Blood warming, pump heating and haemolysis in low-flow extracorporeal life support; an in vitro study using freshly donated human blood

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Blood warming, pump heating and haemolysis in low-flow extracorporeal life support; an in vitro study using freshly donated human blood

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Abstract

Low-flow extracorporeal life support can be used for cardiopulmonary support of paediatric and neonatal patients and is also emerging as a therapy for patients suffering from exacerbation of chronic obstructive pulmonary disease. However, pump heating and haemolysis have proven to negatively affect the system and outcome. This in vitro study aimed at gaining insight into blood warming, pump heating and haemolysis related to the performance of a new low-flow centrifugal pump. Pump performance in the 400–1,500 ml/min flow range was modulated using small-sized dual-lumen catheters and freshly donated human blood. Measurements included plasma free haemoglobin, blood temperature, pump speed, pump pressure, blood flow and thermographic imaging. Blood warming ($\Delta T_{\max}=0.5^{\circ}\text{C}$) had no relationship with pump performance or haemolysis ($R^2_{\max}=0.05$). Pump performance-related parameters revealed no relevant relationships with haemolysis ($R^2_{\max}=0.36$). Thermography showed no relevant heat zones in the pump ($T_{\max}=36^{\circ}\text{C}$). Concerning blood warming, pump heating and haemolysis, we deem the centrifugal pump applicable for low-flow extracorporeal circulation.

Keywords

centrifugal pump; extracorporeal life support; pump heating; haemolysis; normalized index of haemolysis

Introduction

Extracorporeal life support (ECLS) has proven a successful technique for providing cardiopulmonary assistance in adult patients, using supporting blood flows of 3–5 l/min.^{1–3} Adapted towards a low-flow application using supporting blood flows of approximately 0.5 to 1.5 l/min, ECLS can be used for the support of paediatric and neonatal patients^{4–6} or as an emerging therapy for patients suffering from exacerbation of chronic obstructive pulmonary disease.^{7–11}

With centrifugal pump-based ECLS, the hydraulic resistance of small-size catheters and/or an increased patient demand can be compensated for by increasing the pump speed.¹² Pump speed, however, is found to be an independent risk factor for haemolysis.⁶ Simply increasing pump speed may force the centrifugal pump to operate outside its best efficiency zone.¹² Moreover, a study using early generation pumps has shown that increasing pump speed while the flow remains relatively low can result in unstable support flow and severe pump

heating.¹³ In contrast, a recently introduced, new-generation, low-flow, dedicated centrifugal pump has

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Figure 1. Schematic representation (left), photograph (middle) and thermographic image (right) of the mock circulation which allowed for the measurement of flow and both temperature (T) and pressure (p) at the inlet and outlet of the pump. The warmest areas visible are the large housing of the heater unit and the infusion bag containing approximately 200 ml of blood. The average temperature within the circular area covered by the crosshair is given in the upper left corner, i.e. in this example 23.0°C.

demonstrated excellent hydrodynamic stability.¹⁴ Data on performance of that pump in relation to blood warming, pump heating and haemolysis, however, have, to the best of our knowledge, not yet been reported.

The aim of this *in vitro* study using freshly donated human blood was to gain insight into blood warming, pump heating and haemolysis related to the performance of a new low-flow dedicated centrifugal pump.

Materials and Methods

The study was approved by the medical ethical committee of the Maastricht University Medical Centre. Written informed consent was obtained from all blood donors. The study was registered at the Dutch Trial Register, trial number NTR4874.

Mock circulation

A mock circulation was built to investigate blood warming, pump heating and haemolysis in relationship to pump performance as modulated by catheter design and size. The mock circulation (Figure 1) consisted of a double-lumen catheter inserted into a 100 ml infusion bag, ¼ inch polyvinyl chloride tubing (Medtronic, Minneapolis, MN, USA) and a low-flow centrifugal pump (Rotassist 2.8) with drive adapter (sn: 90425123) and CardioHelp drive unit (sn: 90410012, firmware ver. 3.04.02, Maquet Cardiopulmonary AG, Hirrlingen, Germany). The circuit had a total volume of approximately 300 ml. The tubing was guided through a water

bath kept at 37°C using a heater unit (Hypo-hyperthermia model CF1, GranuLab International B.V., Amersfoort, the Netherlands). Flow was measured using a ¼ inch ultrasound flow probe (sn: 90045055) that came with the pump drive unit. Pressures and blood temperatures were measured in-line at the inlet and outlet of the centrifugal pump using disposable pressure transducers (PX604, TruWave, Edwards Lifesciences, Irvine, CA, USA; zeroed towards atmosphere) and temperature probes (Capiiox Luer Thermistor, Terumo Corp., Tokyo, Japan), respectively. A custom-built data acquisition system (PASAQ, Instruments Development Engineering & Evaluation, Maastricht University Medical Centre, Maastricht, the Netherlands) provided pressure and blood temperature read-out.

A calibrated thermographic camera (ThermaCAM SC2000, Flir Systems, Inc., Wilsonville, Oregon, USA) enabled visualisation of pump heating by recording surface temperature distribution of both centrifugal pump and drive unit. During each pump run, the water bath, tubing, infusion bag and catheter were covered with aluminium foil to reduce heat loss by radiation and to maintain circuit temperature. The drive unit, centrifugal pump and temperature sensors remained uncovered. The ambient temperature was 20°C.

Catheters

Figure 2 shows four different small-size, double-lumen catheters, ranging from 13 to 18 French (4.3 to 6 mm). Their varying hydraulic resistance was used to modulate pump performance in terms of pumping

Figure 2. Double-lumen catheters of various sizes. From top to bottom: 13 French (Maquet), 15 French (OriGen, Biomedical, Austin, TX, USA), 16 French (Maquet) and 18 French (OriGen).

efficiency and pump head, with resultant blood warming and pump heating.

Protocol

For donation, approximately 250 ml human whole blood was collected into a blood collection bag containing citrate solution (CompoFlex CPDA-1, Fresenius Kabi AG, Bad Homburg, Germany), according to institutional protocol for blood donation. Subsequently, the fully anticoagulated whole blood was diluted down to a haematocrit of 30% using sodium chloride 0.9%. After mounting one of the four catheters, the circuit was primed using the diluted blood. Centrifugal pump speed (in rpm, rotations per minute) was adjusted to induce a flow rate of either 400 ml/min, 700 ml/min, 1,000 ml/min or 1,500 ml/min by using the mounted catheter as a resistance. Citrated blood samples were drawn from the circuit in duplicate after 5 minutes and after 6 hours of pump run. Samples were immediately centrifuged (3,000 rpm, 12 minutes, 4°C), and sent to the laboratory for plasma free haemoglobin (Hb_{free}) assay. After 3 and 6 hours of the pump run, pump speed, pump flow rate, blood temperature and pressure read-outs were recorded. A thermographic image was taken after 6 hours. Each catheter size-flow rate combination was tested in triplicate and used single-donor blood and new sterile circuit tubing, tube connectors and infusion bag. The centrifugal pump and catheter were reused after being thoroughly rinsed by a 0.9% NaCl solution and dried at atmosphere.

Data processing and statistical analysis

Average Hb_{free} levels were calculated for the two samples taken from the circuit after 5 minutes of pump

run and after 6 hours of pump run. The difference in plasma free haemoglobin (ΔHb_{free}) was determined by subtracting the 6-hour average by the 5-minute average. A normalized index of haemolysis¹⁵ was calculated for each pump run and corrected for catheter size, according to

$$NIH_{corrected} = \frac{\Delta Hb_{free} \cdot V_{total} \cdot \left(1 - \left(\frac{Hct}{100}\right)\right) \cdot 100}{\Delta t \cdot flow \cdot catheter\ size}$$

in which $NIH_{corrected}$ =catheter size-corrected normalized index of haemolysis in grams per 100 litre per French; ΔHb_{free} =difference in plasma free haemoglobin in grams per litre; V_{total} =total circulating volume in litres; Hct =haematocrit; Δt =time elapsed between the two samples in minutes; $flow$ =pump flow rate in litres per minute; $catheter\ size$ =outer lumen catheter diameter in French.

Blood heating was represented by a blood temperature gradient, calculated by the subtraction of the blood temperature measured at the pump outlet by that measured at the inlet. The pump performance-related factors, pumping efficiency and pump head, were calculated by dividing pump flow by pump speed and by calculating the absolute pressure difference between the pump inlet and pump outlet, respectively. Blood temperature gradient, pumping efficiency and pump head were calculated twice for each test run: after 3 and 6 hours. Scatter plots were used to indicate a possible relationship between blood temperature gradient and pumping efficiency, pump head and $NIH_{corrected}$. The proportion of variance was described by regression analysis. A Student t-test was used to test for differences between the 3 hour and 6 hour groups of blood temperature gradient, pumping efficiency and pump head. Statistical analyses were performed using SPSS Statistics 22 (IBM Corp., Armonk, NY, USA). A p-value <0.05 was considered statistically significant.

Results

The largest catheter (18 French) with the maximum flow rate tested (1.5 l/min) required the highest pump speed of all the experiments (3,600 rpm) whereas the smallest catheter (13 French) enabled a maximum flow rate of 400 ml/min at a pump speed of 2,300 rpm. Pumping efficiency ranged from 0.17 ml/rotation to 0.43 ml/rotation whereas the pump head varied from 41 mmHg to 322 mmHg. The highest measured blood temperature gradient between the pump inlet and pump outlet amounted to 0.5°C. Figure 3 shows blood temperature data to reveal no clinically relevant relationships with respect to pump performance-related parameters, pumping efficiency ($R^2_{3h}=0.00$, $p_{3h}=0.94$;

Figure 3. Scatterplot indicating relationships between pumping efficiency and blood temperature gradient (a), pump head and blood temperature gradient (b), pumping efficiency and catheter size-corrected normalized index of haemolysis ($NIH_{corrected}$) (c), pump head and $NIH_{corrected}$ (d) and blood temperature gradient and $NIH_{corrected}$ (e). Graphs a and b use the data of both 3 hours (dashed line) and 6 hours (continuous line) of pump run whereas graphs c, d and e use the data of 6 hours of pump run.

$R^2_{6h}=0.00$, $p_{6h}=0.79$) and pump head ($R^2_{3h}=0.02$, $p_{3h}=0.49$; $R^2_{6h}=0.05$, $p_{6h}=0.24$). Neither pumping efficiency, nor pump head showed a relevant relationship to $NIH_{corrected}$ ($R^2_{6h}=0.24$, $p_{6h}=0.01$ and $R^2_{6h}=0.36$, $p_{6h}=0.00$, respectively). No relationship was found between the blood temperature gradient and $NIH_{corrected}$ ($R^2_{6h}=0.02$, $p_{6h}=0.41$). Furthermore, there were no significant differences between the 3 hour and 6 hour groups with respect to blood temperature gradient, pumping efficiency and pump head ($p>0.92$ for all).

Figure 4 shows 'normal' and thermographic imaging of the drive unit with the pump mounted onto the drive adapter. The thermographic images show the temperature distribution of the console, drive adapter and pump in the outer ranges of pumping efficiency and pump head. The warmest heat zones were found in the housing covering the impeller of the centrifugal pump and were near 36°C, regardless of the pumping efficiency or pump head. The black housing of the drive adapter was warmest close to the pump volute and its temperature amounted to 29°C at maximum. The temperature of the drive unit did not exceed 30°C.

Discussion

This study aimed at gaining insight into blood warming, pump heating and haemolysis in relation to the performance of a centrifugal pump for low-flow applications.

Blood warming and pump heating proved within safe ranges and showed no relationship with pump performance and red cell damage. In addition, there was no relationship between pump performance and red cell damage. No clinically relevant heat zones were found in the console, drive adapter or pump.

In contrast to full-blown extracorporeal life support (ECLS) that uses supporting blood flow rates of 3–6 l/min during refractory acute lung and/or cardiac failure, low-flow ECLS uses supporting blood flows of approximately 0.5 to 1.5 l/min and much smaller catheters. Low-flow ECLS can either be used for the support of paediatric and neonatal patients^{4–6} or as an emerging therapy for patients suffering from exacerbation of chronic obstructive pulmonary disease.^{7,9,16} This study on hydrodynamically simulated low-flow ECLS used a variety of dual-lumen catheters and blood flow rates ranging from 13 to 18 French and 0.4 to 1.5 l/min, respectively. To overcome catheter flow resistance and achieve those supporting blood flow rates, centrifugal pump rotational speeds of up to 3,600 rpm were required. Resulting pumping efficiencies, however, were relatively low, with a maximum value of 0.43 ml per rotation (Figure 3). Under such pumping conditions, Ganushchak et al. demonstrated support instability and severe heating of the pump, its surrounding components and the pumped fluid¹³ whereas Takami et al. demonstrated loss in pumping power.¹⁷ Our data on varying pumping conditions, however, did not show

Figure 4. A 'normal' picture of the rear of the drive unit (a) shows the black drive adapter with the centrifugal pump mounted. The thermographic images show heat distribution with the pump operating in its low (b) and high (c) pumping efficiency range, as well as during pumping in its low (d) and high (e) pump head range.

any relevant heating, neither of the pump nor of the drive adapter, console or the blood being pumped. Moreover, a previous study on the current low-flow pump with respect to hydraulic performance showed excellent support stability.¹⁴ An explanation for those contrasting results may be found in pump design. The pumps used by Ganushchak et al. were of a much older generation and originally intended for high-flow applications like cardiopulmonary bypass. Moreover, they featured completely different designs, using either metal bearings with the risk of running hot or plastic shaft sealing risking leakage when worn off whereas others required sufficient pump flow to achieve adequate motor cooling. The low-flow pump used in this study, in contrast, contains a low-friction, fluid-submersed, point bearing without shaft sealing. Furthermore, as in fully levitated pumps, it uses static coils for both impeller stabilization and driving.

Next to a lowered burden for the initiation of low-flow ECLS, small-sized catheters offer the advantage of improved patient comfort and easier access to bedside physiotherapy in the pursuit of maintaining or regaining physical fitness. Several studies have investigated the implementation of low-flow applications of ECLS using relatively small catheters. Batchinsky et al. and Karagiannidis et al., in pre-clinical studies, applied blood flows of 0.5 l/min using 15.5 French dual-lumen catheters⁷ and blood flow rates of 0.3 to 1.0 l/min using a 19 French dual-lumen catheter,¹⁸ respectively. Next to those pre-clinical investigations on low-flow ECLS, several clinical studies have been reported. Burki et al. used 15.5 French dual-lumen catheters with supporting flows of 0.4 l/min⁹ and Mani et al. reported blood flow rates of up to 0.6 l/min when using the same catheter size.¹⁹ Sharma et al. supported patients, using pump flow rates of 0.5 l/min and dual-lumen catheters ranging from 12 to 24 French in size.¹⁶ Unfortunately, and in contrast to our study, none of those studies provided data on pump rotational speed, hence, rendering a direct data comparison regarding pumping efficiency among studies impossible. However, since our study applied a wide range of both catheter sizes and low-flow blood flow rates, it is most likely that the pumping conditions applied in both pre-clinical and clinical studies mentioned above are comparable with the pumping efficiency data of the current study.

The studies of Batchinsky, Burki and Mani included blood cell damage in terms of haemolysis.^{7,9,19} In contrast to Burki et al. and Mani et al. who used human blood, Batchinsky et al. used porcine blood, which shows a lower osmotic fragility.²⁰ Nevertheless, none of the three studies could demonstrate any relevant red cell damage. Lou et al., in another study, searched for risk factors of haemolysis in pediatric ECLS patients

being supported at an estimated pumping efficiency of 0.4 ml/rotation. They found pump speed to be an independent risk factor for the occurrence of haemolysis.⁶ In contrast to those studies quantifying absolute plasma free haemoglobin levels as an outcome measure, our study calculated relative haemolysis expressed by the NIH and searched for a linkage with the centrifugal pump. We found no significant relationship between NIH and the pump-related parameters pumping efficiency, pump head and fluid warming. Based on the promising results of this experimental study and taking into account the results from our previous study on hydrodynamic pump performance,¹⁴ this new low-flow dedicated centrifugal pump can be considered for low-flow ECLS.

Conclusion

With no relevant heat zones found in the console, drive adapter or pump and with no meaningful relationships among pump performance, blood warming and haemolysis, we deem the Rotassist 2.8 centrifugal pump applicable for low-flow extracorporeal circulation.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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References

1. Bartlett RH, Roloff DW, Custer JR, et al. Extracorporeal life support: the University of Michigan experience. *JAMA* 2000; 283: 904–908.
2. Chung SY, Sheu JJ, Lin YJ, et al. Outcome of patients with profound cardiogenic shock after cardiopulmonary resuscitation and prompt extracorporeal membrane oxygenation support. A single-center observational study. *Circ J* 2012; 76: 1385–1392.
3. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009; 374: 1351–1363.
4. Pettignano R, Fortenberry JD, Heard ML, et al. Primary use of the venovenous approach for extracorporeal

- membrane oxygenation in pediatric acute respiratory failure. *Pediatr Crit Care Med* 2003; 4: 291–298.
5. Paden ML, Conrad SA, Rycus PT, et al. Extracorporeal Life Support Organization Registry Report 2012. *ASAIO J* 2013; 59: 202–210.
 6. Lou S, MacLaren G, Best D, et al. Hemolysis in pediatric patients receiving centrifugal-pump extracorporeal membrane oxygenation: prevalence, risk factors, and outcomes. *Crit Care Med* 2014; 42: 1213–1220.
 7. Batchinsky AI, Jordan BS, Regn D, et al. Respiratory dialysis: reduction in dependence on mechanical ventilation by venovenous extracorporeal CO₂ removal. *Crit Care Med* 2011; 39: 1382–1387.
 8. Terragni P, Maiolo G, Ranieri VM. Role and potentials of low-flow CO₂ removal system in mechanical ventilation. *Curr Opin Crit Care* 2012; 18: 93–98.
 9. Burki NK, Mani RK, Herth FJF, et al. A novel extracorporeal CO₂ removal system: results of a pilot study of hypercapnic respiratory failure in patients with COPD. *CHEST* 2013; 143: 678–686.
 10. Gattinoni L, Pesenti A, Mascheroni D, et al. Low-frequency positive-pressure ventilation with extracorporeal CO₂ removal in severe acute respiratory failure. *JAMA* 1986; 256: 881–886.
 11. Pesenti A, Pelizzola A, Mascheroni D, et al. Low frequency positive pressure ventilation with extracorporeal CO₂ removal (LEPPV-ECCO₂R) in acute respiratory failure (ARF): technique. *Trans Am Soc Artif Intern Organs* 1981; 27: 263–266.
 12. Bachus L, Custodio A. *Know and understand centrifugal pumps*. Elsevier, Oxford. 2003.
 13. Ganushchak YM, van Marken Lichtenbelt W, van der Nagel T, et al. Hydrodynamic performance and heat generation by centrifugal pumps. *Perfusion* 2006; 21: 373–379.
 14. Simons AP, Martens EGHJ, Ganushchak YM. Centrifugal pump performance during low-flow extracorporeal CO₂ removal; safety considerations. *Perfusion* 2015; 30: 17–23.
 15. American Society for Testing and Materials (ASTM) F1841–97. Standard practice for assessment of hemolysis in continuous flow blood pumps; Book of standards. 2005.
 16. Sharma AS, Weerwind PW, Strauch U, et al. Applying a low-flow CO₂ removal device in severe acute hypercapnic respiratory failure. *Perfusion* 2016; 31: 149–155.
 17. Takami Y, Nakazawa T, Makinouchi K, et al. Pump power loss and heat generation in a pivot bearing-supported Gyro centrifugal pump (C1E3). *Artif Organs* 1996; 20: 794–797.
 18. Karagiannidis C, Kampe KA, Sipmann FS, et al. Venovenous extracorporeal CO₂ removal for the treatment of severe respiratory acidosis: pathophysiological and technical considerations. *Crit Care* 2014; 18: R124.
 19. Mani RK, Schmidt W, Lund LW, et al. Respiratory dialysis for avoidance of intubation in acute exacerbation of COPD. *ASAIO J* 2013; 59: 675–678.
 20. Matsuzawa T, Ikarashi Y. Haemolysis of various mammalian erythrocytes in sodium chloride, glucose and phosphate-buffer solutions. *Lab Anim* 1979; 13: 329–331.

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Presenter, Antoine Simons

CO-MODERATOR JOSEPH DEPTULA (Omaha, Nebraska): With the catheter that was collapsing as you described, did you use a new catheter or did you reuse the catheters?

DR. ANTOINE SIMONS (Maastricht, the Netherlands): The catheters we used are expensive so we had to reuse them. We cleaned them and rinsed them thoroughly. For the catheter that collapsed under the extreme experiment after two minutes, we just rinsed it thor-

oughly and then held it under some hot tap water to get it back into shape. Once it cooled down, one could tap it on the table again because it was hard again. We were very surprised that this catheter was so rigid and hard once it cooled down. You could not even squeeze it, which was so remarkable. We had just seen this catheter collapse in the circuit and the bag. It was so rubbery. We were very surprised about that finding.