The Influence of Allogeneic Red Blood Cell Transfusion Compared with 100% Oxygen Ventilation on Systemic Oxygen Transport and Skeletal Muscle Oxygen Tension After Cardiac Surgery

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In this study we investigated the effects of allogeneic red blood cell (RBC) transfusion on tissue oxygenation compared with those of 100% oxygen ventilation by using systemic oxygen transport variables and skeletal muscle oxygen tension ($P_{ti}O_2$). Fifty-one volume-resuscitated, mechanically ventilated patients with a nadir hemoglobin concentration in the range from 7.5 to 8.5 g/dL after elective coronary artery bypass grafting were allocated randomly to receive 1 unit (transfusion 1; $n = 17$) or 2 units (transfusion 2; $n = 17$) of allogeneic RBCs and ventilation with 40% oxygen or pure oxygen ventilation (100% oxygen; $n = 17$) and no allogeneic blood for 3 hours. Invasive arterial and pulmonary artery pressures and calculations of oxygen delivery (oxygen delivery index) and consumption indices (oxygen consumption index) were documented at 30-min intervals. $P_{ti}O_2$ was measured continuously by using implantable polarographic microprobes. Systemic oxygen transport variables and $P_{ti}O_2$ were similar between groups at baseline. The oxygen delivery index increased significantly with transfusion of allogeneic RBCs and 100% oxygen ventilation, whereas the oxygen consumption index remained unchanged. Oxygen 100% ventilation increased $P_{ti}O_2$ significantly (from 24.0 ± 5.1 mm Hg to 34.2 ± 6.2 mm Hg), whereas no change was found after transfusion of allogeneic RBCs. Peak $P_{ti}O_2$ values were 25.2 ± 5.2 mm Hg and 26.3 ± 6.5 mm Hg in the transfusion 1 and 2 groups, respectively. Transfusion of stored allogeneic RBCs was effective only in improving systemic oxygen delivery index, whereas 100% oxygen ventilation improved systemic oxygen transport and $P_{ti}O_2$. This improved oxygenation status was most likely due to an increase in convective oxygen transport with a large driving gradient for diffusion of plasma-dissolved oxygen into the tissue.

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Perioperative anemia in patients undergoing cardiovascular surgery may increase the risk of cardiac-related morbidity, mortality, and functional impairment through inadequate oxygenation of tissues (1–3). For this reason, cardiac surgery has historically been associated with a high probability of allogeneic red blood cell (RBC) transfusion (4,5).

Correcting or improving deficient oxygen delivery (Do_2) by increasing the oxygen-carrying capacity of circulating blood is believed to be the major indication for allogeneic RBC transfusion (6). This approach assumes that an increase in hemoglobin (Hb) concentration with RBC transfusion will increase the oxygen content of blood and, thus, systemic Do_2. Through this increase, regional Do_2 should also increase, resulting in improved oxygen availability to tissues and organ function (6). However, the beneficial effects of RBC transfusion on tissue oxygenation have not been demonstrated convincingly (7–10). In fact, there is a growing body of evidence that RBCs stored for prolonged periods may not be effective oxygen carriers and may even compromise oxygenation of tissues and organ function (9,10).

Instead of RBC transfusion, ventilation with high inspiratory fractions of oxygen may increase the oxygen content of blood by increasing the amount of physically dissolved oxygen in the plasma compartment (11,12). This plasma-dissolved oxygen is highly

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diffusible and therefore preferentially used for tissue oxygenation (11,12). For this reason, 100% oxygen ventilation has emerged as a simple and effective intervention to increase oxygen tension in tissues and may be used to compensate for the decreased oxygen-carrying capacity during isovolemic anemia (11–13).

This study was designed to assess the oxygenation status of moderately anemic cardiac surgery patients after transfusion of 1 or 2 units of allogeneic RBCs by evaluating systemic oxygen transport variables and skeletal oxygen tension ($P_{ti}o_2$). We further tested the hypothesis that increasing oxygen-carrying capacity by 100% oxygen ventilation would be equally effective or even superior to RBC transfusion in improving tissue oxygenation in the immediate postoperative period.

Methods

After approval by the local human ethics committee and after written, informed consent was obtained, 51 patients scheduled for elective primary coronary artery bypass grafting (CABG) with use of cardiopulmonary bypass (CPB) were enrolled in this randomized, prospective, open-label trial. Exclusion criteria consisted of recent (<6 wk) myocardial infarction, unstable angina, severe (>70%) left main coronary artery stenosis, severe alteration of left ventricular function (ejection fraction <30%), significant carotid artery stenosis (>70% or symptomatic), combined coronary and valvular surgery, chronic obstructive pulmonary disease necessitating bronchodilator therapy, severe respiratory insufficiency (arterial oxygen tension <60 mm Hg when breathing room air), liver dysfunction (alanine aminotransferase or aspartate aminotransferase >40 U/L), renal insufficiency (creatinine >2.0 mg/dL), uncontrolled diabetes mellitus (fasting blood glucose concentrations>140 mg/dL despite treatment with oral hypoglycemic drugs and/or insulin), preoperative anemia (Hb concentration <12 g/dL), and abnormal blood coagulation tests (activated partial thromboplastin time >40 s, international normalized ratio >1.25, fibrinogen concentration <1 g/L, or platelet count $<150 \cdot 10^9$/L). Patients were not excluded on the basis of advanced chronological age.

After cardiac surgery, mechanically ventilated and volume-resuscitated patients who had a nadir Hb concentration in the range from 7.5 to 8.5 g/dL within 3 h after arrival at the intensive care unit (ICU) were randomly assigned to 1 of 3 groups by using a closed envelope system. Patients in Group 1 (transfusion 1; $n = 17$) and 2 (transfusion 2; $n = 17$) received infusions of 1 and 2 units of allogeneic RBCs (each given over 30 min) and were mechanically ventilated with an inspired fraction of oxygen (F_{IO_2}) of 0.4, whereas Group 3 patients (100 oxygen; $n = 17$) received ventilation with 100% oxygen over 3 h and no allogeneic RBCs. In the case of hypovolemia with hemodynamic instability, patients in all groups were treated with additional intravascular volume (4% modified gelatin; Gelafundin™; B. Braun, Melsungen, Germany) to maintain pulmonary wedge pressure (PWP) between 10 and 14 mm Hg. Lactated Ringer's solution (B. Braun) was administered to compensate for fluid loss by sweating, gastric tubes, and urine output or as a solvent for drugs (e.g., antibiotics) at 3–5 $mL \cdot kg^{-1} \cdot h^{-1}$ in all patients. Inadequate cardiac output (cardiac index [CI] <2.0 $L \cdot min^{-1} \cdot m^{-2}$ and mean arterial blood pressure [MAP] <60 mm Hg despite sufficient volume infusion) was treated with epinephrine. Norepinephrine was given when systemic vascular resistance was <700 $dynes \cdot s^{-1} \cdot cm^{-5}$ and MAP was <60 mm Hg. If excessive acute blood loss occurred in any group (defined as chest tube drainage >200 mL/h for two consecutive hours) or Hb decreased to less than 7 g/dL, transfusion of 1 unit of allogeneic RBCs was mandated. Fresh frozen plasma and platelet concentrates were transfused for correction of microvascular bleeding in the presence of abnormal blood coagulation values (activated partial thromboplastin time >1.5 times normal, international normalized ratio >1.5, fibrinogen concentration <1 g/L, and platelet count $<50 \times 10^9$/L). Patients received (leukocyte-depleted, buffy coat-free) saline-adenine-glucose-mannitol RBCs (German Red Cross Bloodbank, Hagen, Germany; 320 ± 20 mL/unit; hematocrit 60% ± 5%). RBC units were stored at 4°C for <14 days according to a standardized transfusion protocol of our hospital. After the study period, all patients received blood products according to the guidelines of the American Society of Anesthesiologists (6).

Surgery was performed in a single surgical unit with a standard operative technique. Anesthesia was induced and maintained according to the patient's need, by using weight-related dosages of midazolam (0.07 mg/kg), sufentanil (1.5 μg/kg), and pancuronium (0.1 mg/kg). After intubation of the trachea, the lungs were ventilated with 50% oxygen in air. Ventilation was controlled with a tidal volume of 8–10 mL/kg and a positive end-expiratory pressure of 5 mm Hg. The ventilatory rate was adjusted to maintain an arterial partial pressure of carbon dioxide ($Paco_2$) of 32 to 42 mm Hg and arterial pH between 7.35 and 7.45. CPB was performed with a Sarns 9000 CPB machine (Sarns Inc., Ann Arbor, MI) and a hollow-fiber membrane oxygenator (Cobe Optima XP™; Cobe Laboratories, Planegg-Martinsried, Germany). In all patients, the circuit was primed with 1000 mL of lactated Ringer's solution and 500 mL of gelatin (4% modified gelatin; Gelafundin). Temperature was kept at mild hypothermia (bladder temperature >33°C), and a CPB flow rate of 2.4 $L \cdot min^{-1} \cdot m^{-2}$ was used. Packed RBCs (PRBCs) were added when the hematocrit was <20%. During weaning off bypass, as much pump blood as necessary to

maintain PWP between 10 and 14 mm Hg was infused. The residual blood remaining in the CPB circuit was processed through a cell-saving device and retransfused after sternal closure. All patients were admitted to the ICU, and controlled mechanical ventilation was continued during the following 6 h at minimum. After the patients showed stable systemic hemodynamics (MAP >70 mm Hg, CI >2.0 $L \cdot min^{-1} \cdot m^{-2}$, and PWP between 10 and 14 mm Hg) for 30 min, the study protocol was begun as previously described. In the ICU, mechanical ventilation was maintained with a tidal volume of 8–10 mL/kg, a respiratory frequency of 10–14 breaths/min, a positive end-expiratory pressure of 5 mm Hg, and the designated F_{IO_2}. After the study period, tracheal extubation was performed when systemic hemodynamics remained stable for 30 min, body temperature was >36°C, and the patients breathed spontaneously with adequate blood gas variables (P_{aCO_2} <42 mm Hg and P_{aO_2} >75 mm Hg at an F_{IO_2} <0.35). Physicians directly caring for the patients were aware of the group allocation, but they took no part in subsequent data collection and analysis.

Patients were monitored in the ICU until the first postoperative day. Perioperative monitoring included pulse oximetry, continuous monitoring of leads II and V_5 of the electrocardiogram, automated ST segment analysis, continuous invasive measurement of MAP, and central venous pressure. Body temperature was continuously monitored by the thermistor of a pulmonary artery catheter. Each cardiac output was determined at least in triplicate by the thermodilution technique by using 10 mL of cold saline (<10°C). Derived hemodynamic data (CI and systemic vascular resistance index) and oxygen transport data (D_{O_2} index and oxygen consumption [$\dot{V}_{O_2}$] index) were calculated with standard formulas (Appendix 1) (14). A Licox CMP™ system (Integra NeuroSciences Ltd., Andover Hampshire, UK), a digital bedside monitor that displays tissue oxygen tension values directly, together with a graphical trend, and flexible minimally invasive microsensoric catheters (Revoxode™; Integra NeuroSciences Ltd.) were used for continuous assessment of tissue oxygenation. The Revoxode consists of a closed polarographic cell that is precalibrated at the time of manufacture and supplied with individual calibration data electronically stored on a "smart card." The $P_{ti}O_2$ is determined at the tip of the probe in a cylindrical tissue layer located concentrically along the axis of the microcatheter. Revoxode probes average the heterogeneous local tissue oxygen tension values over their probe area of 14 mm^2, which eliminates random positioning error of microprobe sensors. Oxygen diffuses from the tissue through the polyethylene wall of the catheter into its inner electrolyte chamber, where the Revoxode enables reversible electrolyte reactions to occur at the Clark electrode. This property of the Revoxode preserves sensitivity and offset within a narrow range (5%) over a 5-day period of operation (15). The P_{O_2}-sensitive area of the precalibrated catheter was inserted approximately 25 mm into the deltoid muscle via a 20-gauge guiding cannula (Vasofix™; B. Braun). To avoid tissue damage or compression of capillaries, which might influence the $P_{ti}O_2$ measurement, the guiding cannula was retracted by approximately 10 mm. For correction of the $P_{ti}O_2$ data, the temperature within the deltoid muscle was measured simultaneously with a second probe (CC-10; Integra NeuroSciences Ltd.) implanted alongside the tissue oxygen sensor. Both tissue oxygen and temperature sensors interface with a laptop computer, allowing data to be recorded on a continuous basis and stored electronically. This technique and equipment are well established for the measurement of tissue oxygen tensions (16,17). Arterial and mixed venous blood samples were analyzed in an automatic multiwavelength blood gas tension analyzer (Rapidlab™ 860; Bayer HealthCare, Leverkusen, Germany) in 30-min intervals for Hb, arterial and mixed venous oxygen saturation, P_{aO_2}, venous partial pressure of oxygen (P_{vO_2}), P_{aCO_2}, pH, and lactate concentrations. Hemodynamics, $P_{ti}O_2$ values, systemic oxygen transport, and blood gas variables are reported at a nadir Hb in the range of 7.5 to 8.5 g/dL before any intervention (baseline) and at 30, 60, 90, 120, and 180 min after increasing the F_{IO_2} to 1.0. In Group 1 and 2 patients, time points 30 and 60 min denote the completion of infusion of 1 and 2 units, respectively, of allogeneic RBCs. In addition, plasma concentrations of cardiac troponin T (by using a commercial monoclonal-monoclonal double antibody and one-step sandwich enzyme immunoassay; Boehringer Mannheim, Germany; normal value, <0.1 μg/L) were measured as a marker of myocyte necrosis at baseline and 60 and 180 min thereafter.

Primary outcome measures were $P_{ti}O_2$ and systemic oxygen transport variables in response to either RBC transfusion or 100% oxygen ventilation. The number of patients to be studied was determined with a power analysis according to data from a previous experimental study on the effects of 100% oxygen ventilation on tissue oxygenation (11). In this study, switching ventilation from 21% oxygen to 100% oxygen improved organ oxygen tensions and provided an amount of oxygen equivalent to augmenting Hb by approximately 1.5 g/dL, which is clinically significant because this corresponds to transfusion of 1 unit of PRBCs in a 70-kg patient (11). Using the SD of $P_{ti}O_2$ and assuming that the administration of oxygen is at least as effective as transfusion of erythrocytes in increasing tissue D_{O_2}, we calculated that 17 patients needed to be enrolled in each group to obtain an 80% chance of detecting such an effect at the $P < 0.05$ level of significance.

All data are presented as mean ± SD unless otherwise stated. The MedCalc 4.30 (MedCalc Software,

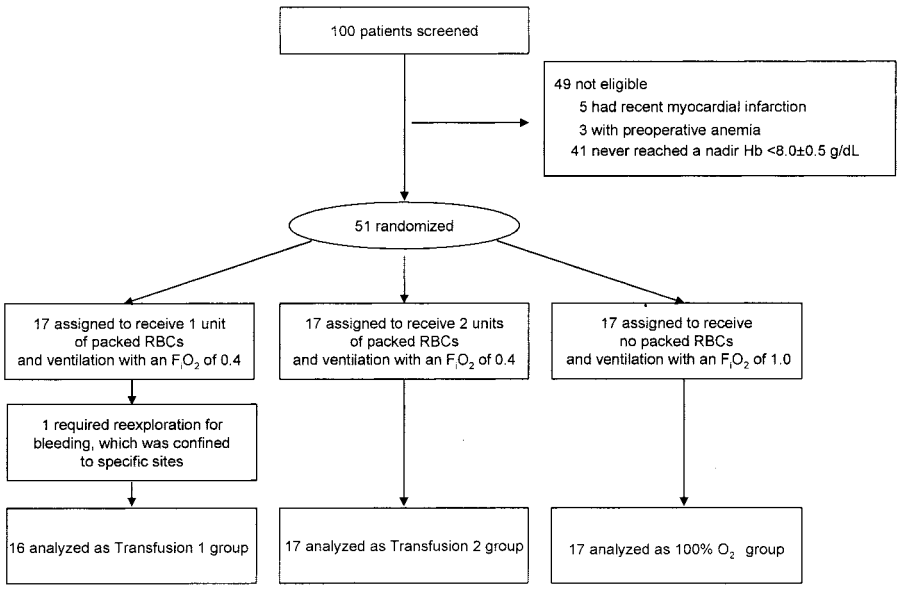

Figure 1. Participant flow diagram. Hb = hemoglobin concentration; RBC = red blood cell; F_{IO_2} = inspired fraction of oxygen.

Table 1. Patient Demographics and Data from the Perioperative Period

Variable	Transfusion 1 (n = 16)	Transfusion 2 (n = 17)	100% Oxygen (n = 17)
Age (yr)	66 (7) [46–75]	68 (8) [48–80]	66 (8) [48–85]
Sex (male/female)	10/6	12/5	11/6
Weight (kg)	78 (12)	77 (15)	75 (13)
Body-surface area (m^2)	1.89 (0.2)	1.86 (0.21)	1.85 (0.19)
Preoperative medication (n)			
ACEI	7	9	9
β-Blockers	13	12	13
Nitroglycerine	9	11	12
Diuretics	4	4	5
Calcium channel blockers	7	9	8
Preoperative LVEF (%)	61 (10)	60 (12)	63 (8)
Duration of			
Anesthesia (min)	185 (40)	177 (35)	182 (42)
Surgery (min)	150 (35)	155 (39)	146 (31)
CPB (min)	72 (9)	77 (11)	71 (9)
Postoperative ventilation (hrs)	8.5 (2.1)	8.2 (1.2)	8.1 (1.1)
No. bypass grafts	2.5 (0.8)	2.6 (0.7)	2.6 (0.8)
Patients receiving IMA grafts (n)	16	17	17
Reoperation for bleeding (n)	1	0	0
No. patients receiving catecholamines (dose range)			
Dobutamine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	4 (2–7)	3 (2–6)	3 (2–7)
Epinephrine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0	1 (0.05–0.15)	1 (0.05–0.15)
Norepinephrine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	4 (0.05–0.1)	3 (0.05–0.1)	4 (0.05–0.15)
Time study began after arrival in ICU (min)	78 (14) [60–150]	83 (16) [62–155]	75 (19) [55–160]
ICU length of stay (d)	2.0 (0.8)	1.5 (0.7)	1.7 (0.7)
Survivors			
Study period	16	17	17
Hospital	16	17	17

ACEI = angiotensin-converting enzyme inhibitor; LVEF = left ventricular ejection fraction; CPB = cardiopulmonary bypass; IMA = internal mammary artery; ICU = intensive care unit. Values are expressed as mean (SD) [range] or number of patients.

Mariakerke, Belgium) software package was used for statistical analyses. The Kolmogorov-Smirnov test was used to check the normality assumption. Continuous variables with a normal distribution were compared by applying Student's t-test, and if not normally distributed, they were compared by using a Wilcoxon test. One-way and two-way analysis of variance with repeated measures and *post hoc* Scheffé tests were used

Table 2 Blood Loss and Perioperative Fluid Management

Variable	Transfusion 1 ($n = 16$)	Transfusion 2 ($n = 17$)	100% Oxygen ($n = 17$)
Intraoperative blood loss (mL)	755 [400–1150]	810 [450–1200]	745 [450–1050]
Chest tube drainage			
0–12 postoperative hours	455 [250–855]	470 [250–920]	460 [190–880]
0–24 postoperative hours	865 [410–1250]	925 [490–1225]	890 [475–1195]
Urinary output (mL)			
Intraoperative	850 (510)	811 (475)	879 (612)
0–12 postoperative hours	1220 (690)	1332 (620)	1378 (722)
0–24 postoperative hours	2551 (742)	2645 (701)	2725 (821)
Volume infusion			
Intraoperative			
Crystalloids (mL)	2545 (611)	2413 (568)	2402 (737)
Colloids (mL)	1020 (453)	1090 (512)	1150 (397)
0–12 postoperative hours			
Crystalloids (mL)	1345 (310)	1410 (375)	1789 (410)*
Colloids (mL)	710 (243)	705 (202)	895 (253)*
0–24 postoperative hours			
Crystalloids (mL)	2990 (725)	3020 (685)	3599 (750)
Colloids (mL)	1550 (382)	1485 (410)	1690 (550)
Median number of allogeneic packed RBCs transfused per patient (units)			
Intraoperative	0 [0–2]	0 [0–2]	0 [0–2]
0–12 postoperative hours	1 [1–3]	2 [2–3]	0 [0–3]*
0–24 postoperative hours	1 [1–3]	2 [2–3]*	1 [0–3]
Perioperative[a]	1 [1–3]	2 [2–3]*	1 [0–3]
Median storage age of transfused RBCs (d)	10 [6–14]	9 [5–14]	10 [6–14]

Values are expressed as median [range], mean (SD), or total.
RBCs = red blood cells.
[a] Includes all allogeneic erythrocyte transfusions from the start of surgery until discharge from the hospital.
[b] Does not include fluids used to prime and added to the extracorporeal circuit during cardiopulmonary bypass.
* $P < 0.05$ compared with other groups.

to determine the effects of group and time and group-time interactions. The χ^2 analysis and Fisher's exact test were used to compare proportions. Pearson's correlation coefficients, simple linear regression analyses, and forward stepwise regression analyses were used to compare associations between continuous variables. Associations between continuous and categorical variables were examined with a Mann-Whitney ranked sum test. Accounting for the 6 time points, a Bonferroni-corrected value of $P < 0.05/6$ was used as the criterion for statistical significance.

Results

One-hundred eligible patients were approached for inclusion in this study. Forty-nine percent of routine elective CABG patients were not randomized because of failure to satisfy our preestablished inclusion/exclusion criteria (Fig. 1). Of 51 patients randomized, data were not collected in 1 patient in the transfusion 1 group because of postoperative surgical lesion bleeding that required reoperation for hemostasis. The enrolled patients were started on their specific treatment within 3 h after arrival in the ICU (Table 1). All patients were comparable with respect to biometric data, preexisting disease, and procedure-related variables (Table 1). None of the patients showed signs of myocyte necrosis, and cardiac troponin T levels were <0.1 μg/L throughout the study period. Intraoperative blood loss, chest tube drainage, and urinary output during the first 24 h after surgery were similar among study groups (Table 2). The amount of crystalloids and colloids received during the first 12 h after surgery was significantly larger in the 100% oxygen group compared with the other two groups. During the hospital stay, patients in the transfusion 2 group received significantly more units of allogeneic PRBCs (37 units) than patients in the two other groups (transfusion 1, 26 units; 100% oxygen, 23 units) (Table 2). Hemodynamic variables did not differ among patients, except for CI, which was significantly higher in the 100% oxygen group (Table 3). Upon onset of 100% oxygen ventilation, Pao_2, Pvo_2, and plasma oxygen content were significantly increased in the 100% oxygen group when compared with the other groups. No changes in lactate concentrations were observed in any group throughout the study period (Table 4). Baseline values of systemic oxygen transport variables and $P_{ti}o_2$ were comparable among the groups (Fig. 2). The Do_2 index increased significantly with transfusion of allogeneic PRBCs and 100% oxygen ventilation (transfusion 1: from 278 ± 41 mL $\cdot$ min^{-1} $\cdot$ m^{-2} to 325 ± 45 mL $\cdot$ min^{-1} $\cdot$ m^{-2}; transfusion 2: from 273 ± 36 mL $\cdot$ min^{-1} $\cdot$ m^{-2} to 353 ± 39 mL $\cdot$ min^{-1} $\cdot$ m^{-2};

Table 3. Hemodynamic Variables

Time	HR (bpm)	MAP (mm Hg)	CVP (mm Hg)	MPAP (mm Hg)	PWP (mm Hg)	CI ($L \cdot min^{-1} \cdot m^{-2}$)	SVRI ($dynes \cdot s^{-1} \cdot cm^{-5} \cdot m^{-2}$)
Baseline							
Transfusion 1	72 (7)	73 (10)	11 (4)	22 (6)	13 (2)	2.4 (0.3)	2116 (321)
Transfusion 2	74 (8)	75 (12)	11 (3)	25 (7)	12 (1)	2.4 (0.2)	1774 (357)
100% oxygen	71 (10)	76 (8)	10 (4)	23 (5)	14 (2)	2.3 (0.3)	1818 (331)
30 min							
Transfusion 1	73 (10)	75 (9)	12 (5)	24 (5)	14 (3)	2.4 (0.2)	1990 (347)
Transfusion 2	73 (7)	72 (11)	11 (5)	22 (7)	13 (2)	2.5 (0.3)	2028 (425)
100% oxygen	75 (9)	77 (11)	12 (4)	26 (3)	14 (1)	2.7 (0.4)*	1713 (259)
60 min							
Transfusion 1	75 (8)	74 (9)	10 (3)	25 (3)	14 (1)	2.4 (0.2)	2276 (331)
Transfusion 2	74 (2)	71 (12)	12 (4)	24 (6)	13 (2)	2.4 (0.4)	2025 (365)
100% oxygen	76 (9)	75 (8)	10 (5)	22 (5)	14 (2)	2.6 (0.4)	1602 (347)
90 min							
Transfusion 1	73 (9)	75 (9)	12 (5)	23 (6)	15 (3)	2.4 (0.1)	2001 (353)
Transfusion 2	76 (8)	71 (10)	13 (5)	19 (4)	14 (1)	2.4 (0.2)	2062 (178)
100% oxygen	75 (11)	76 (12)	11 (3)	25 (7)	15 (2)	2.7 (0.3)*†	1805 (289)
120 min							
Transfusion 1	71 (10)	74 (5)	12 (2)	20 (5)	14 (2)	2.4 (0.2)	2181 (296)
Transfusion 2	75 (6)	75 (11)	13 (3)	21 (3)	14 (0)	2.4 (0.2)	2040 (225)
100% oxygen	77 (11)	76 (9)	12 (5)	23 (4)	13 (3)	2.6 (0.2)*†	1623 (331)
180 min							
Transfusion 1	74 (7)	72 (9)	12 (5)	25 (2)	14 (1)	2.5 (0.3)	1957 (399)
Transfusion 2	73 (9)	73 (8)	13 (3)	22 (6)	13 (1)	2.4 (0.3)	2114 (269)
100% oxygen	79 (12)	75 (11)	12 (2)	24 (2)	14 (2)	2.7 (0.4)*	1755 (237)

HR = heart rate; MAP = mean arterial blood pressure; CVP = central venous pressure; MPAP = mean pulmonary artery pressure; CI = cardiac index; PWP = pulmonary wedge pressure; SVRI = systemic vascular resistance index.

Values are reported at a nadir hemoglobin concentration in the range from 7.5 to 8.5 g/dL (baseline) at 30, 60, 120, and 180 min after increasing the inspired fraction of oxygen to 1.0. Time points 30 and 60 min denote the completion of infusion of 1 and 2 units of packed erythrocytes in the transfusion groups, respectively.

* $P < 0.05/6$ (Bonferroni corrected): significantly different from baseline.

† $P < 0.05/6$ (Bonferroni corrected) compared with the other groups.

100% oxygen: from 267 ± 33 $mL \cdot min^{-1} \cdot m^{-2}$ to 332 ± 39 $mL \cdot min^{-1} \cdot m^{-2}$), whereas the $\dot{V}o_2$ index remained unchanged (Fig. 2). Oxygen 100% ventilation increased $P_{ti}o_2$ significantly (from 24.0 ± 5.1 mm Hg to 34.2 ± 6.2 mm Hg). No significant change in $P_{ti}o_2$ was found after transfusion of allogeneic blood (transfusion 1: from 25.2 ± 5.2 mm Hg to 24.4 ± 3.9 mm Hg; transfusion 2: from 22.7 ± 6.1 mm Hg to 26.3 ± 6.5 mm Hg) (Fig. 2). Routine chest radiographs after exposure to 100% oxygen did not show any evidence of clinically relevant pulmonary atelectasis or injury. No significant correlations were found between systemic and regional oxygen kinetics and transfusion-related variables.

Discussion

In this study, we used direct and indirect techniques to assess oxygen kinetics of moderately anemic cardiac surgery patients in response to either RBC transfusion or 100% oxygen ventilation. Transfusion of stored allogeneic blood was effective only in improving systemic Do_2, whereas 100% oxygen ventilation improved systemic oxygenation and $P_{ti}o_2$. One possible explanation for the improvement of systemic oxygenation by 100% oxygen ventilation is that oxygen in plasma is carried by direct solubility and the contribution to total blood oxygen content is directly proportional to Pao_2. In our patients breathing 100% oxygen, approximately 13% of systemic Do_2 and 38% of systemic $\dot{V}o_2$ was due to physically dissolved oxygen. Similar results were reported by Habler et al. (11), who evaluated systemic oxygenation status in anesthetized dogs undergoing normovolemic hemodilution while breathing 100% oxygen. They found that at an Hb concentration of 7.0 g/dL, almost 15% of Do_2 and 47% of $\dot{V}o_2$ was due to physically dissolved oxygen. Circulatory adaptations to dilutional anemia, such as a compensatory increase of cardiac output, might further explain the increase in systemic Do_2 that was observed in our patients who received 100% oxygen ventilation. The increase in cardiac output might be related to a reduction in blood viscosity resulting in increased venous return and decreased ventricular afterload, as well as an increased sympathetic stimulation of the heart (18–20).

The significantly larger amount of intravascular volume (colloids and crystalloids) received during the first 12 hours after surgery might be another contributing factor for the higher cardiac output observed in those patients placed on 100% oxygen. It should be noted, however, that the physiologic adjustments to a

Table 4. Blood Gas Variables

Time	Hb (g/dL)	Pao_2 (Hg)	$Paco_2$ (Hg)	Pvo_2 (Hg)	BE	Cao_2 (mL/dL)	Hb-O_2 (mL/dL)	Plasma O_2 (mL/dL)	Lactate (mmol/L)
Baseline									
Transfusion 1	8.2 (0.3)	137 (28)	34.7 (1.2)	40.1 (2.2)	1.2 (0.5)	11.7 (1.4)	11.0 (0.4)	0.4 (0.05)	1.2 (0.8)
Transfusion 2	8.1 (0.3)	141 (27)	35.2 (1.5)	41.3 (2.1)	0.6 (0.9)	11.4 (1.1)	11.0 (0.4)	0.4 (0.03)	1.0 (0.6)
100% oxygen	8.2 (0.2)	143 (21)	34.6 (1.2)	41.5 (1.4)	1.0 (1.2)	11.6 (1.1)	11.1 (0.5)	0.4 (0.03)	0.9 (0.9)
30 min									
Transfusion 1	9.3 (0.4)*	142 (30)	34.5 (1.3)	41.3 (2.2)	1.2 (0.8)	13.1 (1.1)*	12.7 (0.5)*	0.4 (0.01)	1.3 (0.4)
Transfusion 2	9.1 (0.4)*	129 (21)	35.5 (1.4)	42.2 (3.2)	0.4 (0.9)	13.0 (1.2)*	12.7 (0.6)*	0.4 (0.02)	1.1 (0.8)
100% oxygen	8.0 (0.4)	512 (45)*†	35.1 (1.6)	43.5 (1.6)*	1.1 (0.6)	12.6 (0.8)*	11.1 (0.5)*	1.6 (0.01)*†	1.3 (0.7)
60 min									
Transfusion 1	9.2 (0.5)*	142 (30)	34.8 (2.2)	40.4 (2.5)	0.3 (0.6)	12.9 (1.3)	12.4 (0.4)*	0.4 (0.02)	0.9 (0.6)
Transfusion 2	10.2 (0.5)*†	135 (25)	35.3 (2.1)	42.2 (2.0)	0.3 (0.7)	14.2 (1.3)*†	13.8 (0.6)*	0.4 (0.01)	1.0 (0.5)
100% oxygen	8.1 (0.4)	499 (37)*†	35.2 (2.4)	44.1 (2.3)*	1.0 (0.6)	12.7 (0.9)	11.2 (0.5)†	1.5 (0.01)*†	0.9 (0.2)
90 min									
Transfusion 1	9.1 (0.3)*	140 (21)	34.9 (2.0)	42.0 (2.2)	1.1 (0.7)	12.8 (0.9)	12.2 (0.6)*	0.4 (0.01)	1.0 (0.6)
Transfusion 2	10.1 (0.7)*†	141 (19)	34.5 (2.1)	42.2 (2.4)	0.5 (0.8)	14.0 (1.5)*†	13.7 (0.4)*	0.4 (0.02)	1.1 (0.3)
100% oxygen	7.9 (0.2)	497 (56)*†	34.9 (2.6)	44.4 (3.1)*	1.1 (0.9)	12.6 (0.9)*	10.9 (0.3)†	1.5 (0.01)*†	1.2 (0.5)
120 min									
Transfusion 1	9.0 (0.4)*	137 (22)	35.0 (1.3)	41.3 (2.4)	1.1 (0.6)	12.7 (1.1)	12.1 (0.4)*	0.4 (0.01)	1.2 (0.6)
Transfusion 2	9.9 (0.6)*†	131 (17)	35.3 (2.1)	42.2 (2.5)	0.7 (0.7)	13.9 (1.3)*†	13.4 (0.4)*	0.4 (0.02)	1.0 (0.7)
100% oxygen	8.0 (0.4)	522 (49)*†	34.9 (1.9)	45.1 (2.2)*†	1.3 (0.7)	12.7 (0.8)*	11.0 (0.3)†	1.6 (0.01)*†	1.2 (0.7)
180 min									
Transfusion 1	8.9 (0.4)	129 (17)	35.0 (2.2)	40.8 (2.4)	1.0 (0.3)	12.5 (0.9)	12.0 (0.3)*	0.4 (0.01)	1.2 (0.6)
Transfusion 2	9.8 (0.5)*†	138 (30)	35.9 (1.9)	42.1 (2.3)	0.8 (0.5)	13.7 (1.2)*†	13.3 (0.3)*	0.4 (0.01)	1.1 (0.5)
100% oxygen	7.9 (0.4)	517 (65)*†	36.4 (2.7)	44.3 (3.1)*	0.9 (0.6)	12.6 (0.9)*	10.9 (0.3)†	1.6 (0.01)*†	0.9 (0.7)

Hb = hemoglobin concentration; Pao_2 and $Paco_2$ = arterial partial pressure of oxygen and carbon dioxide; Pvo_2 = venous partial pressure of oxygen; BE = base excess; Cao_2 = arterial oxygen content; Hb-O_2 = hemoglobin-bound oxygen content; plasma O_2 = plasma oxygen content.

Values are reported at a nadir hemoglobin concentration in the range from 7.5 to 8.5 g/dL (baseline) and at 30, 60, 120, and 180 min after increasing the inspired fraction of oxygen to 1.0. Time points 30 and 60 min denote the completion of infusion of 1 and 2 units of packed erythrocytes in the transfusion groups, respectively.

* $P < 0.05/6$ (Bonferroni corrected): significantly different from baseline.

† $P < 0.05/6$ (Bonferroni corrected) compared with the other groups.

decrease in blood oxygen-carrying capacity are influenced by several factors, such as comorbidity, the use of anesthetics or medications with cardiac or peripheral vascular effects, and, most important, the patient's intravascular volume status (18–20). For this reason, a strict anesthesia and volume-replacement scheme with predefined hemodynamic goals was followed in all patients during the entire study period to allow for full exploitation of the compensatory mechanisms to dilutional anemia. Previous studies have not consistently demonstrated that increasing Do_2 by RBC transfusion was followed by a parallel increase in $\dot{V}o_2$ or improved tissue oxygenation (7–10). In this study, $\dot{V}o_2$ and $P_{ti}o_2$ remained unchanged in patients who received blood transfusions. Augmentation of blood oxygen content by 100% oxygen ventilation also failed to increase $\dot{V}o_2$ but was followed by an immediate increase in $P_{ti}o_2$. There are several reasons that may explain the absence of a beneficial effect of RBC transfusion and 100% oxygen ventilation on systemic $\dot{V}o_2$.

First, systemic $\dot{V}o_2$ was not dependent on oxygen supply before a blood transfusion or 100% oxygen ventilation, which might be attributed to the absence of a true oxygen deficit in these patients. It should be noted, however, that an almost 70% reduction of Hb concentration from baseline is necessary to induce oxygen supply dependency in experimental animals (9). Thus, it is not surprising that there is no pathologic oxygen supply dependency in most clinically resuscitated patients with an Hb concentration more than 7–8 g/dL (21). Moreover, anemic patients usually do not exhibit signs of tissue hypoxia or anaerobic metabolism before transfusion unless they also have acute circulatory failure (22). Indeed, all patients in this study had normal pretransfusion lactate levels and exhibited no signs of myocardial ischemia. Because there is no consensus regarding the degree of tolerable anemia in cardiac surgical patients, we chose a transfusion trigger that would not expose our patients unduly to complications caused by a critically decreased hematocrit. Second, long-term blood storage decreases RBC concentrations of adenosine triphosphate and 2,3-diphosphoglycerate, resulting in decreased erythrocyte membrane deformability and an increased affinity of Hb for oxygen (23,24). These storage effects may interfere with the ability of RBCs to transport and unload oxygen at the capillary level (9,10). Third, transfusion of RBCs is associated with an increase in hematocrit and a concomitant increase

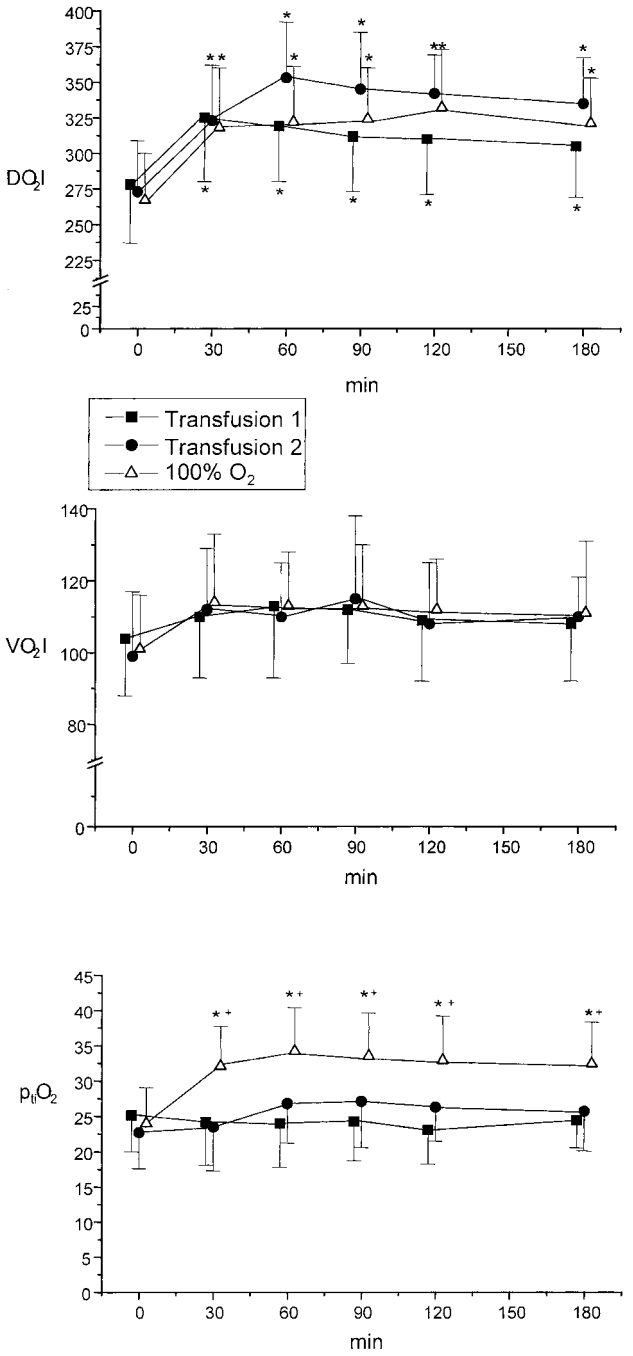

Figure 2. Changes in systemic oxygen delivery index (Do_2I), systemic oxygen consumption index (Vo_2I), and skeletal muscle Po_2 ($P_{ti}o_2$). Values are reported at a nadir hemoglobin concentration in the range from 7.5 to 8.5 g/dL (baseline) at 30, 60, 120, and 180 min after increasing the inspired fraction of oxygen to 1.0. Time points 30 and 60 min denote the completion of infusion of 1 and 2 units, respectively, of packed erythrocytes in the transfusion groups. $^{*}P < 0.05/6$ (Bonferroni corrected): significantly different from baseline; $^{+}P < 0.05/6$ (Bonferroni corrected) compared with other groups.

in blood viscosity, a major determinant of capillary blood rheology. Consequently, any increase in blood viscosity by increases in RBC mass may alter capillary RBC flux, and this may decrease tissue Do_2. Thus, a lower hematocrit, as during moderate isovolemic anemia, may actually be more beneficial to microcirculatory blood flow and tissue oxygenation (25).

Convective transport of oxygen in the plasma phase should become important in enhancing tissue Do_2 with the higher oxygen solubility produced by 100% oxygen ventilation (11). In the presence of a high Pao_2, the Po_2 gradient between arterial blood (500–600 mm Hg) and the peripheral tissues (15–40 mm Hg) is increased, and more of the oxygen transported in the blood is available for consumption in tissues. This increase in partial pressure difference should provide an additional driving gradient for diffusion of dissolved oxygen into the tissues and provide more oxygen for local mitochondrial metabolism (26). Increases in Pao_2, Pvo_2, plasma oxygen content, and total arterial oxygen content in the current patients who received 100% oxygen ventilation imply an increase in oxygenation at the peripheral capillary beds and, therefore, an overall higher driving pressure for diffusion of oxygen from the capillaries into the tissues. The end result was an increase in $P_{ti}o_2$ and, thereby, an improvement in tissue oxygenation, which has been shown to be associated with important clinical outcomes, such as a decreased incidence of surgical wound infections or the delay of blood transfusions (16,27). The latter might be of particular importance for cardiac surgical patients during rewarming in the first few postoperative hours. Hemodilution often occurs at that time because of the administration of crystalloids and colloid solutions, causing a hematocrit nadir at which transfusion decisions are usually made (5). In the hours that follow the surgical procedure, diuresis and fluid mobilization result in hemoconcentration and an increase in hematocrit. Thus, cardiac surgical patients may benefit from pure oxygen ventilation as a temporary "oxygen transport bridge" until hemoconcentration occurs.

There are several limitations to this study. First, our study group was restricted to hemodynamically stable, low-risk patients without excessive bleeding. Therefore, the results of this study may not be extended to patients who exhibit a pathologic oxygen supply dependency or have perfusion failure (i.e., circulatory shock). Second, 100% oxygen ventilation is not completely risk free. Potential harmful effects of a high Fio_2 would be injury to various organs because of the direct interaction of reactive species of oxygen with proteins, lipids, and nucleic acid (28). Furthermore, the administration of 100% oxygen has been shown to induce absorptive atelectasis in the immediate postoperative period, although the extent to which this atelectasis impairs pulmonary function and gas exchange is controversial (28–31). The exposure to

100% oxygen in our study was only of short duration, and routine chest radiographs after the procedure did not show any evidence of clinically relevant pulmonary atelectasis or injury. However, it might be argued that ordinary chest radiography is a rather insensitive tool for detecting and quantifying postoperative atelectasis formation. Third, the clinical usefulness of 100% oxygen ventilation as a temporary oxygen transport bridge might be limited by the fact that a spontaneous increase of hematocrit after cardiac surgery may take 12–24 hours or even longer. This would require prolonged intubation and ventilation with 100% oxygen or the administration of a high F_{IO_2} by the use of a tight-fitting mask to take advantage of the increased oxygen-carrying capacity provided by plasma-dissolved oxygen. This in turn may increase the risk for adverse pulmonary effects, although the toxic F_{IO_2} threshold—length of exposure and level—is still under debate. Fourth, tissue oxygenation was measured in only a single organ (skeletal muscle) and at only one specific area of muscle; therefore, other tissues or organs might get oxygenated differently than the site we measured. Another major problem with monitoring tissue gas tensions in clinical practice is that normal and critically abnormal values have not been established. In previous clinical studies, "normal" values for $P_{ti}O_2$ have been reported to be 14 to 25 mm Hg in patients undergoing CABG with use of CPB (32), 28 mm Hg in ICU patients with limited infection, 48 mm Hg in critically ill patients with severe sepsis, and 22 mm Hg in patients with cardiogenic shock (30). However, there is heterogeneity in microvascular blood flow and oxygenation between organs and at the level of each organ (33). This heterogeneity increases further during shock, sepsis, or other states of critical illness. Consequently, a common dysoxic threshold for skeletal muscle or any given tissue remains undefined.

In summary, we found that transfusion of stored allogeneic RBCs was effective only in improving systemic Do_2, whereas 100% oxygen ventilation improved systemic oxygenation and $P_{ti}O_2$ in volume-resuscitated, moderately anemic cardiac surgery patients. This improved oxygenation status seems to be most likely due to an increase in convective oxygen transport with an increased driving gradient for diffusion of plasma-dissolved oxygen into the tissues.

Appendix 1

Calculations Used in Hemodynamic and Oxygen Transport Measurements (14)

Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)

$CI = CO/\text{body surface area}$,

where CI denotes cardiac index and CO, cardiac output.

Systemic vascular resistance index ($dynes \cdot s \cdot cm^{-5} \cdot m^2$)

$(MAP - CVP) \cdot 79.96/CI$,

where MAP denotes mean arterial blood pressure, CVP denotes central venous pressure, and CI denotes cardiac index.

Arterial oxygen content (mL/dL)

$Cao_2 = (Hb \cdot 1.39 \cdot Sao_2) + (0.0031 \cdot Pao_2)$,

where Cao_2 denotes arterial oxygen content, Hb denotes hemoglobin concentration, Sao_2 denotes arterial oxygen saturation, and Pao_2 denotes arterial partial pressure of oxygen: 1.39 is the oxygen-carrying capacity of hemoglobin (mL O_2/gram Hb); 0.0031 is the solubility coefficient of oxygen in plasma (mL O_2/mm Hg Po_2).

Mixed venous oxygen content (mL/dL)

$Cvo_2 = (Hb \cdot 1.39 \cdot Svo_2) + (0.0031 \cdot Pvo_2)$,

where Cvo_2 denotes mixed venous oxygen content, Hb denotes hemoglobin concentration, Svo_2 denotes venous oxygen saturation, and Pvo_2 denotes venous partial pressure of oxygen.

Oxygen consumption ($mL \cdot min^{-1} \cdot m^{-2}$)

$\dot{V}o_2I = (Cao_2 - Cvo_2) \cdot Cl \cdot 10$,

where $\dot{v}o_2I$ denotes oxygen consumption index, Cao_2 denotes arterial oxygen content, Cvo_2 denotes venous oxygen content, and CI denotes cardiac index.

Oxygen delivery ($mL \cdot min^{-1} \cdot m^{-2}$)

$Do_2l = Cao_2 \cdot Cl \cdot 10$,

where Do_2l denotes oxygen delivery index, Cao_2 denotes arterial oxygen content, and CI denotes cardiac index.

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