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Efficacy of Flow monitoring during ECMO

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Abstract

The hypothesis that blood flow monitoring could serve as an effective early indicator of distal obstruction during ECMO was tested under controlled experimental conditions. The ECMO circuit typically includes (or could be easily modified to include) a shunt that bifurcates from the main line returning a small amount of blood back to the pump with access points for drug infusions. Distal circuit obstructions in the oxygenator and beyond will result in an increased diversion of flow from the distal line to the shunt. Thus, elevations in flow through the shunt can serve as a marker for distal circuit obstruction. An ECMO training circuit was adapted with a resistance chamber that simulates controlled and varying levels of distal obstructions. Experiments were conducted under pediatric and adult pump target flow rates simulating different levels of distal obstructions while documenting the shunt flow and pressure drop across the obstruction. There was measurable and statistically significant elevation in shunt flow at all flow rates due to different levels of obstruction from baseline values and hence consistent with the hypothesis that shunt flow can serve as an indicator of distal obstruction in the ECMO circuit. Flow monitoring is over the tube, hands-free, continuous and easy to implement. Therefore, it has the potential to serve as an early non-specific indicator of elevated distal resistance in the ECMO circuit which can then trigger other measurements (such as pressure drop across the oxygenator) for a more specific assessment of the source for distal resistance.

Keywords

ECMO; flow; pressure drop; fluid mechanics

Introduction

Extracorporeal membrane oxygenation (ECMO) is a prolonged partial heart-lung bypass strategy for selected critically ill patients with severe cardiac and/or respiratory failure as a life support therapy to convalescence or as a bridge to mechanical assist device or organ transplant. Internationally, 5037 patients at 251 centers were reported to the Extracorporeal

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Life Support Organization (ELSO) registry¹ in 2014 as being placed on ECMO. Oxygenator-related complication rates are relatively high (18%) in all age groups with very high mortality (40–80%)¹. The risk of failure is common with prolonged duration of ECMO support, especially in the neonatal and pediatric population. At the University of Iowa Hospitals and Clinics over the last decade, it was found that pediatric patients had a greater incidence of and a higher mortality associated with oxygenator events compared to adult patients. In the last 10 years at our institution, there were 98 ECMO runs in pediatric patients and 106 in adult patients. Oxygenator clot was documented in 22.4% of pediatric patients and 7.5% of adult patients. Oxygenator failure was documented in 10.0% of pediatric patients and 9.4% of adult patients. Depending upon the underlying pathophysiology, patients may also need significant ventilator and/or inotropic support. Therefore, monitoring ECMO circuit and identifying potential complications early is of utmost importance. The current strategy for monitoring ECMO circuit involves hourly measurement of pressure drop across the oxygenator. These measurements are performed manually by health care practitioners. They are reasonably effective, but some challenges exist. For example, use of in-dwelling pressure monitoring lines elevate the risk of infection, clot formation/embolization and air entrainment. The non-continuous periodical nature of measurements (once per hour in our practice) delays identification of complications such as oxygenator obstruction and subsequent replacement efforts. It is also important to recognize that while pressure drop is effective for oxygenator-specific monitoring, it is not an indicator for other sources of distal circuit resistance such as, an elevated systemic vascular resistance, a recovering heart (for veno-arterial circuits) or elevated venous pressure.

Flow monitoring, however, is not routinely performed. It is reasonable to expect that the near-constant flow pumps (be they centrifugal or rotary pumps) used in ECMO will attempt to maintain target flow rates irrespective of any elevations in downstream resistance (e.g., due to oxygenator clot). Thus, flow rate in the ECMO circuit cannot serve as a marker for such complications and may explain the lack of flow monitoring. Drawing from fluid mechanics principles, we submit that, while flow monitoring in the main line is indeed unlikely to serve as a useful marker, the flow in the low-flow shunt that is commonly used to provide an easy access point for drug infusion can indeed serve as a marker of developing distal resistances in the circuit. Unlike pressure monitoring, flow monitoring is continuous, operator-free, and over-the-tube rather than in-line. Flow monitoring, if shown to be effective in identifying complications in the ECMO circuit, may be easily implemented into current ECMO practice. And since it is continuous, it has the potential to serve as a non-specific initial warning of elevated distal resistance. When the alarm is set off, it may then trigger additional, more specific tests such as pressure drop measurements across the oxygenator, thus reducing greatly the need for periodic manual measurements and its associated risks. Ultimately, the premise here is that, since flow monitoring presents with no additional risks or interferences to the current ECMO practice, but has the potential to serve as a new sensitive marker of distal circuit resistance, it is only reasonable that its utility be explored and documented. The objective of this study is to assess whether and to what extent, flow in the shunt can serve as a marker for obstructions in the circuit. We developed an experimental ECMO circuit and simulated controlled levels of obstructions in the circuit to evaluate shunt flow monitoring.

Methods

Principle behind flow monitoring

The case for using elevated pressure drop across the oxygenator as an indicator of oxygenator clotting is obvious. Any obstruction will cause increased oxygenator resistance resulting in elevated pressure drop across it². However, the case for flow monitoring as an indicator of elevated distal resistance due to oxygenator obstruction or other causes (e.g., elevated patient systemic vascular resistance, arterial cannula tip obstruction, native cardiac recovery, elevated venous pressure, etc.) is not so obvious because the pump in the ECMO circuit is designed to attain the target flow rate irrespective of downstream resistances. However, we submit that certain unique aspects of the ECMO circuit may be leveraged such that flow monitoring can indeed serve as a marker of elevated resistance in the circuit. To understand the underlying principle, consider the ECMO circuit (Figure 1). It contains an inflow cannula for venous drainage, which passes through a mechanical pump to an oxygenator for gas exchange before returning to the patient via an outflow cannula to the venous or arterial circulation. The oxygenated blood then re-enters the patient's circulation. Distal to the pump, but proximal to the oxygenator, a shunt returns a small amount of blood back to provide an access point for infusion of drugs and blood parameter sensors. This shunt, which under normal conditions recirculates a small and inconsequential amount of blood back to the reservoir, is the key to flow monitoring. And if this shunt is not part of the standard circuit, due to institutional variations in ECMO circuit design, it is easily added just for purposes of flow monitoring with negligible impact on the main circuit. From a fluid mechanics perspective, if a tube (main trunk) with a fixed flow bifurcates into two branches, an increased resistance in one branch would inevitably increase the flow in the other branch. Accordingly, say if an oxygenator obstruction develops, the increased resistance at the oxygenator would result in decreasing the flow to it thus increasing the flow through the shunt. Thus, elevations in the flow rate in the shunt would be a result of obstruction in the oxygenator or downstream to it. Since measuring flow in the small diameter shunt tubing can be difficult, shunt flow (Q_S) may be measured as the flow drop across the shunt bifurcation point, defined as the difference between the flow rates in the main circuit before and after the shunt bifurcation ($Q_S = Q = Q_{preS} - Q_{postS}$). As with pressure drop, there will be a baseline shunt flow under normal conditions and a threshold may be identified which, when breached, would be indicative of oxygenator obstruction. But unlike pressure drop, the threshold for shunt flow will likely need to be normalized to the pump target flow rates such that low pump flow rates for smaller patients require a lower Q_S threshold while larger adult patients would require a higher Q_S threshold for indicating oxygenator obstruction. While the theoretical reasoning is sound, it may be put to use during ECMO runs only if it can be shown that the shunt flow under realistic levels of oxygenator obstructions is elevated by measurable amounts and comparable to pressure drop under the same conditions. This is precisely the objective of this study. If Q_S may be demonstrated to be a reliable marker for a problem such as oxygenator obstruction, then flow monitoring need to be evaluated as one more marker, albeit one that may be accomplished with over-the-tube transonic probes with no interference in the circuit or manual efforts. Early identification of elevated distal resistances may then trigger more specific tests such as pressure drop measurements and blood gas analysis to measure paO_2 rise when blood passes through the oxygenator to

identify if the cause of elevated resistance is oxygenator obstruction or from other distal sources such as elevated SVR.

Ex vivo mock ECMO circuits have been used historically for assessing oxygenator performance³. An experimental flow loop used in our laboratory for ECMO training purposes was used to assess the proof-of-concept that shunt flow (across the shunt) may serve as a marker for elevated resistance at or distal to the oxygenator. If shown to be true, such non-invasive monitoring could be used in concert with current pressure drop measurements to enhance safety of the ECMO run.

Apparatus

An *ex vivo* ECMO circuit (see Figure 2) was created in the laboratory using the same tubings, connectors, pump (Maquet cardiopulmonary AG centrifugal pump, Hirrlingen, Germany), oxygenator (Maquet cardiopulmonary AG HFMO oxygenator, Hirrlingen, Germany), reservoir, shunt with manifold CDI sensor (Terumo Cardiovascular Systems Corporation, Michigan, USA), and pressure sensors (Medtronic Inc., Minneapolis, USA) as those in clinical practice. The circuit was augmented/modified in the following manner: 1) Flow sensors (Transonic Systems Inc. Ithaca, NY) were placed proximal to the shunt (Q_{PreS} , the flow out of the pump), and immediately distal to the shunt (Q_{postS} , flow through the oxygenator). The over-the-tube ultrasound flow meters had a resolution of 0.001 L/min; 2) A ‘resistance chamber’ was positioned distal to the oxygenator (see Figure 2) with which to simulate the elevated resistance due to oxygenator obstruction at predetermined levels in a reversible manner. This resistance chamber is a compressible tube that may be constricted equi-radially using an external concentric clamp. The greater the controlled tube diameter reduction (constriction), the higher the resistance induced, simulating a greater degree of obstruction in the oxygenator. To minimize the effect of flow disturbances generated by resistance on the measurement of the flow rate, we have placed the ultrasonic flow meter approximately 24–30 inch away from the clamp obstruction. Specifically, we used diameter tube reductions of 0%, 25%, 50% and 75% to simulate baseline, mild obstruction, moderate obstruction and severe obstruction respectively; It is important to note that the descriptors, “mild”, “moderate” and “severe” obstructions are rather relative and the clinical significance of each depends on the pump target flow rates and 3) 0.9% saline was used as the experimental fluid instead of blood.⁴

Adapting an existing ECMO circuit allowed for high fidelity in our simulation as the components in the loop are identical to those used in an actual ECMO circuit, except for the patient. In addition, the standard ECMO circuit has ports for in-line pressure sensing proximal (P_{preO_2}) and distal (P_{postO_2}) to the oxygenator (Figure 2), which also were retained in the experimental loop. Since patients of different sizes are present in the population, ECMO circuits typically use varying target flow rates ranging from 0.5 L/min (infant) to 5 L/min (adult). With larger pump target flow rates (above 2 L/min), the tubing size used in the ECMO circuits is increased from 1/4 inch to 3/8 inch tubes. The experimental flow loop used the appropriate tubing sizes based on pump target flow rates, congruent with clinical practice.

Experiments

Experiments were conducted with the experimental ECMO circuit by simulating varying levels of oxygenator obstruction to study how the changes in shunt flow across the shunt (Q_S), the proposed marker, compared to changes in pressure drop across the oxygenator (P), the conventional marker. The experiments were conducted for conditions simulating patients of varying sizes, from an infant to an adult, by repeating all measurements at 0.5, 1, 1.5, 2, 3, 4, and 5 L/min pump target flow rates. For a given pump target flow rate, measurements of pressure (P_{preO2} and P_{postO2}) and flow rates (Q_{preS} and Q_{postS}) were documented under reference conditions with no constriction. The resistance tube constrictor clamp was then used to effect approximately 25% diameter reduction, which simulated a mild oxygenator obstruction. After allowing 3 minutes of delay for the flow to adjust to the set conditions, the pressures and flow rates were documented. We independently confirmed that the 3 minute delay before taking measurements was sufficient to ensure that the flow has steadied in the system. Next, pressure and flow measurements were similarly recorded with the resistance tube constricted to 50% and then 75% (moderate and severe oxygenator obstruction, respectively). The experiment and measurements were then repeated for pump target flow rates of 0.5 through 5 L/min. From the measured pressures and flow rates, P and Q_S were calculated. P and Q_S measurements at four levels of simulated obstructions (none, mild, moderate, and severe) for each of varying pump target flow rates (infant to adult) were repeated 10 times ($n=10$) to document reproducibility. Thus, we measured P and Q_S for each of seven pump target flow rates (patient size) at each of four obstruction levels in each of 10 repeat experiments.

Data analysis and statistical treatment

The hypothesis that shunt flow is a marker for oxygenator obstruction may be quantitatively framed to state that Q_S will be significantly higher at mild, moderate and severe obstructions than at baseline (no obstruction) for each of the pump target flows assigned for differing patient age/size requirement. Nonparametric paired statistical tests (Wilcoxon signed rank test) comparing Q_S at mild, moderate and severe obstruction with baseline (no obstruction) at each pump target flow were performed. Statistical significance was defined as one-tailed $p < 0.05$. As a comparison, the statistical tests were repeated for the conventional marker, P as well.

Results

We performed 10 *ex vivo* experiments simulating mild, moderate and severe oxygenator obstructions at pump target flow rates ranging from 500 to 5000 mL/min. There was clear and measurable elevation in Q_S at all flow rates with increasing obstruction (Figure 3). These elevations were statistically significant under Wilcoxon signed rank test ($p < 0.05$) for all levels of obstructions (mild, moderate and severe) and for all pump target flow rates (500, 1000, 1500, 2000, 3000, 4000, 5000 mL/min). The conventional marker, P also showed a clear elevation under mild, moderate and severe obstruction for all flow rates with statistical significance (Figure 4).

The large range of baseline values in shunt flow and pressure drop for pump flow rates below 2000 mL/min (see Figure 3 and 4) is likely due to the fact that the experimental ECMO circuit was cleaned and renovated after the first 3 experiments reducing overall resistance in the circuit. Despite changes in baseline values, paired statistical comparisons reveal the clear effect of mild, moderate and severe obstruction (as confirmed by $p < 0.05$ under Wilcoxon Signed rank tests).

Discussion

Monitoring blood flow in the ECMO circuit – especially, the flow in the shunt – has the potential to serve as an additional marker for elevations in resistance at or distal to the oxygenator. Unlike monitoring of other quantities such as pressure drop or paO_2 across the oxygenator, flow monitoring is easily performed, continuous, and over-the-tube. While flow monitoring cannot replace those other more specific measurements, it can serve as another useful piece of independent information about the caliber of the ECMO circuit. If shown to be sensitive and specific enough to common ECMO events such as oxygenator obstruction, return cannula obstruction, elevated systemic vascular resistance (SVR), or even substantive changes in venous pressure, flow monitoring may permit an automated monitoring approach during ECMO. This offers several advantages. For example, it may allow for identification of SVR elevations if subsequent pressure drop and/or paO_2 measurements eliminate the oxygenator as the cause. It can be a valuable tool during ambulatory ECMO where other more manual monitoring methods are less practical. Furthermore, in patients on ECMO after cardiac surgery, the recovery of native cardiac function and consequent prograde cardiac output should oppose the retrograde ECMO arterial flow and thus will elicit an incremental elevation in shunt flow. This could potentially serve as an early indication of suitability for weaning from ECMO. Finally, it may enhance safety in the use of constant-flow rotary pumps that some recent studies suggest may be less hemolytic^{5,6} but require especially careful and continuous monitoring to ensure that elevated distal resistances – not just from oxygenator obstructions, but any source – be managed quickly and reliably. But ultimately, flow measurement provides a new piece of information about the ECMO circuit and it would only be prudent to study it further. We have leveraged the inclusion of the small shunt to hypothesize that the shunt flow will be elevated by elevated resistance at or distal to the oxygenator. This study was an attempt at testing the elevated shunt flow hypothesis and comparing it to pressure drop as a marker.

In our experiment, we refer to our simulated resistance elevations as ‘oxygenator obstruction’ to permit a controlled comparison with pressure drop. The results are consistent with the hypothesis that flow in the shunt quantified as $Q_S = Q_{\text{preS}} - Q_{\text{postS}}$ is a marker of elevated distal resistance and serves as a proof-of-concept for flow monitoring during ECMO runs (Figure 3). Both Q_S and P show statistically significant elevations at all flow rates with statistical significance ($p < 0.05$) at mild, moderate and severe oxygenator obstruction levels. However, the results suggest some key differences between pressure monitoring and flow monitoring that are worth noting. Firstly, P appears to have less noise than Q_S , but this may be attributable to the resolution of the sensors used. Whereas pressure measurement has been optimized for clinical practice, we used the flow sensors that were readily available in this early-stage study. Flow sensors with appropriately chosen precision

are likely to result in less noise. It is remarkable that despite this limitation, shunt flow remained a valid marker for circuit obstruction. Secondly, the threshold P for indicating impending oxygenator failure is independent of the pump target flow rate (i.e., patient size). But since elevations in Q_s will be higher at higher pump target flow rates, the flow-based threshold for indicating downstream obstruction should be normalized to pump target flow rate (i.e., patient-size). The precise flow metric and threshold for indicating impending oxygenator failure are best ascertained using flow data measured in human subjects during ECMO runs. We will therefore refrain from proposing a specific threshold using data from this *ex vivo* study. And finally, it is worth considering that flow monitoring, rather than replacing pressure monitoring, serves to complement it. By serving as a continuous, operator-free metric of the blood flow circuit caliber, flow monitoring can help guide periodic pressure monitoring, thus reducing the need even for hourly pressure measurements using the in-dwelling access lines. Alternatively, it is worth noting that, while pressure drop across the oxygenator can only reveal obstructions in the oxygenator, shunt flow will be elevated by obstructions in the oxygenator and/or anywhere distal to it as well. Thus, flow monitoring is sensitive to a wider range of ECMO circuit anomalies and may serve as a new marker during ECMO runs.

Limitations of this study are worth noting and indicate the need for further investigation in human subjects. Saline was the medium used in experiments. The viscosity of saline (~1cP) is far less than that of blood (~3.5 cP), which impacts the observed pressure drop and changes in flow differential in response to elevated oxygenator resistance. The fluid mechanics principles driving our hypothesis is essentially independent of the fluid type and therefore, we expect similar findings if blood were the fluid medium. Additionally, a tube constrictor was used to simulate oxygenator obstruction. The pinch clamp may be creating asymmetric and non-concentric compressions, resulting in less control over simulated obstructions in the oxygenator. Directly creating oxygenator obstructions would be more realistic, but would not be reversible. Ideally, obstructions would need to be reversible so that the same oxygenator may be used for multiple experiments. Furthermore, higher precision flow meters may reduce noise at lower flow rates. Finally, although various pump target flow rates were simulated, there are other conditions, such as differing venous pressures, that may need to be perturbed to ensure Q_s remains a reliable marker for oxygenator obstruction under all possible conditions. Ultimately, such findings need to be tested under clinical conditions to ensure Q_s is an accurate and feasible method of predicting distal ECMO circuit obstructions. In addition, rotations per minute (RPMs) recorded by the centrifugal pump may increase with increased downstream resistance. Theoretically, RPMs may also be a surrogate to increased downstream resistance in the centrifugal pump system. It may represent a poor marker especially for roller pump systems as it lacks the negative feedback loop to decrease RPMs with increased resistance and also may not be sensitive enough to downstream resistance. Q_s is sensitive to all levels of increased resistance and can be implemented in both roller and centrifugal pump system.

Since flow differential is not a specific indicator of oxygenator obstruction, but rather an indicator of any obstruction at or distal to the oxygenator, it may be prudent to not simply view flow monitoring as a substitute for pressure monitoring. Rather, flow monitoring may be better viewed as an important newly measured variable that could supplement current

ECMO monitoring to improve care. For example, flow measurement could be configured as the first line of continuous, non-contact monitoring of the ECMO circuit. When shunt flow (normalized to pump flow rate) breaches a pre-determined threshold, it could trigger pressure and blood parameter measurements for a more specific assessment of any new developments in the ECMO circuit or the patient. Overall, therefore, it is our case that flow monitoring has the real potential to provide useful new information that can make ECMO care more efficient, effective and safe than current practice.

Conclusion

Our experimental study suggests that monitoring the flow through the shunt, measured as the flow drop between before and after the shunt bifurcation, has the potential to serve as an effective indicator of elevated resistance at or distal to the oxygenator during ECMO. Flow monitoring is safe, hands-free, and continuous. If shown to be an effective marker in human subjects, implementing flow monitoring in the ECMO clinical setting is feasible and straightforward.

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Figure 1.
Schematic of the ECMO circuit

Figure 2. Schematic of experimental ECMO circuit. The clinical circuit was modified by including an adjustable over-the-tube constrictor distal to the oxygenator and flow meters distal and proximal to the shunt bifurcation.

Figure 3.

Comparison of shunt flow between none, moderate and severe (simulated) obstructions for various pump flow rates (500 through 5000 mL/min) in the ECMO circuit for 10 experiments. Boxes refer to quartiles and whiskers refer to minimum and maximum values with outliers shown as data points. Note the clear and measurable elevation in the shunt flow with increasing levels of obstruction. For all pump target flow rates, the shunt flow under mild, moderate and severe obstructions were higher than that at baseline (no obstruction) with statistical significance ($p < 0.05$) under Wilcoxon signed rank test which is consistent with our hypothesis that elevated shunt flow is an indicator of obstruction.

Figure 4.

Comparison of pressure drop between none, moderate and severe (simulated) obstructions for various pump flow rates (500 through 5000 mL/min) in the ECMO circuit for N=10 experiments. Boxes refer to quartiles and whiskers refer to minimum and maximum values with outliers shown as data points. As expected, there was clear and measurable elevation in the pressure drop with increasing levels of obstruction. For all pump target flow rates, the pressure drop under mild, moderate and severe obstructions were higher than that at baseline (no obstruction) with statistical significance ($p < 0.05$) under Wilcoxon signed rank test which is consistent with the current understanding of elevated pressure drop as an indicator of obstruction.