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Original Articles

Contemporary Oxygenator Design Relative to Hemolysis

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Abstract: Hemolysis is a well-known phenomenon during cardiovascular surgery and generally attributed to cardiopulmonary bypass, particularly when using high-resistant oxygenators. This study aimed at investigating whether transoxygenator pressure drop can be considered an independent factor of hemolysis. Additionally, intraoxygenator blood distribution and shear stress were assessed. A low-resistant (LR, n = 3), a moderate-resistant (MR, n = 3), and a high-resistant (HR, n = 3) clinically used membrane oxygenator were tested in vitro using a roller pump and freshly drawn heparinized porcine blood. Flow rates were set to 2 and 4 L/min and maximum flow compliant to the oxygenator type for 1 hour each. As a control, the oxygenator was excluded from the system. Blood samples were taken every 30 minutes for plasma-free hemoglobin assay and transoxygenator pressure was measured inline. Intraoxygenator blood distribution was assessed using an ultrasound dilution technique. Despite the relatively broad spectrum of pressure drop and resultant transoxygenator pressure drops (LR: 14–41 mmHg, MR: 29–115 mmHg, HR: 77–284 mmHg, respectively), no significant association (R^2 = .074, p = .22) was found with the normalized index of hemolysis. The shear stress of each oxygenator at maximum flow rate amounted to 3.0 N/m^2 (LR), 5.7 N/m^2 (MR), and 8.4 N/m^2 (HR), respectively. Analysis of blood flow distribution curves (kurtosis and skewness) revealed intraoxygenator blood flow distribution to become more homogeneous when blood flow rates increased. Contemporary oxygenators were shown not to be a predominant factor for red blood cell damage. **Keywords:** transoxygenator pressure drop, shear stress, flow distribution, normalized index of hemolysis. *JECT. 2014;46:212–216*

In cardiovascular surgery, blood cell damage in terms of hemolysis is a well-known phenomenon and commonly attributed to cardiopulmonary bypass, particularly when using high-resistant oxygenators. Literature related to pressure drop of oxygenators, however, shows diverging opinions regarding transoxygenator pressure drop and hemolysis (1–3).

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Experimentally derived evidence providing more clarity concerning this highly discussed topic is still lacking. In addition, intraoxygenator blood distribution and shear stress may affect oxygenator-induced hemolysis. Intra-device blood flow visualization of oxygenators has been reported previously (4). Such methods, however, are elaborate and do not provide direct quantitative information. Theoretical mathematical modeling of oxygenators may estimate numerical data on blood flow distribution and shear stress (5), but, to the best of our knowledge, no direct linkage has been made toward experimentally derived data on oxygenator-induced hemolysis.

The aim of this in vitro study was to investigate whether transoxygenator pressure drop can be considered an independent factor of hemolysis. Additionally, shear stress modeling was applied, and an ultrasound dilution

technique was used to provide insight into intraoxygenator blood distribution.

MATERIALS AND METHODS

Test Circuitry and Oxygenators

To assess hemolytic characteristics and intradevice blood distribution of oxygenators, a mock circuitry was assembled (Figure 1). The circuit contained a roller pump (COBE, Lakewood, CO), a 1/2 * 3/32-inch silicone pump raceway tubing (Maquet Cardiopulmonary AG, Hirrlingen, Germany), 3/8 * 3/32-inch polyvinyl chloride (PVC) tubing (Maquet), a JVR 1900 soft-shell reservoir (Maquet), and a Capiox SX venous hard-shell cardiotomy reservoir (Terumo Corp., Tokyo, Japan). Tubing and the soft-shell reservoir were Bioline-coated (Maquet), whereas the venous hard-shell cardiotomy reservoir was X-coated (Terumo). The circuit featured either one of the three tested oxygenators or a 20 cm 3/8 * 3/32-inch PVC tubing (Maquet) in those control series without oxygenator. The three oxygenator types used in the test circuit were: a low-resistant oxygenator (LR, n = 3) with a membrane surface area of 1.3 m^2 (Quadrox-i BE HMO 50,000; Maquet), a moderate-resistant oxygenator (MR, n = 3) with a membrane surface area of 1.5 m^2 (Capiox RX15; Terumo), and a high-resistant oxygenator (HR, n = 3) with a membrane surface area of 1.4 m^2 (Inspire 6; Sorin S.p.A., Mirandola, Italy). Priming volumes were 175 mL, 135 mL, and 184 mL, respectively. Blood flow was monitored at the outlet of the roller pump using an ultrasonic flow meter (HT110 Bypass Flow meter with 3/8-inch HXL sensor; Transonic Systems Inc., Ithaca, NY). Pressures were measured at the inlet and outlet of the oxygenator using pressure transducers, which were zero-calibrated to the atmosphere (PX604 TruWave; Edwards Lifesciences, Irvine, CA). Probes for ultrasound dilution (HD03; Transonic Systems Inc.) were placed 5 cm before the inlet and 5 cm after the outlet of the oxygenator, respectively.

Protocol

The circuit was primed with 1100 mL saline solution, after which priming was replaced with freshly drawn heparinized (25,000 IU/L) porcine blood. Every experiment used single-donor blood and a new sterile circuit. After blood priming, mean hematocrit was 41.9 ± .4%, and the mean free hemoglobin concentration was .028 ± .002 g/dL. Blood flow rates were set to 2 L/min, 4 L/min, and maximum flow compliant to the oxygenator type for 1 hour each. Blood samples were drawn 3 minutes after flow was initiated, and every 30 minutes, up to 180 minutes. Samples for plasma-free hemoglobin assay were immediately centrifuged for 12 minutes at 3000 rpm and 4°C.

After the last blood sample, intraoxygenator blood distribution was assessed using ultrasound dilution. The technique uses saline infusion and detects resultant changes in the average cross-sectional velocity of an ultrasound beam that illuminates the blood flow (6). A 30-mL saline bolus was controllably infused within 5 seconds upstream of the oxygenator inlet probe using a cardioplegia roller pump. After bolus infusion, a 30-second period was allowed for dilutional curve recordings at the outlet of the oxygenator. The injected saline at the inlet of the oxygenator interacts

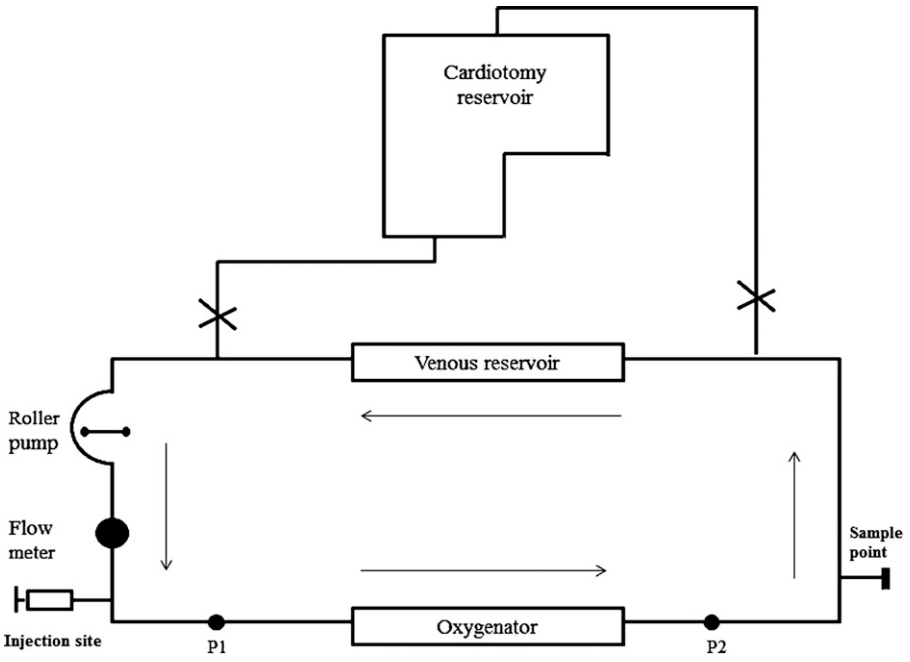

Figure 1. Schematic diagram of the mock circulation used to determine hemolytic characteristics and intraoxygenator blood distribution. In the control experiments, the oxygenator was replaced by a 20-cm 3/8 * 3/32-inch polyvinyl chloride tube. P 1, inlet pressure probe; P 2, outlet pressure probe.

with surrounding blood depicted by dilutional curves. A predominantly skewed curve results from less homogenous flow distribution within the oxygenator, which is explained by higher recirculation. On the other hand, a platykurtotic curve signifies a more homogenous flow distribution within the oxygenator.

Data Processing and Statistical Analysis

A value for transoxygenator pressure drop was calculated for each flow rate using the pressures measured at inlet and outlet of the oxygenator. A normalized index of hemolysis (NIH) was calculated according to American Society for Testing and Materials standards (7) by using the free hemoglobin data retrieved from blood sampling (Formula 1). A relation between NIH and transoxygenator pressure drop was tested by a scatterplot and the proportion of variance was described by regression (Excel 2010; Microsoft Corp., Redmond, WA) and the power of association was analyzed (IBM Corp. released 2012; IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY). A $p \leq .05$ was considered statistically significant. Shear stress was calculated according to the Mockros formula (Formula 2) by using the transoxygenator pressure drop values (8,9). The measurements calculated in Gaussian-cgs units were converted to international system of units ($1\ N/m^2 = 10\ dynes/cm^2$).

RESULTS

Transoxygenator pressure drop calculation of the various oxygenators resulted in a broad spectrum of pressure drop values from 2.0 LPM to the oxygenators rated flow (LR: 14–41 mmHg, MR: 29–115 mmHg, HR: 77–284 mmHg). Despite the relative broad spectrum of pressure drop, congruent NIH analysis did not reveal a statistically significant association to resultant transoxygenator pressure drop or in the control group ($R^2 = .074$, $p = .22$), as shown in Figure 2.

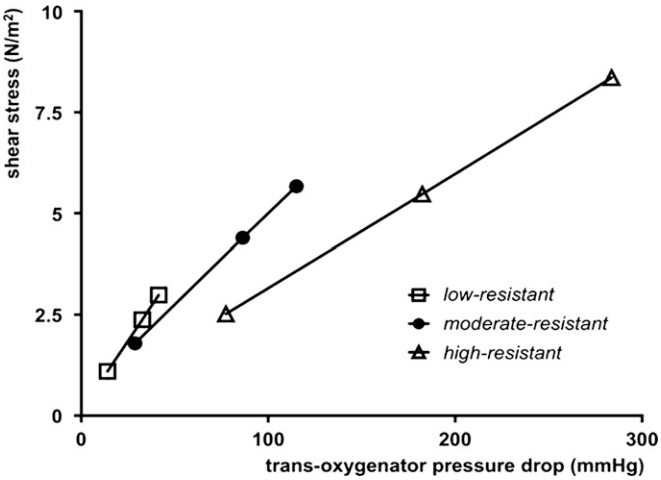

Figure 3. Shear stress in relation to transoxygenator pressure drop. The maximum shear stresses calculated were 3.0 N/m^2 (low-resistant oxygenator), 5.7 N/m^2 (moderate-resistant oxygenator), and 8.4 N/m^2 (high-resistant oxygenator), respectively.

Figure 3 depicts the results of shear stress calculation in relation to transoxygenator pressure drop for each oxygenator. Maximum shear stress values amounted to 3.0 N/m^2, 5.7 N/m^2, and 8.4 N/m^2 for the LR, MR, and HR oxygenators, respectively.

Figure 4 shows data (kurtosis) on ultrasound dilution assessment of the intraoxygenator blood distribution. The figure illustrates the kurtosis of the dilution curves

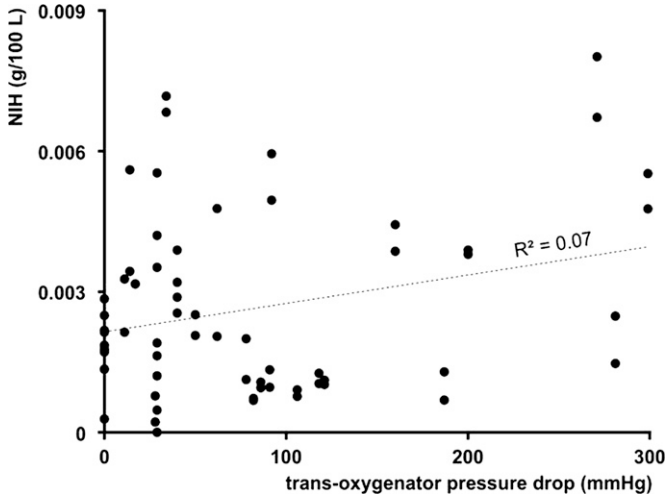

Figure 2. The effect of transoxygenator pressure drop on normalized index of hemolysis (NIH). The varying pressure drop among (low, moderate, and high) resistant oxygenators had no significant effect on NIH or in the control group ($R^2 = .07$, $p = .22$).

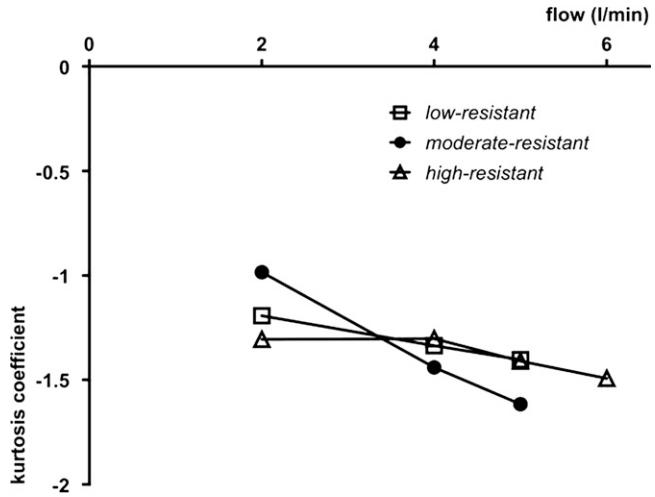

Figure 4. Effect of flow on ultrasound dilution assessment of the intraoxygenator blood distribution (kurtosis). The blood distribution within the oxygenator improves (most evident in the moderate-resistant oxygenator) with the increase in blood flow rate.

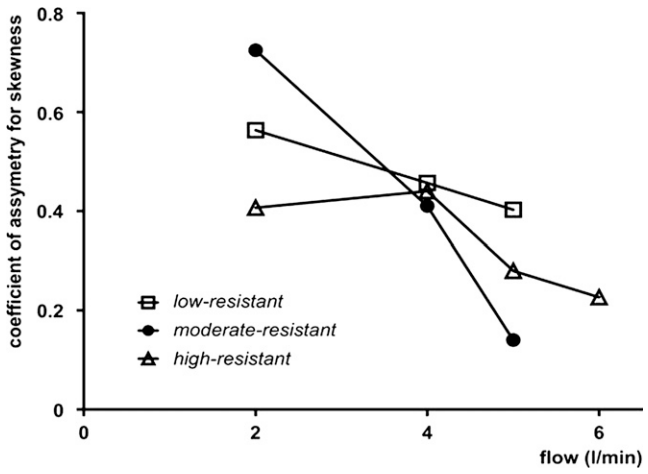

Figure 5. Effect of flow on ultrasound dilution assessment of the intraoxygenator blood distribution (skewness). Increase in blood flow rate decreases the skewness (less recirculation) of the dilution curve.

changing with increment in blood flow rate. As blood flow increased, curve kurtosis decreased (platykurtosis), which was most prominent for the MR oxygenator, followed by comparable values for the LR and HR oxygenators.

Figure 5 shows data (skewness) on ultrasound dilution assessment of the intraoxygenator blood distribution. The figure illustrates the skewness of the dilution curves changing with increment in blood flow rate. Skewness of the curve decreased as flow increased, an effect most prominently seen with the MR oxygenator followed by the HR oxygenator and LR oxygenator, respectively.

DISCUSSION

This study searched for an association of transoxygenator pressure drop and hemolysis using oxygenators featuring various pressure drop and assessed shear stress and blood flow distribution. Despite large differences in resistance, NIH values and blood flow distribution curves proved unaffected by pressure drop, although shear stress varied between 1.0 and 8.4 N/m^2.

Despite various studies on the effect of transoxygenator pressure drop on red blood cells, there is still no consensus regarding this subject. Hemolysis as a result of cardiovascular surgery using cardiopulmonary bypass is generally attributed to the pressure drop caused by the oxygenator. Adamant proof confirming this belief, however, is still lacking. In that context, Kawahito et al. (10) introduced the normalized index of hemolysis, which used plasma-free hemoglobin, but corrects for variations in blood flow, hematocrit, blood volume, and time between measurements. They concluded hemolytic characteristics of oxygenators to have a close relationship to pressure drop. The pressure drops induced by the oxygenators used in their study, however, were relatively low, and ranged from 3 to 44 mmHg only. Segers et al. (2) compared oxygenators in a clinical setting and used plasma-free hemoglobin assay. They concluded that oxygenators inducing a high pressure drop did not increase hemolysis compared with oxygenators inducing a low pressure drop but omitted NIH calculations. Recently, De Somer (1) reviewed the influence of contemporary oxygenator design on hemolysis and concluded that oxygenator design-dependent hemolysis was no longer an issue. Unfortunately, experimental evidence was not provided to either confirm this conclusion or create unambiguity. We, in contrast to Kawahito et al. (10), used a wide range of transoxygenator pressure drop and, unlike Segers et al. (2), included the NIH. No significant association could be found linking oxygenator resistance to hemolysis (Figure 2). Furthermore, the presence of hemolysis in the absence of oxygenators (control) confirms that transoxygenator pressure drop as evidenced in the study had no effect on red blood cell damage.

At the moment, it is well known that shear stress as a result of blood traversing through an extracorporeal circuit plays an important role in activating cellular blood components (11,12). With pressure drop over a certain length of tubing known, calculating shear stress in tubing is feasible and straightforward. Calculating shear stress on a given blood element during transit through the oxygenator, however, remains extremely challenging because the blood flow path is tortuous and complex (1). Despite various formulae being available to estimate shear stress, the results of those calculations remain a rough approximation. Our estimations of shear stress amounted to 8.4 N/m^2 at maximum. Shear stress induced activation of platelets and leukocytes to occur at approximately 8 N/m^2 and 10 N/m^2, respectively (13,14). Although red blood cell activation starts at 150 N/m^2 (15), which re-emphasizes that the contemporary oxygenator design is unlikely to be a predominant factor for inducing red cell lysis.

When a saline bolus is injected into the blood path, it will to some extent mix (dilute) with the surrounding blood. This process can be visualized by dilution curves resulting from ultrasound dilution. When injecting such a bolus near the oxygenator inlet, the shape of the dilution curve with respect to kurtosis and skewness retrieved at the oxygenator outlet relates to the intraoxygenator blood flow distribution. A preferred oxygenator outlet dilution curve shows a platykurtosis and near-zero skewness, i.e., a more homogeneous blood distribution with less recirculation. Analysis of the blood flow distribution curves revealed intraoxygenator blood distribution to become more homogeneous when blood flow rates increased. All tested oxygenators gave comparable distribution curves despite their large differences in transoxygenator pressure drop. Consequently, given the problems regarding calculating shear stress calculations in oxygenators, which represents merely an approximation rather than exact

reality, the application of the ultrasound dilution technique may provide a simple and valuable additional tool to assess blood distribution within oxygenators, although more research regarding quantification and relation to shear stress and blood damage needs to be done. Furthermore, it needs to be ascertained if changing the priming solution would influence the NIH, because porcine blood is more susceptible to osmotic fragility (16).

CONCLUSION

Our results suggest that transoxygenator pressure drop cannot be considered an independent factor of hemolysis, because no such association was found. The assertion that a high transoxygenator pressure drop is harmful to erythrocytes, as considered by some clinicians, may therefore be consigned to the realms of fantasy.

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Formula 1. Calculation of normalized index of hemolysis (NIH).

$$NIH = \frac{\Delta Hb_{free} \times V_{total} \times \left(1 - \left(\frac{Hct}{100}\right)\right) \times 100}{\Delta t \times Q}$$

in which NIH is measured in g/100 L; ΔHb_{free}, increase in plasma-free hemoglobin between two samples, in g/L; V_{total}, total circulatory volume, in L; Hct, hematocrit of sample; Q, flow rate, in L/min; Δt, time between two samples, in minutes.

Formula 2. Calculation of shear stress.

$$\tau_{oxy} = \sqrt{\left(\frac{\eta \times Q \times \Delta P}{V_{priming}}\right)}$$

in which τ_{oxy}, shear stress in the oxygenator, in dynes/cm^2; η, absolute viscosity of the blood, in Pa*s; Q, flow rate, in L/min; ΔP, transoxygenator pressure drop, in Pa; $V_{priming}$, priming volume oxygenator, in mL.