Cerebral Oximetry Monitoring to Maintain Normal Cerebral Oxygen Saturation during High-risk Cardiac Surgery

A Randomized Controlled Feasibility Trial

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ABSTRACT

Background: Cerebral oxygen desaturation during cardiac surgery has been associated with adverse perioperative outcomes. Before a large multicenter randomized controlled trial (RCT) on the impact of preventing desaturations on perioperative outcomes, the authors undertook a randomized prospective, parallel-arm, multicenter feasibility RCT to determine whether an intervention algorithm could prevent desaturations.

Methods: Eight Canadian sites randomized 201 patients between April 2012 and October 2013. The primary outcome was the success rate of reversing cerebral desaturations below 10% relative to baseline in the intervention group. Anesthesiologists were blinded to the cerebral saturation values in the control group. Intensive care unit personnel were blinded to cerebral saturation values for both groups. Secondary outcomes included the area under the curve of cerebral desaturation load, enrolment rates, and a 30-day follow-up for adverse events.

Results: Cerebral desaturations occurred in 71 (70%) of the 102 intervention group patients and 56 (57%) of the 99 control group patients ($P = 0.04$). Reversal was successful in 69 (97%) of the intervention group patients. The mean cerebral desaturation load (SD) in the operating room was smaller for intervention group patients compared with control group patients (104 [217] %.min *vs.* 398 [869] %.min, mean difference, –294; 95% CI, –562 to –26; $P = 0.03$). This was also true in the intensive care unit ($P = 0.02$). There were no differences in adverse events between the groups.

Conclusions: Study sites were successful in reversal of desaturation, patient recruitment, randomization, and follow-up in cardiac surgery, supporting the feasibility of conducting a large multicenter RCT. **(Anesthesiology 2016; 124:826-36)**

NEAR infrared-reflected spectroscopy (NIRS) has been used extensively over the past two decades as a noninvasive continuous monitor of the balance between cerebral oxygen delivery and consumption.[1,2] Originally used as a monitor in both adult[1] and pediatric[3] cardiac surgery, it has also been studied in a wide range of clinical settings including neurology,[4] neurosurgery,[5] vascular surgery,[6] and trauma.[7] Multiple reports have outlined the usefulness of NIRS in preventing potentially catastrophic neurologic events that would otherwise have been undetected with other conventional monitoring.[1,8]

Cardiac surgery patients with significant decreases in regional cerebral oxygen saturation (rSO_2) from baseline values

What We Already Know about This Topic

- Cerebral oxygen desaturation during cardiac surgery is associated with adverse perioperative outcomes
- The authors, therefore, conducted a randomized feasibility trial to determine whether an intervention algorithm can prevent cerebral desaturation

What This Article Tells Us That Is New

- Eight Canadian centers randomized 201 patients
- Cerebral desaturation (10% relative reduction from baseline) was common and nearly always reversible
- Consequently, saturation was far better preserved in patients randomized to intervention than routine care

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have been shown to be at increased risk of postoperative cognitive decline,[9–11] delirium,[12] longer intensive care unit (ICU) and hospital length of stay,[10,13] and an increase in overall major organ dysfunction.[13] These findings have led clinicians to use strategies to reverse decreases in rSO_2 during cardiac surgery to enhance both cerebral oxygenation and global tissue perfusion in an attempt to reduce the incidence of postoperative complications.[14] However, the few interventional studies that have investigated the impact of preventing intraoperative decreases in rSO_2 on postoperative outcomes have had mixed results.[10,13,15] In major vascular surgery, preventing cerebral desaturations resulted in shorter recovery room and hospital length of stay.[16] In cardiac surgery, there was a decrease in major organ dysfunction and shorter ICU length of stay.[13] However, poor compliance with the protocolized interventions limited the interpretation of outcomes in another study.[10]

To standardize strategies to reverse decreases in rSO_2 during cardiac surgery, we developed a physiologic algorithm[8] that we used in a small (n = 48) single-center randomized interventional trial. We showed reversal of desaturations in 93% of patients and an 80% reduction in cerebral desaturation load (CDL, defined as the cumulative area under the curve of desaturation over time for decreases in rSO_2 values below 20% relative to baseline) in the group with interventions.[17] However, the study was underpowered to examine perioperative outcomes. Accordingly, to determine the impact of reversing decreases in rSO_2 on postoperative outcomes, a large multicenter randomized controlled trial (RCT) is needed. However, before such a trial can take place, it is necessary to determine the feasibility in potential participating sites of successfully using the algorithmic approach to prevent decreases in rSO_2.

The purpose of this study was to examine the feasibility of undertaking such a trial. Our primary hypothesis was that academic centers participating in the NORMal cerebral Oxygen SATuration (NORMOSAT) in high-risk cardiac surgery trial will have at least an 80% success rate in reversing decreases in rSO_2 in patients during high-risk cardiac surgery by implementing the same algorithmic strategy. We also wished to demonstrate that participating centers would also be able to recruit and follow-up a sufficient number of patients so as to make a future large-scale RCT feasible.

Materials and Methods

Study Design
The NORMOSAT study is a prospective, multicenter, parallel-arm, and RCT endorsed by the Canadian Perioperative

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Anesthesia Clinical Trials group.[18] The study was conducted between April 2012 and October 2013 in compliance with the Declaration of Helsinki and the International Conference on Harmonization and on Guidelines for Good Clinical Practice. Institutional Research Ethics Board approval was obtained (see appendix 2) in every participating center, and a written informed consent was obtained from every patient. The trial was registered at clinicaltrials.gov (NCT01432184) in August 2011, with Dr. Deschamps as the principal investigator, and the overall design and patient flow is illustrated in figure 1.

Patients were eligible to participate in the NORMOSAT trial if they were 18 yr or older, had a cumulative EuroScore II[19] more than or equal to 10, and/or were undergoing high-risk surgery defined as combined surgery (coronary bypass plus valve replacement or repair), or multiple valve replacement and/or redo surgery. Patients were excluded if they were unable to read French or English, were undergoing off-pump coronary artery bypass surgery, emergency surgery (*i.e.*, less than 6 h after diagnosis) or planned deep hypothermic circulatory arrest, acute endocarditis, or the presence of active delirium or encephalopathy.

Patients were randomly assigned to either a control group or an intervention group. Designated research coordinators from each site logged onto the secure study website of the coordinating central office where randomization was performed in a 1:1 ratio using a computer-generated random number table with permuted random blocks stratified by hospital sites. Research technicians recruited patients the day before the surgery, but to avoid enrolling patients who subsequently did not undergo surgery (*e.g.*, surgical cancellation), randomization took place on the day of surgery just before the induction of anesthesia. Once randomized, patients were followed up and analyzed within the group to which they were allocated regardless of whether they receive the assigned intervention or not (*i.e.*, intention-to-treat principle).

All patients had bilateral NIRS probes applied to the forehead before the induction of anesthesia. Research sites used one of the three Health Canada approved rSO_2 monitoring devices for the study: FORE-SIGHT (CAS Medical Systems Inc., USA; 1 site, 9% of patients), EQUANOX Classic 7600 (Nonin Medical Inc., USA; M, 2 sites, 28% of patients), and INVOS 5100C-PB (Covidien, USA; 5 sites, 62% of patients). NIRS values were obtained from the patients while breathing room air as well as on supplemental oxygen (4 l/min O_2 *via* nasal prongs). The rSO_2 values with supplemental oxygen were used as the baseline values for the study. Once baseline measures were obtained, rSO_2 values were recorded continually and saved on the devices' memory and then exported to Excel files that were then transferred to a secure online databank for analysis by the coordinating center.

Patients allocated to the control group had cerebral oximetry probes applied to the forehead but did not have NIRS values displayed on the monitor (*i.e.*, anesthesiologists were
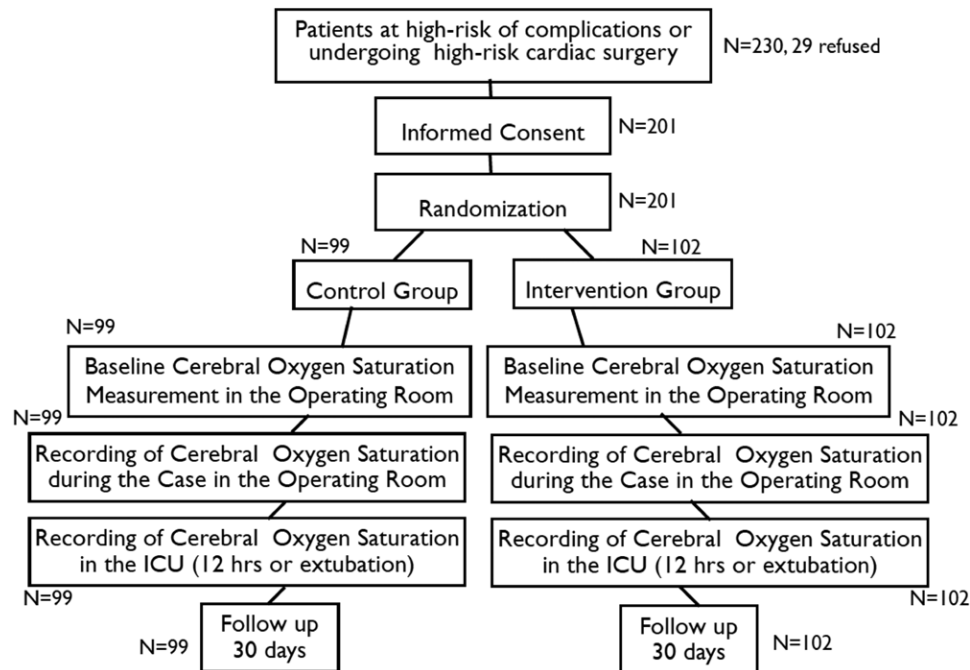
Fig. 1. Flow chart of the Normal Cerebral Oxygen Saturation study. Two hundred thirty patients were recruited, and 29 refused. Randomization was done on 201 patients, 99 in the control groups and 102 in the intervention group. All 201 patients completed the study. ICU = intensive care unit.

blinded to rSO_2 values). Anesthesiologists relied on standard monitoring for the management of these cases.

Patients allocated to the intervention group had NIRS values displayed on the monitor. At an intervention threshold of a 10% decrease in rSO_2 value relative to baseline for a duration exceeding 15 s, anesthesiologists used an interventional algorithm (fig. 2) to reverse desaturations.[8] The 10% threshold level was chosen so as to intervene as early as possible to maintain rSO_2 at baseline values throughout the surgery and avoid an *a priori* defined clinically significant decreases in rSO_2 value below 20% relative to baseline.[13,17] Every desaturation occurrence along with its intervention (success or failure) was noted.

The anesthetic management of patients was in accordance with Canadian guidelines,[20] whereas surgical and perfusion techniques including cardiopulmonary bypass as well as the postoperative care were left to the discretion of the clinical caregivers from each individual center. After surgery, all patients were transferred intubated to the ICU with NIRS sensors in place. In the ICU, rSO_2 was monitored continuously for 12 h (or until tracheal extubation whichever came first) with the monitor displays hidden from the ICU staff (blinded to group assignment).

Outcome Measures

Daily assessment of patients for postoperative complications was recorded by each site's research coordinator until patients were discharged from the hospital or for 30 days whichever came first. (Table 1 lists the definitions used for outcome variables.) Discharged patients were contacted by telephone on the 30th postoperative day for a final follow-up interview. The primary endpoint of the study was the success

rate of reversing decreases in rSO_2 (below 10% of baseline values) in patients undergoing high-risk cardiac surgery with cardiopulmonary bypass.

The principal secondary endpoints of the NORMOSAT trial included the enrolment rate (defined as the number of patients enrolled per week), the between-group difference CDL (%.min), the between-group difference in major organ morbidity and mortality (MOMM) score, a composite endpoint of stroke, renal failure requiring dialysis, prolonged mechanical ventilation more than 48 h, deep sternal wound infection, reoperation, and death. Other predefined endpoints examined included the rate of 30-day follow-up, defined as the proportion of all randomized patients who participated in the 30-day follow-up interview and the incidence of decreases in rSO_2 more than 20% of baseline in the first 12 h in the ICU (or until tracheal extubation).

For the NORMOSAT study to be considered feasible, we determined that every center would need to be able to reverse decreases in rSO_2 in at least 80% of patients, and there would need to be at least two patients recruited per month at each site for a total of 200 patients in a 12-month period.

Statistical Analysis

Results are presented as means (SD) for continuous variables and as frequencies (percentages) for categorical variables. Groups were compared using a Student's *t* test for continuous variables and Pearson chi-square test for categorical variables. As this was a feasibility trail, no corrections (*e.g.*, Bonferroni) were used for controlling multiplicity of testing of the secondary endpoints. The sample size for
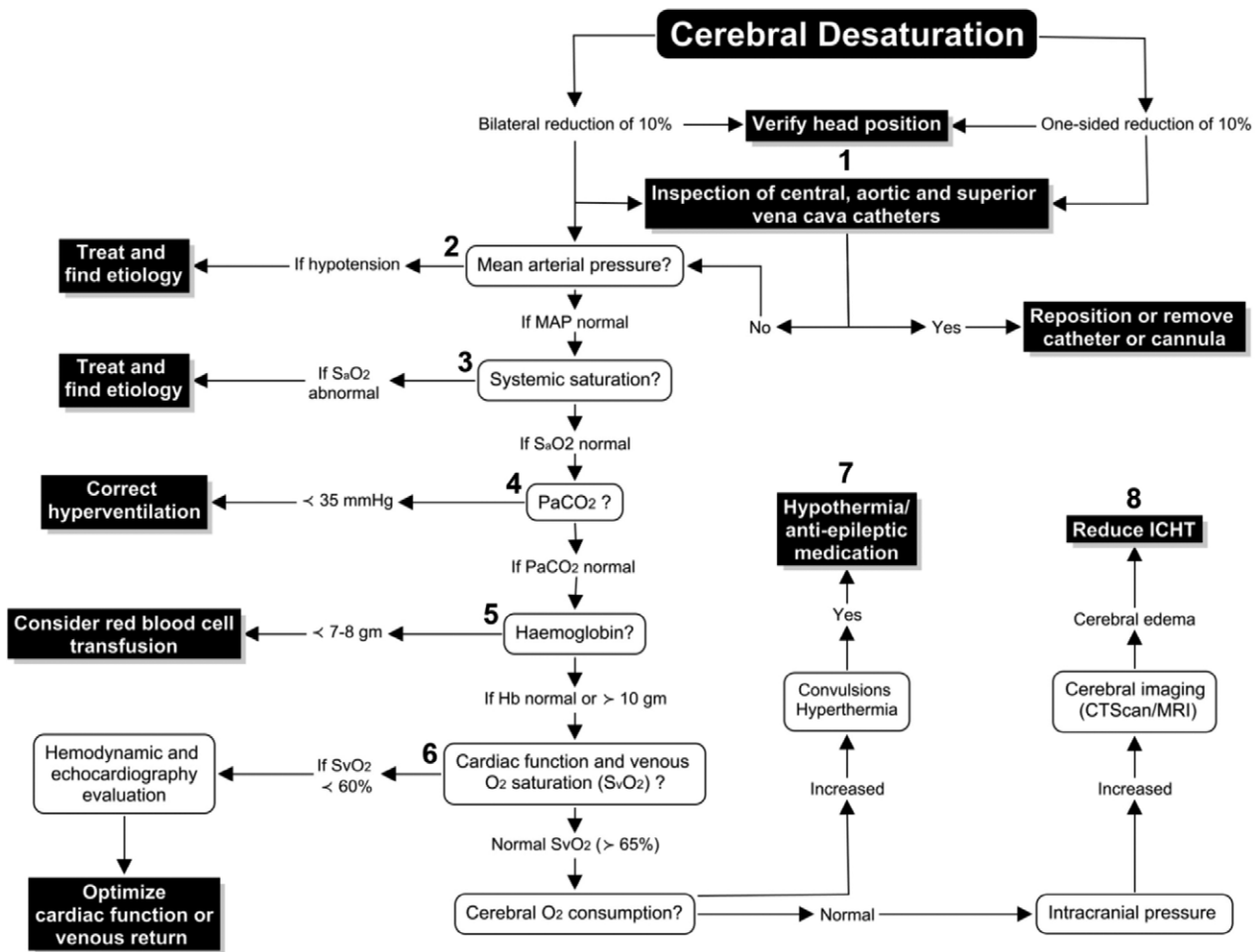
Fig. 2. Physiologic algorithmic approach to the reversal of decreases in cerebral oxygen saturation. Step 1: Verify head position and position of vascular catheters. Step 2: Adjust blood pressure to within 20% of baseline values. Step 3: Increase inspired oxygen fraction to correct low oxygen saturation values. Step 4: Adjust ventilator parameters to increase arterial end tidal carbon dioxide levels within normal ranges (35 to 45 mmHg). Step 5: Consider giving blood transfusions to patients with low hemoglobin level when steps 1 to 4 have not increased cerebral oxygen saturation within 20% of baseline values. Step 6: Consider improving ventricular function in the presence of low output state. Step 7: Rule out hypothermia, seizures, and light anesthesia. Step 8: Consider cerebral edema and increased intracranial pressure. CT Scan = computed tomography scan; Hb = hemoglobin; ICHT = IntraCranial HyperTension; MAP = mean arterial pressure; MRI = magnetic resonance imaging; $PaCO_2$ = arterial carbon dioxide tension; SaO_2 = arterial oxygen saturation; SvO_2 = mixed venous oxygen saturation.

our feasibility endpoint was based on convenience, and no *a priori* calculation was conducted. Statistical analyses were performed using SPSS, version 21.0 (SPSS Inc., USA). Significance level was set at 0.05 for all tests.

Results

Eight centers participated in the study, and 201 patients were recruited. Although recruitment was planned for 1 yr, the total number of patients was recruited over 18 months due to delays in research ethics review board approval (see appendix 2). However, once recruitment began, all centers recruited at the expected recruitment rate. The distribution of patient recruitment between sites and rates of enrolment are shown in table 2. The average enrolment rates across sites varied from 2.1 to 3.3 patients per month. Randomization resulted

in 99 patients in the control group and 102 patients in the intervention group. Before study closure, one center included one more patient than required into the intervention group. One patient randomized to the control group was treated as in the intervention group in error. All patients were included for analysis in the group to which they were randomized.

Demographic data, medical conditions and perioperative risk estimates, and perioperative data are presented in table 3. The rSO_2 data are presented in table 4. Baseline rSO_2 values without supplemental oxygen did not differ between the control and intervention groups. With supplemental oxygen, there was an overall statistically significant increase in rSO_2 values in both groups ($P < 0.001$).

Cerebral desaturation below 10% relative to baseline occurred in 71 of the 102 intervention group patients (69.6%) and 56 of the 99 control group patients (56.6%, $P = 0.04$). In

Table 1. Definition of Clinical Outcomes

MOMM composite index	
Death	Death at 30 d
Cerebrovascular accident	Focal neurologic deficit lasting > 24 h and confirmed by cerebral computed tomography or magnetic resonance imaging
Reoperation	Return to the operating room, all reasons
Respiratory failure	Duration of tracheal intubation exceeding 48 h or reintubation of the tracheal for a pulmonary cause
Dialysis	Any episode of ≥ 1 dialysis
Wound infection	Deep infection requiring specific antibiotic coverage
Other outcomes	
Readmission to the hospital	Any cause within 30 d
Arrhythmia	New onset of postoperative arrhythmia (any cause) requiring treatment by medication or cardioversion
Blood products	Use of any blood product within the first 30 d after surgery
Delirium	As defined by the DSM-IV criteria and diagnosed by a psychiatrist
Gastrointestinal complications	Ischemia detected on angiography Bleeding-based abdominal radiological evidence and surgical exploration
Clinical seizures	Either clinical signs of seizures or electroencephalographic evidence of seizures and absence of organic pathology on cerebral computed tomography or magnetic resonance imaging
Myocardial infarction	Presence of (1) an increase of troponin-I levels over 20 times normal values, (2) new Q waves in two contiguous electrocardiogram leads, or (3) confirmed graft occlusion within the first 30 d after surgery
Renal failure	As defined by the RIFLE criteria

DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; MOMM = 30-d major organ morbidity and mortality; RIFLE = risk, injury, failure, loss, end-stage renal disease.

the intervention group, the total number of interventions was 535, with a mode of 5 interventions per patient (range, 1 to 91, 25 to 75% percentile, 2 to 8). The total number of patients with decreases in rSO_2 below 10% was 127, and the total number of desaturations was 979. Of these, 23 patients had more than one desaturation, 12 patients had more than 3 desaturations, and 3 patients had more than 10 desaturations during the course of surgery. Desaturations were successfully reversed in 69 (97%) of the intervention group patients. The success rate of reversing any desaturation below 10% was 63.5% (219 of 345 desaturations).

Interventions at the 10% threshold level appear to have prevented progression of desaturations below 20% relative to baseline (defined as a clinically significant desaturation).[17] Only 34 of 71 (48%) patients in the intervention group had desaturations below 20% of baseline as opposed to 46 of 56 (82%) patients in the control group ($P < 0.0001$). Also, the total number of desaturations below 20% of baseline was significantly less in

Table 2. Number of Patients Recruited by Participating Centers, Number of Months Centers Participated, and the Rate of Enrolment

Participating Center	No. of Patients Recruited (Total Patients = 201)	No. of Months of Participation	Enrolment Rate: Patients/Month
1	40	12	3.3
2	24	9	2.7
3	30	11	2.7
4	19	9	2.1
5	21	9	2.3
6	21	9	2.3
7	26	9	2.9
8	20	9	2.2

the intervention group (134) compared with the control group (300, $P = 0.012$). The mean (SD) CDL in the operating room (OR) was 104 (217) %.min in the intervention group compared with 398 (869) %.min in the control group ($P = 0.03$; table 4).

The average number of decreases in rSO_2 below 20% relative to baseline in the different participating centers was 2.0 ± 1.0 (range, 0.6 to 3.7) desaturations/patient recruited, and an average of $37 \pm 16\%$ (range, 13 to 63%) of patient recruited had cerebral desaturations at the 20% level. The number of decrease in rSO_2 below 20% with the different NIRS devices was 1.5, 1.7, and 2.3 desaturations/patient recruited with the FORE-SIGHT, EQUANOX Classic 7600, and INVOS 5100C-PB, respectively.

The data for decreases in rSO_2 in the ICU are shown in table 5. In total, there were 1,120 episodes of rSO_2 below 20% relative to baseline in 66 patients in the ICU. Thirty-four of these patients were in the control group and account for 70% of all desaturations in the ICU. The remaining 32 patients in the intervention group accounted for 30% of all desaturations in the ICU ($P = 0.08$). All 66 patients who had decreases in rSO_2 below 20% of baseline in the ICU also had desaturations below 10% in the OR. Of the patients who had cerebral desaturations below 20% of baseline in the OR, 39 (49%) also had decreases in rSO_2 below 20% of baseline in the ICU (23 the control group and 16 in the intervention group, $P = 0.79$). The CDL in the ICU was 58% smaller in the intervention group, 454 (870) %.min compared with the control group, 1,070 (1,961) %.min ($P = 0.02$; table 5).

Follow-up to 30 days was successful in all 201 patients in the study. The time on mechanical ventilation, ICU length of stay, hospital length of stay, MOMM score, and other adverse events are shown in table 6. No significant differences

Table 3. Demographic Data, Medical Conditions, Perioperative Risk Estimates, and Perioperative Data

Demographic Data	All Patients (N = 201)	Control (N = 99)	Intervention (N = 102)	P Value (Control vs. Intervention)
Age (yr), mean ± SD	71 ± 11.2	72 ± 9.4	69 ± 12.6	0.12
Men	145 (72.1%)	71 (71.7%)	74 (72.6%)	0.90
Obstructive lung disease	20 (9.9%)	9 (9.1%)	11 (10.8%)	0.69
Hypertension	160 (79.6%)	84 (84.9%)	76 (74.5%)	0.07
Smoker	23 (11.4%)	10 (10.1%)	13 (12.8%)	0.56
Diabetes	59 (29.4%)	29 (29.3%)	30 (29.4%)	0.99
Congestive heart failure	54 (26.9%)	23 (23.2%)	31 (30.4%)	0.25
Myocardial infarct in the past	9 (4.5%)	5 (5.1%)	4 (3.9%)	0.70
Chronic renal failure	28 (13.9%)	14 (14.1%)	14 (13.7%)	0.93
EuroScore II, mean ± SD	5.28 ± 4.9	5.18 ± 4.7	5.37 ± 5.1	0.78
EuroScore II ≥ 10*	27 (13.4%)	13 (13.1%)	14 (13.7%)	NS
Redo surgery*	38 (18.1%)	19 (19.2%)	18 (18.6%)	NS
Combined coronary bypass and valvular surgery*	141 (70.1%)	73 (73.7%)	68 (66.7%)	NS
Multiple valvular surgeries*	57 (28.2%)	30 (30.3%)	27 (26.5%)	NS
Cardiopulmonary bypass time (min), mean ± SD (range)	135.9 ± 54.2 (38–375)	132.0 ± 50.2 (38–375)	139.6 ± 57.8 (48–334)	0.31
Aortic cross clamp time (min), mean ± SD (range)	105.8 ± 42.4 (14–277)	100.8 ± 34.6 (14–225)	110.6 ± 48.5 (32–277)	0.10

*There is some patient overlap in these categories.
NS = not significant.

Table 4. Cerebral Desaturation Data in the Operating Room

Cerebral Saturation Data	All Patients (N = 201)	Control (N = 99)	Intervention (N = 102)	P Value (Control vs. Intervention)
Baseline cerebral saturation at room air, mean ± SD (range)	62.5 ± 8.0 (28–81)	62.8 ± 7.0 (43–80)	62.2 ± 8.9 (28–81)	0.60
Baseline cerebral saturation with supplemental oxygen, mean ± SD (range)	66.1 ± 8.1* (42–84)	66.5 ± 7.0* (48–81)	65.7 ± 8.9* (42–84)	0.47
Number of patients with increases in baseline cerebral saturation with supplemental oxygen	183	92	91	0.85
Number of cerebral desaturations below 10% relative to baseline (mean per patient; range)	979 (4.77; 0–85)	634 (6.3; 0–66)	345 (3.3; 0–85)	0.06
Number of patients with desaturations below 10% relative to baseline	127 (63.2%)	56 (56.6%)	71 (69.6%)	0.04
Number of cerebral desaturations below 20% relative to baseline (mean per patient; range)	434 (2.2; 0–47)	300 (3.2; 0–47)	134 (1.3; 0–15)	0.02
Number of patients with cerebral desaturations below 20% relative to baseline	80 (39.8%)	46 (46.5%)	34 (33.3%)	0.06
CDL (%.min), mean ± SD (95% CI of mean)		398 ± 870 (140–656)	104 ± 217 (28–179)	0.03

Baseline cerebral saturation increased significantly with oxygen.
*$P < 0.001$ compared to room air, paired t test.
CDL = cerebral desaturation load, cumulative area under the curve of desaturation over time for decreases in rSO_2 values below 20% relative to baseline.

between groups were found. The impact of interventions to reverse decreases in rSO_2 on the components of the composite index, MOMM, is shown in table 7.

Discussion

The primary goal of the NORMOSAT trial was to determine whether decreases in rSO_2 in cardiac surgery patients could be prevented using a NIRS-guided intervention algorithm in the setting of a multicenter prospective randomized study. Our results confirm the feasibility of reversing decrease in rSO_2 below 10% baseline in patients in all sites included in

the trial. Although 63% of all patients had decreases in rSO_2 below 10% baseline in the trial, only 40% of the patients progressed to desaturations below 20% of baseline mainly because fewer patients continued to desaturate in the intervention group. Only 48% of patients progressed to desaturations below 20% of baseline in the intervention group as opposed to 82% of patients in the control group. These data confirm the feasibility of using early interventions to prevent further cerebral desaturations in this patient population.

This trial also further confirms that interventions to reverse decreases in rSO_2 also result in a reduction in the overall

Table 5. ICU Cerebral Saturation Data

	All Patients	Control	Intervention	P Value (Control vs. Intervention)
Number of cerebral desaturations below 20% relative to baseline (mean per patient; range)	1,120 (5.6; 0–240)	789 (7.97; 0–240)	331 (3.2; 0–66)	0.14
Number of patients with desaturations below 20% relative to baseline	66 (32.8%)	34 (34.3%)	32 (31.4%)	0.65
Number of patients with cerebral desaturations below 10% relative to baseline in the operating room and below 20% relative to baseline in the ICU	66 (32.8%)	34 (34.3%)	32 (31.4%)	0.65
Number of patients with cerebral desaturations below 20% relative to baseline in the operating room and below 20% relative to baseline in the ICU	39 (19.4%)	23 (23.2%)	16 (5.9%)	0.79
CDL (%.min), mean ± SD (95% CI of mean)		1070±961 (386–1754)	454±870 (140–767)	0.02

No intervention was made for cerebral desaturations in the ICU. Control and intervention relate to the groups of patient in the operating room.
CDL = cerebral desaturation load, cumulative area under the curve of desaturation over time for decreases in rSO_2 values below 20% relative to baseline; ICU = intensive care unit.

Table 6. Time on Mechanical Ventilation, ICU Length of Stay, Hospital Length of Stay, MOMM Score, and Other Adverse Events at 30 Days Postcardiac Surgery for Patients Who Did Not Have Cerebral Desaturations (No Desaturation) and for Patients in the Control Group and the Intervention Group Who Had Cerebral Desaturations

Adverse Events	No Desaturation (N = 121)	Control (N = 46)	Intervention (N = 34)	P Value (Control vs. Intervention)
Time on mechanical ventilation (h), mean ± SD (25–75 percentile)	27.7±76.0 (7–20)	22.5±6.7 (5.8–17.3)	17.4±27.6 (5–16)	0.57
ICU length of stay (h), mean ± SD (25–75 percentile)	74.4±100.2 (22.5–95.5)	80.5±86.8 (24.8–97)	63.0±58.3 (22–85.5)	0.31
Hospital length of stay (d), mean ± SD (25–75 percentile)	10.7±8.0 (6–12.5)	9.9±5.8 (6–14.3)	11.0±7.2 (6.8–12.5)	0.46
Number of patients with MOMM	18 (14.9%)	10 (21.7%)	6 (17.6%)	0.65
Number of patients with readmissions	9 (7.4%)	5 (10.9%)	4 (11.8%)	0.90
Number of patients with delirium	14 (11.6%)	7 (15.2%)	4 (11.8%)	0.66
Number of patients with seizures	2 (1.7%)	1 (2.2%)	0 (0%)	0.39
Number of patients with renal failure	46 (38.0%)	17 (37.0%)	12 (35.3%)	0.88
Number of patients with blood products transfusions	87 (72.5%)	34 (73.9%)	25 (73.5%)	0.969
Number of patients with new-onset arrhythmias	41 (34.2%)	19 (41.3%)	18 (52.9%)	0.85
Number of patients with gastrointestinal complications	5 (4.2%)	0 (0%)	0 (0%)	1.000
Number of patients with new myocardial infarction	0 (0%)	0 (0%)	0 (0%)	1.000

ICU = intensive care unit; MOMM = major organ morbidity and mortality.

severity of desaturation as defined by the CDL. Because prolonged low rSO_2 values during cardiac surgery have been associated with significantly higher risks of early postoperative cognitive decline,[10] the reduction in CDL seen in the intervention group could potentially lead to a reduction in overall complications in an appropriately powered trial.

In addition to the primary feasibility endpoint, this study also demonstrated the feasibility of conducting a multicenter RCT in several Canadian cardiac anesthesia sites using an algorithm for decision-making and treatment in the OR. Specifically, the transfer of data from research sites to the coordinating center through the NORMOSAT website was easily achieved. Supervision of the application of the algorithm in the OR ensured that all attempts were made to reverse decreases in rSO_2, and follow-up of patients for 30 days postsurgery was successful in all centers. The quality of the cerebral saturation data collected did not appear to be influenced by the type of device used, although this needs to be confirmed with more sites using the different devices. Our results suggest that it would be possible to conduct a large-scale randomized clinical trial with a similar design to examine the effect of preventing decreases in rSO_2 on meaningful clinical outcomes such as a composite outcome measure consisting of cardiovascular mortality, new-onset neurologic events, atrial fibrillation, and postoperative myocardial infarction. Previous studies have shown

Table 7. Impact of Interventions to Reverse Cerebral Desaturations on the Components of the Major Organ Morbidity and Mortality Composite Endpoint

Adverse Events	All Patients (N = 80)	Control (N = 46)	Intervention (N = 34)	P Value
Death	10 (12.5%)	6 (13.0%)	4 (11.8%)	0.49
Cerebrovascular accident	3 (3.8%)	2 (14.3%)	1 (2.9%)	0.54
Reoperation	9 (11.3%)	5 (10.9%)	4 (11.8%)	0.70
Respiratory failure	16 (20.0%)	8 (17.4%)	8 (23.5%)	0.95
Dialysis	11 (13.8%)	6 (13.0%)	5 (14.7%)	0.80
Wound infection	5 (6.3%)	3 (5.4%)	2 (5.9%)	0.63

some benefits of reversing cerebral saturation during cardiac surgery on outcomes[10–15] but not in a high-risk population of patients for whom NIRS is most often used. A large-scale RCT would clarify the benefit of reversing cerebral desaturations in this population of patients.

As previously described,[17] a large proportion of patients (75%) also had desaturations in the ICU. Interestingly, patients without desaturations in the OR continued to be free of desaturations in the ICU. Also, there was a significant decrease in the CDL of patients in the intervention group compared with the control group in the ICU. Because no interventions were made in the ICU to reverse decreases in rSO_2, these results suggest that reversing cerebral desaturations in the OR might protect patients by reducing the severity of decreases in rSO_2 in the ICU. The effect of combining interventions in the OR and in the ICU on the CDL should be the subject of further investigation.

There were several limitations in our study. For example, it was not powered to measure the impact of reversal of decreases in rSO_2 in the OR on perioperative adverse events. Patients who had a low baseline rSO_2 have been observed to have poor outcome at 1 month and 1 yr after cardiac surgery.[21] The same appears to be true for patients who do not increase their baseline rSO_2 values with supplemental oxygen.[21] We were unable to show an association between increased rSO_2 values with supplemental oxygen and outcomes because 100% of our patients had increases in rSO_2 values when supplemental oxygen was added in the OR. One possible reason may be the difference in sample size between the studies. We were also unable to find a relationship between postoperative delirium and low baseline rSO_2 values or large decreases in intraoperative rSO_2 values as others have.[12] Our definition of delirium may be at the source of this difference because it was obtained from the charts and not from a systematic screening of the patients in the ICU. For most adverse events measured in this study, the number of events in patients with desaturations was very similar to the number of events in patients who did not have significant decreases in rSO_2. Furthermore, successful interventions to reverse decreases in rSO_2 had very little impact on reducing the occurrence of adverse events (tables 6 and 7). One reason may the lack of power of the feasibility trial, but we also have to consider the possibility that our patient population may have been so high risk that interventions to reverse decreases in rSO_2 have very little impact on outcomes. We preferentially used a high-risk

population of patients for two reasons. One, these complex surgeries in high-risk patients tend to have a greater incidence of technical complications resulting in catastrophic events better detected by NIRS than any other available device.[1,8] Second, cardiac anesthesiologists tend to reserve the use of NIRS for this patient population believing that the cost–benefit ratio is greater than the use of NIRS in healthier patients.

As for sample size estimates for future outcomes studies, this feasibility trial suggests that 3,080 patients in total would be needed to detect a significant decrease in mortality, 4,638 patients for a decrease in stroke rate, and 1,610 patients for a decrease in the rate of delirium. However, the use of a composite endpoint as a primary outcome, other than MOMM because it was not shown to improve with interventions to reverse cerebral desaturations, could help to reduce the sample size in the large-scale RCT. A definitive RCT would give important information on outcomes and on the numbers needed to treat in this patient population. In parallel, a study could be undertaken to show a benefit of NIRS monitoring in a healthier population, but the number of patients with cerebral desaturations would decrease significantly, thus increasing the total number of patients to be studied.

In conclusion, in this multicenter prospective randomized study, we determined that the use of a physiologic algorithmic approach to management of intraoperative decrease in rSO_2 was feasible. There was a high success rate with the algorithmic approach to the reversal of significant decreases in rSO_2 in high-risk cardiac surgery patients in all participating centers. Early interventions in the OR had a significant impact on further progression of cerebral oxygen desaturations and on the overall cerebral oxygen desaturation load in these patients. Interventions to reverse decreases in rSO_2 in the OR appear to protect patient from desaturations in the ICU. A large multicenter RCT trial would be needed to measure the impact of intraoperative reversal of decreases in rSO_2 on clinical outcomes in high-risk cardiac surgery patients, and this study suggests that such a trial is feasible.

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Competing Interests

Dr. Deschamps has received speaking honoraria for educational seminars on the use of cerebral saturation monitoring in cardiac surgery patients sponsored by the companies Nonin Medical Inc., Plymouth, Minnesota, and Covidien Inc. (now a part of Medtronic), Boulder, Colorado. Dr. Denault has received speaking honoraria for educational seminars on the use of cerebral saturation monitoring in cardiac surgery patients sponsored by Covidien Inc. (now a part of Medtronic). NONIN Medical Inc. provided equipment and sensors for one of the centers implicated in the study. The other authors declare no competing interests.

Reproducible Science

Full protocol available from Dr. Deschamps: deschamps.a@gmail.com. Raw data available from Dr. Deschamps: deschamps.a@gmail.com.

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Appendix 2: Research Ethics Review Board

Center	RERB Approval Date
1	August 2011
2	December 2011
3	February 2012
4	March 2012
5	April 2012
6	May 2012
7	July 2012
8	October 2012

There was a span of 14 months between Research Ethics Review Board (RERB) approval between the first and the last site to start recruitment for the study. This is the reason why more than 12 months were needed to complete the study and also the reason why the number of patients recruited per site was different.