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Efficacy of Near-Infrared Spectrometry for Monitoring the Cerebral Effects of Severe Dilutional Anemia

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ABSTRACT

Introduction: Clear guidelines for red cell transfusion during cardiac surgery have not yet been established. The current focus on blood conservation during cardiac surgery has increased the urgency to determine the minimum safe hematocrit for these patients. The aim of this study was to determine whether monitoring of cerebral regional oxygen saturation (rSO_2) via near-infrared spectrometry (NIRS) is effective for assessing the cerebral effects of severe dilutional anemia during elective coronary arterial bypass graft surgery (CABG).

Methods: The prospective observational study involved patients who underwent cerebral rSO_2 monitoring by NIRS during elective isolated first-time CABG: an anemic group (*N*=15) (minimum Hemoglobin (Hb) <7 g/dL at any period during cardiopulmonary bypass (CPB) and a control group (*N*=15) (Hb >8 g/dL during CPB). Mean arterial pressure (MAP), pump blood flow, blood lactate level, pCO_2, pO_2 at five time points and cross-clamp time, extracorporeal circulation time were recorded for each patient. Group results statistically were compared.

Results: The anemic group had significantly lower mean preoperative Hb than the control group (10.3 mg/dL versus 14.2 mg/dL; *P* = .001). The lowest Hb levels were observed in the hypothermic period of CPB in the anemic group. None of the controls exhibited a >20% decrease in cerebral rSO_2. Eleven (73.3%) of the anemic patients required an increase in pump blood flow to raise their cerebral rSO_2.

Conclusions: In this study, the changes in cerebral rSO_2 in the patients with low Hb were within acceptable limits, and this was in concordance with the blood lactate levels and blood-gas analysis. It can be suggested that NIRS monitoring of cerebral rSO_2 can assist in decision making related to blood transfusion and dilutional anemia during CPB.

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INTRODUCTION

Hemodilution and anemia during cardiovascular surgery are associated with postoperative morbidity and mortality [Goodnough 1989]. There has been much debate regarding the minimum safe hematocrit during CPB. The limited experimental available data suggests that hematocrit as low as 10% may be safe during hypothermic CPB [Rand 1964]; however, clear guidelines for red cell transfusion during CPB have not yet been established. Surgeons and anesthesiologists frequently rely on personal experience and anecdotal accounts to develop their own transfusion practices during CPB [Goodnough 1989; Gordon 1975; Kuduvalli 2005]. The current emphasis on blood conservation during cardiac surgery has increased the need to establish the minimum safe hematocrit for this patient group. The systemic response to hemodilution and anemia under non-CPB conditions is well described. Under physiologic conditions, levels of systemic and regional oxygen consumption are independent of oxygen delivery [Welch 1992; Goodnough 1995; Messmer 1975]. During moderate hemodilution and anemia, oxygen delivery and consumption are maintained via increased cardiac output and tissue blood flow, as well as increased tissue oxygen extraction [Welch 1992; Goodnough 1995; Messmer 1975]. However, for individual organs and for the body as a whole, there is a critical hematocrit value at which oxygen consumption becomes delivery-dependent. Under physiologic conditions, dogs are able to maintain constant systemic oxygen with hematocrit of approximately 10% [Fan 1980]. The same physiology may be extrapolated to humans during CPB, as whole body oxygen balance is actively manipulated by changes in hematocrit, temperature, and pump blood flow under CPB conditions. During moderate hemodilution, as occurs in CPB, total body oxygen delivery is kept in the physiologic range via increased tissue blood flow that occurs as a consequence of reduced blood viscosity and decreased vascular resistance [Chapler 1986; Cain 1977]. In addition, implementation of moderate hypothermia during CPB decreases oxygen demand and reduces the need for blood transfusion.

Oximetry is a process in which rSO_2 is measured using NIRS. Over the past decade, cerebral oximetry has emerged as a new noninvasive technique for monitoring oxygen levels in cerebral tissue, which is very sensitive to ischemia, throughout cardiac operations under CPB. Our aim was to

determine whether monitoring of rSO_2 via NIRS is effective for assessing the cerebral effects of severe dilutional anemia during elective CABG.

MATERIALS AND METHODS

Patient Selection: The investigation was a prospective observational study, and the Ethics Committee of Acibadem University approved the protocol. The subjects were selected from among 70 adults who underwent elective, isolated, first-time CABG and had cerebral oxygen saturation monitored via NIRS. Two groups were established: "Anemic" patients (*N*=15) with low Hb (≤7 g/dL) recorded during CPB, and control patients (*N*=15) who maintained high Hb (≥8 g/dL) throughout CPB. The control patients were chosen from among the remaining 55 patients (Hb ≥8 g/dL) with demographic properties similar to the patients in the anemic group. Patients with >50% carotid artery stenosis were excluded.

Anesthesia: During CPB, MAP and pump flow were kept at 50 mmHg to 80 mmHg and 2.2-2.5 L/m^2, respectively. Adequacy of tissue perfusion was monitored based on venous-to-arterial carbon dioxide difference (Pv-aCO_2), lactate level, urine output, and base deficit. Cerebral rSO_2 was monitored via NIRS throughout each operation (see detailed methods below).

Midazolam 125 µg/kg IM was administered 30 minutes before the operation. Anesthetic induction consisted of Midazolam 50 µg/kg, Pancuronium 0.15 mg/kg, and Fentanyl 25 µg/kg to 35 µg/kg. After endotracheal intubation, 50% O2, 50% N2O, and 3% to 4% Desflurane were used for all hemodynamically stable patients. Maintenance anesthesia and muscle relaxation were accomplished with Midazolam and Vecuronium 80 µg/kg/h, for both. Moderate hypothermia was maintained during CPB. The doses of Midazolam and Vecuronium both were decreased to 60 µg/kg/h when body temperature reached 32°C. Rewarming was initiated during left internal mammary artery grafting. When body temperature reached 36.5°C and the patient was hemodynamically stable, CPB was discontinued and Heparin was reversed with Protamine Sulfate. Infusions of Midazolam and Vecuronium were restored to 80 µg/kg/h during rewarming, reduced to 50 µg/kg/h after termination of CPB, and then discontinued at skin closure.

During the operation, the following stepwise interventions were carried out when there was >10% decrease in cerebral rSO_2:

1. For patients with Hb ≤5 g/dL during hypothermia and/or Hb ≤6 g/dL during rewarming, at least one red blood cell transfusion was administered.
2. For patients with Hb higher than the above limits:
   a. If partial oxygen pressure (pO_2) was <100 mmHg, the inspiratory oxygen fraction (FiO_2) was increased.
   b. If the reservoir level was adequate, pump blood flow was increased from 2.0-2.5 L/m^2/min to 2.5-3.0 L/m^2/min.
   c. If the reservoir level was low, venous return was increased by one or more of the following: Placing the patient in Trendelenburg position, applying vacuum-assisted venous suction, repositioning the venous cannula, or adding crystalloid.
   d. If MAP was ≤60 mmHg, repeated intravenous boluses of 25 µg Noradrenaline were administered to achieve MAP >60 mmHg.
   e. Transfusions of erythrocyte suspension were administered to achieve Hb >7 g/dL.

Transfusion strategies were based on most the recent published guidelines [Society of Thoracic Surgeons Blood Conservation Guideline Task Force 2011].

Near-Infrared Spectroscopy: The NIRS method was performed using an *in vivo* optical spectroscopy (INVOS) system (Invos Somanetics 5100 C, Somanetics Corp., Troy, MI, USA) that consisted of sensors placed on the right and/or left side of the patient's forehead, one or two preamplifiers, reusable sensor cables, and a monitor. The probe for this unit has one light source and two photo detectors. A photo detector close to the light source absorbs light reflected from superficial tissues. The second photo detector located distant from the light source absorbs light reflected from deeper tissues, such as watershed zones of the brain.

The basic principles of oxymetric studies are related to the Beer Lambert Law, which is expressed as:

$A = -log(I1/I0) = \alpha 1 \times C \times L$

A=attenuation, *I0*=incident light intensity, *I1*=detected light intensity, α=specific extinction coefficient (µM-1.cm^{-1}), *L*=distance over which light enters and leaves the solution (cm).

The device is designed to measure oxygen in brain or tissues that are directly beneath the sensor. Specifically, it uses two wavelengths, 660 nm and 940 nm, to measure changes in rSO_2. Measuring the quantity of returning photons as a function of wavelength allows the operator to infer the spectral absorption of the underlying tissue and, thus, make conclusions about the average percentage oxygenation of the tissue.

Data collection: Monitoring data (MAP, pump blood flow, blood lactate level, pCO_2, and pO_2) and durations of the stages of each surgery (cross-clamp time and extracorporeal circulation time) were recorded for each patient. During each operation, blood samples were drawn for blood-gas analysis at 5 time points: Before anesthetic induction (T1), five minutes after initiation of CPB (T2), 20 minutes after initiation of CPB (which usually coincided with 15th minute of cross-clamp time) (T3), immediately after cross-clamp release (T4), and just before termination of CPB (T5). For each patient, the blood-gas values that coincided with the lowest recorded Hb level were used for statistical analysis.

Statistical Analysis: Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc, Chicago, IL, USA). Results were recorded as percentages or as mean ± standard deviation. Univariate comparisons were made using chi-square or Fisher's exact test for categorical variables and unpaired t-tests for continuous variables. *P* values less than .05 were considered significant.

RESULTS

None of the patients in either group suffered neurological, cardiac, pulmonary, renal, gastrointestinal, or infectious

Table 1. Demographic characteristics and operative details for the two study groups

	Anemic group (*N*=15)	Control group (*N*=15)	*P Value*
Age (years)	64.2 ± 7.7	56.8 ± 9.3	.02
Females/Males (%)	80/20	20/80	.03
Preop Hemoglobin (g/dL)	10.3 ± 0.9	14.2 ± 1.3	.001
Extracorporeal circulation time (min)	65 ± 23	53 ± 19	NS
Cross-clamp time (min)	40 ± 21	35 ± 17	NS
Postoperative volume balance (mL)	1226 ± 524	947 ± 584	NS

Table 2. Group results for hemoglobin level prior to anesthetic induction, minimum hemoglobin during extracorporeal circulation, and hemodynamic and arterial blood gas values at time of minimum Hb during extracorporeal circulation.

	Anemic group (*N*=15)	Control group (*N*=15)	*P Value*
Hemoglobin (g/dL) at T1	10.3 ± 0.9	14.2 ± 1.3	.001
Min. Hemoglobin during extracorporeal circulation (g/dL)	6.2 ± 0.4	10.3 ± 1.3	.001
Mean arterial pressure (mmHg)	65 ± 5	56 ± 7	.001
Lactate level (mmol/dL)	1.1 ± 0.3	1.1 ± 0.5	NS
Pump blood flow (L/min/m^2)	2.5 ± 0.2	2.2 ± 0.2	.001
pO_2 (mmHg)	202 ± 43	145 ± 42	.001
pCO_2 (mmHg)	33 ± 3	39 ± 2	.001

pO_2: partial oxygen pressure; pCO_2: partial carbon dioxide pressure; T1: prior to anesthetic induction; NS: Non-sufficient.

complications. There was no postoperative mortality. Demographic characteristics and operative data for each group are listed in Table 1. The mean age of the anemic group was significantly older than that of the control group (64.2 ± 7.7 years vs. 56.8 ± 9.3 years; P = 0.02). The mean preoperative Hb level in the anemic group was significantly lower than that in the control group (10.3 ± 0.9 g/dL vs. 14.2 ± 1.3 g/dL; P = 0.001). The minimum Hb level during extracorporeal circulation (ECC) in the anemic group was significantly lower than that in the control group (6.2 ± 0.4 g/dL vs. 10.3 ± 1.3 g/dL; P = 0.001). The control group means for MAP, pump blood flow, and pO_2 all were significantly lower than the corresponding means in the anemic group, whereas the control group's mean pCO_2 was significantly higher (Table 2). In both hemispheres, the change in rSO_2 from T1 to time of lowest

Table 3. Oxygen saturation findings and their change in time for the right and left cerebral hemispheres, respectively, in the two study groups.

	Anemic group (N=15)	Control group (N=15)
Right hemisphere:		
rSO_2 (%) at T1	52 ± 9	66 ± 6
rSO_2 (%) at time of lowest Hemoglobin during ECC	49 ± 7	58 ± 6
Change in rSO_2 from T1 to lowest Hemoglobin during ECC (%)	5.7	12
Left hemisphere:		
rSO_2 (%) at T1	54 ± 6	69 ± 7
rSO_2 (%) at time of lowest Hemoglobin during ECC	50 ± 7	58 ± 6
Change in rSO_2 from T1 to lowest Hemoglobin during ECC (%)	7.4	11.5

ECC: extracorporeal circulation; rSO_2: regional oxygen saturation; T1: prior to anesthetic induction.

Hb during ECC did not exceed 20% in either the control group or the anemic group (Table 4). Table 4 details the interventions that were required during CPB for each patient in the anemic group.

DISCUSSION

Human life expectancy has increased in accordance with recent substantial developments in the knowledge, equipment, and practice of CABG. Also, as patients undergoing CABG tend to be older, many have other health issues combined with cardiac illness. In addition to the requirement for longer stay in the intensive care unit after cardiac operations, older age is associated with greater risk and complication rates in cardiac surgery and is considered an important risk factor in the CABG patient group specifically [Cane 1995]. Neurological problems ranging from personality changes to stroke occur in 7% to 10% of elderly patients who undergo CABG, a rate higher than observed in younger patients [Roach 1996]. To some extent, this higher incidence of postoperative problems in older patients can overshadow the success of the surgery. Whereas age is beyond the surgeon's control, pump blood flow, MAP, pO_2, pCO_2, and hematocrit are modifiable parameters that are known to contribute to patient outcome in CABG surgery [Roach 1996; Schwartz 1995; Soma 1989; Murphy 2007; Mehdi 2009]. Despite 50 years of experience with CABG, the optimum values for hemodynamic and blood gas parameters such as MAP, pO_2, and pCO_2 during CABG are still being debated. It has been documented that cerebral blood flow remains constant if MAP is kept between 30 mmHg -100 mmHg [Schell 1993]; however, there is no consensus on a specific optimum value for MAP during CABG.

Table 4. Interventions required during cardiopulmonary bypass for each patient in the anemic group.

Patient no.	Increased FiO_2	Increased pump blood flow	Noradrenaline boluses to achieve MAP >60 mmHg	Crystalloid administration	Erythrocyte transfusion
1		+		+	
2			+		
3	+	+			
4	+	+			
5	+	+			
6		+		+	
7	+				
8					
9		+		+	
10	+	+		+	
11		+	+		+
12	+	+		+	
13					
14		+		+	
15	+	+			

FiO_2: inspiratory oxygen fraction; MAP: mean arterial pressure.

Whereas some studies have shown that maintaining MAP at >60 mmHg during CABG has positive effects on outcome parameters [Roach 1996; Schwartz 1995; Soma 1989; Murphy 2007; Mehdi 2009], other research has revealed no correlation between changes in MAP during CABG and neurological or other outcome parameters [Schell 1993; Taylor 1990; Schwartz 1995]. During CPB, the systemic flow rate (typically 1.6-2.4 L/min/m^2) is usually based on body surface area and the degree of hypothermia and is adjusted according to indicators of organ perfusion (e.g. arterial blood gas (ABG) findings. It also has been claimed that higher pump blood flow rates during CABG (2.4-3.0 L/min/m^2) improve outcome; however, analysis has revealed no significant positive correlations between higher pump blood flow rates and outcome parameters [Messmer 1975]. Patients who exhibit alterations in cerebral blood pressure and autoregulation of cerebral blood flow disturbances preoperatively are considered to be at high risk for neurological problems after CABG. These disturbances may not be noticed or monitored during CABG. Sometimes, even patients who exhibit no changes in hemodynamic parameters during the operation show postoperative neurological problems. Mean arterial pressure may be the single most important determinant of cerebral perfusion in these patients. It is well understood that parameters monitored during cardiac surgery, such as MAP and pump blood flow, provide indirect data that reflect the adequacy of tissue perfusion during CABG. However, the optimum values for these parameters vary for each individual and this reduces confidence in them as monitoring tools during cardiac surgery.

Hemoglobin levels during CABG are another topic of debate for surgeons and anesthetists. Maintaining adequate Hb levels can be very challenging in this "bloody" surgery. Adding hemodilution to the changes that already occur within the process of CPB makes accurate monitoring even more complex. Hemodilution during CPB is known to increase microcirculation and provide more blood to tissues; however, because optimal values for MAP and pump blood flow are difficult to determine, clinicians focus on maintaining adequate tissue perfusion. They prefer to administer blood transfusions during CABG as a means of maintaining tissue perfusion and keeping Hb at levels that ensure adequate oxygenation. When research revealed adverse effects of blood transfusion on mortality and morbidity other than the known side effects, indications for transfusion during CABG were revised and lower Hb values were tolerated [Messmer 1975]. However, there is still no consensus on what constitutes a safe level of dilutional anemia during CPB. In practice, there is wide variation in transfusion practices and decisions depend more on the clinician's education and institution than on his or her level of theoretical knowledge [Messmer 1975; Chapler 1986; Cain 1977]. Delivery of oxygen (DO_2) to the tissues can be calculated using the following formula:

DO_2 = pump blood flow (L/min) x Hb (g/dL) × 1.34 × arterial oxygen saturation (SaO_2) × 10

One also can use this equation to calculate the oxygen extraction ratio (OER, maximum of 66%) if the approximate oxygen consumption (VO_2) is known. Target VO_2 is 95±20 mL/min/m^2 during normothermia [Cavaliere 1998; Long 2003], 49.9±17.7 mL/min/m^2 during hypothermia (30°C)

[Long 2003], and 133±40 mL/min/m^2 during rewarming [Jakobsena 2012]. For example, for a patient with pump blood flow 5 L/min, SaO_2 99%, and Hb 5 g/dL, DO_2/VO_2 during the normothermic, hypothermic, and rewarming periods of CPB would be 330/163, 330/85, and 330/226, respectively. The corresponding OER values would be 49%, 26%, and 66%. According to DO_2/VO_2 and OER, this pump blood flow and oxygenation are adequate during normothermia and hypothermia for a patient with 5 g/dL Hb level, but not for rewarming. The results for DO_2/VO_2 and OER with Hb 6 g/dL would be 397/226 and 57%, which are adequate for the rewarming period. In other words, slightly higher minimum Hb (6 g/dL) is necessary for adequate oxygen delivery during the rewarming period. Despite this theoretical knowledge, in daily practice it tends to be difficult to follow theoretical guidelines. Considering that the brain requires 20% of cardiac output and is very vulnerable to ischemia, during the anemic period of CPB, most clinicians tend to evaluate the parameters that support theoretical knowledge, but make conservative adjustments to ensure the patient's safety.

The impaired vasomotor reactivity and disturbed autoregulation of cerebral blood flow that occur during CPB may preclude adequate changes in cerebral perfusion pressure in response to altered MAP and shifts in Hb levels; however, monitoring of MAP, CPB flow rate, and/or Hb can be relied upon as bases for estimating and intervening to adjust cerebral blood flow. In contrast, evaluating cerebral hemodynamics by NIRS measurement of cerebral blood flow velocity and rSO_2 may be more accurate and valuable, especially in combination with MAP, since NIRS monitoring reveals changes in cerebral blood flow and cerebral oxygenation.

Noninvasive measurement and monitoring of oxygenation of brain tissue by NIRS provides very important data related to the adequacy of brain tissue perfusion, which can be altered significantly by any decrease in DO_2 during CPB. In addition, this technique provides data about systemic tissue perfusion. In previous studies, NIRS has been used to evaluate brain rSO_2 during various types of events that alter cerebral hemodynamics [Edmonds 2002; Iglesias 2003]. Near-infrared spectrometry can be used to follow changes and overall trends in rSO_2, and thus is a qualitative monitoring modality. This simple, noninvasive monitoring method has been shown to permit rapid detection of regional cerebral hypoxia, has been validated for this purpose in volunteers, and has been suggested to have an important application in cardiac surgery [Edmonds 2002; Iglesias 2003]. When coupled with other vital physiologic data, monitoring of rSO_2 trends can improve patient management through continuous assessment of the balance between cerebral oxygen consumption and the delivery of oxygenated Hb. Sudden decreases in global cerebral oxygen content may provide the feedback necessary to maintain adequate oxygenation.

In our study, we found that, according to NIRS monitoring of cerebral rSO_2 and arterial blood gas results, low Hb values that had been considered theoretically safe during CPB also were clinically safe. Decreases in cerebral rSO_2 of >20% from baseline are considered significant and the above mentioned interventions were applied. However, even when Hb levels were at the lowest value in any period during CPB, the decrease in cerebral rSO_2 was not >20% from baseline. The anemic patients exhibited acceptable changes in cerebral rSO_2. The observed decreases were lower than expected in the setting of profound anemia, and we attribute this to the interventions that were applied in 13 patients (87%) of the anemic group (Table 4). We also observed that lactate levels remained within the normal range in both patient groups, and we consider this another significant indicator tissue perfusion was maintained during anemia in CPB.

As a conclusion, our findings suggest that NIRS monitoring of cerebral rSO_2 is an effective method that can assist in decision-making related to blood transfusions aimed at addressing dilutional anemia during CPB.

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