The effect of oxygenator membranes on blood: a comparison of two oxygenators in open-heart surgery

Joseph Noora¹,², Andre Lamy¹,³, Kelly M Smith¹,³, Rosanne Kent¹,³, Dianne Batt², John Fedoryshyn² and Xiaoyin Wang²,³

¹McMaster University, Hamilton, Ontario, Canada; ²Hamilton Health Sciences, Hamilton, Ontario, Canada; ³CADENCE Research Group, Hamilton, Ontario, Canada

The interaction between the cardiopulmonary bypass (CPB) and the blood may result in complications such as hemodynamic instability, pulmonary edema, gastrointestinal dysfunction, and myocardial edema or fluid retention, as well as possible early or late neurological deficits.¹⁻⁷ In addition to these possible complications, the blood-to-surface interaction may induce a whole body inflammatory response, or coagulopathy, leading to increased postoperative morbidity.²,³,⁵,⁶⁻¹⁰

Membrane oxygenators have evolved over the past decade and now represent the gold standard for CPB.³,⁴,⁹ Continual research and development in the field of CPB has promoted the re-engineering of membrane oxygenators, with the new models designed to reduce the comorbidities associated with their predecessors. Manipulations of surface properties and mechanical improvements in circuitry have resulted in a reduction of the detrimental platelet–surface interactions. However, the ultimate potential of these maneuvers to improve the morbidity associated with CPB is limited.¹¹,¹² Because of this, the development of an oxygenator membrane coating designed to protect blood components has come to the forefront.

The use of a heparin coating on the surfaces of the CPB circuit has evolved, reducing the deleterious blood-to-surface interactions during open-heart surgery (OHS).¹¹,¹³⁻¹⁸ To further the field of oxygenator development, a surface coating (Trillium Biopmiasive) has been developed to minimize the absorption of protein and the attachment of cells to the CPB surfaces, thus effectively reducing the activation of the contact and cellular systems of the blood.

The Hamilton Health Sciences – General Site routinely uses two types of membrane oxygenators during OHS, the Medtronic Affinity NT (coated) and...
the Cobe Optima XP (noncoated). The purpose of the present study is to evaluate the performance of each membrane oxygenator and assess their influence on the blood components during OHS.

Materials and methods

Study design

This is a prospective randomized controlled trial with a two-group, repeated measures design. Patients were approached at the Hamilton Health Sciences – General Site between January and July 2001. The Hamilton Health Sciences – General Site is a university affiliated, tertiary care center and is the Regional Heart Center serving a population of approximately two million Canadians. The Cardiac Surgical Group performs approximately 1400 OHS procedures annually. All seven surgeons and eight perfusionists participated in the study. The Research Ethics Board of McMaster University and the Hamilton Health Sciences approved the study.

Patients

All adult patients undergoing elective or urgent OHS who were expected to be on CPB for greater than 45 min and able to give written informed consent were eligible to participate in the study. Exclusion criteria included active endocarditis, hematological disease, allergy to heparin or protamine, pregnancy, emergent surgery (surgery within 4 to 6 hours of referral), low body weight (below 50 kg), intra-aortic balloon pump (IABP) insertion prior to surgery, patients with low preoperative platelet counts (< 100,000 × 10^6/L), or patients enrolled in another study.

Sample size

The sample size for the study was calculated to detect a difference in platelet count of 20,000 × 10^6/L between the two oxygenators. Data from a pilot study conducted at the Hamilton Health Sciences – General Site were used to calculate the sample size for the present study. It was determined that a sample size of 120 patients per group would yield significant differences between the oxygenators with \( \beta = 0.80 \) and \( \alpha = 0.05 \). A total of 256 patients were recruited to account for dropout, surgical mortality, and loss to follow-up.

Outcomes

Blood work. Measurements obtained prior to surgery, 15 min after initiating CPB, and every 30 min thereafter while on CPB included hemoglobin concentration, white blood cell count, platelet count, and electrolytes. These measurements are routinely conducted immediately following OHS and at regular intervals in the intensive care unit.

Hemodynamics and oxygenation. Measurements included pump flow and sweep, input and outflow pressures (mmHg), FiO₂ and arterial and venous oxygen content, which were recorded at 15, 45, and 75 min while on CPB. Data obtained from the arterial (SaO₂) and venous (SvO₂) oxygen saturation, hemoglobin content, arterial and venous pO₂, and inlet (Pi) and outlet (Po) blood path pressures were used to calculate oxygen transfer (calculated per FiO₂), arteriovenous oxygen difference (A-VO₂), and blood path pressure drop (see Appendix).

Postoperative measurements. The number and volume of transfused units of blood products in the operating room and intensive care unit were recorded. Total blood loss from pericardial and chest tubes was measured (mL) and recorded at 6 and 12 hours postoperatively.

Procedure. The CPB circuit consisted of a hard-shell membrane oxygenator (Affinity NT, Medtronic or Optima XP, Cobe, Denver, Colorado), a Stockert roller pump (Stockert Instrumente, GmbH, Munchen, Germany), a 37-μm arterial line filter (Medtronic Cardiopulmonary, Anaheim, CA, USA), and a 4:1 blood cardioplegia (Myotherm, Medtronic Cardiopulmonary, Anaheim, CA, USA). The Affinity NT had a membrane area of 2.5 m² and a priming volume of 285 mL. The Optima had a membrane area of 1.9 m² and a priming volume of 262 mL. The pump was primed with 2 L of lactated Ringer’s solution, 2000 IU of Hepalean heparin (Organon Tecknica, Inc), 24 g of mannitol and 100 mL of 8.4% sodium bicarbonate. Oxygen transfer was measured by arteriovenous oxygen difference per FiO₂ and flow. The Trillium Biopassive surface, incorporated into the Affinity NT, is a coating process that involves two polymers. Polymer A strongly bonds to the surface of most materials used for disposable products in OHS and polymer B is then bound to the primer coat and consists of polyethylene oxide chains, sulfonate groups and heparin that are covalently bonded into the coating. A standard heparin dosage of 400 U/kg was administered to each patient. The activated clotting times were measured pre-CPB and every 20–30 min on CPB using Hemochron ACT tubes (International Technidyne Corporation, Edison, NJ, USA). Activated clotting times were maintained above 480 seconds and supplemented with additional heparin.
as needed. Patients received an antifibrinolytic (Amicar or Cyclokapron) as per our routine.

Statistical analysis. Descriptive statistics were used to describe subject characteristics and demographic variables. Categorical variables were analyzed using Chi-square or Fisher’s Exact Test. Continuous variables were analyzed using Student’s \( t \)-test or repeated measures analysis of variance (to assess group-by-time interactions). Multivariate analysis of variance was completed when appropriate. An \( \alpha \leq 0.05 \) was considered significant. Significant differences were evaluated using Scheffe’s post hoc test. Outcomes are reported as mean ± standard deviation unless otherwise noted.

Results

Patient flow
Between January and July 2001, 559 patients were referred for OHS at the Hamilton Health Sciences – General Site and initially considered to be eligible for participation in the study. Of these, 242 were ineligible due to: already in another study (138), scheduled to undergo off-pump surgery (64), weight below 50 kg (12), were not expected to exceed CPB of 45 min (22), had an IABP inserted preoperatively (four), or had low preoperative platelet counts (two). Consequently, 317 patients were approached for participation in the study, of these, 61 declined to participate for language, religious, and personal reasons. Two hundred and fifty-six patients were randomized to the Medtronic Affinity NT (\( n = 128 \)) or Cobe Optima XP (\( n = 128 \)). Three patients were subsequently removed from the study, at the time of surgery, at the request of their surgeon. There were no patient complications or morbidity related to oxygenator performance.

All devices were primed according to manufacturers’ instructions as outlined in the product insert. There were no difficulties encountered in either circuit set up or priming, and there were no patient complications or morbidity related to oxygenator performance.

Subject characteristics
Table 1 outlines subjects’ characteristics. The baseline characteristics were similar between the two groups. Of the 253 patients completing the study, 55 (21.7%) were women, 198 (78.3%) were men and the group had a mean age of 66.5 ± 10.7 years. The type of surgery completed and their relative distributions were similar between the groups and are detailed in Table 2. Isolated CABG surgery was the greatest surgery reported in either group, with 86.7% of Affinity NT and 88.8% of Optima patients undergoing isolated CABG surgery. The use of calcium channel blockers, \( \beta \)-blockers and ACE inhibitors was also similar between the two groups.

Fluid balance
There were no significant differences between the Affinity NT and Optima XP groups for the pump prime volume or for the time on CPB. Fluid balance during surgery was not significantly different (\( p = 0.267 \)). Total fluid volume given to and excreted from the patient was not significantly different among the groups. The total fluid balance likewise was similar in both groups, as were the types and volumes of transfusions given postoperatively. All patients had postoperative pleural and/or pericardial tube bleeding recorded at 6 and 12 hours in the intensive care unit. The mean output for the Affinity NT and Optima XP were 346 ± 277 mL and 353 ± 249 mL, respectively, at 6 hours (\( p = 0.849 \)) and 512 ± 398 mL and 574 ± 441 mL, respectively, at 12 hours (\( p = 0.254 \)). No significant difference was found between the two groups at either time period.

Hematology
Baseline platelets, hemoglobin, hematocrit, and leukocyte levels were similar between the groups (Table 3). A significant main effect for time was found in all blood variables studied (\( p < 0.001 \)). There was a significant decline in leukocytes, hemoglobin, and hematocrit from baseline at each measurement point. This decline was similar for the Affinity NT and Optima oxygenators. A clear rise in platelet count was noted from 15 min to 75 min on CPB (\( p < 0.001 \)) and was similar for both oxygenators. Examination of the data for leukocyte count, hemoglobin, hematocrit, and platelets at each of the time periods measured while on CPB, demonstrated that there were no significant differences between groups, or within group differences for any these variables (Table 3).

Oxygenation blood path resistance
The arterial and venous oxygen content levels were recorded for all patients at each of the measurement time points. The A-VO\(_2\) difference was determined for each patient and compared with respect to fraction of oxygen saturation and rate of flow through the membrane. The oxygen transfer was also recorded and compared with respect to oxygen saturation. There were no significant differences between the two groups for these measures (Table 4 and Figure 1).

The input and output pressures were measured in the first 130 patients in the study. The blood path pressure drop was significantly different between
the two oxygenators (\( p < 0.001 \)). The Affinity NT oxygenator demonstrated a smaller drop in pressure across its membrane at each time point (Table 1). As seen here, the Affinity NT demonstrated a smaller blood path pressure drop from 15 min to 75 min of CPB time (47.5 \( \pm \) 63.0 mmHg at 15 min and 23.4 \( \pm \) 81.0 mmHg at 75 min) than did the Optima (106 \( \pm \) 67.0 mmHg at 15 min and 91.4 \( \pm \) 79.0 mmHg at 75 min). The difference was accompanied by a clear trend for the blood path pressure drop to decrease with time. This trend was similar in both groups.

### Table 1 Subject characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Medtronic Affinity NT</th>
<th>Cobe Optima XP</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male, ( n ) (%)</td>
<td>101 (51.0)</td>
<td>97 (49.0)</td>
</tr>
<tr>
<td></td>
<td>Female, ( n ) (%)</td>
<td>27 (49.1)</td>
<td>28 (50.9)</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>67.12 (10.74)</td>
<td>65.90 (10.76)</td>
<td>0.370</td>
</tr>
<tr>
<td>Height (cm), mean (SD)</td>
<td>170.62 (9.49)</td>
<td>170.41 (8.66)</td>
<td>0.851</td>
</tr>
<tr>
<td>Weight (kg), mean (SD)</td>
<td>81.47 (12.82)</td>
<td>82.91 (14.00)</td>
<td>0.396</td>
</tr>
<tr>
<td>BSA (m(^2)), mean (SD)</td>
<td>1.93 (0.18)</td>
<td>1.94 (0.18)</td>
<td>0.616</td>
</tr>
</tbody>
</table>

BSA: body surface area.

### Table 2 Surgery completed

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Medtronic Affinity NT</th>
<th>Cobe Optima XP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated-CABG</td>
<td>111 (86.7%)</td>
<td>111 (88.8%)</td>
</tr>
<tr>
<td>Combined procedure</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Aortic valve</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Mitral valve</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Redo-CABG</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Tricuspid valve</td>
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<td>1</td>
</tr>
</tbody>
</table>

CABG: coronary artery bypass graft.

### Table 3 Hematology

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time</th>
<th>Medtronic Affinity NT</th>
<th>Cobe Optima XP</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>Baseline</td>
<td>114</td>
<td>15</td>
<td>114</td>
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<tr>
<td></td>
<td>15 min</td>
<td>79</td>
<td>12</td>
<td>78</td>
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<td></td>
<td>45 min</td>
<td>83</td>
<td>13</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>75 min</td>
<td>84</td>
<td>12</td>
<td>83</td>
</tr>
<tr>
<td>Platelets (10(^9)/L)</td>
<td>Baseline</td>
<td>204</td>
<td>62</td>
<td>202</td>
</tr>
<tr>
<td></td>
<td>15 min</td>
<td>137</td>
<td>49</td>
<td>138</td>
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<td></td>
<td>45 min</td>
<td>146</td>
<td>51</td>
<td>149</td>
</tr>
<tr>
<td></td>
<td>75 min</td>
<td>150</td>
<td>57</td>
<td>161</td>
</tr>
<tr>
<td>Leukocytes (10(^9)/L)</td>
<td>Baseline</td>
<td>6.14</td>
<td>1.91</td>
<td>6.24</td>
</tr>
<tr>
<td></td>
<td>15 min</td>
<td>4.30</td>
<td>1.75</td>
<td>3.99</td>
</tr>
<tr>
<td></td>
<td>45 min</td>
<td>5.55</td>
<td>2.23</td>
<td>5.78</td>
</tr>
<tr>
<td></td>
<td>75 min</td>
<td>6.90</td>
<td>3.29</td>
<td>7.85</td>
</tr>
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</table>

**Discussion**

To the best of our knowledge, this is one of the largest randomized controlled trials comparing oxygenators completed to date. The large number of patients recruited allowed for a large degree of statistical power through balanced randomization and resulted in two well-balanced groups being compared. This is demonstrated by the lack of a significant difference between the two groups in demographic variables. The study found that both membrane oxygenators performed well and that there was no difference between the two oxygenators on their effects on blood components during OHS.

The Affinity NT and Optima oxygenators performed similarly with respect to the primary outcome; hence, they both had a similar effect on platelet counts during OHS. The Affinity NT demonstrated an immediate decline in platelets from baseline of 32.7%, a subsequent slow recovery at 45 min of CPB time to 28.5% of baseline and further recovery at 75 min to 26.3%. Accordingly, the Optima XP oxygenator demonstrated a similar pattern, with reductions in platelets from baseline of
remaining in the recirculated blood may lose their ability to aggregate in response to ADP and epinephrine within 2 min of the start of recirculation. Thromboxane B\_2, the stable end product of thromboxane A\_2, appears and progressively increases. Lastly, acid phosphatase, a lysosomal enzyme, is released in progressively increasing amounts during the first 2 hours of recirculation. This physiology suggests that platelets become less adherent and are released from the membrane over time; therefore, improving the resistance of the oxygenator. Taken together, the above might explain the findings of the present study, that platelet levels increased with time on pump after the initial drop from preoperative levels.

The present study also demonstrates a significant reduction in the hematological measures after 15 min of CPB. This reduction persisted at 45 and 75 min and was similar across both groups. This phenomenon may be secondary to a hemodilution effect caused by fluid administration preoperatively, during the monitoring line insertion, during the induction of anesthesia and by the perfusionists during CPB. This finding of a similar effect on blood components by both oxygenators is also supported by the finding of similar levels of postoperative blood loss between the two study groups.

The most critical function of the CPB system is to supply the tissues with oxygen, which is achieved by the membrane of the oxygenator. Factors involved in oxygen transfer include hemoglobin concentration, transit time, diffusion, partial pressure difference, blood path thickness, and membrane characteristics. For the purpose of this study, A-VO\_2 difference and oxygen transfer were used to compare this function in the two oxygenators. No significant differences were found between the Affinity NT and Optima oxygenators for either oxygen transfer or A-VO\_2 difference. A recent study comparing nine oxygenators found that the Affinity NT had significantly higher oxygen transfer than the Optima, although the validity of this study was hampered by its relatively small sample size (90 patients total; 10 for each oxygenator investigated).

### Table 4 Oxygen transfer per FiO\_2

<table>
<thead>
<tr>
<th>Oxygen transfer/FiO_2, 15 min</th>
<th>Oxygenator</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affinity NT</td>
<td>128</td>
<td>148.52</td>
<td>53.78</td>
<td>0.221</td>
<td></td>
</tr>
<tr>
<td>Optima XP</td>
<td>125</td>
<td>140.00</td>
<td>56.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen transfer/FiO_2, 45 min</td>
<td>Affinity NT</td>
<td>127</td>
<td>153.55</td>
<td>50.44</td>
<td>0.278</td>
</tr>
<tr>
<td>Optima XP</td>
<td>122</td>
<td>160.79</td>
<td>54.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen transfer/FiO_2, 75 min</td>
<td>Affinity NT</td>
<td>100</td>
<td>172.70</td>
<td>75.71</td>
<td>0.979</td>
</tr>
<tr>
<td>Optima XP</td>
<td>87</td>
<td>172.94</td>
<td>48.04</td>
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</tbody>
</table>

Figure 1 Arteriovenous oxygen difference.

Figure 2 Pressure drop.
One intriguing finding of the present study was the substantial difference of blood path pressure drop between the two oxygenators (Figure 2). The findings of the present study are supported by the findings of Segers and colleagues, who reported similar trends in the transmembrane pressures of the Affinity NT and Optima oxygenators in their comparison of nine oxygenators, as were found in this study. Although their findings were based on small patient numbers, coupled with the findings of the present study, they support the need for further investigation of this phenomenon and its significance in OHS.

Another study comparing three oxygenators in 26 patients found that the oxygenator with a reduced blood path diffusion distance had a lower blood path pressure drop than the others. The trade-off of increasing gas exchange performance by reducing gas diffusion distances is usually an increase in blood path pressure. Additional studies have examined the relationship between blood path pressure and its adverse effect on blood rheology and found that a correlation is difficult to make without taking the dimensions of the oxygenators and membrane manufacturing into account. Thus, the fact that the two membranes investigated here are constructed differently may play a role in the difference in blood path pressure changes between the two oxygenators observed in the present study.

Our study found that blood path pressure drop decreased with time in both oxygenators. This finding coincided with a rise in platelet count with time on CPB. Palanzo et al. previously demonstrated that platelet trapping and high trans-oxygenator pressures occur when albumin is not used in the pump prime. In fact, the phenomenon of increase in oxygenator inlet pressure due to fibrin formation occurring in the presence of therapeutic ACTs has been well described in the literature. The rise in platelets with time on CPB observed in the present study may have three potential explanations. The first relates to the increase in thromboxane \( \text{B}_2 \) and other platelet aggregation inhibitors with time on the pump as described above. The second relates to rewarming of the patient, potentially leading to the dissolution of cryofibrinogen, thus reducing the impact of the platelet-trapping phenomenon. The third explanation relates to platelet function. If platelets adhering to the oxygenator eventually lose their function and are then released into circulation, this could account for this rise in platelet count.

The present study has several strengths. As the Hamilton Health Sciences – General Site is a tertiary care, university-affiliated institution, serving a large diverse population, the findings of the present study may be readily extrapolated to other cardiac surgical centers across Canada. In addition to this, the large sample size adds power to the overall findings of the study. There are, however, limitations to the present study. First, it is a single institution study and, thus, a sample bias may be reflected in the findings of the study. Secondly, for ethical reasons, we had to exclude patients based on emergent surgery due to their already compromised state. The hemodynamics and pressure characteristics found in this study may not hold true for emergent patients, and the findings cannot be generalized to this patient group.

The Affinity NT was brought to our institution as a replacement for its predecessor, which had no Trillium coating. Several concerns regarding the noncoated Affinity, particularly the clinical finding that its use was consistent with a drop in platelet counts, led to its replacement with the Affinity NT. These concerns were confirmed by the results of an unpublished study at our institution comparing the noncoated Affinity to three other oxygenators in 280 patients. Such concerns were validated by a recently published randomized trial of 98 patients that found the use of the Trillium-coated Affinity oxygenators resulted in improved patient outcomes compared with noncoated Affinity oxygenators. The present study should alleviate any further concerns regarding the Affinity NT.

This study clearly demonstrates that the Medtronic Affinity NT and the Cobe Optima XP oxygenators produce comparable results with respect to their effects on blood components, but were significantly different with respect to the degree of transmembrane pressure drop during OHS using CPB. Future studies should concentrate on platelet function, temperature and transmembrane pressure changes and their effect on the overall outcomes for patients undergoing OHS.

Acknowledgements

The authors would like to acknowledge the surgeons and perfusionists at the Hamilton Health Sciences for their excellent collaboration in this project. This study was funded by a grant from Medtronic of Canada Ltd. The funding agency had no role in the conduct of the study, the analysis of the results or in the decision to submit the manuscript for publication. The authors retain complete scientific independence including design of the study, data collection, analysis, and development of the manuscript.
References

Appendix

Calculations for oxygen transfer (mL/min), arterio-venous oxygen difference and pressure drop (mmHg)

Oxygen transfer (mL/min)
\[ = \left(\left[\text{SaO}_2 - \text{SvO}_2\right] \times \text{Hb} \times 1.34 \times Q_b \times 10\right) \]

(calculated per FiO\textsubscript{2} at each time period).

\[ \text{A-VO}_2 = \text{CaO}_2 - \text{CvO}_2 \]

Pressure drop (mmHg) = Pi – Po

where Pi = inlet pressure (mmHg) and Po = outlet pressure.
CaO\textsubscript{2}: arterial oxygen content (mL \text{O}_2/dL)
CvO\textsubscript{2}: venous oxygen content.