METABOLIC GAS EXCHANGE IN CRITICALLY ILL SURGICAL PATIENTS

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METABOLIC GAS EXCHANGE IN CRITICALLY ILL SURGICAL PATIENTS

physical, methodological, therapeutic and prognostic aspects

UITWISSELING VAN METABOLE GASSEN BIJ ERNSTIG ZIEKE CHIRURGISCHE PATIENTEN

fysische, methodologische, therapeutische en voorspellende aspecten

PROEFSCHRIFT

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"It is possible ro recognize, in nature, beauty not only in form but in function."
(Rasmussen, Science, 1970)

"Clinicians rarely enjoy the luxury of perfection and frequently must proceed substituting pragmatism for purity."
(Harken, Surg. Gynecol. Obstet., 1976)

To Julie, our parents and our child

CONTENTS

Part A
INTRODUCTION

Chapter 1

HISTORY AND BIOLOGICAL SIGNIFICANCE OF METABOLIC GAS-EXCHANGE

Jean-Baptiste van Helmont (the Netherlands, 1577-1644) is considered to be the discoverer of carbon dioxide (1). He added acid to limestone and collected the liberated "air". It was found to kill dogs and to extinguish flames. He calles it "gas sylvestre", deriving "gas" from the word "chaos" to describe its disordering nature. More than a hundred years later, in 1771, Joseph Priestley (England, 1733-1804) put a plant into a quantity of air in which a candle had burned out. He found that ten days later another candle burned perfectly well in it and concluded, that plants, instead of affecting the air, reverse the effects of breathing. He had discovered what Lavoisier in 1779 would name "oxygine" (< ὀξυς = acid and γιγνομαι = to arise, to originate; oxygen produces acids on combination with certain substances).

Long before Van Helmont and Priestley it was already realized, that respiration and cumbustion are highly similar. Roman diggers, working underground, took along a lighted lamp; only if the lamp continued to burn, the air was considered safe enough to breathe. From such observations the term Flamma Vitae originates, the Fire of Life (1). Lavoisier (France, 1743-1794) was the first to point out clearly, that fire and man both consume oxygen which, after combination with organic substance, will produce water and carbon dioxide (2).

In the human body oxygen uptake (and in inversed sequence carbon dioxide output) depends on a great number of vital functions. The pulmonary and cardiovascular system *deliver* oxygen to the peripheral capillaries, bound to hemoglobin in the red blood cells. After *dissociation* of the oxyhemoglobin complex oxygen has to *diffuse* through the capillary wall and the extracellular fluid into the peripheral cell. Finally it is *utilized* in the complex system of biochemical pathways.

Especially in critically ill patients different organ functions are frequently disturbed simultaneously. Under these circumstances each step in the vital process of gas-exchange may be hampered. Metabolic gas-exchange reflects not only the metabolic state, but also the different underlying organ

functions. This thesis describes physical, methodological, therapeutic and prognostic aspects of metabolic gas-exchange in critically ill, surgical patients.

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Chapter 2

PHYSICAL AND METHODOLOGICAL ASPECTS OF METABOLIC GAS-EXCHANGE MEASUREMENT

2.1 Technical requirements in critically ill patients

In the intensive treatment of critically ill patients accurate determination of both short term and long term gas-exchange values is desirable (Chapter 3). The ideal monitor should provide continuous, quantitative information, be inexpensive and simple to use and have a minimal chance of causing harm to the patient. Several techniques have been developed to monitor oxygen consumption and carbon dioxide production. These different techniques as well as their advantages and disadvantages will be discussed in paragraph 2.2.

2.2 Survey of different techniques

2.2.1 *Indirect metabolic gas-exchange measurement*

The indirect method is based on the Fick principle, relating the amount of oxygen consumed or carbon dioxide produced to arterio-venous gas-content difference and cardiac output:

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

$$\dot{V}_{CO_2} = CO \times (C_{\bar{v}}CO_2 - C_aCO_2)$$

CO	=	cardiac output [l/min]
C_aO_2	=	arterial oxygen content [ml/l, STPD]
$C_{\bar{v}}O_2$	=	mixed venous oxygen content [ml/l, STPD]
$C_{\bar{v}}CO_2$	=	mixed venous carbon dioxide content [ml/l, STPD]
C_aCO_2	=	arterial carbon dioxide content [ml/l, STPD]
$\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$	=	oxygen consumption and carbon dioxide production [ml/min, STPD]

The indirect method has several disadvantages. It is time-consuming and can only be performed intermittently. It requires a pulmonary artery catheter which is known to have various complications (pneumothorax, arrhythmias, sepsis, etc.). Moreover, cardiac output is usually assessed by the indicator dilution technique (1) which has several important error sources resulting in miscalculations of cardiac output as great as 20-40% (2-6). Recently, oxygen consumption was shown to be miscalculated with an average of −11% (range −35% to +23%) as compared to the more reliable direct, open circuit method (see below) (7). One of the advantages of the indirect method is the possibility of regional measurements by selective catheterization of different organs (3, 8).

2.2.2 *Direct metabolic gas-exchange measurement*

Whole body gas-exchange values can be determined by means of direct, non-invasive analysis of inspiratory and expiratory gases. For this purpose two different systems have been developed. In the *closed circuit,* so-called "rebreathing" method the subject is completely cut off from the outside air and breathes through a closed system, originally containing pure oxygen. During the expiration water and carbon dioxide are constantly removed (3). Oxygen consumption rate is calculated either from the decrease of gas volume (9) or from the amount of oxygen which has to be added to the system in order to maintain the starting amount of oxygen (10, 11). With this closed-circuit method both inspiratory and expiratory leaks produce errors (12). Other great disadvantages of many closed circuit systems are, that they do not allow determination of carbon dioxide production and that they can hardly be cleaned bacteriologically after use.

In the *open circuit* method, the subject is permitted to breathe air from the outside, while the expired air is either collected for later analysis(Fig. 2.1: Douglas bag; Tissot spirometer) (12, 13) or immediately and continuously analyzed by an automatic metabolic device (5, 14, 15). In case of open-circuit analysis of expired air, inspiratory overflow does not produce errors. For this reason, the open circuit method is generally more reliable than the closed circuit system (12). Because the Douglas bag method is cumbersome and its sampling capacity limits the recording time, optimal measurement of both $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ could be performed by continuous, automatic analysis of expired air. For this purpose a relatively inexpensive metabolic device was designed and tested in collaboration with the Research and Development Unit of the University Hospital Workshop (Fig. 2.2A+B). Subsequently it was validated at the surgical Intensive Care Unit of the Dijkzigt University

Hospital (Appendix I) (14). This device was primarily constructed for application in mechanically ventilated patients.

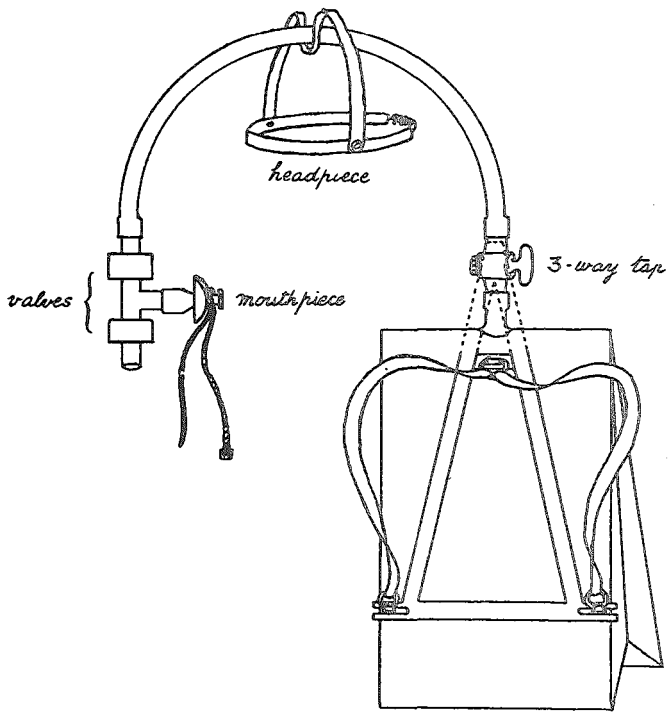

Figure 2.1. A portable apparatus for the determination of the total respiratory exchange in man. The wedge-shaped gas bag is lined with vulcanised rubber and has a capacity of about 50 liters. After collection of expired air over a definite period volume and concentrations of gases are determined. From: Douglas, C.G., 1911 (ref.nr. 13).

Both for the closed and for the open circuit method accurate gas-connections are essential, for which various systems have been developed. Respiratory chambers have been used (16,17; Fig. 2.3), but apart from incubators for newborn infants they can hardly be applied in clinical situations. A facemask or a mouthpiece/noseclip is only acceptable for short periods and frequently leads to undesirable, temporary overventilation or underventilation. A rigid, transparant head canopy allows more prolonged registrations (18-20), but for short recording periods it does not lead to more accurate results as compared to the mouthpiece/noseclip system (21). If the inspiratory oxygen concentration does not correspond

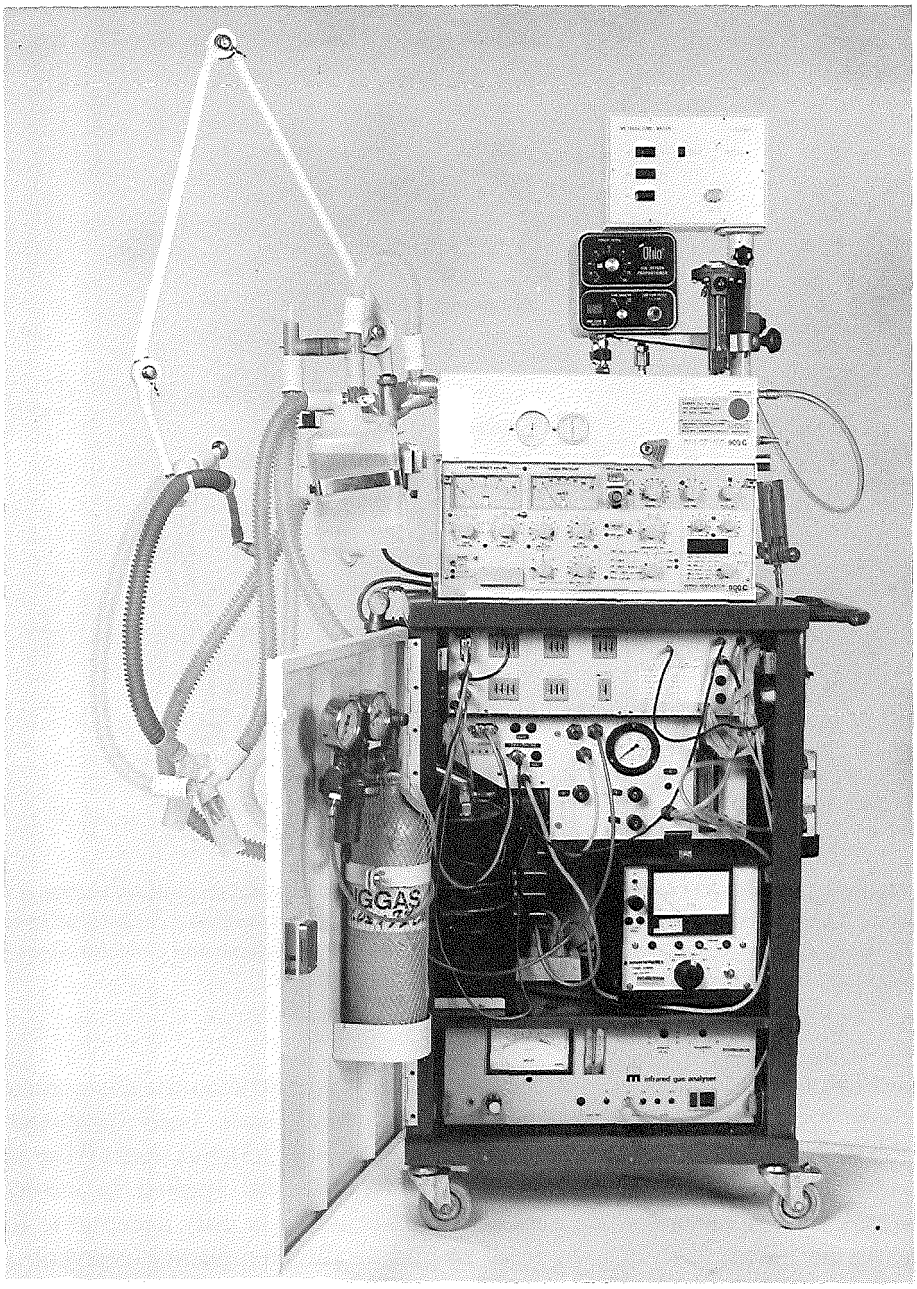

Figure 2.2A. The automatic metabolic device for continuous expired air analysis in combination with a ventilator (Siemens Servo 900-C). The device has been constructed in collaboration with the Research and Development Unit of the Dijkzigt University Hospital Workshop. Any ventilator with an expiratory port without internal gas loss can be connected to the metabolic cart.

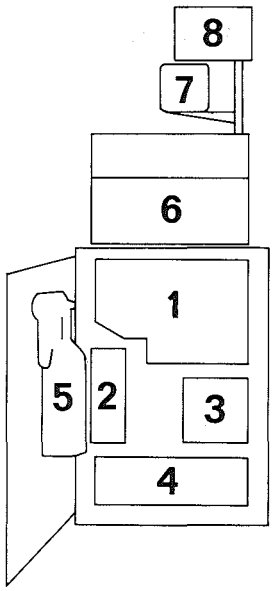

Figure 2.2B. Diagram of figure 2.2A. 1 = control unit; 2 = volumetric flow meter (Dordrecht); 3 = paramagnetic oxygen analyzer (Taylor Servomex OA 273); 4 = infrared gas analyzer (Mijnhardt UG 51); 5 = calibration gas; 6 = servo ventilator (Siemens-Elema 900-C); 7 = air oxygen proportioner (Ohio SJ 01); 8 = display.

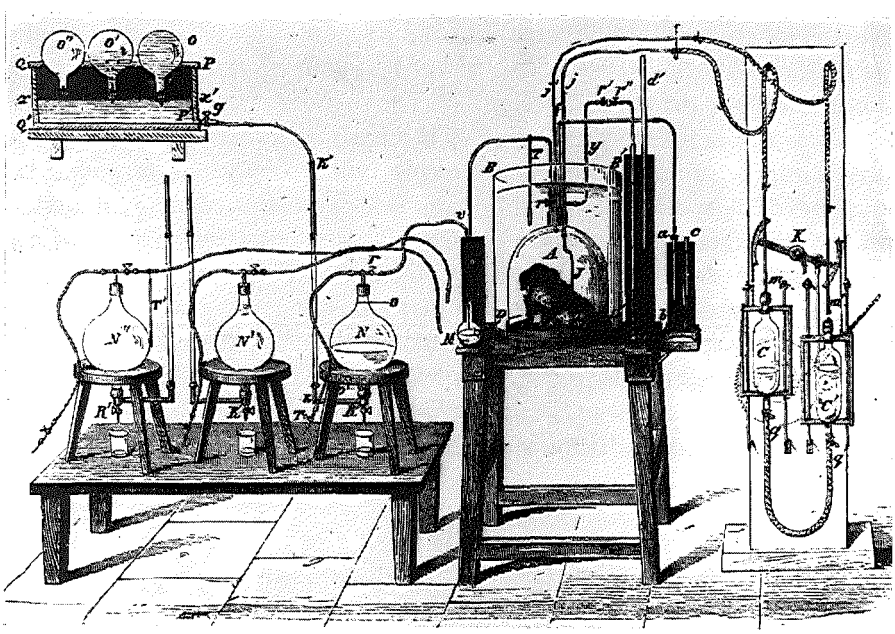

Figure 2.3. The closed circuit metabolism apparatus of Regnault and Reiset, 1849 (ref.nr. 16).

with the ambient concentration, the head canopy must be combined with an additional neck seal. In case of mechanically ventilated patients the expired air can easily be collected from the ventilator.

2.2.3 *Metabolic gas-exchange measurement in aquatic animals*

In aquatic animals oxygen consumption and carbon dioxide production can be measured directly from the changes of gas-concentrations in the ambient water (22, 23). Under these circumstances measurement of CO_2-production is extremely difficult because CO_2 is partly bound to the carbonate buffer system. More accurate results can be obtained by measuring $^{14}CO_2$-output from homogeneously labelled animals, fed with ^{14}C-labelled food (22).

2.2.4 *Measurement of carbon dioxide production by means of the doubly labelled water method*

In free living subjects long term carbon dioxide production can be estimated non-invasively by means of the doubly labelled water method (24). This method was suggested by the finding that the oxygen of respiratory carbon dioxide is in isotopic equilibrium with the oxygen of body water; at least a large majority of utilized molecular oxygen is soon converted to body water and not to carbon dioxide (25) (Fig. 2.4). The turnover rate of the oxygen of the body water is greater than that of the hydrogen, because hydrogen is almost entirely removed via water alone, while oxygen is removed by respiratory CO_2 as well. Hence carbon dioxide production can be calculated from the difference between the turnover rates of the hydrogen and the oxygen of the doubly labelled body water (D_2O^{18}). The greatest disadvantage of the doubly labelled water method is, that oxygen consumption can only be approximated from an estimated R.Q. value, preferably based on the diet composition during the recording period (26, 27). Both in human (20) and in animal studies (28) the difference between the doubly labelled water estimates and the respiratory gas-exchange values appeared to be within 10%.

2.3 **Factors with a disturbing influence on direct, open circuit gas-exchange measurement**

Direct, open circuit gas-exchange measurements can be disturbed by various factors:

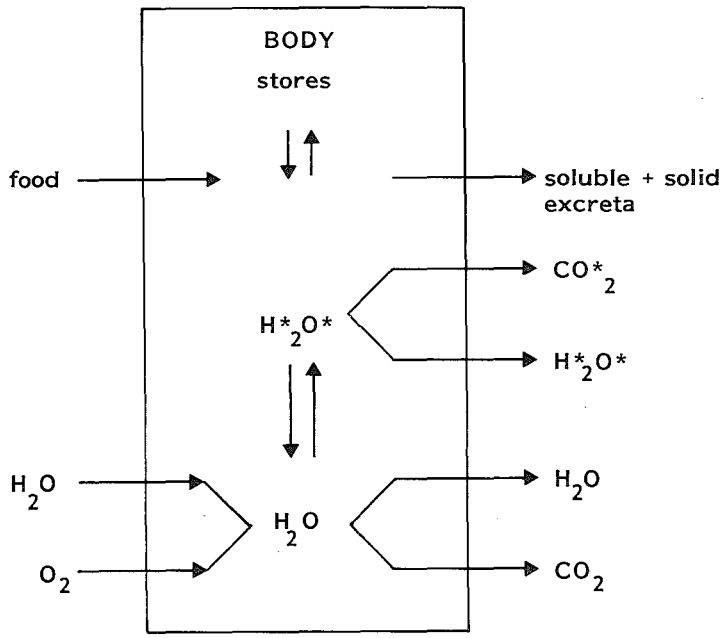

Figure 2.4. Diagram of the material balance in humans and animals after the administration of doubly labelled water ($H^*_2O^* = D_2O^{18}$).

- High inspired oxygen concentrations (>60%) induce an increased sensitivity of the Haldane transform algorithm to sensor errors.
- Several O_2-mixers give off an oxygen concentration which is flow-dependent and pressure-dependent; this will lead to great errors (Appendix I).
- If expiratory flow ($\dot{V}_E$) and gas fractions (F_EO_2 and F_ECO_2) are measured at different locations in the ventilator tubing system, overestimation of lung $\dot{V}_E$ is not corrected by an opposite error in F_EO_2 and F_ECO_2 (29).
- If specific gases (e.g. gaseous anesthetics) are exchanged, the Haldane transform algorithm can not be applied, unless the differences in inspiratory and expiratory fractions of these gases are taken into account.
- Certain gaseous anesthetics (e.g. nitrous oxide) interfere with the paramagnetic O_2-sensor.
- In mechanically ventilated patients artifacts can be introduced by patient-ventilator disconnections. We developed an automatic algorithm, which detects and suppresses such disconnections (Appendix II) (30).
- Profuse bleeding and abundant transfusion disturb the buffer capacity and the body gas stores.

- Hemodialysis leads to extrapulmonary CO_2-loss, especially if acetate is used as a buffer in the dialysate (Appendix III) (31).
- If expiratory air leaks through thoracic drains, cuff of endotracheal tube, noseclip/mouthpiece, head canopy, etc., gas-exchange measurements will be disturbed (Fig. 2.5).

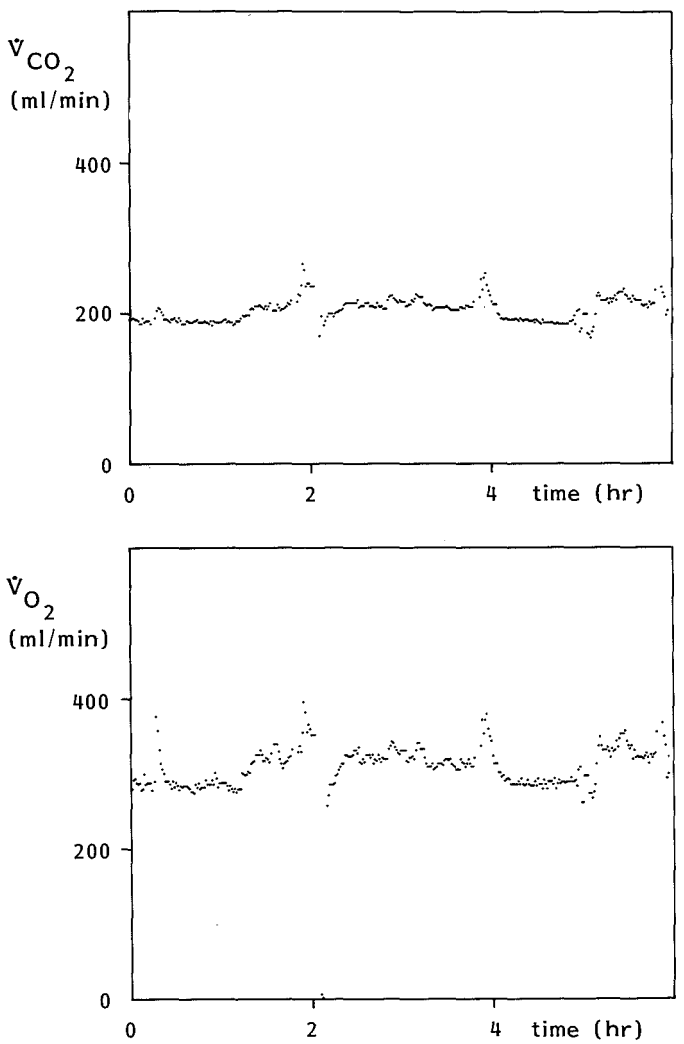

Figure 2.5. Continuous recording of carbon dioxide output ($\dot{V}_{CO_2}$) and oxygen uptake ($\dot{V}_{O_2}$), measured from the expired air in a patient with a thoracic drain. Abundant air leakage during expiration leads to an erroneously low $\dot{V}_{CO_2}$ resp. high $\dot{V}_{O_2}$, resulting in an unreal R.Q. of 0.65.

2.4 Intermittent vs continuous gas-exchange measurement

Frequently gas-exchange measurements can only be performed during short periods of the day due to technical limitations. In these situations total diurnal gas-exchange values have to be extrapolated from such short recording periods, by which both stochastic and systematic errors can be introduced. We quantified the errors of such extrapolations at different duration and number of the recording periods and analyzed the influence of a possible diurnal rhythm in gas-exchange (Chapter 5) (32).

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Chapter 3

CLINICAL APPLICATIONS

3.1 **Indirect calorimetry**

3.1.1 *Basic principles*

In the 19th century it was still generally accepted, that living organisms could generate energy spontaneously. Not untill the turn of this century it was irrefutably demonstrated by Rubner (1) and by Atwater and Benedict (2), that the Law of Conservation of Energy is valid not only in inanimate reactions, but in living organisms as well (3):

$$E_{in} = E_{out} + E_{stored}$$

where E_{in} is the total amount of ingested energy, E_{out} is the total amount of energy which is given off and E_{stored} is the net amount of energy which is stored in the body. In healthy adults body composition is considered to be more or less constant; consequently, E_{stored} can be neglected. Under these circumstances the chemical energy which is ingested by the food is identical to the amount of energy, which is dissipated and excreted in urine + faeces:

$$E_{in} = E_{food} = E_{dissipated} + E_{urine,\ faeces}$$

Dissipation of energy is necessary for thermoregulation (E_{therm}), maintenance of the body ($E_{maintain}$) and motor activity ($E_{activity}$). E_{therm}, $E_{maintain}$ and $E_{activity}$ are ultimately liberated as external heat.

After a period of severe weight loss body composition can rapidly change under hypercaloric feeding. Like the rapid growth of newborn infants, such restoration of body mass not only requires the energy which is present in the basic components ($E_{components}$), but also requires energy to synthetize these components to more complex substances ($E_{synthesis}$, e.g. from amino acids to proteins):

$$E_{restore} = E_{components} + E_{synthesis}$$

In general, $E_{components}$ is much greater than $E_{synthesis}$. Dependent on the efficiency of the synthesis process $E_{synthesis}$ will partly remain in the body

($E_{synth-int}$) and partly be liberated as external heat ($E_{synth-ext}$). In case of rapid increase of body mass the energy balance can be presented as follows:

$$E_{in} = E_{dissipated} + E_{urine,faeces} + E_{synth-int} + E_{components}$$

where $E_{dissipated}$ is composed of E_{therm}, $E_{maintain}$, $E_{activity}$ and $E_{synth-ext}$.

Direct calorimetry is the direct physical measurement of total heat transfer between an organism and its environment (4); it corresponds with $E_{dissipated}$. *Indirect calorimetry* measures the amounts of oxygen consumed and carbon dioxide produced from which energy expenditure can be calculated. Of course the terms direct/indirect calorimetry should not be confused with the direct/indirect method of metabolic gas-exchange measurement (paragraphs 2.2.1 and 2.2.2). The indirectly measured energy expenditure is considered to correspond with $E_{dissipated} + E_{synth-int}$. By simultaneous direct and indirect calorimetry $E_{synth-int}$ can be calculated (5).

Apart from situations of rapid changes in body composition the results of direct and indirect calorimetry correspond excellently in groups of patients (6-8), although in individual measurements substantial differences have been found which still remain unexplained (8).

3.1.2 *Analysis of combustion mixture*

The ratio between the amounts of carbon dioxide produced and oxygen consumed is called respiratory quotient (R.Q.). It depends on the combustion mixture and can easily be derived from the different chemical reactions (Fig. 3.1). Carbohydrates are oxidized with R.Q. = 1.00, while mean dietary fat and protein are burned with R.Q. = 0.71 and 0.80 respectively (9). A rise of nonprotein R.Q. above 1.00 indicates net conversion of carbohydrates to fat (lipogenesis). Although theoretically R.Q. can vary considerably in the long term (10), its mean physiological range is limited from 0.70 to 1.20 (11).

Protein break-down can be quantified from the total amount of liberated nitrogen. After simultaneous measurement of urea nitrogen production and gas-exchange specification of the combustion mixture is possible by using the following formulas (12):

$$dP = 6.25\ N$$

$$dF = 1.805\ \dot{V}_{O_2} - 1.805\ \dot{V}_{CO_2} - 1.681\ N$$

$$dS = 4.061\ \dot{V}_{CO_2} - 2.855\ \dot{V}_{O_2} - 2.468\ N$$

dP, dF and dS	total amount of metabolized protein, fat resp. carbohydrate [gram/min]
N	urea nitrogen production [gram/min]
$\dot{V}_{O_2}$	oxygen consumption [ml/min]
$\dot{V}_{CO_2}$	carbon dioxide production [ml/min]

These calculations can be disturbed by net lipogenesis (10) and by aberrant calory sources e.g. alcohol (Fig. 3.1: R.Q. = 0.67) or sodium acetate (Appendix III). Furthermore, if gas-exchange is only measured during short periods, serious errors can be introduced by temporary overventilation or underventilation due to the great difference in body gas stores of oxygen (about 1 l, STPD) and carbon dioxide (about 20 l, STPD) (13-15). In clinical practice urea nitrogen production is frequently calculated from the urinary urea output (12), although in fact a careful urea-balance should be preferred.

$C_6H_{12}O_6$ glucose glycogen	+	$6\,O_2$	→	$6\,CO_2$	+	$6\,H_2O$	R.Q. $= \frac{6}{6} =$	1.00
$C_{57}H_{104}O_6$ triolene	+	$80\,O_2$	→	$57\,CO_2$	+	$52\,H_2O$	R.Q. $= \frac{57}{80} =$	0.71
$2\,C_3H_7O_2N$ alanine	+	$6\,O_2$	→	$5\,CO_2$	+	$5\,H_2O$ + $(NH_2)_2CO$	R.Q. $= \frac{5}{6} =$	0.83
C_2H_5OH ethanol	+	$3\,O_2$	→	$2\,CO_2$	+	$3\,H_2O$	R.Q. $= \frac{2}{3} =$	0.67

Figure 3.1. Combustion reactions of various nutrients with the corresponding respiratory quotients (R.Qs.).

3.1.3 *Determination of energy expenditure*

The quantity of energy which is liberated per liter of oxygen is roughly equal in the combustion of carbohydrates, fats and proteins (5.02, 4.63 and 4.83 kcal/l resp.) (9). On the other hand, per liter of carbon dioxide produced the amount of liberated energy varies considerably. Therefore, measurement of oxygen consumption is more essential for the determination of energy expenditure than the measurement of carbon dioxide production.

Accurate determination of energy expenditure is possible by means of the Weir formula (16):

$$\text{energy expenditure} = 3.94\ \dot{V}_{O_2} + 1.11\ \dot{V}_{CO_2} - 2.17\ N$$

energy expenditure	[kcal/24 h]
$\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$	oxygen consumption and carbon dioxide production [1/24 h, STPD]
N	urea nitrogen production [gram/24 h]

By avoiding the cumbersome nitrogen correction only a small error of less than 2% is introduced in the application of the abbreviated Weir formula (17, 18).

The accuracy of conventional indirect calorimetry is limited (19). Skin respiration is neglected. Numerous complex metabolic pathways are reduced to a few simple biochemical reactions of synthesis and combustion. The composition of combustion mixture is rather assumed than exactly known; differences between animal/human fat and starch/glycogen are neglected. Calorimetric measurements are disturbed by changes in body gas stores during unsteady states (10, 14, 20); temporary hypo- or hyperventilation with secondary changes in body gas stores can simulate actual alterations in metabolic rate and combustion mixture. The abbreviated Weir formula does not take into account the specific contribution of protein metabolism. Because the summated effect of these inaccuracies and oversimplifications is relatively small, indirect calorimetry is widely applied and the abbreviated Weir formula is generally accepted as a reliable method for the determination of energy expenditure.

3.1.4 *Calculation vs measurement of energy expenditure*

Basal energy expenditure (BEE) is defined as the energy expenditure in a neutral thermal environment, at least 12 h postprandially, with the healthy subject at ease both mentally and physically. BEE can be calculated by means of the empirical Harris-Benedict formula, based on the sex, height, weight and age of the subject (21):

♂ BEE = 66 + 13.8W + 5H - 6.8A [kcal/24h]
♀ BEE = 655 + 9.7W + 1.8H - 4.7A [kcal/24h]

W = weight [kg]
H = height [cm]
A = age [yr]

After ingestion of food BEE is elevated with about 10% partly due to the specific dynamic action (SDA) especially of proteins (22). Since total energy expenditure (TEE) also depends on the motor activity and the clinical condition of the patient, it has been suggested to apply an activity factor and a clinical correction factor (23), for which the guidelines are summarized in Table 3.1. TEE can, thus, be calculated by the following formula (23):

$$TEE = [(100 + af)/100] \times [(100 + cf)/100] \times BEE + SDA$$

af = activity factor [%]
cf = clinical correction factor [%]

It has been suggested, that SDA represents the energy cost of growth (in particular of protein synthesis) and therefore it only plays a role in young or undernourished subjects (24). It is doubtful, whether or not SDA has to be added to the Harris-Benedict formula, since the original study was performed under resting (i.e. non-fasting) instead of under basal conditions (23, 25, 26).

Table 3.1. Contribution (percentages above 100%) of various activity levels to the activity factor (25, 84) and of various stress components to the clinical correction factor (20, 23, 71, 75, 85, 86) according to different authors.

Activity Factor	
spontaneously breathing + bedridden	10%
sedentary	20%
ambulatory	25-50%
Clinical Correction Factor	
elevated body temperature (per °C above 37°C)	12%
severe infection/sepsis	10-30%
recent extensive operation	10-30%
fracture/trauma	10-30%
burn wounds	50-150%
respiratory distress syndrome	20%

Presently, due to technical limitations in daily clinical practice continuous indirect calorimetry for TEE-determination is hardly ever possible. In such situations TEE can either be extrapolated from intermittent gas-exchange recordings (paragraph 2.4) or calculated by means of the corrected Harris-Benedict formula. We determined the accuracy of both methods as compared to the "gold standard" of continuous indirect calorimetry in a group of critically ill, surgical patients (Chapter 6).

3.1.5 *Isocaloric parenteral feeding*

At the turn of this century malnutrition was already supposed to have a detrimental influence on postoperative recovery of surgical patients (27, 28). In several animal studies this supposition has been affirmed (29-32). Hypoalimentation can lead to delayed wound repair (29-32) and decreased resistance to infection (33). Since in surgical treatment oral feeding is often impossible, alternative routes for nutritional support have been investigated. Rectal feeding (27) did not appear to be effective (34). Administration of hypertonic solutions in peripheral veins was tried, but hampered by inevitable phlebitis. The combination of peripheral high volume intake (5-7 l/24 h of isotonic fluids) plus high output induced by diuretics was abandoned because of the risk of overhydration and the severe loss of electrolytes (35). Thanks to the introduction of central venous catheters (36) and of a variety of parenteral nutrients intravenous alimentation became applicable eversince the late 1960s. Dudrick and Wilmore were the first to describe the possibility of anabolism and normal growth during long term parenteral nutrition (37, 38).

Yet, only few prospective trials have been executed, analyzing the effect of total parenteral nutrition (TPN) under highly specific clinical conditions (39-45). Despite the controversial outcome of these trials TPN has acquired an important role in a broad area of today's surgical treatment. In the early seventies the primary goal was to reach a positive nitrogen balance. In this period extremely high quantities of calories were administered, up to 5,000-6,000 kcal/day (46).

The last few years it has been clearly demonstrated, that such hyperalimentation has serious side-effects. It can induce hepatic dysfunction (47, 48), hyperglycemia and elevated levels of BUN, cholesterol and triglycerides (46). It has been shown, that the intravenous administration of triglycerides (e.g. Intralipid) can lead to increased serum levels of free fatty acids (FFA), especially when it is combined with heparin, which activates lipoprotein lipase (49). Increased serum levels of FFA have the risk of arrhythmias (49), endothelial damage (50) and generalized vasodilatation (51), although other data suggest that this putative risk may have been exaggerated (52, 53). Excessive quantities of fat inhibit the reticuloendothelial function (54-56). If glucose is partly substituted by fructose in order to diminish the required quantity of insulin, liver adenosine triphosphate (ATP) and inorganic phosphate (P_i) are rapidly depleted resulting in a severe hypoglycemia (57, 58). A carbohydrate overload can lead to pulmonary decompensation or delayed ventilatory weaning due to an increased CO_2-production (59-61). Based on these data it has been advised to prevent both hypo-

and hyperalimentation and to adapt the caloric supply to the actual energy expenditure of the individual patient (12, 46, 62). To plan individually tailored, isocaloric feeding TEE must be determined for each patient. Many hospitals do not have the equipment, necessary to perform indirect calorimetry. In such situations one can use the anthropometric formulas, which can be corrected for the motor activity and the clinical condition. For practical reasons of simplicity, however, a standard nutritional support regimen is frequently used (63). We analyzed to what extent such standard regimen leads to hypo- or hyperalimentation. For this purpose a standard caloric supply of 2875 kcal/day was compared to TEE, measured by means of continuous indirect calorimetry. Furthermore it was examined, whether the caloric supply could have been matched more properly to TEE by basing the nutritional support upon the basic or the corrected Harris-Benedict formula instead of upon the standard regimen of 2875 kcal/day (Chapter 7) (64).

3.2 **Outcome prediction in critically ill patients**

Oxygen consumption depends on a great number of vital organ functions. After oxygen has been delivered to the capillaries by the pulmonary and cardiovascular system, it has to diffuse across the capillary wall and the extracellular fluid into the peripheral cells before it can be utilized. Under pathological conditions the oxygen demand of the peripheral cells increases. However, this will only lead to an actual increase of oxygen consumption, if the organism is able to enhance all intermediate steps. Several authors have suggested, that the inability of augmenting $\dot{V}_{O_2}$-index (i.e. oxygen consumption/body surface area) in answer to exogenous stress-factors discriminates nonsurvivors from survivors (65-69). In a heterogeneous group of critically ill surgical patients we determined the prognostic value of $\dot{V}_{O_2}$-index on their ultimate outcome and we compared this value with that of an established physiological scoring system. Furthermore, it was analyzed, whether the reliability of this scoring system can be improved by adding $\dot{V}_{O_2}$-index as a supplemental physiological variable (Chapter 8) (70).

3.3 **On line monitoring of oxygen consumption**

Critical illness is usually accompanied by an increased oxygen demand (23, 71), whereas oxygen delivery, oxyhemoglobin dissociation and oxygen diffusion are often seriously hampered (72-79; Chapter 1). In such situa-

tions a peripheral O_2-deficit may occur, followed by a hazardous production of lactate (80-82). In case of an impending O_2-deficit it is of crucial therapeutic interest to restore homeostasis not ony by increasing the O_2-transport to the cells, but also by lowering the O_2-demand. By relieving the cardiopulmonary system reduction of O_2-demand can help to avoid the detrimental side-effects of excessive inotropic agents and of toxic inspiratory oxygen concentrations. For the evaluation of therapeutic interventions aimed to reduce the oxygen-demand on line monitoring of oxygen consumption is indispensable (Chapter 9) (83).

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Chapter 4

OBJECTIVES OF INVESTIGATION

In the following chapters and appendices different studies are described. The aims of these studies are:

- To design and to validate an automatic instrument for the measurement of oxygen consumption ($\dot{V}_{O_2}$), carbon dioxide production ($\dot{V}_{CO_2}$) and respiratory quotient (R.Q.) (Appendix I).
- To assess the influence of artifacts in metabolic gas-exchange recordings due to patient-ventilator disconnections and to validate a new method for automatic detection and suppression of these artifacts (Appendix II).
- To survey the disturbing influences of several clinical circumstances (especially of acetate hemodialysis) on metabolic gas-exchange measurements (Appendix III).
- To quantify the stochastic and systematic errors, which are introduced when diurnal values of $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and R.Q. are extrapolated from short recording periods (Chapter 5).
- To analyze the systematic influence of a possible diurnal rhythm in gas-exchange on such extrapolations (Chapter 5).
- To determine the discrepancy between (Chapter 6):
  a. Basal Energy Expenditure (= BEE; i.e. the energy expenditure under basal conditions) calculated by means of the anthropometric uncorrected Harris-Benedict formula and Total Energy Expenditure (= TEE) measured by means of continuous indirect calorimetry;
  b. TEE calculated by means of the corrected Harris-Benedict formula and continuously measured TEE;
  c. intermittently measured TEE and continuously measured TEE.
- To analyze to what extent a standard nutritional regimen leads to hypo- or hyperalimentation and to determine whether a tailored caloric supply based on anthropometric data gives a better match to energy expenditure than a standard supply (Chapter 7).
- To determine whether $\dot{V}_{O_2}$-indices of survivors are different from those of nonsurvivors and to analyze whether the potency of a frequently used

system to predict the patient's ultimate outcome (SAPS) can be improved by addition of $\dot{V}_{O_2}$-index as a supplemental physiological variable (Chapter 8).

- To survey the present nutritional, mechanical and pharmacological methods to reduce metabolic rate (Chapter 9).

Part B

ORIGINAL STUDIES

Chapter 5

EXTRAPOLATION ACCURACY OF INTERMITTENT METABOLIC GAS-EXCHANGE RECORDINGS AND ITS RELATION TO THE DIURNAL RHYTHM IN CRITICALLY ILL PATIENTS

This chapter has been submitted for publication.

Parts of this chapter have been presented at the 15th Annual Symposium of the Society of Critical Care Medicine (Crit. Care Med. 14: 409, 1986) and at the 8th Congress of the European Society of Parenteral and Enteral Nutrition (Clin. Nutr. [Suppl.] 5: 121, 1986).

EXTRAPOLATION ACCURACY OF INTERMITTENT METABOLIC GAS-EXCHANGE RECORDINGS AND ITS RELATION TO THE DIURNAL RHYTHM IN CRITICALLY ILL PATIENTS

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Abstract

In the intensive treatment of critically ill patients it is frequently important to know the values of total diurnal O_2-consumption and CO_2-production. However, often only short term values can be achieved, from which the diurnal values must be extrapolated. In this way both stochastic and systematic errors can be introduced. This study analyzes the systematic influence of a possible diurnal rhythm of gas-exchange and quantifies the extrapolation accuracy of 16 frequently used recording protocols (1, 2, 3, or 4 times/day during 5, 15, 30 or 60 min) in critically ill patients. For this purpose continuous gas-exchange measurements were performed during 24 h/day in 50 ventilated patients. Only a small diurnal rhythm was found. The extrapolation accuracy depended on the duration and number of the recording periods. Generally, the impact of number predominated over the effect of duration. In clinical practice 24-h values can be estimated with sufficient accuracy by extrapolation from measurements of 2×15 min during the day.

Introduction

In the management of critically ill patients metabolic gas-exchange measurements are performed for various purposes. In the first place they can be applied for the clinical evaluation of therapeutic interventions, aimed to diminish the metabolic demands (1-4).

Secondly the $\dot{V}_{O_2}$-index (i.e. oxygen consumption/body surface area) is frequently used to indicate the severity of illness and to predict the ultimate outcome of the patients. Oxygen consumption index depends on a great number of interrelated factors and its vital significance is reflected by the postulated predictive value concerning survival (5-11).

A third application of metabolic gas-exchange measurements lies in the field of tailoring nutritional therapy. In planning daily individualized nutritional support the caloric supply should be based upon diurnal total energy expenditure (TEE) in order to prevent both hypo- and hyperalimentation (12-14). TEE can be determined most accurately by means of continuous indirect calorimetry during 24 h/day and summation of all $\dot{V}_{O_2}$ (i.e. oxygen consumption) and $\dot{V}_{CO_2}$ (i.e. carbon dioxide production) values (10, 13-16). However, in many studies the expired air is collected in a Douglas bag, which allows sampling only during a limited period. In non-intubated patients gas-collection time is also limited due to the badly tolerated application of a head-canopy (17,18) or a mouthpiece/noseclip. In order to calculate TEE from short recording periods, the assessed $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ values must be extrapolated to a 24-h period. In this way both stochastic and systematic errors can be introduced. The magnitude of these errors has not yet been investigated.

The aim of the present study is twofold: 1. to analyze the systematic influence of a possible diurnal rhythm of gas-exchange in critically ill surgical patients; 2. to quantify the stochastic and systematic errors introduced by extrapolations from short recording periods with various duration and number in these patients. Thus it might be possible to determine in this type of patients which sampling protocol is suitable to get an acceptable estimate of diurnal $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and Respiratory Quotient (R.Q. $= \dot{V}_{CO_2}/\dot{V}_{O_2}$).

Methods and materials

Patient selection

In a surgical intensive care unit 50 patients were selected on the following criteria:

1. continuous mechanical ventilation (Intermittent Positive Pressure Ventilation, Continuous Positive Pressure Ventilation or Intermittent Mandatory Ventilation); 2. inspired oxygen concentration of 60% or less; 3. no air-leakage (no cuff-leakage, no leakage through thoracic drains etc.); 4. at least 6 h postanesthesia to exclude the disturbing influence of nitrous oxide etc.; 5. absence of profuse bleeding; 6. absence of dialysis.

The clinical data of the patients are summarized in Table 5.1. Severity of illness was quantified by the Simplified Acute Physiology Scoring system (SAPS-system) (19). In case of enteral and/or parenteral nutrition the administration was always performed on a continuous basis.

Table 5.1. Survey of clinical data (n = 50).

Mean age ± SE (range)	55 ± 18 (15-83) yrs
Sex: ♂/♀	40/10 (80%/20%)
Body temperature (mean ± SE)	38.2 ± 0.9°C)
Infection/sepsis	n = 29 (58%)
Recent major operation (< 5 days)	n = 22 (44%)
Fracture/trauma	n = 12 (24%)
Respiratory distress syndrome	n = 10 (20%)
Enteral nutrition only	n = 15 (30%)
Parenteral nutrition only	n = 22 (44%)
Enteral + parenteral nutrition	n = 2 (4%)
Hospital mortality	n = 20 (40%)
Mean ± SE of S.A.P.-score* (n = 49)	14 ± 5 (range: 3-26)

*S.A.P.-score = Simplified Acute Physiology score (19)

Measurements

During 24 h/day $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ were determined each minute by means of open circuit respirometry with an automatic metabolic cart (20). All minute-values of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ were sent to a remote computer (DEC, pdp 11/73) and stored for later use. Artifacts due to calibration and patient/ventilator-disconnections were automatically suppressed (13).

Analyses

Total diurnal values of $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and R.Q. as well as the mean values per minute were computed for each patient by summation of all minute values per day. In order to analyze the diurnal rhythm the 24-h recording period was divided into 8 intervals of 3 h each. For each patient the mean minute values of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ in each interval were calculated and expressed as a percentage of the mean diurnal values of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ respectively. To determine for each interval whether the percentages were significantly different from 100%, the Student t-test was used. In the same way for each interval the mean absolute R.Q. values were compared with the mean diurnal R.Q. values.

Total diurnal $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and R.Q. were estimated by extrapolation from simulated short recording periods with different durations (5-15-30-60 min) and numbers (1 interval/day, starting at 12.00; 2 intervals/day, starting at 08.00 and 17.00; 3 intervals/day, starting at 08.00, 12.00 and 17.00; 4 intervals/day, starting at 00.00, 08.00, 12.00 and 17.00). The choice of durations and numbers was based upon procedures which are often applied in metabolic studies (Table 5.2). The simulated short recording periods were always chosen at least 30 minutes after any alteration of ventilatory therapy or a disconnection of patient and ventilator. If necessary the timing of the mentioned periods was delayed for this reason.

Table 5.2. Durations and numbers of gas-exchange measurements in various metabolic studies.

Author	(ref.nr.: year)	duration per period [min]	number
Fernandez Mondejar	(52: 1982)	2	1
Rhodes	(56: 1985)	3	1
Knox	(54: 1983)	5	1
Smith	(55: 1984)	5	1
Barlett	(51: 1977)	3-5	1-2
Quebbeman	(53: 1982)	10-15	1
Nordenström	(58: 1983)	20-40	3-5
Elwyn	(57: 1979)	40-60	3-5
Weissman	(22: 1984)	40-60	3-5
Ravussin	(15: 1982)	1440	1
Carlsson	(10: 1984)	1440	1

To express the accuracy of the extrapolation from the described 16 sampling protocols (1-4 × 5′/15′/30′/60′) two different statistical procedures were performed. Firstly the accuracy for the **individual** patient was expressed as the absolute value of the percentage difference (= APD) between the extrapolated and the real, continuously measured diurnal $\dot{V}_{O_2}$:

$$APD = \frac{| \dot{V}_{O_2} \text{ extrapol} - \dot{V}_{O_2} \text{ contin} |}{\dot{V}_{O_2} \text{ contin}} \times 100\%.$$

In the same way the APDs for $\dot{V}_{CO_2}$ and R.Q. were determined. For comparison of the accuracies of the different extrapolation protocols the Wilcoxon rank-sum test was applied.

Secondly for each of the 16 investigated extrapolation protocols the linear correlation between the continuously measured values and the extrapolated values was calculated with the Jackknife method (R = mean Jackknife coefficient of correlation) (21). By means of linear regression analysis a best fit (expressed as $y = bx + a$, with a = intercept and b = slope) was computed. In this way, for the **group** of patients the stochastic error of each sampling protocol was quantified by R and the systematic error was quantified by a and b.

Results

The 3-h values of both averaged $\dot{V}_{O_2}$ and averaged $\dot{V}_{CO_2}$ were slightly lower during the night than during the day (Fig. 5.1). At some intervals the deviation from the mean diurnal values (i.e. 100%) of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ was statistically significant, but at each interval this deviation was smaller than 3%. The diurnal curve of averaged R.Q. was very constant (Fig. 5.1); there was no significant difference between the averaged R.Q. value of any 3-h interval and the mean diurnal R.Q. value (= 0.87).

The accuracy (expressed as mean APD), with which diurnal $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and R.Q. of the **individual** patient was extrapolated from short recording periods, is visualized with pseudo 3-dimensional plots (Fig. 5.2). The smaller the APD, the more accurate the extrapolation. For the *oxygen-consumption* the accuracy was improved both by an increase of the duration and by an increase of the number of measurements. In case of one single measurement the accuracy (A) was improved substantially by increasing the duration of the recording period ($\dot{V}_{O_2}$: $A_{1\times30'} > A_{1\times5'}$, $p < 0.05$); if one measured twice a day, increase in duration had a similar effect ($\dot{V}_{O_2}$: $A_{2\times30'} > A_{2\times5'}$, $p < 0.01$). Measuring twice instead of once a day appeared to improve the accuracy significantly ($\dot{V}_{O_2}$: $A_{2\times5'} > A_{1\times5'}$, $p < 0.005$). This effect tended to predominate over the effect of increased duration in case of one single recording period ($\dot{V}_{O_2}$: $A_{2\times5'} > A_{1\times15'}$, $p < 0.05$). Further increase in number raised the accuracy only slightly ($\dot{V}_{O_2}$: no significant difference between $A_{2\times5'}$ and $A_{3\times5'}$). For the *carbon dioxide production* the accuracy of the extrapolation was less dependent on the duration of recording periods than the accuracy of the $\dot{V}_{O_2}$-extrapolation ($\dot{V}_{CO_2}$: no significant difference between $A_{1\times60'}$ and $A_{1\times5'}$). However, increase in number led to significantly better results ($\dot{V}_{CO_2}$: $A_{2\times5'} > A_{1\times5'}$, $p < 0.05$). For the *respiratory quotient* the accuracy of extrapolation was even more influenced by duration and number than the accuracy of the $\dot{V}_{O_2}$-extrapolation (R.Q.: $A_{1\times30'} > A_{1\times5'}$, $p < 0.01$; $A_{2\times5'} > A_{1\times5'}$, $p < 0.0005$).

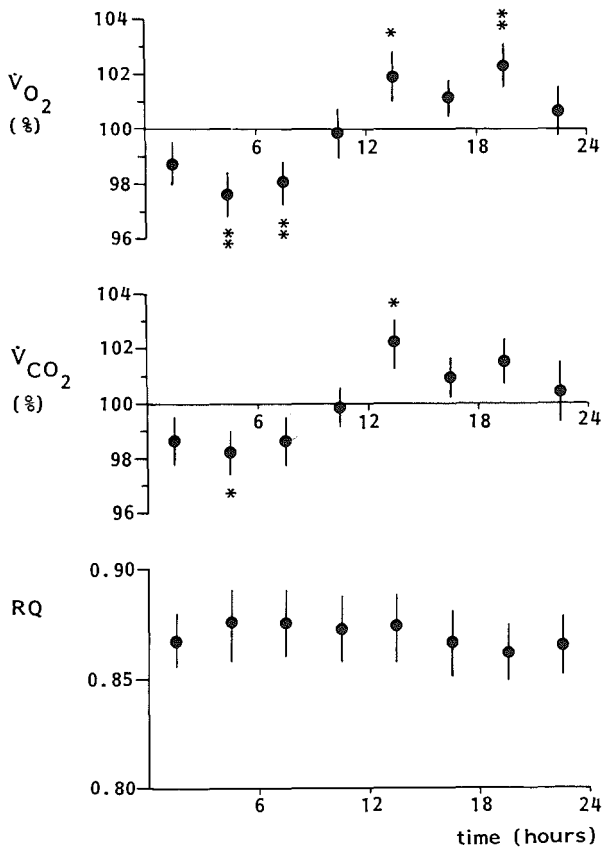

Figure 5.1. Three hour averages (dots) of $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and R.Q. in 50 patients. SD is indicated by bars. Significant deviations from the mean diurnal values (i.e. 100% resp. 0.87) are marked (* = $p < 0.05$, ** = $p < 0.01$).

For the total **group** of patients the mean coefficient of correlation (R) between the extrapolated and the continuously measured values is an indication of the stochastic part of the extrapolation-error; for $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and R.Q. R varied with both the duration and the number of the recording periods (Fig. 5.3A, 5.3B, 5.3C). The systematic part of the extrapolation-error, quantified by the intercept (a) and the slope (b) of the best linear fit, varied in the same way: the intercept tended to zero and the slope tended to one with increasing duration and with increasing number of recording periods (Fig. 5.3D, 5.3E, 5.3F resp. Fig. 5.3G, 5.3H, 5.3I) for $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and R.Q..

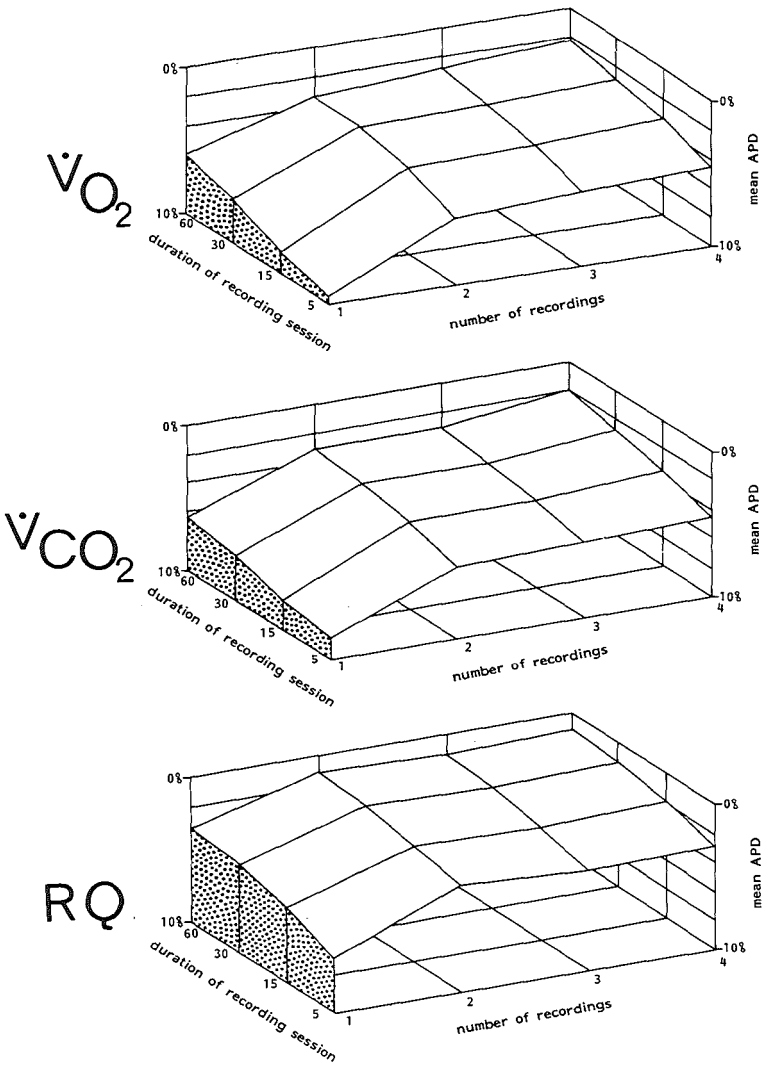

Figure 5.2. The mean APDs of $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and R.Q. in relation to the 16 different extrapolation protocols (1, 2, 3 or 4 times/day during 5, 15, 30 or 60 min).

The extrapolations of $\dot{V}_{CO_2}$ tended to be slightly more accurate than the estimates of $\dot{V}_{O_2}$ with the same extrapolation protocol (Fig. 5.3A vs Fig. 5.3B; Fig. 5.3D vs Fig. 5.3E; Fig. 5.3G vs Fig. 5.3H).

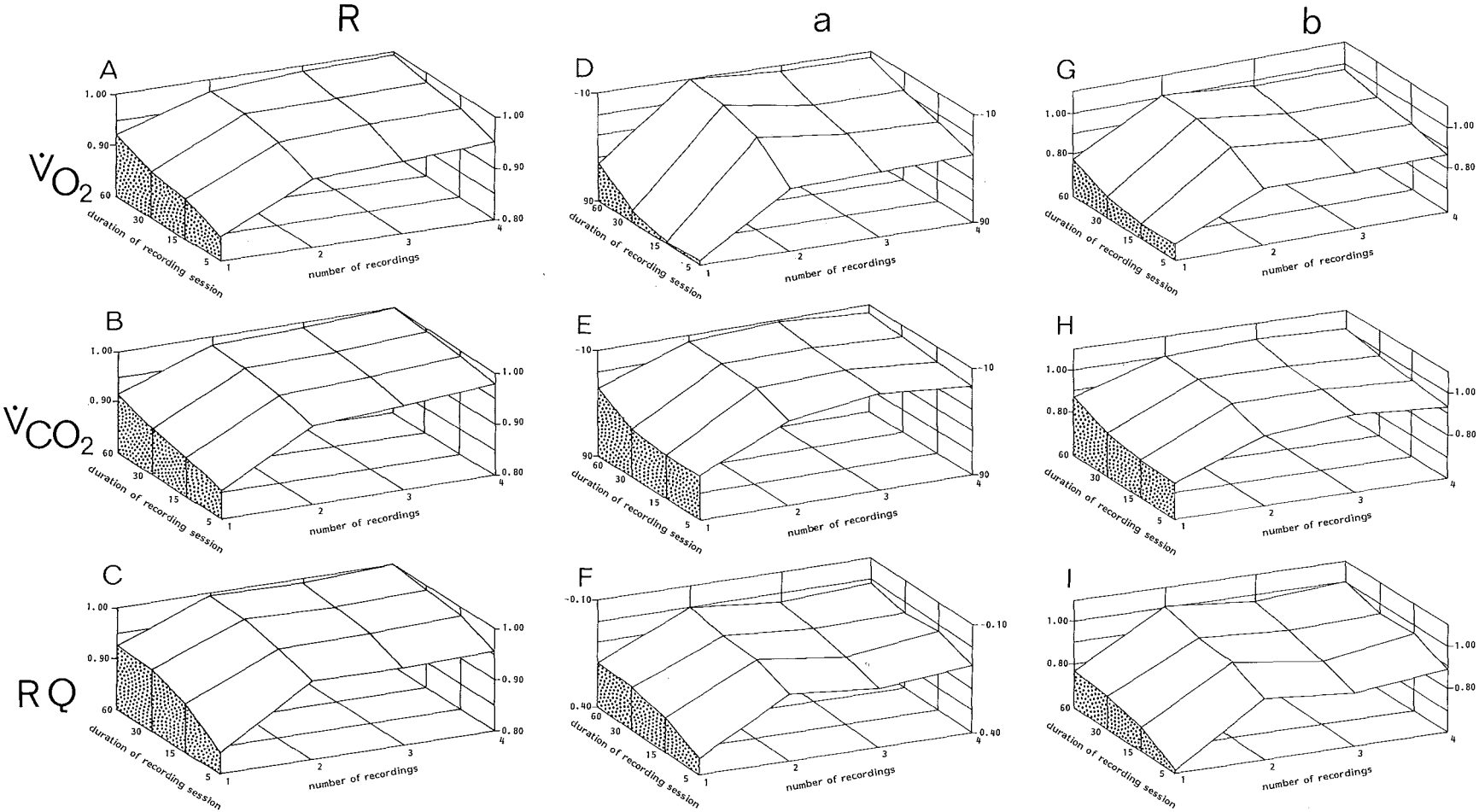

Figure 5.3. The mean Jackknife coefficient of correlation (R) between the extrapolated and the continuously measured values of $\dot{V}_{O_2}$ (Fig. 5.3A), $\dot{V}_{CO_2}$ (Fig. 5.3B) and R.Q. (Fig. 5.3C). The mean intercept (a) and the mean slope (b) of the best linear fit for $\dot{V}_{O_2}$ (Fig. 5.3D, 5.3G), $\dot{V}_{CO_2}$ (Fig. 5.3E, 5.3H) and R.Q. (Fig. 5.3F, 5.3I).

Discussion

Since we have demonstrated, that in critically ill surgical patients the amplitude of the diurnal rhythm of metabolic gas-exchange is only about 3%, nocturnal gas-exchange measurements are not necessary to get reliable 24-h estimates of metabolic gas-exchange. Despite the absence of a considerable diurnal rhythm we found, that the accuracy of the 24-h estimates still depends on the duration and number of the short recording periods. Apparently, in the individual patient large fluctuations in metabolic gas-exchange occur, which for the whole group are spread more or less equally over the day and night. Short term variations can be introduced by changes in the body gas stores. Because the oxygen store and to a lesser extent the carbon dioxide store are kept within relatively narrow limits, long term variations of gas-exchange must be of metabolic origin. Fluctuations in metabolic rate can be induced by a number of different factors.

1. *Motor activity.* The amount of voluntary movements and respiratory labour may be highly variable during the day (16, 22). Activity energy expenditure averages about 25% of Resting Energy Expenditure (REE) in ambulatory patients (23). 2. *Nutrition.* Caloric intake and diet-composition influence the Specific Dynamic Action (SDA) of food, which normally causes an increase of about 10% in Basal Energy Expenditure (BEE) to give REE (23). An excessive carbohydrate intake can lead to an increased production of CO_2, released by the conversion of glucose to fat (24, 25). 3. *Clinical condition.* Fever, sepsis, operations, burns, etc. have an increasing effect on metabolic rate (18, 26-30). Essential changes of the clinical condition (e.g. rapid development of fever) will have implications for the patient's metabolic rate. 4. *Medication.* A number of drugs such as beta-blocking agents (31, 32), morphine (2, 22), barbiturates (4) and muscle relaxants (3, 22, 33) have been described to decrease metabolic rate. 5. *Discomfort/pain.* Fluctuations in $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ can be induced by discomfort and pain (34). 6. *Diurnal rhythm.* In healthy persons the influence of physiological variables causes a cyclic diurnal rhythm due to two basic components: the vegetative rhythm of BEE and the activity rhythm (35). Diurnal rhythm is influenced by sound (36), light intensity (35-38), ambient temperature (36, 37) and appears in a number of physiological variables such as core temperature, hormonal blood levels and renal function (39).

The first aim of this study was to analyze whether or not a cyclic diurnal metabolic rhythm is still detectable in critically ill patients. The choice of the 3-h sampling intervals has to be considered as a compromise. On the one

hand detection of a possible diurnal rhythm requires a division of the 24-h period into shorter intervals. On the other hand longer intervals would be desirable to eliminate changes in body gas stores and to exclude the effect of subtle differences in the phases of the individual rhythms. The difference between day and night appears to have almost totally disappeared in comparison with healthy, intermittently fed persons, in whom these deviations are at least 35% (SDA + motor activity) (23). In our **group** of patients alimentation is given on a continuous basis and apparently the summated influence of motor activity, medical/nursing care, light intensity etc. is spread more or less equally over the day and night.

In the **individual** patient all above-mentioned factors may cause considerable fluctuations in metabolic rate (10, 22, 40, 41). In intrapatient or interpatient comparisons, it is essential to measure strictly under standard conditions. In healthy persons metabolic rate can be determined under basal conditions, i.e. at least 12 h postprandially, in a neutral thermal environment, and these persons must be at ease both mentally and physically (28, 42). In an intensive care patient it is hardly ever possible/acceptable to establish these basal conditions; therefore gas-exchange measurements are usually performed under resting conditions, i.e. with the continuation of nutrition and with the patients supine, resting and awake (22, 41). Because of the adverse effects of hypoalimentation (43-47) and hyperalimentation (12, 24, 48) is has been advised to adapt the caloric supply to the actual energy expenditure of the individual patient (12-14). In our opinion, when planning a nutritional regimen, the caloric supply should be emphatically based on the total diurnal energy expenditure rather than on the basal or resting energy expenditure. An exact calculation of TEE is possible by continuous measurement of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ during 24 h/day (10, 15) and subsequent application of the abbreviated Weir-formula (49, 50).

For practical reasons TEE is only rarely based on continuous gas-exchange measurements during 24 h/day. The Douglas bag has a limited sampling capacity and the head-canopy or mouthpiece/noseclip is not tolerated for prolonged periods. Therefore, $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ are frequently recorded for relatively short periods, during which disturbing changes in the body gas stores can be introduced due to hyperventilation. From these short recording periods the diurnal values are estimated by extrapolation. In different studies these periods are chosen more or less arbitrarily and vary in length from a few minutes (51-56) to several hours (22, 57, 58) (Table 5.2). From our findings it can be concluded that the accuracy of this extrapolation depends on the duration and number of the recording periods. The slightly better accuracy of $\dot{V}_{CO_2}$ than that of $\dot{V}_{O_2}$, when the same extrapolation protocol is used, can be explained by the greater buffering capacity

for carbon dioxide changes (34, 37, 59); in comparison with the small gas-store of oxygen (circa 1 l, STPD) the carbon dioxide store in the human body is relatively large (circa 20 l, STPD). Furthermore, it becomes clear that an increase in number of measurements tends to be more effective than an increase in duration of measurements, apparently due to the diurnal metabolic fluctuations of the individual patient. The choice of the protocol depends on the available instrument (Douglas bag, automatic metabolic cart etc.) as well as on the desired accuracy. Measuring more than e.g. 2×15'/day is rather cumbersome and time-consuming, and in metabolic studies it does not lead to a beneficial increase in extrapolation accuracy.

The contradictory outcome of some earlier metabolic studies might be explained by a difference in the applied extrapolation protocols (Table 5.2), leading to a limited validity of the ultimate results (14).

Conclusion

A diurnal rhythm can hardly be recognized within this **group** of critically ill, surgical ICU patients. The difference in metabolic gas-exchange during the day and night has almost totally disappeared. On the other hand a great number of factors cause substantial diurnal variations in the metabolic rate of the **individual** patient. Total diurnal $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and R.Q. can be estimated by extrapolation from intermittent gas-exchange measurements. However, due to the changes of metabolic rate and the variations in body gas stores of the individual patient the accuracy of this extrapolation depends on the duration and number of the recording periods. In general, the impact of number predominates over the effect of duration. In daily clinical practice estimation of total diurnal $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and R.Q. can be satisfactorily achieved by extrapolation from gas-exchange recordings of 2×15 min during the day, considering the small amplitude of the diurnal rhythm.

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Chapter 6

CALCULATION vs MEASUREMENT OF TOTAL ENERGY EXPENDITURE

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CALCULATION vs MEASUREMENT OF TOTAL ENERGY EXPENDITURE

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Abstract

In severely ill patients both hypo- and hyperalimentation must be avoided by adjusting caloric intake to total energy expenditure (TEE). We determined the discrepancy between basal energy expenditure (BEE) calculated from the basic Harris-Benedict formula and TEE measured by continuous indirect calorimetry in a heterogeneous group of mechanically ventilated surgical patients. We also compared the accuracy of TEE calculated from the corrected Harris-Benedict formula or estimated by intermittent indirect calorimetry to that of TEE measured by continuous indirect calorimetry. The poor correlation between calculated BEE and measured TEE was significantly ($p < .05$) improved by a correction factor based on each patient's clinical condition. The mean absolute difference between calculated TEE and measured TEE was 8.9 ± 9.6 (SD) %. Calculations were significantly ($p < .05$) improved by estimating TEE from two 5-min recording periods. This suggests that continuous indirect calorimetry may not always be necessary to guide caloric replacement.

Introduction

Appropriate caloric intake is essential for critically ill patients in the ICU, since both hypo- and hyperalimentation can cause adverse effects (1). For example, starvation delays wound healing and decreases resistance to infection, while hyperalimentation can cause hepatic dysfunction, hyperglycemia, elevated levels of BUN, cholesterol or triglycerides, and respiratory distress due to increased CO_2 production. Consequently, caloric intake should be adapted to each patient's calculated, estimated, or measured total energy expenditure (TEE) (2).

The Harris-Benedict formula (3) is used frequently to calculate basal energy expenditure (BEE). TEE is the product of BEE and a factor that depends on the patient's clinical condition (2, 4). TEE can also be determined by indirect calorimetry. Until recently this method was too complicated for daily clinical use; however, fully automatic instruments now allow intermittent or continuous measurements of TEE (5, 6). This study determined the discrepancy between formula-calculated BEE and continuously measured TEE in mechanically ventilated, critically ill ICU patients. It also compared the accuracy of TEE calculations and intermittent TEE estimations with that of continuous TEE measurements obtained by indirect calorimetry.

Patients and methods

The study population was composed of 25 patients in a surgical ICU. Patient ages ranged from 15 to 83 yr (mean 56); 19 were male. All patients were ventilated mechanically with an inspired oxygen concentration of 60% or less. They were at least 6 h postanesthesia, in order to eliminate the disturbing influence of nitrous oxide on gas-exchange measurements. Seven were heavily sedated and five were treated with muscle relaxants. Patients with active bleeding, air leakage, subcutaneous emphysema or dialysis were excluded from the study.

Indirect calorimetry

Oxygen consumption ($\dot{V}_{O_2}$) and carbon dioxide production ($\dot{V}_{CO_2}$) were recorded continuously in all patients for 24 h, using a previously described metabolic cart (6). Each minute the computed $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ values were sent automatically to a remote computer (DEC, pdp 11/23+) and stored for later use. Diurnal $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ were determined by summing all the minute-figures during the recording period. Artifacts due to ventilatory disconnections were removed automatically by an algorithm; this algorithm identifies every period with an expiratory minute volume of less than 2 l/min and suppresses automatically all detected periods plus the next 5 min and the last minute just before the detected artifact from the summing procedure (7). The 24-h TEE (kcal/24 h) was assessed from $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ using the abbreviated Weir formula (8):

$$TEE = 3.9\ \dot{V}_{O_2} + 1.1\ \dot{V}_{CO_2}$$

where $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ are expressed in liters per 24 h at STPD. This equation

was also used to assess three estimates of TEE from short sections of the 24-h recording: one 5-min interval starting at 8 AM, one 10-min interval starting at 8 AM, and the average of two 5-min intervals starting at 8 AM and 5 PM, respectively. These intervals always began at least 30 min after a ventilatory intervention.

Basic Harris-Benedict formula and its correction factor

BEE is defined as the energy expenditure in a neutral thermal environment at least 12 h postprandially, at ease both mentally and physically (9). We used the Harris-Benedict formula (3) to calculate BEE (kcal/24 h) as follows:

$$\text{male:} \quad BEE = 66 + 13.8W + 5H - 6.8A$$
$$\text{female:} \quad BEE = 655 + 9.7W + 1.8H - 4.7A$$

where W is weight (kg), H is height (cm), and A is age (yr). Because energy expenditure depends on the patient's clinical condition (10), TEE was determined by multiplying BEE times a correction factor derived from clinical judgment and routine hematologic, biochemical, radiographic, and bacteriologic data for each patient (4, 11-15). The guidelines for determining the correction factor are given in Table 6.1. Infections, recent extensive

Table 6.1. Percent contribution of various stress components to the correction factor (percentages above 100%) according to different authors (4, 11-15).

Elevated body temperature (per °C above 37°C)	12%
Severe infection/sepsis	10-30%
Recent extensive operation	10-30%
Fracture/trauma	10-30%
Burn wounds	50-150%
Respiratory distress syndrome	20%

operations, respiratory distress syndrome, burn wounds, and elevation of body temperature all have a comparable influence (2, 4, 11-16); the contribution of each stress component depends on its severity. For each patient the correction factor was determined before the 24-h continuous recording of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$.

Statistical analysis

The linear correlations between the measured TEE values and the calculated BEE values and between the measured TEE values and the TEE

values obtained by the other methods were determined with an advanced technique in order to be able to compare the statistical significance of two different correlation coefficients by the Student's t-test (17). A best fit was computed by linear regression analysis.

Results

There was a great discrepancy between BEE calculated from the basic Harris-Benedict formula and TEE measured by continuous indirect calorimetry in this group of critically ill patients (Fig. 6.1A). The coefficient of correlation between calculated BEE and measured TEE was relatively low (Table 6.2).

Table 6.2. Statistical comparison of calculated BEE, calculated TEE, and estimated TEE to measured TEE.

	Correlation coefficient		± SEM	Intercept ± SD	Slope ± SD
Calculated BEE	0.5	†	± 0.2	850 ± 580	0.9 ± 0.4
Calculated TEE	0.82	*	± 0.07	−68 ± 320	1.0 ± 0.2
5-min TEE estimate	0.90	*	± 0.04	250 ± 200	0.9 ± 0.1
10-min TEE estimate	0.92	*	± 0.03	274 ± 170	0.9 ± 0.1
Average of two 5-min TEE estimates	0.95	†	± 0.03	210 ± 140	0.9 ± 0.1

*not significant.
†$p < .05$.

The clinical diagnoses of the 25 patients and the contributions of the individual correction factors are surveyed in Table 6.3. The mean correction factor was 46 ± 17% (SD). The corrected Harris-Benedict calculations of TEE are compared to continuous calorimetric measurements of TEE in figure 6.1B. Most data points are closer to the regression line as compared to figure 6.1A. This is reflected in a significantly ($p < .05$) improved correlation and a better linear fit (Table 6.2). The mean absolute difference between calculated and measured TEE was 8.9 ± 9.6% (SD). As can be seen from Table 6.4, this difference was less than 10% in 19 patients; the discrepancy exceeded 30% in only one patient, whose metabolism was disturbed by a severe proteinuria for which bilateral nefrectomy was ultimately performed.

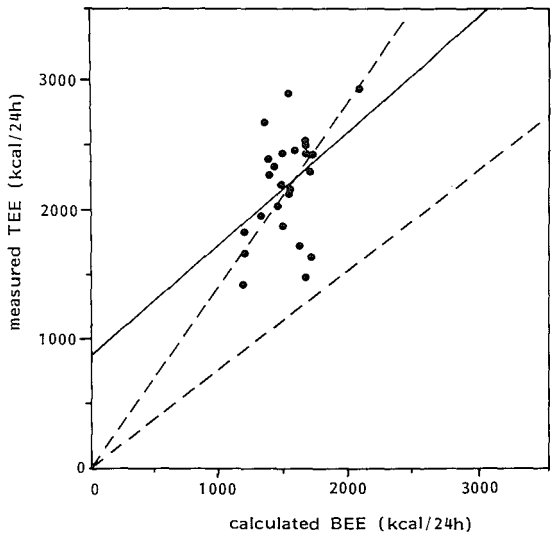

Figure 6.1A. Calculated BEE compared to measured TEE. The area between the *dashed lines* corresponds to calculated BEE/measured TEE ratios between 0.7 and 1.3. Mean TEE based on continuous calorimetric measurements was 2160 kcal/24 h (range 1408 to 2895).

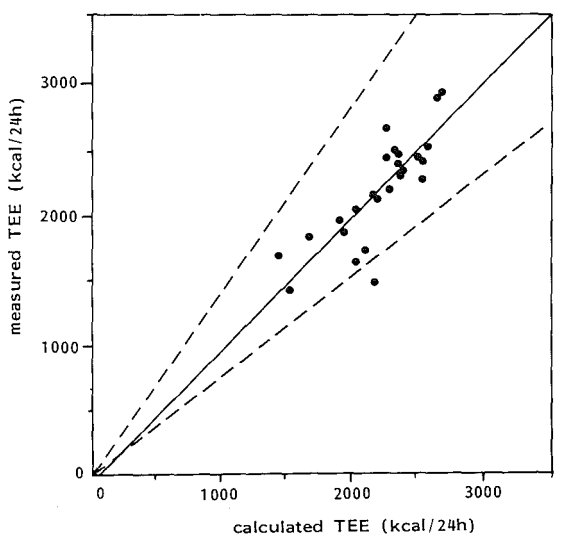

Figure 6.1B. Calculated TEE compared to measured TEE. The area between the *dashed lines* corresponds to calculated/measured TEE ratios between 0.7 and 1.3. In all but one patient the difference between the two values was less than 30%.

Table 6.3. Survey of the clinical conditions and the contribution of individual correction factors according to the guidelines of Table 6.1.

Pat. nr	CLINICAL DIAGNOSIS	Trauma	Fever	Infection/ Sepsis	Recent Operation	Respiratory Distress Syndrome	Total correction Factor (% above 100%)
1	Bifurcation prosthesis, pneumonia, respiratory distress syndrome		19	15		20	54
2	Multiple fractures, pneumonia	10	16	30			56
3	Total gastrectomy 3 days before, respiratory distress syndrome		5		5	20	30
4	Bilateral nefrectomy 1 day before				30		30
5	Acute pancreatitis, laparotomy		25	20	10		55
6	Generalized peritonitis due to colonic perforation		22	30		20	72
7	Aortic tube prosthesis, pneumonia		25	15			40
8	Multiple gunshot wounds	25	15				40
9	Acute pancreatitis		18	30			48
10	Aortic prosthesis, pneumonia		20	30			50
11	Multiple fractures, pneumonia	30	24	20			74
12	Esophageal resection, gastric tube, respiratory distress dynrome		24		25	20	69
13	Acute pancreatitis, laparotomy for drainage of abscesses		30	30	25		85
14	Anastomotic leakage of esophagocolostomy		20	20			40
15	Multiple fractures	30					30
16	Drainage of abscess, pneumonia		15	25			40
17	Anastomotic leakage of ileocolostomy, respiratory distress syndrome		28	20		20	68
18	Peritonitis, laparotomy for drainage of abscess		9	30	5		44
19	Ileal perforations due to allergic vasculitis/periarteritis nodosa		24	15			39
20	Adhesiolysis, colostomy				30		30
21	Respiratory distress syndrome after esophageal resection					20	20
22	Bifurcation prosthesis, respiratory distress syndrome		12		10	20	42
23	Respiratory insufficiency after hemihepatectomy		29				29
24	Thyroidectomy, pneumonia			20			20
25	Esophageal resection, colonic interposition, respiratory distress syndrome				10	20	30

Table 6.4. Distribution of the percent differences between calculated BEE and measured TEE and between four different TEE values and measured TEE.

Percent Difference	Number of Patients				
	BEE	Calculated TEE	Estimated TEE		
			5-min	10-min	Average of two 5-min
Below _10%	2	19	18	20	25
10% to 20%	3	3	7	5	2
20% to 30%	7	2	—	—	—
Above 30%	13	1	—	—	—

Estimated and measured TEE values are compared in figure 6.2. The correlation was slightly but not significantly improved by extending the interval from 5 to 10 min, and somewhat further improved by averaging values from the two 5-min periods (Table 6.2). Of these three estimates, only the last-named produced TEE values significantly ($p < .05$) more accurate than calculated TEE values.

Discussion

Some authors deny the existence of a relevant hypermetabolic state and the necessity of a clinical correction factor (18, 19); however, we found a significant discrepancy between calculated BEE and measured TEE, which was decreased by supplemental application of the clinical correction factor (calculated TEE). In our group of mechanically ventilated surgical patients, application of the Harris-Benedict formula combined with careful judgment of the clinical condition led to an average difference between calculated and continuously measured TEE of $8.9 \pm 9.6\%$. Rutten et al. (20) proposed multiplying BEE by 1.75 to provide a better calculation of caloric needs compared to the basic Harris-Benedict formula in acutely ill patients; however, this overestimates caloric needs by 50% to 60% (21).

As an alternative to using BEE with a correction factor, indirect calorimetry has its methodologic limitations (22, 23) and the abbreviated Weir formula (8) does not take into account the specific contribution of protein combustion. However, this method is generally accepted as reliable for TEE determination. Indirect calorimetry has been used with recording periods varying from a few minutes (18, 22, 24) to several hours per day (25). Continuous 24-h measurement also has been advocated (26), because $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ in critically ill patients can fluctuate substantially with circadian

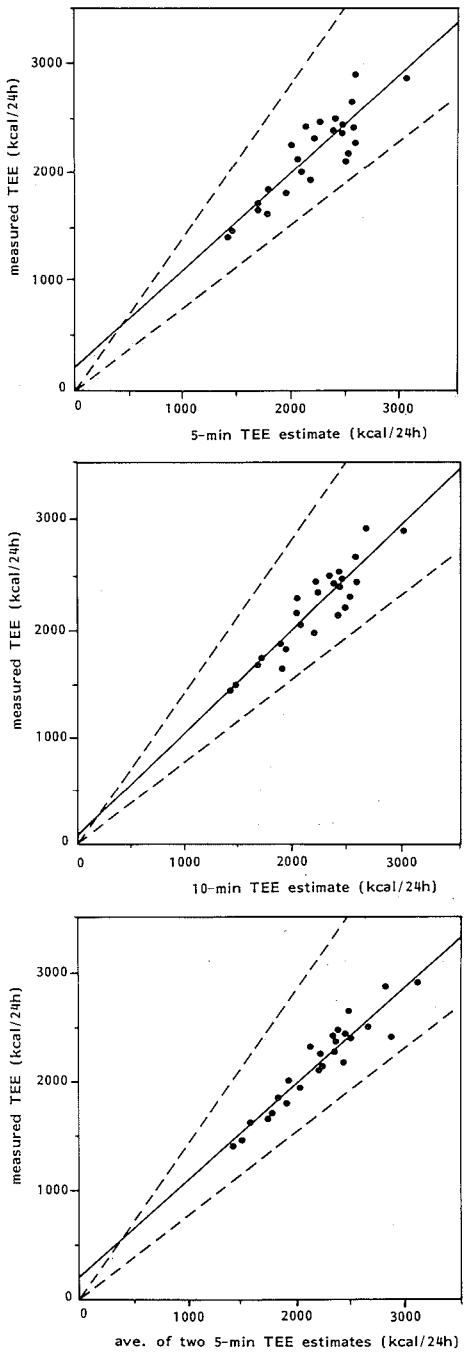

Figure 6.2. Five-min (*top*), 10-min (*middle*), and average of two 5-min (*bottom*) estimates of TEE compared to measured TEE. In each figure, the area between the *dashed lines* corresponds to estimated/measured TEE ratios between 0.7 and 1.3.

rhythm (9), changes in body temperature (11), discomfort and pain (23), medication (27, 28) and nutrition (24, 29). This suggests that if continuous measurements are not used, the reliability of intermittent metabolic recordings will be related to their duration and frequency, which is confirmed by the results of this study (Table 6.2). Our results suggest that increased frequency is more important than increased duration: the accuracy of two 5-min periods at 8 AM and 5 PM was slightly better than one 10-min period at 8 AM.

Apart from a more accurate determination of TEE, indirect calorimetry has a second advantage over the calculation method. By combining indirect calorimetry with a determination of the urea production, it is possible to quantify protein metabolism and to differentiate the remaining caloric expenditure into a carbohydrate and a fat component. However, in the daily management of critically ill surgical patients, reliable determination of the urea production is very difficult and time-consuming due to the complexity of several disturbing factors (e.g., variations in third space, transfusion of blood or plasma).

Our results should be interpreted with caution because they describe a highly heterogeneous group of surgical ICU patients; further investigations are necessary to determine whether the discrepancy between calculated and continuously measured TEE is clinically relevant; in that case indirect calorimetry is required to assess the individual caloric needs in daily practice. It might be possible, that in well-defined subpopulations (e.g., uremia) less accurate results can be achieved by application of the calculation method. In spontaneously breathing patients the obligatory use of a head canopy or a mouthpiece/noseclip probably requires metabolic gas-exchange measurements over a longer period, because these techniques frequently lead to a disturbance of the patient's steady state by changing the body gas stores.

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Chapter 7

TOTAL PARENTERAL NUTRITION IN CRITICALLY ILL SURGICAL PATIENTS: FIXED vs TAILORED CALORIC REPLACEMENT

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TOTAL PARENTERAL NUTRITION IN CRITICALLY ILL SURGICAL PATIENTS: FIXED vs TAILORED CALORIC REPLACEMENT

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Abstract

In critically ill patients accurate measurement of total energy expenditure (TEE) is possible by means of continuous indirect calorimetry. Since in many ICUs the necessary equipment is not available, the Harris-Benedict formula (HB) is frequently used to calculate TEE. Supplemental application of a clinical correction factor (HBc) has been advised. In this study we assessed the reliability of both methods of calculation and of a standard nutritional regimen, all three compared to the calorimetrically measured TEE (gold standard). Although the basic HB-formula did not perform better than the standard regimen, significantly better results were obtained by supplemental application of the clinical correction factor (HBc). It is left undecided, whether or not indirect calorimetry is actually to be preferred in daily clinical practice.

Introduction

Although at the beginning of this century *hypoalimentation* was already supposed to have a deleterious effect upon patient's recovery (1), it was not possible to supply total parenteral nutrition (TPN) until the late 1960s (11, 48). Ever since the introduction of central venous catheters (32) and the availability of various parenteral nutrients, parenteral hyperalimentation has been extensively applied both to restore and to maintain the patient's nutritional condition. Besides proteins, calories were initially supplied in excessive quantities in order to prevent auto-cannibalism and to obtain a positive nitrogen-balance (2, 41, 49).

During the last few years, however, it has become clear that, especially in critically ill patients, *hyperalimentation* may have detrimental influences as well (2-4, 12, 30, 42). Therefore both hypo- and hyperalimentation should be avoided by adjusting the caloric supply to the individual patient's total energy expenditure (TEE) (2, 24, 36, 37). Bedside assessment of the caloric expenditure is possible by means of the empirical Harris-Benedict formula (20, 35), which can be corrected for the specific clinical condition (5, 9, 19, 26, 27, 29, 45). On the other hand the individual caloric needs can be measured by means of indirect calorimetry, for which fully automatic, but rather expensive instruments are commercially available.

For practical reasons, however, in many hospitals a standard nutritional support regimen is frequently used (38). The aim of this study was to analyze to what extent a standard regimen leads to hypo- or hyperalimentation. For this purpose a standard caloric supply was compared to TEE, measured by means of continuous indirect calorimetry. It was further examined, whether the caloric supply could have been matched better to TEE by basing the nutritional support on the basic or the corrected Harris-Benedict formula, instead of the standard regimen.

Methods and materials

Patient selection and determination of caloric supply

The study was performed in 20 artificially ventilated, surgical patients. Patients with active bleeding, dialysis, air-leakage or subcutaneous emphysema were excluded; they had to be at least 6 h postanesthesia in order to exclude the disturbing influence of nitrous oxide on the gas-exchange measurements. The individual anthropometric and clinical data are summarized in Table 7.1. Bed sheets were used without blankets and/or bed clothing. The set-point of the air-conditioning system was fixed at 24°C. Sedatives and/or muscle relaxants were only used in case of severe restlessness in order to prevent an excessive, undesired increase of metabolic rate. All patients received TPN, basically according to a standard nutritional support regimen (Table 7.2). Patients with (additional) enteral feeding were not allowed to enter the study in order to exclude the variable contribution in calorie uptake due to incomplete digestion or incomplete absorption. In this way it was possible to determine the actual caloric supply (aCS) per patient, which may deviate from the prescribed caloric quantity (i.e. 2875 kcal/day) due to the variable needs of fluid administration in ICU patients.

Since the issue of the protein-flux was beyond the scope of this study, nitrogen-balance determination was not performed.

Table 7.1. Anthropometric and clinical data of the patients (n = 20). The individual body temperature can be derived from the contribution of fever to the clinical correction factor (12% per °C above 37°C).

		ANTHROPOMETRIC DATA					CLINICAL DATA								
Pat. nr	CLINICAL DIAGNOSIS	sex	height (cm)	weight (kg)	weight (% IBW)	age (years)	fever (% c.f.)	trauma/fractures (% c.f.)	sepsis/infection (% c.f.)	recent operation (% c.f.)	resp. distress synd. (% c.f.)	total correction factor (% above 100%)	duration TPN at start (days)	sedation	paralysis
1	Bifurcation prosthesis, pneumonia, respiratory distress syndrome	M	170	75	112	75	19	—	15%	—	20%	54%	8	—	+
2	Multiple fractures, pneumonia	M	170	60	90	15	16	10%	30%	—	—	56%	2	—	+
3.	Total gastrectomy 3 days before, respiratory distress syndrome	M	180	80	103	70	5	—	—	5%	20%	30%	0	+	+
4.	Bilateral nefrectomy 1 day before	M	175	65	90	29	—	—	—	30%	—	30%	0	—	—
5.	Acute pancreatitis, laparotomy	M	180	64	82	65	25	—	20%	10%	—	55%	1	—	—
6.	Multiple gunshot wounds	M	170	85	127	65	15	25%	—	—	—	40%	0	—	—
7.	Acute pancreatitis	M	174	75	106	40	18	—	30%	—	—	48%	0	—	—
8.	Aortic prosthesis, pneumonia	M	176	78	107	68	20	—	30%	—	—	50%	1	—	+
9.	Acute pancreatitis, laparotomy for drainage of abscesses	F	170	65	107	50	30	—	30%	25%	—	85%	1	+	—
10.	Drainage of abscess, pneumonia	F	172	65	103	37	15	—	25%	—	—	40%	0	—	—
11.	Anastomotic leakage of ileocolostomy, respiratory distress syndrome	M	172	60	87	51	—	—	20%	—	20%	40%	0	—	—
12.	Ileal perforations due to allergic vasculitis/periarteritis nadosa	F	156	60	122	71	24	—	15%	—	—	39%	5	+	—
13.	Respiratory insufficiency after hemihepatectomy	F	155	55	115	68	29	—	—	—	—	29%	0	—	—
14.	Esophageal resection, colonic interposition, respiratory distress syndrome	M	179	64	83	53	—	—	—	10%	20%	30%	0	+	—
15.	Multiple fractures, peritonitis due to colonic perforation	M	185	77	93	33	25	30%	20%	—	—	75%	0	+	+
16.	Pneumonia after hemicolectomy, respiratory distress syndrome	M	182	60	75	67	4	—	20%	—	20%	44%	1	—	—
17.	Relaparotomy for peritonitis after ileal resection	F	170	82	134	62	—	—	30%	10%	—	40%	2	—	—
18.	Mediastinitis after esophageal resection	M	180	65	83	58	—	—	20%	—	—	20%	8	—	—
19.	Esophageal resection and colonic interposition 5 days before, pneumonia	M	169	54	82	65	5	—	30%	5%	—	40%	4	—	—
20.	Peritonitis due to ileal perforation (non-Hodgkin lymphoma), ileal resection	M	172	52	75	64	12	—	30%	8%	—	50%	2	—	—

Table 7.2. Standard regimen for total parenteral nutrition.

1000 ml glucose 50%	1875 kcal/24 h (7850 kJ)
500 ml fat emulsion 10% (Intralipid®)	550 kcal/24 h (2300 kJ)
750 ml amino-acid solution (Azonutril®)	450 kcal/24 h (1880 kJ)
Non-protein caloric supply	2425 kcal/24 h (10150 kJ)
Total caloric supply	2875 kcal/24 h (12030 kJ)
Caloric carbohydrate/fat ratio	3.4
Nitrogen/non-protein calorie-ratio	1/130
Short acting insulin	+
Electrolytes	+
Fat-soluble vitamins	+
Water-soluble vitamins	+
Trace elements	+

Measurement of TEE by means of continuous indirect calorimetry

In all patients continuous indirect calorimetry was performed for 24 h with a previously described metabolic cart (14). Each minute oxygen consumption ($\dot{V}_{O_2}$) and carbon dioxide production ($\dot{V}_{CO_2}$) were measured and stored on a remote computer. Diurnal $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ were calculated by summing all minute figures. Artifacts due to ventilatory disconnections were automatically removed (15). Diurnal TEE (kcal/day) was determined by means of the abbreviated Weir formula (17, 46):

$$TEE = 3.9\ \dot{V}_{O_2} + 1.1\ \dot{V}_{CO_2}$$

with $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ in l/24 h (STPD-conditions).

Bedside-calculation of TEE using the uncorrected and the corrected Harris-Benedict formula

Before starting the continuous calorimetric measurements total energy expenditure was calculated with the Harris-Benedict formula (HB) (20, 35):

$$\text{male:} \quad HB = 66 + 13.8W + 5H - 6.8\ A \qquad \text{(kcal/24 h)}$$
$$\text{female:} \quad HB = 655 + 9.7W + 1.8H - 4.7A \qquad \text{(kcal/24 h)}$$

where W = weight (kg); H = height (cm); A = age (year).

Ideal body weight (IBW) was determined according to Paauw (35). If the actual body weight of a patient exceeded IBW by more than 10%, the Harris-Benedict formula was applied in two different ways; the HB-calculation was made both with the actual body weight and with IBW + 10%.

Subsequently for each patient the Harris-Benedict formula was corrected (HBc) for the clinical condition by multiplying HB with an individual correction factor (cf):

$$HBc = cf \times HB \qquad (kcal/24\ h)$$

This clinical correction factor was determined according to the guidelines, summarized in Table 7.3 and adapted from different authors (5, 9, 19, 26, 27, 29, 45). The contribution of the different stress-components to the correction factor is assumed to depend on their actual severity. As the Harris-Benedict study was performed under resting rather than under fasting or basal conditions (17, 29), no correction was made for the specific dynamic action in our study.

Table 7.3. Guidelines for the determination of the clinical correction factor (percentages above 100%).

Elevated body temperature (per °C above 37°C)	12%
Severe infection/sepsis	10-30%
Recent extensive operation	10-30%
Fracture/trauma	10-30%
Burn wounds	50-150%
Respiratory distress syndrome	20%

Statistical analysis

It seems likely, that the clinical effect of over- or under-feeding depends on the relative rather than the absolute discrepancy between the caloric supply and the caloric expenditure. For this reason, not the absolute value of the difference but the absolute value of the percentage difference (= APD) between the actual caloric supply (aCS) and the calorimetrically measured total energy expenditure (CIC) was determined for each patient ($APD = |(aCS-CIC)/CIC| \times 100\%$). In the same way APD was determined between the calculated HB and the measured CIC and between the calculated HBc and the measured CIC. These three groups of APDs were compared with the Wilcoxon rank-sum test.

Results

A survey of the most important figures is given in Table 7.4. The actually administered caloric supply (2853 ± 396 kcal/day) was very near to the prescribed supply of the standard regimen (i.e. 2875 kcal/day). The

measured total energy expenditure (CIC) was 2095 ± 378 kcal/day, which was significantly less than the standard support of 2875 kcal/day. Apparently, for this group of patients the chosen caloric replacement was too large and thus aCS exceeded the expenditure in 17 of the 20 patients. The uncorrected Harris-Benedict formula largely underestimated the total energy expenditure (1475 ± 184 vs 2095 ± 378 kcal/day). The APDs between the uncorrected HB-values and the measured CIC-values (Table 7.4b: | (HB-CIC)/CIC | × 100% = 29.6 ± 10%) were not better than those between the actual caloric supply and the CIC-values (Table 7.4b: | (aCS-CIC)/CIC | × 100% = 44.4 ± 30%; Fig. 7.1), provided that under- and overfeeding are considered equally deleterious.

The mean of the CIC/HB ratio was 1.43 (SD = ± 0.21) expressing the hypermetabolic state of the patient group. Application of the clinical correction factor led to a significant difference ($p < 0.01$) between the APDs of HBc and the APDs of HB with CIC (Fig. 7.1). Furthermore a significant difference ($p < 0.01$) existed between the APDs of HBc and the APDs of aCS with CIC.

The distribution of the APDs between CIC on the one hand and aCS, HB resp. HBc on the other hand is given in Table 7.4c. Again it becomes clear,

Table 7.4. *a.* Values (mean ± SD) of the actual caloric supply (aCS) and total energy expenditure calculated with the uncorrected and corrected Harris-Benedict formula (HB and HBc) and measured by means of continuous indirect calorimetry (CIC). *b.* The absolute values (mean ± SD) of the percentage differences (APDs) between CIC on the one hand and aCS, HB and HBc on the other hand. *c.* The distribution (number of patients) of the APDs between CIC on the one hand and aCS, HB and HBc on the other hand.

a.

aCS	2853 ± 396 (kcal/day)
HB	1475 ± 184 (kcal/day)
HBc	2138 ± 383 (kcal/day)
CIC	2095 ± 378 (kcal/day)

b.

|(aCS-CIC)/CIC| × 100%	= 44.4 ± 30%
|(HB -CIC)/CIC| × 100%	= 29.6 ± 10%
|(HBc-CIC)/CIC| × 100%	= 8.9 ± 10%

c.

	aCS	HB	HBc
<10%	3	1	15
10-20%	1	3	3
20-30%	3	5	1
>30%	13	11	1

that the application of the uncorrected Harris-Benedict formula did not lead to superior results as compared to the standard nutritional regimen. Only after supplemental correction for the clinical condition the caloric supply would have been tailored more correctly to the individual needs.

The patients were 99 ± 17% of their IBW. In five obese patients the actual body weight exceeded IBW in more than 10% (patient nos. 1, 6, 12, 13 and 17). If in the Harris-Benedict formula a maximal body weight of 1.10× IBW is taken into account, the results of the statistical comparisons, summarized in figure 7.1, remain unchanged.

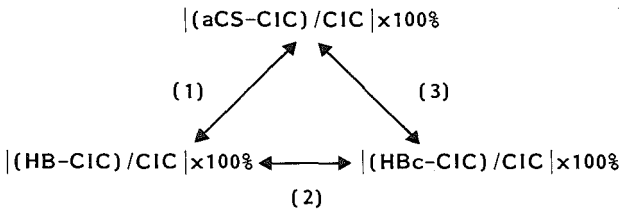

Figure 7.1. Statistical comparison of the three groups of APDs with the Wilcoxon rank-sum test: (1) not significant ($p > 0.05$); (2) and (3) significant ($p < 0.01$). aCS = actual caloric supply; CIC = total energy expenditure measured by means of continuous indirect calorimetry; HB = total energy expenditure calculated by means of the uncorrected Harris-Benedict formula; HBc = total energy expenditure calculated by means of the corrected Harris-Benedict formula.

Discussion

Only few prospective trials have been executed, analyzing the effect of TPN under different clinical conditions (7, 21-23, 33, 34, 44). Despite the controversial outcome of these trials, TPN has acquired an important role in today's surgical treatment. During the first half of the last decade much attention has been paid to the protein requirements; the primary goal was to attain a positive nitrogen balance. In this period extremely high doses of parenteral nutrition were advocated up to 5000-6000 kcal/day in order to restore the lean body mass of malnourished patients (2, 24, 41, 49). With a "safety margin" of 1.5× to 2.0× basal energy expenditure (19, 29, 40) the increased caloric demands of severely ill patients could be sufficiently covered to prevent auto-cannibalism and to reach a positive nitrogen-balance with 95% confidence (40).

Recent publications have stressed the detrimental effects of such hyper-alimentation, especially in critically ill patients. Excessive caloric supply

may lead to hepatic dysfunction (30, 42), hyperglycemia, elevated levels of BUN, cholesterol or triglycerides (2) and delayed ventilatory weaning due to an increased CO_2-production up to twice fasting-level (3, 4, 12). In this way hyperalimentation is a metabolic stress rather than a nutritional support, which is reflected in an increased urinary output of catecholamines (3, 13). Therefore it has been advised to avoid both underfeeding and overfeeding by adjusting the caloric supply to the energy expenditure of the individual patient (2, 31, 36).

If one is interested in inter-patient or intra-patient comparisons, energy expenditure should be determined under basal or resting conditions (basal energy expenditure = BEE; resting energy expenditure = REE) in order to minimize the disturbing influence of a great number of variable factors (motor activity, medication etc.) (47). However, in case of nutritional assessment caloric supply should be based upon total energy expenditure, taking into account the total effect of all these factors. Reliable determination of TEE is possible by means of indirect calorimetry (14, 15). However, in many intensive care units an automatic metabolic cart is not available due to the considerable costs. The Douglas-bag method (10, 16) is considered to be both too unreliable and too time-consuming for daily practice. This study was to analyze to what extent standardization of the caloric supply leads to under- or overfeeding in critically ill patients and how much improvement is gained by simple bedside-calculation of total energy expenditure in situations, where the necessary equipment for reliable indirect calorimetry is not available.

The average caloric requirement for the adult, critically ill, surgical patient can be estimated at 2500-3000 kcal/day (28, 38, 43). Therefore a standard regimen was chosen containing 2875 kcal/day. The actual caloric supply (2853 $\pm$ 396 kcal/day) was only slightly different from the prescribed quantity, which means that in spite of the variable needs of fluid administration it was possible to effect the regimen. The measured total energy expenditure (CIC = 2095 $\pm$ 378 kcal/day) was significantly less than the actual caloric supply. Apparently, at least for this group of patients the chosen caloric support regimen was too large, which of course could not have been known at the beginning of the study.

In figure 7.1 it can be seen, that the application of the uncorrected Harris-Benedict formula does not lead to a better adjustment of the caloric supply to the individual needs. This conclusion corresponds with those of previous studies, indicating that under various clinical conditions the basic Harris-

Benedict formula is not able to predict the individual energy expenditure accurately (18, 37, 45). However, significantly better results can be obtained with the supplemental application of the clinical correction factor in combination with the Harris-Benedict formula. This is in contrast to several recent calorimetric studies (6, 35, 36, 39), denying the existence of a clinically important hypermetabolic state in stressed, traumatized or septic patients. In our group of patients the CIC/HB ratio (reflecting the hypermetabolic state) was 1.43 ± 0.21 (mean ± SD) which is remarkably high. In spite of great diurnal fluctuations in gas-exchange (8), most investigators perform intermittent indirect calorimetry under resting rather than "representative" conditions and based upon short recording periods, which is less accurate than the continuous measurements in this study. It is unclear, whether or not this can explain the above-mentioned discrepancy with respect to the existence of a hypermetabolic state.

Because an excessive quantity of adipose tissue does not lead to a proportional increase of metabolic rate, it has been advised to use a maximal body weight of 1.10× IBW in the Harris-Benedict formula (25). Although the body weight of five obese patients exceeded 1.10× IBW, supplemental application of this restrictive guideline did not lead to significant changes in the ultimate results of the study.

In *conclusion*, in our category of surgical patients the application of the uncorrected Harris-Benedict formula has no advantages over a more simple standard nutritional regimen. If the necessary equipment for indirect calorimetry is not available, we advise tailoring of caloric replacement based upon the corrected Harris-Benedict formula. No data are available to answer the question, to what extent a discrepancy between caloric supply and caloric expenditure can be accepted without any danger. Although the HBc method seems to be more satisfactory, it remains unresolved, whether or not indirect calorimetry is actually to be preferred in daily clinical practice.

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Chapter 8

OUTCOME PREDICTION IN CRITICALLY ILL PATIENTS BY MEANS OF OXYGEN CONSUMPTION INDEX AND SIMPLIFIED ACUTE PHYSIOLOGY SCORE

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OUTCOME PREDICTION IN CRITICALLY ILL PATIENTS BY MEANS OF OXYGEN CONSUMPTION INDEX AND SYMPLIFIED ACUTE PHYSIOLOGY SCORE

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Abstract

Both oxygen consumption index ($\dot{V}_{O_2}$-index) and Simplified Acute Physiology Score (SAPS) are reported to be reliable predictors of the ultimate outcome in critically ill patients. The purpose of this study was to verify whether survivors and nonsurvivors have different $\dot{V}_{O_2}$-indices and whether the prognostic potency of SAPS can be improved by addition of $\dot{V}_{O_2}$-index as a supplemental physiological variable. In 50 mechanically ventilated, surgical ICU patients with heterogeneous underlying diseases SAPS was calculated and $\dot{V}_{O_2}$-index was determined by continuous 24-h measurement of oxygen consumption. The $\dot{V}_{O_2}$-indices of survivors and nonsurvivors were not significantly different ($p > 0.05$), which is in contrast to the results of earlier studies. This contrast may be explained by a difference both in methods of $\dot{V}_{O_2}$-measurement and in study populations. SAPS was significantly lower in survivors than in nonsurvivors ($p < 0.005$) and was able to classify the patients correctly into groups of increasing probability of death. However, SAPS failed to be a helpful prognosticator in the individual patient. The addition of $\dot{V}_{O_2}$-index to SAPS as a supplemental physiological variable did not substantially improve the prognostic potency. Because a higher $\dot{V}_{O_2}$-index did not necessarily indicate a better survival chance, there is no argument for therapeutic interventions aimed exclusively at increasing $\dot{V}_{O_2}$-index, as suggested previously.

Introduction

In the intensive treatment of critically ill patients outcome prediction is of great interest. Firstly it can describe the severity of illness and facilitates

comparisons between *groups* of patients; it is therefore indispensable for ICU-trials and for the determination of the departmental performance rate (16). Secondly, the recognition of differences between the physiological patterns of survivors and nonsurvivors leads to a better understanding of host defense mechanisms and can introduce new therapeutic modalities (33). Thirdly, in *individual* patients highly reliable mortality prediction may reduce human suffering and partly solve the dilemma how to spend limited resources.

In recent years many efforts have been made to design a simple, physiologically based classification system in order to indentify groups of patients on the basis of severity of illness and probability of death. The laborious APACHE-system using 34 variables (22) was successfully simplified to 14 easily obtainable variables (Simplified Acute Physiology Scoring-system = SAPS-system), without any significant loss of prognostic potency (16).

Contradictory data are available about the prognostic potency of $\dot{V}_{O_2}$-index (i.e. oxygen consumption/body surface area = $\dot{V}_{O_2}$/BSA) on survival rate. Neither the APACHE-system, nor the SAPS-system takes into account $\dot{V}_{O_2}$-index. On the one hand, several authors have suggested, that the inability of augmenting $\dot{V}_{O_2}$-index in answer to exogenous stress-factors discriminates nonsurvivors from survivors (5, 8, 41). As a predictor of outcome $\dot{V}_{O_2}$-index is said to be more reliable than e.g. mean arterial pressure (31) or cardiac output (37). On the other hand, similar hemodynamic profiles have been described both for survivors and for nonsurvivors (38) without any prognostic value of $\dot{V}_{O_2}$-index (19). It is unclear, how these contradictory results must be explained.

The purpose of this study was (1) to determine whether $\dot{V}_{O_2}$-indices of survivors are different from those of nonsurvivors and (2) to analyze whether the potency of the SAPS-system to predict the patient's ultimate outcome can be improved by addition of $\dot{V}_{O_2}$-index as a supplemental physiological variable.

Material and methods

Patient selection

In a surgical intensive care unit 50 mechanically ventilated patients were studied. The clinical data of these patients are summarized in Table 8.1. Patients were allowed to enter the study, if they were expected to need mechanical ventilation during at least 24 h. Factors with a disturbing influence on gas-exchange measurements led to the following exclusion-

criteria: 1. active bleeding; 2. hemodialysis; 3. incorrectable, expiratory air leakage (cuff, thoracic drain, etc.); 4. first 6 h postanesthesia; 5. inspiratory oxygen concentration > 60%.

Table 8.1. Clinical profile of the patients (pts) under study.

Number of patients (♂/♀)	50 (38/12)
Mean age ± SD (range)	53.5 ± 17 (15-83)
Body temperature (mean ± SD)	38.2 ± 0.9°C
Infection/sepsis	29 pts (58%)
Recent major operation (< 5 days)	22 pts (44%)
Fracture/trauma	13 pts (26%)
Respiratory distress syndrome	10 pts (20%)
Enteral nutrition	17 pts (34%)
Parenteral nutrition	21 pts (42%)
Enteral + parenteral nutrition	2 pts (4%)

Monitoring of oxygen consumption index

In each patient continuous gas-exchange measurements were performed during 24 h by open circuit respirometry with a fully automatic metabolic cart (12). Every minute the oxygen consumption was determined and the assessed $\dot{V}_{O_2}$-value was sent to a remote computer for later use. After automatic artifact suppression (13) and summation of all diurnal minute-values mean $\dot{V}_{O_2}$-index was calculated for each patient. BSA was determined from the individual height and weight with a surface area nomogram; $\dot{V}_{O_2}$-index was calculated from the following quotient: mean $\dot{V}_{O_2}$/BSA.

Simplified Acute Physiology Score and mortality rate

At the start of the gas-exchange measurements various organ functions were individually scored according to the SAPS-system (16), for which the guidelines are summarized in Table 8.2: the more severily ill the patient, the higher the score. None of the patients suffered from severe head injury, but since many of them had to be sedated and some had to be paralyzed, scoring of the central nervous system was hardly possible. To acquire a total score which can be compared with other studies, the Glasgow coma score was assumed to be equal to the mean value of the other 13 variables.

Mortality rate was determined for four different periods following the recording day: (1) the total hospital stay, (2) the first week, (3) the second week and (4) the rest of the hospital stay.

Table 8.2. Scoring values for the 14 physiological variables of the SAPS-system (reprinted with permission) (16).

	HIGH VALUES						LOW VALUES		
SAP-Scoring values	4	3	2	1	0	1	2	3	4
Variables of SAPS-system									
1. Age (yr)	>75	66-75	56-65	46-55	≤45				
2. Heart rate (beat/min)	≥180	140-179	110-139		70-109		55-69	40-54	<40
3. Systolic blood pressure (mmHg)	≥190		150-189		80-149		55-79		<55
4. Body temperature (°C)	≥41	39.0-40.9		38.5-38.9	36.0-38.4	34.0-35.9	32.0-33.9	30.0-31.9	<30.0
5. Spontaneous respiratory rate (breath/min) or	≥50	35-49		25-34	12-24	10-11	6-9		<6
Ventilation or CPAP								yes	
6. Urinary output (L/24 h)			>5.00	3.50-4.99	0.70-3.49		0.50-0.69	0.20-0.49	<0.20
7. Blood urea (mMol/L)	≥55.0	36.0-54.9	29.0-35.9	7.5-28.9	3.5-7.4	<3.5			
8. Hematocrit (%)	≥60.0		50.0-59.9	46.0-49.9	30.0-45.9		20.0-29.9		<20.0
9. White blood cell count ($10^3/mm^2$)	≥40.0		20.0-39.9	15.0-19.9	3.0-14.9		1.0-2.9		<1.0
10. Serum glucose (mMol/L)	≥44.5	27.8-44.4		14.0-27.7	3.9-13.9		2.8-3.8	1.6-2.7	<1.6
11. Serum potassium (mEq/L)	≥7.0	6.0-6.9		5.5-5.9	3.5-5.4	3.0-3.4	2.5-2.9		<2.5
12. Serum sodium (mEq/L)	≥180	161-179	156-160	151-155	130-150		120-129	110-119	<110
13. Serum HCO_3^- (mEq/L)		>40.0		30.0-39.9	20.0-29.9	10.0-19.9		5.0-9.9	<5.0
14. Glasgow coma score					13-15	10-12	7-9	4-6	3

Statistical analysis

Both the SAP-Scores and the $\dot{V}_{O_2}$-indices were compared for survivors and nonsurvivors with the Wilcoxon rank-sum test.

The prognostic potency of (1) $\dot{V}_{O_2}$-index, (2) SAPS and (3) the combination of $\dot{V}_{O_2}$-index and SAPS were determined by the technique of receiver operating characteristic (ROC) curve analysis. This requires that the cut-off value for a test is varied and that at each cut-off value the true and false positive ratios are calculated. Plotting true against false positive ratio gives the ROC curve. A better test gives an ROC curve which lies closer to the ordinate, i.e. gives a high true positive ratio, before the false positive ratio rises and corrupts the results (4).

Results

Seven out of the 50 patients (14%) died within one week after the recording day; 3 patients (6%) died during the second week and 8 patients (16%) during the rest of the hospital stay. Thirteen of the 18 patients (72%), who died during the total hospital stay, had multiple system organ failure according to the criteria listed by Fry (15); one patient died probably due to an acute myocardial infarction and four patients died due to pulmonary infections.

From the contribution of the 14 variables to the total SAP-Score it appears, that those variables which can be corrected for by relatively simple therapeutic interventions (e.g. serum electrolytes, serum glucose) were roughly in the normal range (Table 8.3). In general, variables which are less easily controllable (e.g. heart rate, blood pressure) deviated more from normal values and therefore contributed more to the total score. For the 50 patients this resulted in an SAP-Score of 13.5 ± 4 (mean ± SD; range = 4-26). The SAP-Score in survivors (mean ± SD = 12.2 ± 4) was significantly lower than the Score in nonsurvivors (15.9 ± 5; one-tailed $p < 0.005$). The SAPS-system was even able to classify the patients correctly into groups of increasing probability of death, irrespective of the primary diagnosis (Table 8.4). However, at the optimal cut-off value of 17 the accuracy of the SAPS-system to predict the hospital mortality was only 74%; 12 patients (24%) ultimately died despite a score < 17 (i.e. false negative) and one patient (2%) survived despite a score > 17 (i.e. false positive).

While for the total group of 50 patients mean $\dot{V}_{O_2}$-index was 168 ml/min.m^2 (SD = ± 27; range = 112-230), the $\dot{V}_{O_2}$-indices in survivors were not significantly different from those in nonsurvivors (Table 8.5: two-tailed $p > 0.05$). Division of the patient-group into subpopulations based on the time-

interval between gas-exchange measurements and day of decease did not produce a significant difference between survivors and nonsurvivors either.

The ROC curve for $\dot{V}_{O_2}$-index approximated the 45° diagonal (y = x), indicating the absence of prognostic potency (Fig. 8.1). The ROC curve for SAPS was superior to that for $\dot{V}_{O_2}$-index. The ROC curves for SAPS alone and for the combination of $\dot{V}_{O_2}$-index and SAPS were highly similar; the addition of $\dot{V}_{O_2}$-index to SAPS as a supplemental physiological variable did not substantially improve the prognostic potency.

Table 8.3. Contribution of the 14 physiological variables to the total SAP-Score.

	HIGH VALUES		LOW VALUES
SAP-Scoring values	4 — 3 — 2	1 — 0 — 1	2 — 3 — 4
Variables of SAPS-system			
1. Age	—	25	25
2. Heart rate	41	6	3
3. Systolic blood pressure	25	22	3
4. Body temperature	18	32	0
5. Spont. respir. rate/artif. ventil.	—	—	50
6. Urinary output	1	45	4
7. Blood urea	6	44	—
8. Hematocrit	0	38	12
9. WBC count	8	42	0
10. Serum glucose	1	47	2
11. Serum potassium	0	50	0
12. Serum sodium	2	47	1
13. Serum HCO_3^-	0	50	0
14. Glasgow coma score	—	47	3

Table 8.4. The relation between SAP-Score and hospital mortality rate.

SAP-Score	Nr. of patients	Hospital mortality rate (%)
< 13	19	2/19 (= 11%)
13-18	24	10/24 (= 42%)
> 18	7	6/7 (= 86%)

Table 8.5. $\dot{V}_{O_2}$-index (mean ± SD) of survivors (S) and nonsurvivors (nS). The mortality rate during the total hospital stay is further differentiated over three different periods after the recording day.

Period after recording day		$\dot{V}_{O_2}$-index (ml.min^{-1}.m^{-2})	
total hospital stay	S (32 pts)	171 ± 26	*
	nS (18 pts)	162 ± 28	
⩽ 7 days	S (43 pts)	169 ± 26	*
	nS (7 pts)	162 ± 33	
8-14 days	S (40 pts)	168 ± 26	*
	nS (3 pts)	181 ± 14	
>14 days	S (32 pts)	171 ± 26	*
	nS (8 pts)	154 ± 26	

*not significant (two tailed: $p > 0.05$) (Wilcoxon rank-sum test).

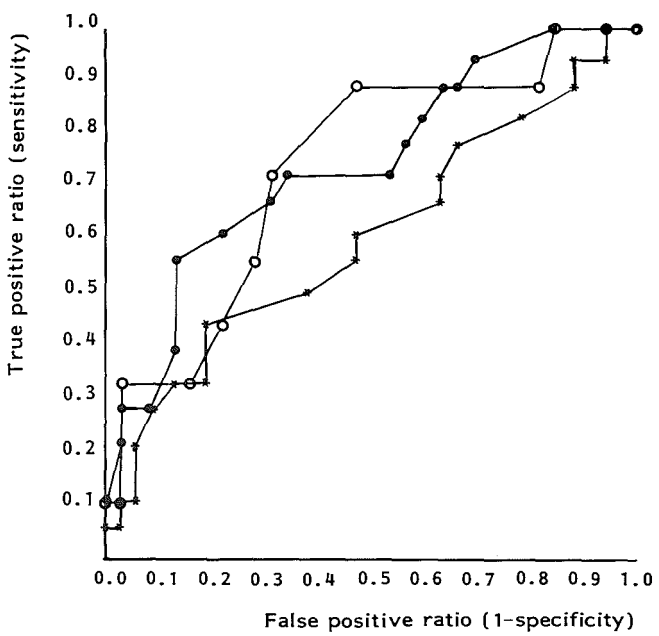

Figure 8.1. The receiver operating characteristic (ROC) curve for $\dot{V}_{O_2}$-index (*), SAPS (○), and the combination of $\dot{V}_{O_2}$-index and SAPS (●) as predictors of decease.

Discussion

From these results it can be concluded, that in contrast to previous studies $\dot{V}_{O_2}$-indices in survivors are not significantly different from those in nonsurvivors, regardless of the interval between the gas-exchange measurement and the day of decease. Furthermore, the prognostic potency of the SAPS-system can not be improved by addition of $\dot{V}_{O_2}$-index as a supplemental physiological variable.

Sir William Osler (1849-1920) already stated, that patients rarely die of their primarily diagnosed illness; more often they die of physiological complications (33). Therefore it is tempting to predict the ultimate outcome of patients by describing their clinical conditions based on physiological variables rather than on their underlying diseases. Such a physiologically based classification system has been developed, using 14 easily obtainable variables (16). This SAPS-system was able to classify our patients correctly in groups of increasing probability of death (Table 8.4). However, in the individual patient it failed to predict the ultimate outcome reliably. With an accuracy of only 74% it can not be helpful to take warranted decisions on the discontinuation of treatment.

It is still unclear, which moment is most suitable to score the condition of the patients. In previous studies the condition was usually scored during the first 24 h after admission to the ICU (1, 16). This is a highly variable moment in the course of illness, since it depends on the available ICU capacity and on the therapeutic facilities in the rest of the hospital. In this study the moment of scoring was mainly determined by the necessity of mechanical ventilation, by which a comparable variability is introduced. Other investigators classify the patients on every day of ICU treatment (23).

Oxygen consumption depends on a number of factors (17). 1. In patients with cardiopulmonary disease, severe hypovolemia etc. $\dot{V}_{O_2}$ may be hampered by an insufficient *O_2-supply* (defined by the product of cardiac output and arterial oxygen content), which results in a so-called oxygen-supply dependency (36). 2. In critically ill patients the *O_2-extraction rate* (defined by the relative difference between arterial and mixed venous oxygen content $= C_a - C_{\bar{v}}/C_a$) is frequently limited due to a left shifted oxyhemoglobin saturation curve (18, 39), capillary blocking, peripheral endothelial swelling and tissue edema. Consequently, the diffusion area is diminished and the diffusion distance is enlarged (9, 26, 30). 3. In patients with profound ischemia or sepsis *O_2-utilization* might be disturbed even if oxygen is abundantly available in the cells (7, 9, 11, 25, 36).

Earlier studies have suggested that $\dot{V}_{O_2}$-index is an important discriminator between survivors and nonsurvivors (5, 6, 8, 31, 35, 37, 41, 42).

This was explained by the fact that oxygen consumption is dependent on so many vital organ functions. However, in our group of patients the $\dot{V}_{O_2}$-index was not different between survivors and nonsurvivors (Table 8.5). Our findings correspond with recent other data, suggesting that survivors and nonsurvivors have similar hemodynamic profiles (38) and that $\dot{V}_{O_2}$-index is not a reliable prognosticator of outcome (19).

Various factors can explain why the results of the present and recent other studies differ from those of earlier studies. The first reason may be a different composition of the study *populations* with respect to the stage of illness (14). Secondly, oxygen consumption was measured with different *techniques*. In the old studies $\dot{V}_{O_2}$ was mainly determined indirectly with the Fick principle, by which errors up to 40% are introduced (19-21, 29). If $\dot{V}_{O_2}$ was measured directly by expired air analysis, this was nearly always performed during relatively short periods of the day despite great diurnal fluctuations of $\dot{V}_{O_2}$ (5, 10, 24, 27, 40). Since in the present study continuous respirometry during 24 h/day was used, the above described errors were excluded. Automatic artifact suppression supplemented further accuracy (13).

In situtations, where the oxygen consumption is limited by an insufficient oxygen transport, therapeutic interventions such as an alteration of mechanical ventilation or a blood transfusion can be evaluated from the subsequent rise in $\dot{V}_{O_2}$-index (32). However, as we have found, that a higher $\dot{V}_{O_2}$-index does not necessarily indicate a better survival chance, there is no theoretical argument for therapeutic interventions aimed exclusively at bringing the $\dot{V}_{O_2}$-index above a certain level, as suggested previously (33-35). On the contrary, in case of an impending, uncorrectable O_2-deficit, it may be even more essential to decrease oxygen demand with a subsequent fall of oxygen consumption (2, 3, 28, 40).

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Chapter 9

EFFICACY OF THERAPEUTIC REDUCTION OF METABOLIC RATE IN CRITICALLY ILL PATIENTS

This chapter has been submitted for publication.

EFFICACY OF THERAPEUTIC REDUCTION OF METABOLIC RATE IN CRITICALLY ILL PATIENTS

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Summary

Therapeutic interventions, aimed to decrease the metabolic demands in critically ill patients with an impending O_2-deficit, can be monitored by continuous recording of O_2-consumption and CO_2-production. This paper presents an outline of the present nutritional, mechanical and pharmacological methods to reduce metabolic rate with typical gas-exchange recordings. Future pharmacological developments are suggested.

Introduction

Until recently recording of oxygen-consumption ($\dot{V}_{O_2}$) and of carbon dioxide-production ($\dot{V}_{CO_2}$) could hardly be performed in daily clinical practice. The Douglas-bag system was considered too time-consuming and the indirect Fick method was too inaccurate due to errors as large as 20-40% (1, 2). We designed and validated an automatic metabolic device, which offers the advantages of continuous, metabolic gas-exchange recordings with an accuracy within 3% of the minute values (3, 4). Applications of metabolic gas-exchange recordings have been described for tailoring nutritional therapy (5) and for predicting outcome of critically ill patients (6, 7). A third important application is the monitoring of the efficacy of therapeutic interventions, aimed to reduce the metabolic rate in severely ill, hypermetabolic patients. In these patients the oxygen demand is markedly increased (8), whereas the oxygen-delivery and the oxygen-extraction are often seriously hampered (9-11). Especially in patients with a limited cardiorespiratory reserve a peripheral O_2-deficit can occur, followed by a hazardous production of lactate (12-14). In case of an impending O_2-deficit it is of crucial therapeutic interest to restore homeostasis not only by

increasing the O_2-delivery and the O_2-extraction, but also by lowering the O_2-demand. This paper surveys the different therapeutic methods to suppress the increased metabolic demands in critically ill patients. Attention will be paid to 1. nutritional supply; 2. respiratory labor, other motor activity and pain; 3. fever and 4. future pharmacological developments. Various effects will be illustrated by examples of continuous gas-exchange recordings to evaluate the therapeutic result.

Nutritional supply

In order to prevent severe weight-loss enteral and parenteral feeding are frequently administered in excessive quantities to critically ill patients. However, overfeeding should be avoided because it has detrimental side-effects. It can lead to hepatic dysfunction (15), hyperglycemia and elevated BUN-levels (16). A carbohydrate- (17-19) and a protein-overload (20) can lead to respiratory failure. In hypermetabolic patients a *carbohydrate-overload* results in an increase of both $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$. As indicated by a respiratory quotient (R.Q. $= \dot{V}_{CO_2}/\dot{V}_{O_2}$) smaller than 1.00, the carbohydrate-overload is not converted to fat, but is deposited as glycogen in unphysiologically high quantities. However, in normometabolic, depleted patients a carbohydrate-overload results in an R.Q. larger than 1.00, indicating net conversion of carbohydrate to fat. While $\dot{V}_{O_2}$ remains more or less constant, $\dot{V}_{CO_2}$ rises dramatically. In these situations hyperalimentation results in a metabolic stress rather than providing nutritional support, as reflected by an increased urinary output of catecholamines (17, 21). Figure 9.1 shows the favorable decrease in $\dot{V}_{CO_2}$, induced by reduction of the caloric supply to the caloric expenditure in a depleted patient.

Central nervous respiratory drive is said to be influenced by nutrition, especially by protein-intake. Patients with semistarvation have a diminished respiratory response to hypoxemia (22), whereas the respiratory response to an artificial increase of inspired pCO_2 is enhanced by protein enriched parenteral nutrition. In a patient with pulmonary dysfunction a *protein-overload* should be avoided; it can lead to an unnecessary increase in respiratory effort, because the patient attempts to decrease the resting level of arterial pCO_2 (20).

The quantity of energy liberated per liter of oxygen is almost equal for the combustion of carbohydrate, protein or fat (23). However, CO_2-production is lower for the combustion of *fat* than for that of carbohydrate or protein. This results in a mean R.Q. of 0.71 when fat is oxidized, whereas carbohydrates and proteins are burned with an R.Q. of 1.00 and 0.80 respectively.

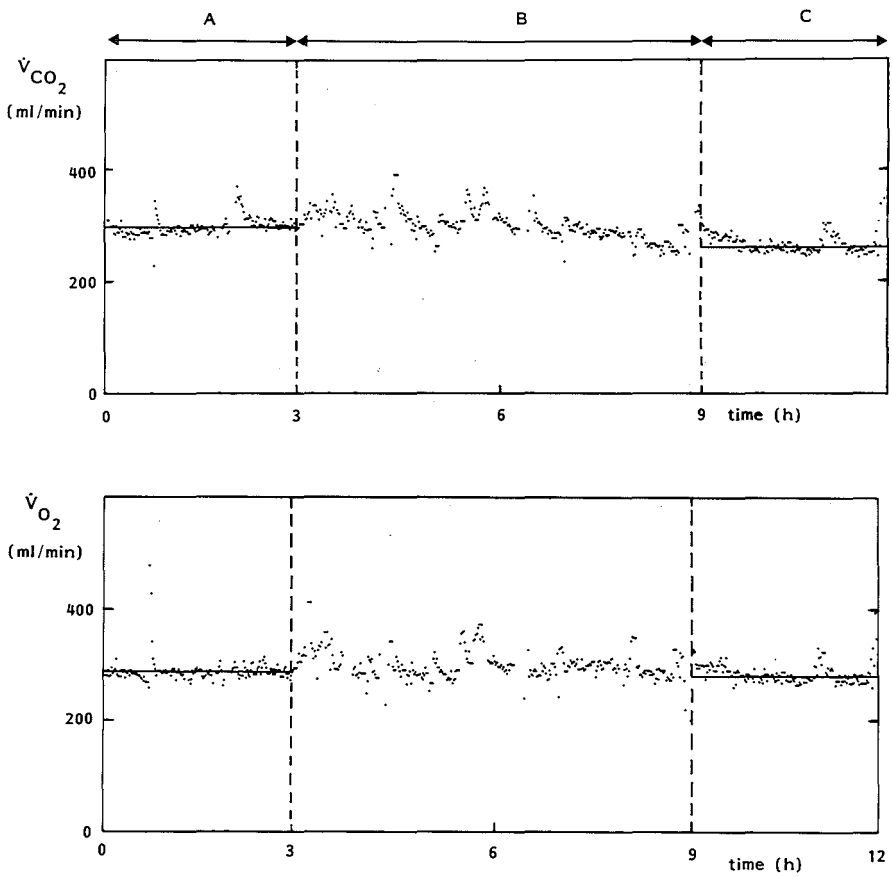

Figure 9.1. Alterations in metabolic gas-exchange induced by adjustment of the caloric supply to the caloric expenditure in a depleted patient. During *period A* by mistake an elementary diet of 4200 kcal/day (= 17,550 kJ/day) was administered on a continuous basis, resulting in R.Q. = 1.04. Subsequently the administration rate was lowered and during the transitional *period B* the net caloric intake was gradually adapted to his actual energy expenditure (2100 kcal/day = 8,775 kJ/day). Ultimately $\dot{V}_{CO_2}$ dropped about 10%, resulting in R.Q. = 0.94 *(period C)*. Solid lines indicate mean $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ during the different periods.

For this reason CO_2-production can be reduced, if carbohydrates and proteins are replaced by an isocaloric amount of fat as a calorie-source (24).

It can be concluded that:

1. a carbohydrate-overload has to be avoided in order to prevent a useless increase of $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$;

2. a protein-overload is also undesirable due to its postulated, superfluous stimulation of respiratory drive;
3. isocaloric replacement of carbohydrate and protein by fat as a calorie-source can further reduce CO_2-production.

Respiratory labor, other motor activity, and pain

Under normal conditions only about 2% of $\dot{V}_{O_2}$ is consumed in respiratory muscles. However, in case of severe cardiorespiratory disease this percentage can rise considerably due to both an increase in labor and a decrease in efficiency (25). In critical situations of failing O_2-delivery mechanical ventilation can take over *respiratory labor* resulting in a decrease in $\dot{V}_{O_2}$ varying from 24 to 40% (26). Generally, cardiac output remains more or less unchanged, but 20% of total blood flow is not sent any longer to the respiratory muscles and a redistribution of blood flow occurs in favor of other vital organs (27). Lactic acidosis is lessened, which can lead to a higher survival rate (28, 29). For these reasons one should be cautious in weaning a patient with a severely diminished cardiorespiratory reserve from the ventilator (30).

Attention should not only be paid to respiratory labor, but also to other kinds of *motor activity*, which can be abolished by muscle relaxants. Frequently, the simultaneous relief of *pain* can further decrease metabolic rate. The repeated, combined administration of pancuronium bromide and fentanyl is able to decrease $\dot{V}_{O_2}$ markedly in a restless and painful, ventilated patient (Fig. 9.2). Postoperative hypothermia and bacteremia frequently evoke a shivering response, which can not only be suppressed by muscle relaxants (31), but also by opiates (11). Apart from the prevention of shivering opiates have a sedative and analgetic effect in critically ill patients, leading to a decrease in $\dot{V}_{O_2}$ varying from 9 to 20% (32-34). An example of such an opiate-effect is given in figure 9.3. In patients with severe head injury oxygen consumption can be diminished by as much as 40% by administering barbiturates, probably due to suppression of muscular hypertonicity (35). In a more heterogeneous group of ICU patients, however, a comparable effect of barbiturates on $\dot{V}_{O_2}$-level could not be confirmed (36).

Routine nursing care and chest physical therapy can increase the metabolic rate of intensive care patients. A rise of 35% in $\dot{V}_{O_2}$ has been described, which can be attributed to a variety of factors including motor activity and pain (32). Of course chest physical therapy is essential in the prevention of pulmonary complications, but it should be executed with caution especially in patients with a limited cardiorespiratory reserve.

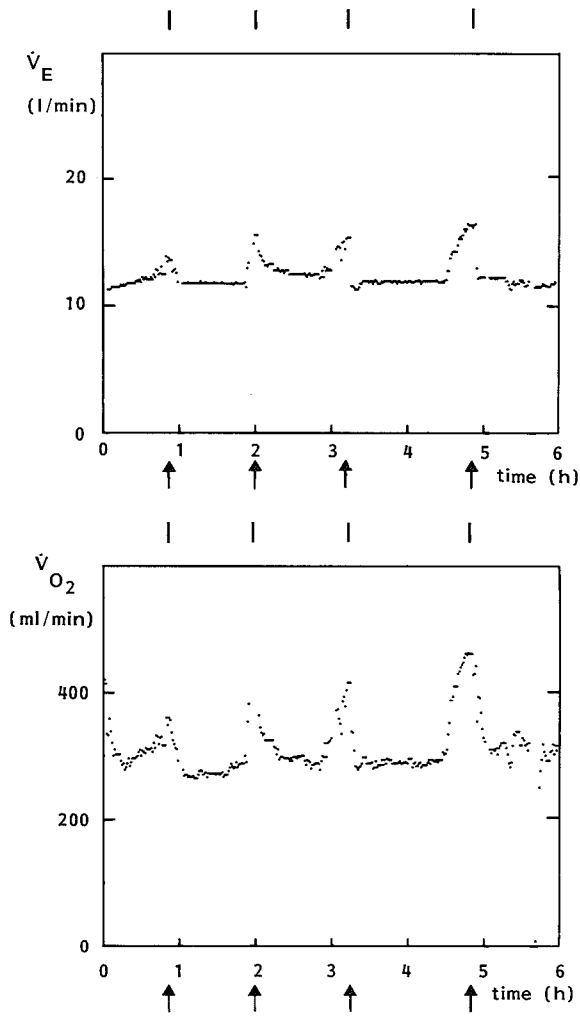

Figure 9.2. The repeated influence of 4 mg pancuronium bromide and 0.1 mg fentanyl citrate i.v. (arrows) on expiratory minute volume ($\dot{V}_E$) and oxygen consumption ($\dot{V}_{O_2}$) in a ventilated patient with severe restlessness. Excessive voluntary movements and fighting against the ventilator were prevented and pain was relieved, resulting in a marked decrease of $\dot{V}_{O_2}$.

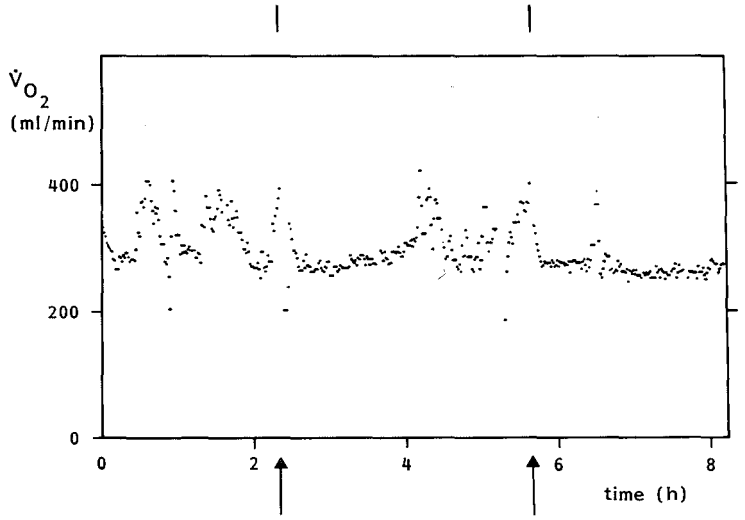

Figure 9.3. Great fluctuations of oxygen consumption ($\dot{V}_{O_2}$) in a restless patient due to pain. Reduction of $\dot{V}_{O_2}$ can be recognized after the repeated administration of 5 mg morphine i.v. (arrows).

Fever

Fever is the most ancient and widely spread hallmark of disease. Its recognition as a sign of disease goes back at least as far as Hippocrates (37, 38). Yet until recently its natural role in the combat against disease was unclear (39). It was supposed to have a favorable influence on the process of healing, otherwise it would not have survived in evolution. In all warm-blooded animals fever occurs and the poikilothermic reptiles seek a warm environment in case of illness. The importance of such warm environment was first stressed by Kluger and co-workers (40). They found that lizards injected with bacteria had a significantly better survival rate, if they were allowed to seek a warm environment. Ever since increasing evidence exists, that fever is a crucial mechanism of adaptation. It elevates mitogenesis of thymocytes and production and activity of lymphokines (38).

Fever is accompanied by an increase in metabolic rate of about 12% per degree Centigrade, as described by DuBois in 1936 (41). In critically ill patients with a limited cardiorespiratory reserve this hypermetabolic reaction can lead to a detrimental O_2-deficit. Whether or not suppression of fever is useful in such situations remains questionable. The administration

of antipyretic agents has serious disadvantages: the complicated activation of the immunological system is disturbed and a reliable parameter of the course of illness is lost. On the other hand application of antipyretics has the advantage that many patients feel much better. Furthermore, antipyretics diminish the stress upon the cardiorespiratory system by reducing the metabolic rate (42). From animal studies it has been suggested, that fever above 38.5°C has a negative effect on survival rate (43, 44). Treatment with antipyretic drugs could therefore increase survival rate, partly because of the improvement of hemodynamics (45-47).

Figure 9.4 demonstrates, how the rapid onset of fever increases oxygen consumption; subsequently it shows the lowering effect of the antipyretic agent pyrazolon.

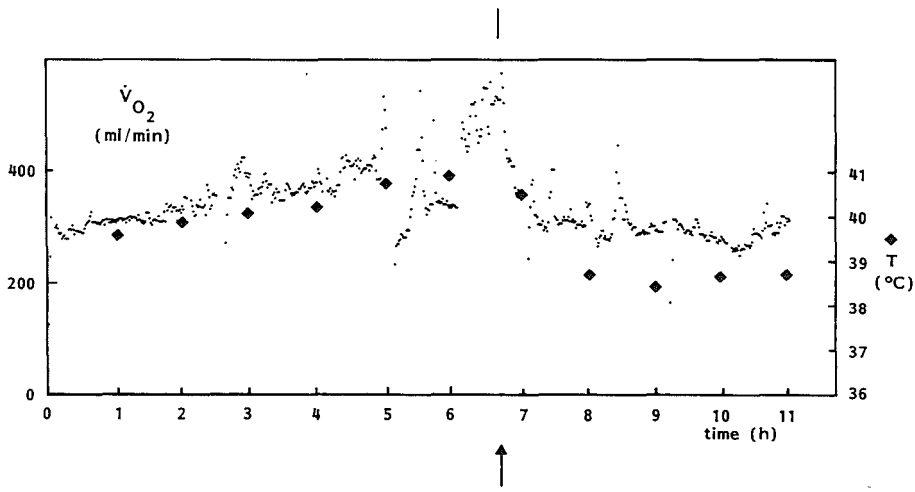

Figure 9.4. The relation between body-temperature (♦) and oxygen consumption ($\dot{V}_{O_2}$). At first a rapid onset of fever was associated with a concomitant rise in $\dot{V}_{O_2}$, which was subsequently suppressed by the administration of 1 g pyrazolon i.v. (arrow).

Future pharmacological developments

Calcium-cations (Ca^{2+}) play a central role both in the neural and in the hormonal regulation of biological processes (48, 49). A variety of stimuli can lead to an increased concentration of cytosolic Ca^{2+}. Subsequently Ca^{2+} is bound to cytosolic proteins and in particular to calmodulin, which has been shown to be present in all eukaryotic cells. The calcium-calmodulin complex is able to activate a great number of intracellular

enzymes (48, 50, 51). Due to the central position of Ca^{2+} and calmodulin in the cellular control system, it might be assumed, that at least in part the hypermetabolic reaction to stress-factors is regulated through this mechanism. Abundant indirect evidence is available, that severe, preterminal conditions are characterized by Ca^{2+} overload in the cell. Several experimental and clinical studies have confirmed the favorable influence of Ca^{2+} overload inhibition on prevention of cell death (52-57).

If the hypermetabolic reaction to stress is related to an increase in the cytosolic Ca^{2+} concentration, it may be possible to reduce the concomitant increase of oxygen-demand in such patients by Ca^{2+} entry blockers. Within the heterogeneous group of Ca^{2+} entry blockers, however, Ca^{2+} slow channel blockers such as nifedipine or verapamil have undesirable hemodynamic (i.e. negative inotropic and chronotropic) effects. They can therefore hardly be applied in critically ill patients. Ca^{2+} overload blockers such as flunarizine selectively inhibit the pathological Ca^{2+} overload without interfering with the physiological Ca^{2+} entry (58, 59). For this reason, Ca^{2+} overload blockers might be useful for reducing $\dot{V}_{O_2}$ in critically ill patients.

We clinically tested flunarizine on its hemodynamic influences and on its effect on $\dot{V}_{O_2}$ in seven, hemodynamically stable, hypermetabolic patients with heterogeneous underlying diseases (protocol approved by the Committee on Human Experimentation of the institution). Flunarizine was administered intravenously as a booster of 0.1 mg/kg in 15 min, followed by

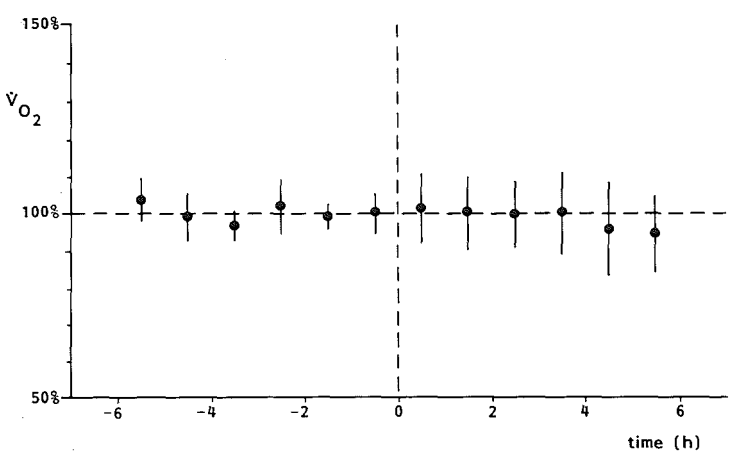

Figure 9.5. The effect of i.v. flunarizine (booster of 0.1 mg/kg in 15 min starting at vertical dashed line, followed by the same dose over a period of 6 h) on oxygen consumption ($\dot{V}_{O_2}$) in 7 hypermetabolic patients. Baseline (i.e. 100%) was calculated from the values before administration. Mean values are indicated by dots, SD is indicated by bars.

the same dose over a period of 6 h. As expected, hemodynamics remained unchanged after the administration of flunarizine (data unpublished). However, oxygen consumption did not change either (Fig. 9.5). The absence of undesirable hemodynamic side-effects justifies further studies on the effect of Ca^{2+} overload blockers in critically ill patients.

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Part C

GENERAL DISCUSSION AND SUMMARY

Chapter 10

GENERAL DISCUSSION AND SUMMARY

This thesis describes several aspects of metabolic gas-exchange in critically ill surgical patients. In Chapter 2 different techniques for metabolic gas-exchange measurement are described. It is concluded, that presently direct measurement of metabolic gas-exchange is the method of choice in the management of critically ill patients. The literature on the clinical applications of metabolic gas-exchange measurements is reviewed in Chapter 3. The main part of this thesis consists of our experimental work, described in eight studies (Chapter 5, 6, 7, 8 and 9; Appendix I, II, and III). The objectives of these studies are surveyed in Chapter 4.

The main conclusions of these studies are summarized and their interrelations are discussed in this chapter. Moreover, some challenging questions which remain to be answered are emphasized.

10.1 **Physical and methodological conclusions**

In mechanically ventilated patients continuous gas-exchange measurements can be performed by means of a newly developed, fully automatic, open circuit device. This non-invasive and safe technique allows simultaneous measurement of oxygen consumption ($\dot{V}_{O_2}$), carbon dioxide production ($\dot{V}_{CO_2}$) and expiratory minute volume ($\dot{V}_E$). The accuracy of the one-minute values both for $\dot{V}_{O_2}$ and for $\dot{V}_{CO_2}$ was within 3% of the real values (Appendix I).

Gas-exchange measurements can be severely disturbed by patient-ventilator disconnections. Both short term and long term metabolic gas-exchange measurements only lead to reliable results, if the inevitable disconnection-artifacts are sufficiently suppressed. We designed and validated a method for automatic suppression of such artifacts, by which the disturbing influence on continuously measured diurnal $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ was reduced from up to 10% to a maximum of 1% (Appendix II).

Besides patient-ventilator disconnections several other clinical circumstances, such as hemodialysis, air leakage, and profuse bleeding can disturb gas-exchange measurements. The influence of hemodialysis on gas-exchange measurements is reviewed in Appendix III.

Although continuous gas-exchange measurements are certainly feasible in clinical practice, intermittent determinations are often performed. Under these circumstances diurnal values are extrapolated from short recording values. We investigated the extrapolation accuracy of 16 different non-continuous recording protocols in a group of 50 critically ill patients. In the individual patient the extrapolation accuracy depended on the duration and number of the short recording periods, which can be explained by changes in metabolic rate and by variations in body gas stores. The choice of the non-continuous recording protocol should be based on the desired accuracy of the diurnal gas-exchange values. For the group of patients the diurnal amplitude of the metabolic gas-exchange appeared to be very small (i.e. $< 3\%$); for this reason nocturnal determinations are not strictly necessary to attain reliable 24-h estimates (Chapter 5).

10.2 **Therapeutic and prognostic conclusions**

10.2.1 *Implications for nutritional therapy*

Favorable effects of nutritional support therapy can only be concluded from significant decreases of morbidity and/or mortality in prospective and controlled clinical trials (1). Although only few such trials have been executed and their outcome is highly controversial, nutritional therapy is frequently applied in today's treatment of critically ill patients.

It has been demonstrated that both severe hypo- and severe hyperalimentation during prolonged periods can have unfavorable effects. Based on these data it is now generally accepted, that the caloric supply to critically ill patients should be adapted to the individual caloric expenditure. However, no decisive data are available whether hypo- and hyperalimentation are equally deleterious. It is undecided to what extent a mismatch between caloric supply and caloric expenditure is acceptable. Even under normal conditions it is not exactly known, how much food man requires (2, 3). Large proportions of the world's population are undernourished according to current standards, but are often surprisingly well able to perform normal activities. At the same time, many obese persons have great difficulties in loosing weight despite moderate energy intake. Apparently, there is a great diversity of mechanisms by which homeostasis is maintained.

Further investigations are needed to determine whether isocaloric feeding leads to better clinical results than moderate hypo- or hyperalimentation. In any case determination of the individual energy expenditure is indispensable for individually tailored nutrition.

This individual energy expenditure can be *calculated* by means of the anthropometric Harris-Benedict formula or *estimated* from short term calorimetric measurements (intermittent indirect calorimetry). In a heterogeneous group of 25 surgical ICU patients the *calculated* results of the Harris-Benedict formula could be significantly improved by supplemental application of a correction factor, based on a number of specific clinical conditions of the patient. The accuracy of *estimation* by means of intermittent indirect calorimetry depended on the duration and number of the recording periods. Estimation of the energy expenditure from two 5-min recording periods at 08.00 and 17.00 appeared to be more accurate than calculation by means of the corrected Harris-Benedict formula (Chapter 6).

In our group of patients application of the corrected Harris-Benedict formula appeared to provide reasonably accurate calculation results. It seems likely, that this accuracy is clinically acceptable. However, such results can not be attained under all clinical circumstances. Further investigations are in progress to identify groups of patients for whom indirect calorimetry is probably to be preferred to calculation by means of the corrected Harris-Benedict formula. These investigations may lead to new guidelines for the composition of the clinical correction factor.

For practical reasons in many hospitals a standard nutritional regimen is frequently used in critically ill patients. We have quantified the individual discrepancy between energy expenditure and energy intake in case of a standard nutritional support regimen of 2875 kcal/day in a heterogeneous group of 20 surgical ICU patients (Chapter 7). In this group of patients it was further examined, whether the caloric supply could have been matched better to the caloric expenditure by basing the nutritional support on the basic or the corrected Harris-Benedict formula instead of the standard regimen. Calculation by means of the basic Harris-Benedict formula did not perform better than the standard regimen, but significantly better results were attained by supplemental application of the clinical correction factor. Since a standard nutritional regimen is more simple, less time-consuming and cheaper than an individually tailored system, individualization of nutritional therapy is only preferable, if the caloric mismatch resulting from a standard regimen leads to unacceptable side-effects. Preliminary results do not seem to indicate important differences between a carefully chosen fixed caloric supply and an individually tailored caloric supply (4), but further investigations are necessary to allow more definite conclusions.

10.2.2 *Relation between oxygen consumption index and survival rate*

In recent years many efforts have been made to design simple classification systems in order to identify groups of patients on the basis of severity of illness and probability of decease. The Simplified Acute Physiology Scoring system (SAPS-system) scores the patient's status by the deviation of 14 routinely available physiological variables from the normal range. It appears to be able to classify patients in groups of increasing probability of decease.

Previous studies have also demonstrated a great prognostic potency of oxygen consumption index on the ultimate outcome of critically ill patients: a high $\dot{V}_{O_2}$-index is said to be related to a high survival rate. We verified in a heterogenous group of 50 mechanically ventilated patients, whether survivors and nonsurvivors have different $\dot{V}_{O_2}$-indices (Chapter 8). Moreover, it was examined whether the prognostic potency of the SAPS-system could be improved by adding the $\dot{V}_{O_2}$-index as a supplemental physiological variable. In our study the $\dot{V}_{O_2}$-indices of survivors and nonsurvivors appeared to be not significantly different and addition of $\dot{V}_{O_2}$-index to SAPS did not improve its prognostic potency.

As can be concluded from the abbreviated Weir formula (paragraph 3.1.3), $\dot{V}_{O_2}$ is positively related to energy expenditure. Therefore, the existence of a relationship between $\dot{V}_{O_2}$ and survival rate would also imply a similar relationship between energy expenditure and survival rate. However, in our group of patients the absence of the supposed relationship between $\dot{V}_{O_2}$ and survival rate (Chapter 8) can explain that the corrected Harris-Benedict formula was able to calculate energy expenditure quite accurately without taking into account any supplemental factors associated with organ failure (Chapter 6 and 7).

From animal studies it has been suggested that nonsurvivors have a fixed substrate utilization pattern and that they are unable to adapt their combustion processes to the composition of the nutritional regimen (5). Under clinical circumstances substrate utilization patterns can be analyzed by simultaneous measurement of urea-production and metabolic gas-exchange (paragraph 3.1.2). For the prognostic discrimination of surviving and nonsurviving patients it might be worthwile to determine the response of their utilization patterns to sudden changes in dosage or composition of the nutritional regimen.

10.2.3 *Evaluation of therapeutic interventions*

In seriously ill patients with an (impending) peripheral O_2-deficit, therapy can be directed to an increase of oxygen-transport (6). Frequently, however, improvement of one component of the O_2-transport system results in an impairment of an other component. For example, arterial oxygen content can be increased by massive transfusion of old blood. At the same time peripheral vascular resistance will be increased by a rise in blood viscosity and oxyhemoglobin dissociation will be hindered by a left shifted oxyhemoglobin saturation curve. In situtations, where the oxygen consumption is limited by an insufficient oxygen transport, the net result of interventions which are aimed to increase oxygen-transport could be quantified by on-line gas-exchange measurements.

Previously it has been postulated, that due to the possible relationship between $\dot{V}_{O_2}$-index and survival rate therapy should be directed primarily to increase oxygen consumption above the level of 170 $ml.min^{-1}.m^{-2}$ (7). However, in our group of patients a high $\dot{V}_{O_2}$-index did not indicate a good chance of survival (Chapter 8). In our opinion, there can be two essentially different therapeutic goals in case of an (impending) peripheral O_2-deficit. Firstly, the oxygen transport can be improved with a possible rise in $\dot{V}_{O_2}$. Secondly, the metabolic demands can be reduced with a subsequent redistribution of O_2-delivery or fall of $\dot{V}_{O_2}$. Therapeutic manoeuvres aimed to reduce metabolic rate can be evaluated by on-line gas-exchange measurements as well. A survey of the present nutritional, mechanical and pharmacological methods for reduction of $\dot{V}_{O_2}$ and metabolic rate is presented in Chapter 9.

It might be hypothetized, that at least in part the hypermetabolic reaction to stress is regulated by an increase of the cytosolic Ca^{2+} concentration and that therefore Ca^{2+} overload blockers might be useful for reducing $\dot{V}_{O_2}$ in hypermetabolic patients. For this purpose we clinically tested the Ca^{2+} overload blocker flunarizine. In the applied dosage it did not appear to change $\dot{V}_{O_2}$ under hypermetabolic circumstances (Chapter 9).

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Chapter 11

ALGEMENE DISCUSSIE EN SAMENVATTING

Dit proefschrift behandelt een aantal aspecten van de uitwisseling van metabole gassen bij ernstig zieke, chirurgische patiënten. In Hoofdstuk 2 worden verschillende meetmethoden beschreven; op dit moment blijkt de directe meetmethode de techniek van voorkeur te zijn bij de behandeling van ernstig zieke patiënten. Een literatuur-overzicht betreffende de klinische toepassingen van gasuitwisselingsmetingen wordt gegeven in Hoofdstuk 3. Het belangrijkste gedeelte van dit proefschrift wordt gevormd door ons experimentele onderzoek, dat wordt beschreven in acht studies (Hoofdstuk 5, 6, 7, 8 en 9; Appendix I, II en III). Een overzicht van de doelstellingen van deze studies wordt gegeven in Hoofdstuk 4.

Onderstaand worden de belangrijkste conclusies uit deze studies samengevat en in hun samenhang besproken. Daarnaast worden een aantal wezenlijke vragen die onbeantwoord zijn gebleven aan de orde gesteld.

11.1 **Fysische en methodologische conclusies**

Bij kunstmatig beademde patiënten kunnen gasuitwisselingsmetingen continu worden uitgevoerd met behulp van recent ontwikkelde, volautomatische apparatuur waarbij gebruik gemaakt wordt van een open systeem. Deze niet-invasieve en veilige techniek maakt gelijktijdige meting mogelijk van zuurstofconsumptie ($\dot{V}_{O_2}$), kooldioxideproduktie ($\dot{V}_{CO_2}$) en expiratoir minuutvolume ($\dot{V}_E$). De nauwkeurigheid van de 1-minuuts waarden voor zowel de $\dot{V}_{O_2}$ als de $\dot{V}_{CO_2}$ was binnen 3% van de juiste waarden (Appendix I).

Gasuitwisselingsmetingen worden ernstig gestoord, wanneer de beademingsmachine wordt losgekoppeld van de patiënt. Metingen gedurende zowel kortere als langere tijd leiden alleen dan tot betrouwbare resultaten, indien de door loskoppeling geïnduceerde artefacten voldoende worden onderdrukt. Wij ontwierpen een methode voor automatische suppressie van dergelijke artefacten. Vervolgens werd deze methode klinisch getest,

waarbij bleek dat de storende invloed op de continu gemeten 24-uurs waarden van $\dot{V}_{O_2}$ en $\dot{V}_{CO_2}$ werd teruggebracht van maximaal 10% tot maximaal 1% (Appendix II).

Ook velerlei andere klinische omstandigheden, zoals hemodialyse, luchtlekkage en ernstig bloedverlies, kunnen gasuitwisselingsmetingen verstoren. De storende invloed van hemodialyse wordt behandeld in Appendix III.

Hoewel in de klinische praktijk continue gasuitwisselingsmetingen zeker mogelijk zijn, worden toch vaak slechts intermitterend metingen uitgevoerd. 24-uurs Waarden worden dan geëxtrapoleerd van waarden die zijn verkregen over korte perioden van de dag. Wij onderzochten voor 16 verschillende niet-continue meetprotocollen hoe nauwkeurig dergelijke extrapolaties zijn in een groep van 50 ernstig zieke patiënten. Voor de *individuele* patiënt hing de betrouwbaarheid van de extrapolatie af van de duur en het aantal van de verschillende metingen, hetgeen kan worden verklaard door veranderingen in het stofwisselingsniveau en in de gasvoorraden van het lichaam. De keuze van het niet-continue meetprotocol dient gebaseerd te worden op de gewenste nauwkeurigheid van de geëxtrapoleerde 24-uurs waarden van $\dot{V}_{O_2}$ en $\dot{V}_{CO_2}$. Voor de *groep* patiënten bleek de 24-uurs amplitude van de gasuitwisseling zeer klein te zijn (< 3%); nachtelijke metingen zijn daarom niet strikt noodzakelijk ter verkrijging van betrouwbare 24-uurs schattingen (Hoofdstuk 5).

11.2 **Therapeutische en prognostische conclusies**

11.2.1 *Implicaties voor voedingstherapie*

Gunstige effecten van voedingstherapie kunnen alleen worden afgeleid uit een significante vermindering van morbiditeit en/of mortaliteit in prospectieve en gecontroleerde klinische studies (1). Hoewel slechts een zeer beperkt aantal van dergelijke studies zijn uitgevoerd en de resultaten hiervan zeer tegenstrijdig zijn, wordt voedingstherapie in de huidige behandeling van ernstig zieke patiënten uitgebreid toegepast.

Het is aangetoond, dat zowel ernstige ondervoeding als ernstige overvoeding, indien toegepast gedurende lange perioden, ongunstige effecten kunnen hebben. Op grond hiervan is het thans algemeen aanvaard, dat de toediening van calorieën aan ernstig zieke patiënten dient te worden aangepast aan het individuele calorieverbruik. Er zijn echter geen eensluidende gegevens voorhanden, die aangeven of ondervoeding en overvoeding even

schadelijk zijn. Het is onbekend, welke discrepantie tussen calorieaanbod en calorieverbruik klinisch acceptabel is. Zelfs onder normale omstandigheden is niet precies bekend, hoeveel voedsel de mens nodig heeft (2, 3). Grote delen van de wereldbevolking zijn naar Westerse maatstaven ondervoed terwijl zij desondanks verrassend goed in staat zijn hun normale activiteiten uit te voeren. Te zelfder tijd hebben veel mensen die lijden aan vetzucht grote moeite gewicht te verliezen ondanks het feit, dat zij slechts een matige hoeveelheid calorieën tot zich nemen. Blijkbaar bestaat er een grote diversiteit aan mechanismen ter handhaving van een energie-evenwicht.

Nader onderzoek is nodig om aan te geven of isocalorische voeding tot betere klinische resultaten leidt in vergelijking met matige ondervoeding of overvoeding. In alle gevallen is het voor een geïndividualiseerde voeding noodzakelijk het individuele energieverbruik vast te kunnen stellen.

Dit individuele energieverbruik kan worden *berekend* met behulp van de anthropometrische Harris-Benedict formule of worden *geschat* op basis van kortdurende calorimetrische bepalingen (intermitterende indirecte calorimetrie). Voor een heterogene groep van 25 chirurgische intensive care patiënten konden de *rekenresultaten* van de Harris-Benedict formule significant worden verbeterd door aanvullende toepassing van een correctiefactor, gebaseerd op een aantal specifieke klinische condities van de patiënt. De nauwkeurigheid die kon worden bereikt door *schatting* van het energieverbruik op basis van intermitterende indirecte calorimetrie was afhankelijk van de duur en het aantal meetperioden. Schatting van het energieverbruik op basis van 2 meetperioden om 08.00 en 17.00 uur van elk 5 min bleek nauwkeuriger te zijn dan berekening met behulp van de gecorrigeerde Harris-Benedict formule (Hoofdstuk 6).

Binnen onze groep patiënten bleek toepassing van de gecorrigeerde Harris-Benedict formule betrekkelijk nauwkeurige rekenresultaten te verschaffen. Het lijkt waarschijnlijk, dat deze nauwkeurigheid klinisch acceptabel is. Dergelijke resultaten kunnen echter niet onder alle klinische omstandigheden worden bereikt. Nader onderzoek vindt plaats om patiëntengroepen te identificeren, voor wie waarschijnlijk aan indirecte calorimetrie de voorkeur dient te worden gegeven boven berekening van het energieverbruik met behulp van de gecorrigeerde Harris-Benedict formule. Op grond hiervan kunnen wellicht nieuwe richtlijnen worden geformuleerd voor de samenstelling van de klinische correctiefactor.

Om praktische redenen wordt bij ernstig zieke patiënten in vele ziekenhuizen vaak een standaard voedingsschema gebruikt. Wij hebben voor een

heterogene groep van 20 chirurgische intensive care patiënten vastgesteld, hoe groot de individuele discrepantie bedraagt tussen energieverbruik en energieaanbod in geval van een standaard voedingsschema van 2875 kcal/dag (Hoofdstuk 7). Voor deze groep patiënten werd bovendien nagegaan, of het energieaanbod beter afgestemd had kunnen worden op het energieverbruik door het voedingsschema te baseren op de basale of de gecorrigeerde Harris-Benedict formule in plaats van het standaardschema. Gebruik van de basale Harris-Benedict formule leidde niet tot een geringere calorische discrepantie dan het standaardschema, maar significant betere resultaten werden bereikt door aanvullende toepassing van de klinische correctiefactor. Aangezien een standaard voedingsschema eenvoudiger, minder tijdrovend en goedkoper is dan een geïndividualiseerd systeem, verdient individualisatie van voedingstherapie slechts de voorkeur, indien de calorische discrepantie in geval van een standaard schema tot onacceptabele neveneffecten leidt. De eerste, voorlopige resultaten lijken geen belangrijke verschillen aan te geven tussen toediening van een zorgvuldig gekozen, gefixeerde hoeveelheid calorieën enerzijds en een geïndividualiseerde calorietoediening anderzijds (4). Nader onderzoek is echter nodig alvorens meer definitieve conclusies kunnen worden getrokken.

11.2.2 *Relatie tussen zuurstofconsumptie-index en kans op overleving*

Vele auteurs hebben getracht een eenvoudig systeem te ontwerpen dat groepen patiënten kan classificeren op basis van de ernst van hun ziekten en hun kans op overlijden. Het "Simplified Acute Physiology Scoring"-systeem (SAPS-systeem) kwantificeert de conditie van de patiënt op basis van de afwijking van 14 routinematig beschikbare, fysiologische variabelen van de referentiewaarden. Het systeem blijkt goed in staat te zijn patiënten in te delen in verschillende groepen met een toenemende kans op overlijden.

Eerdere studies hebben eveneens een belangrijke prognostische waarde aangetoond van de zuurstofconsumptie-index voor de uiteindelijke afloop van ernstig zieke patiënten: een hoge $\dot{V}_{O_2}$-index zou wijzen op een grote kans op overleving. Wij verifieerden in een heterogene groep van 50 beademde patiënten, of overlevers en niet-overlevers verschillende $\dot{V}_{O_2}$-indices hebben (Hoofdstuk 8). Bovendien werd nagegaan of de prognostische waarde van het SAPS-systeem verbeterd zou kunnen worden door toevoeging van de $\dot{V}_{O_2}$-index als aanvullende variabele. In onze studie bleken de $\dot{V}_{O_2}$-indices van overlevers en niet-overlevers echter niet significant verschillend te zijn en leidde toevoeging van de $\dot{V}_{O_2}$-index aan het SAPS-systeem niet tot een verbetering van de voorspellende waarde van dit systeem.

Uit de vereenvoudigde Weir-formule kan worden afgeleid (paragraaf 3.1.3), dat de zuurstofconsumptie van een patiënt positief gerelateerd is aan zijn energieverbruik. Om die reden zou de aanwezigheid van een relatie tussen zuurstofconsumptie en kans op overleving een zelfde relatie impliceren tussen energieverbruik en kans op overleving. Bij onze groep patiënten vormt echter de afwezigheid van de veronderstelde relatie tussen zuurstofconsumptie en kans op overleving (Hoofdstuk 8) een goede verklaring voor het feit, dat de gecorrigeerde Harris-Benedict formule in staat was het individuele energieverbruik alleszins nauwkeurig te berekenen zonder extra factoren te verdisconteren, die geassocieerd zijn met het falen van orgaansystemen (Hoofdstuk 6 en 7).

Dierexperimenteel zijn aanwijzingen voorhanden die aangeven dat niet-overlevers volgens een gefixeerd patroon energetische substraten verbruiken en niet in staat zijn hun verbrandingsprocessen aan te passen aan de samenstelling van de toegediende voeding (5). Onder klinische omstandigheden kan men patronen van substraatsutilisatie analyseren door gelijktijdige meting van de ureumproduktie en de uitwisseling van metabole gassen (paragraaf 3.1.2). Bij de voorspelling van het al dan niet in leven blijven van patiënten is het wellicht de moeite waard de verschuiving van hun utilisatiepatronen te bepalen ten gevolge van plotselinge veranderingen in dosis of samenstelling van de toegediende voeding.

11.2.3 *Evaluatie van therapeutische handelingen*

Bij ernstig zieke patiënten met een (dreigend) perifeer zuurstoftekort kunnen therapeutische maatregelen worden gericht op verhoging van het zuurstoftransport (6). Vaak echter resulteert verbetering van één component van het zuurstof-transporterend systeem in een verslechtering van een andere component. Zo kan ten gevolge van uitgebreide transfusie van oude rode bloedcellen de hoeveelheid in het arteriële bloed aanwezige zuurstof hoger worden. Tegelijkertijd zal de perifere vaatweerstand stijgen door een toename van de viscositeit van het bloed en zal de dissociatie van het zuurstof-hemoglobine complex nadelig worden beïnvloed door een linksverschuiving van de zuurstofsaturatie-curve. In situaties, waarbij de zuurstofconsumptie wordt beperkt door een ontoereikend zuurstoftransport, zou het netto resultaat van zuurstoftransport-verhogende handelingen kunnen worden gekwantificeerd door continue meting van de metabole gasuitwisseling.

Op grond van de vermeende relatie tussen $\dot{V}_{O_2}$-index en kans op overleving heeft men in het verleden gepleit voor het nemen van therapeutische-

maatregelen met het primaire doel de zuurstofconsumptie boven het niveau van 170 $ml.min^{-1}.m^{-2}$ te brengen (7). Bij onze groep patiënten vormde een hoge $\dot{V}_{O_2}$-index echter geen aanwijzing voor een goede kans op overleving (Hoofdstuk 8). Naar onze mening kunnen er twee verschillende doelstellingen worden nagestreefd in het geval van een (dreigend) perifeer zuurstoftekort. In de eerste plaats kan het zuurstoftransporterend vermogen worden verhoogd, gepaard gaande met een mogelijke stijging van de $\dot{V}_{O_2}$. Ten tweede kan de metabole vraag naar zuurstof worden verlaagd, met dientengevolge een herverdeling van de zuurstofleverantie op capillair niveau danwel een daling van de $\dot{V}_{O_2}$. Ook therapeutische handelingen ter verlaging van het stofwisselingsniveau kunnen worden geëvalueerd door continue registratie van de metabole gasuitwisseling. Een overzicht van de huidige mechanische en farmacologische methoden alsmede van de methoden op het gebied van de voeding ter verlaging van het zuurstofverbruik en het stofwisselingsniveau wordt gegeven in Hoofdstuk 9.

Hypothetisch zou tenminste ten dele de hypermetabole reactie op stress kunnen worden gereguleerd door een toename van de in de cytosol aanwezige Ca^{2+} concentratie. Om die reden zouden Ca^{2+} overload blockers bruikbaar kunnen zijn ter verlaging van de zuurstofconsumptie bij hypermetabole patiënten. Met dit oogmerk hebben wij de Ca^{2+} overload blocker flunarizine klinisch getest. Flunarizine bleek echter in de gebruikte dosering niet in staat de zuurstofconsumptie onder hypermetabole omstandigheden te veranderen (Hoofdstuk 9).

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APPENDICES

Appendix I

DESIGN AND VALIDATION OF AN AUTOMATIC METABOLIC MONITOR

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DESIGN AND VALIDATION OF AN AUTOMATIC METABOLIC MONITOR

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Abstract

A self-calibrating fully automatic instrument for the measurement of oxygen consumption, carbon dioxide production and the respiratory quotient of mechanically ventilated patients has been developed. The instrument is based on commercially available conventional oxygen and carbon dioxide gas analysers and a domestic natural gas volumetric flow meter. The distribution of the different gas flows, i.e. calibration gases, the inspiratory mixture sample and the expiratory mixture sample, are controlled by an inexpensive microprocessor, which also performs the necessary calculations. The accuracy of the instrument has been validated by bench tests. The present prototype has been in use for over 3000 h without major failures.

Introduction

Indirect calorimetry has been described as a tool for the determination of the nutritional needs of the artificially ventilated, critically ill patient. According to this method a subject's caloric expenditure and the contribution of the three types of energy sources (i.e. carbohydrates, fat and proteins) can be calculated from oxygen uptake, carbon dioxide release and the production of urea in the body (1). This may be done by calculating protein metabolism from urea production and subsequently by computation of carbohydrate and fat utilization from the remaining amounts of oxygen consumption and carbon dioxide production. These calculations have been described in detail (8, 13).

It appears to be favourable to adapt the nutritional supply to the actual expenditure of the patient. Underfeeding can lead to endogeneous protein loss and may inhibit wound healing. On the other hand, a caloric excess of carbohydrates apparently can be converted into endogeneous fat or lead to steatose (5, 12). This biochemical process releases large amounts of carbon dioxide, additional to normal production. This may be an unnecessary burden on ventilation and circulation in the critically ill patient (2).

Measurement systems and protocols for the assessment of oxygen and carbon dioxide exchange have been described (11, 14). Although suitable for research purposes, routine clinical application of indirect calorimetry is severely hampered by the costs of the commercial instruments (13), and the complicated measurement and calibration procedures (6).

This paper describes the design and bench test validation of a fully automated self-calibrating measurement system, which can be connected to a commercial ventilator.

Principles of measurements

The metabolic monitor has been designed to measure inspiratory oxygen concentration, expiratory oxygen and carbon dioxide concentrations with flow (ATPS), temperature and pressure of the expiratory mixture. Expiratory flow is converted to STPD conditions by means of a correction for temperature and water vapour, according to:

$$\dot{V}_E = \dot{V}_e \cdot \frac{273}{273+t} \cdot \frac{P-Pw}{100} \qquad (1)$$

with: t : expiratory gas temperature in °C
$\dot{V}_E$: expiratory flow (STPD)
$\dot{V}_e$: expiratory flow (ATPS)
P : expiratory gas pressure in kPa
Pw : water vapour partial pressure in kPa from

$$Pw = 1.450 - 0.052 \cdot t + 0.005 \cdot t^2 \qquad (2)$$

Using the Haldane transform, oxygen consumption $\dot{V}_{O_2}$, carbon dioxide production $\dot{V}_{CO_2}$ and respiratory quotient RQ are calculated:

$$\dot{V}_{CO_2} = \dot{V}_E \cdot F_{ECO_2} \tag{3}$$

$$\dot{V}_{O_2} = \dot{V}_E \cdot \frac{F_{IO_2} - F_{EO_2} - (F_{IO_2} \cdot F_{ECO_2})}{(1 - F_{IO_2})} \tag{4}$$

$$RQ = \frac{\dot{V}_{CO_2}}{\dot{V}_{O_2}} \tag{5}$$

with: F_{IO_2} : inspiratory oxygen fraction
F_{EO_2} : mixed expiratory oxygen fraction
F_{ECO_2} : mixed expiratory carbon dioxide fraction

Design of the instrument

The inspiratory mixture is acquired in an Ohio air-oxygen proportioner (Fig. I.1). Pressurized air is first led through a pressure regulator, while the blender output flow is stabilized by means of a flow controller. These two provisions are important to eliminate the variations of flow and input pressure of the blender, which would otherwise induce severe fluctuations in the inspired oxygen concentration (3). This acquired inspiratory mixture is presented to the ventilator, to an external IMV circuit (4) and through the

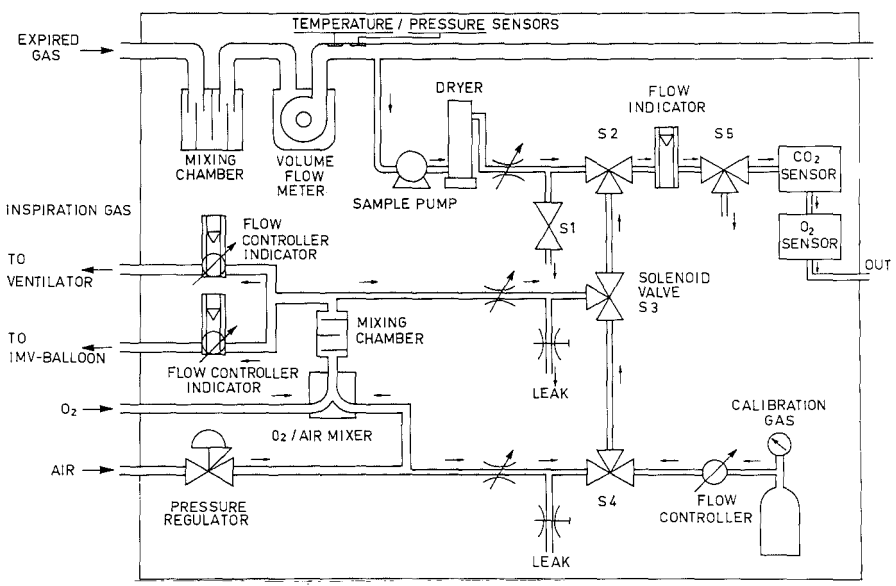

Figure I.1. Block diagram of the metabolic monitor.

S3, S2 and S5 valves to the gas analysers (see Figs. I.1 and I.2). In case of ventilation with a positive end expiratory pressure, a PEEP valve can be mounted on the expiratory output of the metabolic monitor as indicated in figure I.2.

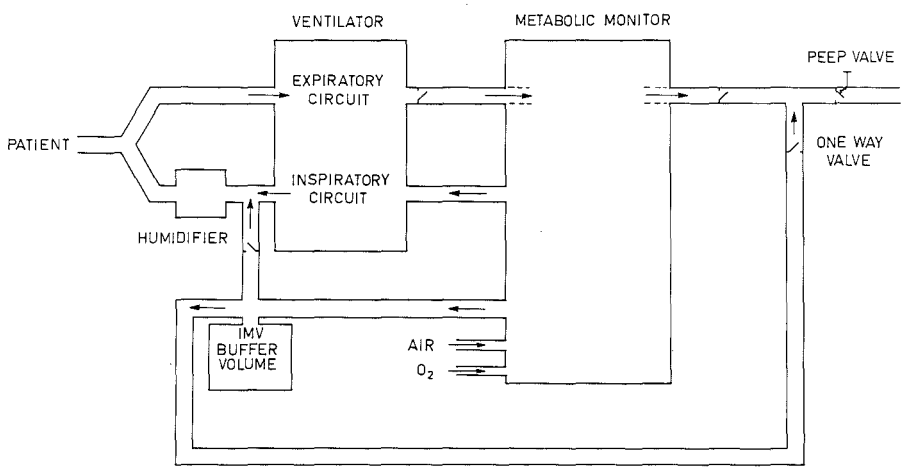

Figure I.2. Connections of the metabolic monitor to a ventilator with external PEEP and IMV system.

The expiratory gas flows through a 4-l mixing chamber before entering a Dordrecht volumetric flow meter. This volume meter, which is normally used for domestic natural gas, was modified by replacing the mechanical counter by an opto-electrical encoder (stated accuracy within 0.5% from 1 to 50 l/min). After the flow meter a 150 ml/min sample flow is pumped through a $CaCl_2$-filled dryer column either through S2 and S5 to the analyser circuit or through S1 to ambient by an Austen L12 diaphragm pump. This design feature prevents airway pressure fluctuations influencing the operation of the gas analysers, which are pressure sensitive.

The analyser circuit consists of a paramagnetic O_2 instrument (Taylor Servomix OA 273) and an infrared type capnograph (Mijnhardt UG51), modified to match the slower response time of the O_2 recorder. Gas analysis of the system is controlled by a single board microprocessor which commands the solenoid valves S1-S5 in such a way that:

1. once every 2 h or on demand the gas analysis instruments are calibrated with two test gases: the calibration gas (usually 7% CO_2, 40% O_2 in N_2) and pressurized dried air, both with known concentrations of oxygen and carbon dioxide;

2. the inspiratory gas mixture is sampled once every 12 min;
3. the expiratory mixture is sampled 8 times a minute.
Calculated values for oxygen consumption, carbon dioxide production and expiratory minute volume are available once every minute on the bedside display and on a communication line to a printer or a remote computer for storage and additional analysis, including artefact suppression, trending, 24-h averages and metabolic calculations.

Test methods

The accuracy of the metabolic monitor has been tested with laboratory simulations, where a 2-l balloon was connected to the ventilator metabolic monitor combination. The expiratory flow was compared with a Dordrecht wet gas volume meter (precision 0.2% of actual value), while constant flows were blown through both systems.

To simulate the exchange of CO_2 we injected a predetermined amount of this gas in the balloon in addition to the gas mixture coming from the ventilator (Siemens-Elema 900A). The injected CO_2 was controlled by a Brooks mass flow controller system, which was previously calibrated against a Dordrecht wet gas meter. To simulate the oxygen exchange we added a certain flow of nitrogen $\dot{V}_{N_2}$ to the balloon, also by means of a Brooks mass flow system. This nitrogen dilution simulates oxygen consumption (9) according to:

$$\dot{V}_{O_2} = \dot{V}_{N_2} \cdot \frac{F_{IO_2}}{(1\text{-}F_IO_2)} \qquad (6)$$

In order to test the overall accuracy of the respiratory quotient (RQ) we simultaneously injected both CO_2 and N_2 by means of a Godart gas mixture pump. In all simulations the minute volume of the ventilator was set at 11.5 l/min, the frequency at 20/min, the Inspiratory Pause Expiratory ratio at 25:10:65. In some of the simulations the humidifier was switched on.

Statistical analysis was done on a Digital PDP 11/23+ computer using an advanced correlation technique (10) and conventional linear regression analysis.

Test results

The determination of the $\dot{V}_E$ at different minute volumes up to 20 l/min appeared to be within 0.4% of the actual values. By means of linear

regression we found a good consistancy between the metabolic monitor and the test method as is shown in Table I.1.

Table I.1. Accuracy of metabolic monitor determinations against controlled injections.

Variable	Correlation	Slope ± SD	Intercept ± SD	n
$\dot{V}_E$	0.999	1.00 ± 0.02	−0.12 ± 0.2 l/min	16
$\dot{V}_{O_2}$	0.999	0.97 ± 0.01	7.2 ± 4 ml/min	32
$\dot{V}_{CO_2}$	0.999	1.00 ± 0.01	3.5 ± 5 ml/min	16
RQ	0.999	0.96 ± 0.01	0.029 ± 0.01	15

Each particular determination of the $\dot{V}_{O_2}$ and of the $\dot{V}_{CO_2}$ was repeated 9 times by the metabolic monitor and from these determinations the mean values and standard deviations were estimated. The mean values were compared with the values of the injection method. This was done for four different values of the inspiratory oxygen concentration (21%, 40%, 60%, 80%), since we may expect that for the higher range of inspiratory oxygen fractions the errors of the metabolic monitor will increase. The correlation between the metabolic monitor mean results and the injection test method appeared to be 0.999 for $\dot{V}_{O_2}$ and for $\dot{V}_{CO_2}$ (Table I.1). The standard deviation of the metabolic monitor determinations of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$, indicating the random error of the instrument, appeared to be independent on the values of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$. However, these standard deviations do increase for the higher inspiratory oxygen concentrations (Table I.2).

Table I.2. Standard deviation of metabolic monitor determinations (n = 9 for all cases).

F_IO_2 (%)	21	40	50	60	80
$\dot{V}_{O_2}$ (ml/min)	2	2	3	4	8
$\dot{V}_{CO_2}$ (ml/min)	2	2	3	3	4
RQ	0.01	0.01	0.01	0.01	0.02

To investigate further the accuracy of our instrument we have plotted the differences between both methods in figure I.3 for the oxygen consumption and in figure I.4 for the carbon dioxide production. It appears that the differences in the $\dot{V}_{O_2}$ have a mainly random character and are less than 3% as long as the inspiratory oxygen fraction is 60% or less. It increases for an inspiratory oxygen fraction of 80%. The differences in the $\dot{V}_{CO_2}$, which are also less than 3% in all cases, follow a curved relationship with the injected amount of carbon dioxide.

From our tests with simultaneous injection of carbon dioxide and nitrogen to establish the accuracy of the RQ we found a correlation of 0.999 and good

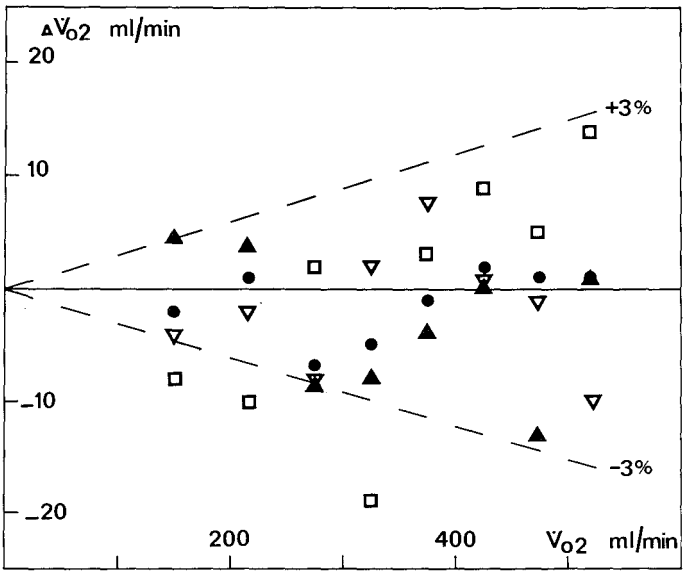

Figure I.3. Oxygen consumption errors $\Delta\dot{V}_{O_2}$ at different levels of inspiratory oxygen concentration. Filled circles-21%, filled triangles-40%, open triangles-60%, open squares-80%.

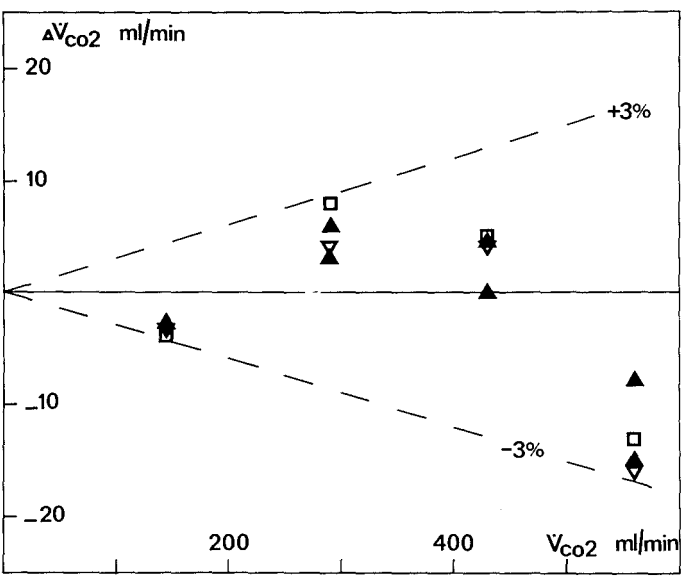

Figure I.4. Carbon dioxide production errors $\Delta\dot{V}_{CO_2}$ at different levels of inspiratory oxygen concentration. Filled circles-21%, filled triangles-40%, open triangles-60%, open squares-80%.

consistancy (Table I.1). In the range of physiologically possible values (0.6-1.5) the absolute differences between both methods appeared to be less than 0.03.

The influence of a higher mean airway pressure was tested by the application of PEEP. The influence of a PEEP of 20 cm H_2O was less than the resolution of the metabolic monitor (1 ml/min for both $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$). The corrections for the H_2O content of the expiratory gases was tested by switching on the humidifier establishing water vapour saturation at 33°C. These results were in agreement with manual corrections.

Discussion

The accuracy of the metabolic monitor was determined with laboratory tests, simulating the conditions, flows and gas-exchange that may be expected in an ICU environment. The results indicate that the accuracy of the instrument is within 3% for $\dot{V}_{CO_2}$. For $\dot{V}_{O_2}$ the accuracy is also better than 3%, provided that the inspiratory oxygen percentage is 60% or less. The increase of the errors for the higher inspiratory oxygen is inherent to the Haldane transform algorithm, which is particularly clear in the limit case of 100% inspiratory oxygen when the computation of $\dot{V}_{O_2}$ by means of formula (4) is impossible. The distribution of the errors in the measurement of $\dot{V}_{O_2}$ appeared to be mainly random over all measurements, while the errors in $\dot{V}_{CO_2}$ show a curved relation with the $\dot{V}_{CO_2}$ and therefore with F_{ECO_2}. We consider that an imperfect linearization of the capnograph caused this error distribution. The absolute error in RQ appeared to be less than 0.03 in the physiological range.

For the estimation of the metabolic carbon dioxide production and oxygen consumption it is necessary to average the value of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ over longer periods than a minute, in order to decrease the influence of a variation in ventilation on the contents of the buffering capacity of the body. Therefore the above mentioned errors are acceptable for clinical purposes, including estimation of the caloric expenditure of critically ill patients.

Other systems for the measurement of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ have been described in the literature, as reviewed by Westenskow (13). Our system is advantageous over the classical systems, based on spirometers or on Douglas bag collection, which can obtain a similar accuracy but obviously cannot be used for continuous recordings. Also they require manual control and calibration by trained operators. Comparable continuously recording instruments are mostly more expensive, especially when they require the use of a mass spectrometer (11) or still require some manual control (7).

The instrument described here has now been used for research and routine application in the estimation of our ICU patients' nutritional needs for over 3000 h without major failures. Since only an inspiratory sample and the expired gas are needed for the performance of this apparatus, it does not interfere with any type of ventilation and can be coupled to many ventilators currently used in intensive care departments. The instrument was assembled from mechanical and electrical parts of about US $900 and $1100 respectively, a mixer ($800) and two gas analysers (oxygen analyser $1350, capnograph $3100), which is considerably less expensive than a commercial instrument.

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Appendix II

ARTIFACTS IN THE ASSESSMENT OF METABOLIC GAS-EXCHANGE

This article has been published before in Intensive Care Med. 12: 312-316, 1986.

ARTIFACTS IN THE ASSESSMENT OF METABOLIC GAS-EXCHANGE

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Abstract

In mechanically ventilated patients metabolic gas-exchange recordings are frequently influenced by routine patient therapy. In this study the influence of such artifacts is investigated and a method for automatic detection and suppression proposed. This method reduced the influence of artifacts on diurnal oxygen and carbon dioxide exchange from up to 10% to a maximum of 1%.

Introduction

During the last decade critical care physicians expressed an increasing interest in the bedside measurement of metabolic gas-exchange, i.e. oxygen uptake ($\dot{V}_{O_2}$) and carbon dioxide output ($\dot{V}_{CO_2}$). This has led to the construction and validation of a variety of instruments (7, 16, 23, 24), some of which are commercially available. At present this equipment has been widely used for three main clinical problems.

The concern for achieving a daily balance between total energy expenditure (TEE) and nutritional caloric supply revived the application of indirect calorimetry as a tool to assess TEE from metabolic gas-exchange. It was known that underfeeding could induce protein loss and deterioration of wound healing (9). However, it became apparent from indirect calorimetric studies that hyperalimentation with carbohydrate may lead to excess hepatic fat and glycogen deposition (13, 18) with increased carbon dioxide production (1). It has been advocated, therefore, that indirect calorimetry may guide caloric replacement in the individual critically ill patient, receiving enteral or parenteral nutrition (15). The metabolic rate of the severely ill patient is subject to large fluctuations especially related to

patient activities (4, 22). Therefore, accurate determination of daily TEE requires the continuous recording of oxygen uptake and carbon dioxide output. However, the established sampling method, using a Douglas bag for the collection of expired gas, allows only for short-term gas sampling and thus merely yields an instantaneous energy expenditure which cannot simply be extrapolated to diurnal TEE (11, 12). Due to the technical limitations of the old collection methods, resting energy expenditure (REE) was conventionally measured for nutritional purposes under standardized conditions. However, REE is more suitable to compare the metabolic rate of different patient categories rather than to design a nutritional regimen for the individual patient. REE is usually lower than TEE (22). Therefore, if caloric supply would be based upon REE, in some patients hypoalimentation may occur.

The second clinical problem relates to the critical issue of the short-term balance between supply and demands for oxygen. Since the total buffering capacity of the body for oxygen is relatively small, a variation in the oxygen exchange minute value is directly related to the oxygen extraction by the tissues. $\dot{V}_{O_2}$ can therefore yield significant extra information besides hemodynamic and blood gas data in patients with impaired oxygen extraction, such as in ARDS (3, 10) or in sepsis (14), in which satisfactory arterial blood gas values alone do not imply adequate tissue oxygenation. In this type of application a continuous monitoring of metabolic gas-exchange seems to be important and may be used to evaluate the actual effect of therapeutic $\dot{V}_{O_2}$ reduction on gas-exchange (6, 17), in the case of an impending O_2 deficit.

Furthermore, it has been postulated that $\dot{V}_{O_2}$ has a highly predictive value in the ultimate outcome of the patient (19).

For these reasons the recording of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ should be on a continuous basis and obviously the influence of all kinds of artifacts should be minimized. Our strategy is that artifacts if possible should be *prevented* in the first place, as in all monitoring of vital physiological signals. This may either depend upon proper design of the machinery (2, 7, 23), or upon the measurement protocol (5). Artifacts which cannot be prevented should be *detected* and their influence on the measured values suppressed if possible. This paper describes some artifacts in metabolic gas-exchange recordings due to common patient care in the ICU. Furthermore, a method for automatic detection and suppression is demonstrated.

Materials and methods

Patient selection

In a surgical intensive care unit 25 mechanically ventilated adult patients were selected between October 1983 and December 1984 on the following basis: *inclusion criteria:* [1] a prediction, based on clinical judgement, of at least 24 h mechanical ventilation; [2] patient at least 6 h post anesthesia (to prevent interaction of N_2O with the O_2 sensor in the metabolic cart); [3] inspired oxygen concentration of 60% or less; *exclusion criteria:* [4] active bleeding; [5] dialysis; [6] air leakage (e.g. thoracic or cuff leakage); [7] unavailability of the equipment (not more than one patient at a time in the trial). After application of the above criteria no other (arbitrary) selection of the patients was performed. This resulted in the study population sample of Table II.1.

Table II.1. Survey of the clinical data.

		Number	Percentage
Sex:	male	19	76%
	female	6	24%
Condition:	respiratory distress syndrome	8	32%
	trauma	4	16%
	recent operation*	9	36%
	infection	15	60%
Average age:		56 (15-83)	

*between 1 and 5 days before recording date.

Patient care

All necessary therapy was administered to the patient as usual, by physicians and nurses who were unaware of the specific purpose of this study. Therapy affecting the recordings included broncho-pulmonary toilet, replacement of ventilator parts and bronchoscopy. During these time intervals the direct connection between patient, ventilator and metabolic monitor was temporarily impossible, causing artifacts in the gas-exchange values ($\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$), but also in the expiratory minute volume ($\dot{V}_E$). All therapeutic interventions were documented on a case report form (CRF).

Recordings and analyses

The gas-exchange values and $\dot{V}_E$ were determined each minute by an automatic metabolic monitor (7). The obtained minute values were transmitted to a remote computer (DEC, pdp 11/23+) and stored for later analyses.

Diurnal $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ were determined by summating the recorded minute values, which were previously processed by artifact suppression algorithms. Three different artifact suppression methods were applied to the same data for comparison. [1] A complete exclusion of artifacts guided by the CRF in combination with visual inspection of the data. [2] An automatic algorithm, detecting ventilator disconnection by a $\dot{V}_E$ value below a certain threshold (minute value less than 2 l/min), and suppressing all detected periods plus the next 5 min and the last minute just before the detected artifact from the summation procedure. This period was chosen and tested empirically serving as a compromise between recovery of gas concentrations in lungs, blood and tissues to the previously existing values on the one hand and not loosing too many data on the other. [3] No suppression at all. In the first and second algorithm the missing minute values were replaced by average values to obtain a 24-h total.

The first method is the most accurate technique and is considered as our standard by which the second method, an algorithm which can easily be automated, and the third method, can be judged. A small difference between the first and the second method might be expected since the manual suppression method allows for individual choice of the duration of suppressed periods, depending upon the actual recovery of the gas-exchange values. This could also influence the number of artifacts, since two succeeding artifacts with a short interval between them may be classified as a single one of longer duration depending upon the recovery time chosen in the first method.

Results

A typical record of $\dot{V}_E$, $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ is depicted in figure II.1A, which shows the signals without artifact suppression. Apart from the interruptions in the signals every 2 h due to automatic calibration of the metabolic cart (indicated by the marker trace) two artifacts are visible at 1 h 42 min and at 4 h 18 min respectively, both caused by disconnecting the ventilator in order to perform a broncho-pulmonary toilet. The same data are included in figure II.1B, however, after automatic artifact suppression. Both artifacts are recognized correctly and excluded from the diurnal gas-exchange

calculation. In this way exclusion of the artifacts increased diurnal $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ with 5.1% and 4.1% respectively for this patient.

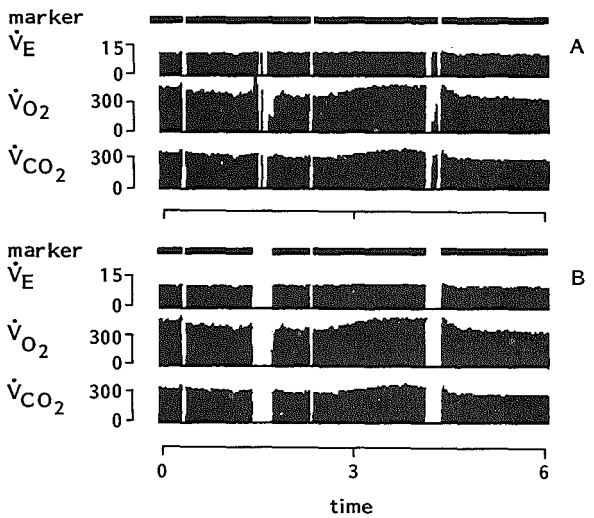

Figure II.1. *A.* Record of $\dot{V}_E$ [l/min], $\dot{V}_{O_2}$ [ml/min] and $\dot{V}_{CO_2}$ [ml/min] without artifact suppression. Marker interruptions indicate time [h] intervals where no data are available due to calibration of the metabolic cart. *B.* Same data after application of automatic artifact suppression. Marker interruptions indicate time intervals where no data are available due to calibration or artifacts.

In order to get an impression of the impact of artifacts due to therapy induced ventilator/patient disconnection, the total number of artifacts per patient over 24 h found by [1] manual and [2] automatic detection is depicted in histogram form in figure II.2A. Similarly the total duration of these artifacts, expressed in percentage of total recording-time, is presented in figure II.2B. The manual artifact suppression method detected between 4 and 21 artifacts per patient, resulting in a suppression of 2.5-18% of all recorded minute values. The automatic method found between 2 and 22 artifact periods, and excluded 2-18% of the total recording time (24 h) per patient. Differences between both methods in number and total duration of artifacts were small, even for the individual cases studied.

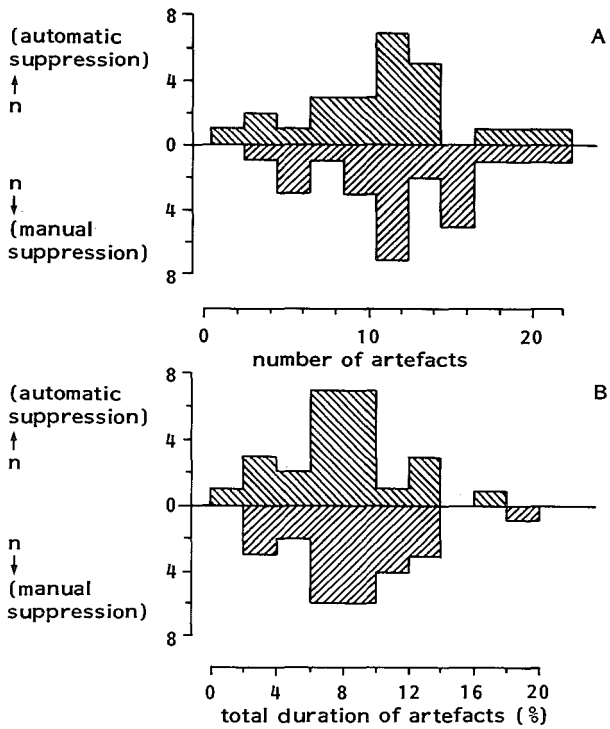

Figure II.2. *A.* Distribution of number of artifacts per patient in 24 hours, for automatic (upwards) and manual (downwards) detection. *B.* Distribution of total fraction [%] of recording time lost by artifacts per patient, for automatic (upwards) and manual (downwards) detection.

The influence of these artifacts on diurnal $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and RQ were evaluated by means of relative errors ($\Delta\dot{V}_{O_2}$, $\Delta\dot{V}_{CO_2}$) and the absolute error ΔRQ.

Without artifact processing diurnal $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ were underestimated up to 11% and 10% respectively, compared to our standard (data with manual artifact suppression), as shown for all patients in histogram form in figure II.3A,B. This is dramatically improved ($p < 0.001$, Wilcoxon rank-sum test) by application of the automatic artifact suppression method, which gave errors between −1% and +1% for both $\Delta\dot{V}_{O_2}$ and $\Delta\dot{V}_{CO_2}$.

RQ was only slightly overestimated without artifact suppression (up to 2%) which improved by the application of automatic artifact algorithm (Fig. II.3C).

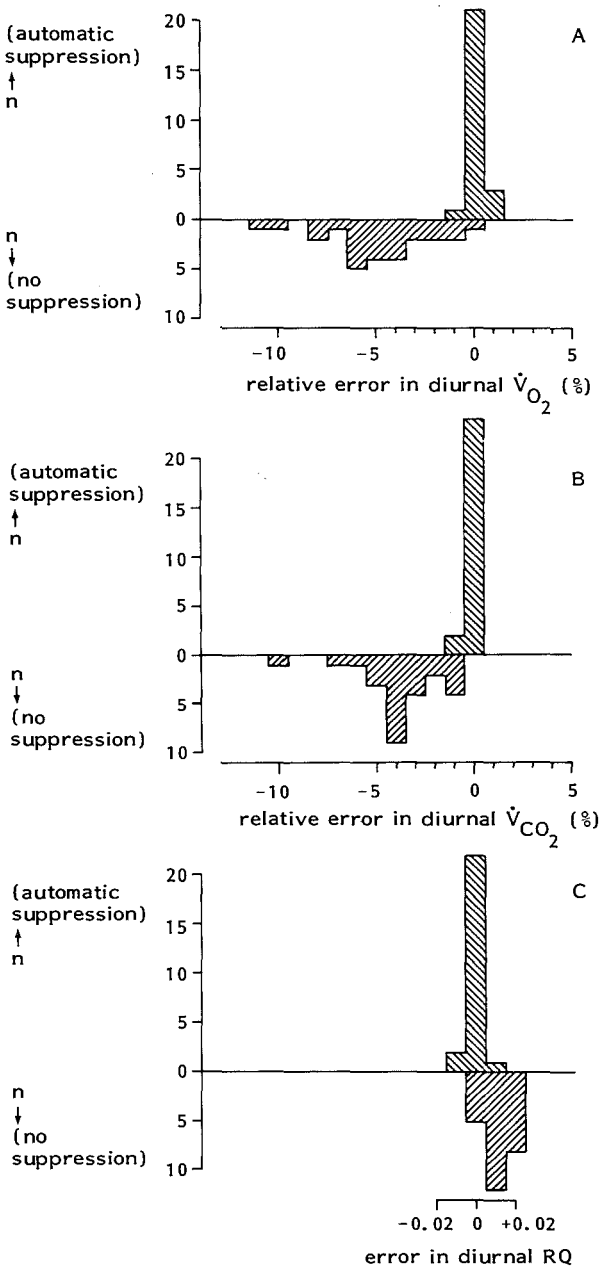

Figure II.3. *A.* Distribution of relative error in $\dot{V}_{O_2}$ with automatic artifact suppression (upwards) and without artifact suppression (downwards). *B.* Distribution of relative error in $\dot{V}_{CO_2}$ with automatic artifact suppression (upwards) and without artifact suppression (downwards). *C.* Distribution of error in RQ with automatic artifact suppression (upwards) and without artifact suppression (downwards).

Discussion

Gas-exchange measurements have been demonstrated to be useful in clinical research and practice. Their accuracy will depend not only on the design of the available instruments, but also on a number of factors dependent on the purpose of the measurements and the clinical therapy of the patient population.

Implications for short-term monitoring

For applications requiring instantaneous or minute-values of the gas-exchange, such as in case of cardiac output monitoring by the Fick principle, it is essential that a steady state is achieved concerning the gas-exchange in the patient and the connected gas collecting instruments. Therapeutic interventions such as changes in inspiratory oxygen concentration, breathing pattern, tidal volume, or changes in mental and physical effort may bring the patient from a steady state to a new situation with new blood gas values and associated changes in body gas stores. The impact of such a disturbance was demonstrated by Damask et al. (5), who found an almost twofold increase in $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ suddenly after percutaneous muscle biopsies were performed under local anesthesia. Besides these fluctuations induced by therapeutic changes and patient activities, we have shown that artifacts in gas-exchange values are caused by normal ventilatory therapy and nursing care during a considerable period of measurement (up to 18% of total time). It is beyond question that this would reduce the value of gas-exchange data for vital physiological monitoring unless certain artifact processing is performed.

The classical approach for individual energy replacement is based on the measurement of REE by means of indirect calorimetry (8). However, this is a complex and exacting task that requires an astute observer and much patience, because several factors such as patient activities may increase the actual energy expenditure considerably compared to REE (22). Since the basic objective of individualized caloric replacement is to obtain a balance between expenditure and nutritional intake, and since REE is usually lower than TEE, we prefer to measure gas-exchange continuously over the day to calculate diurnal TEE as the basis for energy intake. We have shown that using such recordings underestimations of TEE by up to 10% can be prevented by simple artifact suppression. This is even more important in monitoring the effects of therapeutic decrease in metabolic rate (6, 17), which can be indicated in case of an impending O_2-delivery deficit.

Conclusion

Clinical employment of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ measurements is severely hampered by instrumentation related errors. This study demonstrates that routine therapy for critically ill, ventilated patients frequently causes artifacts in gas-exchange measurements. An adequate detection of these artifacts and suppression of their influence on derived values seems to be indispensable. Routine implementation in a clinical setting is only practical when this is realized without manual operation. The automated artifact suppression mechanism presented here, can easily be incorporated into a microprocessor, that forms a part of most metabolic recording instruments for control purposes.

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Appendix III

THE INFLUENCE OF ACETATE HEMODIALYSIS ON ARTERIAL OXYGENATION AND INDIRECT CALORIMETRY

A slightly different, dutch version of this article has been published before in Klin. Fysica 3: 137-140, 1986.

THE INFLUENCE OF ACETATE HEMODIALYSIS ON ARTERIAL OXYGENATION AND INDIRECT CALORIMETRY

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Abstract

The influence of acetate hemodialysis on arterial oxygenation and indirect calorimetry is surveyed.

During acetate dialysis carbon dioxide is lost across the dialyzer membrane, leading to hypocapnia. This hypocapnia induces hypoventilation and ultimately results in secondary hypoxemia. Generally, the decrease of arterial O_2-tension is well tolerated, but in patients with a poor cardiopulmonary reserve it can lead to a critical situation.

Moreover, acetate dialysis has a disturbing influence on conventional indirect calorimetry. Carbon dioxide entering the dialysate across the membrane is not recorded and consequently carbon dioxide production ($\dot{V}_{CO_2}$) and respiratory quotient (R.Q.) seem to be erroneously low. Real changes in total energy expenditure (TEE) and R.Q. can be induced by anxiety, motor activity and acetate metabolization.

Introduction

Hypoxemia during hemodialysis is a frequently described phenomenon, for which various causes have been postulated (1). In the first place the generation of micro-aggregates during the extracorporal circulation could affect the pulmonary circulation (2). Furthermore, hemodialysis could activate complement-mediated leukostasis in the lungs with secondary pulmonary dysfunction (3, 4). When acetate is used as a buffer, hemodialysis might also lead to myocardial depression (5). However, the main cause of dialysis-induced hypoxemia is considered to be the carbon dioxide loss

across the membrane (6, 7), especially during acetate dialysis. The dialysate (about 75 l in case of recirculation dialysis) is saturated with oxygen. Due to the physical properties of the membrane, only small quantities of oxygen will pass, although the oxygen-tension in the dialysate is higher than that in the blood. On the other hand carbon dioxide can easily pass across the membrane. Its relatively high tension in the blood and its low tension in the dialysate cause a continuous flow of carbon dioxide from the body into the dialysate.

This preferential CO_2-elimination has two important consequences: hypoventilation with secondary hypoxemia and disturbing influences on indirect calorimetry.

Hypoventilation with a secondary hypoxemia

In 1905 Haldane already suggested that under normal conditions the regulation of the alveolar ventilation depends on the CO_2-tension rather than on the O_2-tension in the respiratory center (8). Many years later this was confirmed in animal models (9-10). Only under pathological conditions the respiratory center is mainly stimulated by a decreased O_2-tension. This phenomenon occurs in patients with chronic obstructive pulmonary disease, who are used to a chronically increased arterial CO_2-tension; in these situtions the administration of large quantities of oxygen should be avoided, because it would eliminate the respiratory drive, resulting in CO_2-coma.

In a group of seven spontaneously breathing patients it was demonstrated by Patterson et al., that during acetate-dialysis an average of 30 ml $CO_2.m^{-2}$ BSA.min^{-1} (i.e. approximately 25% of whole body carbon dioxide production) is removed across the membrane (7). This extrapulmonary CO_2-loss induces hypocapnia and leads to hypoventilation with a secondary hypoxemia. Generally, this decrease of arterial O_2-tension is well tolerated, but it may be detrimental in patients with a limited cardiopulmonary reserve. For this reason it has been advised to use a bicarbonate-buffer in borderline patients (4). However, the use of bicarbonate can also lead to a secondary hypoventilation, which can be explained in that bicarbonate passing across the membrane into the blood induces a pH-rise and thus inhibits the respiratory center (11).

The disturbing influences on indirect calorimetry

By means of calorimetry one can determine the total amount of energy expenditure. This can be performed by measuring *directly* the total heat production. In case of *indirect* calorimetry the oxygen consumption ($\dot{V}_{O_2}$) and carbon dioxide production ($\dot{V}_{CO_2}$) are determined, from which the liberated energy can be derived (12). We designed and validated an automatic metabolic monitor, measuring both $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ with an accuracy within 3% of the minute values (13, 14). In case of long term recordings, errors in $\dot{V}_{O_2}$ will be further reduced due to their random distribution. The abbreviated Weir-formula relates the amounts of oxygen consumed and carbon dioxide produced to the total energy expenditure (15):

$$TEE = 3.9\ \dot{V}_{O_2} + 1.1\ \dot{V}_{CO_2}$$

TEE = total energy expenditure [kcal/24 h]
$\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ = oxygen consumption and carbon dioxide production [1/24 h, STPD-conditions]

If at the same time the urea-production is calculated, one can determine the contributions of the different nutrients (carbohydrate, protein, fat) to the total combustion mixture.

Despite its intrinsic limitations (16) indirect calorimetry is generally considered a reliable method. However, under certain clinical conditions the calorimetric measurements are inacceptably disturbed (17). Table III.1 gives a survey of these situations, including hemodialysis. Across the

Table III.1. Survey of various clinical situations with their disturbing influences on indirect calorimetry.

hemodialysis	CO_2-loss across dialyzer and/or metabolic shifts
profuse bleeding or abundant transfusion	changes of buffer capacity and body gas stores
certain gaseous anesthetics (e.g. nitrous oxide)	interference with paramagnetic O_2-sensors
F_IO_2 above certain level	sensitivity of Haldane transform algorithm to sensor noise
air-system not closed	air-leakage through noseclip/mouthpiece, head canopy, cuff of endotracheal tube, thoracic drain etc.

dialyzer membrane carbon dioxide is lost, which is not taken into account in case of conventional indirect calorimetry. Consequently $\dot{V}_{CO_2}$ and therefore TEE seem to be erroneously low. The influence on the respiratory quotient is even more misleading, because its physiological range is extremely small and relatively subtle changes lead to highly fallacious conclusions (18).

During hemodialysis two different factors can lead to further changes in TEE and R.Q.. First of all a rise in energy expenditure has been postulated due to an increase of anxiety and movement (7). Secondly, when acetate is used as a buffer, it passes across the dialyzer membrane, enters the body and is metabolized with an R.Q. of 1.00: for the oxidation of each molecule of acetate two molecules of oxygen are needed and two molecules of carbon dioxide are produced (Fig. III.1A). The introduction of this energy source can change whole body R.Q..

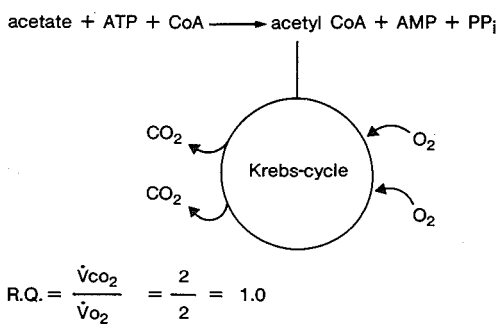

Figure III.1A. Schematic presentation of the metabolization of acetate.

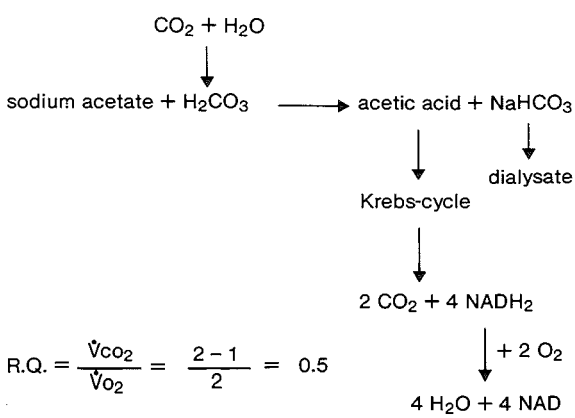

Figure III.1B. Schematic presentation of the metabolization of acetate according to Oh (19). The initial step is erroneously supposed to be its conversion to acetic acid. In reality it is nót the acetic acid molecule, but the acetate ion that enters the Krebs-cycle after it has been converted to acetyl CoA (Fig. III.1A).

Previously, it has been erroneously postulated (1, 19, 20), that the initial step in acetate metabolization involves its conversion to acetic acid before it is further broken down in the Krebs-cycle. This initial step would ultimately lead to a decrease of R.Q. (Fig. III.1B). However, it should be realized, that the acetate ion (and nót the acetic acid molecule) enters the Krebs-cycle after it has been converted to acetyl-CoA.

Figure III.2 and figure III.3 illustrate two examples of continuous calorimetric recordings in dialyzed patients; the calorimetric indices before, during and after dialysis are given in Table III.2 and Table III.3 respectively. Some of the previously mentioned effects of dialysis can be recognized. The first patient (Fig. III.2) is treated with intermittent mandatory ventilation (IMV), which remains unchanged during the total recording period. Apart from the mandatory ventilation IMV-therapy allows additional spontaneous breathing. The variations in total expiratory minute volume ($\dot{V}_E$) before and after dialysis indicate, that the patient is partly breathing spontaneously, which leads to a small increae of total $\dot{V}_E$. During dialysis total $\dot{V}_E$ is more or less equal to the mandatory level from which can be concluded, that the patient is not stimulated to breathe spontaneously during this period. The diminished metabolic cost of breathing might explain the slight decrease of $\dot{V}_{O_2}$ (Table III.2). The more pronounced decrease of $\dot{V}_{CO_2}$ accompanied by a net fall of R.Q. suggests extrapulmonary CO_2-loss.

Table III.2. Calorimetric indices during the 2 h previous to the dialysis of figure III.2, during the dialysis and during the 2 h following the dialysis ($\dot{V}_E$ = expiratory minute volume, $\dot{V}_{CO_2}$ = carbon dioxide production, $\dot{V}_{O_2}$ = oxygen consumption, R.Q. = respiratory quotient).

	the previous 2 h	during dialysis	the subsequent 2 h
$\dot{V}_E$ [l/min]	8.16	7.35	8.74
$\dot{V}_{CO_2}$ [ml/min]	317	275	330
$\dot{V}_{O_2}$ [ml/min]	423	392	451
R.Q.	0.75	0.70	0.73
Estimated TEE [kcal/day]	2880	2640	3050

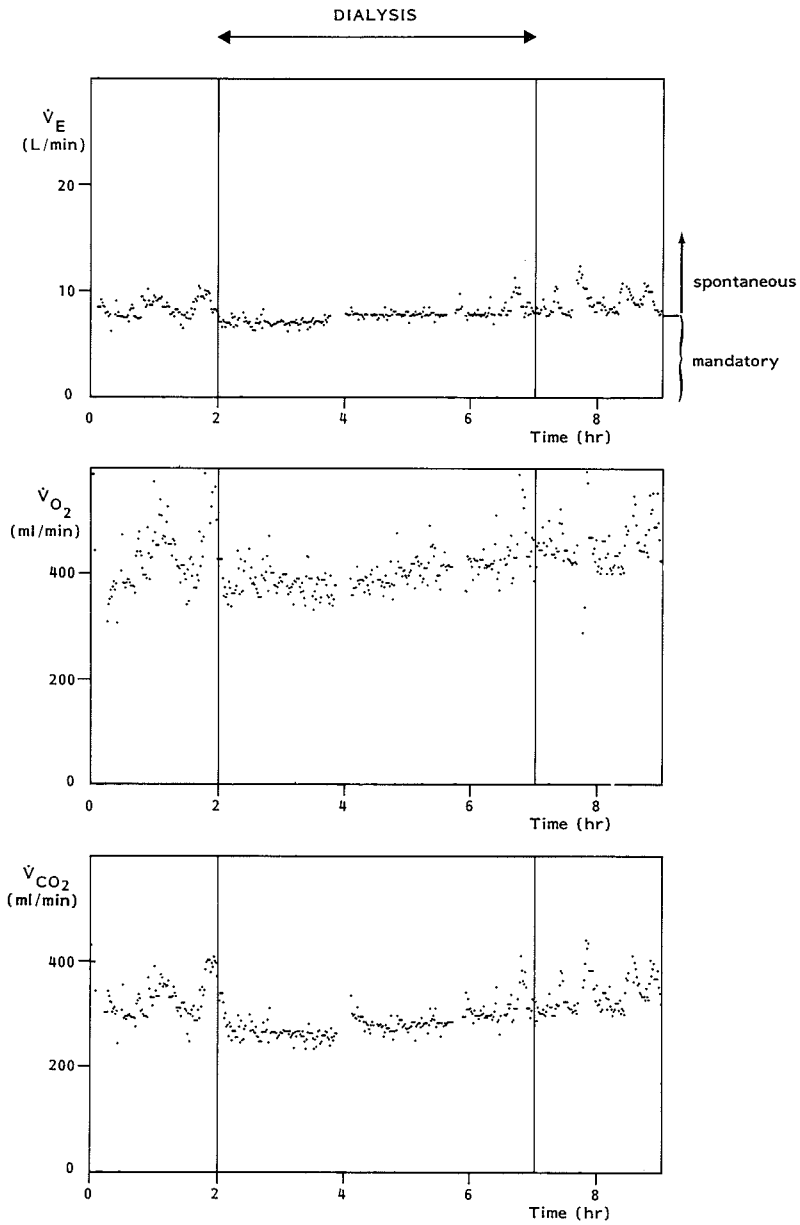

Figure III.2. Typical example of a continuous calorimetric recording before, during and after acetate dialysis.

The second patient (Fig. III.3) is also ventilated artificially. During the total recording period spontaneous breathing hardly occurs. Consequently, the decrease of $\dot{V}_{O_2}$ during dialysis is absent and is even replaced by a slight increase, possibly induced by anxiety or movement (Table III.3) (7). However, $\dot{V}_{CO_2}$ decreases with 14%. The simultaneous increase of $\dot{V}_{O_2}$ and decrease of $\dot{V}_{CO_2}$ explain the important fall of R.Q.. The actual R.Q. (i.e. the R.Q. before and after dialysis) is greater than 1.00; the actual nonprotein R.Q. must be even higher, indicating net lipogenesis. The patient receives TPN which is apparently administered in excessive quantities, leading to a superfluous CO_2-production. Of course this situation should be avoided in a circulatorily or pulmonarily compromised patient, in whom gas-exchange is already hampered. Interpretation of the R.Q. values during dialysis (< 1.00) would lead to erroneous conclusions, since the hypercaloric feeding would not have been recognized. This case illustrates the disturbing and misleading influence of hemodialysis on indirect calorimetry.

Table III.3. Calorimetric indices during the 2 h previous to the dialysis of figure III.3, during the dialysis and during the 2 h following the dialysis ($\dot{V}_E$ = expiratory minute volume, $\dot{V}_{CO_2}$ = carbon dioxide production, $\dot{V}_{O_2}$ = oxygen consumption, R.Q. = respiratory quotient).

	the previous 2 h	during dialysis	the subsequent 2 h
$\dot{V}_E$ [l/min]	8.09	8.31	8.43
$\dot{V}_{CO_2}$ [ml/min]	258	221	269
$\dot{V}_{O_2}$ [ml/min]	252	270	258
R.Q.	1.03	0.82	1.04
Estimated TEE [kcal/day]	1820	1870	1870

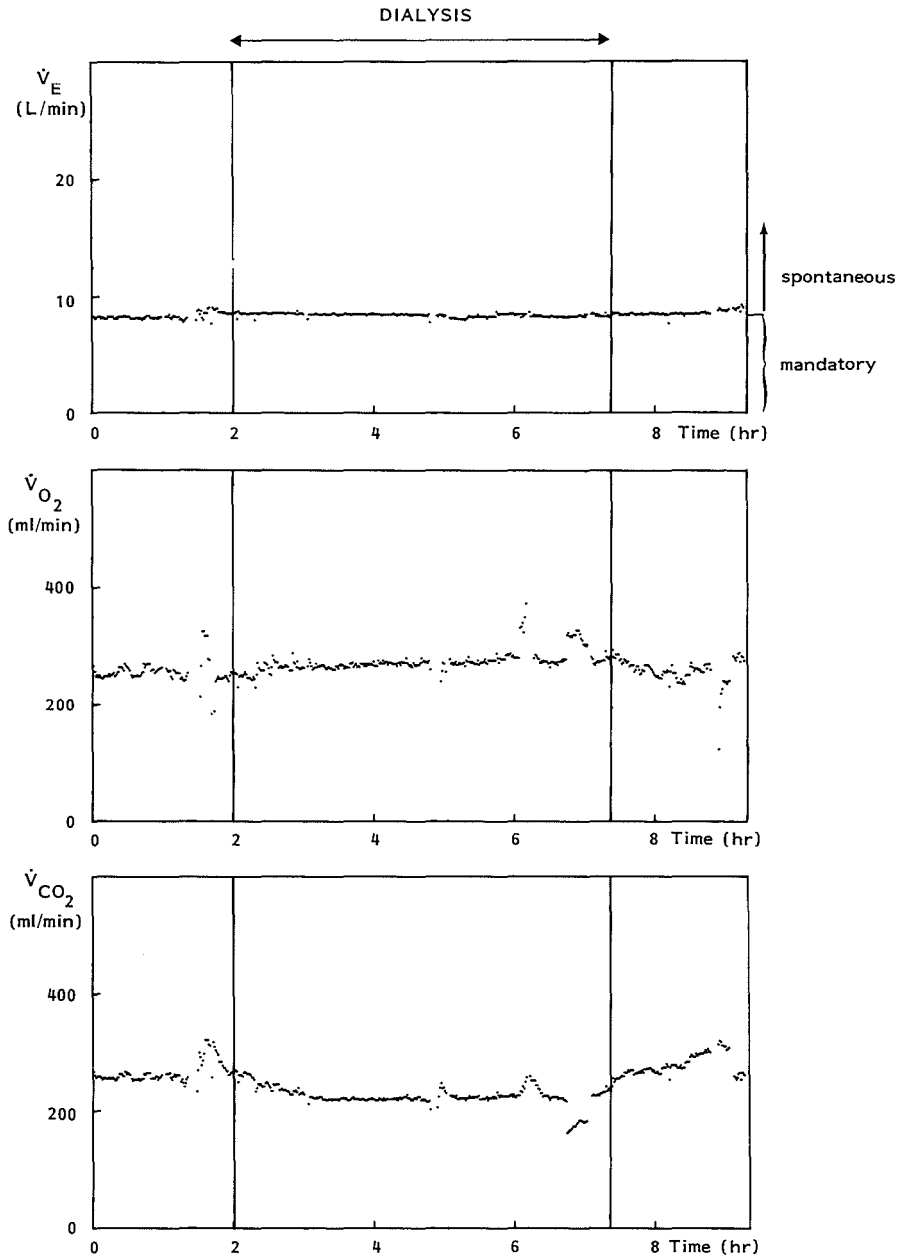

Figure III.3. Typical example of a continuous calorimetric recording before, during and after acetate dialysis.

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LIST OF ABBREVIATIONS

a	intercept of best linear fit in $y = bx + a$
A	accuracy or age
aCS	actual caloric supply
af	activity factor
APACHE	acute physiology and chronic health evaluation
APD	absolute value of percentage difference
ARDS	adult respiratory distress syndrome
ATP	adenosine triphosphate
ATPS	ambient temperature and pressure; saturated
ave	average
b	slope of best linear fit in $y = bx + a$
BEE	basal energy expenditure
BSA	body surface area
BUN	blood urea nitrogen
C_a	arterial content
Ca^{2+}	calcium cation
$CaCl_2$	calcium chloride
cf	clinical correction factor
CIC	continuous indirect calorimetry
CO	cardiac output
CO_2	carbon dioxide
$^{14}CO_2$	carbon-labelled carbon dioxide
CRF	case report form
$C_{\bar{v}}$	mixed venous content
dF	amount of metabolized fat
D_2O^{18}	doubly labelled water = $H^*_2O^*$
dP	amount of metabolized protein
dS	amount of metabolized carbohydrate
$\Delta\dot{V}_{CO_2}$	carbon dioxide production error
$\Delta\dot{V}_{O_2}$	oxygen consumption error
$E_{activity}$	energy required for motor activity
$E_{components}$	energy present in the basic components of food
$E_{dissipated}$	dissipated energy

E_{food}	energy ingested by food
E_{in}	ingested energy
$E_{maintain}$	energy required for maintenance of the body
E_{out}	energy given off
$E_{restore}$	energy required for restoration of body mass
E_{stored}	energy stored in the body
$E_{synthesis}$	energy required to synthetize the basic components to more complex substances
$E_{synth-ext}$	part of $E_{synthesis}$ which is liberated as external heat
$E_{synth-int}$	part of $E_{synthesis}$ which remains in the body
E_{therm}	energy required for thermoregulation
$E_{urine,faeces}$	energy excreted in urine and faeces
F_ECO_2	mixed expiratory carbon dioxide fraction
F_EO_2	mixed expiratory oxygen fraction
FFA	free fatty acids
F_IO_2	inspiratory oxygen fraction
h	hour
H	height
HB	Harris-Benedict formula
HBc	Harris-Benedict formula corrected for clinical condition
HCO_3^-	bicarbonate anion
H_2O	water
$H^*_2O^*$	doubly labelled water = D_2O^{18}
IBW	ideal body weight
ICU	intensive care unit
IIC	intermittent indirect calorimetry
IMV	intermittent mandatory ventilation
n	number
N	urea nitrogen production
N_2	nitrogen
nS	nonsurvivors
O_2	oxygen
p	level of significance
P	pressure
PEEP	positive end expiratory pressure
P_i	inorganic phosphate
pts	patients
P_w	water vapour partial pressure
R	mean coefficient of correlation
REE	resting energy expenditure

ROC	receiver operating characteristic
RQ	respiratory quotient
S	survivors
SAPS	simplified acute physiology score
SD	standard deviation
SDA	specific dynamic action
SE(M)	standard error of the mean
STPD	standard temperature and pressure; dry
t	temperature
TEE	total energy expenditure
TPN	total parenteral nutrition
$\dot{V}_{CO_2}$	carbon dioxide production; carbon dioxide output
$\dot{V}_e$	expiratory flow (ATPS)
$\dot{V}_E$	expiratory flow (STPD)
$\dot{V}_{O_2}$	oxygen consumption; oxygen uptake
$\dot{V}_{O_2}$-index	oxygen consumption/body surface area
W	weight
WBC	white blood cell
yr	year

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Cover design by Kees de Vries: diagram of oxygen and carbon dioxide molecule (after: The Modern World Encyclopedia, published by Kodansha Ltd.).