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# Analysis of $P_{50}$ and oxygen transport in patients after cardiac surgery

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**Abstract** *Objective*: To determine whether standard $P_{50}$ after cardiac surgery decreases and whether decreased $P_{50}$ is related to the transfusion of red blood cells (RBCs), acid-base changes, body temperature, oxygen parameters and/or duration of cardiopulmonary bypass (CPB).
*Design*: Pilot study in cardiac surgery patients.
*Setting*: University hospital.
*Patients*: 12 consecutive elective cardiac surgery patients.
*Interventions*: Blood was taken before surgery, after CPB and in the intensive care unit until 18 h postoperatively. Cardiac output and oxygen consumption were measured. Buffy coat-poor RBCs were transfused, anticoagulated with citrate-phosphate-dextrose buffer and stored in saline-adenine-glucose-mannitol at 4 °C, when haemoglobin was $< 5.6$ mmol·l$^{-1}$.
*Measurements and results*: Standard $P_{50}$ was calculated from measured partial pressure of oxygen and of carbon dioxide, pH and oxygen saturation in mixed venous blood ($SvO_2$) using the Severinghaus formula. Median length of RBC storage was 25 days. Standard $P_{50}$ after surgery was significantly lower than baseline value ($p = 0.0001$). The number of RBC units transfused and duration of CPB were conjointly associated with $P_{50}$ ($R^2 = 0.72$). Patients who received more RBCs consumed more oxygen.
*Conclusion*: Cardiac surgery patients receiving more RBC units have lower standard $P_{50}$ and consume more oxygen. $P_{50}$ decreased more when the CPB took longer. Because a decrease in $P_{50}$ implies a low ratio of mixed venous oxygen tension ($PvO_2$) to $SvO_2$, a shift in $P_{50}$ should be taken into account when using $SvO_2$ as a measure of global oxygen availability. When a direct measurement of $SvO_2$ is not available, $PvO_2$ should be used instead of calculated $SvO_2$.

**Key words** $P_{50}$ · Blood transfusion · Oxygen transport · Oxygen availability · Cardiac surgery

## Introduction

After cardiac surgery, oxygen demands are increased as a result of ischaemia, subsequent reperfusion and a systemic inflammatory response [1, 2]. Concurrently, oxygen delivery ($DO_2$) to tissues may be limited by myocardial depression [3] and regional disturbances in the microcirculation [4] due to vasoconstriction and vascular disease. If $DO_2$ fails to meet the metabolic demands, tissue hypoxia may ensue and this may ultimately lead to organ damage. Tissue hypoxia might be limited by the correction of hypovolaemia and the infusion of inotropic agents or vasodilators [5–7]. Anaemia from blood loss during surgery may be another factor restricting post-operative $DO_2$. Several investigators have shown that the transfu-

sion of red blood cells (RBCs), although correcting anaemia, does not improve oxygen consumption ($VO_2$) [8] and can even be associated with splanchnic ischaemia [9, 10]. This could be the result of poor deformability of the transfused RBCs, leading to disturbances in the microcirculation [10]. This might also result from an increased affinity of stored haemoglobin for oxygen impairing the ability of transfused haemoglobin to release oxygen to the tissues.

The oxygen affinity of haemoglobin is determined by changes in the partial pressure of carbon dioxide ($PCO_2$), the concentration of the hydrogen ion [$H^+$], haemoglobin, temperature, and by the 2,3-diphosphoglycerate (2,3-DPG) and adenosine triphosphate (ATP) concentration in the RBCs [11, 12]. The oxygen affinity of haemoglobin can be expressed in $P_{50}$. Standard $P_{50}$ is the partial pressure of oxygen ($PO_2$) associated with 50% oxygen saturation of haemoglobin (pH 7.4, $PCO_2$ 40 mmHg and temperature 37 °C) [12]. This value is used to quantify the oxygen affinity of haemoglobin under standard conditions. $P_{50}$ in vivo is determined by standard $P_{50}$ and superimposed acute changes of $P_{50}$ due to changes in $H^+$ ion concentration (Bohr effect) and temperature.

To monitor the patients' oxygen status, mixed venous oxygen saturation ($SvO_2$) is generally used, as well as $VO_2$ calculated by the Fick formula. Although the variability of oxyhaemoglobin affinity in intensive care patients is well known, clinicians frequently rely on the value of $SvO_2$ obtained from routine blood gas analysis that calculates $SvO_2$ assuming normal oxyhaemoglobin affinity. When comparing calculated $SvO_2$ with measured $SvO_2$ in patients after cardiac surgery, we observed a clinically significant difference which could be explained by an increased oxyhaemoglobin affinity. We hypothesized that this increased affinity is related to blood transfusion. However, during cardiac surgery, many of the factors influencing oxyhaemoglobin affinity are changing. The aim of this study was to determine whether standard $P_{50}$ after cardiac surgery falls, and whether decreased $P_{50}$ is related to acid-base changes, body temperature, haemoglobin concentration, $DO_2$ and $VO_2$, $SvO_2$, duration of cardiopulmonary bypass (CPB) and/or transfusion of RBCs.

## Methods

### Patients

Twelve consecutive patients (eight men and four women) undergoing elective cardiac surgery in the Hospital of the Free University in Amsterdam were included in the study. Mean age was 63 years (SD 10). Patients undergoing elective cardiac surgery were included when myocardial function was not severely disturbed (end-diastolic pressure <20 mmHg, ejection fraction >40%, or absence of cardiac decompensation in the patients with aortic valve surgery) and other organ functions were normal. Two patients underwent aortic valve replacement, one patient mitral valve replacement and the other patients coronary bypass grafting. The average duration of aortic cross-clamping was 66 min (SD 30) and of cardiopulmonary bypass 104 min (SD 36). The study was approved by the Ethical Committee of the Free University Hospital in Amsterdam. Since 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

Patients were studied in a prospective way. Arterial and mixed venous blood were sampled after induction of anaesthesia before surgery, 30 min after termination of CPB, 30 min, 2 h, 4 h, 8 h and 18 h after the patient's admission to the intensive care unit for measurement of pH, $PCO_2$, $PO_2$, haemoglobin concentration (Hb) and direct measurement of $SvO_2$. Concomitantly, cardiac output and $VO_2$ were measured. Standard $P_{50}$, base excess (BE) and $DO_2$ were calculated from measured variables. The time of transfusion of RBCs was recorded.

Haemodynamic, oxygen, haemoglobin, acid-base and transfusion data were related to $P_{50}$. A fall in $P_{50}$ was observed, and this fall was significantly related to RBC transfusion. It was subsequently investigated whether the level of $VO_2$ after transfusion was related to RBC transfusion. The increase in post-operative $VO_2$ ($\Delta VO_2$) is multifactorial. Others have shown that the increase in $VO_2$ in the first hours after surgery is associated with rewarming [13]. We have shown that $\Delta VO_2$ in the first hours after surgery may be associated with an endotoxin-related inflammatory response [4]. To get around these factors, $VO_2$ was examined after full rewarming and haemodynamic stabilisation and when self-breathing was without effort (late $VO_2$).

### Anaesthesia, CPB and intensive care treatment

Patients were treated according to a standard protocol. After premedication with lorazepam and usual anti-anginal medication, anaesthesia was induced with fentanyl, pancuronium and diazepam and maintained with supplemental doses of these drugs. A pulmonary artery catheter was inserted after induction of anaesthesia and intubation, and all patients received dexamethasone 1 $mg \cdot kg^{-1}$.

CPB was performed with moderate systemic hypothermia (28–30 °C), non-pulsatile flow and cold crystalloid cardioplegia for myocardial protection. The CPB circuit consisted of a membrane oxygenator (Avecor, Plymouth, Minn., USA), a roller pump (Stockert) with an arterial filter and polyvinyl tubing. The circuit was primed with 2000 ml Ringer's lactate, 200 ml human albumin 20%, 100 ml mannitol 20%, 50 ml sodium bicarbonate 8.4% and 5000 IU bovine heparin. During CPB, pH was regulated by means of the α-stat method.

After release of the aortic cross-clamp, nitroglycerin 2 $mg \cdot h^{-1}$ plus dopamine 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ were started. The dopamine and nitroglycerin doses were increased when cardiac index (CI) was lower than 2.0 $l \cdot min^{-1}$. CPB was continued until central body temperature was restored to 36 °C, and patients were externally warmed with a heating mattress until rectal temperature exceeded 36.5 °C and the difference between rectal and toe temperature was less than 5 °C. Patients were on controlled mechanical ventilation at least 8 h post-operatively. Patients were sedated with morphine and diazepam i.v. during the first 8 post-operative hours to relieve pain and stress, prevent shivering and obtain a reliable value of $VO_2$ and cardiac output. Thereafter, when rewarming was complete, and tem-

perature and circulation remained stable, pressure support ventilation was started and continued if self-breathing was not associated with an increase in $VO_2$. Patients were extubated as soon as possible. All patients were discharged from the ICU on the first day after surgery.

### Blood preservation, storage and transfusion

During collection, whole blood was anticoagulated with citrate-phosphate-dextrose and rapidly cooled to ambient temperature [14]. Whole blood was centrifugated within 18 to 24 h after collection, and buffy coat-poor RBCs were stored with saline-adenine-glucose-mannitol at 4 °C. RBCs were transfused to maintain Hb above 4.4 $mmol \cdot l^{-1}$ during CPB and above 5.5 $mmol \cdot l^{-1}$ in the ICU.

### Biochemical measurements

After sampling, measurements of pH, $PO_2$ and $PCO_2$ in arterial and mixed venous blood were performed immediately using a pH/blood gas analyser (Corning 178). Oxygen saturation was measured separately with a co-oximeter (Corning 2500), and Hb was also measured separately (Coulter). Blood for calculation of standard $P_{50}$ was taken from the distal port of the pulmonary artery catheter. In this study, $P_{50}$ refers to standard in vitro $P_{50}$, calculated for the standard conditions of pH 7.4, $PCO_2$ 40 mmHg and temperature 37 °C, using the Severinghaus formula [15, 16] (see Appendix), and not the $P_{50}$ measured under in vivo conditions.

### Clinical methods

#### *Haemodynamic measurements*

Haemodynamic measurements included heart rate, mean arterial blood pressure, central venous pressure, pulmonary artery and pulmonary artery wedge pressure and cardiac output. Cardiac output was measured by the thermodilution method using room temperature injectate with a Tramscope 12 (Marquette, Milwaukee, Wisc., USA). The mean of four measurements with a correct dilution curve was calculated. CI was calculated from cardiac output: CI = cardiac output/total body surface area.

#### *Oxygen consumption*

$VO_2$ was measured continuously during mechanical ventilation by respiratory gas analysis with an open circuit indirect calorimeter (Deltatrac, Datex Instrumentarium, Helsinki, Finland). This calorimeter has been validated previously [17, 18] and has been described in detail [19]. Fractional inspired oxygen ($FIO_2$) was consistently less than 50%, and minute volume and $FIO_2$ remained constant within the 60 min before measurements were taken. Calibrations were made before starting, after transport of the patient and the instrument to the ICU 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. Deltatrac averages $VO_2$ measurements over 1 min, and the mean of at least five values was taken. These values were additionally compared with the continuously printed values to exclude short-term variability. Values of $VO_2$ were adjusted for the total body area ($ml \cdot min^{-1} \cdot m^{-2}$).

For calculated $VO_2$ the Fick formula was used:

$VO_2\text{-Fick} = CO \times \{[(1.39 \times \text{haemoglobin} \times \text{arterial oxygen saturation}) + (0.003 \times PaO_2)] - [(1.39 \times \text{haemoglobin} \times SvO_2) + (0.003 \times PvO_2)]\}$.

#### *Oxygen supply*

Oxygen supply was calculated with the following equations: $DO_2 = CI \times [(1.39 \times \text{haemoglobin (g/dl)} \times \text{arterial oxygen saturation}) + (0.003 \times PaO_2)]$.

#### *Mixed venous oxygen saturation*

$SvO_2$ was directly measured from pulmonary artery blood ($mSvO_2$), and this value was compared with the value calculated from measured pH, $PO_2$ and $PCO_2$ under standard conditions, assuming a normal oxygen affinity for Hb ($cSvO_2$). This value is routinely available from the Corning blood gas analyser.

### Data analysis

Statistical analysis was performed using Statview SE+Graphics computer software (Abacus Concepts). Results are presented as mean (SD), except for the duration of RBC storage, which is presented as median and range, because this variable was not distributed normally. Differences between consecutive measurements were analysed using a one-way analysis of variance (ANOVA) with the Dunnett test for comparison of individual measurements.

To identify the significant determinants of decreased $P_{50}$, forward stepwise regression analysis was done ($F$-to-enter $>4$) using the following variables: pre-operative $P_{50}$, duration of CPB, number of units of RBCs transfused, Hb, pH, BE, body temperature, CI, $VO_2$, $DO_2$ and $SvO_2$.

To investigate whether the level of $VO_2$ after transfusion was significantly related to the transfusion RBCs or $P_{50}$, regression analysis was performed. Other explanatory variables were studied as well: duration of CPB, Hb, pH, BE, body temperature, CI and $DO_2$.

A probability ($p$) level less than 0.05 was considered statistically significant.

## Results

In the 12 patients, a total of 63 $P_{50}$ measurements were performed, providing at least five values per patient. $P_{50}$ after CPB was significantly lower than baseline value with ANOVA for repeated measures ($p = 0.0001$) (Fig. 1). Differences between patients were also significantly different ($p = 0.0001$), indicating that the range of values was wide and that factors other than the surgical intervention affected $P_{50}$. For individual measurements, $P_{50}$ measured 4 h and 8 h after ICU admission was significantly lower than baseline value. The within-patient variability of $P_{50}$ in time ranged from 0.5 to 5.8 mmHg. Post-operative Hb ($p = 0.0001$), BE ($p = 0.03$) and $PvO_2$ ($p = 0.03$) were significantly lower, and post-operative CI ($p = 0.0001$) and $VO_2$ ($p = 0.006$) were significantly high-

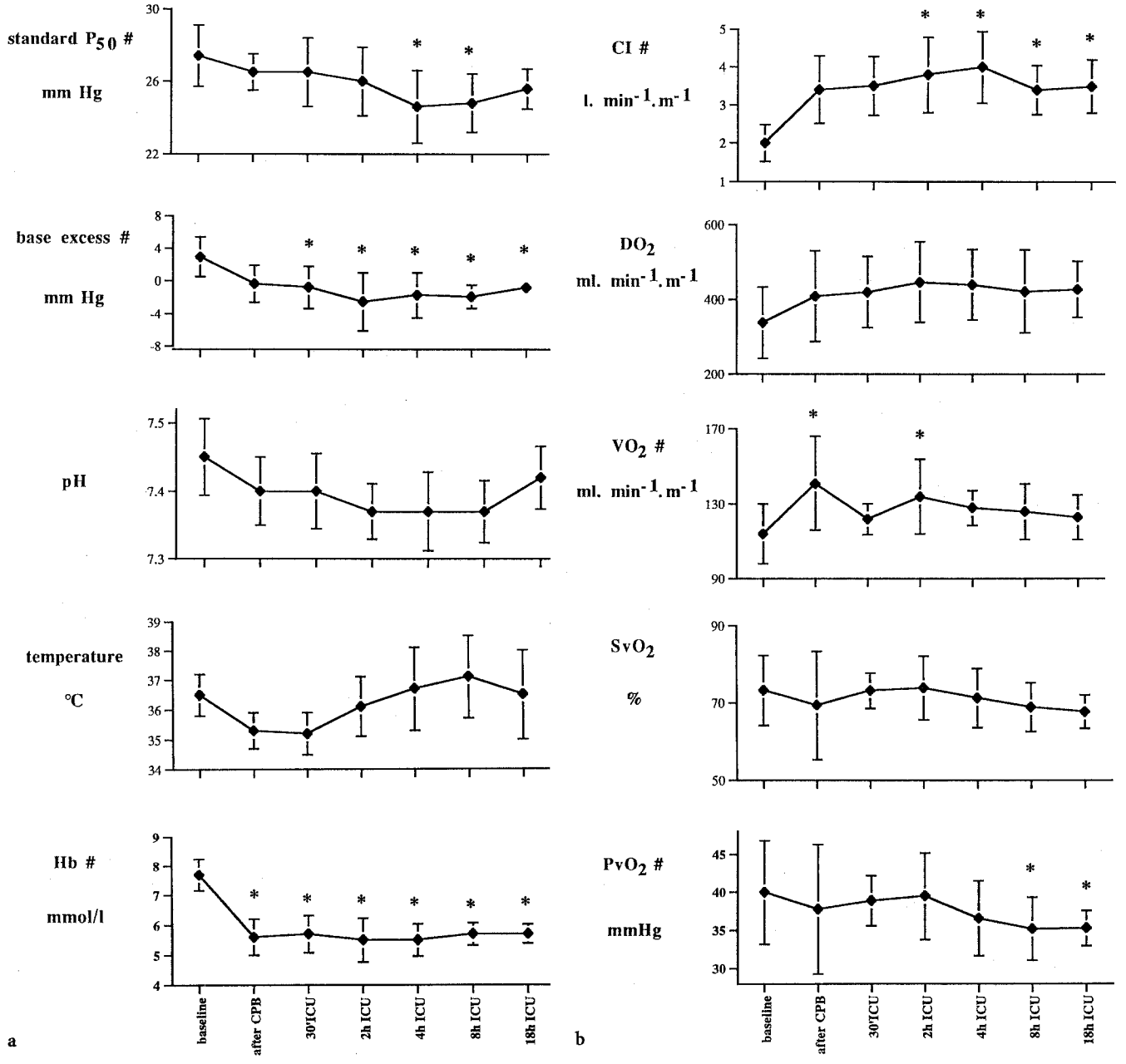


**Fig. 1a, b** Values of standard $P_{50}$, base excess *BE*, pH, haemoglobin *Hb*, cardiac index *CI*, oxygen delivery $DO_2$, oxygen consumption $VO_2$, mixed venous oxygen saturation $SvO_2$ and mixed venous oxygen tension $PvO_2$ are plotted against time. # Repeated measures are significantly different from baseline (ANOVA). * Individual value is significantly different from baseline value (Dunnett test)

er, than baseline value (Fig. 1). Post-operative values of $DO_2$, oxygen extraction, $SvO_2$, pH and central body temperature were not significantly different from pre-operative values. Differences between patients were significant for $DO_2$ ($p = 0.004$), $VO_2$ ($p = 0.049$), $PvO_2$ ($p = 0.0005$) and $SvO_2$ ($p = 0.005$).

In Fig. 2, the number of transfused units of RBCs are plotted against time. Median length of RBC storage was 25 days, ranging from 8 to 31 days.

To identify which of the measured variables might explain decreased $P_{50}$, regression analysis was performed for the $P_{50}$ 4 h after ICU admission, the first of the individual samples that was significantly lower than baseline value. Of all measured variables, the number of RBC units transfused was the only single variable that was significantly associated with $P_{50}$ 4 h after ICU admission (Fig. 3). To identify whether the addition of other variables might explain the variability of post-operative $P_{50}$ better, stepwise regression analysis was performed next.

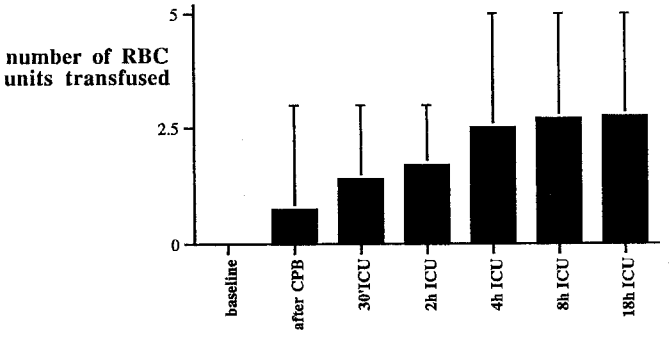


**Fig. 2** The number of units of transfused red blood cells *RBC* is plotted against time

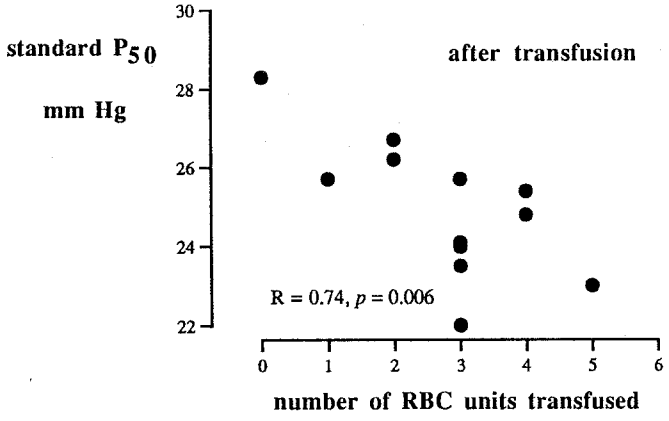


**Fig. 3** Relation between the standard $P_{50}$ after transfusion and the number of units of transfused red blood cells *RBC*. Each patient is represented by a single $P_{50}$ measurement

Since some of the patients received the RBC transfusion later than 4 h after admission, stepwise regression analysis was performed for the $P_{50}$ measured after transfusion of the last RBC unit. Stepwise selection showed that 55% of the variability of this $P_{50}$ could be attributed to the transfusion of RBCs. Adding the duration of CPB increased the predictability of $P_{50}$ after transfusion to 70%. $P_{50}$ decreased by 1 mmHg for each unit of RBCs transfused and for each 40 min of CPB (Table 1). The transfusion of RBCs and the duration of CPB were not significantly interrelated. None of the following variables explained the variability of $P_{50}$ significantly: pH, BE, body temperature, Hb, CI, $VO_2$, $DO_2$, and $SvO_2$ ($F<2$). In vivo pH and BE after transfusion were not related to RBC transfusion.

We further investigated whether $VO_2$ was related to the transfusion of RBC. The increase in post-operative oxygen consumption early after ICU admission was significantly related to the duration of CPB (2 h after

**Table 1** Forward stepwise selection for $P_{50}$ after transfusion (*CPB* cardiopulmonary bypass)

| Independent variable | Coefficient | Standard error | *F*-test |
|---|---|---|---|
| Constant | 30 | | |
| Duration CPB (min) | −0.02 | 0.01 | 5.9 |
| Number of RBC units | −1 | 0.26 | 18 |

$R^2 = 0.72$; *F*-test of the model = 9

ICU admission: $R=0.58$, 4 h after ICU admission $R = 0.0074$), and not to circulatory variables, $DO_2$ or temperature at that time. To eliminate the influence of rewarming and recovery from CPB on $VO_2$, $VO_2$ before extubation (late $VO_2$) was used to analyse the relation between $VO_2$ and RBC transfusion. Regression analysis identified the number of RBC units transfused as the most significant factor explaining late $VO_2$ (Fig. 4). The relation with $P_{50}$ at that time was also significant, but was dependent on the number of RBC units transfused. Late $VO_2$ was not significantly related to the duration of CPB, Hb, pH, BE, body temperature, CI or $DO_2$ ($R<0.2$).

To visualise the implications of a change in $P_{50}$ when using $SvO_2$ or $VO_2$-Fick for clinical monitoring, the difference between the $mSvO_2$ as measured directly and $cSvO_2$ as calculated by the blood gas analyser, assuming a normal oxygen affinity for Hb is plotted against standard $P_{50}$ (Fig. 5). The difference between $VO_2$-Fick using $cSvO_2$ and $VO_2$-Fick using $mSvO_2$ is also plotted against standard $P_{50}$. The bias is greater when standard $P_{50}$ is lower, and rises to 12 mmHg for $SvO_2$ and to 59 $ml \cdot min^{-1} \cdot m^{-2}$ for $VO_2$-Fick in our patients. When $P_{50}$ falls, calculated $SvO_2$ is falsely low, and $VO_2$-Fick using $cSvO_2$ is falsely high.

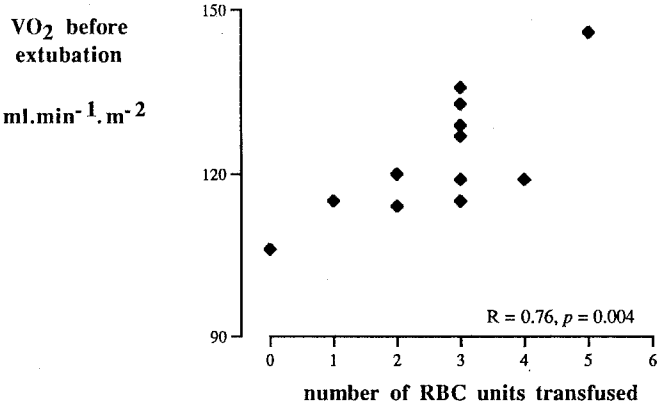


**Fig. 4** Relation between oxygen consumption $VO_2$ measured before extubation after rewarming, stabilisation of circulation, and after transfusion, and the number of units of red blood cell *RBC* transfused

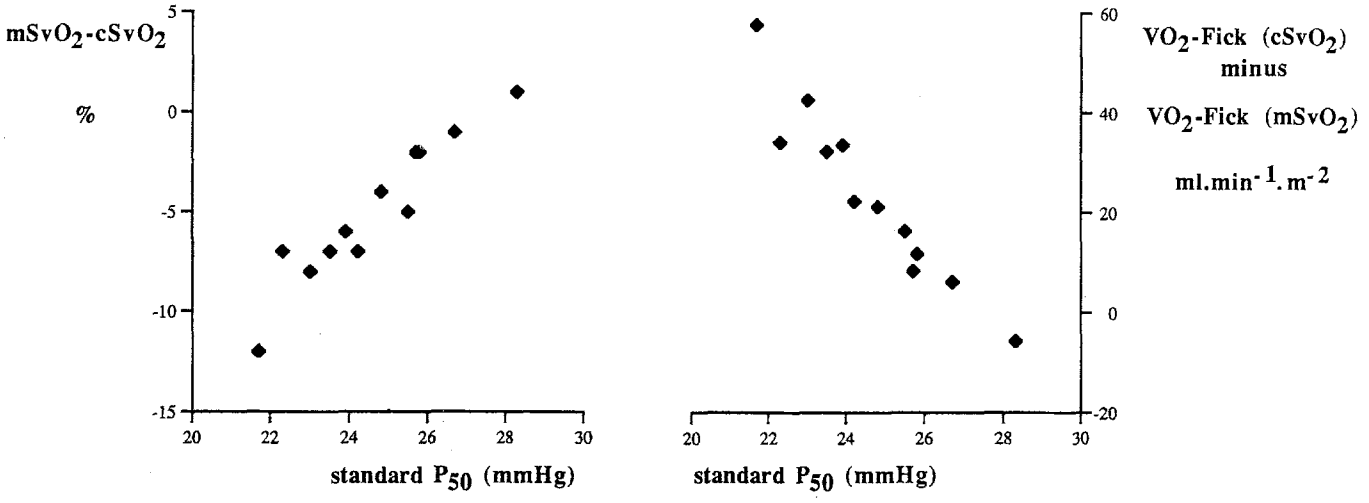


**Fig. 5** Relation between the difference between the $SvO_2$ as measured directly $mSvO_2$ and as calculated from $PaO_2$ assuming a normal oxygen affinity for haemoglobin $cSvO_2$ and standard $P_{50}$, and the relation between the difference between $VO_2$-Fick using $cSvO_2$ and $VO_2$-Fick using $mSvO_2$ and standard $P_{50}$. In these scattergrams, the measurements from 4 h after ICU admission are shown. $P_{50}$ at this time was the first $P_{50}$ after surgery that was significantly lower than baseline

## Discussion

This study shows that standard $P_{50}$ after elective cardiac surgery may decrease. The transfusion of RBCs was the most significant factor explaining decreased $P_{50}$. The transfusion of each unit of RBCs was associated with a fall in $P_{50}$ of 1 mmHg. Transfusion of RBCs restores the oxygen carrying capacity of blood, but not the oxygen releasing capacity in the first hours after transfusion. The decrease in $P_{50}$ after transfusion of RBCs is mainly caused by loss of 2,3-DPG in RBCs during storage. The rate of recovery of 2,3-DPG in the transfused cells in vivo depends upon the quality of the transfused cells and the metabolic condition of the patient, and takes at least 24 h [21].

2,3-DPG diminishes oxygen affinity to haemoglobin, by binding to the $\beta$-chain of one of the four chains of desoxyhaemoglobin to induce a structural change [22]. The concentration of 2,3-DPG depends on the anticoagulant and red cell additive solution used, the length and temperature of storage before component preparation, the method of cooling and the length of time the RBCs are stored at 4 °C [23]. Although the ATP content of the present bank blood is well preserved, the 2,3-DPG content is decreased to half of the initial value after 18 h and to a third 24 h after collection. A further decrease is observed during storage at 4 °C. After two weeks, 2,3-DPG values are too low to be measured [14]. The median length of RBC storage in our patients was 25 days. The longer storage time of the RBCs in our patients may explain the discrepancy between the present results and those of Coetzee and Swanepoel [24]. They used RBCs of less than 3 days old and found that 8 h after CPB the $P_{50}$ returned to baseline values. Apart from the influence of 2,3-DPG on standard $P_{50}$, low $P_{50}$ in stored RBCs can also be caused by the low temperature and the low concentration of anorganic ions such as phosphate in stored blood. The influence of the acidosis on oxygen affinity in stored blood is dual. The pH of the presently used blood falls in vitro to 7.03 after collection, and to 6.50 after 3 weeks' storage [23, 25]. By inhibiting glycolysis, acidosis contributes to low 2,3-DPG levels. On the other hand, low pH increases $P_{50}$ by the Bohr effect, which partially counteracts low standard $P_{50}$ in vitro. Despite acidosis, the net oxyhaemoglobin affinity in blood stored for more that 2 weeks is high. In the present patients, in vivo pH, BE and body temperature were not related to RBC transfusion. Although, in vivo $P_{50}$ was not measured in our patients, $PvO_2$ decreased significantly, while $SvO_2$ did not decrease (Fig. 1), and calculated $SvO_2$ differed significantly from the measured value (Fig. 5). These findings indicate that in vivo $P_{50}$ was low in our patients as well.

Besides the transfusion of RBCs, $P_{50}$ was associated with the duration of CPB. $P_{50}$ was lower after prolonged CPB. A fall in $P_{50}$ after prolonged CPB might be caused by a low ADP/ATP ratio in the circulating RBCs, as reported after CPB [26]. This fall in ADP/ATP ratio is the consequence of ischaemia. ATP and 2,3-DPG compete for the common substrate 1,3-diphosphoglycerate [22, 27]. A fall in $P_{50}$ after prolonged CPB might also be related to a fall in plasma phosphate concentration after CPB [26]. After CPB, the metabolic need for phosphate is high. Phosphate is required for regeneration of 2,3-DPG and cellular ATP stores, and for buffering of

acid. Hypophosphataemia causes low $P_{50}$ by limiting 2,3-DPG production. In addition, phosphate has a direct and rapid effect on the recovery of $P_{50}$ [27].

From the present results it also appears that late $VO_2$ was higher when more RBC units were transfused. Late $VO_2$ was inversely related to $P_{50}$. Although the design of this study and the regression analysis are not meant to imply causation, the relation might be used for hypothesis generation. The level of $VO_2$ in a patient is primarily determined by metabolism but might be limited by oxygen supply. In the present patients, late $VO_2$ was not related to concomitant Hb, CI or global $DO_2$. The higher level of $VO_2$ might therefore be related to increased metabolism. Increased metabolism after cardiac surgery is multifactorial and might be explained by a rise in body temperature [13], physical or emotional stress, wound healing, replenishment of cellular oxygen stores, inflammation [2], or the formation of oxygen-derived free radicals. In the present patients, late $VO_2$, which was measured after full rewarming, was not related to body temperature nor to the duration of CPB, BE or pH. The statistical relation between late $VO_2$ and the number of RBCs transfused might be related to an increased metabolism of the transfused RBC themselves. After 3 weeks' storage, lactate concentration is as high as 27.7 mmol/l and potassium 42.8 mmol/l [14]. Estimating the amount of oxygen needed for the recovery of the RBCs [25] remains speculative. After transfusion, RBCs need oxygen for rewarming to body temperature (about 150 ml $O_2$ per 2 RBCs per °C), for repletion of 2,3-DPG and ATP stores (repletion of 13 µmol 2,3-DPG per g Hb from glucose would cost 115 ml $O_2$ per 2 RBCs, and of 5.88 µmol ATP – if depleted – 390 ml $O_2$), for reconversion of lactate (complete reconversion of 19 mmol per 2 RBCs to glucose would cost 604 l $O_2$; however, an unknown proportion of lactate will be converted to pyruvate and enter the citric acid cycle providing energy), for re-establishment of the Na/K equilibrium, replenishment of cellular protein, glycogen and membrane phospholipids, and for oxygenation to arterial blood (200 ml/2 RBC units). The increased oxygen consumption might also be related to the release of cytokines from transfused leucocytes that increase metabolism [28]. Buffy coat-poor RBCs were used in this study. To what extent these processes will increase $VO_2$ depends on the temperature of the transfused RBCs, the duration of storage, the time of recovery and the white blood cell content. Although no causative relation is shown, from our results it appears that transfusion of RBCs after 25 days' storage is associated with increased $VO_2$ without evidence for a global delivery-limited $VO_2$.

The clinical implications of low $P_{50}$ are related to monitoring of the patients' oxygen state, and to local physiological adaptations which are multifactorial in the critically ill patient and cannot easily be measured directly. When $P_{50}$ falls, the ratio of $PvO_2$ to $SvO_2$ decreases. Since tissue oxygenation is more dependent on capillary oxygen tension than on capillary oxygen content, a change in $P_{50}$ should be considered when using $SvO_2$ for clinical monitoring. When $P_{50}$ falls, as occurs during hypothermia, alkalosis or massive transfusion of stored blood, and measurement of $SvO_2$ is not available, $PvO_2$ should be used for monitoring global oxygen availability to tissues instead of the unreliable $SvO_2$. This has been emphasized by others before [29, 30]. To what extent low $P_{50}$ might impair tissue oxygenation remains speculative. A fall in standard $P_{50}$ requires an adaptive increase in blood flow or capillary recruitment to sustain $DO_2$. Available data indicate that a decrease in $P_{50}$ in otherwise normal animals increases blood flow to the heart and brain at the expense of renal and intestinal flow [31], without evidence for organ dysfunction [32]. However, increased oxyhaemoglobin affinity under conditions of marginal $DO_2$ or diminished adaptive responses, might produce alterations in organ function [29]. Patients with vascular disease or vasoconstriction may be at particular risk, because they lack the ability to increase local tissue perfusion. Conclusions about the effect of a decrease in $P_{50}$ cannot be drawn from this study. The fall in $P_{50}$ in cardiac surgery patients coincides with anaemia, increased oxygen demand and ischaemic myocardial depression. All of these factors may lower $SvO_2$, and some of these are known to elicit a compensatory rise in $P_{50}$ [33, 34]. This compensation will be restricted by low standard $P_{50}$. If, in addition to increased oxyhaemoglobin affinity, the microcirculation is disturbed, the transfer of oxygen to tissues may be hampered substantially in the individual patient. Low $PvO_2$ might warn the clinician in this situation.

Limitation of a fall in $P_{50}$ after cardiac surgery should primarily be obtained by techniques limiting the transfusion of homologous erythrocytes [35–37]. In high risk patients, a fall in $P_{50}$ could be limited by the transfusion of RBCs with a short storage time, or even of 2,3-DPG-enriched blood cells [38]. The correction of hypophosphataemia can increase $P_{50}$ significantly [39, 40]. The increase in oxygen consumption associated with RBC transfusion may be limited by rewarming of the RBCs before transfusion and perhaps by using blood filters that limit the number of leucocytes transfused.

In conclusion, cardiac surgery patients receiving more RBC units (median storage 25 days) have lower standard $P_{50}$ and consume more oxygen. $P_{50}$ decreases more when CPB takes longer. Because a decrease in $P_{50}$ implies a low ratio of $PvO_2$ to $SvO_2$, a shift in $P_{50}$ should be considered when using $SvO_2$ as a measure of global oxygen availability. When direct measurement of $SvO_2$ is not available, $PvO_2$ should be used instead of calculated $SvO_2$.

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## Appendix

*Formula for calculation of $P_{50}$ (Severinghaus):*
$PO_2$, pH, $PCO_2$ are measured at 37 °C. $PO_{2C}$ is $PO_2$ measured at 37 °C corrected to pH 7.4 and $PCO_2$ 40 mmHg. S is oxyhaemoglobin saturation (%). $PO_{2S}$ is $PO_2$ corresponding to measured $SaO_2$ on standard oxygen haemoglobin dissociation curve.

$$P_{50} = 26.6 \times PO_{2C}/PO_{2S} \text{ (mmHg)}$$

when: $PO_{2S} = e^{(x)}$

$$\times = 0385 \times \ln(1/S - 1)^{-1} + 3.32 - (72 \times S)^{-1} - (S^6/6)$$

$$PO_{2C} = PO_2 \times 10^{0.48 \times (pH - 7.4) + 0.06 \times (\log 40 - \log PCO_2)}$$