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Goal-Directed Perfusion Methodology for Determining Oxygenator Performance during Clinical Cardiopulmonary Bypass

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Abstract: New generation oxygenators incorporate arterial line filtration either sequential to, or directly in, the gas exchange module. This unique design may affect gas exchange performance by altering the operational characteristics of the device. The present study was designed to evaluate three oxygenators in a clinical setting using a goal-directed perfusion algorithm during cardiopulmonary bypass (CPB). After institutional review board approval, 60 adult patients undergoing cardiac surgery for acquired heart disease were matched for disease state and body size into three groups based on oxygenator type: Terumo SX18™ (n = 20), Terumo FX15™ (n = 20), and LivaNova Inspire6F™ 6 Dual (n = 20). An external arterial line filter was used with the FX15, whereas the SX18 and Inspire6F had integrated arterial filters. All perfusion, anesthetic and postoperative care management was standardized using institutional goal-directed patient management processes. Data were collected and stored according to quality improvement guidelines. There were no differences in demographics or type of surgical procedure performed among groups. The Inspire6F patients required lower fraction of inspired oxygen values as compared to the SX18 (67.9% ± 6.2% vs. 75.4% ± 6.5%, $p < .005$) and FX15 (79.1% ± 8.4%, $p < .0001$) groups. Arterial oxygen content and oxygen delivery were slightly higher in the FX15 group as compared to SX18 (13.1 ± 1.4 mL O_2/dL vs. 12.4 ± 1.1 mL O_2/dL, 611.1 ± 150.4 mL O_2 vs. 528.2 ± 102.3 mL O_2, $p < .05$). The FX15 patients had significantly higher CPB hematocrits compared to SX18 patients (30.3% ± 3.9% vs. 27.7% ± 2.6%, $p < .05$), but were not different when compared to the Inspire6F group (28.8% ± 3.5%, $p < .50$). There were no differences in intraoperative transfusion rates, but a higher percent of patients received postoperative transfusions in the SX18 group as compared to either FX15 or Inspire6F groups ($p < .039$). There were no differences in postoperative morbidity or complications in any group. In conclusion, the use of the SX18 was comparable to newer generation oxygenators in regard to gas exchange performance and the degree of hemodilution. **Keywords:** oxygenator, performance, clinical study, gas transfer, outcomes. *J Extra Corpor Technol. 2017;49:81–92*

Adequate perfusion is dependent on a number of factors that include the delivery of nutrients, their uptake and metabolism, the metabolic rate of tissue, and the removal of waste products. This delivery is dependent on the physical process of fluid movement through intact and functioning cardiopulmonary and vascular tissue beds. During extracorporeal circulation with cardiopulmonary bypass (CPB), these intrinsic systems are supplemented through the use of the heart–lung machine that is comprised of various synthetic devices that serve to temporarily replace biological functions (1). Although, as in any complex multifaceted process, all aspects of the system must perform as expected, it is the interaction of the pump and oxygenator that essentially make extracorporeal circulation a reality. During the 60 plus years that CPB has been used, many changes have occurred to the essential devices of the heart–lung machine, but arguably, the most dramatic developments have occurred to the oxygenating systems (2,3).

Over the past several decades, many of the design changes to oxygenators focused on minimizing surface area and improving biocompatibility (4,5). Such alterations served to reduce hemodilution and ensuing anemia, and curtail the systemic inflammatory response elicited when

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blood is exposed to foreign surfaces (6). At the same time, changes to the surfaces within an oxygenator (gas exchange bundle, heat exchanger, venous/cardiotomy reservoir, and filters) included the incorporation of surface modifying agents to reduce thrombotic potential and reduce inflammation (7–9).

The quest for continued reduction in prime volumes for extracorporeal circuits has resulted in the production of oxygenators that have integrated arterial line filters either directly in the membrane module, or incorporated into a sequential design to it (10–12). This design modification removed the external arterial line filter simplifying the CPB circuit, leading to considerable debate within the perfusion community. Concerns about air handling for the removal of gaseous emboli have arisen questioning the intrinsic safety of these devices as compared to their predecessors (13–17). An additional concern is the potential catastrophic effect of thrombus formation within the integrated filter media which cannot be bypassed such as possible with the use of external filters with a shunt line placed around the filter.

During the past decade, several prospective randomized trials have evaluated oxygenators (6,18–21) but few have examined gas exchange performance as a critical metric. Recent research in the importance of reducing postoperative renal dysfunction has examined the roles of allogeneic transfusion and oxygen delivery as mitigating and modifiable factors. This has served as a foundation for a goal-directed modality for perfusion and is predicated upon oxygenator performance and oxygen delivery during CPB (22–25). Therefore, the purpose of this study was to examine oxygenator performance in a clinical setting comparing three commercially available oxygenators.

MATERIALS AND METHODS

Patient Population

All patients undergoing cardiac surgery with CPB at a single center over an 18-month period from January 2013 to July 2014 were considered for the study. Inclusion criteria included patients greater than 19 years of age undergoing surgery for acquired heart disease such as coronary revascularization, valve repair or replacement surgery, and combined procedures involving both valvular surgery and coronary revascularization. Exclusion criteria included patients undergoing emergent cardiac surgery, patients with congenital heart disease, patients with preoperative anemia as determined by either an intraoperative postheparinization hematocrit less than 28%, or patients who required priming of the CPB circuit with allogeneic packed red blood cells (PRBCs). Patients with preexisting coagulopathies as determined by abnormal presurgical coagulation screens or those currently receiving oral anticoagulants were not eligible for the study, nor were patients with preoperative platelet counts under 125,000/uL.

All patients were operated upon by members from the same surgical team that included one cardiac surgeon, two cardiovascular anesthesiologists, and two perfusionists. Standardized protocols were implemented as a means of reducing inter-clinician variation. After review of published guidelines and current best practices in cardiac surgery, anesthesia, and perfusion, protocols were devised and agreed upon by the surgical team. This mechanism for standardization became the basis for a goal-directed approach to patient management which was implemented across all surgeries.

CPB Circuit

A standard modular heart–lung machine (Advanced Perfusion System 1, Terumo Cardiovascular, Ann Arbor, MI) with a central control monitor was used for all patients with the following safety devices in place: centrifugal blood pump, air and level detection systems, pressure monitoring for the arterial line, cardioplegia circuit, and both antegrade and retrograde cardioplegia administration. All safety devices had preprogrammed limits of operation that were not altered throughout the experimental time period. Vacuum-assist venous drainage was used only for minimally invasive aortic valve procedures with negative pressure not exceeding −40 mmHg. The CPB circuit contained a membrane oxygenator with or without an integrated arterial filter, a tip-to-tip coated tubing pack (XCoating®, Delphin® Pump, Terumo Cardiovascular), a 4–1 blood to crystalloid cardioplegia circuit (Capiox CP50®,Terumo Cardiovascular), and in-line arterial and venous blood gas monitor (CDI 500®, Terumo Cardiovascular). Intraoperative autotransfusion (IAT) was used on every case (CATS®, Terumo Cardiovascular) with autotransfusate reinfused through a 20-micron blood filter. The prime constituents included a balanced physiologic crystalloid solution (Plasma-Lyte® 148; Baxter Healthcare Corp., Chicago, IL) (initial 2,000 mL), 8.4% sodium bicarbonate (50 mL), porcine heparin (10,000 IU), 25% salt-poor albumin (100 mL), 25% mannitol (50 mL), and epsilon aminocaproic acid (EACA) (10 g in 20 mL). Autologous priming (AP) was performed on every patient by using the patients' own blood to displace volume from the arterial line, oxygenator, and venous line through the recirculation line into collection bags. The AP process began postheparinization when the activated clotting time (ACT) was above 300 seconds, and rising. The final prime volume ranged from 800 to 900 mL. Albumin, mannitol, and EACA were added after the volume was displaced from the circuit by AP. Blood gas management

was maintained using an alpha-stat methodology with core blood temperature (bladder) allowed to drift-cool to approximately 34°C. Rewarming was achieved on a gradual basis with arterial blood temperature not exceeding 37°C, and core temperature rewarmed to approximately 36.5–37°C prior to separation from CPB. CPB blood flow ($CPBQ_b$) was kept between 1.8 and 2.4 L/min/m^2, and mean arterial pressure (MAP) was kept between 50 and 80 mmHg. Arterial blood gas parameters were maintained as follows: pH, 7.30–7.45; PaO_2, 150–250 mmHg; $PaCO_2$, 35–55 mmHg; HCO_3, 23–27 mEq; base excess, −2 to 2; and mixed venous oxygen saturation (SvO_2) greater than 65%. Desflurane was administered to all patients throughout the CPB period and was maintained between 1% and 3%. Porcine heparin was initially administered at 400 IU/kg body weight, with a targeted ACT maintained above 500 seconds. Additional heparin was titrated throughout the CPB period to achieve these minimal ACT values. Heparin was reversed with protamine administered at a ratio of 100 mg to every 10,000 IU of total heparin.

All devices, including oxygenators, were obtained through the hospital's negotiated purchasing agreements that had been previously established, by non-clinicians with manufacturers, without any input from any clinician involved in this study. No device was donated, nor obtained, at a rate below what the hospital's purchasing department had previously established. At no time during, or after this study, were conversations held with any manufacturer of any device used within this study.

Surgical Technique

Surgery was performed through a median sternotomy except for minimally invasive procedures for aortic valve surgery where a hemi-sternotomy was used. For coronary artery bypass graft surgery, a left internal thoracic artery was always used with greater saphenous vein harvesting performed endoscopically by physician assistants. Cannulation was achieved with a 24-Fr aortic cannula (EZF24TA®, Edwards Lifesciences, Irvine, CA), a 36/46 Fr triple-stage venous cannula (TF364602A®, Edwards Lifesciences), and both antegrade (ARO14V®, Edwards Lifesciences) and retrograde (RCO14IT®, Edwards Lifesciences) cardioplegia cannulae. Venting of the heart was achieved with a 20-Fr catheter (12,112, DLP®, Medtronic, Minneapolis, MN) placed either into the right superior pulmonary vein and advanced in to the left ventricle, or placed in the pulmonary artery.

Anesthetic Technique

There was no change in clinical practice during the study period. All patients were anesthetized with a balanced technique combining narcotics and inhalation gases. Indwelling catheters were placed for the measurement and continuous monitoring of arterial and pulmonary artery blood pressures (BPs). Additional continuous monitoring included electrocardiogram, near infrared spectroscopy (NIRS) (INVOS™ 5100, Covidien Corporation, Mansfield, MA), and urine output. Premedication consisted of intravenous midazolam, and anesthesia was induced with either propofol or etomidate as a hypnotic, fentanyl as the narcotic, rocuronium for muscle paralysis, and maintained with inhalational agent desflurane or sevoflurane. The anesthetic agents were titrated to effect during surgery based on vital signs (heart rate, BP) and Bispectral (BIS) (Bispectral Index™, Covidien) values, and muscle relaxant supplemented based on the train-of-four response. Certain patients who were anticipated to undergo rapid extubation also received a continuous infusion of dexmedetomidine dependent on the pre-operative clinical assessment, which was initiated upon institution of CPB. Ventilation was achieved to normocapnia under volume control at a frequency of 10–12 breaths per minute, and a tidal volume of 8–10 mL/kg of ideal body weight, and positive end-expiratory pressure maintained at 5 cm H_2O. Glycemic control throughout the perioperative period was achieved by maintaining glucose levels at 120–150 mg/dL by the use of insulin infusion, or bolus, as necessary. At the conclusion of surgery, patients were transported to the cardiovascular intensive care unit (CVICU) with oxygen and monitoring of arterial blood pressure, heart rate, and pulse oximetry. Patients were weaned from CPB as per standard protocols. NIRS and BIS analysis monitoring were routinely used with interventions for improving cerebral saturation instituted once levels dropped below 25% of baseline (pre-anesthetic induction) levels, or if saturation values were to fall below 40%. These interventions included increasing cardiac output, increasing MAP, increasing $PaCO_2$ levels, administering additional anesthetic agents, correcting hemodilution through urine output, or the administration of PRBC.

Transfusion of Allogeneic Blood Products

The intraoperative transfusion threshold for PRBC administration was set at a nadir hematocrit of 24%, with either a drop in SvO_2 below 65% and/or NIRS decline to 25% below baseline, or an absolute value under 40% unresponsive to increased $CPBQ_b$ or increased depth of anesthesia. Transfusion of PRBC in the CVICU was achieved when patients had a low hematocrit (<24%) and a concurrent hypoxic indication unresponsive to changes in ventilator settings, such as a reduced SvO_2 or low cardiac index (less than 2 L/min/m^2). Intraoperative transfusion of other blood products occurred when excessive bleeding was encountered, as assessed by the surgeon, and postoperatively when chest tube output exceeded 300 mL/h for two consecutive hours. Fresh frozen plasma (FFP) was given when international normalized ratio

(INR) exceeded 1.5, with two units administered initially before repeat INR assessment. Single-donor platelets (SDP) platelets were used for platelet counts lower than 100,000/uL of blood with patients receiving one SDP prior to reassessment. Cryoprecipitate (CRYO, 10 pack units) was administered if fibrinogen levels were below 100 mg/dL. These criteria were the same for the entire hospital stay.

Study Groups

The three study groups were treated consistently other than the use of a membrane oxygenator: SX18—Capiox® SX18, FX15—FX15® (FX15RE40 4,000-mL hard shell reservoir, Terumo Cardiovascular), and Inspire6F—Inspire6F 6F® HVR Dual (LivaNova, Arvada, CO) (Table 1). All oxygenators were assembled and primed following the manufacturer's instructions for use (IFU). The only modification to the perfusion circuit occurred in SX18 patients where the external arterial line filter had system line pressure measured off a side port of a three-way stopcock, whereas the FX15 and Inspire6F used a high-pressure port on the oxygenator for line pressure determination. The external arterial line filter (AF125X, Terumo Cardiovascular) used with the SX18 consisted of a 37-micron filter media and a polycarbonate housing, and had a prime volume of 125 mL. This was a non-randomized, sequential study with the SX18 patients operated upon during the initial phase of the study, and FX15 and Inspire6F following immediately thereafter. SX18 patients did not overlap with FX15 and Inspire6F. Patients having either the FX15 or Inspire6F were alternatively placed into either group by sequential circuit preparation, and no clinical decision was made to use one device over another for any patient.

All patients were stratified according to risk through the utilization of readily available models, which calculated a patient's risk for morbidity and mortality. In the initial phase of the study where the SX18 was used, patients were risk stratified using the European System for Cardiac Operative Risk Evaluation (Euroscore II) classification methodology. Prior to the use of either the FX15 or the Inspire6F, a decision was made to shift to the Society of Thoracic Surgeons (STS) risk stratification calculator (http://www.sts.org/quality-research-patient-safety/quality/quality-performance-measures). All patients in the latter two groups had this method of determining risk. Although not powered as an outcomes study, quality performance metrics as described by the STS national measures were analyzed as part of the institutional quality improvement process.

End Points

The primary end points were oxygenator performance, which included fraction of inspired oxygen (FiO_2) and ventilating gas flow (sweep rate). Oxygenation parameters included arterial oxygen content (CaO_2), venous oxygen content (CvO_2), delivery of oxygen (DO_2), oxygen consumption (VO_2), and oxygen extraction (%). Secondary end points included intra- and postoperative fluid management, transfusion rates of allogeneic blood products (PRBC, FFP, SDP, and CRYO), and chest tube output. Additional data collected included clinical outcome data such as incidence of perioperative myocardial infarction, acute lung injury, new-onset atrial fibrillation, respiratory insufficiency, renal insufficiency, acute renal failure, neurological complications, hospital length of stay, 30-day postoperative readmission, and 30-day mortality rates.

All data were obtained from the Perfusion Electronic Medical Record (PEMR) with data extracted and entered into the Electronic Perfusion Quality Improvement Perfusion Database (EQUIPD). The function of the EQUIPD is fundamentally a means to reduce unwanted variation among clinicians performing repetitive, protocol-driven procedures (26). All data were continuously analyzed and compared to benchmarked values to assure compliance to

Table 1. Oxygenator operating and performance characteristics.

	SX18	FX15	Inspire6F
Manufacturer	Terumo Cardiovascular	Terumo Cardiovascular	LivaNova
Surface area (m^2)	1.8	1.5	1.4
Priming volume	270	144	284
Blood flow range (L/min)	.5–7.0	.5–5.0	.5–6.0
Heat exchange surface area (m^2)	.22	.14	.43
Heat exchange material	Stainless steel	Stainless steel	Polyurethane
Coating	X Coating™	X Coating™	Phisio™
Integrated filter surface area (cm^2)	—	360	68
Integrated filter pore size (υ)	—	32	38
O_2 transfer (mL/min) at 5 L/min—FiO_2 100%	305	330	318
CO_2 transfer (mL/min) at 5 L/min–1:1 gas-to-blood flow ratio	200	235	273
Pressure drop (mmHg) at 5 L/min	125	115	174

All values taken from manufacturers' IFU.

accepted standards. The variable used was hematocrit obtained from historical controls using the first on-CPB level (25.2%) and expecting a 2.0% increase with the implementation of the integrated arterial filter oxygenators. The power of the test was set at .80 and the standard deviation (SD) was 5.5. The calculated sample size using these conditions was calculated to be 60. The local Research Ethics Committee of Wright Center for Graduate Medical Education, Institutional Review Board, Scranton, PA, approved the research and determined that informed consent was not necessary for the study (study no. PMC061814AL).

Statistical Analysis

Data are presented as mean and SD or median and 25th–75th percentile if continuous, and as percent if categorical. All data were analyzed using a commercially available statistical package (LP, STATA/IC®, StataCorp, College Station, TX). All non-categorical data were analyzed using a one-way analysis of variance with Bonferroni correction for multiple measurements. Categorical data were analyzed using a Fisher's exact test. Statistical significance was accepted at the $p < .05$ level.

RESULTS

All three groups of patients were evenly matched without significant difference in any preoperative demographic variable or surgical procedure (Table 2). Intergroup comparison of risk stratification revealed no differences between FX15 and Inspire6F patients. During CPB, there were no differences for either bypass or cross-clamp times and no patients underwent a circulatory arrest period. Fluid management varied among groups with significantly more on-CPB crystalloid solution administered to the SX18 patients compared to the FX15 and Inspire6F groups. Total perfusion volume (defined as all volume added during CPB) was also greater milliliters in this group (SX18, 2,870 ± 1,308 mL vs. FX15, 2,058 ± 740 mL, $p < .025$). Ultrafiltration was only used in a small number of patients (SX18, $n = 0$; FX15, $n = 2$ and Inspire6F, $n = 1$), with no differences between groups. There were no on-CPB differences in PRBC transfusion rate nor volume, but a trend toward higher allogeneic transfusion volumes was seen in the SX18 patients both for FFP ($p < .054$) and for SDP ($p < .073$) (Table 3). Transfusion volumes are displayed as intraoperative, postoperative, and total volume and are shown in Figure 1A–C and in Table 5. Postoperative PRBC transfusion volume was significantly higher in the SX18 (306.5 ± 381.8 mL) vs. FX15 (58.8 ± 165.0 mL, $p < .011$) Total transfusion volume was higher in SX18 patients for PRBC vs. FX15 (639.9 ± 672.0 mL vs. 243.9 ± 335.2 mL, $p < .042$), and for FFP SX18 vs. Inspire6F (208.1 ± 381.6 mL vs. 15.3 ± 66.8 mL, $p < .029$. Transfusion rates were higher in the postoperative period for SX18 patients but did not differ among groups at any other time (Figure 2). Higher quantities of IAT processed volumes and anticoagulant volumes were seen in the SX18 vs. Inspire6F groups (3,763 ± 1,206 mL vs. 2,995 ± 1,052 mL, $p < .05$, 410.0 ± 149.2 mL vs. 315.0 ± 58.7 mL, $p < .017$), respectively. A greater volume of autotransfusate was returned to the SX18 patients (1,334.7 ± 656.2 mL) compared to either FX15 (844.3 ± 338.8 mL, $p < .010$) and Inspire6F groups (915.8 ± 480.1 mL, $p < .035$). Urine output during CPB did not vary among groups, but the anesthesia urine output (not including CPB) was higher in the SX18 patients (539.5 ± 342.5 mL) when compared to

Table 2. Demographic data for all patients.

	SX18	FX15	Inspire6F	*p* Value
Number	20	20	20	—
Gender (% male)	65.0	55.0	60.0	.812
Age (years)	65.3 ± 13.1	69.4 ± 11.3	70.7 ± 12.7	.364
Weight (kg)	84.9 ± 19.9	89.4 ± 28.3	88.0 ± 15.0	.798
Height (cm)	169.7 ± 10.7	169.2 ± 10.3	169.1 ± 13.3	.985
BSA	1.9 ± .3	2.0 ± .3	2.0 ± .2	.717
Operative procedures	CABG (9) CABG/valve (6) Isolated valve (5)	CABG (8) CABG/valve (4) Isolated valve (8)	CABG (7) CABG/valve (7) Isolated valve (7)	
Preoperative EF (%)	49.3 ± 14.5	49.8 ± 13.5	53.0 ± 9.8	.604
Mortality risk*	—	.023 ± .028	.026 ± .021	.606
Morbidity risk*	—	.159 ± .104	.178 ± 0.094	.540
Risk for long length of stay*	—	.669 ± .057	.079 ± .054	.495
Permanent stroke risk*	—	.016 ± .016	.017 ± .011	.726
Prolonged ventilation risk*	—	.099 ± .080	.104 ± .059	.775
Renal failure risk*	—	.046 ± .052	.057 ± .047	.466
Reoperation risk*	—	.063 ± .029	.071 ± .030	.405

CABG, coronary artery bypass graft surgery; EF, ejection fraction. All data are mean ± SD.
*Comparison only made between FX15 and Inspire groups using STS risk stratification calculator, which was not available in SX18 group.

Table 3. Operative data for all patients.

	SX18	FX15	Inspire6F	*p* Value
Number	20	20	20	—
CPB time (minute)	115.7 ± 57.9	101.7 ± 47.8	108.3 ± 33.4	.651
XC time (minute)	69.7 ± 49.7	67.1 ± 44.7	67.6 ± 41.2	.982
AP volume (mL)	1,018 ± 271	1,145 ± 150	985 ± 282	.097
Prime crystalloid (mL)	940 ± 185	855 ± 150	1,015 ± 282	.067
CPB crystalloid (mL)	590 ± 660	360 ± 390	323 ± 407	.001*
CPB 25% albumin (mL)	7.5 ± 18.1	.0 ± .0	7.5 ± 25.5	.307
CPB 5% albumin (mL)	150 ± 170	62.5 ± 137.5	50 ± 102.6	.061
CPB PRBC (mL)	300.0 ± 456.5	152.5 ± 253.1	243.0 ± 349.0	.436
CPB $NaHCO_3$ (mEq)	2.6 ± 11.2	.0 ± .0	11.5+26.4	.079
CPB urine (mL)	331.8 ± 222.5	299.5 ± 183.2	342.1 ± 22.5	.771
Ultrafiltration (mL)	.0 ± .0	90.0 ± 279.0	50.0 ± 223.6	.391
IAT volume processed (mL)	3,763 ± 1,206	3,060 ± 730	2,995 ± 1,052	.036†
IAT anticoagulant volume (mL)	410.0 ± 149.2	380.0 ± 83.4	315.0 ± 58.7	.018‡
IAT returned volume (mL)	1,334.7 ± 656.2	844.3 ± 338.8	915.8 ± 480.1	.007§
Total perfusion volume in (mL)	2,869 ± 1,307.6	2,058.1 ± 739.6	2,261 ± 613.5	.022‖
Total perfusion volume out (mL)	331.8 ± 222.5	389.5 ± 328.4	392.1 ± 284.3	.747
Anesthesia crystalloid (mL)	1,693 ± 526	1,775 ± 820	1,820 ± 698	.840
Anesthesia PRBC (mL)	46.8 ± 150.2	45.0 ± 146.8	.0 ± .0	.391
Anesthesia FFP (mL)	75.0 ± 191.6	0.0 ± 0.0	.0 ± .0	.054
Anesthesia SDP (mL)	75.0 ± 165.1	22.5 ± 73.4	.0 ± .0	.073
Anesthesia CRYO (mL)	.0 ± .0	.0 ± .0	.0 ± .0	.999
Anesthesia urine (mL)	539.5 ± 342.5	218.5 ± 110.3	307.9 ± 194.7	.002¶
Total anesthesia volume in (mL)	1,993 ± 914	1,929 ± 914	1,985 ± 769	.964
Total volume in (mL)	4,799 ± 1,455	3,987 ± 1,259	4,118 ± 897	.089
Total volume out (mL)	871.3 ± 416.8	608.0 ± 337.5	700.0 ± 390.6	.097
Fluid balance (mL)	3,991 ± 1,430	3,379 ± 1,218	3,418 ± 978	.216
Operative time (hours:minutes)	3:54 ± 0:48	3:36 ± 1:00	3:29 ± 0:44	.312

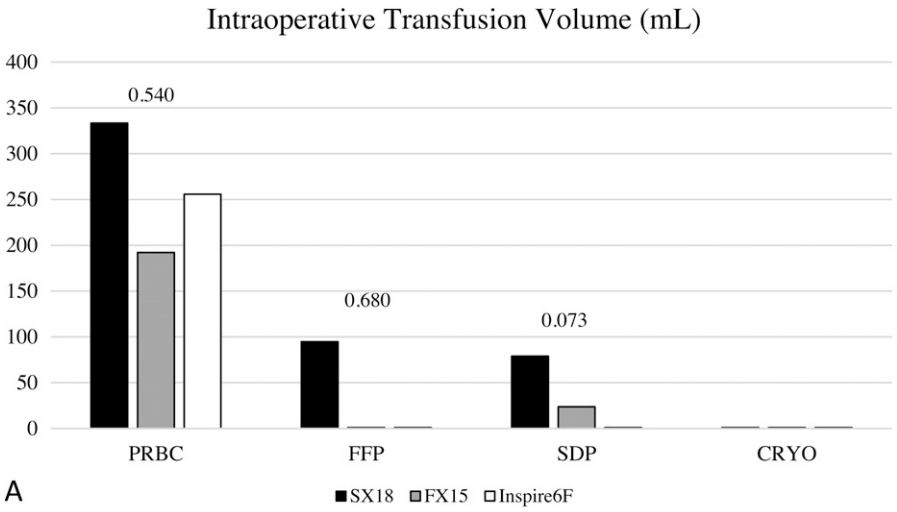
XC, cross clamp. All data are mean ± SD.
*SX18 vs. FX15 ($p < .004$) and Inspire ($p < .02$).
†SX18 vs. Inspire ($p < .05$).
‡SX18 vs. Inspire ($p < .017$).
§SX18 vs. FX15 ($p < .01$) and Inspire ($p < .04$).
¶SX18 vs. FX15 ($p < .001$) and Inspire ($p < .009$).
‖SX18 vs. FX15 ($p < .025$).

FX15 (218.5 ± 110.3 mL, $p < .001$) and Inspire6F (307.9 ± 194.7 mL, $p < .009$) patients.

During CPB, there were no significant differences in CPB bypass parameters including average CPB blood flow, SvO_2, systemic venous resistance (SVR), CPB sweep ate, arterial venous oxygen (AVO_2) difference, DO_2/body surface area (BSA), VO_2, VO_2/BSA, and O_2 extraction (Table 4). However, significant differences between oxygenator groups were found in FiO_2, CaO_2, CvO_2, and DO_2. Average circuit line pressure also varied, but was determined to be a factor of differential pressure monitoring techniques due to the presence of a separate arterial line filter in conjunction with pressure monitoring off a side luer port on a stopcock mounted at the top of the filter.

There were no hematocrit differences among groups in any pre-CPB time period nor did the percent change in hematocrit vary between groups (Figure 3). However, absolute values did change during CPB associated with oxygenator type, and the requirement for additional crystalloid fluids on CPB (Table 2). The FX15 group had the highest on CPB hematocrits vs. the SX18 group (30.3% ± 3.9% vs. 25.8% ± 2.3%, $p < .05$), as well as higher end-CPB values (28.6% ± 3.8% vs. 25.8% ± 2.3%, $p < .01$), and higher last-in-room values (28.5% ± 4.4% vs. 25.8% ± 2.9%, $p < .05$). There were no differences between FX15 and Inspire6F patients at any sample period, and no differences at any postoperative time. Platelet counts were similar across all groups throughout the study period (Figure 4).

Postoperative data for transfusion and chest tube output are shown in Table 5. FX15 patients had lower chest tube output at 24 hours vs. Inspire6F ($p < .026$), whereas total chest tube output was significantly higher in SX18 patients when compared to FX15 ($p < .048$). There were no occurrences of acute renal failure or postoperative dialysis. One patient in each group had a prolonged ventilation period resulting from pulmonary dysfunction. New-onset atrial fibrillation was found in 25% of FX15 and SX18 patients, and in 40% of Inspire6F patients ($p < .490$). Four patients underwent reoperation for bleeding during the hospital admission (FX15, $n = 1$ and Inspire6F, $n = 3$, $p < .153$). There was one hospital death (Inspire6F) resulting from multiorgan system failure and



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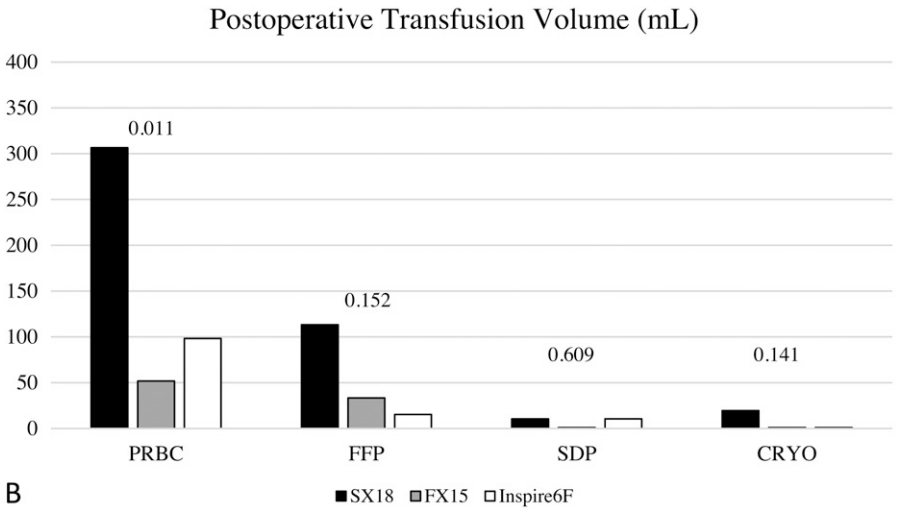

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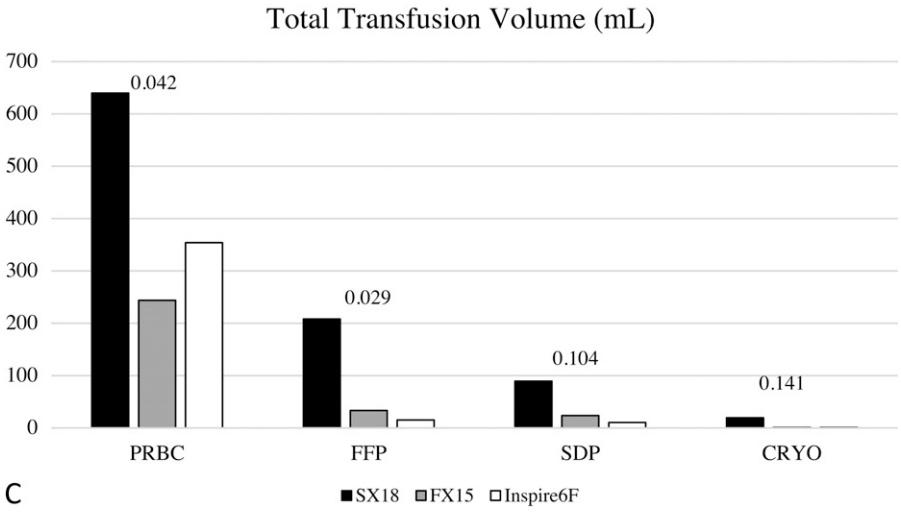

C

Figure 1. (A) Intraoperative, (B) postoperative, and (C) total transfusion volumes for allogeneic blood products.

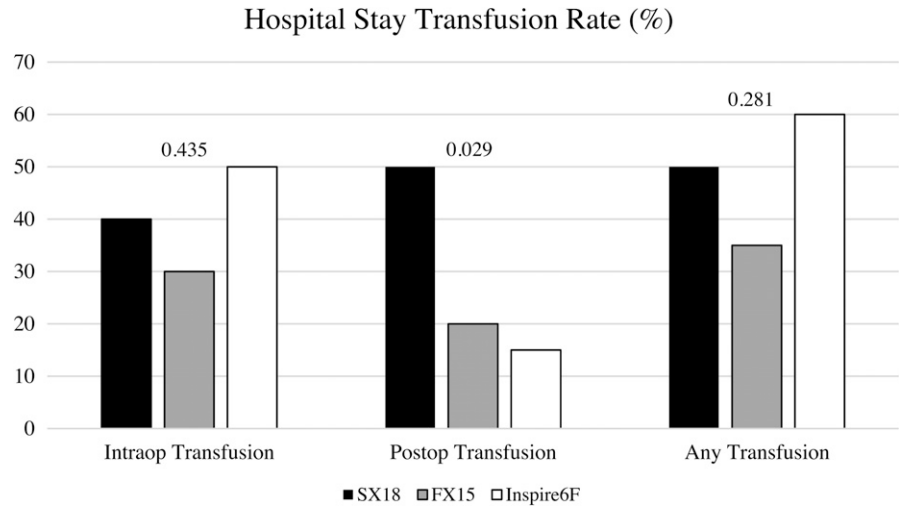

Figure 2. Rate of transfusion for allogeneic blood products during hospital stay.

cardiac arrest ($p < .362$). Total length of stay did not vary among groups.

DISCUSSION

The primary function of an oxygenator is to safely and non-traumatically arterialize venous blood while preserving circulating formed elements in an effort to reduce the activation of inflammatory pathways. Other critical functions include temperature regulation with the use of integrated heat exchangers, and removing particulate contaminants through filtration. The historical development of oxygenators has been replete with engineering milestones in the progression from direct contact systems to those functioning as microporous, semipermeable membranes. Much of the effort in reducing the imprint that oxygenators have on extracorporeal circuits is to reduce the total surface area that blood comes in contact with by redesigning both gas and blood flow patterns throughout the device. A more recent step in this evolution has been to incorporate the once external arterial line filter into the oxygenation bundle in an effort to reduce surface area and improve air handling capacity. The challenges in designing an integrated system have been considerable and the clinicians have been slow to embrace these technologies in clinical practice.

During the past decade, few researchers have prospectively performed randomized clinical trials to evaluate oxygenators (6,18–21), and even fewer have examined

Table 4. Patient variables during CPB and oxygenator performance.

	SX18	FX15	Inspire6F	*p* Value
Number	20	20	20	—
Blood flow (L/min)	4.3 ± .6	4.5 ± .6	4.5 ± .5	.302
SvO_2 (%)	79.4 ± 5.8	82.5 ± 3.4	81.9 ± 5.4	.116
SVR	1,374 ± 340	1,350 ± 205	1,316 ± 339	.771
CPB mean line pressure (mmHg)	160.4 ± 20.9	209.0 ± 43.4	192.1 ± 24.6	.0001*
CPB mean sweep rate (L/min)	2.3 ± .6	2.4 ± .9	2.5 ± .5	.607
CPB mean FiO_2 (%)	74.5 ± 6.54	79.1 ± 8.4	69.1 ± 7.9	.0005†
CaO_2 (mL O_2/dL)	12.4 ± 1.1	13.6 ± 1.7	13.1 ± 1.4	.049‡
CvO_2 (mL O_2/dL)	9.5 ± 1.2	10.7 ± 1.5	10.3 ± 1.5	.021§
AVO_2 difference (mL O_2/dL)	2.9 ± .6	2.8 ± .5	2.8 ± .6	.800
DO_2 (mL O_2/min)	528.2 ± 102.3	611.1 ± 150.4	603.0 ± 80.6	.049¶
DO_2/BSA (mL O_2/min/m^2)	291.1 ± 56.1	297.5 ± 38.7	288.4 ± 34.1	.799
VO_2 (mL O_2)	125.2 ± 32.6	127.4 ± 35.2	129.4 ± 31.1	.921
VO_2/BSA (mL O_2/min/m^2)	67.9 ± 14.0	65.3 ± 12.1	65.7 ± 15.8	.810
O_2 extraction	.24 ± .07	.21 ± .03	.22 ± .05	.133

All data are mean ± SD.
*SX18 vs. FX15 ($p < .0001$) and Inspire ($p < .006$).
†Inspire vs. SX18 ($p < .034$) and FX15 ($p < .0001$).
‡SX18 vs. FX15 ($p < .047$).
§SX18 vs. FX15 ($p < .019$).
¶SX18 vs. FX15 ($p < .049$).

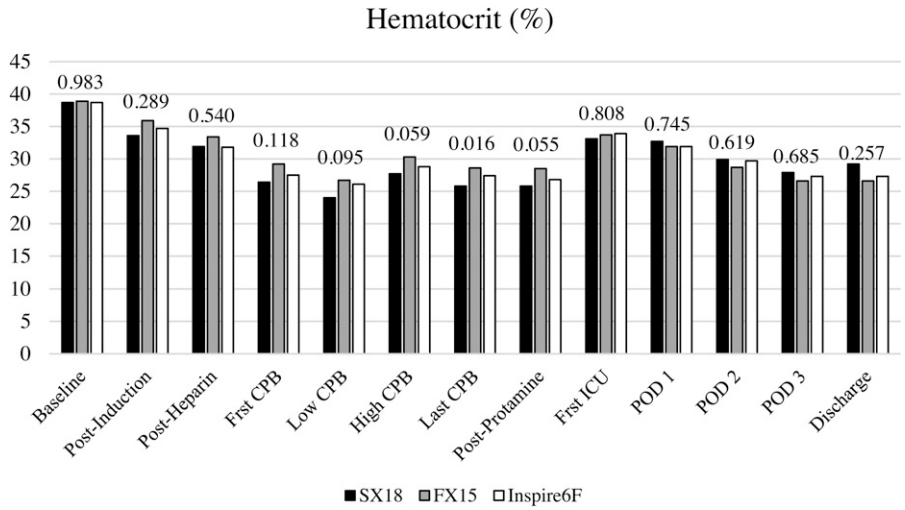

Figure 3. Hematocrit during hospital stay.

gas exchange performance as a critical metric. Perhaps the reason for this has been the meticulous engineering and manufacturing processes that cardiopulmonary device companies must implement while developing new devices to assure that they meet minimum performance criteria. It is rare that individual hospitals have the resources to conduct preclinical evaluations on these devices. Perfusionists often rely on anecdotal information regarding oxygenator performance such as vendor-supplied white papers, word-of-mouth assessments from colleagues, or after manufacturer-sponsored "wet labs" to demonstrate ergonomic attributes and product familiarization. Often these result in non-scientific and anecdotal observations on how easy the oxygenator primes. Oxygenator performance is not often studied but several papers have examined flow geometries across the oxygenator for markers of hemolysis and the biocompatibility to reduce the systemic inflammatory responses associated with extracorporeal flow (6,27,28). Therefore, clinicians who try to use the best available evidence to evaluate advancements in oxygenator technology are at a distinct disadvantage with many decisions based on cost instead of value. Therefore, the question becomes, "have oxygenators become a commodity susceptible to low-bid pricing structures or aggressive marketing strategies, or both?"

The focus of this study was not primarily on reducing transfusions, especially since we did not follow a restrictive transfusion protocol and administered PRBC to patients whose hematocrits were 24% or lower. Nevertheless, the use of an aggressive AP protocol resulted in a reduction in hematocrit from pre-CPB to first on-CPB of only 12–15%. Of note was our initial interest in the Inspire6F dual chamber reservoir. This allows the clinician the ability to sequester the mediastinal shed blood in the cardiotomy reservoir keeping it separate from the

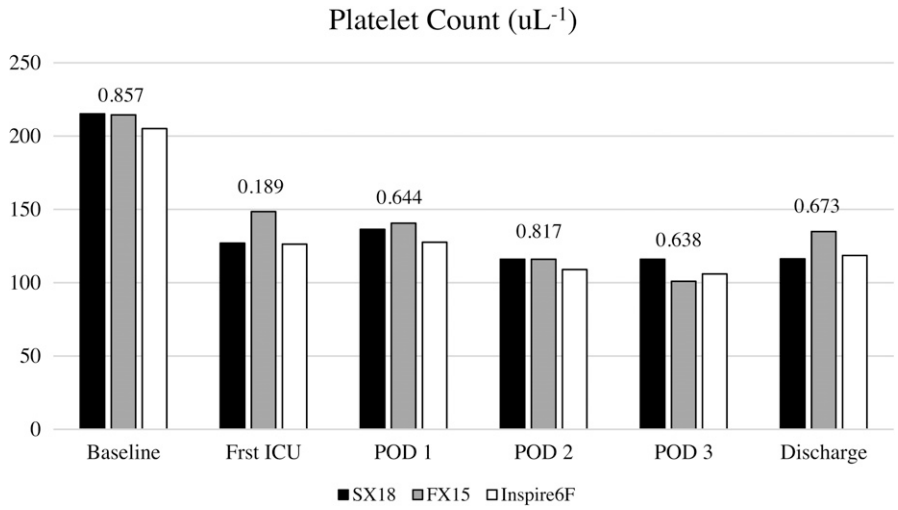

Figure 4. Platelet count during hospital stay.

Table 5. Postoperative data for all patients.

	SX18	FX15	Inspire6F	*p* Value
Number	20	20	20	—
CVICU PRBC (mL)	306.5 ± 381.8	58.8 ± 165.0	113.2 ± 216.1	.011*
CVICU FFP (mL)	107.7 ± 227.6	31.7 ± 141.8	14.6 ± 65.1	.154
CVICU SDP (mL)	10.0 ± 44.7	.0 ± .0	10.0 ± 44.7	.609
CVICU CRYO (mL)	18.6 ± 58.4	.0 ± 10.3	.0 ± .0	.142
CVICU CTO 12 hours (mL)	463.8 ± 354.6	325.3 ± 143.9	469.5 ± 258.6	.163
CVICU CTO 24 hours (mL)	739.0 ± 442.1	518.5 ± 183.9	819.7 ± 359.7	.024†
CVICU CTO total (mL)	1,465.3 ± 1,194.5	818.9 ± 342.4	1,278.1 ± 693.9	.046‡
LOS (days)	5.0 ± 1.6	5.3 ± 2.5	5.3 ± 1.8	.086

CTO, chest tube output; LOS, length of stay. All data are mean ± SD.
*SX18 vs. FX15 ($p < .011$).
†FX15 vs. Inspire ($p < .026$).
‡SX18 vs. FX15 ($p < .048$).

venous reservoir. Although some have advocated such sequestration as an anti-inflammatory measure, we were more concerned at using this design as a means of optimizing AP of the circuit. Our thought was by separating the cardiotomy and venous reservoirs we would achieve a more controlled process for AP, which would result in a greater volume of sanguineous fluid removal and a concomitant higher first on-CPB hematocrit. To accomplish this, the cardiotomy reservoir bypass valve was closed, which allowed the surgical team to use the aspiration suckers after achieving an adequate ACT, and concurrent with the process of AP. The fact that no difference was seen questions the benefit of the dual reservoir as an adjunct to AP.

The devices that we evaluated are commercially available and, except for the SX18, are considered small (mid-level) adult oxygenators for gas exchange and rated blood flow. Historically we used the SX18 and found this device to meet, and exceed, the needs of our patient population. Prior to the clinical evaluation described in this study, we reviewed our EQUIPD and found that for the previous several years (n = 256 patients), the median CPB blood flow was 4.6 L/min (interquartile range [IQR] 4.3–4.8), median on-CPB $NaHCO_3$ dose of .0 mEq (IQR .0–7.5), and a median SvO_2 of 83.6% (IQR, 79.4–85.6). We were unable to identify any consistent metric for subadequate perfusion, which included blood gas indicators for metabolic acidosis or compromised oxygen ($rScO_2$) delivery. Therefore, we opted to use the mid-level devices instead of the larger, higher performing oxygenators available from each of the manufacturers. This reduced patient exposure to excessive device surface area and lowered prime volumes, further reducing iatrogenic anemia. Lahanas and colleagues compared two mid-level oxygenators in small BSA patients (<1.8 m^2) and found that patients who had the FX15 had a lower rate of PRBC transfusion when compared to those who had the D905 EOS oxygenator (Dideco, Mirandola, Italy) (29). In the present study, we observed a significantly higher volume of PRBC given to patients in the SX18 group as compared to FX15 patients, which was consistent with the higher CVICU total chest tube output in this group.

In an editorial by Myers on off-label use of oxygenators, he states some of the reasons that perfusionists tend to use devices that exceed the IFU recommended by the manufacturer and the cautionary note when such is accomplished (30). One of the devices in the present study did have a lower maximum rated blood flow (FX15, 5 L/min) and in three patients we exceeded this (mean $CPBQ_b$, 5.6, 5.3, and 5.4 L/min) with a mean FiO_2 of 99.1, 79.5, and 97.1 and sweep rates of 5.1, 3.0, and 3.2 L/min, respectively. The highest mean oxygen consumption for a patient in this group was 201.3 mL/min and the DO_2 averaged 1,010 mL. The patient was a 45-year-old male undergoing coronary revascularization who weighed 156.4 kg with a body mass index of 46.8. In retrospect, he would have been better served with a larger oxygenator or perhaps the Inspire6F. With the use of the Inspire6F, no patients exceeded the maximum flow range of 6.0 L/min and only once during the entire study period did the FiO_2 ever exceed 85%, with the mean being 69.1%. In this study, the Inspire6F resulted in adequate oxygen delivery over all encountered conditions and was found to be suitable for a wider range of patients. The FX15 performed well in the majority of situations, but reached its predicted performance in highly metabolic patients, causing us to carefully evaluate its use in a patient whose predicted blood flow was at or near that of the maximum rated flow for the oxygenator. For this reason, we have decided to maintain a small inventory of higher performing devices (FX25 and Inspire8F), but use the mid-level units in the majority of patients served.

The present study demonstrated that the Inspire6F had the highest performance for gas transfer of any of the devices tested. The lower FiO_2 and similar sweep rates resulted in similar oxygen delivery to the FX15 and the SX18. This was also shown by Stanzel and Henderson

who evaluated several commercially available oxygenators and found the Inspire6F to outperform the FX15 in oxygen transfer but not in CO_2 removal (31). However, the Inspire6F had a higher pressure drop that may be related to the flow path across the fluid path of the membrane module.

Another aspect of evaluating oxygenators with integrated arterial filters is the importance of the purge line, which all commercially available devices contain. Purge lines are used to divert gaseous emboli from the circuit to reduce air from entering the arterial line. As part of their functionality, they shunt blood away from the patient, therefore requiring careful assessment of various parameters (DO_2, VO_2, SvO_2, pH, etc.) as most important in assuring the adequacy of perfusion then predicted blood flows. Clearly, the quantity of embolic load will vary under test conditions, and would be related to hydrodynamic principles of flow, pressure, and viscosity that change frequently especially in the clinical environment. In the present study, we did not assess the air handling capacity of any tested device, yet the low occurrence of adverse events or clinical sequelae across patient groups did not result in any indication for potential concern. Additional prospective research in a randomized fashion will result in increased knowledge on concerns related to the air handling capacity of oxygenators with integrated arterial filters.

The present study has several imitations. First, it is a retrospective study without randomization using an alternating means of applying either the FX15 or Inspire6F devices for patients. Therefore, we cannot state cause and effect and concede that the lack of randomization may have influenced results. Second, although there were not differences in our preoperative risk stratification calculation, the fact that the SX18 patients used the Euroscore II method, we are unable to show that they would have been similar to the FX15 and Inspire6F groups who used the STS risk calculator. Although the SX18 group was finished immediately before the use of the integrated arterial line filter oxygenators, there was no change in the cardiac team members nor patient management during the entire study period, which provided a consistent study period.

CONCLUSIONS

In this small comparison of prospectively collected data between several commercially available oxygenators, small differences were seen in several perfusion parameters during CPB related to oxygen delivery, and with transfusion rates in the postoperative period. Although the selection of oxygenators based on clinical performance and physical characteristics may result in improved perfusion delivery and outcomes to patients undergoing extracorporeal circulation, additional research is necessary to support such a finding.

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APPENDIX

Calculations used throughout the study. Arterial oxygen content (CaO_2)

$$CaO_2 = Hb(gm/dL) \times 1.34\,mL\,O_2/gm\ Hb \times SaO_2 + PaO_2 \times (.003\,mL\,O_2/\,mm\,Hg/dL)$$

Venous oxygen content (CvO_2)

$$CvO_2 = Hb(gm/dL) \times 1.34\,mL\,O_2/gm\ Hb \times SvO_2 + PvO_2 \times (.003\,mL\,O_2/\,mm\,Hg/dL).$$

Oxygen delivery (DO_2)

$$DO_2 = CaO_2 \times Q \times 10$$

Oxygen consumption (VO_2)

$$VO_2 = Q(CaO_2 - CvO_2)10$$

Oxygen extraction ratio (OER)

$$OER = VO_2/DO_2$$

where Hb is hemoglobin, PaO_2 is the partial pressure of O_2 in arterial blood, Q is flow, SaO_2 is saturation of oxygen in arterial blood, SvO_2 is saturation of oxygen in venous blood.