The Effects of Flow Rate on Mixed Venous Oxygen Content and Saturation in Veno-Venous Extracorporeal Life Support: A Comparison of a Computer Simulation and an in vitro Analysis

by

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Abstract

Extracorporeal life support (ECLS) is the extended use of cardiopulmonary bypass (CPB) to support patients suffering from reversible cardiac and/or respiratory failure. Veno-venous ECLS (VV ECLS) is used to support patients suffering from only respiratory failure. Because the drainage and reinfusion cannulae for VV ECLS are both located in the venous circulation, a phenomenon known as recirculation occurs where oxygenated blood will be drained out again and recirculated through the ECLS circuit. This study compared a MATLAB simulation of recirculation with an experiment to characterize the relationship between ECLS drainage blood oxygen content and recirculation.

A MATLAB graphical user interface (GUI) was created which accepts user-specified values for saturation (SO_2) and partial pressure of oxygen (PO_2) for oxygenated and deoxygenated blood, as well as hemoglobin concentration, recirculation fraction, and the pH of the drainage blood. This model then predicts, based on conservation equations, the oxygen content and saturation of ECLS drainage blood. Two in vitro CPB circuits were also constructed, one for oxygenation and one for deoxygenation. The blood was then mixed in different proportions to simulate different levels of recirculation, and the oxygen content and saturation were measured and compared to model predictions.

The results illustrate that a linear relationship exists between recirculation fraction and ECLS drainage blood oxygen content ($p < 0.001$), and that the MATLAB model is a very accurate predictor of ECLS drainage blood oxygen content and saturation, based on comparison to experimental data. It was also determined that hemoglobin concentration and pH of the drainage blood can have a dramatic effect on the ECLS drainage blood oxygen content and saturation, respectively.

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Nomenclature

Abbreviations

$(A\text{-}a)DO_2$	Alveolar-Arterial Oxygen Gradient
AAP	Average Airway Pressure
ARDS	Acute Respiratory Distress Syndrome
CPB	Cardiopulmonary Bypass
CPD	Citrate Phosphate Dextrose
CPR	Cardiopulmonary Resuscitation
CPS	Cardiopulmonary Support
C_VO_2	Venous oxygen content
$ECCO_2R$	Extracorporeal CO_2 Removal
ECLS	Extracorporeal Life Support
ECMO	Extracorporeal Membrane Oxygenation
F_iO_2	Fraction of Inspired Oxygen
GUI	Graphical User Interface
OI	Oxygen Index
P_AO_2	Arterial Partial Pressure of Oxygen
PCIRV	Pressure Controlled Inverse Ratio Ventilation
PEEP	Positive End-Expiratory Pressure
PIP	Peak Inspiratory Pressure
RR	Respiratory Rate
S_VO_2	Venous Oxygen Saturation
VA ECLS	Veno-arterial ECLS

VI	Ventilation Index
VV ECLS	Veno-venous ECLS

1. Introduction

Extracorporeal life support (ECLS) is the use of prolonged extracorporeal cardiopulmonary bypass. It is comprised of various methods to provide temporary cardiopulmonary support (CPS) for days or weeks. It can be used for strictly CPS, extracorporeal carbon dioxide removal ($ECCO_2R$), and extracorporeal membrane oxygenation (ECMO) [1]. ECLS is currently used in patients suffering from acute, reversible cardiac and/or respiratory failure that is unresponsive to medical and/or pharmacological treatment [2]. It is also used as a bridge-to-transplantation and is used to support pediatric patients suffering from a congenital heart defect until corrective surgery can be performed. Although this modality is traditionally known as ECMO, the name ECLS is currently the favored acronym due to it encompassing treatments other than just oxygenation. For instance, hemofiltration can be integrated into the circuit to aid in renal support. Additionally, ECLS has also been employed for hepatic support in patients suffering from liver failure [3, 4].

Specifically, ECLS is typically used to support patients requiring post-cardiopulmonary bypass (CPB) support as well as to aid in the treatment of patients suffering from acute myocardial failure and/or myocarditis, acute respiratory distress syndrome (ARDS), atelectasis, pneumonia (as a result of a bacterial or viral infection, or aspiration), post-lung transplant dysfunction, and post-pneumonectomy pulmonary edema [1, 5]. However, patients suffering from right or left ventricular failure may have a ventricular assist device placed as ECLS is not a treatment in itself; it merely provides support for the patient while the pathophysiologic conditions heal or resolve naturally via medical, pharmacological, or surgical intervention, or via organ transplantation, and,

therefore, should only be used in the treatment of conditions which are considered reversible [2]. ECLS takes the pressure off of the patient's body to provide cardiac and/or respiratory support in order to help induce healing. It also prevents any harmful effects from increased air pressures and fraction of inspired oxygen (F_iO_2) that result from conventional ventilator support which could exacerbate any existing lung injury [2]. Although similar in many ways, traditional CPB and ECLS differ in key areas. During CPB, the heart is often arrested and systemic perfusion is executed at decreased flows. Because of this decreased flow rate, as well as blood contacting foreign surfaces, complete systemic anticoagulation is required (typically with heparin). ECLS may also require systemic anticoagulation, but usually to a lesser extent due to higher flow rates. If heparin-bonded circuits are used, systemic anticoagulation can possibly be averted completely for short durations [6]. Additionally, ECLS can support patients for days and weeks, as opposed to CPB, which supports patients for hours [1].

1.1. Indications for ECLS

In general, ECLS is indicated for patients suffering from acute respiratory failure and/or cardiac failure from which they can be expected to recover within two to four weeks [2]. Although inclusion criteria typically vary between institutions, two criteria are used at nearly all ECLS centers. Oxygen index (OI) is based on the arterial partial pressure of oxygen (P_AO_2), average airway pressure (AAP), and F_iO_2, and is calculated based on Equation (1) [7]:

$$OI = (AAP \times F_iO_2 \times 100)/P_AO_2. \quad (1)$$

Many institutions have assessed the OI equation and have established that an OI of greater than 40 implies the need for ECLS [8]. Additionally, the post-ductal alveolar-arterial oxygen gradient ((A-a)DO_2) is typically used as a criterion in ECLS centers. An (A-a)DO_2 of 610 Torr or greater is another indication for ECLS treatment [9].

Many other criteria are used in various ECLS centers worldwide. Ventilation index (VI) was also determined to be a predictor for the need of ECLS based on its prediction of mortality, with its value calculated using Equation (2) [10]:

$$VI = (RR \times P_A CO_2 \times PIP)/1000, \quad (2)$$

where RR is respiratory rate (in breaths/minute) and PIP is the peak inspiratory pressure on a mechanical ventilator. A VI of greater than 40 suggests the need for ECLS [10].

Generally, for respiratory failure, ECLS is indicated for patients in whom optimal ventilator treatment is inadequate (a shunt of greater than 30% with an applied F_iO_2 of greater than 60%), patients whose lung compliance has greatly decreased (less than 0.5 mL/cm H_2O/kg; normal compliance is approximately 2.5 mL/cm H_2O/kg), severe hypoxemia that does not respond to conventional mechanical ventilation, and a Murray score (which is a function of the P_AO_2/F_iO_2 ratio, positive end-expiratory pressure (PEEP) on a mechanical ventilator, lung compliance, and the appearance of fluid and/or congestion on a chest X-ray) of at least 3.0 or hypercapnia that cannot be corrected with a blood pH of less than 7.0 and a PIP setting of greater than 40 cm H_2O (the greatest inspiratory pressure used) [2, 5]. Specifically for cardiac failure, ECLS is indicated for patients suffering from cardiogenic shock whom most likely would not recuperate without support as exhibited by increasing hypotension, cardiac arrest, inadequate

peripheral perfusion, increasing diastolic pressures, decreasing renal function, decreased venous oxygen saturation (S_VO_2), and continuing acidosis [1, 5].

1.2. Contraindications for ECLS

Because ECLS is an important life-saving treatment, it is important to also have criteria to eliminate patients who will most likely not benefit from its use. For neonatal ECLS, a gestational age of less than 32 weeks is a contraindication due to a greatly increased risk in premature babies for intracranial bleeding which can be exacerbated by systemic anticoagulation [2]. In all patients, ECLS is contraindicated in patients with an intracranial hemorrhage greater than grade II, respiratory failure and mechanical ventilator treatment for greater than seven days, patients requiring cardiopulmonary resuscitation (CPR) for more than 30 minutes, multiple (more than two) organ system failure/irreversible organ damage/underlying severe chronic pulmonary and/or cardiac diseases, bleeding disorders, profound neurologic injury, immunodeficiency, sepsis, unknown etiology of the disease, and any condition that is not compatible with either short- or long-term survival [2, 5].

2. Background

2.1. History of ECLS for Respiratory Support

Ashbaugh *et al.* first reported on ARDS in adults in 1967, and in 1973, a Bramson membrane lung was used in the support of a patient suffering from ARDS [11, 12]. However, initial ECLS trials in adult patients were discouraging. A National Institutes of Health-sponsored randomized controlled trial of ECLS in adults in 1979 studied 90 patients divided evenly between a control group and an ECLS group; it was discovered that the treatment had no impact on the survival of patients suffering from ARDS [13]. Despite the disappointing results, institutions worldwide persisted in investigating ECLS as a treatment. In the mid-1980s, two Italian studies reported the successful usage of $ECCO_2R$ combined with pressure controlled inverse ratio ventilation (PCIRV; a technique in which not all inspired air is exhaled, thus creating PEEP and permitting constant inflation of the lungs) to treat patients suffering from ARDS [14, 15]. The two studies reported survival rates of 63% and 49% in patients receiving treatment with ECLS and PCIRV, respectively; however, because the studies were not randomized, other factors influencing the results of the study, such as patient selection, could not be ruled out [14, 15]. Morris *et al.* attempted to recreate the two Italian studies as a randomized controlled trial with patients divided between conventional treatment and PCIRV with $ECCO_2R$ [16]. In the first 40 patients, the ECLS group showed a statistically insignificant ($p = 0.8$) difference in survival rate of 30% versus 42% in the conventional ventilator treatment group, and the trial was subsequently terminated due to the ineffectiveness of ECLS [16].

Despite the initial disappointing results observed in adults, ECLS proved promising in pediatrics. It was first used successfully in 1975 in a newborn suffering from respiratory failure [17]. Because pulmonary hypertension in newborns had a mortality rate of approximately 80% in American and European hospitals, physicians began using ECLS for treating babies born with this condition [18]. By 1982, 45 newborns suffering from respiratory failure were treated with ECLS; a survival rate of 55% and short-term normal growth and development in 80% of surviving newborns were achieved [19]. Three studies were conducted that contrasted conventional mechanical ventilation against ECLS for treating newborns suffering from respiratory insufficiency [7, 20, 21]. Each of these three studies presented a considerable improvement in patient survival when treated with ECLS compared to the control groups, notwithstanding a predicted mortality rate of 80-90% in the patient population [7, 20, 21]. Timmons *et al.* organized a study examining various treatment methods for pediatric patients suffering from respiratory failure and determined that ECLS was the only treatment that indicated improved outcomes [22]. Green and others assessed Timmons *et al.*'s work and found a 74% survival rate in ECLS patients compared to 53% in patients treated with conventional methods, and determined that ECLS was associated with a reduced mortality rate ($p = 0.0082$) [23]. The Collaborative UK ECMO Trial was occurring simultaneously, but separately, with Green's work [24]. This study not only examined the mortality rate of ECLS patients and those managed with conventional treatment; it also followed the infant patients up through their first birthday. A 68% and 41% survival rate were observed in the ECLS and conventional treatment groups at each patient's one

year birthday, respectively, and determined that ECLS "reduces the risk of mortality without a major concomitant rise in severe disability by about 45%." [24]

Because of the encouraging results observed in the pediatric population, many other trials persisted in examining ECLS treatment for adults. Despite the continued successful usage of ECLS in pediatrics, ECLS has yet to prove itself as the best treatment available for adults suffering from respiratory failure. Table 1 summarizes the results of these adult studies.

Table 1: Adult ECLS Study Survival Rates.

Study Author	Year	Number of ECLS Patients	ECLS Survival Rate	Conventional Treatment Survival Rate
Egan [25]	1988	17	24%	NA (not available)
Wagner [26]	1990	76	50%	NA
Brunet [27]	1993	23	52%	NA
Brunet [28]	1994	11	73%	NA
Manert [29]	1996	21	81%	77%
Guinard [30]	1996	10	40%	50%
Peek [31]	1997	50	66%	NA
Lewandowski [32]	1997	49	55%	89%
Ullrich [33]	1999	13	62%	83%
Mols [34]	2000	62	55%	61%
Linden [35]	2000	17	76%	NA
Liebold [36]	2000	20	60%	NA
Frenckner [37]	2002	38	66%	NA
Hemmila [38]	2004	280	52%	NA
Cordell-Smith [39]	2006	28	71%	NA
Peek [40]	2009	68	63%	47%

Furthermore, during the H1N1 influenza ("swine flu") epidemic of 2009, ECLS was used to successfully treat many patients suffering from pneumonia resulting from H1N1 [41].

2.2. Methods of ECLS

There are two main methods for ECLS based on the pathophysiological condition: Veno-arterial and veno-venous treatment. Each method has different cannulation techniques and provides patient support for different disorders.

2.2.1. Veno-Arterial (VA) ECLS

VA ECLS treatment is used in patients suffering from isolated cardiac or cardiac and respiratory failure. When ECLS was first being developed, it was also used for patients suffering from respiratory failure. VA ECLS can provide up to 60 to 80% of a patient's normal cardiac output and it still permits blood flow through the pulmonary circulation to prevent any (further) lung injury [42, 43]. Venous blood is drained from the inferior vena cava (IVC) via the femoral vein or right internal jugular vein. Arterial blood is infused into patients via the right common carotid, femoral, or axillary artery. Direct cannulation of the right atrium (for venous drainage) and aorta (for arterial infusion) may be required for patients who cannot be weaned from CPB. Figure 1 illustrates one cannulation configuration for VA ECLS.

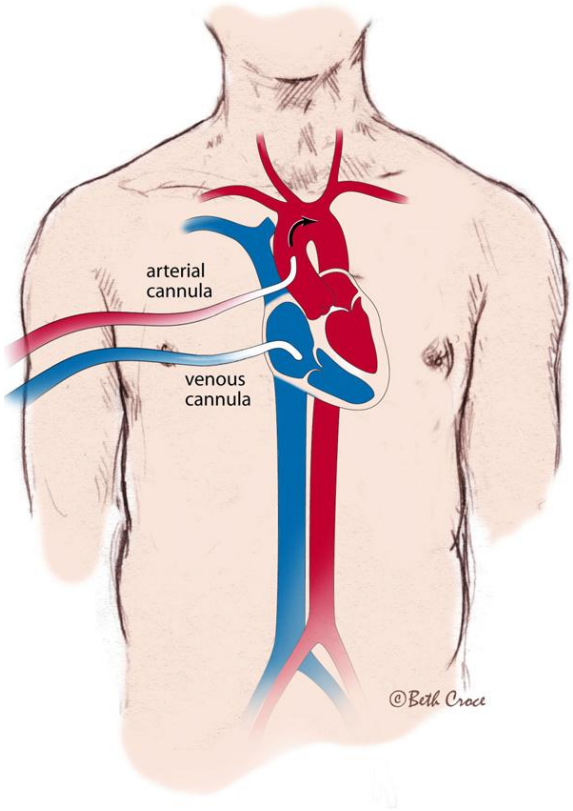

Figure 1: Cannulation for VA ECLS [44]. In this configuration, venous blood is drained from the right atrium, and arterial blood is reinfused into the ascending aorta.

2.2.2. Veno-Venous (VV) ECLS

As previously stated, VV ECLS is used for patients suffering from respiratory failure only; it does not provide any cardiac support. As ECLS techniques and technologies have improved, institutions have moved away from using VA ECLS for the treatment of respiratory failure due to the advantages of the VV treatment. Cannulation for VV ECLS is typically in a femoral vein and/or the right internal jugular vein depending on the use of two single-lumen cannulae or a single dual-lumen cannula. When dual-cannulation is used, it is best to use the femoral vein for drainage and the right internal jugular vein for reinfusion of oxygenated blood (called femoro-arterial VV

ECLS) as it results in higher flow rates, pulmonary arterial mixed blood venous saturation, and better drainage over atrio-femoral VV ECLS [45]. Figure 2 illustrates the cannulation of the right internal jugular vein in a pediatric patient with the use of a single dual-lumen cannula for VV ECLS, and Figure 3 illustrates dual-cannulation in atrio-femoral VV ECLS.

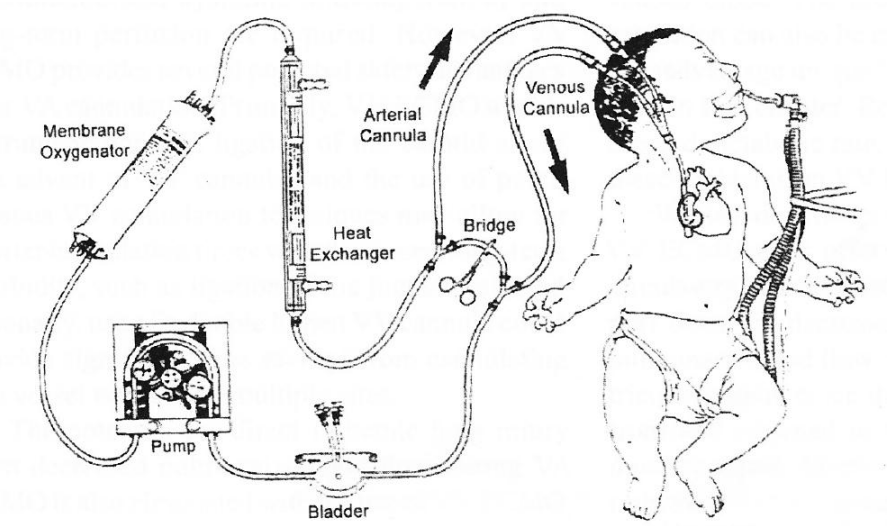

Figure 2: Cannulation for a Dual-Lumen VV ECLS Setup [42]. A bladder is used in some institutions to help control pump flow, and the bridge is used when weaning patients off of ECLS.

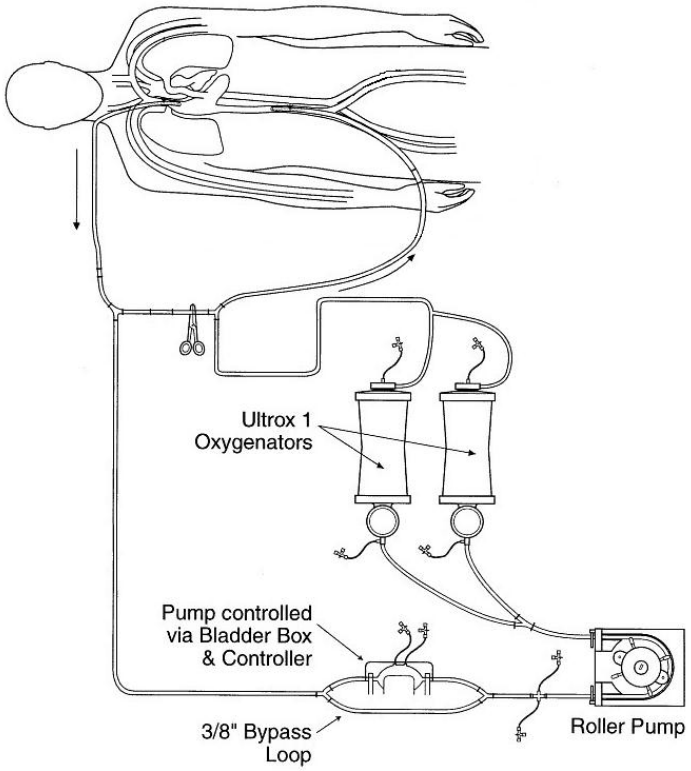

Figure 3: Dual-Cannulation for Atrio-Femoral VV ECLS [46].

Because of the creation of percutaneous cannulation and the fact that a major artery does not have to be cannulated, VV ECLS can result in shorter cannulation times and decrease the risk of long-term morbidity [42]. Furthermore, the use of a dual-lumen cannula offers potentially additional time-saving due to the need to cannulate only a single vein [42]. Moreover, VV ECLS can be better than VA for the lungs and brain; it prevents direct ischemic lung damage because of the sustained flow of oxygenated blood through the lungs, thereby also reducing lung inflammation, and it prevents any emboli resulting from cannulation or the circuit from flowing to the brain [42]. The main disadvantage of this treatment method is that oxygenation could be decreased due to the reinfused blood mixing with systemic venous blood, which can also be exacerbated by a phenomenon known as recirculation. Recirculation is defined as "the portion of blood

returning to the ECLS circuit immediately after being infused to the patient from the circuit." [42, 47] Recirculation is depicted in Figure 4 in a dual-lumen cannula.

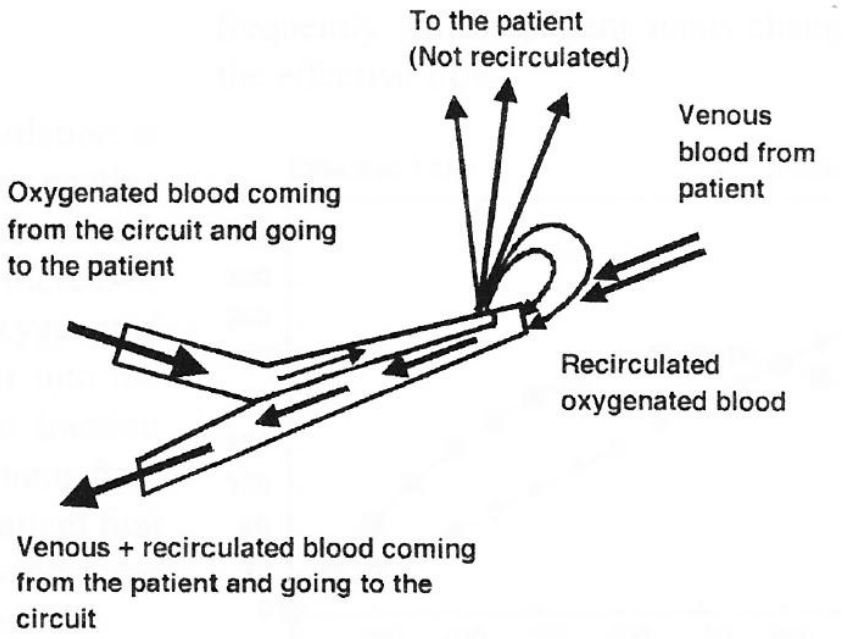

Figure 4: Depiction of Recirculation in a Dual-Lumen Cannula [42].

Recirculation fraction can be calculated using Equation (3) [42, 47, 48, 49, 50]:

$$R = \left(S_{Pre-oxygenator} - S_V O_2\right) / \left(S_{Post-oxygenator} - S_V O_2\right) \times 100\%, \quad (3)$$

where R is recirculation fraction (in percent), $S_{Pre\text{-}oxygenator}$ is the mixed venous oxygen saturation of the blood being drained into the circuit from the patient, S_VO_2 is the actual mixed venous oxygen saturation in the patient, and $S_{Post\text{-}oxygenator}$ is the oxygen saturation of the blood entering the patient from the circuit. Recirculation is affected by four elements: Pump flow rate, cannula positioning, patient cardiac output, and size of the right atrium. It can result in increased pulmonary vascular resistance, increased myocardial oxygen demand and a decreased supply, and a decrease in oxygen delivery to

all organs and tissues [47]. Recirculation can present as decreasing patient S_AO_2, increasing $S_{Pre\text{-}oxygenator}$, decreasing (A-a)$DO_2$, and metabolic acidosis [42]. Recirculation can result in a false measured value of S_VO_2 as it can appear greater than the patient's actual S_VO_2. However, because there is always some amount of recirculation, it is currently not possible to measure a patient's true S_VO_2 without stopping ECLS oxygenation [47]. Because ECLS patients are typically unstable, however, this is not a viable option. Measuring the S_VO_2 in a patient's inferior or superior vena cava can serve as an approximation, but these values do not accurately represent global S_VO_2 [47]. One potential solution to reducing recirculation would be to increase the distance between the cannulae; however, this could result in decreased drainage of the venous blood and/or result in an increased amount of venous blood mixing with blood entering from the ECLS and into the right atrium.

Thirty percent recirculation is the typical value observed during VV ECLS, and at approximately 50% recirculation and greater, the effective flow (the effective oxygen delivery) begins to decrease [42]. Effective pump flow is expressed numerically in Equation (4) [42]:

$$EF = TF - (TF \times R), \tag{4}$$

where EF is effective pump flow, TF is total pump flow, and R is recirculation fraction. Effective flow can be increased by increasing pump flow rate. However, there is a limit, depending on individual patient anatomy, in which the increased pump flow rate will increase the negative pressure on the venous drainage cannula to a point in which it will begin pulling even more of the oxygenated blood back into the circuit [42]. Dual-lumen cannulae have been shown to decrease the recirculation fraction (especially if the venous

drainage holes are moved farther back from the tip of the cannula; however, the size of the internal jugular vein and overall size of the patient can be limiting factors with respect to cannula size and can result in a dual-lumen cannula unable to allow for adequate blood flow rates in adult patients [51, 52, 53, 54, 55, 56]. Other benefits for using a dual-lumen cannula include increased patient mobility by cannulating only the right internal jugular vein, and decreased risk of infection [51, 52, 53, 54, 55, 56].

Techniques have been created at attempting to correct recirculation. Two studies examined the effects of creating a curve at the distal end of the reinfusion cannula and found that it not only helps to improve systemic oxygenation, but it also helps to reduce the time of ECLS treatment and the number of ECLS-related complications [57, 58]. Figure 5 illustrates the ends of the tips near the right atrium for one of the studies.

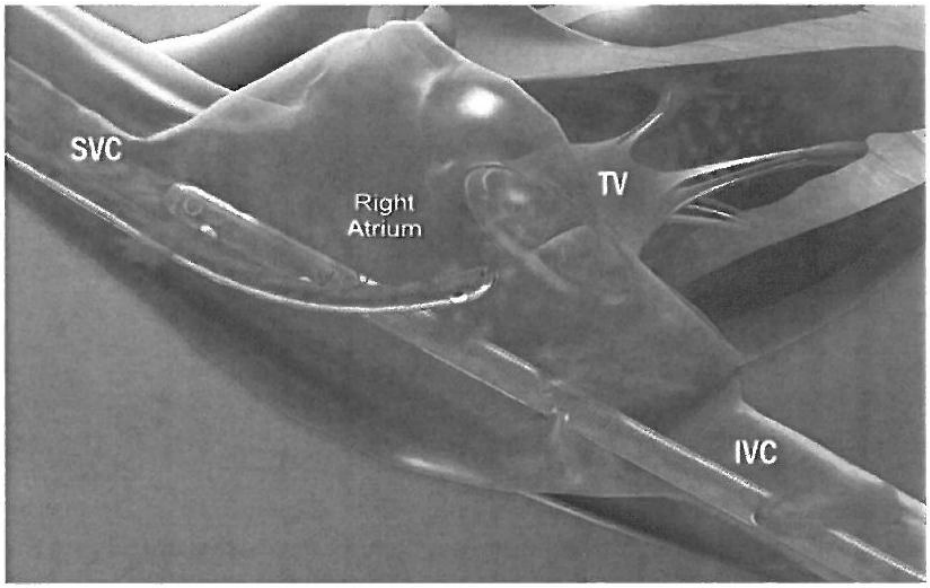

Figure 5: VV ECLS Cannulation Illustrating the Desired Locations of the Tips of the Cannulae in the "X-configurgation" [57]. TV = tricuspid valve.

Another method added a second drainage cannula into a dual-cannulation VV ECLS setup [46]. In this study, the patients were treated with atrial-femoral (right internal jugular vein drainage and femoral vein reinfusion). A second, short drainage cannula was inserted into the left femoral vein for supplemental drainage. This three-cannulae setup resulted in decreased recirculation, thereby improved systemic oxygenation compared to normal atrial-femoral ECLS [46]. However, as previously discussed, femoro-atrial ECLS achieves similar positive results compared to atrial-femoral VV ECLS, and it also avoids the need for a third cannula.

Physicians and perfusionists can use measurements of recirculation to help improve the ECLS treatment. However, it can be a difficult task. It has typically been performed with a technique known as ultrasound dilution [49, 50, 59, 60, 61]. This technique is performed with two ultrasonic sensors, one is attached to the ECLS circuit reinfusion line, and the other is attached to the patient drainage line. A small bolus of saline is injected into the reinfusion line of the ECLS circuit and a dilution curve is created. Another dilution curve is created when the recirculated saline and blood flows past the sensor on the patient drainage line. The two curves are then compared and a percent of recirculation is calculated. This technique was found to be accurate, offers rapid measurements of recirculation, and can be helpful in the optimization of patient care while on VV ECLS [50, 59, 60, 61]. Measuring the arterial and venous PO_2 directly from the cannulae can also provide a sense of the degree of recirculation; if P_VO_2 is within physiologic range (35-45 mmHg) and less than 10% of P_AO_2, then any recirculation can be considered as clinically irrelevant [62].

Lindstrom *et al.* compared the use of oxygen content of the blood to the use of saturation to calculate recirculation. They modified Equation (3) to include content based on an oxygen mass balance rather than saturation, as shown in Equation (5) [48]:

$$R = \left(C_{Pre-oxygenator} - C_V O_2\right)/\left(C_{Post-oxygenator} - C_V O_2\right) \times 100\%. \quad (5)$$

They determined that using oxygen content instead of saturation produced a more accurate model of recirculation. They plotted content- and saturation-derived recirculation calculations against known recirculation values and found a greater correlation between the use of content ($R^2 = 0.87$) and the actual recirculation value when compared to the use of saturation ($R^2 = 0.64$) [48]. When looking at the oxyhemoglobin dissociation curve (which is a plot of the relationship between the oxygen saturation of hemoglobin and the PO_2 in the blood), this finding is fathomable; the relationship between oxygen saturation and PO_2 is not linear, as shown in Figure 6.

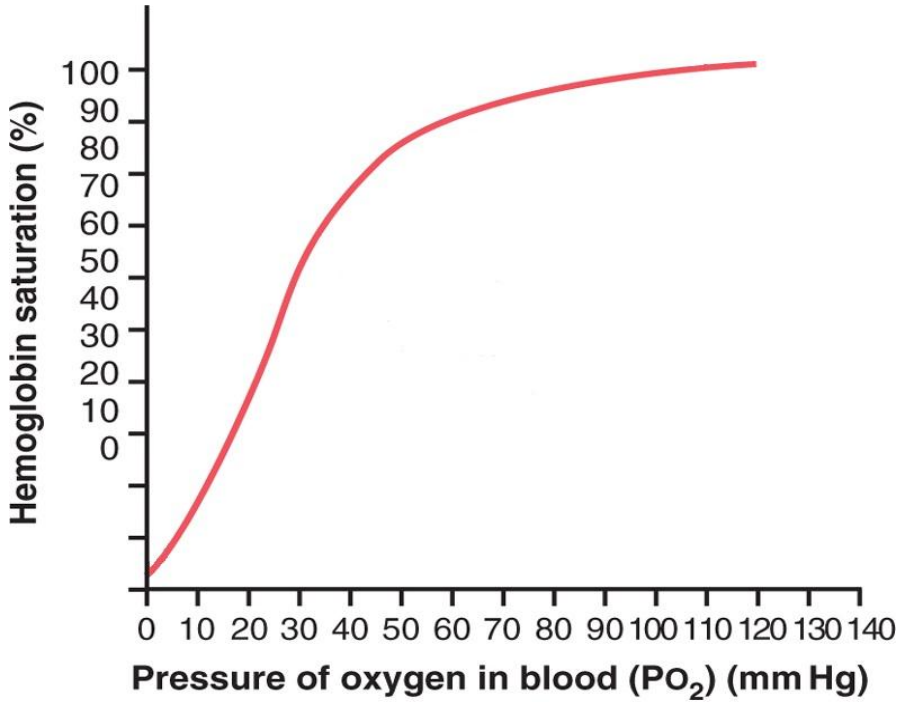

Figure 6: Oxyhemoglobin Dissociation Curve [63].

In order to appropriately predict the saturation of ECLS drainage blood, the PO_2 of it must be determined. Oxygen content is calculated as a function of saturation and PO_2 and shown in Equation (6):

$$Oxygen\ Content = (1.34)([Hgb])(SO_2) + (0.003)(PO_2), \quad (6)$$

where 1.34 is the amount of oxygen that can bind to hemoglobin (in mL of oxygen/g hemoglobin), [Hgb] is the concentration of hemoglobin in the blood (in g Hgb/dL of blood), and 0.003 is the amount of oxygen dissolved in the blood plasma per unit of pressure (in mL of oxygen/(dL of blood × mmHg)). An equation for SO_2 as a function of PO_2 at a pH of 7.4 was determined and found to be very accurate (the greatest error was +0.55% at 98.77% saturation, and a mean absolute error of 0.26%; these were determined over a PO_2 range of 0 to 500 mmHg and a SO_2 range of 0.60% to 99.72%); the relationship is shown in Equation (7) [64]:

$$SO_2 = \left((23{,}400((PO_2)^3 + 150PO_2)^{-1}) + 1\right)^{-1}. \quad (7)$$

During normal physiologic conditions, the oxygen dissolved in plasma is a relatively small amount: Assuming 105 mmHg for P_AO_2, 12 g Hgb/dL Blood, 100% S_AO_2, it accounts for only 1.9% of total oxygen content [63]. Therefore, Equation (3) works well for and is applicable when the PO_2 is approximately 100 mmHg or less. However, patients on ECLS often have a P_AO_2 in excess of 300 or 400 mmHg, which, under the same conditions, can account for up to 5-7% of total oxygen content in the blood.

Walker and colleagues experienced these problems when attempting to improve on Equation (3) [47]. They attempted to improve this equation by mixing arterial and venous blood in different proportions, ranging from 10% to 90% arterial blood and subsequently measuring each mixture's oxygen saturation and hemoglobin concentration.

After completing measurements and outsourcing their results for analysis, the resulting model shown in Equation (8) was returned for determining a patient's true S_VO_2:

$$S_VO_2 = \frac{S_{pre-oxygenator} - (R \times S_{post-oxygenator})}{1-R} - (0.005 \times R) - (0.163 \times R \times P_AO_2). \quad (8)$$

2.3. Hypothesis

As previously discussed, the model for recirculation shown in Equation (3) is really only applicable with a PO_2 of about 100 mmHg or less, and it is not currently possible to determine a patient's true S_VO_2. As a result, the content of the resultant mixture must be determined, and Equation (7) can be used to determine the resultant saturation. This study investigated the effects of recirculation on mixed venous oxygen content and saturation, and compared calculated S_VO_2 to a patient's true S_VO_2. This was tested by mixing oxygenated and deoxygenated blood in different proportions and measuring the resultant oxygen content and saturation of the mixture. A model was created based on these measurements. These data were used to test the following hypothesis: A linear relationship exists between mixed venous oxygen content and recirculation fraction. Additionally, MATLAB can be used to accurately create a simple, noninvasive model for determining the effects of recirculation on ECLS drainage blood oxygen content and saturation. This model would be verified with a physical experiment, and could then serve as a theoretical framework for future analyses.

3. Materials and Methods

3.1. Computer Simulation

Initially, a graphical user interface (GUI) simulation was created in MATLAB to calculate the content and saturation of the different mixtures of blood. It allows users to enter in values for the SO_2, PO_2, concentration of hemoglobin, recirculation fraction, and pH for the drainage blood, as shown in Figure 7.

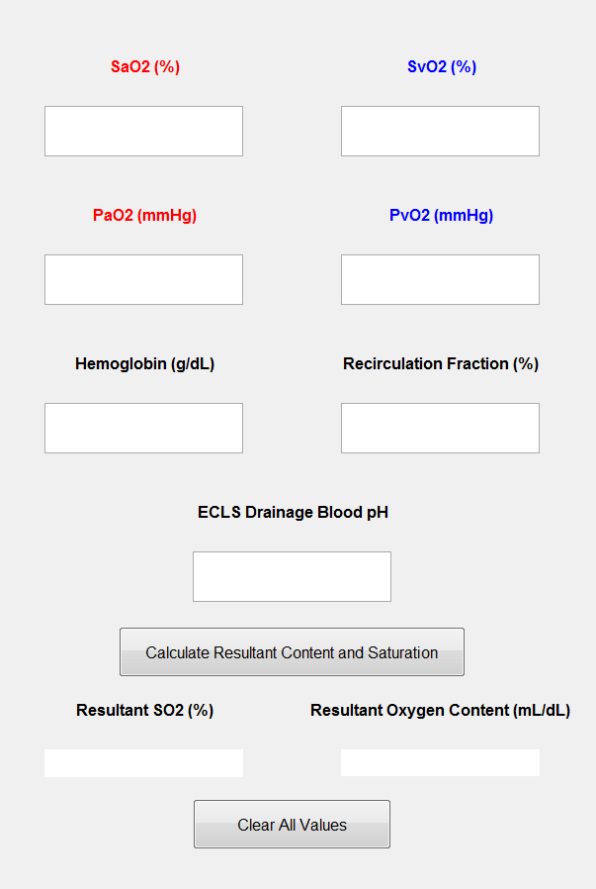

Figure 7: MATLAB GUI.

Firstly, the oxygen content was calculated for the two blood saturations using Equation (6). Again, because of the oxyhemoglobin dissociation curve (Figure 5), the saturation of

mixed blood would not produce a linear relationship. Therefore, the content had to be calculated, and the resultant content was determined based upon the recirculation fraction by using an oxygen content mass balance, as shown in Equation (9):

$$C_R O_2 = (RF)(C_A O_2) + (1 - RF)(C_V O_2), \quad (9)$$

where C_RO_2 is the resultant content, RF is the recirculation (in decimal form), and C_AO_2 and C_VO_2 are the contents for the oxygenated and deoxygenated blood, respectively. Once C_RO_2 was calculated, a separate function was called in MATLAB. This function used the oxygen content equation – Equation (6) –rearranged to solve for SO_2 as a function of PO_2, as shown in Equation (10):

$$S_R O_2 = \frac{C_R O_2 - (0.003)(P_R O_2)}{(1.34)([Hgb])}, \quad (10)$$

where S_RO_2 and P_RO_2 are the resultant saturation and partial pressure of oxygen, respectively. Thereafter, Equation (7), which calculates SO_2 as a function of PO_2, was called. However, PO_2 had to be corrected for the pH of the ECLS drainage blood, and was corrected using Equation (11) [64]:

$$-0.48 = \left(log \left(\frac{PO_{2,obs}}{PO_{2(7.4)}} \right) \right) / (pH_{obs} - 7.4), \quad (11)$$

where $PO_{2,obs}$ is the actual pH-corrected value, $PO_{2(7.4)}$ is the value at a pH of 7.4, and pH_{obs} is the observed/measured pH. However, because neither $PO_{2,obs}$ nor $PO_{2(7.4)}$ of the drainage blood are known, Equation (11) was rearranged to calculate the ratio of $PO_{2,obs}$ and $PO_{2(7.4)}$, as shown in Equation (12):

$$\frac{PO_{2,obs}}{PO_{2(7.4)}} = 10^{-0.48 \times (pH_{obs} - 7.4)}. \quad (12)$$

PO_2 in Equation (7), which would be its value at a pH of 7.4, was multiplied by this ratio to solve for the actual pH-corrected PO_2, and SO_2 using Equation (7) was calculated

based on the pH-corrected PO_2. Finally, Equations (7) and (10) were solved simultaneously and the PO_2 was determined from this result. This number is then sent back to the main GUI function. SO_2 is calculated based off of the PO_2 from the simultaneous solving of Equations (7) and (10), and is displayed in the GUI window along with C_RO_2.

3.2. Circuit Design

Two separate CPB circuits were created to achieve the desired blood gas values, which are shown in Table 2. The values for the deoxygenated blood were determined from the FDA's regulations for oxygenator testing, while arterial values were set based on values typically seen in a patient on ECLS [65].

Table 2: Values for Simulating Oxygenated and Deoxygenated Blood.

Parameter	Oxygenated Blood	Deoxygenated Blood
SO_2 (%)	100	70-80
PO_2 (mmHg)	250-300	45-55
PCO_2 (mmHg)	35-45	45-60
pH	7.4-7.5	7.3-7.45
Temperature (°C)	35	
Hematocrit (%)	30	
Hemoglobin (g/dL blood)	9.9	

Two CPB circuits were primed with 1.5 liters of Plasma-Lyte A. This prime was chased out with 1.5 liters of fresh bovine blood from Lampire Biological Laboratories (which was anticoagulated with citrate phosphate dextrose (CPD) to prevent any negative anticoagulant-platelet interaction) in each circuit. The two circuits were set up nearly identically, each with a Terumo CAPIOX RX25 oxygenator and reservoir, Pemco roller

pump, Terumo CDI 500 blood gas analyzer cuvette, and a Sarns heater-cooler, as shown in Figure 8 (the saturation probe was only used in the deoxygenation circuit, however; this probe was used to measure hematocrit, hemoglobin, and saturation).

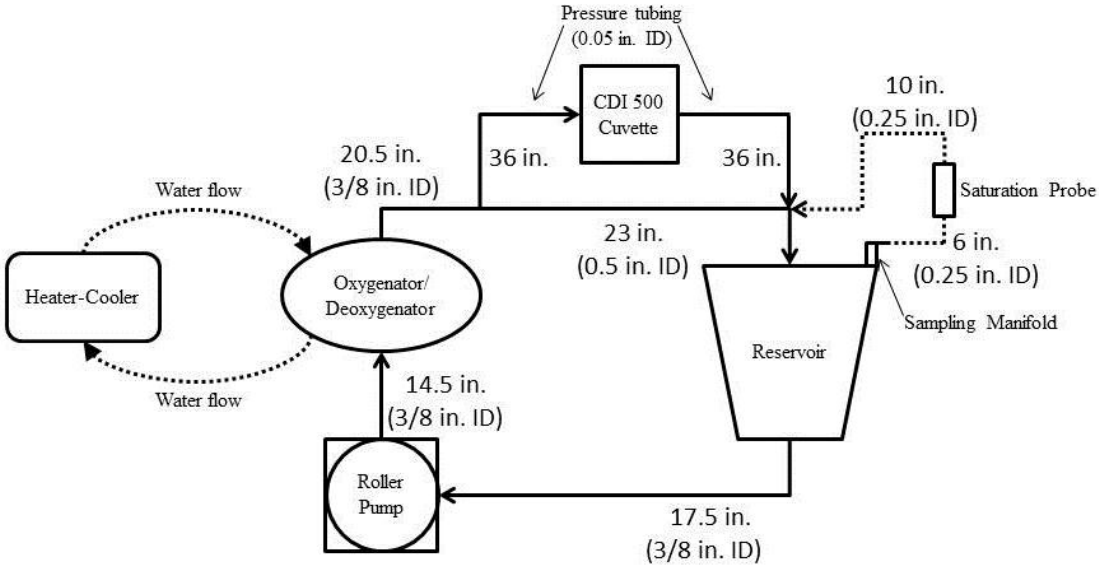

Figure 8: Experimental CPB Circuit Diagram. Tubing lengths indicated. ID = Internal Diameter.

pH of the blood was adjusted as necessary with 1 mEq/mL of sodium bicarbonate. Resembling previous experiments, the deoxygenation was achieved with a mixture of nitrogen and carbon dioxide flowing into the gas inlet of the oxygenator, with 100% oxygen and carbon dioxide used to make final adjustments [47, 66]. The CDI 500 units, which use optical fluorescence for measurements, were monitored for the parameter values in Table 2. Once the values in were achieved, sample volumes corresponding to recirculation fractions were withdrawn from each circuit into 60 mL syringes. For example, to simulate 10% recirculation, 6 mL of oxygenated blood and 54 mL of deoxygenated blood were drawn into the syringes. Once blood was drawn from the

oxygenation circuit, a stopcock in the line to the CDI cuvette was opened to flush the blood out of the cuvette with air. The blood from the deoxygenation circuit was then drawn into the syringes and the syringes were then rotated multiple times to ensure proper mixing of the blood. Once the deoxygenated blood was drawn, a stopcock between the sampling manifold and saturation probe was opened and the saturation probe cuvette was drained of blood. One syringe was then completely injected into this stopcock and, subsequently, the saturation probe in order to properly measure and record the oxygen saturation. The other syringe was then completely injected into the CDI cuvette previously emptied in the oxygenation circuit, and the PO2, PCO_2, and pH were measured and recorded. This process was executed five times for each level of recirculation. Recirculation levels of 10% to 70%, increasing in 10% increments, were measured. pH and PCO_2 were measured to ensure proper physiologic conditions.

3.3. Statistical Analyses

The data for oxygen content were entered into Minitab 16 Statistical Software for analysis. Assumptions for a linear regression analysis were tested (linearity, normality of residuals, independence of residuals, and homogeneity of variance), and the regression analysis was subsequently performed to examine the relationship between recirculation level and oxygen content. Tests were performed at the $\alpha = 0.05$ level.

4. Results

4.1. Regression Analysis

A linear regression test was performed using Minitab 16 statistical software, which was used to test the hypothesis in Section 2.3. The relationship between ECLS drainage blood oxygen content and recirculation fraction was determined to be linear ($p < 0.001$) with a significant constant ($p < 0.001$). The equation for the relationship is shown in Equation (13):

$$C_R O_2 = 0.0424 \times RF + 9.9 \ \frac{mL\ O_2}{dL\ Blood}\,. \tag{13}$$

The relationship was determined to have a strong correlation, with a coefficient of determination of $R^2 = 97.2\%$, indicating that 97.2% of the variance for C_RO_2 is explained by recirculation. The model also passed a pure error lack-of-fit test ($p = 0.097$) and no autocorrelation was found (Durbin-Watson statistic of 1.9421). A scatterplot of the data can be seen in Figure 9.

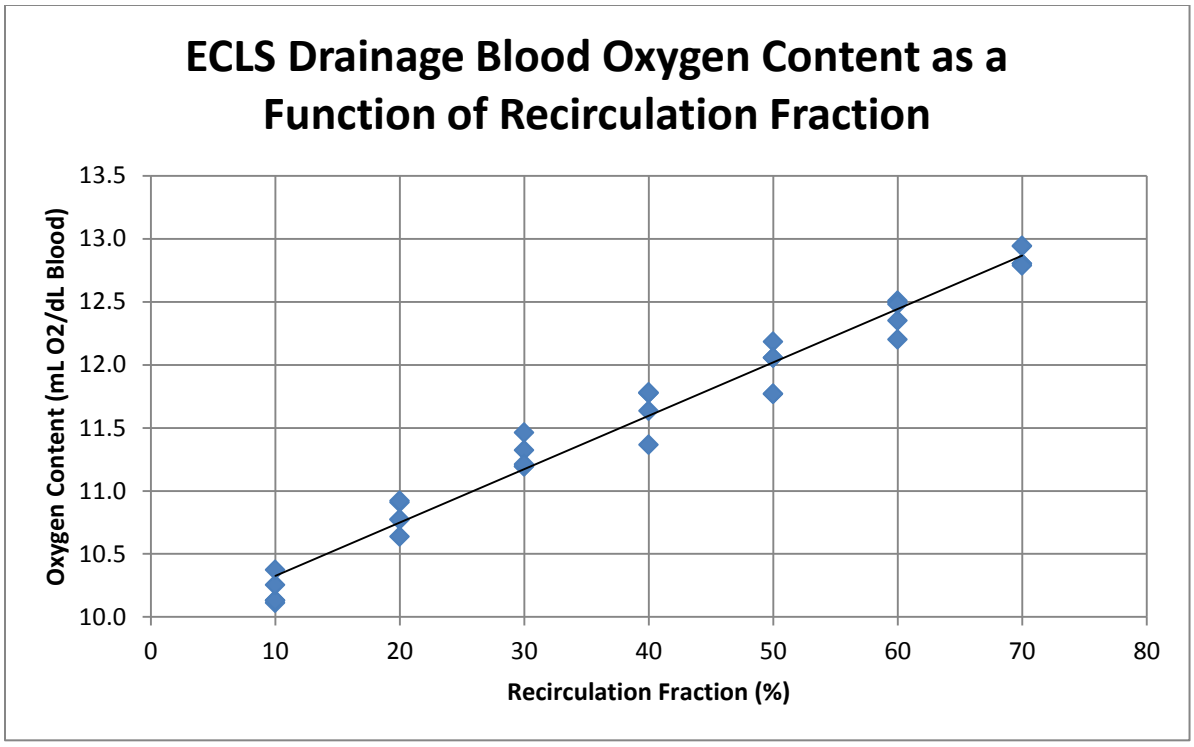

Figure 9: Scatterplot of Oxygen Content as a Function of Recirculation Fraction with Linear Regression Trendline.

4.2. Assumption Testing

As discussed in Section 3.3, four assumptions were tested to support the Minitab regression analysis. The scatterplot in Figure 9 shows that the data are at least reasonably linear. The residuals were not found to be normal (Anderson-Darling statistic of 0.812, p = 0.032), but this is a minor violation and can be disregarded. The residuals were independent and the variance was determined to be homogenous.

4.3. Comparison of MATLAB and Experimental Results

The results for the experiment were compared with the MATLAB simulation with identical numbers entered into the GUI (SO_2, PO_2, pH, hemoglobin concentration, and

recirculation fraction). The percent difference between the measured resultant content values and those calculated in MATLAB was calculated. The average percent difference at each recirculation fraction is shown in Figure 10.

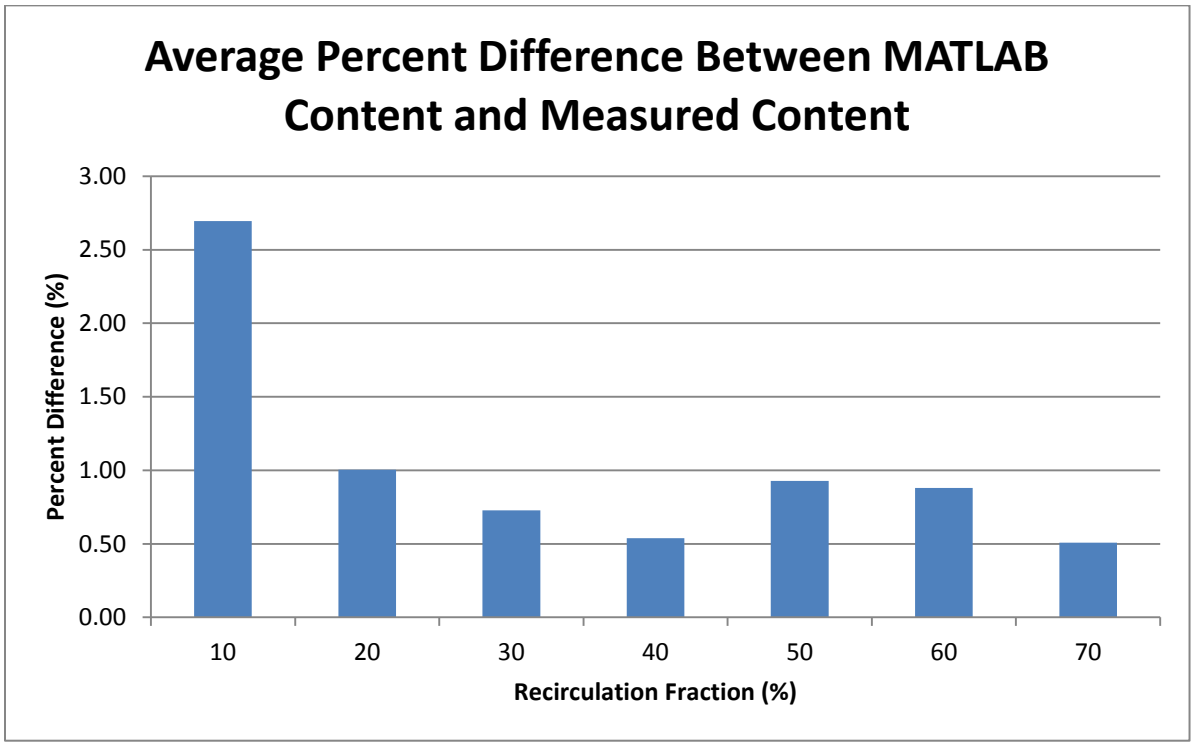

Figure 10: Average Percent Difference Between MATLAB Calculated Resultant Oxygen Content and Measured Resultant Oxygen Content. Five trials were performed at each recirculation level.

5. Discussion

The determination of a linear model for ECLS drainage blood oxygen content as a function of recirculation was expected due to the mathematics used in the MATLAB model. After calculating oxygen content from the oxygen and deoxygenated blood, a simple mass balance calculation was used to determine the mixture oxygen content. For example, for 10% recirculation, the resultant mixture oxygen content would be comprised of 10% of the oxygenated blood and 90% of the deoxygenated blood. Minitab also determined that the relationship between recirculation and resultant mixture oxygen saturation was also linear ($p < 0.001$) with a significant constant ($p < 0.001$). The equation for this relationship is shown in Equation (14):

$$S_R O_2 = 0.299 \times RF + 73.7\%. \quad (14)$$

The relationship was determined to have a strong correlation, with a coefficient of determination of $R^2 = 96.8\%$, indicating that 96.8% of the variance for S_RO_2 is explained by recirculation. However, this model failed a pure error lack-of-fit test ($p = 0.035$), suggesting that the model does not accurately fit the data. This nonlinearity is most likely a result of the Bohr Effect, which creates the oxyhemoglobin dissociation curve (Figure 6). Conversely, when the ECLS drainage blood oxygen saturation is plotted as a function of recirculation, the plot appears to fit well. A scatterplot of the relationship between resultant mixture oxygen saturation and recirculation is shown in Figure 11.

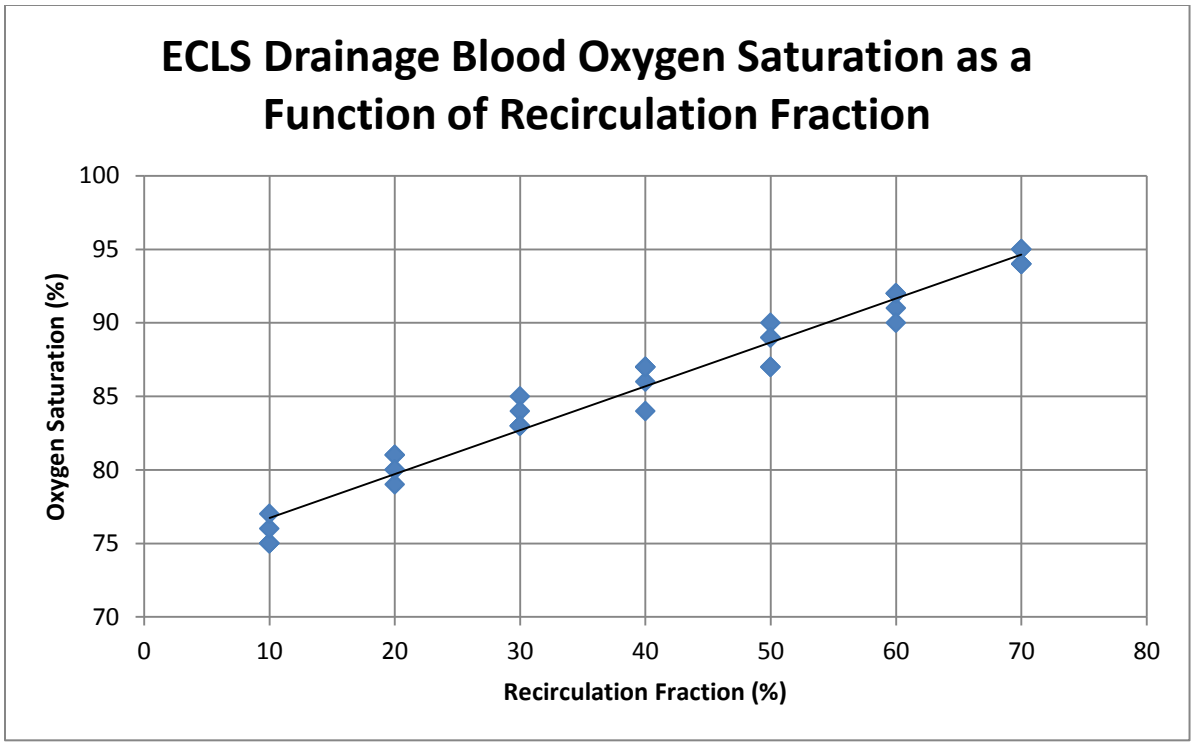

Figure 11: Scatterplot of Oxygen Saturation as a Function of Recirculation Fraction with Trendline.

Resembling Figure 10, the results for the experiment were compared with the MATLAB simulation with identical numbers entered into the GUI. The percent difference between the measured resultant saturation values and those calculated in MATLAB were calculated and the average percent difference at each recirculation fraction is shown in Figure 12.

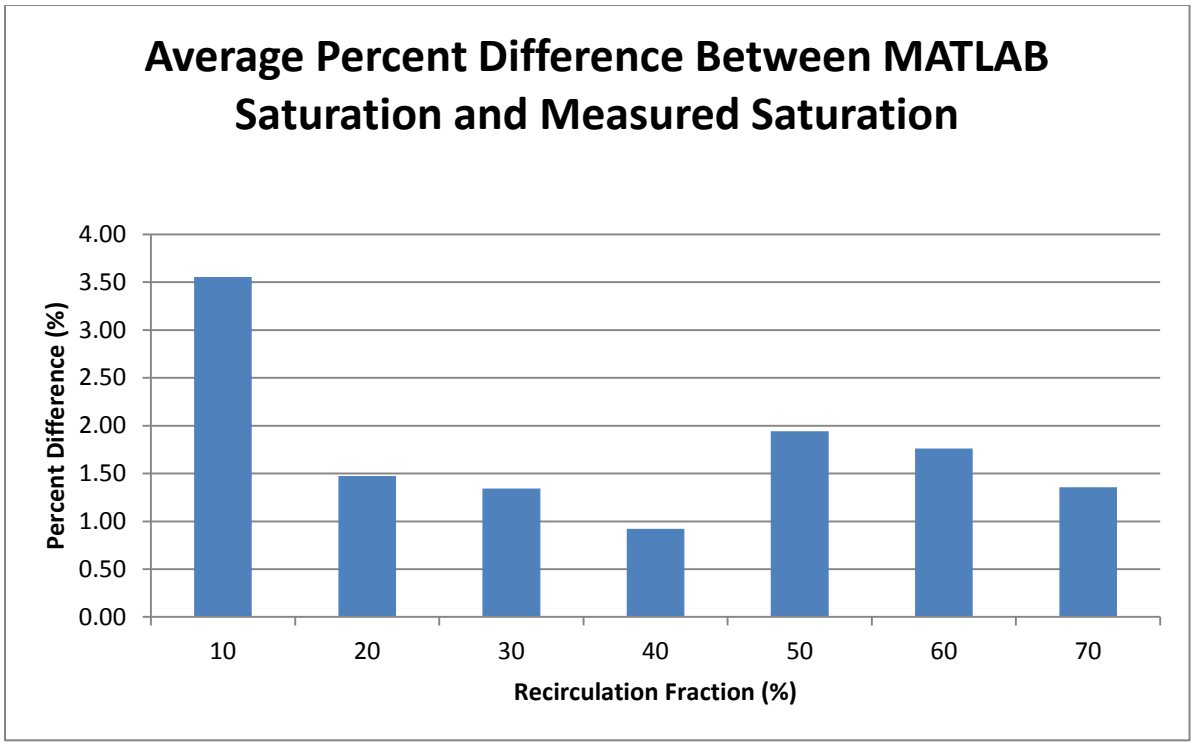

Figure 12: Average Percent Difference Between MATLAB Calculated Resultant Oxygen Saturation and Measured Resultant Oxygen Saturation.

As shown in Figures 10 and 12, the MATLAB GUI is an accurate tool for modeling recirculation during VV ECLS. However, the fourth trial for the 10% recirculation fraction appears to be an outlier as it is nearly six times the standard deviation from the average value (0.720 versus 0.128 for oxygen content, and 6.60 versus 1.14 for oxygen saturation). The percent difference between the MATLAB calculated and the actual measured values for content and saturation were 7.03% and 7.99%, respectively. The PO_2 of the oxygenated blood for this trial was also outside of the range displayed in Table 2 (239 mmHg), which could have also resulted in incorrect/odd results. With this trial removed from the average percent difference calculations, the MATLAB model appears to be even more accurate, as shown in Figures 13 and 14.

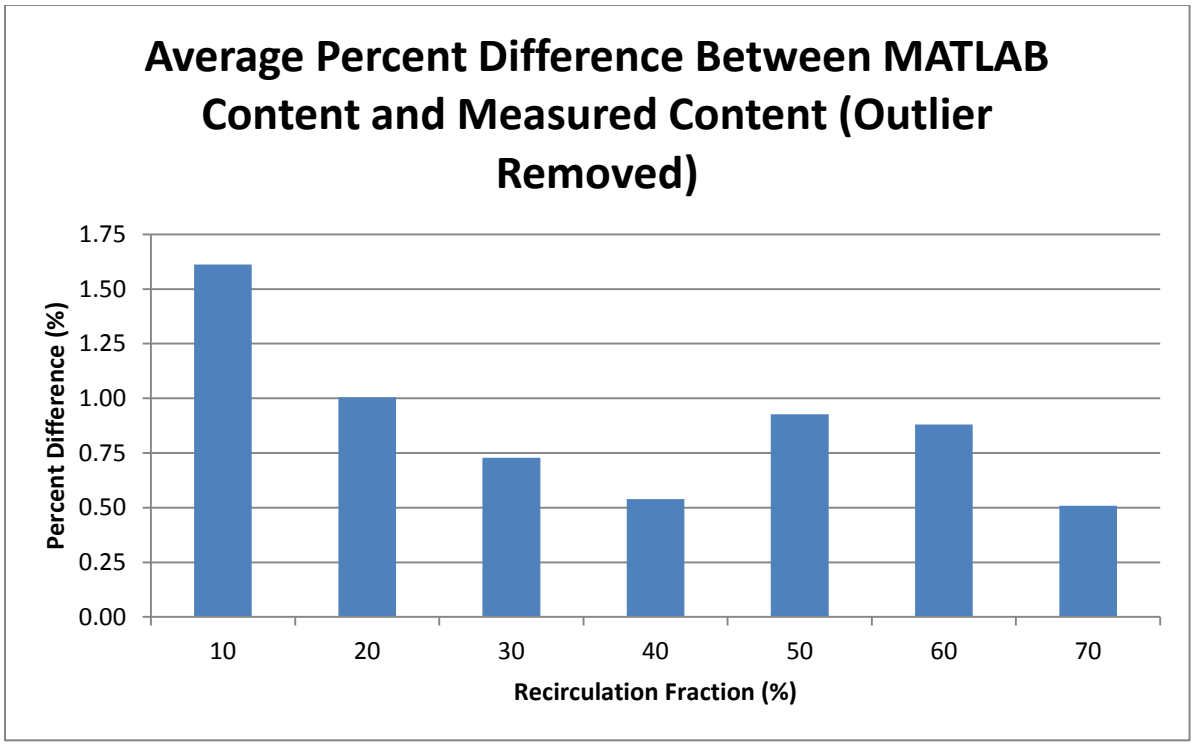

Figure 13: Average Percent Difference Between MATLAB Calculated Resultant Oxygen Content and Measured Resultant Oxygen Content With Trial 4 for 10% Recirculation Removed.

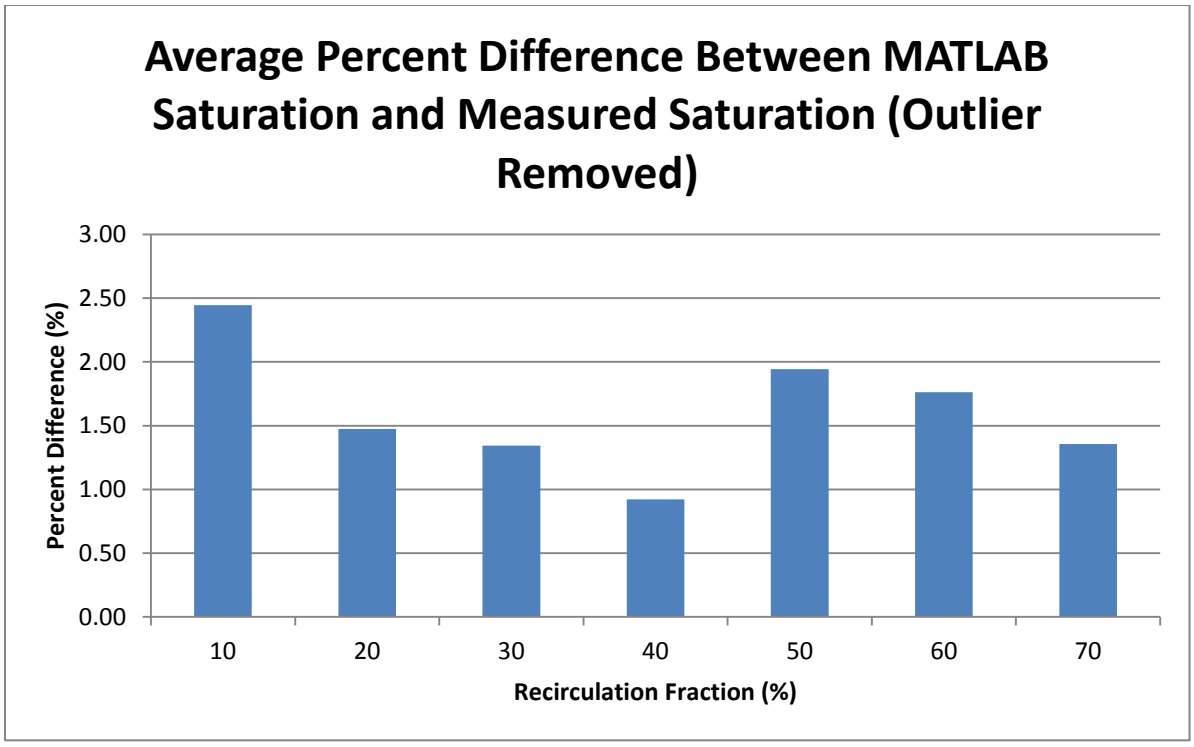

Figure 14: Average Percent Difference Between MATLAB Calculated Resultant Oxygen Saturation and Measured Resultant Oxygen Saturation With Trial 4 for 10% Recirculation Removed.

An additional model was created in MATLAB to examine the effects of hemoglobin concentration on the resultant mixture oxygen content. Since nearly all of the oxygen in arterial blood in humans is bound to hemoglobin, it was expected that increasing its concentration, while keeping other parameters constant, would result in an increase in oxygen content. The values kept constant in the model are shown in Table 3.

Table 3: Values Used in Examining the Effects of Hemoglobin Concentration on ECLS Drainage Oxygen Content.

Parameter	Value
S_VO_2	75%
P_VO_2	50 mmHg
S_AO_2	100%
P_AO_2	275 mmHg
Drainage pH	7.4

This was tested over the same range of recirculation fractions (10-70%). The plots of these can be seen in Figure 15.

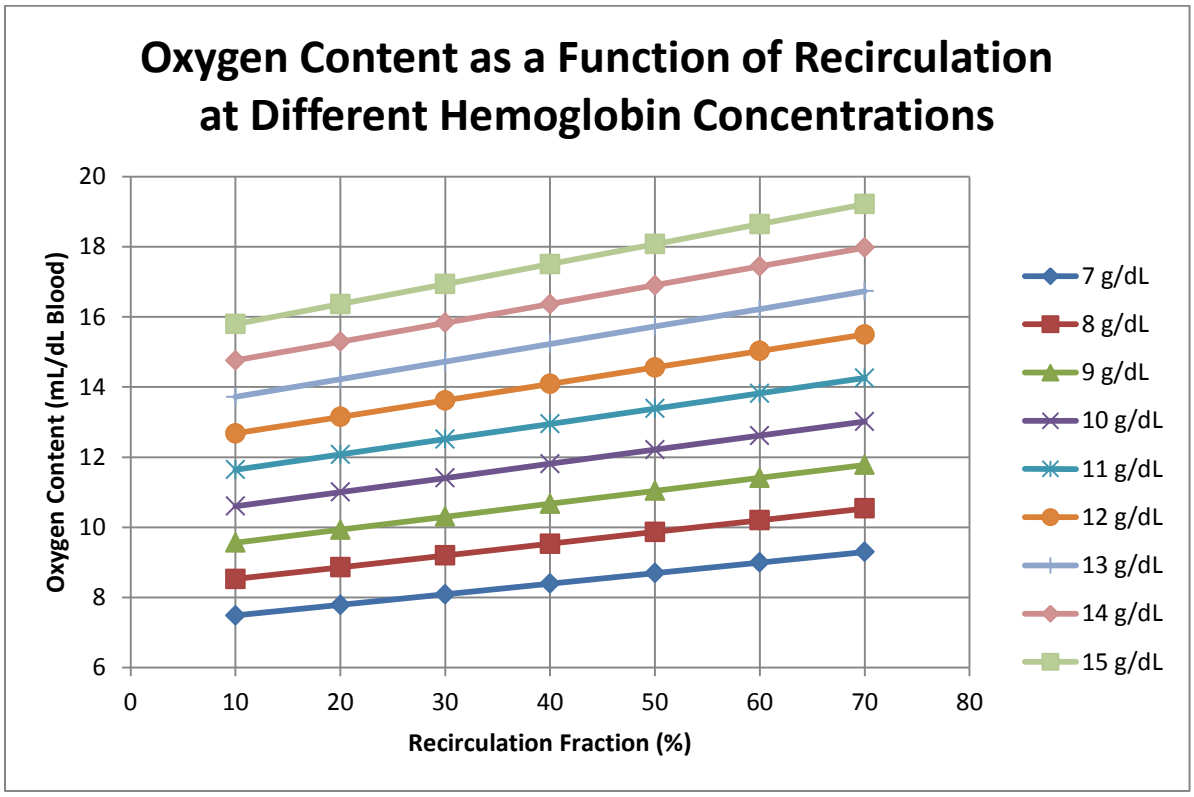

Figure 15: Plots of Oxygen Content as a Function of Recirculation at Different Concentrations of Hemoglobin.

The plot in Figure 15 illustrates that a higher hemoglobin concentration results in a higher oxygen content. This makes sense because more oxygen can be carried in the blood. This result indicates that maintaining a higher hemoglobin concentration can aid in patient treatment. Additionally, because an increase in hemoglobin has a much greater effect than an increase in PO_2 – see Equation (6) – it is better to increase an ECLS patient's hemoglobin as opposed to increasing the F_iO_2 on the ECLS circuit. However,

because the risk of mortality increases with each blood transfusion, increasing the F_iO_2 should be examined first. If this is insufficient, a blood transfusion should be considered.

In addition to recirculation, the pH of the ECLS drainage blood also had a dramatic effect on the oxygen saturation of the resultant mixture. Despite total oxygen content remaining the same throughout each pH value, the oxygen saturation was different in each trial. This was also examined in the MATLAB model, similar to the effect of hemoglobin concentration on resultant mixture oxygen content. The values kept constant are shown in Table 4, and the plots of resultant mixture oxygen saturation at different pH values are shown in Figure 16.

Table 4: Values Used in Examining the Effects of pH on ECLS Drainage Oxygen Saturation.

Parameter	Value
S_VO_2	75%
P_VO_2	50 mmHg
S_AO_2	100%
P_AO_2	275 mmHg
Hemoglobin Concentration	12 g/dL

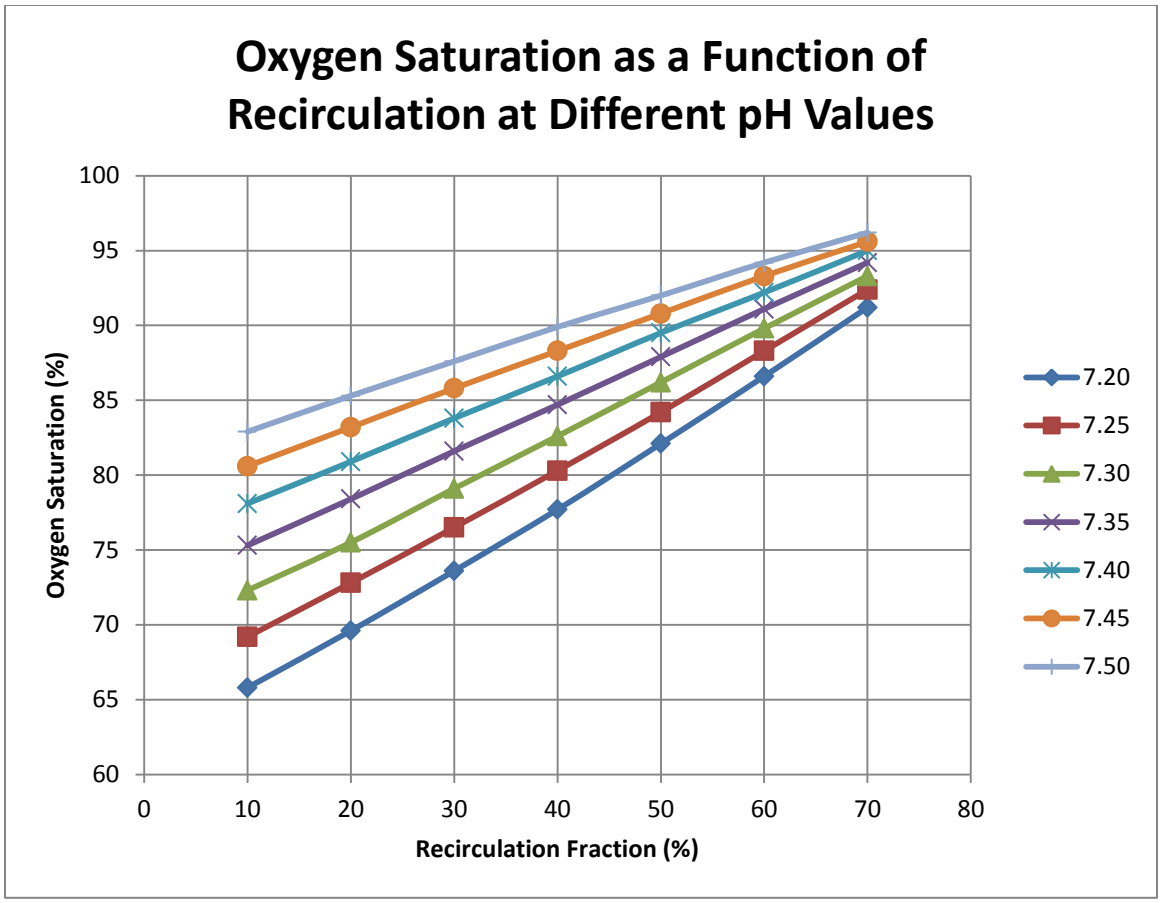

Figure 16: Plots of Oxygen Saturation as a Function of Recirculation at Different pH Values.

The plot in Figure 16 indicates that a higher pH will result in higher oxygen saturation. However, increasing the blood pH also increases hemoglobin's affinity for oxygen. This means that the hemoglobin does not want to release the oxygen to the tissues. At first glance, it appears that maintaining a more basic pH could aid in patient treatment. However, because a more basic pH would also increase hemoglobin's oxygen affinity, less oxygen would be released to the tissues. Therefore, maintaining a normal physiologic pH (7.35-7.45) would provide the best balance between oxygen saturation and hemoglobin's oxygen affinity. However, because of the Bohr Effect, the relationship between saturation and recirculation may not be linear in practice.

6. Conclusion

6.1. Limitations

Despite this experiment resulting in excellent results, some limitations were associated with the investigation. First and foremost, the CDI 500 unit used could not be calibrated with results from a blood gas analyzer due to one being unavailable at the time of the experiment. Aside from calibrating the unit with an apparatus from Terumo before use, the CDI 500 also requires calibration with input from a separate blood gas analyzer to produce more accurate measurements. A blood gas analyzer would also most likely have resulted in more accurate numbers from the mixture samples. Additionally, a potential source of systematic error is the fact that bovine blood was used in the experiment and compared with the human dissociation curve. The bovine and human dissociation curves are not identical; therefore, this could have produced some of the witnessed error.

Regarding the MATLAB program, it would have to be converted into an executable program that could operate regardless of platform. It would be difficult to convince institutions to purchase all of MATLAB just for this one program. Moreover, the program would also have to be altered to be more resistant to errors; as it stands, users can enter invalid parameters into the program, and will attempt to run, resulting in an error being produced in the main MATALB window (outside of the GUI).

6.2. Clinical Applications

Although the MATLAB model is very accurate, it probably could not be used clinically by itself. There are too many unknowns in a VV ECLS patient to enable the

clinical use of this model. One could argue that a measured oxygen content combined with the known hemoglobin concentration can result in determining the recirculation from Figure 15. However, since a VV ECLS patient's true S_VO_2 cannot be determined, nor can their P_VO_2 or venous oxygen content, it would not necessarily be an accurate measurement. A low S_VO_2 and P_VO_2 combined for a low venous oxygen content along with a high recirculation fraction could result in a drainage blood oxygen content similar to a lower recirculation fraction with venous numbers closer to physiologically normal, but this program could not indicate this situation. However, combining the MATLAB program with the use of ultrasound dilution could be used to improve recirculation measurements. The ECLS drainage blood oxygen content could be measured and then recirculation could be estimated using ultrasound dilution. These measurements could then be confirmed using the plot in Figure 15, and the recirculation treated accordingly, such as with the adjustment of cannulae position.

6.3. Summary

This study established that the relationship between recirculation fraction and VV ECLS drainage blood oxygen content is linear over the range of conditions investigated and that the MATLAB GUI model is accurate at calculating the oxygen content and saturation of the drainage blood, and this theoretical analysis can, therefore, be used in future studies. Additionally, it determined that the relationship between recirculation fraction and VV ECLS drainage blood oxygen saturation may actually be linear. It also determined that hemoglobin concentration and pH can have a strong effect on the oxygen content of the drainage blood.

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Appendix A. Raw Data.

Table A1: Raw Data for Oxygenated Blood for all Trials.

Oxygenated Blood					
RF (%)	**PO_2 (mmHg)**	**SO_2 (%)**	**Content (mL O_2/dL Blood)**	**pH**	**PCO_2 (mmHg)**
10	252	100	14.022	7.49	35
10	250	100	14.016	7.5	35
10	300	100	14.166	7.48	37
10	239	100	13.983	7.47	38
10	262	100	14.052	7.45	40
20	273	100	14.085	7.45	40
20	252	100	14.022	7.46	39
20	254	100	14.028	7.47	38
20	252	100	14.022	7.47	38
20	253	100	14.025	7.48	37
30	262	100	14.052	7.49	36
30	276	100	14.094	7.48	37
30	252	100	14.022	7.45	40
30	256	100	14.034	7.45	41
30	250	100	14.016	7.45	40
40	263	100	14.055	7.48	37
40	250	100	14.016	7.48	36
40	295	100	14.151	7.47	38
40	261	100	14.049	7.44	41
40	289	100	14.133	7.44	41
50	270	100	14.076	7.45	40
50	259	100	14.043	7.45	39
50	252	100	14.022	7.46	38
50	254	100	14.028	7.47	38
50	257	100	14.037	7.47	37
60	292	100	14.142	7.44	41
60	278	100	14.1	7.44	40
60	263	100	14.055	7.45	39
60	250	100	14.016	7.46	38
60	274	100	14.088	7.47	37
70	295	100	14.151	7.47	37
70	268	100	14.07	7.43	42
70	277	100	14.097	7.43	41
70	281	100	14.109	7.44	40
70	268	100	14.07	7.45	39

Table A2: Raw Data for Deoxygenated Blood for all Trials.

Deoxygenated Blood					
RF (%)	**PO_2 (mmHg)**	**SO_2 (%)**	**Content (mL O_2/dL Blood)**	**pH**	**PCO_2 (mmHg)**
10	52	74	9.97284	7.35	56
10	55	73	9.84918	7.32	60
10	50	73	9.83418	7.31	60
10	53	79	10.63914	7.4	48
10	49	75	10.0965	7.42	45
20	49	75	10.0965	7.4	47
20	52	78	10.50348	7.38	50
20	47	73	9.82518	7.39	49
20	48	74	9.96084	7.4	48
20	47	72	9.69252	7.38	52
30	51	78	10.50048	7.4	48
30	51	74	9.96984	7.34	57
30	53	77	10.37382	7.37	53
30	50	75	10.0995	7.39	49
30	52	75	10.1055	7.37	53
40	55	76	10.24716	7.34	56
40	49	73	9.83118	7.36	52
40	47	74	9.95784	7.41	45
40	50	75	10.0995	7.39	48
40	49	75	10.0965	7.38	49
50	47	70	9.4272	7.36	51
50	53	78	10.50648	7.4	47
50	47	73	9.82518	7.39	48
50	52	76	10.23816	7.35	53
50	52	78	10.50348	7.37	50
60	52	78	10.50348	7.35	53
60	51	76	10.23516	7.37	49
60	49	74	9.96384	7.39	47
60	48	73	9.82818	7.37	50
60	47	73	9.82518	7.4	45
70	49	75	10.0965	7.37	49
70	50	75	10.0995	7.36	50
70	51	75	10.1025	7.37	49
70	51	77	10.36782	7.37	49
70	47	72	9.69252	7.37	49

Table A3: Raw Data for Mixture Blood for all Trials.

Mixture Blood					
RF (%)	**PO_2 (mmHg)**	**SO_2 (%)**	**Content (mL O2/dL Blood)**	**pH**	**PCO_2 (mmHg)**
10	54	75	10.1115	7.37	56
10	61	75	10.1325	7.34	59
10	60	75	10.1295	7.33	63
10	57	76	10.25316	7.42	49
10	53	77	10.37382	7.42	48
20	54	81	10.90746	7.42	49
20	59	81	10.92246	7.4	52
20	52	79	10.63614	7.4	51
20	53	80	10.7718	7.41	50
20	54	80	10.7748	7.4	51
30	62	85	11.4621	7.43	47
30	61	83	11.19378	7.37	55
30	60	84	11.32344	7.39	52
30	62	83	11.19678	7.4	50
30	67	83	11.21178	7.4	52
40	79	87	11.77842	7.39	51
40	74	84	11.36544	7.4	49
40	75	86	11.63376	7.43	45
40	78	87	11.77542	7.41	48
40	79	87	11.77842	7.41	47
50	76	87	11.76942	7.41	47
50	81	90	12.1824	7.43	45
50	76	87	11.76942	7.43	44
50	83	89	12.05574	7.4	47
50	83	89	12.05574	7.42	46
60	96	92	12.49272	7.41	46
60	101	92	12.50772	7.41	45
60	93	91	12.35106	7.43	44
60	87	90	12.2004	7.42	44
60	92	92	12.48072	7.44	42
70	111	94	12.80304	7.44	41
70	111	94	12.80304	7.44	41
70	113	95	12.9417	7.42	45
70	113	95	12.9417	7.41	44
70	106	94	12.78804	7.42	44

Appendix B. Statistical Output From Minitab Testing.

Regression Analysis: Mixture Content versus RF

The regression equation is
Mixture Content = 9.90 + 0.0424 RF

Predictor	Coef	SE Coef	T	P	VIF
Constant	9.90170	0.05567	177.87	0.000	
RF	0.042368	0.001245	34.04	0.000	1.000

S = 0.147284 R-Sq = 97.2% R-Sq(adj) = 97.1%

Analysis of Variance

Source	DF	SS	MS	F	P
Regression	1	25.131	25.131	1158.51	0.000
Residual Error	33	0.716	0.022		
Lack of Fit	5	0.194	0.039	2.08	0.097
Pure Error	28	0.522	0.019		
Total	34	25.847			

Unusual Observations

Obs	RF	Mixture Content	Fit	SE Fit	Residual	St Resid
11	30.0	11.4621	11.1728	0.0278	0.2893	2.00R

R denotes an observation with a large standardized residual.

Durbin-Watson statistic = 1.94210

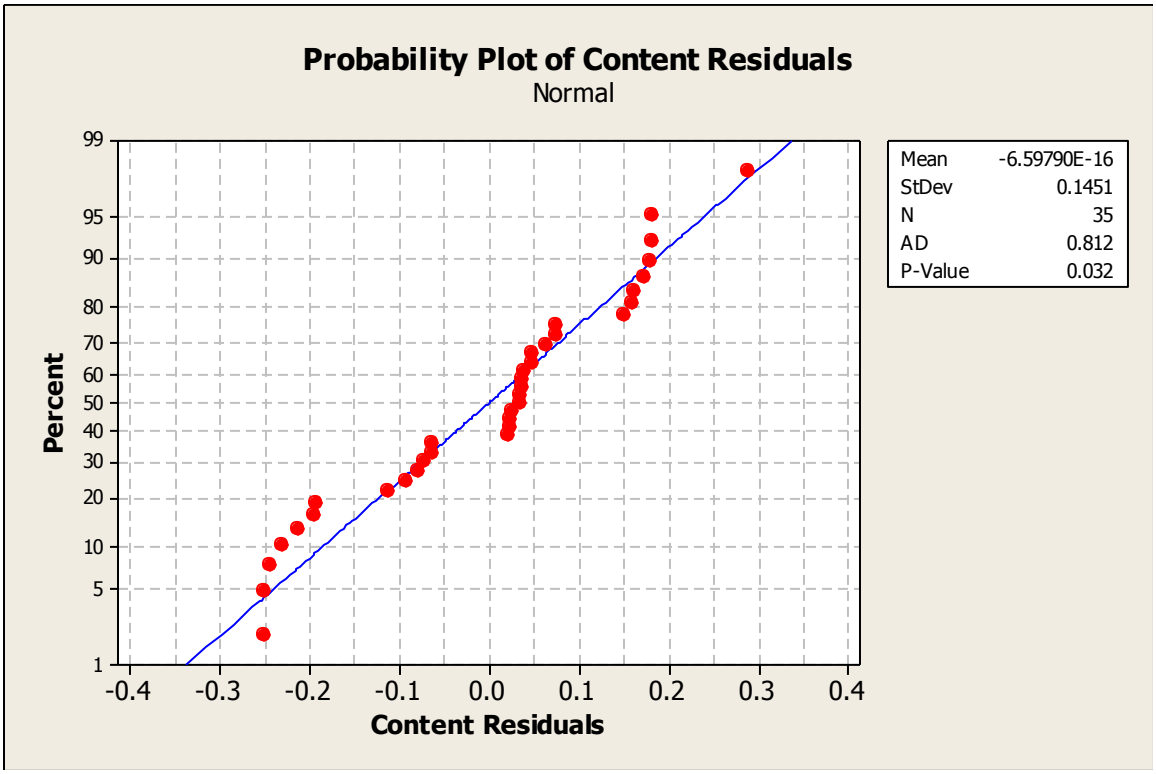

Figure B1: Minitab Probability Plot Testing for Normality of the Residuals (Failed – Non-Normal).

Regression Analysis: Mixture Saturation versus RF

The regression equation is
Mixture Saturation = 73.7 + 0.299 RF

Predictor	Coef	SE Coef	T	P	VIF
Constant	73.7429	0.4239	173.95	0.000	
RF	0.298571	0.009479	31.50	0.000	1.000

S = 1.12161 R-Sq = 96.8% R-Sq(adj) = 96.7%

Analysis of Variance

Source	DF	SS	MS	F	P
Regression	1	1248.0	1248.0	992.07	0.000
Residual Error	33	41.5	1.3		
Lack of Fit	5	13.9	2.8	2.82	0.035
Pure Error	28	27.6	1.0		
Total	34	1289.5			

Unusual Observations

Obs	RF	Mixture Saturation	Fit	SE Fit	Residual	St Resid
11	30.0	85.000	82.700	0.212	2.300	2.09R

R denotes an observation with a large standardized residual.

Durbin-Watson statistic = 1.75846

Appendix C. MATLAB Code for VVECLS03112012.m (Main GUI).

```
function varargout = VVECLS03112012(varargin)
% VVECLS03112012 MATLAB code for VVECLS03112012.fig
%      VVECLS03112012, by itself, creates a new VVECLS03112012 or
raises the existing
%      singleton*.
%
%      H = VVECLS03112012 returns the handle to a new VVECLS03112012 or
the handle to
%      the existing singleton*.
%
%      VVECLS03112012('CALLBACK',hObject,eventData,handles,...) calls
the local
%      function named CALLBACK in VVECLS03112012.M with the given input
arguments.
%
%      VVECLS03112012('Property','Value',...) creates a new
VVECLS03112012 or raises the
%      existing singleton*.  Starting from the left, property value
pairs are
%      applied to the GUI before VVECLS03112012_OpeningFcn gets called.
An
%      unrecognized property name or invalid value makes property
application
%      stop.  All inputs are passed to VVECLS03112012_OpeningFcn via
varargin.
%
%      *See GUI Options on GUIDE's Tools menu.  Choose "GUI allows only
one
%      instance to run (singleton)".
%
% See also: GUIDE, GUIDATA, GUIHANDLES

% Edit the above text to modify the response to help VVECLS03112012

% Last Modified by GUIDE v2.5 11-Mar-2012 13:45:37

% Begin initialization code - DO NOT EDIT
gui_Singleton = 1;
gui_State = struct('gui_Name',       mfilename, ...
                   'gui_Singleton',  gui_Singleton, ...
                   'gui_OpeningFcn', @VVECLS03112012_OpeningFcn, ...
                   'gui_OutputFcn',  @VVECLS03112012_OutputFcn, ...
                   'gui_LayoutFcn',  [] , ...
                   'gui_Callback',   []);
if nargin && ischar(varargin{1})
    gui_State.gui_Callback = str2func(varargin{1});
end

if nargout
    [varargout{1:nargout}] = gui_mainfcn(gui_State, varargin{:});
else
    gui_mainfcn(gui_State, varargin{:});
end
```

```
% End initialization code - DO NOT EDIT


% --- Executes just before VVECLS03112012 is made visible.
function VVECLS03112012_OpeningFcn(hObject, eventdata, handles,
varargin)
% This function has no output args, see OutputFcn.
% hObject    handle to figure
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    structure with handles and user data (see GUIDATA)
% varargin   command line arguments to VVECLS03112012 (see VARARGIN)

% Choose default command line output for VVECLS03112012
handles.output = hObject;

% Update handles structure
guidata(hObject, handles);

% UIWAIT makes VVECLS03112012 wait for user response (see UIRESUME)
% uiwait(handles.figure1);


% --- Outputs from this function are returned to the command line.
function varargout = VVECLS03112012_OutputFcn(hObject, eventdata,
handles)
% varargout  cell array for returning output args (see VARARGOUT);
% hObject    handle to figure
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    structure with handles and user data (see GUIDATA)

% Get default command line output from handles structure
varargout{1} = handles.output;



function sao2_Callback(hObject, eventdata, handles)
% hObject    handle to sao2 (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    structure with handles and user data (see GUIDATA)

% Hints: get(hObject,'String') returns contents of sao2 as text
%        str2double(get(hObject,'String')) returns contents of sao2 as
a double


% --- Executes during object creation, after setting all properties.
function sao2_CreateFcn(hObject, eventdata, handles)
% hObject    handle to sao2 (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    empty - handles not created until after all CreateFcns
called

% Hint: edit controls usually have a white background on Windows.
%       See ISPC and COMPUTER.
```

```
if ispc && isequal(get(hObject,'BackgroundColor'),
get(0,'defaultUicontrolBackgroundColor'))
    set(hObject,'BackgroundColor','white');
end



function svo2_Callback(hObject, eventdata, handles)
% hObject    handle to svo2 (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    structure with handles and user data (see GUIDATA)

% Hints: get(hObject,'String') returns contents of svo2 as text
%        str2double(get(hObject,'String')) returns contents of svo2 as
a double


% --- Executes during object creation, after setting all properties.
function svo2_CreateFcn(hObject, eventdata, handles)
% hObject    handle to svo2 (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    empty - handles not created until after all CreateFcns
called

% Hint: edit controls usually have a white background on Windows.
%       See ISPC and COMPUTER.
if ispc && isequal(get(hObject,'BackgroundColor'),
get(0,'defaultUicontrolBackgroundColor'))
    set(hObject,'BackgroundColor','white');
end



function artph_Callback(hObject, eventdata, handles)
% hObject    handle to artph (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    structure with handles and user data (see GUIDATA)

% Hints: get(hObject,'String') returns contents of artph as text
%        str2double(get(hObject,'String')) returns contents of artph as
a double


% --- Executes during object creation, after setting all properties.
function artph_CreateFcn(hObject, eventdata, handles)
% hObject    handle to artph (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    empty - handles not created until after all CreateFcns
called

% Hint: edit controls usually have a white background on Windows.
%       See ISPC and COMPUTER.
if ispc && isequal(get(hObject,'BackgroundColor'),
get(0,'defaultUicontrolBackgroundColor'))
```

```
    set(hObject,'BackgroundColor','white');
end



function venph_Callback(hObject, eventdata, handles)
% hObject    handle to venph (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    structure with handles and user data (see GUIDATA)

% Hints: get(hObject,'String') returns contents of venph as text
%        str2double(get(hObject,'String')) returns contents of venph as
a double


% --- Executes during object creation, after setting all properties.
function venph_CreateFcn(hObject, eventdata, handles)
% hObject    handle to venph (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    empty - handles not created until after all CreateFcns
called

% Hint: edit controls usually have a white background on Windows.
%       See ISPC and COMPUTER.
if ispc && isequal(get(hObject,'BackgroundColor'),
get(0,'defaultUicontrolBackgroundColor'))
    set(hObject,'BackgroundColor','white');
end



function hgb_Callback(hObject, eventdata, handles)
% hObject    handle to hgb (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    structure with handles and user data (see GUIDATA)

% Hints: get(hObject,'String') returns contents of hgb as text
%        str2double(get(hObject,'String')) returns contents of hgb as a
double


% --- Executes during object creation, after setting all properties.
function hgb_CreateFcn(hObject, eventdata, handles)
% hObject    handle to hgb (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    empty - handles not created until after all CreateFcns
called

% Hint: edit controls usually have a white background on Windows.
%       See ISPC and COMPUTER.
if ispc && isequal(get(hObject,'BackgroundColor'),
get(0,'defaultUicontrolBackgroundColor'))
    set(hObject,'BackgroundColor','white');
end
```

```
function rf_Callback(hObject, eventdata, handles)
% hObject    handle to rf (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    structure with handles and user data (see GUIDATA)

% Hints: get(hObject,'String') returns contents of rf as text
%        str2double(get(hObject,'String')) returns contents of rf as a
double


% --- Executes during object creation, after setting all properties.
function rf_CreateFcn(hObject, eventdata, handles)
% hObject    handle to rf (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    empty - handles not created until after all CreateFcns
called

% Hint: edit controls usually have a white background on Windows.
%       See ISPC and COMPUTER.
if ispc && isequal(get(hObject,'BackgroundColor'),
get(0,'defaultUicontrolBackgroundColor'))
    set(hObject,'BackgroundColor','white');
end


% --- Executes on button press in sro2calc.
function sro2calc_Callback(hObject, eventdata, handles)
% hObject    handle to sro2calc (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    structure with handles and user data (see GUIDATA)
%
%
% Created by Adam Richman, 2/22/2012
%
% Revisions:  2/29/2012
% Re-entered the papersat eqn because of calculation errors.  Changed
it so
% the final saturation is displayed in its respective window instead of
% final PO2.  Changed resultant saturation and content windows to
static
% text (instead of edit boxes).  Added a "clear all values" button.
Also
% changed it so the pH is entered into the boxes (it was originally
created
% with the PO2 values entered in).  It now corrects PO2 values for a
given
% pH and uses the corrected PO2 values.
%
% Revisions:  3/2/2012
% Changed GUI so users enter in PO2 values.  Then corrected these PO2
% values based on entered pH.
%
```

```
% Revisions:  3/11/2012
% Changed GUI so users only enter in pH for the ECLS drainage blood.
The
% function calcpo2 then corrects po2 for the pH.
%
%
%Get values and convert strings to numbers.
%
global CR hgb ph
%
rf = str2num(get(handles.rf,'String'));
sao2 = str2num(get(handles.sao2,'String'));
svo2 = str2num(get(handles.svo2,'String'));
hgb = str2num(get(handles.hgb,'String'));
ph = str2num(get(handles.bloodph,'String'));
pao2 = str2num(get(handles.pao2,'String'));
pvo2 = str2num(get(handles.pvo2,'String'));
%
%
% Calculate contents for oxygenated and deoxygenated blood
cao2 = (1.34*hgb*(sao2/100)) + (0.003*pao2);
cvo2 = (1.34*hgb*(svo2/100)) + (0.003*pvo2);
%
%
% Calculate resultant oxygen content
CR = (rf/100)*(cao2) + (1-(rf/100))*(cvo2);
%
% Set resultant content into window
set(handles.cro2,'String',CR)
%
%
% Call function calcpo2 to calculate mixture PO2
finalpo2=fzero('calcpo2',0);
%
% Calculate resultant so2 based on calculated po2
finalso2=100*(23400*(finalpo2.^3+150*finalpo2).^-1+1).^-1;
%
set(handles.sro2,'String',finalso2);
%
guidata(hObject, handles);


function sro2_Callback(hObject, eventdata, handles)
% hObject    handle to sro2 (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    structure with handles and user data (see GUIDATA)

% Hints: get(hObject,'String') returns contents of sro2 as text
%        str2double(get(hObject,'String')) returns contents of sro2 as
a double


% --- Executes during object creation, after setting all properties.
function sro2_CreateFcn(hObject, eventdata, handles)
% hObject    handle to sro2 (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
```

```
% handles    empty - handles not created until after all CreateFcns
called

% Hint: edit controls usually have a white background on Windows.
%       See ISPC and COMPUTER.
if ispc && isequal(get(hObject,'BackgroundColor'),
get(0,'defaultUicontrolBackgroundColor'))
    set(hObject,'BackgroundColor','white');
end



function cro2_Callback(hObject, eventdata, handles)
% hObject    handle to cro2 (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    structure with handles and user data (see GUIDATA)

% Hints: get(hObject,'String') returns contents of cro2 as text
%        str2double(get(hObject,'String')) returns contents of cro2 as
a double


% --- Executes during object creation, after setting all properties.
function cro2_CreateFcn(hObject, eventdata, handles)
% hObject    handle to cro2 (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    empty - handles not created until after all CreateFcns
called

% Hint: edit controls usually have a white background on Windows.
%       See ISPC and COMPUTER.
if ispc && isequal(get(hObject,'BackgroundColor'),
get(0,'defaultUicontrolBackgroundColor'))
    set(hObject,'BackgroundColor','white');
end



% --- Executes on button press in clearbutton.
function clearbutton_Callback(hObject, eventdata, handles)
% hObject    handle to clearbutton (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    structure with handles and user data (see GUIDATA)
%
% This button clears all values entered in the windows.
%
set(handles.cro2,'String','');
set(handles.sro2,'String','');
set(handles.rf,'String','');
set(handles.sao2,'String','');
set(handles.svo2,'String','');
set(handles.bloodph,'String','');
set(handles.hgb,'String','');
set(handles.pao2,'String','');
set(handles.pvo2,'String','');
%
```

```
guidata(hObject, handles);



function pao2_Callback(hObject, eventdata, handles)
% hObject    handle to pao2 (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    structure with handles and user data (see GUIDATA)

% Hints: get(hObject,'String') returns contents of pao2 as text
%        str2double(get(hObject,'String')) returns contents of pao2 as
a double


% --- Executes during object creation, after setting all properties.
function pao2_CreateFcn(hObject, eventdata, handles)
% hObject    handle to pao2 (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    empty - handles not created until after all CreateFcns
called

% Hint: edit controls usually have a white background on Windows.
%       See ISPC and COMPUTER.
if ispc && isequal(get(hObject,'BackgroundColor'),
get(0,'defaultUicontrolBackgroundColor'))
    set(hObject,'BackgroundColor','white');
end



function pvo2_Callback(hObject, eventdata, handles)
% hObject    handle to pvo2 (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    structure with handles and user data (see GUIDATA)

% Hints: get(hObject,'String') returns contents of pvo2 as text
%        str2double(get(hObject,'String')) returns contents of pvo2 as
a double


% --- Executes during object creation, after setting all properties.
function pvo2_CreateFcn(hObject, eventdata, handles)
% hObject    handle to pvo2 (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    empty - handles not created until after all CreateFcns
called

% Hint: edit controls usually have a white background on Windows.
%       See ISPC and COMPUTER.
if ispc && isequal(get(hObject,'BackgroundColor'),
get(0,'defaultUicontrolBackgroundColor'))
    set(hObject,'BackgroundColor','white');
end
```

```
function bloodph_Callback(hObject, eventdata, handles)
% hObject    handle to bloodph (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    structure with handles and user data (see GUIDATA)

% Hints: get(hObject,'String') returns contents of bloodph as text
%        str2double(get(hObject,'String')) returns contents of bloodph
as a double


% --- Executes during object creation, after setting all properties.
function bloodph_CreateFcn(hObject, eventdata, handles)
% hObject    handle to bloodph (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    empty - handles not created until after all CreateFcns
called

% Hint: edit controls usually have a white background on Windows.
%       See ISPC and COMPUTER.
if ispc && isequal(get(hObject,'BackgroundColor'),
get(0,'defaultUicontrolBackgroundColor'))
    set(hObject,'BackgroundColor','white');
end
```

Appendix D. MATLAB Code for calcpo2.m (Function Called by GUI).

```
function so2diff=calcpo2(po2)
%
global CR hgb ph
%
% Created by Adam Richman, 2/22/2012
%
% Revisions: 2/29/2012
% Added an if statement per Dr. Tritt to find only the roots greater
than
% zero for the difference equation. Also re-typed the papersat equation
% because of calculation errors.
%
%
% sro2 is the content equation rearranged for saturation as a function
of
% PO2.  It is used to determine where it intersects with the other
equation
% for saturation as a function of PO2 (called papersat; it's called
papersat
% because it's the saturation equation from a paper).
%
sro2=(CR-(po2*0.003))/(1.34*hgb);
%
% multiply this po2 by "R". R=10^-.48*(ph-7.4). This is used to correct
the
% saturation for ph.  R is the ratio of PO2 observed/po2 at ph = 7.4.
R = 10^(-0.48*(ph-7.4));
po2r = po2*R;
papersat=((23400*(po2r.^3+150*po2r).^-1+1).^-1);
%
% Find the difference between the two equations.
%
% If statement per Dr. Tritt
if po2 < 0
   % Always return non-zero value for PO2 < 0.
   so2diff = 1 + -po2;
else
   % Return the difference between the two equations.
   so2diff = sro2 - papersat;
end
```

PERFUSION

THESIS APPROVAL FORM

MASTER OF SCIENCE IN PERFUSION – MSP

MILWAUKEE SCHOOL OF ENGINEERING

This thesis, entitled "The Effects of Flow Rate on Mixed Venous Oxygen Content and Saturation in Veno-Venous Extracorporeal Life Support: A Comparison of a Computer Simulation and an in vitro Analysis," submitted by the student Adam Richman, has been approved by the following committee:

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Dr. Jeffrey LaMack

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