

# Normoxia vs. Hyperoxia: Impact of Oxygen Tension Strategies on Outcomes for Patients Receiving Cardiopulmonary Bypass for Routine Cardiac Surgical Repair

D. Mark Brown, BS, CCP;\*† David W. Holt, MA, CCT, NRABT;† Jeff T. Edwards, BS, CCP;\* Robert J. Burnett III, MD\*

\*Northwest Heart and Lung Surgical Associates, Spokane, Washington/Coeur d'Alene, Idaho; and †Graduate Degree Completion Program, School of Allied Health Professions, University of Nebraska Medical Center, Omaha, Nebraska

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**Abstract:** Oxygen pressure field theory (OPFT) was originally described in the early 1900s by Danish physiologist, Dr. August Krogh. This revolutionary theory described microcirculation of blood gases at the capillary level using a theoretical cylindrical tissue model commonly referred to as the Krogh cylinder. In recent years, the principles and benefits of OPFT in long-term extracorporeal circulatory support (ECMO) have been realized. Cardiac clinicians have successfully mastered OPFT fundamentals and incorporated them into their clinical practice. These clinicians have experienced significantly improved survival rates as a result of OPFT strategies. The objective of this study was to determine if a hyperoxic strategy can lead to equally beneficial outcomes for short-term support as measured by total ventilator time and total length of stay in intensive care unit (ICU) in the cardiopulmonary bypass (CPB) patient at a private institution. Patients receiving traditional blood gas management while on

CPB (group B,  $n = 17$ ) were retrospectively compared with hyperoxic patients (group A,  $n = 19$ ). Hyperoxic/OPFT management was defined as  $\text{paO}_2$  values of 300–350 mmHg and average  $V_{\text{SAT}} > 75\%$ . Traditional blood gas management was defined as  $\text{paO}_2$  values of 150–250 mmHg and average  $V_{\text{SAT}} < 75\%$ . No significant differences between treatment groups were found for patient weight, CPB/AXC times, BSA, pre/post Hgb, pre/post-platelet (PLT) counts, pre/post-creatinine levels, pre/post-BUN, UF volumes, or CPB urine output. Additionally, no significant statistical differences were found between treatment groups for total time in ICU (T-ICU) or total time on ventilator (TOV). Hyperoxic management strategies provided no conclusive evidence of outcome improvement for patients receiving CPB for routine cardiac surgical repair. Additional studies into the impact of hyperoxia in short-term extracorporeal circulatory support are needed. *JECT. 2006;38:241–248*

Oxygen pressure field theory (OPFT) was initially described by Danish physiologist August Krogh early in the 20th century as part of his work on the structure and function of capillaries, for which he won an unshared Nobel Prize in 1920. Unfortunately, the clinical significance of this has not been recognized by the medical community until relatively recently.

The theoretical cylindrical tissue model described in OPFT, now referred to as the Krogh cylinder (Figure 1)

provides speculative microcirculatory mechanisms for blood gases at the capillary level. Krogh suggested that tissue  $\text{pO}_2$  levels are greatest and most closely resemble arterial  $\text{pO}_2$  values nearest the lumen wall on the arterial end of the capillary. Through his cylindrical model, Krogh further showed how tissue  $\text{pO}_2$  is lowest at the outside perimeter of the venous end of the capillary. Consequently, tissue  $\text{pO}_2$  levels progressively decrease while  $[\text{H}^+]$  ion levels progressively increase with capillary length and diameter. As a result, venous ends of thickened, elongated capillaries are at increased risk of critical levels hypoxia and acidosis (1).

If left untreated, these hypoxic and acidotic areas can have lethal effects on cells, tissues, and entire organ systems (2). A thickened Krogh cylinder (Figure 2) shows how “lethal corners” of hypoxia, hypercapnia, acidosis,

Address correspondence to D. Mark Brown, MPS, CCP, NW Heart and Lung Surgical Associates, PS, 2003 Lincoln Way, Suite 300, Coeur D'Alene 83814. E-mail: mark@perfusion.com

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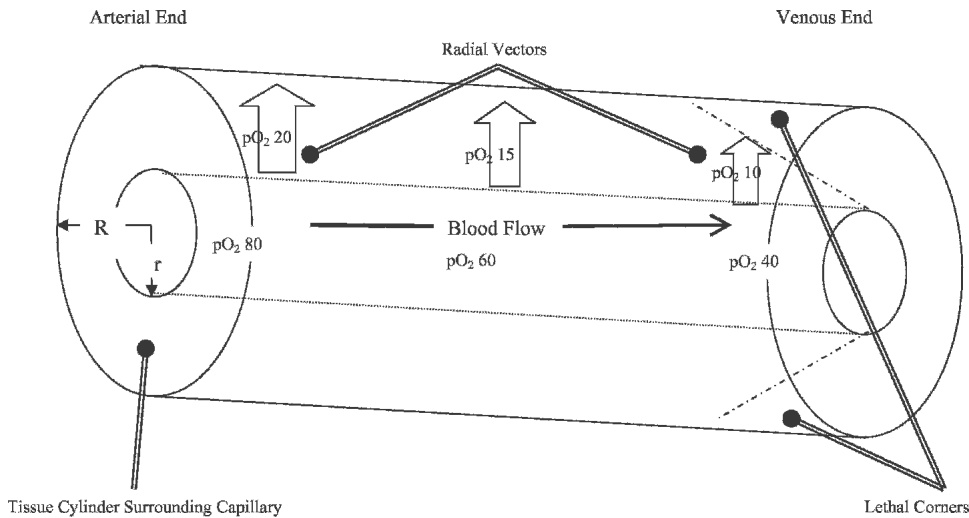


Figure 1. Krogh cylinder.

<b>Radius</b>		
Capillary		$r = 5\mu\text{m}$
Tissue Cylinder		$R = 10\mu\text{m}$
<b>Cross-Sectional Areas</b> ( $A = \pi r^2$ )		
Capillary		$A = (3.14) (5\mu\text{m})^2 = 78.5\mu\text{m}^2$
Tissue Cylinder		$A = (3.14) (10\mu\text{m})^2 = 314\mu\text{m}^2$
<b>Cross Section Ratio</b> (Capillary: Cylinder)		(Capillary / Cylinder) = $(78.5/314) = 0.25 = 1:4$ Ratio
<b>Capillary <math>pO_2</math></b>		
Arterial		80 mmHg
Venous		40 mmHg
<b>Mean Cylinder <math>pO_2</math></b>		
Arterial		20 mmHg
Venous		10 mmHg

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and other metabolic wastes can accumulate within the capillary, rapidly and progressively resulting in tissue death. Krogh's suggestion for preventing or attenuating these lethal corners is primarily bifactorial: create a hyperoxic environment for tissues and minimize tissue edema.

Arterial  $pO_2$  values are elevated beyond normal physiological levels to supersaturated/hyperoxic levels to improve  $O_2$  tissue diffusion along the capillary axis. Theoretically, this diffusion should occur in both radial and axial directions, thus increasing tissue  $pO_2$  further down the length of the capillary toward the venous end. Consequently, capillary perimeters on the venous end should experience improved oxygenation. Tissue edema is minimized to reduce capillary diameter and the resultant distance between capillary lumen and tissue perimeter. This diameter reduction shortens the distance  $O_2$  must travel to functionally perfuse the tissue. This improved tissue perfusion results in improved oxygenation, lower  $[H^+]$  ion concentration, and more efficient removal of metabolic waste products.

Mathematical and physiological studies validate Krogh's fundamental theory and cylindrical tissue model (3–6). Other studies conclude the efficacy of OPFT and hyperoxia in clinical applications (7,8). In cases where deep hypothermic circulatory arrest (DHCA) was used, Pearl et al. (9) concluded that hyperoxia resulted in superior blood gas values regardless of specific blood gas management strategy (i.e., alpha-stat or pH stat). Wittnich et al. (10) concluded that exposure hyperoxia in the presence of ischemia provided an energy-sparing effect during the early ischemic period. However, a correlational increase in ventricular fibrillation was concluded to negate any beneficial hyperoxic effects. Of note, a significant discrepancy in clinical definitions of hyperoxia exists within the literature. This discrepancy ranges from 250 to 700 mmHg (9–13).

In recent years, cardiac surgical clinicians have been implementing OPFT fundamentals and successfully incorporating them into their clinical practice. The principles and benefits of OPFT strategies in long-term extracorpo-

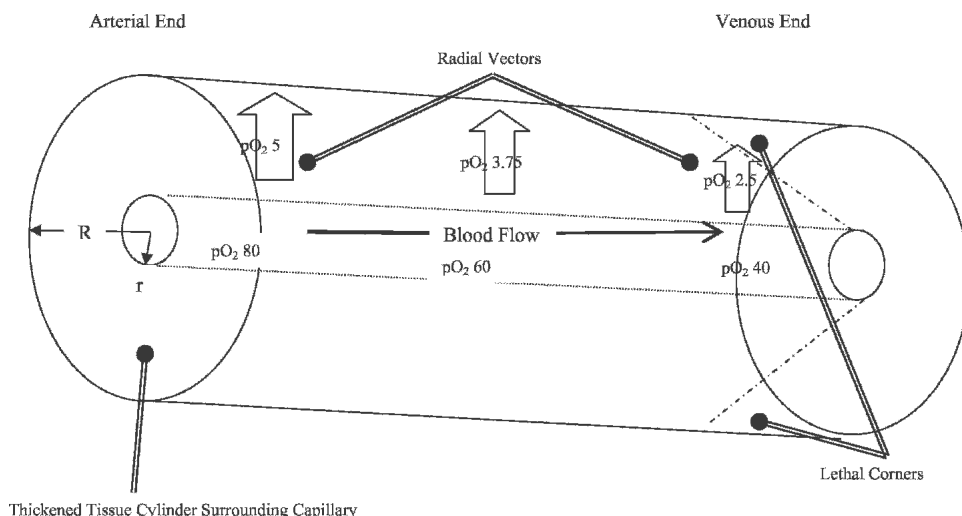


Figure 2. Thickened Krogh cylinder.

<b>Radius</b>	
Capillary	$r = 5\mu\text{m}$
Thickened Tissue Cylinder	$R = 20\mu\text{m}$
<b>Cross-Sectional Areas</b> ( $A = \pi r^2$ )	
Capillary	$A = (3.14) (5\mu\text{m})^2 = 78.5\mu\text{m}^2$
Thickened Tissue Cylinder	$A = (3.14) (20\mu\text{m})^2 = 1256\mu\text{m}^2$
<b>Cross Section Ratio</b> (Capillary: Thickened Cylinder) (Capillary / Cylinder) = $(78.5/1256) = 0.0625 = 1:16$ Ratio	
<b>Capillary pO<sub>2</sub></b>	
Arterial	80 mmHg
Venous	40 mmHg
<b>Mean Cylinder pO<sub>2</sub></b>	
Arterial	5 mmHg
Venous	2.5 mmHg

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real circulatory support, (i.e., extracorporeal circulatory support [ECMO]) have been realized. As a direct result of OPFT strategies, many clinicians have experienced improved patient survival rates (1). OPFT strategies that include the tactic of hyperoxia may reduce morbidity or mortality among selected patients (14–25).

The objective of this study was to determine if a hyperoxia management strategy would result in equally beneficial outcomes for short-term support as measured by total ventilator time and total length of stay in the intensive care unit (ICU).

**MATERIALS AND METHODS**

**Study Design**

This study was designed to collect appropriate data for retrospective analysis of patients receiving one of two perfusion management strategies while on cardiopulmonary bypass (CPB). The different management strategies can be categorized as follows—group A: those patients receiv-

ing blood gas management consistent with hyperoxic/OPFT and management (i.e.,  $\text{paO}_2$  300–350 mmHg and  $V_{\text{SAT}}$  values >75%); group B: those patient receiving traditionally accepted blood gas management while on CPB (i.e.,  $\text{paO}_2$  150–250 mmHg and average  $V_{\text{SAT}}$  values of 70–75%).

**Patient Population/Selection**

A total of 36 patients were selected: 19 from group A and 17 from group B. Of the 19 group A patients, 18 received CABG and 1 received valve replacement. Among the 17 group B patients, 13 received CABG, 3 received valve replacements, and 1 received combined CABG/valve. To be included in the study, each patient had to meet both inclusion and exclusion selection criteria. The criteria for inclusion/exclusion are as follows.

**Inclusion Criteria**

1. Nonemergent cardiac surgical repair necessitating CPB and AXC

2. Age range: 40–80 years
3. BSA 1.6–2.4 m<sup>2</sup>
4. Preoperative HCT > 27%
5. Maximum CPB time 120 minutes
6. Ultrafiltration volume 5500–6500 mL

#### Exclusion Criteria

1. CPB time >120 minutes
2. Recent history, such as neurological deficits (TIA, CVA, head injury etc.)
3. Renal insufficiency presenting to the operating room with anuria or serum creatinine level > 1.5
4. Presence of pre/perioperative intra-aortic balloon pump (IABP)
5. Deep hypothermic circulatory arrest (DHCA)
6. Hypothermia < 28°C
7. Medical history positive for diabetes mellitus, COPD, hypothyroidism

#### Extracorporeal Circuit Design

Patients from both group A and group B received identical extracorporeal circuits (ECCs) run on a Sarns Modular Perfusion System 8000 (Terumo/SARNS, Ann Arbor, MI). The ECC used was a customized pack by Terumo. The pack incorporated a Terumo Capiiox RX-25 hollow fiber oxygenator with open integrated hard shell venous reservoir, Capiiox arterial line filter, and Capiiox HC11 Hemoconcentrator. The oxygenator, venous reservoir, and arterio-venous (A-V) loop were coated with Terumo's bio-passive X-coating. Capiiox disposable centrifugal pumps were used on all cases. The Quest MPS (Quest Medical, Allen, TX) was used for cardioplegia delivery.

Other ancillary equipment consists of Sechrist air/O<sub>2</sub> blender (Sechrist Industries, Anaheim, CA), Hemothem heater/cooler (Cincinnati Sub-Zero, Cincinnati, OH) and a Sarns/Terumo CDI Blood Parameter Monitoring System 500 (Terumo/SARNS) for continuous in-line blood gas monitoring. All ancillary components were used on every patient in both groups.

#### Cardiopulmonary Bypass

All patients received 1200–1800 mL of priming solution (lactated Ringer or Normosol), 10,000 units of porcine-derived heparin, and 50 mEq NaHCO<sub>3</sub>. The use of anti-fibrinolytics and protease inhibitors, such as Amicar and Trasylol, are surgeon-specific and were added as indicated.

All perfusion parameters were mandated by the attending surgeon. As such, patient target temperatures, as well as other relevant physiological parameters, were performed per protocol for that particular surgeon.

Cardioplegia was delivered by the Quest MPS. Arrest and additive agents were administered in accordance with surgeon-directed protocols. Perfusion pressures were

maintained at 55–75 mmHg. If sufficient urine output was not observed during CPB, diuretics were administered per surgeon/anesthesiologist orders.

Inhalation anesthetics (exclusively isoflurane) were routinely administered by the perfusionist during CPB. The range of isoflurane levels administered during CPB were 0.4–1.5 volume % to maintain a bispectral Index (BIS) of 40–60.

Patient hematocrits were maintained between 21% and 30%. Anticoagulation was achieved through the use of porcine-derived heparin. Anticoagulation levels were monitored by Celite-activated clotting times (ACT) and maintained >480 seconds at all times during CPB.

A maximum temperature gradient of 10°C was maintained during periods of patient cooling and rewarming; attempts to wean patients from CPB were not made until core (bladder) temperature of 35–36°C was achieved.

#### Data Collection

Institutional Review Board (IRB) approval was obtained before initiation of study and data collection. All data included in this retrospective analysis were collected in compliance with all applicable guidelines established by the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Each patient was assigned a unique and untraceable identifier. This identifier and corresponding data (demographical, statistical, and otherwise) was entered into a database for appropriate statistical analysis. The patient database was accessible exclusively by the primary investigator. As required by HIPAA regulations, all charts and computer files were locked in a secure area out of view from the general public.

To minimize clinical variation, data was collected from two different clinicians: control data from one and treatment data from another. In terms of clinical technique and overall patient management, the clinicians were virtually identical. The primary variation between clinicians was the pO<sub>2</sub> levels maintained throughout CPB.

To adequately meet the requirements of this study, patient data was collected from three different phases of a patient's hospital stay: preoperatively, intraoperatively, and postoperatively. Specific data to be collected from each phase are as follows.

#### Preoperative Data

1. History and physical
2. Appropriate preoperative laboratory values (Hgb, Plt, Creat, BUN)

#### Intraoperative Data

1. Blood gas and Hgb data
2. Patient hemodynamic data (pressures, temperatures)
3. Perfusion data (blood flow, blender settings)
4. Urine output

**Postoperative Data**

1. Twelve- to 24-hour postoperative laboratory values at (Hgb, Plt, Creat, BUN)
2. Twenty-four-hour urine output
3. Length of time on ventilator (TOV)
4. Length of time in ICU (T-ICU)
5. Postoperative complications/morbidities

**Statistical Analysis**

Appropriate data points were recorded directly from extracorporeal perfusion records and entered into a computer database using Microsoft Excel. Additional data were collected from institutional electronic databases and merged with Excel data.

The Shapiro-Wilk test was used to test for normality of the data for the following continuous variables: ultrafiltration, ICU time, ventilator time, weight, CPB time, AXC time, BSA, urine output during CPB, and the repeatedly measured Hgb, PLT, Creat, BUN, ABG, VBG, and  $V_{sat}$  variables. Normal probability plots were also examined.

Ultrafiltration, weight, CPB time, and AXC time were approximately normally distributed, so a *t* test was used to test for differences in the means between the two treatment groups. A test for equality of variances was performed to determine whether to use a *t* test that assumed equal variances or a *t* test that assumed unequal variances should be used.

ICU time, ventilator time, BSA, and urine output during CPB were slightly skewed, so the nonparametric Wilcoxon test was used to test for differences in the medians between the two treatment groups.

The repeatedly measured variables of Hgb, PLT, Creat, BUN, ABG, VBG, and  $V_{sat}$  were each approximately normally distributed. A repeated-measures mixed general linear model with fixed effects for treatment, time-point, and treatment by time-point interaction was used to analyze these data. Pairwise comparisons were made between treatments at each time-point, and the *p* values were adjusted using the Bonferroni adjustment for multiple comparisons.

Estimates of treatment means, SDs, and SEs are provided for each continuous variable.

Statistical significance was defined as  $p \leq .05$ . Unless otherwise indicated, all data are expressed as mean  $\pm$  SD. PC SAS version 9.1 was used for all analyses.

**RESULTS**

Table 1 shows patient demographic data. Laboratory and other data are outlined in Table 2. In both groups, initial ABG samples were taken 2–3 minutes after initiation of CPB to verify adequate oxygenation before placement of AXC. Subsequent ABG, VBG, and  $V_{sat}$  values were analyzed every 15–25 minutes throughout CPB. For

**Table 1.** Patient demographics.

	Hyperoxic ( <i>n</i> = 19)	Normoxic ( <i>n</i> = 17)	<i>p</i> Value
Patient weight (kg)	86.2 $\pm$ 13.9	87 $\pm$ 16.0	.8754*
Body surface area (m <sup>2</sup> )	2.02 $\pm$ 0.20	1.93 $\pm$ 0.51	.9874†
CPB (min)	94.7 $\pm$ 13.3	86.3 $\pm$ 19.9	.1401*
AXC (min)	72.8 $\pm$ 9.74	66.1 $\pm$ 16.1	.1474*

\**t*-test.

†Nonparametric Wilcoxon (Kruskall-Wallis) test.

**Table 2.** Laboratory and other patient data.

	Hyperoxic ( <i>n</i> = 19)	Normoxic ( <i>n</i> = 17)	<i>p</i> Value
Pre-CPB Hgb (g/dL)	12.2 $\pm$ 1.27	13.1 $\pm$ 1.25	.1014‡
12- to 24-hour postoperative Hgb (g/dL)	9.3 $\pm$ 1.28	10.1 $\pm$ 1.39	.1831‡
Pre-CPB Plt (K/ $\mu$ L)	232 $\pm$ 53	226 $\pm$ 71	1.000‡
12- to 24-hour postoperative Plt (K/ $\mu$ L)	140 $\pm$ 30	139 $\pm$ 28	1.000‡
Pre-CPB creatinine (mg/dL)	0.96 $\pm$ 0.28	0.94 $\pm$ 0.18	1.000‡
12- to 24-hour postoperative creatinine (mg/dL)	1.04 $\pm$ 0.45	1.01 $\pm$ 0.20	1.000‡
Pre-CPB BUN (mg/dL)	16.1 $\pm$ 6.93	14.7 $\pm$ 5.47	.9986‡
12- to 24-hour postoperative BUN (mg/dL)	15.3 $\pm$ 6.28	12.9 $\pm$ 4.46	.4512‡
Ultrafiltrate (mL)	5995 $\pm$ 272	6041 $\pm$ 292	.6241*
CPB urine (mL)	193 $\pm$ 159	240 $\pm$ 130	.0988†
Time in ICU (hr)	38.6 $\pm$ 21.5	29.2 $\pm$ 14.51	.4185†
Time on ventilator (hr)	9.38 $\pm$ 4.75	6.97 $\pm$ 4.81	.0986†

\**t*-test.

†Nonparametric Wilcoxon (Kruskall-Wallis) test.

‡Bonferroni adjusted *p* value.

clarification, subsequent samples were labeled as ABG-1, VBG-1, and  $V_{sat}$ -1. A comparison of sequential ABG and VBG are shown in Figures 3 and 4.

ABG values were statistically significantly higher ( $p < .0010$ ) at every time interval in the OPFT group (Figure 3). VBG-1 ( $p = .0044$ ) and  $V_{sat}$ -1 ( $p < .0010$ ) values were significantly higher in the OPFT group; subsequent VBG and  $V_{sat}$  values revealed no statistically significant differences (Figures 4 and 5).

All laboratory values (Hgb, Plt, Creat, and BUN) exhibited normal distributions and showed no statistically significant differences between treatment groups. Patient weights were found to be normally distributed (means  $\pm$  SD), whereas BSA values were found to be slightly skewed between groups, requiring the use of a nonparametric Wilcoxon test ( $p = .9874$ ). CBP and AXC times were found to be normally distributed between groups with no statistically significant differences noted. Ultrafiltrate (UF) values were slightly higher in the non-OPFT group (6041  $\pm$  292 vs. 5994  $\pm$  272 in the OPFT/hyperoxic group), but revealed no statistical significance. Mean CPB urine outputs in the non-OPFT/normoxic group (240  $\pm$  130) were slightly higher than the OPFT group (193  $\pm$  159), but were not statistically significant. No significant



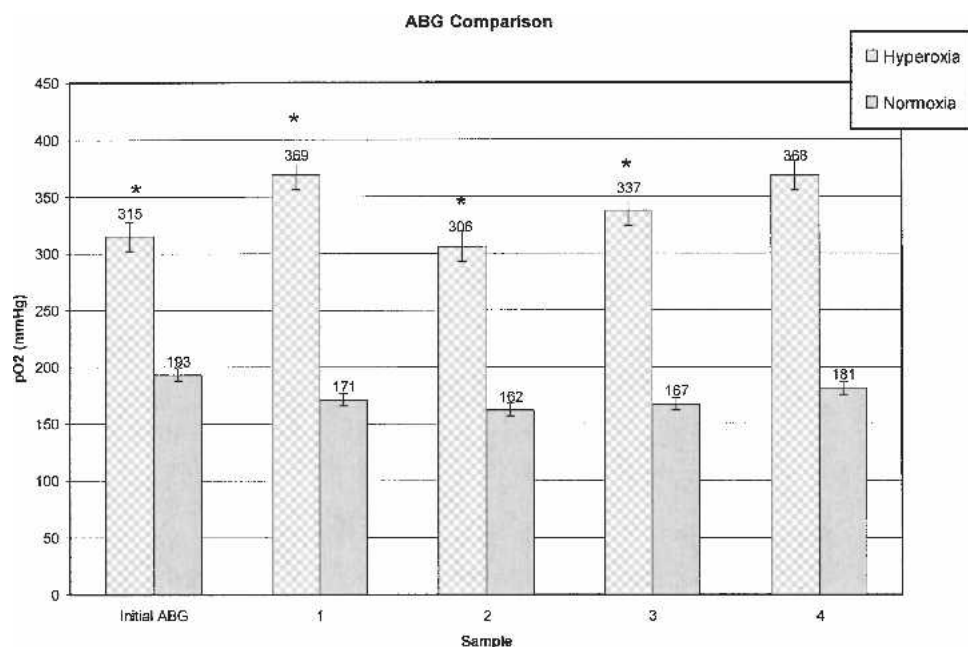


Figure 3. Arterial blood gases.

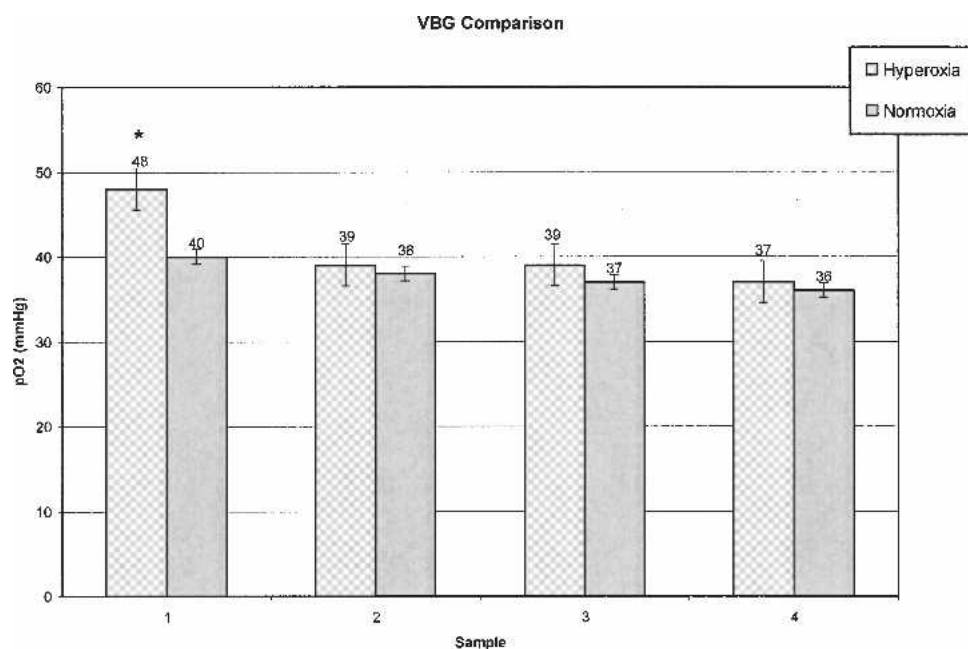


Figure 4. Venous blood gases.

differences were found in T-ICU ( $p = 04185$ ) or TOV ( $p = .0986$ ). T-ICU and TOV data are shown in Figure 6.

Some clinical investigators have concluded OPFT and hyperoxic management results in an increased occurrence of myocardial reperfusion injury caused by excessive free radical and diene production (11–13). These investigators maintain that myocardial reperfusion injuries result in markedly reduced ventricular function/contractility and reduced cardiac output. No evident signs of myocardial reperfusion injury were observed in either group.

## DISCUSSION

By providing tissues with a hyperoxic environment and minimizing fluid overload as theorized by Krogh and shown in his cylindrical model, cardiac clinicians have experienced improved outcomes for their patients undergoing long-term ECMO. The goal of this retrospective study was to determine if OPFT/hyperoxic management strategies had an impact on outcomes for patients receiving CPB for routine cardiac surgical repair. The primary indicators for improved outcomes were T-ICU and TOV.

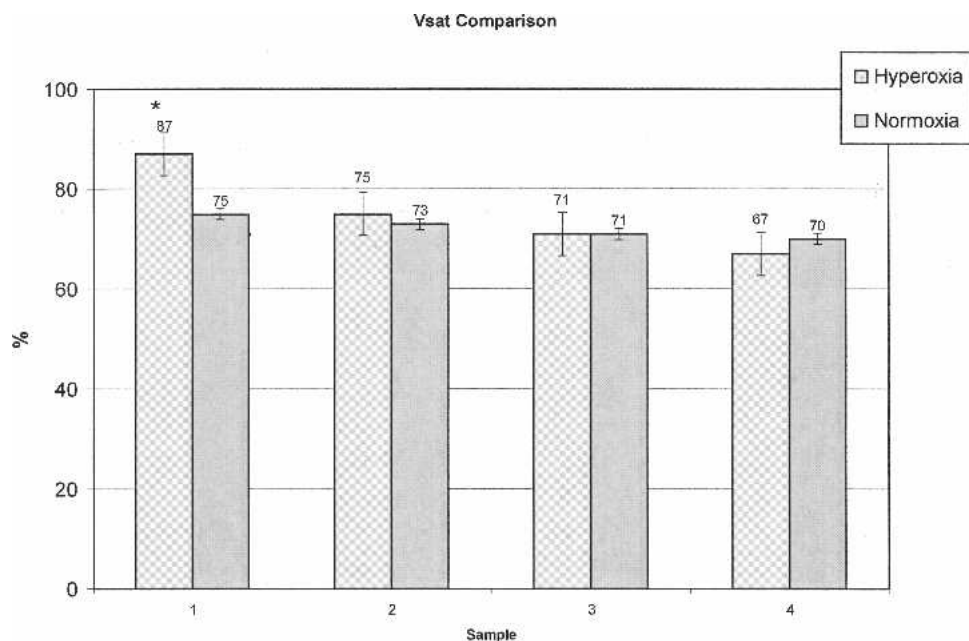


Figure 5. Venous saturations.

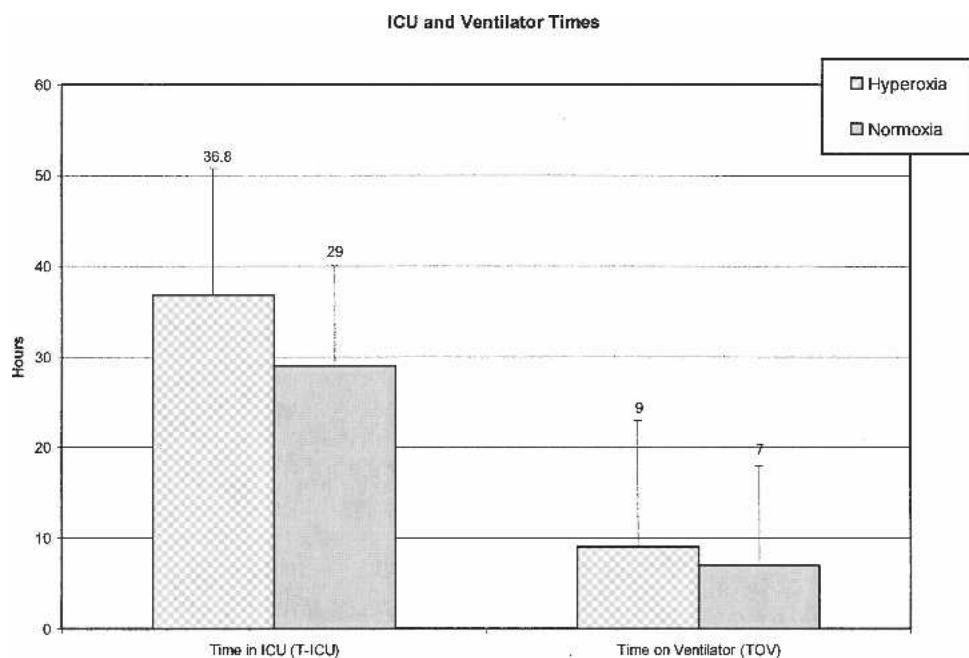


Figure 6. Time in ICU and time on ventilator.

Mean ABG, VBG, and  $V_{sat}$  values were numerically higher at every time interval in the OPFT group except for  $V_{sat}$  at the final interval. Statistically significant higher values of ABG were noted at every time interval in the hyperoxia group; however, only the first VBG and  $V_{sat}$  samples were significantly different.

No statistically significant differences were found in any other variables. Preoperative and postoperative laboratory values for Hgb, Plt, Creat, and BUN were not statis-

tically significant. No statistical differences were found in patient weight, BSA, CPB/AXC times, UF volumes, CPB urine output, T-ICU, or TOV.

In conclusion, our study failed to provide conclusive evidence on the impact of a hyperoxic management on outcomes for patients receiving CPB for routine cardiac surgical repair. Further studies on hyperoxia in short-term extracorporeal circulatory support are warranted.

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