the basis of the present study we cannot exclude that pathologic oxygen supply dependency and "oxygen debt" exist at an earlier stage of sepsis or during septic shock. In experimental studies using direct measurement of $\dot{V}O_2$ and calculation of $\dot{D}O_2$, pathologic oxygen supply dependency was demonstrated during endotoxemia and bacteremia in dogs (32,33,35), but this phenomenon was not found in septic patients in our study.

In patients with septic shock, inadequate tissue perfusion and oxygenation may already be evidenced by the finding of low arterial blood pressure. Then the measurement of $\dot{V}O_2$ and $\dot{D}O_2$, and analysis of their relationship does not provide additional information on tissue oxygenation and may not be useful in guiding therapy or predicting outcome of individual patients.

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Chapter 6

THE EFFECTS OF PROSTAGLANDIN E_1 ON CRITICAL OXYGEN DELIVERY AND ARTERIAL BLOOD LACTATE DURING REDUCTION OF CARDIAC OUTPUT BY POSITIVE END-EXPIRATORY PRESSURE

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Introduction

Under physiologic conditions oxygen uptake ($\dot{V}O_2$) by the body is dependent on metabolic rate and not limited by oxygen delivery. Oxygen delivery ($\dot{D}O_2$) is defined as the product of cardiac output (CO) and oxygen content of arterial blood (C_aO_2). When CO or C_aO_2, or both decrease, $\dot{D}O_2$ decreases but $\dot{V}O_2$ is maintained by increased oxygen extraction. Only below a critical $\dot{D}O_2$, $\dot{V}O_2$ becomes dependent on $\dot{D}O_2$, because increasing oxygen extraction can no longer compensate for the fall in $\dot{D}O_2$. This is called physiologic supply dependency of $\dot{V}O_2$ (1,2). When $\dot{V}O_2$ is limited by $\dot{D}O_2$, anaerobic metabolism and lactate production increase (3).

During sepsis and Adult Respiratory Distress Syndrome (ARDS) $\dot{V}O_2$ may be dependent on $\dot{D}O_2$ over an increased range of $\dot{D}O_2$, compared to normal, so that the critical $\dot{D}O_2$ is increased. This phenomenon is denoted as pathologic oxygen supply dependency (4-6). It is associated with inadequate oxygen extraction (6).

For sepsis and shock, peripheral vasodilation may underlie maldistribution of blood flow, inadequate oxygen extraction, pathologic oxygen supply dependency, lactic acidemia and mortality (7). On the other hand, pharmacologic vasodilation with prostaglandin E_1 (PGE_1) or prostacyclin has been reported to improve $\dot{D}O_2$, $\dot{V}O_2$ (8-11) and oxygen extraction (12) in (postoperative) patients with sepsis and ARDS. The effect of PGE_1 on survival of ARDS patients seems controversial (8,13). In animal models of hypovolemic shock and acute respiratory failure, PGE_1 has a beneficial hemodynamic effect (14-16).

To investigate whether the minimal $\dot{D}O_2$ required to maintain $\dot{V}O_2$ and aerobic metabolism is altered by the vasodilator PGE_1, we measured $\dot{D}O_2$, $\dot{V}O_2$ and arterial blood lactate levels during reduction of CO by ventilation with incremental positive end expiratory pressure.

Methods

We used 12 male Yorkshire pigs, weighing 23±2 kg. Prior to the experiment the animals were fasted for 24 hours but allowed free access to water. Anesthesia was induced with azaperone 2 mg/kg i.m. and pentobarbital 20 mg/kg i.v. and maintained with a continuous infusion of pentobarbital sodium (5 mg/kg/h) and pancuronium bromide (0.2 mg/kg/h) for muscular paralysis. Animals were intubated and ventilated with an air/oxygen mixture (F_IO_2 40%). A Servo 900 B ventilator (Siemens, Stockholm, Sweden) was used with a tidal volume of 15 ml/kg at a frequency of 12 /min. Ventilatory settings were not changed during each experiment. Dextrose 5% in water and 0.9% saline were infused at a rate of 5 ml/kg/h to prevent dehydration.

Instrumentation and measurements

Pigs were studied in the supine position, on a heating blanket. A continuous registration of the electrocardiogram allowed calculation of heart rate (HR, beats/min). A catheter was placed in the right carotid artery for measurement of mean arterial pressure (MAP, mm Hg) and in the right internal jugular vein for fluid administration. A 7F Swan-Ganz catheter (Edwards Laboratories, Santa Ana, Calif.) was advanced into the pulmonary artery via the right external jugular vein for the measurement of central venous pressure (CVP, mm Hg), pulmonary capillary wedge pressure (PCWP, mm Hg) and cardiac output (CO, ml/min/kg), by the thermodilution technique using a computer (REF 1, Edwards Laboratories, Santa Ana, California, USA). The mean of three determinations at end-expiration, using injections of 5 ml iced 5% dextrose, was used. Body temperature (°C) was measured by the thermistor of the pulmonary artery catheter. Arterial blood samples were taken in heparinized syringes for determination of oxygen content. Partial pressure of oxygen (PO_2, mm Hg) was measured by an automated blood gas analyzer (Corning type 175, American Hospital Supply). Haemoglobin (Hb, g/dl) and saturation (SO_2, %) were measured with a Co-oximeter (Instrumentation Laboratories, Lexington, MA). Arterial blood lactate levels (mmol/l) were measured with an UV method (Analytical Chemistry Analyzer, Dupont, Wilmington, DE).

Oxygen uptake ($\dot{V}O_2$, ml/min/kg) was measured with a Deltatrac™ metabolic monitor (Datex, Helsinki, Finland), described previously (17). The metabolic monitor is connected to the outlet of the ventilator to divert all expired gas into a mixing chamber. A paramagnetic differential oxygen sensor measures inspiratory oxygen concentration (F_IO_2) and the O_2-concentration difference between inspired and expired gas (F_IO_2-F_EO_2). The carbon dioxide concentration (F_ECO_2) of the expired gas is measured continuously with an infrared sensor. From these measurements combined with a dilution type flow measurement the Deltatrac calculates $\dot{V}O_2$ with an inaccuracy of less than 2% at F_IO_2 of 40% and PEEP up to 20 cm H_2O, as tested using previously described methods (18).

Prior to measurements the sensors were calibrated with a gas mixture of known composition. Carbon dioxide output ($\dot{V}CO_2$) and $\dot{V}O_2$ are converted to standard temperature and pressure dry gas (STPD) condition.

Calculations

Cardiac output and oxygen uptake were normalized to body weight. Stroke volume was calculated as CO/HR. Arterial oxygen content (C_aO_2, vol %) was calculated from 1.39 x Hb x S_aO_2 + 0.003 x P_aO_2. Oxygen delivery ($\dot{D}O_2$, ml/min/kg) was calculated as CO x C_aO_2 x 10. Oxygen extraction ratio was calculated as $\dot{V}O_2/\dot{D}O_2$. Systemic vascular resistance (SVR) was calculated as (MAP-CVP)/CO x 80 (dynes.sec/cm^5). A five minute average $\dot{V}O_2$ was calculated for each measurement set.

Experimental protocol

Twelve animals were randomly assigned to two groups. One group (N=6) received a continuous intravenous infusion of PGE_1 (Prostin VR, Upjohn Company, Kalamazoo, Mich.) at a dose of 0.2 µg/kg/min during 90 min in the first half of the experiment (t=0-150 min) and an equivalent volume of 0.9% saline during 90 min in the second half of the experiment (t=180-360 min). The other group (N=6) received saline first and PGE_1 in the second period. Since PGE_1 is metabolized to a large extent by normal lungs during a single passage, so that drug concentrations in the systemic circulation may be low (19), PGE_1 was given at a dose of 0.2 µg/kg/min, which is higher than in a previous study in pigs with septic shock (0.1 µg/kg/min) (20), or in clinical studies (25-40 ng/kg/min) (8-11,13).

At 30 min after instrumentation, baseline measurements were performed and blood samples taken. A second set of measurements was performed 15 min later (t=0 min), whereafter infusion of either PGE_1 or saline was started. At t=30 min measurements were repeated, whereafter end-expiratory pressure was increased by 5 cm of H_2O increments at 15 minute intervals up to 20 cm H_2O (t=75 min), each time preceded by a complete measurement set. At t=90 min, PEEP and infusion were discontinued, followed by measurements at t=120 and 150 min. At t=180 min the alternate infusion was started and the same sequence as from t=0-150 min was repeated. After the last measurements (t=360 min) the animal was killed by injection of saturated KCl solution.

Data analysis and statistics

In each animal the critical $\dot{D}O_2$ during PGE_1 or saline was assessed from two series of six measurement sets of $\dot{V}O_2$ and $\dot{D}O_2$ (obtained at t=0-90 and t=180-270 min). Both linear and non-linear regression analysis were used to fit the data, as shown in Fig. 1. The linear regression model uses the intersection of a horizontal plateau of the baseline $\dot{V}O_2$ (mean of the three measurement points at the highest $\dot{D}O_2$) with a regression line formed from points with $\dot{V}O_2$ less than the baseline (1).

In the non-linear model the exponential equation $\dot{V}O_2 = \alpha(1-e^{-\beta \dot{D}O_2})$, that best fits the data is used to determine the critical $\dot{D}O_2$ at the 90th percentile of the plateau (21). We used this model because it is reported to provide a better fit to data than the linear regression approach (22). Prostaglandin E_1 and saline effects were compared after testing for unequal carry-over and time effects (23). Data are expressed as mean±SD. Mann-Whitney tests were used with a p-level of 0.05.

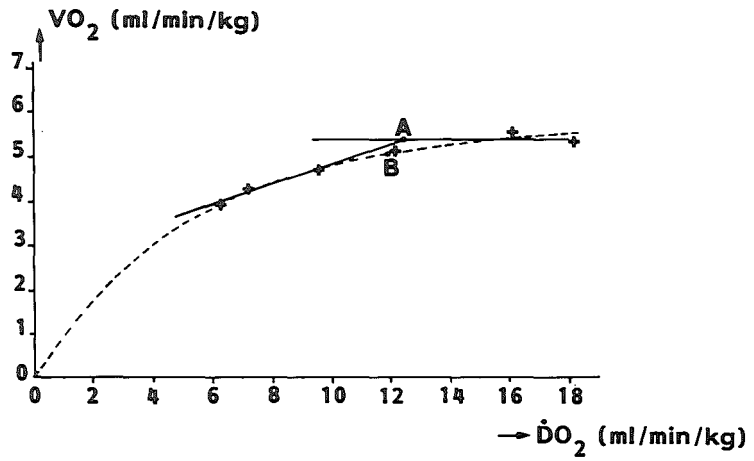

Figure 1. Two methods to calculate the critical $\dot{D}O_2$ level from simultaneous measurements of $\dot{D}O_2$ and $\dot{V}O_2$. Curved line is fit by non-linear model, straight lines are fit by linear model. Pluses indicate actual measurements of $\dot{V}O_2$ and $\dot{D}O_2$ in this animal. The critical $\dot{D}O_2$ levels found by the linear (A) and non-linear (B) model are indicated with dots.

Results

Time-effects and carry-over effects

Some variables changed in time during the experiments. The baseline $\dot{D}O_2$ in the first period (t=0 min) was equal to that in the second (t=180 min), but at t=45 $\dot{D}O_2$ was 11±32% higher than at t=225 ($p<0.005$) and at t=60 10±41% higher than at t=240 min ($p<0.05$). Oxygen uptake during the first and second period was equal, even though body temperature during the first period was lower. At the first baseline (t=0 min) body temperature was 0.8±0.6 °C lower ($p<0.01$) than at the second baseline (t=180 min). At the end of the first period (t=90 min) body temperature was 0.9±0.6 °C lower than at the corresponding measurement in the second period (t=270 min, $p<0.01$). The critical $\dot{D}O_2$ was not significantly different between periods. Oxygen extraction ratio at the critical $\dot{D}O_2$ in the first half of the experiment was 0.48±0.15, in the second half 0.57±0.15 ($p<0.05$). Because there are no unequal carry-over effects, the combined results of the first and second period may be compared for treatment effects.

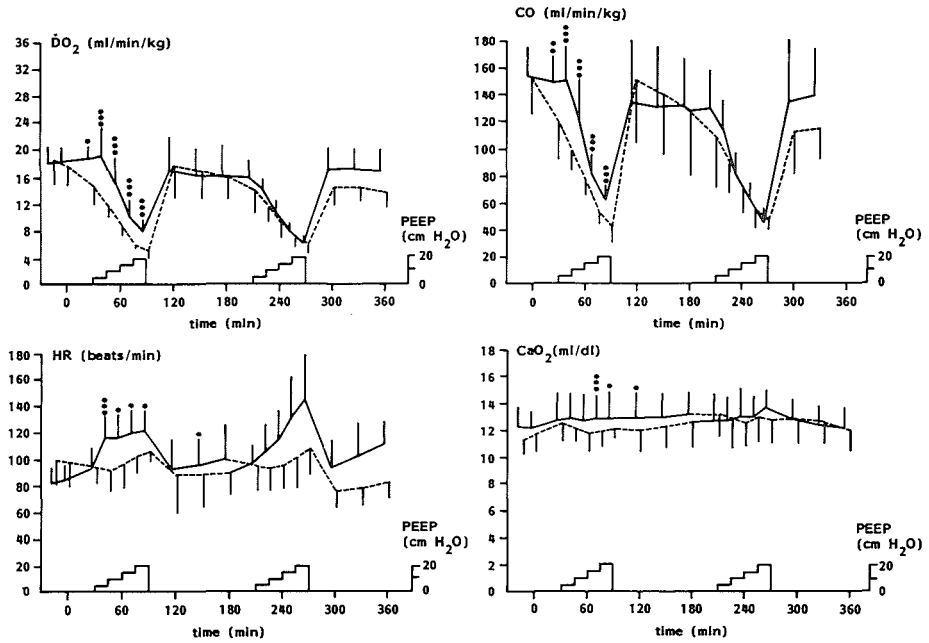

Figure 2A. $\dot{D}O_2$, CO, HR and C_aO_2 (mean±SD) during PGE_1 (interrupted line) and saline (solid line) infusion. Differences between PGE_1 and saline are indicated at the infusion with the highest value (* $p<0.05$, ** $p<0.01$, *** $p<0.005$).

Treatment effects

Oxygen delivery during PGE_1 was lower than during saline infusion before and during PEEP ventilation (Fig. 2A). At t=45/225 min the relative difference was largest, $\dot{D}O_2$ during PGE_1 being 26±17% lower than during saline. Arterial blood oxygen content was lower during PGE_1 infusion than during saline, this was significant at t=75/255, t=90/270 and t=120/300 min, the largest difference being 5.8±8.6% at t=90/270 min. The larger $\dot{D}O_2$ decrease during PGE_1 infusion was mainly due to a larger cardiac output decrease. At t=45/225 min the CO difference was largest: CO was 25±18% lower during PGE_1 than saline. Heart rate (HR) during PGE_1 infusion and PEEP was lower than during saline infusion, the largest difference was found at t=75/255 min, when HR during PGE_1 was 17±17% lower than during saline. Stroke volume (SV) during PGE_1 was lower than during saline at t=30, 45, 60 and 75 min, but was higher during PGE_1 at t=90 min (not statistically significant). Wedge pressure (PCWP) was lower during PGE_1 than during saline infusion, this was significant at t=30/210 (PGE_1 1.7±1.2 vs saline 3.6±2.7 mm Hg, $p<0.05$) and t=60/240 min (PGE_1 7.4±0.9 vs saline 9.3±1.8 mm Hg, $p<0.005$).

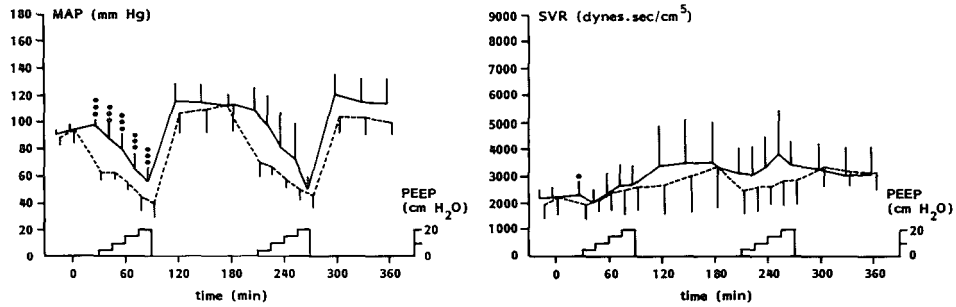

Figure 2B. MAP and SVR (mean±SD) during PGE_1 (interrupted line) and control saline (solid line) infusion. Differences between PGE_1 and saline are indicated at the infusion with the highest value (* $p<0.05$, ** $p<0.01$, *** $p<0.005$).

Compared with saline, the mean arterial blood pressure (MAP) during PGE_1 was at least 18±11% (at t=90) and at most 34±12% (t=30 min) lower than during saline infusion. The lower blood pressure during PGE_1 was partly due to a larger CO decrease, and partly due to a lower systemic vascular resistance (SVR). although the latter was significantly lower only immediately after the start of PGE_1 infusion.

Oxygen uptake ($\dot{V}O_2$) decreased with increased levels of PEEP. As compared with t=0/180 min (baseline), during PGE_1 $\dot{V}O_2$ declined significantly ($p<0.0005$) from t=60/240 on to t=90/270 min, when $\dot{V}O_2$ was 71±5% of the baseline value. During saline $\dot{V}O_2$ declined from t=75/255 min on to 71±7% of baseline at t=90/270 min ($p<0.05$). At t=120/300 min (zero PEEP), $\dot{V}O_2$ was 7.5±8.2% (PGE_1) and 2.8±6.2% (saline) higher than baseline, respectively. A small but statistically significant difference in mean body temperature was noted at t=90/270 min (37.4±1.4 °C during PGE_1 and 37.1±1.3 °C during saline, $p<0.05$). Arterial blood lactate levels were higher during PGE_1 than saline infusion both during and after PEEP ventilation. At t=75/255 min the largest difference was found, when lactate levels were 43±43% higher during PGE_1.

In Fig. 3 the critical $\dot{D}O_2$ determined by linear and non-linear models is shown. With the linear model critical $\dot{D}O_2$ during PGE_1 was 12.5±4.0 and during saline 15.3±4.0 ml/min/kg. Using the non-linear model the critical $\dot{D}O_2$ was 10.5±1.5 (PGE_1) and 13.3±2.7 ml/min/kg (saline). In both models the differences were significant ($p<0.02$). The residual squares sum of the non-linear and linear model was equal, which indicates that the two models fitted equally well to the data. The SD of the critical $\dot{D}O_2$ estimates by the linear model was higher than that of the non-linear model, which may indicate that estimates obtained by the linear model are less accurate. Oxygen extraction ratio (OER) at the critical $\dot{D}O_2$ (linear method) was 0.57±0.15 for PGE_1 and 0.48±0.15 for saline ($p<0.05$). With the non-linear method the critical OER was 0.60±0.07 (PGE_1) and 0.49±0.06 (saline, $p<0.005$).

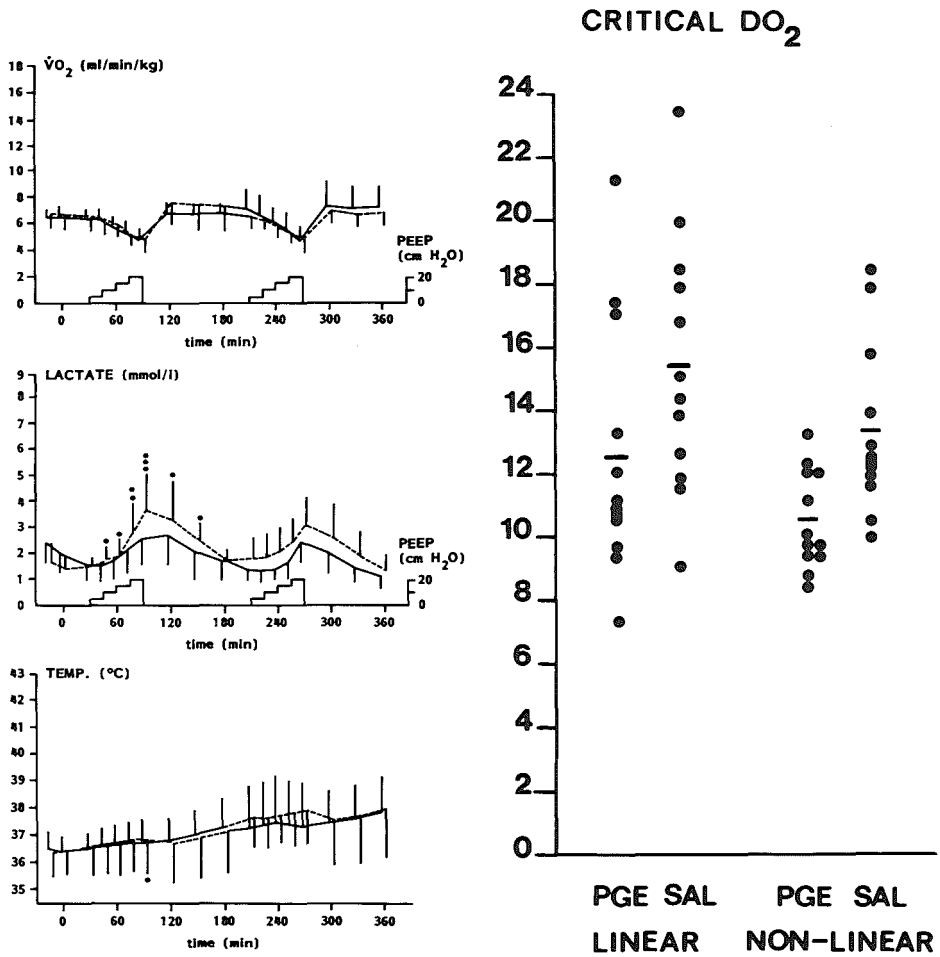

Figure 2C (left). $\dot{V}O_2$, lactate, and body temperature (mean±SD) during PGE_1 (interrupted line) and saline (solid line) infusion. Differences between PGE_1 and saline are indicated at the infusion with the highest value (* $p<0.05$, ** $p<0.01$, *** $p<0.005$).

Figure 3 (right). Critical $\dot{D}O_2$ during PGE_1 and control saline infusion. The critical $\dot{D}O_2$ calculated by linear (L) and non-linear (NL) method are shown. Bars indicate mean.

Discussion

The basis for this study is the observation that vasodilators such as PGE_1 and prostacyclin may increase $\dot{D}O_2$, $\dot{V}O_2$ and oxygen extraction in patients with ARDS and sepsis (8-12). Contrary to this, in sepsis and shock, peripheral vasodilation may underlie maldistribution of blood flow, inadequate oxygen extraction, pathological oxygen supply dependency, lactic acidemia and mortality (7). Studies showing the existence of pathological oxygen supply dependency have been disputed on the basis of methodological considerations (24,25). In an experimental study on sepsis however, it was shown that directly measured $\dot{V}O_2$ is closely related to $\dot{D}O_2$ at higher levels of $\dot{D}O_2$ than normal, implying increased critical $\dot{D}O_2$, caused by impaired oxygen extraction (26).

In the present study, vasodilation with PGE_1 decreased the critical $\dot{D}O_2$ by increasing oxygen extraction. Assuming that the oxygen extraction ratio reflects the balance between the distribution of flow according to tissue needs and the available oxygen exchange surface area (27), our results indicate that this balance is favorably influenced by vasodilation with PGE_1 during reduced oxygen supply. Despite a larger CO decrease, oxygen uptake during PGE_1 infusion was equally well maintained as during saline, so that the oxygen deficit (the difference between oxygen uptake and demand) must have been equal also. A direct effect of PGE_1 to increase oxygen demand and uptake would have been detected after the infusion was started. Furthermore, prostacyclin infused in healthy volunteers did not influence $\dot{V}O_2$ (12).

Arterial lactate concentration was higher during PGE_1. Although the value of the lactate concentration as a measure of tissue hypoxia has been questioned (28,29), lactate rises linearly with oxygen deficit in the tissues and anaerobic metabolism (30-35). Lactate concentration depends on production and on removal from the circulation (36). Therefore, the higher blood lactate during PGE_1 may have been the result of diminished lactate removal due to a lower CO during PGE_1 (36).

Ventilation with PEEP caused a larger decrease in CO with PGE_1 infusion than with saline. Pulmonary capillary wedge pressure and stroke volume (not significant) were lower during PGE_1. The lower heart rate during PGE_1 indicates that PGE_1-induced vasodilation may have resulted in a more pronounced lung stretch depressor reflex. This reflex results in diminished venous return for a given CVP and a lower heart rate and is more pronounced in case of arterial vasodilation (37,38). The decrease of CO during PGE_1 infusion at the onset of the experiment may be explained by decreased venous return due to venous vasodilation and relative hypovolemia.

Whether the effect of PGE_1 to lower the critical $\dot{D}O_2$ by increasing oxygen extraction explains the reported beneficial metabolic and survival effects of PGE_1, cannot be deduced from our study, because in the present study normal pigs were used.

Several other studies employing PGE_1 report increased $\dot{V}O_2$, but no change in oxygen extraction (9-11). Therefore, the increased $\dot{V}O_2$ in these studies was the result of increased $\dot{D}O_2$ and pathological oxygen supply dependency. Bihari et al. found that prostacyclin not only increased $\dot{D}O_2$, but in 10 out of 27 ARDS patients also increased oxygen extraction (12).

In summary, the vasodilator PGE_1 decreases the critical $\dot{D}O_2$ in anesthetized normal pigs. The hypothesis that this may explain the beneficial effect of PGE_1 on $\dot{D}O_2$, $\dot{V}O_2$ and outcome in ARDS/sepsis patients should be evaluated in experimental and clinical studies.

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CHAPTER 7

GENERAL DISCUSSION AND SUMMARY

By determination of oxygen uptake and carbon dioxide output an individual patient's energy expenditure can be calculated, to guide caloric supply (1). It is thereby assumed that the oxygen uptake is sufficient to meet the oxygen demand of aerobic energy metabolism. In critically ill patients however it has been described that oxygen uptake is limited by oxygen supply, which results in "oxygen debt" (2). The "oxygen debt" has been related to lactic acidosis, multiple organ failure and mortality (2-4). The determination of oxygen uptake has been described as a method to detect "oxygen debt" and to optimize ventilatory and circulatory therapy in critically ill patients (2,5,6).

The question arises how the determination of oxygen uptake can be used for the assessment of energy requirements as well as for the detection of an "oxygen debt" of energy metabolism. In this thesis the possible limitation of aerobic energy metabolism by inadequate oxygen uptake is investigated (chapters 4 to 6). Furthermore, two important methodological and clinical problems in the assessment of energy expenditure in spontaneously breathing and mechanically ventilated patients are discussed (chapters 2 and 3). In section 1.2 of the introduction different techniques to determine energy expenditure, oxygen uptake, and carbon dioxide output are discussed.

In chapter 2 the reproducibility of resting energy expenditure determination by indirect calorimetry was investigated in 50 healthy subjects and 10 patients with cirrhosis of the liver. In each subject energy expenditure was measured during 30 minutes, once under standard (basal) conditions and three times under non-standard (resting) conditions. No systematic within-subject difference between the three resting energy expenditure measurements was found. The variation coefficient of these measurements was 5±3% in controls and 5±2% in patients. It is concluded that reproducible measurements of resting energy expenditure can be performed by indirect calorimetry.

In chapter 3 it was investigated whether the energy expenditure of a critically ill patient, measured on a single day reliably estimates energy expenditure on subsequent days of a patient's ICU stay. In 60 patients energy expenditure was measured by indirect calorimetry during two to seven days, and the relation between the clinical condition and energy expenditure was investigated. The clinical condition was scored by daily determination of the simplified acute physiology score (SAP-Score). During one week energy expenditure variations of up to 30% of energy expenditure measured on the first day were observed. These variations of energy expenditure were in part correlated with changes in body temperature. No statistically significant correlation between energy expenditure and clinical condition (SAP-Score) was found.

There was no indication that energy expenditure changed systematically in time. The large day-to-day variability of energy expenditure leads to the conclusion that it is advisable to adapt the caloric supply to the result of daily measurement of energy expenditure if a balance between caloric supply and demand is intended.

Despite the known detrimental effects of overfeeding and underfeeding on a patient's clinical condition, the energy expenditure of individual patients is not routinely measured (7). The alternative method to tailor caloric supply to expenditure, the use of an empiric formula to estimate energy expenditure, yields results which may differ more than 30% from measured energy expenditure, even after correction for the increase of energy expenditure due to disease (8). Therefore it is surprising that commercially available instrumentation for the measurement of energy expenditure in spontaneously breathing and mechanically ventilated patients is only scarcely used. A survey among owners of indirect calorimetry equipment showed that the frequent disuse is due to frequent malfunction, calibration difficulties and technical limitations when measuring in mechanically ventilated patients (7). The instrumentation for oxygen uptake and carbon dioxide measurement used in this thesis was tested and improved in the laboratory prior to its clinical use, and none of the afore-mentioned problems was encountered during clinical use (9).

An important reason for not performing daily energy expenditure measurements is the fact that it is not exactly known how much overfeeding or underfeeding will adversely affect a patient's clinical condition. It is therefore not known whether a beneficial effect on the clinical condition of a patient can be expected if caloric supply is accurately tailored to caloric expenditure. Rhodes et al. found no difference in nitrogen balance between ten patients who received individually adapted caloric supply and ten patients who received a fixed amount of caloric supply of 2600 kcal/day (10). In their study energy expenditure was estimated, and the study was too short to detect a number of metabolic complications associated with parenteral nutrition. A prospective study to evaluate the metabolic and respiratory effects of adaptation of caloric supply to measured energy expenditure is required to allow more definitive conclusions on the need for performing energy expenditure measurements.

In chapters 4 and 5 the relationship between oxygen uptake and oxygen supply of critically ill patients is described. It was investigated whether the aerobic energy metabolism is dependent on oxygen supply, even when oxygen supply is above the normal critical oxygen supply level. In studies reporting that oxygen uptake is limited by oxygen supply in critically ill patients, oxygen uptake was calculated by an indirect method as the product of cardiac output and arteriovenous oxygen content difference (section 1.2). Oxygen supply is calculated as the product of cardiac output and arterial blood oxygen content.

Because the measurement errors in the shared variables cardiac output and arterial blood oxygen content occur in both oxygen uptake and oxygen supply, mathematic coupling of oxygen supply and uptake is introduced. In chapter 4 the influence of this mathematic coupling on the relationship between oxygen uptake and oxygen supply in critically ill patients was investigated.

In 13 postoperative and seven septic patients oxygen uptake was calculated by the Fick method, as well as measured by respirometry. Since the determination of oxygen uptake by respirometry is independent of oxygen supply, no such mathematic coupling can be expected. In 10 (out of 20) patients a close relation between oxygen supply and oxygen uptake calculated by the Fick method was found, but in only two of these 10 patients there was also a close relation between oxygen supply and oxygen uptake measured by respirometry. It was demonstrated that the high correlation and regression coefficient between calculated oxygen uptake and supply was mainly the result of mathematic coupling of these variables. It is concluded that oxygen uptake calculated by the Fick method is unsuitable for the investigation of the relationship between oxygen uptake and oxygen supply. Therefore, the conclusion from previous studies by others (2-4) that oxygen uptake is limited by oxygen supply may have been erroneous.

Only in four patients a close relation between oxygen supply and oxygen uptake measured by respirometry was found. In these patients body temperature increased during the measurement period. The close relation between oxygen uptake and supply in these cases does not represent oxygen supply dependency, but is more likely the result of the change in body temperature and metabolic rate, resulting in simultaneous changes of oxygen uptake and supply (physiologic coupling). A constant metabolic rate is a necessary condition for the assessment of a causal relationship between oxygen uptake and oxygen supply. In critically ill patients however, the metabolic rate may vary considerably during the day (11-13) and from day to day (chapter 3), due to changes in body temperature, level of consciousness, physical activity and medication. To minimize the risk of a change in metabolic rate during measurements, oxygen supply should be changed in a short period of time, e.g. by fluid loading or by medication with a positive inotropic effect (2,3,6). Adrenergic agents might however increase cellular metabolism and oxygen demand, resulting in a simultaneous increase of oxygen supply and uptake.

In chapter 5 it was investigated whether (independently measured) oxygen uptake is limited by oxygen supply in septic and postoperative patients. Also the relationship between a possible limitation of oxygen uptake and arterial blood lactate concentration (as measure of anaerobic metabolism) was studied. In 16 septic and 14 postoperative patients oxygen supply, oxygen uptake (by respirometry) and arterial blood lactate were determined.

The change of oxygen uptake during changes of oxygen supply induced by fluid loading, blood transfusion and changes in vasoactive and inotropic medication was studied. Only in one postoperative and in two septic patients a small positive correlation between oxygen uptake and oxygen supply was found (slopes of the regression lines 0.09, 0.08 and 0.05). The small positive slope may represent oxygen supply dependency or a small change in metabolic rate. As for oxygen supply changes due to changes in cardiac output, the small slope could be partly explained by the delivery-dependent oxygen demand of the heart and kidneys. No relation was found between elevated arterial blood lactate levels and oxygen supply dependency.

It is concluded that either no limitation of oxygen uptake by oxygen supply existed in these patients, or the study of the relationship between oxygen uptake and supply is not a reliable method to detect "oxygen debt". If the first assumption is true, a further therapeutic increase of oxygen supply will not result in an increase of oxygen uptake. This may indicate that there is no beneficial effect on tissue oxygenation, which must be balanced against the possible detrimental effects of therapy to increase oxygen supply. If oxygen uptake is adequate to meet oxygen demand the determination of oxygen uptake remains a valid method to determine energy requirements. If contrary to what has been stated previously by others, an existing "oxygen debt" is not detected by analysis of the relationship between oxygen uptake and oxygen supply, determination of oxygen uptake may be unsuitable to optimize ventilatory and circulatory therapy in critically ill patients.

The studies in chapter 4 and 5 were performed in septic and postoperative patients who were mostly in stable hemodynamic condition. The lack of a positive correlation between oxygen uptake and oxygen supply in these patients does not exclude that in an early phase of sepsis or during septic shock there may be an "oxygen debt" due to oxygen supply dependency. This can only be investigated if a positive correlation between independently measured oxygen uptake and oxygen supply can be demonstrated in patients with septic shock. A positive correlation between directly measured and (calculated) oxygen supply above the normal critical oxygen supply has been found in studies on dogs during bacteremia (14).

In chapter 6 it was investigated whether the minimal oxygen supply required to maintain oxygen uptake and aerobic energy metabolism is altered by the vasodilator PGE_1. Oxygen supply, oxygen uptake and arterial blood lactate concentration were measured during reduction of cardiac output (and oxygen supply) by positive end-expiratory pressure in anesthetized pigs. Vasodilation with PGE_1 reduced the minimally required oxygen supply, but arterial lactate was higher during PGE_1 than during control saline experiments. The higher lactate concentration may have resulted from reduced elimination of lactate, or from increased lactate production compared with controls.

Prostaglandin E_1 may have increased the available exchange surface area for oxygen, and allowed higher oxygen extraction. The vasodilation may have interfered with the adaptation of local perfusion (and oxygen supply) to local oxygen demand, which resulted in higher lactate production than during controls. Additional study of the effect of vasoactive medication on oxygen uptake seems indicated.

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Hoofdstuk 7

ALGEMENE DISCUSSIE EN SAMENVATTING

Door bepaling van de zuurstofopname en kooldioxide afgifte kan het energieverbruik van een individuele patiënt worden berekend om de voeding aan te passen aan het energieverbruik (1). Hierbij wordt er vanuit gegaan dat de zuurstofopname voldoet aan de zuurstofbehoefte van de aerobe energie stofwisseling. Bij ernstig zieke patiënten is echter beschreven dat de zuurstofopname beperkt kan zijn door het zuurstofaanbod, waardoor een zuurstoftekort bestaat (2). Dit zuurstoftekort wordt in verband gebracht met lactaatacidose, multiple orgaan falen en mortaliteit (2-4). De bepaling van de zuurstofopname is beschreven als een methode om bij ernstig zieke patiënten een zuurstoftekort aan te tonen en om de therapie ter ondersteuning van ventilatie en circulatie te optimaliseren (2,5,6).

De vraag dringt zich op hoe het mogelijk is dat de bepaling van de zuurstofopname zowel gebruikt kan worden voor de bepaling van de energiebehoefte als voor het aantonen van een zuurstoftekort in de aerobe energie stofwisseling. In dit proefschrift wordt de mogelijke beperking van de aerobe energie stofwisseling door onvoldoende zuurstofopname onderzocht (hoofdstukken 4 tot 6). Daarnaast worden twee belangrijke methodologische en klinische problemen bij de bepaling van het energieverbruik van spontaan ademende en van ernstig zieke beademde patiënten besproken (hoofdstukken 2 en 3). In deel 1.2 van de inleiding worden de verschillende methoden voor de bepaling van de energie stofwisseling en de zuurstofopname en kooldioxide afgifte besproken.

In hoofdstuk 2 werd de reproduceerbaarheid van de bepaling van het energieverbruik door middel van indirecte calorimetrie bij 50 gezonde vrijwilligers en 10 patiënten met levercirrhose onderzocht. Bij alle proefpersonen werd het energieverbruik één keer gemeten onder standaard ("basale") omstandigheden, en drie keer onder niet-standaard ("rust") omstandigheden, telkens gedurende 30 minuten. In individuele proefpersonen werd geen systematisch verschil tussen de niet-standaard metingen onderling gevonden. De variatie coëfficiënt van deze metingen was 5±3% bij gezonde vrijwilligers en 5±2% bij patiënten. Geconcludeerd wordt dat het energieverbruik reproduceerbaar gemeten kan worden met indirecte calorimetrie onder niet-standaard omstandigheden.

In hoofdstuk 3 werd onderzocht of het energieverbruik van ernstige zieke, beademde patiënten gemeten op een enkele dag, het energieverbruik op daarop volgende dagen van het verblijf op de intensive care kan voorspellen. Bij 60 patiënten werd het energieverbruik gedurende twee tot zeven dagen gemeten met behulp van indirecte calorimetrie, en werd de relatie tussen de klinische conditie en het energieverbruik in deze periode onderzocht. De klinische conditie werd iedere dag beoordeeld met een SAP-Score (Simplified Acute Physiology Score).

In de loop van een week werden veranderingen in het energieverbruik tot 30% van het verbruik gemeten op de eerste dag waargenomen. Deze veranderingen bleken deels gecorreleerd te zijn met veranderingen in de lichaamstemperatuur van patiënten. Er werd geen statistisch significant verband tussen het energieverbruik en de klinische conditie (SAP-Score) gevonden. Ook werd geen aanwijzing gevonden dat het energieverbruik gedurende de opname op de intensive care afdeling systematisch veranderde in de tijd. De grote veranderingen van het energieverbruik op opeenvolgende dagen leiden tot de conclusie dat het aanbeveling verdient het energieverbruik van een ernstig zieke patiënt dagelijks te meten, wanneer wordt beoogd de voeding af te stemmen op het individuele energieverbruik.

Ondanks het feit dat ondervoeding en overvoeding nadelige effecten op de klinische conditie van een patiënt kunnen hebben, wordt het energieverbruik van individuele patiënten niet routinematig gemeten om de voeding af te stemmen op het energieverbruik (7). De andere methode om de voeding aan te passen aan het energieverbruik is schatting van het energieverbruik met een empirische formule. Hierbij worden verschillen van meer dan 30% van het gemeten energieverbruik gevonden, zelfs na toepassing van een klinische correctiefactor (8). Het wekt daarom verbazing dat de beschikbare commerciële apparatuur voor meting van het energieverbruik van zowel spontaan ademende als beademde patiënten weinig wordt gebruikt. Een onderzoek onder instituten die dergelijke apparatuur hebben, toont aan dat er weinig gebruik van wordt gemaakt door frequente storingen, problemen met ijking van de sensoren en technische beperkingen van de apparatuur tijdens meting bij beademde patiënten (7). De apparatuur die in het onderzoek in dit proefschrift werd gebruikt voor meting van zuurstofopname en kooldioxide afgifte, werd getest en verbeterd in het laboratorium voor het klinisch gebruik, zodat geen der voornoemde problemen tijdens klinisch gebruik voorkwamen (9).

Een belangrijke reden om niet dagelijks bij alle patiënten het energieverbruik te meten is dat niet goed bekend is bij welke mate van ondervoeding of overvoeding nadelige effecten op de conditie van een patiënt optreden. Het is niet bekend of een gunstig effect op de klinische conditie van een patiënt wordt verkregen door een nauwkeurig aan het individuele verbruik aangepaste voeding. Rhodes et al. vonden geen verschil in de stikstofbalans bij tien patiënten die individueel aangepaste voeding kregen en tien patiënten die een standaard hoeveelheid calorieën (2600 kcal/dag) kregen (10). In deze studie werd het energieverbruik geschat en de tijdsduur van de studie was te kort om complicaties van parenterale voeding te kunnen aantonen. Een prospectief onderzoek naar de effecten op de gaswisseling en de stofwisseling tijdens aanpassing van de voeding aan het gemeten energieverbruik is vereist om de noodzaak van meting van het energieverbruik aan te tonen.

In de hoofdstukken 4 en 5 wordt het verband tussen het zuurstofaanbod en de zuurstofopname van ernstig zieke patiënten beschreven. Onderzocht werd of de aerobe energie stofwisseling van deze patiënten afhankelijk is van het zuurstofaanbod, wanneer het zuurstofaanbod hoger is dan het normale kritieke zuurstofaanbod niveau. In studies die aantoonden dat bij ernstig zieke patiënten de zuurstofopname beperkt is door het zuurstofaanbod, werd de zuurstofopname berekend als het produkt van hartminuutvolume en arterioveneus zuurstofgehalte verschil (deel 1.2 van de inleiding). Het zuurstofaanbod wordt berekend als het produkt van hartminuutvolume en zuurstofgehalte van arterieel bloed. Doordat de meetfouten in hartminuutvolume en zuurstofgehalte van arterieel bloed zowel in zuurstofopname als in zuurstofaanbod voorkomen, ontstaat een wiskundige koppeling van zuurstofopname en zuurstofaanbod. In hoofdstuk 4 werd de invloed van deze wiskundige koppeling op het verband tussen zuurstofaanbod en zuurstofopname bij ernstig zieke patiënten onderzocht.

Bij 13 postoperatieve en zeven septische patiënten werd de zuurstofopname zowel berekend met de Fick methode, als gemeten met respirometrie. De bepaling van de zuurstofopname met respirometrie geschiedt onafhankelijk van de berekening van het zuurstofaanbod, zodat hierbij geen wiskundige koppeling wordt verwacht. Bij 10 (van de 20) patiënten werd een sterk positieve correlatie gevonden tussen zuurstofaanbod en zuurstofopname berekend met de Fick methode, maar bij slechts twee van deze 10 patiënten bestond ook een positieve correlatie tussen zuurstofaanbod en zuurstofopname gemeten met respirometrie. Aangetoond werd dat de hoge correlatie en de regressie coëfficiënt tussen zuurstofaanbod en berekende zuurstofopname voornamelijk het gevolg is van wiskundige koppeling van deze variabelen. De conclusie is dat de zuurstofopname berekend met de Fick methode ongeschikt is voor het onderzoek van het verband tussen zuurstofopname en -aanbod. Er kan in eerdere studies (2-4) ten onrechte geconcludeerd zijn dat de zuurstofopname afhankelijk is van het zuurstofaanbod, voorzover de zuurstofopname werd berekend met de Fick methode.

Bij vier patiënten werd een sterk positieve correlatie tussen zuurstofaanbod en zuurstofopname gemeten met respirometrie gevonden. De lichaamstemperatuur van deze patiënten veranderde gedurende de opeenvolgende metingen van zuurstofaanbod en zuurstofopname. De sterk positieve correlatie tussen zuurstofaanbod en zuurstofopname berust bij deze patiënten waarschijnlijk niet op afhankelijkheid van de zuurstofopname van het aanbod, maar op de verandering van de lichaamstemperatuur en het stofwisselingsniveau, waardoor het zuurstofaanbod en de zuurstofopname gelijktijdig veranderen (fysiologische koppeling). Een constant stofwisselingsniveau is een noodzakelijke voorwaarde om een oorzakelijk verband tussen zuurstofopname en zuurstofaanbod vast te kunnen stellen.

Bij ernstig zieke patiënten kan het stofwisselingsniveau echter gedurende de dag (11-13) en op opeenvolgende dagen sterk veranderen (hoofdstuk 3), onder invloed van veranderingen in de lichaamstemperatuur, het bewustzijnsniveau, de lichamelijke activiteit en de medicatie. Door het zuurstofaanbod in korte tijd te veranderen, bijvoorbeeld door intraveneuze toediening van vocht of medicatie met positief inotrope werking wordt de kans op een verandering van het stofwisselingsniveau tijdens de meting verkleind (2,3,6). Adrenerge medicatie zou wellicht het stofwisselingsniveau en daarmee de zuurstofbehoefte kunnen verhogen, hetgeen kan leiden tot een gelijktijdige verandering van het zuurstofaanbod en de zuurstofopname.

In hoofdstuk 5 werd onderzocht of de (onafhankelijk gemeten) zuurstofopname van septische en postoperatieve patiënten beperkt is door het zuurstofaanbod. Tevens werd nagegaan of een relatie aantoonbaar is tussen een beperking van de zuurstofopname enerzijds, en de lactaat concentratie als maat voor de anaerobe stofwisseling anderzijds. In een groep van 16 septische en 14 postoperatieve patiënten werden het zuurstofaanbod, de zuurstofopname (respirometrie) en de lactaat concentratie gemeten. De verandering van de zuurstofopname tijdens veranderingen van het zuurstofaanbod door vochttoediening, bloedtransfusie en veranderingen in de medicatie werd onderzocht. Bij slechts één postoperatieve patiënt en bij twee septische patiënten werd een zwakke positieve correlatie tussen zuurstofaanbod en zuurstofopname gevonden (de hellingen van de regressielijnen waren 0,09, 0,08 en 0,05). Deze zwakke positieve correlatie zou kunnen berusten op afhankelijkheid van de zuurstofopname van het zuurstofaanbod of op een geringe verandering van het stofwisselingsniveau gedurende de periode dat de metingen werden verricht. Indien de verandering in het zuurstofaanbod berust op een verandering in het hartminuutvolume, zou de zwakke positieve correlatie gedeeltelijk verklaard kunnen worden door een verhoging van de zuurstofbehoefte van het hart en de nieren ten gevolge van toegenomen hartminuutvolume en glomerulaire filtratie snelheid. Er werd geen verband gevonden tussen een verhoogde lactaat concentratie en afhankelijkheid van de zuurstofopname van het zuurstofaanbod.

Geconcludeerd wordt dat bij de onderzochte patiëntengroep geen beperking van de zuurstofopname door het zuurstofaanbod bestaat, of dat de bestudering van het verband tussen de zuurstofopname en het zuurstofaanbod geen betrouwbare methode is om een zuurstoftekort aan te tonen. In het eerste geval zal een verdere therapeutische verhoging van het zuurstofaanbod niet leiden tot een verhoging van de zuurstofopname. Dit zou kunnen betekenen dat de zuurstofvoorziening van weefsels hierdoor niet gunstig wordt beïnvloed, hetgeen afgewogen moet worden tegen de mogelijke nadelige effecten van therapie die het zuurstofaanbod verhoogt. Indien de zuurstofopname voldoende blijkt te zijn om aan de zuurstofbehoefte te voldoen, dan is meting van de zuurstofopname wel een goede methode om het energieverbruik te bepalen.

Indien in tegenstelling tot wat eerder door anderen werd beweerd (2,5,6), een bestaand zuurstoftekort niet wordt aangetoond door onderzoek van het verband tussen zuurstofopname en -aanbod, dan is de bepaling van de zuurstofopname niet geschikt om de therapie ter ondersteuning van ventilatie en circulatie van ernstig zieke patiënten te optimaliseren.

De studies in de hoofdstukken 4 en 5 werden uitgevoerd bij septische en postoperatieve patiënten die merendeels in stabiele hemodynamische toestand waren. Het ontbreken van een sterk positieve correlatie tussen zuurstofopname en zuurstofaanbod bij deze patiënten sluit uiteraard niet uit dat in een vroege fase van sepsis of tijdens septische shock een zuurstoftekort bestaat. Hierover kan pas uitsluitsel worden verkregen indien bij patiënten met septische shock een sterk positieve correlatie tussen onafhankelijk gemeten zuurstofopname en zuurstofaanbod wordt aangetoond. Een positieve correlatie tussen de direct gemeten zuurstofopname en het (berekende) zuurstofaanbod, bij een zuurstofaanbod boven de normale kritieke zuurstofaanbod grens, werd wel aangetoond in studies bij honden met bacteriëmie (14).

In hoofdstuk 6 werd onderzocht of het minimaal benodigde zuurstofaanbod voor de handhaving van de zuurstofopname en de aerobe energie stofwisseling beïnvloed wordt door vaatverwijding met prostaglandine E_1 (PGE_1). Het zuurstofaanbod, de zuurstofopname en de lactaat concentratie werden gemeten tijdens verlaging van het hartminuutvolume (en het zuurstofaanbod) door positieve eind-expiratoire druk beademing van genarcotiseerde varkens. Vaatverwijding met PGE_1 verlaagde het minimaal benodigde zuurstofaanbod, maar de arteriële lactaat concentratie was tijdens PGE_1 hoger dan tijdens de controle experimenten met fysiologisch zout. De hogere lactaat concentratie zou verklaard kunnen worden door een verminderde lactaat afbraak, of door een verhoogde lactaat productie in vergelijking met de controles. Wellicht dat prostaglandine E_1 het beschikbare diffusieoppervlak voor zuurstof vergrootte, en daardoor een hogere zuurstofextractie mogelijk maakte. Het is mogelijk dat de vaatverwijding interfereerde met de aanpassing van lokale perfusie (en zuurstofaanbod) aan lokale zuurstofbehoefte, waardoor meer lactaat werd geproduceerd dan tijdens de controle experimenten. Nader onderzoek naar het effect van vasoactieve medicatie op de zuurstofopname lijkt aangewezen.

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ABBREVIATIONS

A = age (years)
ABL = arterial blood lactate concentration (mmol/l)
aHb = arterial blood haemoglobin concentration (mmol/l)
ARDS = adult respiratory distress syndrome
BEE = basal energy expenditure (kcal/day)
BSA = body surface area (m^2)
C_aO_2 = arterial blood oxygen content (ml/dl)
CI = cardiac index = CO / BSA ($l/min/m^2$)
CO = cardiac output (l/min)
CO_2 = carbon dioxide
$C_{\bar{v}}O_2$ = mixed venous blood oxygen content (ml/dl)
CVP = central venous pressure (mm Hg)
$\dot{D}O_2$ = oxygen delivery ($ml/min/m^2$)
EE = energy expenditure (kcal/day)
$F_{\bar{E}}CO_2$ = mixed expiratory carbon dioxide concentration (%)
$F_{\bar{E}}O_2$ = mixed expiratory oxygen concentration (%)
F_ICO_2 = inspiratory carbon dioxide concentration (%)
F_IO_2 = inspiratory oxygen concentration (%)
H = height (cm)
HBEE = Harris-Benedict estimation of energy expenditure (kcal/day)
HR = heart rate (beats/min)
ICU = intensive care unit
MAP = mean arterial blood pressure (mm Hg)
MOF = multiple organ failure
N_2 = nitrogen
O_2 = oxygen
OER = oxygen extraction ratio = $\dot{V}O_2$ / $\dot{D}O_2$
OSD = oxygen supply dependency
p = level of statistical significance
P_aO_2 = arterial blood oxygen tension (kPa)
$P_{\bar{v}}O_2$ = mixed venous blood oxygen tension (kPa)
PCWP = pulmonary capillary wedge pressure (mm Hg)
PEEP = positive end-expiratory pressure (cm H_2O)
PGE_1 = prostaglandin E_1
REE = resting energy expenditure (kcal/day)
RQ = respiratory quotient = $\dot{V}CO_2$ / $\dot{V}O_2$
S_aO_2 = arterial blood oxygen saturation (%)
$S_{\bar{v}}O_2$ = mixed venous blood oxygen saturation (%)
SAPS = simplified acute physiology score
SVR = systemic vascular resistance ($dynes.sec/cm^5$)
TEE = total energy expenditure (kcal/day)
$\dot{V}CO_2$ = carbon dioxide output ($ml/min/m^2$)
$\dot{V}_E$ = expiratory minute volume (l/min)
$\dot{V}O_2$ = oxygen uptake ($ml/min/m^2$)

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