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Oxygen consumption after cardiopulmonary bypass – implications of different measuring methods

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Abstract. *Objective:* To determine whether intra-pulmonary oxygen consumption or whole body oxygen consumption is the main determinant of the hypermetabolic response after cardiopulmonary bypass. Secondly, which method of measuring oxygen consumption best quantifies this hyperdynamic response.
Design: We measured oxygen consumption by analysing respiratory gas (VO_2-gas), carbon dioxide excretion (VCO_2), and respiratory exchange ratio (RER = VCO_2/VO_2), and calculated oxygen consumption using the Fick-method (VO_2-Fick) and intra-pulmonary oxygen consumption (VO_2-gas – VO_2-Fick) in patients at fixed times before and after elective cardiac surgery. Next, comparisons were made between methods and also between measurements at different times before and after bypass.
Setting: University hospital.
Patients: 10 elective cardiac surgical patients.
Interventions: None.
Measurements and results: VO_2-gas, VCO_2 and RER were measured with an open circuit indirect calorimeter. VO_2-Fick was calculated: VO_2-Fick = cardiac index × (arterial – mixed venous oxygen content). Intrapulmonary oxygen consumption was calculated as the difference between VO_2-gas and VO_2-Fick. Both VO_2-gas and VO_2-Fick were about 20% higher after bypass than after induction of anaesthesia. Absolute values of VO_2-gas were about 30% higher than VO_2-Fick. Intra-pulmonary oxygen consumption accounted for 32% of whole body oxygen consumption after induction of anaesthesia and did not increase after bypass.
Conclusion: Whole body oxygen consumption and not intra-pulmonary oxygen consumption is the main determinant of the hypermetabolic response after bypass. Increased intra-pulmonary oxygen consumption is not related to bypass. VO_2-gas best quantifies this hypermetabolic response directly after bypass, and not VO_2-Fick, VCO_2 or intra-pulmonary oxygen consumption, since VO_2-Fick excludes intra-pulmonary oxygen consumption and VCO_2 does not reflect metabolism directly after bypass.

Key words: Oxygen consumption – Cardiopulmonary bypass – Pulmonary gas exchange – Energy metabolism – Physiological monitoring – Intra-pulmonary oxygen consumption

The cardiopulmonary bypass procedure used for cardiac surgery can induce a hyperdynamic response. Clinical signs of this response directly after bypass include a high cardiac output with hypotension and a low systemic vascular resistance. Later on in the post-operative period a post-perfusion syndrome [1–4] may develop with symptoms of fever, fluid retention and peripheral and pulmonary edema [5, 6]. This hyperdynamic response, resembling septic shock, is the circulatory compensation for increased metabolism. Several factors during cardiopulmonary bypass contribute to this increased metabolism after bypass. Firstly, hypoperfusion during bypass and ischaemia of heart and lungs during cross clamping require replenishment of cellular energy stores after bypass. Secondly, cardiopulmonary bypass induces a whole body inflammatory response [7, 8] which triggers the formation of oxygen derived free radicals [9–11] and the release of cytokines like tumor necrosis factor [4]. This inflammation increases metabolism. Thirdly, rewarming after hypothermia induces a hypermetabolic response [12]. Therefore, replenishment of cellular oxygen stores, inflammation and rewarming can be the cause of a hyperdynamic response after cardiopulmonary bypass.

Although mortality and morbidity of elective cardiac surgery is low, immediately after surgery all patients require intensive treatment to correct haemodynamic imbalance. Further, when longer bypass times are required a more severe hypermetabolic response can induce organ dysfunction, necessitating extended post-operative support in the intensive care unit. Therefore, technical and therapeutic improvements are required to reduce organ damage and improve patients' outcome, particularly after prolonged bypass.

In order to evaluate these improvements a sensitive clinical indicator is needed, quantifying this hypermetabolic response. Since the hypermetabolic response is associated with increased oxygen demand, changes in oxygen consumption could be a quantitative clinical indicator of the hypermetabolic response induced by cardiopulmonary bypass.

Three methods of monitoring oxygen consumption are available. Firstly, oxygen consumption can be measured directly with an indirect calorimeter by analysis of respiratory gas (VO_2-gas) [13, 14]. Secondly, oxygen consumption can be calculated with the reversed Fick method (VO_2-Fick). Since VO_2-Fick is calculated as the product of the arterio-venous oxygen content difference and cardiac output, it excludes any oxygen consumption in the lung [15]. Intra-pulmonary oxygen consumption is therefore calculated as the difference between VO_2-gas and VO_2-Fick. Thirdly, oxygen consumption can be deduced from carbon dioxide excretion (VCO_2), routinely measured with some ventilators, assuming a constant VCO_2/VO_2 ratio. However, these 3 methods are not interchangeable [16], particularly when oxygen consumption in the lung is increased or the VCO_2/VO_2 ratio is not constant. Normally the lungs use 1% – 4% of the total body oxygen consumption [17]. Increased intra-pulmonary oxygen consumption has been found in dogs with experimental pneumococcal pneumonia [15], in intensive care patients with ARDS [18], sepsis and respiratory failure [19] and after cardiac surgery [14].

The first aim of this study was to determine whether intra-pulmonary oxygen consumption or whole body oxygen consumption is the main determinant of this hypermetabolic response after cardiopulmonary bypass. The second aim was to determine which method of measuring oxygen consumption best quantifies this hyperdynamic response. Therefore we measured VO_2-gas, VO_2-Fick, VCO_2, VCO_2/VO_2 ratio, and intra-pulmonary oxygen consumption (VO_2-gas – VO_2-Fick) in patients at a series of fixed times before and after cardiopulmonary bypass and in the intensive care unit until extubation.

Methods

Patients

Ten patients (5 male, 5 female) undergoing cardiopulmonary bypass for elective cardiac surgery were studied. Mean age was 64 years (range 53 – 75 years). In order to reduce the tumor necrosis factor-related inflammatory response, all patients received dexamethasone 1 mg/kg after induction of anaesthesia [4]. None of the patients showed pre-operative signs of infection or pulmonary dysfunction. Two patients underwent aortic valve replacement and 8 underwent coronary bypass surgery. In 3 patients LIMA-grafts were used. Mean aortic clamp time was 62 min, mean bypass time was 97 min. All patients were extubated the day after surgery and survived. One patient had a major complication, hemiplegia due to cerebral infarction.

The study was approved by the Ethical Committee of the Free University Hospital in Amsterdam. Since the clinical management of patients was unaltered and no extra invasive procedures were needed it was not deemed necessary to obtain consent from individual patients.

Study design

To determine whether pulmonary oxygen consumption or whole body oxygen consumption is the main determinant of this hypermetabolic response after cardiopulmonary bypass, and to determine which method of measuring oxygen consumption best estimates this hypermetabolic response, we measured VO_2-gas, VO_2-Fick, VCO_2, and oxygen consumption in the lung (VO_2-gas – VO_2-Fick) in patients at a series of fixed times before and after cardiopulmonary bypass for elective cardiac surgery. After indexation for body surface area, measurements of oxygen consumption were compared between methods, and within-method between the different points of time.

Technique of anaesthesia, cardiopulmonary bypass and intensive care treatment

Anaesthesia was induced with pancuronium bromide 0.1 mg/kg and fentanyl 50 µg/kg and maintained with a continuous infusion of fentanyl 50 µg/kg/h and midazolam 0.1 mg/kg/h. Neither volatile anaesthetics nor nitrous oxide were used. Patients were ventilated with 40% oxygen and 5 cmH_2O positive end-expiratory pressure. A pulmonary artery catheter was inserted after induction of anaesthesia and intubation.

Cardiopulmonary bypass was performed with moderate systemic hypothermia (28 – 30 °C), non-pulsatile flow and cold cardioplegia. The cardiopulmonary bypass circuit consisted of a membrane oxygenator (Ultrox-1, Scimed Life systems Inc.), a roller pump (Stockert) with filter and polyvinyl tubing. The circuit was primed with 2000 ml Ringer's lactate, 200 ml human albumin 20%, 100 ml mannitol 20% and 50 ml sodium bicarbonate 8.4%. A standard cannulation technique was used with a two-stage venous cannula and subtotal bypass. During CPB pH was regulated by means of the alpha-stat method [20], which aims at normocapnia.

After release of the aortic clamp, mechanical ventilation was resumed using 40% – 50% oxygen and 5 cmH_2O positive end-expiratory pressure, and nitroglycerin 2 mg/h and dopamine 2 µg/kg/h were started. Dopamine dose was increased when cardiac index was low. Bypass was continued until central body temperature was restored to 36 °C. In the intensive care unit all patients were externally warmed with a heating mattress until rectal temperature was higher than 36.5 °C and the difference between rectal and toe temperature was less than 5 °C. Intermittent positive pressure ventilation was continued until temperature and haemodynamics were stable, blood loss from drains was < 50 ml/h and patients were awake. Thereafter pressure support ventilation was started until the moment of extubation, generally on the morning after operation. Packed cells were transfused to keep haemoglobin > 5.6 mmol/l.

During stabilization of circulation and temperature patients were sedated with intermittent morphine and diazepam i.v. Stable patients were allowed to wake up and morphine and valium were only used when needed for pain or restlessness.

Methods of measurement

Oxygen consumption (VO_2-gas), carbon dioxide excretion (VCO_2) and the ratio between VCO_2 and VO_2, i.e. the respiratory exchange ratio ($RER = VCO_2/VO_2$), were measured continuously by respiratory gas analysis with an open circuit indirect calorimeter (Deltatrac, Datex Instrumentarium, Helsinki, Finland). This calorimeter contains a fast response paramagnetic differential oxygen analyzer and an infrared carbon dioxide sensor. The apparatus has been described in detail previously [14]. Briefly, all expired gas from the ventilator enters the four litre mixing chamber from which gas is sampled and analyzed to determine mixed expired O_2 and CO_2 concentrations (FeO_2, $FeCO_2$). The expired gas leaving the mixing chamber is then mixed with room air so that the total flow (Q) is constant. Diluted CO_2 fraction is measured ($Fe \cdot dil \cdot CO_2$), and the CO_2 excretion is calculated: $VCO_2 = Q \times Fe \cdot dil \cdot CO_2$. The RER, or the ratio of VCO_2 and VO_2, is calculated by means of the Haldane transformation:

$$RER = \frac{1 - FIO_2}{(FIO_2 - FeO_2)/FeCO_2 - FIO_2}$$

The FIO_2 and $FICO_2$ are measured in the inspired air, sampled after the humidifier. The VO_2 is subsequently calculated from the RER as: $VO_2 = VCO_2/RER$. Gas volumes are corrected to standard conditions of dry gas, temperature and pressure. Validation of this metabolic monitor demonstrated a relative error within ±5% in the measurement of VCO_2 [14] and of 4.3% ±3.2% in the minute volume measurement [21].

In this study, the artefact suppression mode was used. FIO_2 was always less than 50%. Minute volume and FIO_2 were never changed within 60 min before measurements were taken. Calibrations were made before starting, after transport of the instrument with the patient to the intensive care unit, and at 8-h intervals thereafter. A meticulous check on gas leakage was made and minute volume measured by the ventilator and the calorimeter was routinely checked.

VO_2-Fick was calculated by means of the Fick-formula, in which VO_2-Fick = cardiac output × (arterial − mixed venous oxygen content). Cardiac output was measured by the thermodilution method using a Marquette Tramscope 12. The mean of four measurements was calculated and only measurements with correct dilution curves were used [22]. Arterial and mixed venous oxygen content were calculated using the standard formula (oxygen content = haemoglobin × oxygen saturation $\times 1.39 + 0.003 \times PO_2$). Immediately after measurement of the cardiac output, blood was aspirated slowly from the distal lumen of the pulmonary artery catheter and simultaneously from the arterial line. Gas analysis was performed without delay. Oxygen tension was measured with a pH/blood gas analyser (Corning 178) and oxygen saturation was measured with a co-oximeter (Corning 2500). Haemoglobin was measured separately (Coulter J 666).

Pulmonary oxygen consumption was calculated as the difference between VO_2-gas and VO_2-Fick.

When a stable clinical condition with adequate sedation and appropriate filling pressures had been achieved, measurements as described above were performed at a series of fixed times: after induction of anaesthesia and insertion of the pulmonary artery catheter (before surgery), 30 min after cardiopulmonary bypass, 30, 120, 240 and 480 min after arrival in the intensive care unit and just before extubation.

Statistics

For the determination of the differences within a method between separate times of measurements of VO_2-gas, VO_2-Fick, VCO_2 and RER the Wilcoxon Rank test was used. To determine the difference between the measurements of oxygen consumption obtained with the different methods at the individual points of time, Mann-Whitney-U testing was used. A probability level of $p < 0.05$ was considered statistically significant.

Results

In the 10 patients both VO_2-gas and VO_2-Fick were about 20% higher after cardiopulmonary bypass than after induction of anaesthesia before surgery (Fig. 1). However, absolute values of VO_2-gas were higher than VO_2-Fick. This difference between VO_2-gas and VO_2-Fick was 32% after induction of anaesthesia, and declined gradually from 27% 30 min after bypass to non-important differences at 8 and 18 h after arrival in the intensive care unit.

Intra-pulmonary oxygen consumption, calculated as the difference between VO_2-gas and VO_2-Fick, was high immediately after induction of anaesthesia and before surgery (Fig. 2), accounting for 32% of whole body oxygen consumption. Intra-pulmonary oxygen consumption did not increase further after bypass. It remained high during the first 4 h post-operative, but reached normal values at 8 and 18 h after operation.

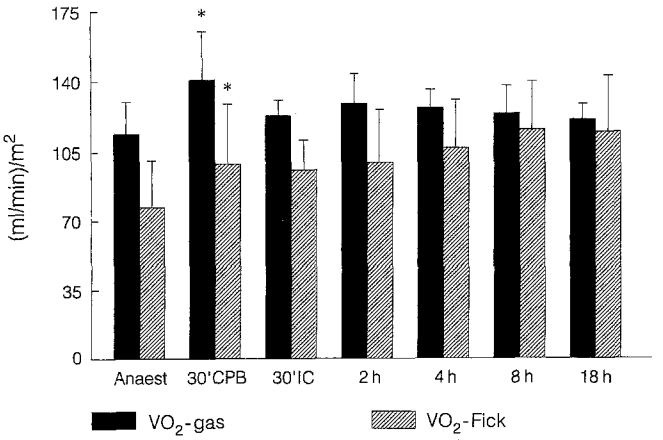

Fig. 1. Oxygen consumption measured by analysis of respiratory gases (VO_2-gas) and oxygen consumption calculated following the reversed Fick method (VO_2-Fick) plotted against times of measurement: after induction of anaesthesia and insertion of the pulmonary artery catheter, 30 min after bypass, 30 min after ICU arrival, 2, 4, 8 and 18 h after ICU arrival or just before extubation. Data are mean values ± SD. $*p < 0.05$ vs. the value after induction of anaesthesia

In contrast with VO_2-gas and VO_2-Fick, VCO_2 was not higher after cardiopulmonary bypass than after induction of anaesthesia. However, 2 h after patients' arrival in the intensive care unit VCO_2 was 9% higher than after bypass (Fig. 3).

RER (VCO_2/VO_2-gas) was very low 30 min after bypass, 0.65 ± 0.10 mean (Fig. 4), a value even below the physiological range (0.70 − 1.0). This trough in RER was due to the post-bypass rise in VO_2-gas which was not accompanied by a rise in VCO_2. By the time the patient arrived in the intensive care unit, RER had returned to physiological values.

Discussion

Our results in elective cardiac surgery patients treated with dexamethasone show that whole body oxygen con-

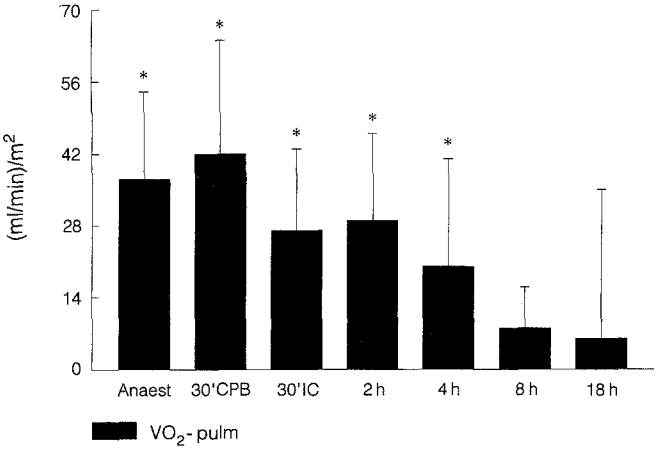

Fig. 2. Intrapulmonary oxygen consumption (VO_2-pulm), calculated as the difference between VO_2-gas and VO_2-Fick plotted against the times of measurement (see legend Fig. 1). Data are mean values ± SD. $*p < 0.05$ for the difference

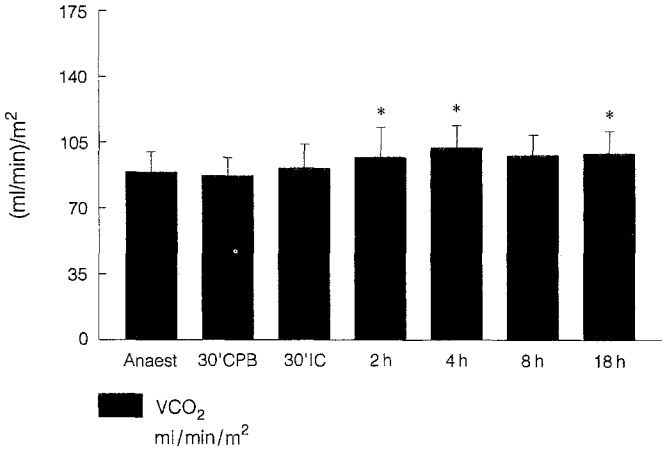

Fig. 3. Carbon dioxide production (VCO_2) measured by analysis of respiratory gases, plotted against the times of measurement (see legend Fig. 1). Data are mean ± SD. $*p < 0.05$ vs. the value after induction of anaesthesia

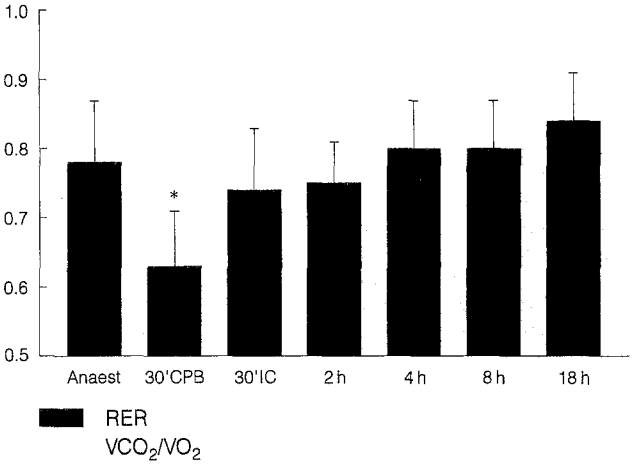

Fig. 4. Respiratory exchange ratio (RER = VCO_2/VO_2) plotted against the times of measurement. $*p < 0.05$ vs. the value after induction of anaesthesia and all succeeding values

sumption and not intra-pulmonary oxygen consumption is the main determinant of the hypermetabolic response after cardiopulmonary bypass. This is evidenced by the fact that both VO_2-gas and VO_2-Fick increased after bypass and intra-pulmonary oxygen consumption did not.

Our results also show that VO_2-gas best quantifies this hypermetabolic response, and not VO_2-Fick, VCO_2 or pulmonary oxygen consumption. There are three different reasons why VO_2-Fick, VCO_2 and intra-pulmonary oxygen consumption do not adequately assess this hypermetabolic response. First, although VO_2-Fick increases after bypass, it underestimates whole body oxygen consumption, due to increased intra-pulmonary oxygen consumption. This intra-pulmonary oxygen consumption, which is excluded in the Fick-method, accounts for about 30% of whole body oxygen consumption before and after bypass. For quantitative reasons therefore, in our study VO_2-Fick is not an adequate measure of the hypermetabolic response after bypass. Secondly, VCO_2 – in contrast with VO_2-gas – does not increase after bypass. This discrepancy between VO_2-gas and VCO_2 indicates that VCO_2 does not reflect metabolism at this moment. VCO_2 increases later, 2 h after the patients' arrival in intensive care. Thus, in our study, due to its delayed increase, VCO_2 is not an adequate method to measure the hypermetabolic response directly after bypass. Thirdly, intra-pulmonary oxygen consumption had already increased before surgery. Although it was high in the first hours after bypass, a bypass-related increase was not observed. For this reason, in our study increased intra-pulmonary oxygen consumption can not be related to the hypermetabolic response induced by cardiopulmonary bypass.

In our patients oxygen consumption increased after bypass, when cellular energy stores are replenished, high levels of inflammatory mediators like elastase and myeloperoxidase [23] can be measured, and oxygen derived free radicals are formed [24, 25]. Our study does not show which of these factors is responsible for this hypermetabolic response. It is unlikely that the early increase in VO_2-gas is caused by a tumor necrosis factor-related inflammatory response, since our patients received dexamethasone. In a previous study [4], we showed that prophylactic use of dexamethasone completely prevented the release of tumor necrosis factor after bypass, and consequently postoperative fever, hypotension and fluid retention.

In contrast with Chiara et al. [12] we did not measure a peak oxygen consumption three hours postoperatively in the period of rewarming. This discrepancy might be attributed to the standard use of nitroglycerine in our patients, resulting in a more homogenous rewarming at the end of bypass. This difference can further be attributed to our strategy of external warming up in the intensive care. However, probably the most important factor for this discrepancy is the prophylactic use of dexamethasone to prevent the tumor necrosis-related inflammatory response.

The importance of this study could be the demonstration of an early increase in oxygen consumption directly after bypass. This increase can only be measured with VO_2-gas. Although other investigators compared different methods of determining oxygen consumption after cardiopulmonary bypass, we are not aware of a study comparing the time-pattern of the three methods used in this study. Our results show that continuous measurement of VO_2-gas provides the possibility to detect and treat a hypermetabolic response directly after bypass in an early phase. In addition, monitoring VO_2-gas offers the possibility to evaluate in future studies technical and therapeutic improvements, which are necessary to reduce organ damage and make patients' outcome better specifically after prolonged bypass.

An rather unexpected finding was the very low RER after bypass. This low RER is caused by the fact that the increase in oxygen consumption after bypass was initially not accompanied by an increase in carbon dioxide excretion. After careful exclusion of measurement errors, a lack of steady state seems to be the most likely explanation for this delayed increase in carbon dioxide-excretion.

In the unsteady state of rewarming and changing ventilation, oxygen and carbon dioxide behave differently [26]. Oxygen consumption as measured corresponds with the rate of aerobic metabolism, since the oxygen store of the body is small (1 l). However, carbon dioxide excretion reflects the metabolic production of CO_2 in steady state conditions only. After alterations in ventilation, temperature, pressure and humidity, the body CO_2-stores will change. The time required for equalization of metabolic CO_2 production and CO_2 excretion may vary from 30 up to 120 min [27]. The observed delay in VCO_2 increase in our patients could therefore indicate CO_2 retention to compensate for acid-base changes like CO_2 depletion, generated during bypass.

Another explanation for the low RER after bypass might be an increased metabolism consuming oxygen without carbon dioxide production. Several metabolic processes, such as formation of oxygen-derived free radicals [11, 24, 25], oxygenase reactions, and loss of oxygen utilization efficiency of the postischemic heart [28] occur during reperfusion. Since these reactions consume oxygen without producing carbon dioxide, their presence can therefore be another explanation for the temporary low CO_2 excretion and RER after bypass.

A second unexpected finding in our study was the high intra-pulmonary oxygen consumption before surgery. At this moment patients were anaesthetized, mechanically ventilated with 40% oxygen, and a pulmonary artery catheter was inserted. Increased intra-pulmonary oxygen consumption was a time-related finding in our patients, since it was at normal levels at eight and eighteen hours after operation. At that time temperature and circulation were generally stable, patients were arousable and pressure support ventilation was started. Although, increased intra-pulmonary oxygen consumption is observed by others [15, 18, 19], its mechanism remains uncertain. High oxygen extraction by metabolically active cells in the lung involved in inflammation was suggested [15, 18]. However, a relation with any aspect of the patients' pulmonary pathology [19] or ventilation/perfusion indices [29] was not found. Likewise, we could not find a relation between increased intra-pulmonary oxygen consumption and cardiopulmonary bypass. Since we observed a high intra-pulmonary oxygen consumption before and after bypass, and physiological values 8 h after operation, our data suggest a relation with anaesthesia and controlled mechanical ventilation. This time-related decline in intra-pulmonary oxygen consumption excludes a systematic measurement error between VO_2-gas and VO_2-Fick, and indicates a pathophysiological explanation for the difference.

In conclusion, our results show that whole body oxygen consumption and not intra-pulmonary consumption is the main denominator of the hypermetabolic response after cardiopulmonary bypass. Increased intra-pulmonary oxygen consumption is not related to bypass. Our results also show that VO_2-gas best quantifies this hypermetabolic response directly after bypass. The reason is that VO_2-Fick excludes intra-pulmonary oxygen consumption and VCO_2 does not reflect metabolism directly after bypass. The importance of this study might be the observation, that continuous measurement of VO_2-gas opens up the possibility of early detection and treatment of this hypermetabolic response directly after cardiopulmonary bypass, while measurement of VCO_2 or VO_2-Fick do not. Furthermore, in future evaluations of technical and therapeutic improvements VO_2-gas can be used as a quantitative indicator of the hypermetabolic response after bypass.

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