

# Effect of Normobaric versus Hypobaric Oxygenation on Gaseous Microemboli Removal in a Diffusion Membrane Oxygenator: An In Vitro Comparison

Matthew Schuldes, MS, RN, CCP;\* Jeffrey B. Riley, MHPE, CCP;†  
Stephen G. Francis, MS, CCP, LP;‡ Sean Clingan, MS, CCP§

\**Mayo Clinic, Rochester, Minnesota*; †*University Hospitals Cleveland Medical Center, Cleveland, Ohio*; ‡*Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio*; and §*Specialty Care, Las Vegas, Nevada*

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**Abstract:** Gaseous microemboli (GME) are an abnormal physiological occurrence during cardiopulmonary bypass and extracorporeal membrane oxygenation (ECMO). Several studies have correlated negative sequelae with exposure to increased amounts of GME. Hypobaric oxygenation is effective at eliminating GME in hollow-fiber microporous membrane oxygenators. However, hollow-fiber diffusion membrane oxygenators, which are commonly used for ECMO, have yet to be validated. The purpose of this study was to determine if hypobaric oxygenation, compared against normobaric oxygenation, can reduce introduced GME when used on diffusion membrane oxygenators. Comparison of a sealed Quadrox-iD with hypobaric sweep gas (.67 atm) vs. an unmodified Quadrox-iD with normal atmospheric sweep gas (1 atm) in terms of GME transmission during continuous air introduction (50 mL/min) in a recirculating in vitro circuit, over a range

of flow rates (3.5, 5 L/min) and crystalloid prime temperatures (37°C, 28°C, and 18°C). GME were measured using three EDAC Doppler probes positioned pre-oxygenator, post-oxygenator, and at the arterial cannula. Hypobaric oxygenation vs. normobaric oxygenation significantly reduced hollow-fiber diffusion membrane oxygenator GME transmission at all combination of pump flows and temperatures. There was further significant reduction in GME count between the oxygenator outlet and at the arterial cannula. Hypobaric oxygenation used on hollow-fiber diffusion membrane oxygenators can further reduce GME compared to normobaric oxygenation. This technique may be a safe approach to eliminate GME during ECMO. **Keywords:** gaseous microemboli, hollow fiber diffusion membrane oxygenator, emboli detection and classification system, extracorporeal membrane oxygenation, extracorporeal life support. *J Extra Corpor Technol. 2016;48:129–136*

Elimination of gaseous microemboli (GME) has been the focus of numerous studies due to the effect GME may have on neurological outcomes, as well as morbidity and mortality for patients undergoing extracorporeal circulation (ECC) (1–5). These efforts have led to better understanding of GME generation, detection, and pathophysiology, as well as techniques and equipment designed for GME reduction (5–10). Unfortunately, most of these GME studies primarily focus on cardiopulmonary bypass (CPB) procedures and related equipment. Current litera-

ture lacks significant evidence reporting the possible risks of microembolism during extracorporeal membrane oxygenation (ECMO) (9). A recent abstract presented by the American Society of Anesthesiologists, however, reports probable link of GME exposure during ECMO to end organ dysfunction(11). In addition, it discusses the failure of ECMO equipment to effectively manage GME. Despite the lack of microembolism protection in current ECMO, implementation of ECMO continues to rapidly increase as a means of long-term support for patients suffering from acute respiratory and cardiac failure (12). ECMO has been shown to be effective in providing support for patients with cardiac or respiratory failure; however, morbidity and mortality rates among these patients remains high, and survivors carry a high risk of subsequent brain injury and functional deficit (13). With the amount of studies correlating GME to post-operative cognitive dysfunction in CPB, it is surprising that equal vigilance

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Address correspondence to: Matthew Schuldes MS, RN, CCP, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. E-mail: schuldes.matthew@mayo.edu

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addressing the role of GME in ECMO circuits has yet to be defined.

Current trends in ECMO are focused on simplifying and minimizing circuits to eradicate the opportunity for error and lessen the risks associated with long-term exposure to the ECC (7). Popular components of an ECMO circuit include venous line, centrifugal pump, hollow-fiber diffusion membrane oxygenator, and an arterial (or venous) return line. Though this approach offers minimal exposure to foreign ECC surfaces, it lacks the two primary components responsible for CPB GME removal, the venous reservoir and the arterial filter. Just as in normobaric oxygenation for ECMO, hypobaric oxygenation uses the oxygenator as the GME removal device (8). Hypobaric oxygenation requires the oxygenator gas phase to be sealed, the addition of vacuum to the gas phase, and the use of 100% oxygen as the sweep gas. This novel approach increases oxygenator GME capture within the oxygenator, as well as enhances reabsorption of GME post-oxygenator by a mechanism termed “undersaturation” (14–16).

Hypobaric oxygenation provides the foundation behind this research. GME have been detected and quantified during ECMO, which may contribute to patient end organ dysfunction, and subsequent morbidity and mortality. Furthermore, the occurrence of GME within the ECMO circuit is largely overlooked, as are methods to ameliorate this occurrence (9,10). It is the premise of this study that using hypobaric oxygenation on hollow-fiber diffusion membrane oxygenators for ECMO will prove more effective than normobaric oxygenation at eliminating introduced GME. This proposition will be investigated by comparing a sealed polymethylpentene (PMP) fiber oxygenator with hypobaric sweep gas vs. an unsealed oxygenator with normobaric sweep gas in terms of GME transmission during air introduction, *in vitro*, over a range of flow rates and prime temperatures.

## MATERIALS AND METHODS

### Test Circuit

A recirculating test circuit was constructed using bi-passive polymer tubing (Terumo X coating, Terumo Cardiovascular, Ann Arbor, MI). The Sorin Revolution centrifugal pump (Sorin Group, Arvada, CO) was used to generate fluid flow and was measured with a Stockert flow probe to the S5 Heart Lung Machine (Sorin Group). Flow then followed into the standard Quadrox-iD oxygenator during control trials, or in an epoxy-sealed Quadrox-iD during experimental trials (Bioline Hollow Fiber Diffusion [PMP] Membrane Oxygenator; Maquet Getinge Group, Goteberg, Sweden); 100% compressed oxygen sweep gas was used at a 1:1 flow:sweep ratio. Gas phase pressure was regulated with vacuum on the epoxy-sealed experi-

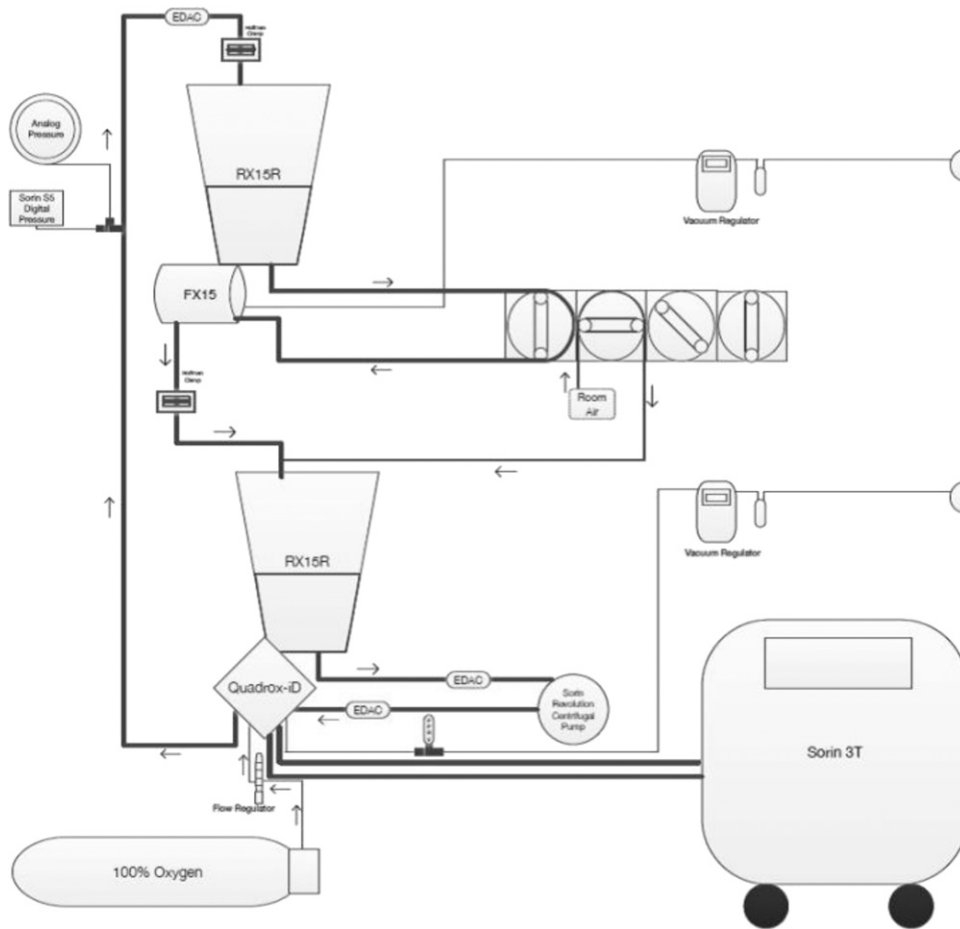
mental Quadrox-iD oxygenator (–250 mmHg or .67 atm) with an Ohmeda regulator attached to suction tubing on the gas outlet (Ohio Medical Corporation, Gurnee, IL). A positive pressure relief valve with 5–15 mmHg opening pressure was placed in line with the suction tubing on the gas outlet of the oxygenator to prevent over-pressurization of the gas phase (Terumo). A 180-cm-long 3/8-inch inside diameter (ID) line followed the oxygenator. A Hoffman clamp regulated the circuit pressure (Humboldt Manufacturing, Elgin, IL). Pressure was transduced digitally with the Sorin S5 heart–lung machine (Sorin). A RX15R hardshell reservoir was placed at the end of the simulated arterial line and acted as a simulated patient. This was the first method used to clear GME. The reservoir drained into a Sorin S5 roller pump that was used to generate fluid flow through an epoxy-sealed FX 15 Microporous Hollow Fiber Oxygenator with X-Coating (Terumo). Vacuum was attached to the gas outlet and regulated the gas phase pressure (–250 mmHg or .67 atm) with an Ohmeda regulator (Ohio). This “deairing” oxygenator was the second method to remove GME that had been introduced into the circuit. From this deairing oxygenator, the fluid flowed into another RX15R hardshell reservoir (Terumo). A Hoffman clamp was used to control the drainage between both reservoirs (Humboldt). A stopcock was placed on a leur port of the second venous reservoir to provide introduction of air. Fluid flow followed through the second venous reservoir and back to the centrifugal pump. The circuit is displayed in Figure 1.

### Prime

The circuit was filled with a Plasmalyte crystalloid prime (Baxter, Deerfield, IL) with both reservoir levels maintained at 600 mL. The crystalloid was either cooled or warmed using the Sorin 3T heater/cooler to the desired temperature (37°C, 28°C, and 18°C). Temperature measurements were made at the arterial outlets of the oxygenators.

### Test Oxygenator; Hypobaric and Normobaric Oxygenation

The Quadrox-iD oxygenator was used to analyze hypobaric oxygenation because of its large use in ECMO. In addition, a true diffusion membrane oxygenator had yet to be studied for hypobaric oxygenation application. The Quadrox-iD oxygenator without modification was used in control trials. During experimental trials, the Quadrox-iD was modified by occluding the exhaust gas port with an epoxy sealant. With the application of vacuum to the gas outlet, the gas phase of the oxygenator was reduced to hypobaric levels. This reduction in pressure of the gas phase creates an increased diffusion gradient for the oxygenator to remove GME. In addition, 100% oxygen sweep gas was used during both the



**Figure 1.** The test circuit designed to evaluate hypobaric oxygenation on a hollow fiber diffusion membrane oxygenator. The bold line represents the circulating fluid pathway through test circuit.

experimental and control trials; 100% oxygen in the oxygenator gas phase creates an environment to rapidly remove nitrogen from GME, which represents the largest percentage of gas present in GME. By eliminating nitrogen, GME are primarily composed of oxygen. Furthermore, the mostly oxygen GME can follow an existing diffusion gradient into the surrounding fluid (undersaturation).

### Air Challenge

Air was continuously entrained via 1/4-inch ID tubing open to air in an occlusive roller head on the Sorin S5 with a flow of 50 mL/min into a leuc lock port on the venous line inlet of the reservoir. GME counts were measured at three circuit positions for 2 minutes during each trial. After each trial and before another was started, the fluid prime was recirculated, deaired, and analyzed to ensure complete GME removal.

### GME Detection

Three EDAC (LUNA Innovations, Roanoke, VA) quantifier probes were used. The probes were placed according to manufacturer's instructions and ensured with quality signals. The first cuvette and probe was

placed 15 cm proximal to the oxygenator to verify quantity of GME entering the oxygenator. The second EDAC cuvette and probe was placed 15 cm distal to the oxygenator to quantify oxygenator GME removal. At 180 cm distal to the second cuvette and probe, the third EDAC cuvette and probe was placed and used to measure GME to the "patient." The difference between EDAC sensors 3 and 2 measured the effect of undersaturation.

### Test Procedure

The experiment was designed to test the effect of hypobaric oxygenation ( $-250$  mmHg suction pressure and exhaust ports sealed to ambient pressure) on a sealed oxygenator gas phase vs. normobaric ventilation (0 mmHg suction pressure, and exhaust ports open to ambient pressure) for GME removal under independent variables of two pump flows (3.5 and 5 L/min), line pressures of 150 and 200 mmHg, and three prime temperature ( $37^{\circ}\text{C}$ ,  $28^{\circ}\text{C}$ , and  $18^{\circ}\text{C}$ ).

Ten control trials were performed for 2 minutes each with pump flows maintained at 3.5 or 5.0 L/min with post-oxygenator pressure of 150 or 200 mmHg, respectively. These trials were repeated at  $37^{\circ}\text{C}$ ,  $28^{\circ}\text{C}$ , and  $18^{\circ}\text{C}$  with

**Table 1.** GME count by blood flow, temperature, and gas phase vacuum.

Blood flow	Temperature	Gas vacuum	Oxy inlet	Oxy outlet	Art cannula
5.0	37	0	16,077	498	196
		-250	12,570	449	31
	28	0	17,062	1,157	890
		-250	12,595	616	62
	18	0	16,110	1,342	1,277
		-250	11,127	823	182
3.5	37	0	21,687	290	27
		-250	17,004	61	2
	28	0	23,996	1,037	166
		-250	17,367	165	8
	18	0	19,860	1,327	298
		-250	16,689	455	73

GME count is reported per minute and the average of 10, 2-minute trials at different fluid flows and temperatures. Oxygenator inlet counts before venous air injection were not equal. Oxygenator outlet and arterial cannula comparisons are significantly different ( $p < .01$ ) at all temperatures and fluid flows in the experimental group. The use of vacuum (-250 mmHg) significantly reduces GME counts at the arterial cannula compared to no gas vacuum.

10 trials done at each temperature and flow/line pressure combination. Thus, there were 120 measurements taken for GME size, count, and volume over the course of the experiment; 60 measurements were taken in the control group, and 60 measurements were taken in the experimental group. In each group (control and experimental), there were 20 measurements taken at each temperature yielding a total of 40 measurements for each of the three temperatures.

### Statistical Analysis

JMP Statistics Software Version 11 (SAS Institute Inc., Cary, NC) was used to generate our descriptive statistics on the effect of vacuum (hypobaric ventilation), temperature, flow, and pressure on the embolic count and volume for each trial in relation to EDAC cuvette position. Mean GME counts and mean GME volume were calculated for each trial and used to create a multiple linear regression model with the independent variables. The data are presented as mean GME counts and mean GME volume. Dependent parameter  $t$  tests and the all-pairs Tukey-Kramer tests were used to compare changes in GME count and GME volume from cuvette positions 1 through 3. Results were considered statistically significant at  $p < .05$ .

### RESULTS

A statistically significant difference was observed between pre-oxygenator GME counts and GME volume when the normobaric were compared against hypobaric trials ( $p < .0001$ ). The variation between the normobaric and hypobaric trials in GME counts and volume pre-oxygenator was unexpected considering that an occlusive roller pump was used to entrain air experi-

mentally. The differences were exhibited in that the pre-oxygenator hypobaric trials all displayed lower GME counts and volume when compared against the pre-oxygenator normobaric trials. The summary data are displayed in Table 1.

A statistically significant difference was observed between post-oxygenator GME counts when comparing hypobaric and normobaric trials ( $p < .0001$ ). The increased significant difference in removal of GME count by the hypobaric oxygenator is summarized in Table 1. GME volume was shown to be statistically insignificant when comparing the normobaric to the hypobaric trials ( $p > .05$ ) (Table 2).

A statistically significant difference was observed between simulated patient GME counts when comparing the normobaric against the hypobaric trials ( $p < .0001$ ). The difference in removal of GME by hypobaric oxygenation and undersaturation is summarized in Table 1. GME volume was again shown to be statistically insignificant when comparing normobaric and hypobaric trials ( $p > .05$ ) (Table 2).

Differences in the pre-oxygenator GME counts and volume in normobaric vs. hypobaric trials was unfavorable for multiple linear regression analysis. For this reason, percentage change in GME count and GME volume was calculated for each trial and used to evaluate hypobaric oxygenation. The percentage change was then used to create our multiple linear regression models and is displayed in Figures 2 and 3.

When control parameters are compared against one another using multiple linear regression in our experimental model, flow, temperature, line pressure, and vacuum accounted for 67% of the variability in percent removal of GME at the simulated arterial cannula when a fixed amount of air was added to the venous inlet of the venous



**Table 2.** GME embolic load by blood flow, temperature, and gas phase vacuum.

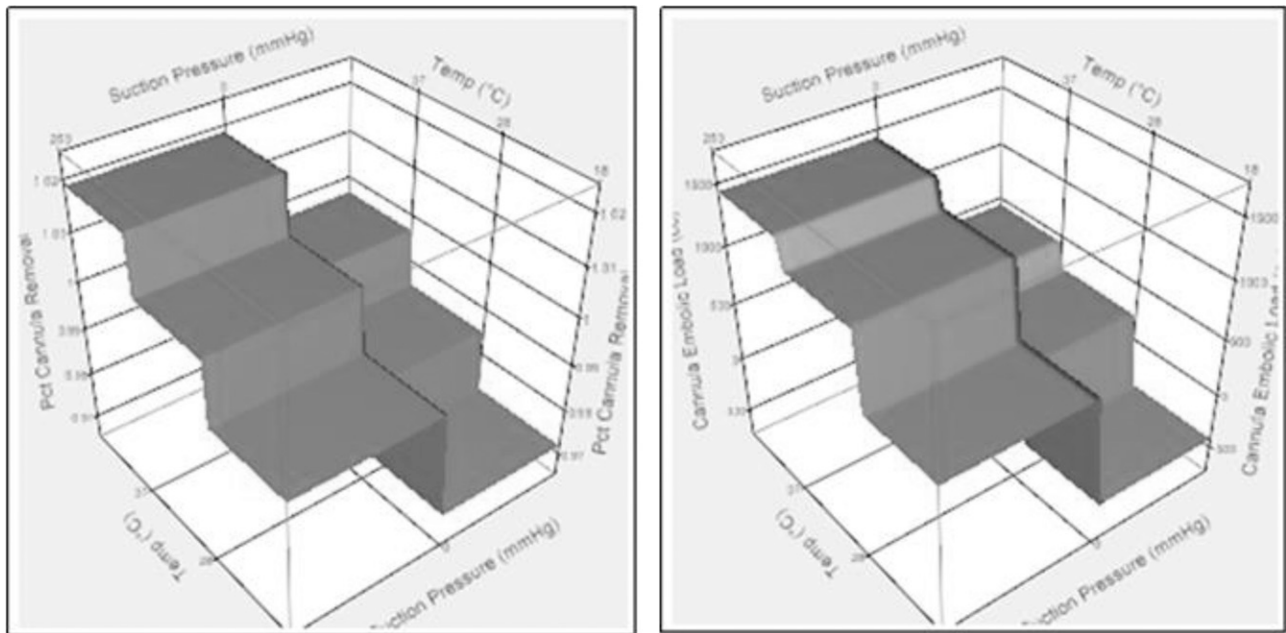
Blood flow	Temperature	Gas vacuum	Oxy inlet	Oxy outlet	Art cannula
5.0	37	0	3.43E-04	8.90E-06	2.82E-06
		-250	1.76E-04	7.83E-06	5.54E-07
	28	0	4.92E-04	2.43E-05	1.66E-05
		-250	1.71E-04	1.12E-05	6.96E-07
	18	0	3.93E-04	2.63E-05	1.94E-05
		-250	1.23E-04	8.23E-06	1.04E-06
3.5	37	0	5.00E-04	3.19E-06	2.12E-07
		-250	2.40E-04	6.18E-07	4.69E-09
	28	0	6.56E-04	1.11E-05	1.83E-06
		-250	2.16E-04	1.04E-06	6.04E-08
	18	0	4.70E-04	1.22E-05	3.02E-06
		-250	1.90E-04	2.02E-06	2.31E-07

GME volume load is reported per minute and the average of 10, 2-minute trials at different fluid flows and temperatures. 1.00E-6 is .000001 mL of air. Oxygenator inlet volumes before venous air injection were not equal. Except for oxygenator inlet, all comparisons are not significantly different at  $p < .05$ . The embolic loads are smaller with the use of vacuum at the arterial cannula, but not significantly different. The smallest arterial cannula embolic load was .000000005 mL at 3.5 L/min and -250 mmHg gas vacuum.

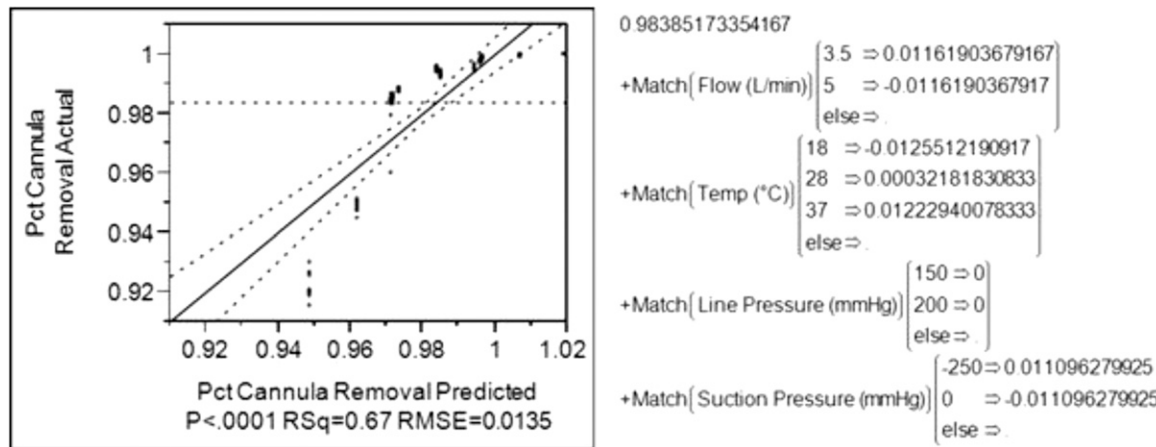
reservoir. The analysis of variance and lack of fit reveal that the chance of error creating the results is less than 1%. When the multiple linear regression models were produced, line pressure had little effect on the statistical outcome. The addition of vacuum to a sealed oxygenator (hypobaric ventilation) produced significant improvement in the oxygenator's ability to reduce GME count and volume ( $p < .0001$ ).

Temperature was a major factor. A temperature at 37°C was shown to favorably influence reduction in

GME count and volume ( $p < .0001$ ), whereas a temperature of 18°C were shown to decrease the oxygenator's ability to reduce GME count and volume ( $p < .0001$ ). A temperature of 28°C compared to 37°C was not shown to statistically affect oxygenator GME removal. Fluid flow played a significant factor in GME removal when keeping the other independent variables constant. In our model, a flow of 3.5 L/min was shown to statistically reduce GME count and volume ( $p < .0001$ ), whereas a flow of 5 L/min was shown to statistically increase GME



**Figure 2.** Surface profiles of the regression model. The surface profiles display the magnitude and direction for the effects of temperature and gas suction pressure on percent GME count removal and GME volume load at the arterial cannula for 5-L/min fluid flow with continuous venous air entrainment.



**Figure 3.** Experimental multiple linear regression model of percent GME removal at the simulated arterial cannula. The graph presents the experimental model for percent GME removal at the arterial cannula with an  $r^2$  value of approximately 67%. The model reliably predicts for the effects of temperature, blood flow, and gas vacuum. The experimental circuit was able to remove approximately 98% of all GME that were entrained. Under optimal conditions our experimental circuit removed 99.8% of GME.

count and volume ( $p < .0001$ ). Higher flows seem to reduce the efficiency of the oxygenator to remove GME. The pump flow effects are summarized in Tables 1 and 2.

## DISCUSSION

Closed ECC systems, particularly in ECMO, lack an air interface and are often thought of as being more air free than CPB. However, because of the lack of GME elimination devices in ECMO circuits, GME entering the venous side can circumvent the oxygenator and pass to the arterial side (9,10).

The oxygenator is the primary component of gas exchange during ECMO, which makes it essential to use as a GME elimination device. Hypobaric oxygenation controls the behavioral tendencies of GME by manipulating physical gas laws. By reducing the total pressure of the gas phase of the oxygenator to hypobaric levels, we reduce the constituent (oxygen, nitrogen, and carbon dioxide) total gas pressures. This manipulation of Dalton's law of partial pressures creates a larger diffusion gradient for gas diffusion from the blood phase to the gas phase of the oxygenator. In addition, reducing the total pressure of the gas phase with vacuum reduces the amount of gas dissolved in a liquid in the blood phase. This is a manipulation of Henry's law. Moreover, by manipulating the ideal gas law and its constituents, we are able to create conditions favorable for GME dissolution. Subatmospheric conditions are created by sealing the oxygenators auxiliary gas vents and applying vacuum to the gas outlet. The Maquet Quadrox-iD has one auxiliary gas vent, and once sealed, it easily facilitates below atmospheric pressure levels.

Hypobaric oxygenation uses 100% oxygen as the sweep gas. This is essential to maintain an adequate diffusion gradient for oxygen from the gas phase to the blood phase once the gas phase pressures have been reduced. A primary benefit of using 100% oxygen sweep gas is to provide a larger diffusion gradient for the removal of nitrogen and oxygen transfer. Nitrogen represents the largest constituent and most insoluble gas present in GME. Moreover, by using 100% oxygen, there is a large diffusion gradient present to liberate nitrogen from GME in the blood phase into the gas phase of the oxygenator, and leave oxygen gas as the primary component of GME. Another benefit of using 100% oxygen and subatmospheric pressures on the oxygenator is a mechanism termed "undersaturation" (16). Once GME have been denitrogenated by the oxygenator, the largest component and thus partial pressure of gas existing within GME is oxygen. Thus, the partial pressure of oxygen gas in GME is greater than the partial pressure of oxygen gas present in the circulating fluid (undersaturation). Oxygen gas then follows the existing diffusion gradient causing oxygen to dissolve into the surrounding liquid until equilibrium is reached (shrinking GME), or total dissolution (dissolving GME) into the circulating fluid occurs. This diffusive (undersaturation) gradient is emphasized with the application of subatmospheric pressures to the gas phase of the oxygenator. Undersaturation is demonstrated in our EDAC data, whereas the GME count and volume present post-oxygenator (sensor 2) is greatly decreased as it reaches the simulated patient (sensor 3).

An important feature of hypobaric oxygenation is the retention of the ability to control  $pO_2$  and  $pCO_2$  independently. A change in the partial pressure of oxygen in the gas phase of the oxygenator will produce measured

effects on how much oxygen can diffuse from the gas phase to the blood phase. By lowering the total gas phase pressure with vacuum, the operator may reduce the max  $pO_2$  of the gas phase, and subsequently decrease the maximum achievable  $PaO_2$  in the blood phase. Moreover, the operator can control the  $PaO_2$  of the blood phase by increasing or decreasing the amount of vacuum applied to the oxygenator. This allows the benefits of using 100% oxygen sweep gas to remove nitrogen, yet allowing control of  $PaO_2$  to the mildly hyperoxic levels associated with ECC and avoiding the damaging effects of hyperoxia (17).  $PaCO_2$  control is preserved with the amount of 100%  $O_2$  "sweep" gas applied to the gas phase of the oxygenator.

Hypobaric oxygenation challenges the oxygenator's safety precautions. By sealing the auxiliary vent ports of an oxygenator, the risk for over pressurization is created. To prevent mass transfer of gas through the PMP fibers from the gas phase to the blood phase, a positive pressure relief valve is essential and must be placed in either the gas inlet line or the vacuum line attached to the oxygenator gas outlet. If suction is hypothetically lost, positive pressure would vent through the valve and not through the PMP fibers.

Previous studies have shown the effective use of hypobaric oxygenation in traditional ECC circuits with an arterial line filter in vivo, as well as an integrated oxygenator in vitro (14,15). Data from this study confirm that hypobaric oxygenation is effective in removing GME within a hollow-fiber diffusion membrane oxygenator. This investigation also supports previous studies testing the feasibility of application and mechanisms of hypobaric oxygenation (14,15). To date, hypobaric oxygenation has proven to be the most effective method for GME elimination, reproducing similar results over a variation of equipment used and test conditions.

This evaluation offers noteworthy data with respect to GME count elimination; however, interpretation of the data is somewhat limited. All the trials in this experiment were conducted in vitro using crystalloid solution. Crystalloid was chosen to reduce overall experimental cost and provide introspection into whether further studies could be validated. This choice may produce measured differences when compared to using blood. Also, data were accrued by manipulating an oxygenator outside of manufacturer's recommendations. Although this was necessary for the study, manufacturer's acquiescence would be required for clinical application of hypobaric oxygenation.

In addition, introduction of GME count and volume into the test circuit needed better control. The hypobaric trials all showed slightly smaller pre-oxygenator GME counts when compared against normobaric trials. It is hypothesized that the proximity of the EDAC cuvette to the experimental oxygenator provided a gradient to dissolve GME before even reaching the oxygenator, which

reduced our experimental pre-oxygenator GME counts. To improve consistency, a specialized injector device could have been used to provide equivalent amounts of air entrainment for each trial. Also, GME count was significantly reduced, but GME volume load was not. There is considerable debate as to how much GME (count or volume) is harmful. Although 50 mL/min of air was entrained experimentally in the test circuit, only a very small amount reached the simulated patient. Until specified GME counts and/or volume can be linked with specific negative sequelae; the contribution of GME to negative outcomes will continue to be overlooked. However, because of GME's unnatural physiology and ability to cause harm, elimination should be desired.

This study was designed with the use of an open venous reservoir. Use of a reservoir served two functions, to simulate a patient and to ensure all GME were cleared from the circuit between each trial. This was a known flaw in the experimental design; however, it was necessary for accurate data acquisition.

An unexpected experimental finding was the effect of differing temperatures on GME. According to the physical gas laws, as the temperature decreases the solubility of GME should increase. However, as temperature was decreased in this experiment, an increase in GME count and volume was observed. Also observed was the inefficient removal of these bubbles by the oxygenator. Hypobaric oxygenation was able to remove more GME at colder temperatures vs. the control ( $p < .0001$ ); however, colder temperature must alter the ability of the oxygenator to filter and remove GME. These findings are similar to findings by Clingan et al. and Sleep et al. (15,18).

Further in vitro research regarding the prolonged effect of hypobaric conditions on the oxygenators is warranted. It is hypothesized that the PMP diffusion membrane oxygenators will better handle hypobaric conditions for prolonged periods vs. polypropylene microporous membrane oxygenators. In addition, in vitro/vivo research using blood is warranted for the advancement of this technique to human use.

## CONCLUSION

This study confirms the efficacy of hypobaric oxygenation in eliminating GME using a modified PMP diffusion membrane oxygenator vs. normobaric oxygenation on an unmodified PMP diffusion membrane oxygenator. Because the working principle is a simple modification of gaseous properties, it can easily be applied in a variety of clinical settings. Because of the unnatural nature of GME, and the role they may have in end organ dysfunction on ECMO, the advancement of this technique is warranted for the possibility of improving patient outcomes. Hypobaric

oxygenation may provide a means to eliminate GME from long-term extracorporeal support practice.

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