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# Heparin Coated Hollow-Fiber Oxygenator Without Systemic Heparinization in Comparison to Classic Bubble and Membrane Oxygenators

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## Abstract

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**Heparin surface coated hollow-fiber oxygenators and tubing sets were evaluated without systemic heparinization (surface) in comparison to conventional uncoated membrane (plate) and bubble oxygenators and tubing sets with systemic heparinization (ACT > 400 s). Thirteen dogs were perfused for 6 hours with a mean flow of 100 ml/kg min. and either surface (42 ± 9 kg), plate (38 ± 12 kg) or bubble oxygenators (41 ± 18: NS) by cavo-aortic cannulation after median sternotomy. Besides continuous monitoring of hemodynamics, blood samples for blood gas, biochemical and hematological analyses were taken before, after mixing and every 30 minutes thereafter. Throughout perfusion, arterial pH, arterial pCO<sub>2</sub>, arterial pO<sub>2</sub> and venous oxygen saturation could be maintained within normal ranges for the three groups. Plasma hemoglobine, however, was significantly lower in heparin-coated equipment (p < 0.005), which allowed cardiopulmonary bypass without systemic heparinization and therefore without return of shed blood.**

## Introduction

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In recent years, new membrane oxygenators with improved performances have been developed. Furthermore the design of these devices was modified so far that their handling became as simple as that of bubble oxygenators. However, prolonged cardiopulmonary bypass is still limited in time<sup>1</sup> by profuse bleeding and hemorrhage during or after cardiovascular surgery with the pump oxygenator is a common problem.<sup>2</sup> One reason for hemorrhage despite improved

oxygenating devices is the still necessary full heparinization during cardiopulmonary bypass. A very promising approach for reducing the dependence of full systemic heparinization during cardiopulmonary bypass is the development of heparin-linked biomaterials. A first step in this direction appears to be heparin surface coatings as introduced by V. Gott in 1963<sup>3</sup> and simplified by Grode.<sup>4</sup> Nowadays improved heparin surface coatings, either ionic<sup>5</sup> or surface immobilized<sup>6</sup> are available, and heparin surface coating of oxygenators, filters and tubing sets is feasible. The present study was designed to evaluate a heparin surface coated oxygenator without systemic heparinization in comparison to classic bubble and membrane oxygenators with systemic heparinization.

## Materials and Methods

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### *Heparin surface coated oxygenators and tubings*

All blood exposed surfaces of standard hollow-fiber membrane oxygenators (Bentley BOS-CM 40) and standard tubing sets were coated with the Bentley Duraflo II which is a water insoluble complex between heparin and the complex agent alkylbenzyltrimethylammonium chloride of the formula (C<sub>6</sub>H<sub>5</sub> CH<sub>2</sub> N (CH<sub>3</sub>)<sub>2</sub> R) Cl, in which R is a precisely defined C<sub>18</sub> chain length alkyl. The resulting complex is insoluble in water and crystalloid prime solutions and has superior retention on surfaces exposed to the blood. Surface coated venous cannulas, coated venous lines, coated venous reservoirs (Bentley BRM 1900), coated pump loops, coated oxygenators including coated heat exchangers, coated arterial lines, coated arterial filters (25 µm: Bentley AF 1025), coated arterial cannulas, coated connectors and coated stop-cocks were prepared. The Bentley BOS-CM 40 hollow fiber membrane oxygenator is made from microporous polypropylene with blood inside and gas outside of the fibers as reported previously<sup>7</sup>.

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### Classic bubble and membrane oxygenators

The classic Polystan Venotherm VT 5000 bubble oxygenator including heat exchanger, oxygenator and arterial reservoir was used in conjunction with a standard Bentley tubing set as reference for low cost *Bubble* oxygenators.

The integrated Cobe CML membrane oxygenator including an open venous reservoir, heat exchanger and oxygenator was also used in conjunction with a standard Bentley tubing set as reference for *Plate* oxygenators.

### Animals

The study included 13 mongrel dogs. Five animals were assigned to the bubble oxygenator group (mean body weight  $41 \pm 18$  kg), 5 animals were assigned to the plate membrane oxygenator group (mean body weight  $38 \pm 12$  kg), and 3 animals were assigned to the surface heparin coated hollow fiber membrane oxygenator group (mean body weight  $42 \pm 9$  kg; NS). All dogs were premedicated with morphine. General anesthesia was started with pentothal and maintained thereafter.

### Cardiopulmonary bypass

After median sternotomy, heparin was given systemically 3 mg/kg for bubble and plate and activated clotting time (ACT) was maintained at 400 seconds throughout bypass. No heparin at all was given for surface. Ascending aorta and right atrium were cannulated and connected to the respective tubing set and oxygenator which were primed previously with 2000 ml of crystalloid priming solution (Hartmann). Complete hemodilution without transfusion of homologous blood was performed. Blood flow was maintained at 100 ml/kg min. over 6 hours. Gas was delivered to the bubble oxygenator with a back pressure compensated anesthetic rotameter. For the membrane oxygenators gas flows were adjusted with gas blenders recommended by the respective manufacturers.

### Measurement

EKG, central venous pressure (microtip pressure transducer), aortic pressure (microtip pressure transducer), core temperature, arterial and venous temperature were recorded continuously. The microtip pressure transducers (Millar) were used to avoid the otherwise necessary heparin drip to keep the blood pressure monitoring lines patent. A standard battery of blood samples, including hematocrit, total hemoglobin, plasma hemoglobin, red and white blood cell count, thrombocytes, arterial and venous blood gas analysis (AVL), Na, K, and activated clotting time was performed beforehand, five minutes after onset of

cardiopulmonary bypass and every thirty minutes thereafter.

### Data analysis

For hemoglobin and formed elements, the results were corrected for hemodilution by changes in hematocrit. Mean and standard deviation were derived for each parameter for the three groups. Students t-test was used to analyze data for statistical significance ( $p < 0.05$ ).

## Results

All animals could be perfused during 6 hours in accordance to the protocol. Mean pH could be maintained in physiologic ranges in all three groups (Figure 1). Mean pH values varied between 7.40 and 7.48 for the heparin surface coated oxygenator group without systemic heparinization versus 7.32 and 7.50 for the bubble oxygenator group with systemic heparinization versus 7.35 and 7.50 for the plate membrane oxygenator group with systemic heparinization. Similar values were achieved in the 3 groups for partial arterial  $\text{CO}_2$  and partial arterial  $\text{O}_2$  pressures which are depicted in Figures 2 and 3. Mean  $\text{paCO}_2$  values varied between 3.90 and 4.13 for surface, versus 3.43 and 4.20 for bubble, versus 3.2 and 3.8 kPa for plate between 1 and 6 hours of perfusion. Mean  $\text{paO}_2$  values varied between 24.0 and 41.8 for surface, versus 35.6 and 61.4 for bubble, versus 31.6 and 42.2 for plate. Mean venous oxygen saturation ( $\text{SvO}_2$ ) could be maintained above 60% in all three groups for at least five hours of cardiopulmonary bypass (Figure 4). Thrombocyte deple-

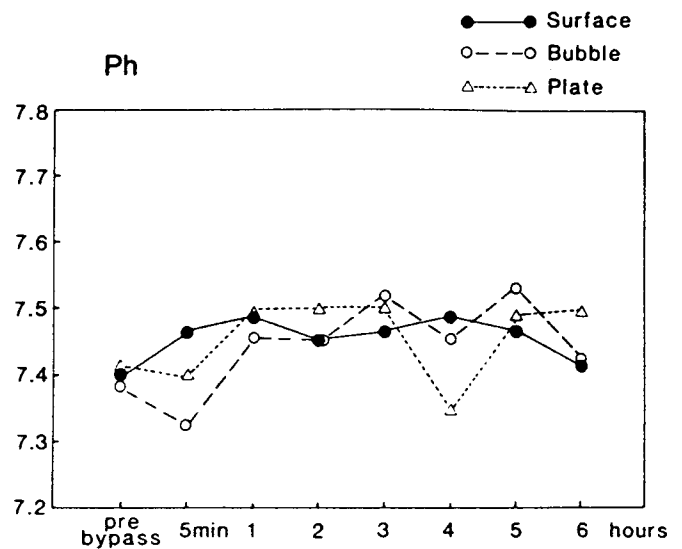


Figure 1: Mean arterial pH values before and throughout the perfusion

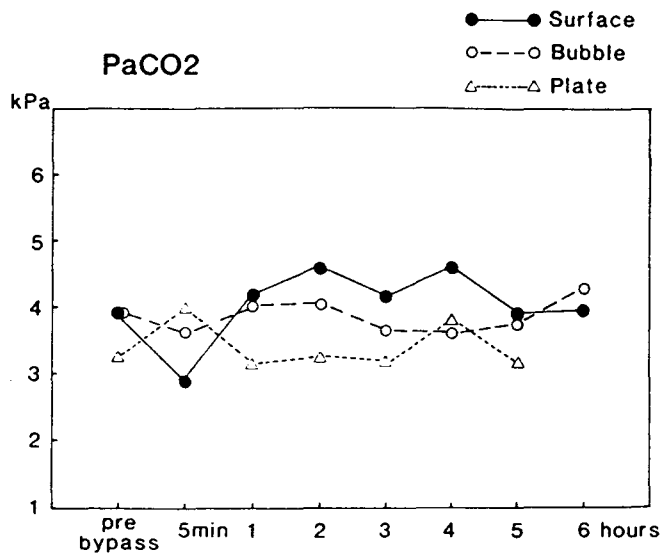


Figure 2: Mean partial arterial CO<sub>2</sub> pressure before and throughout the perfusion

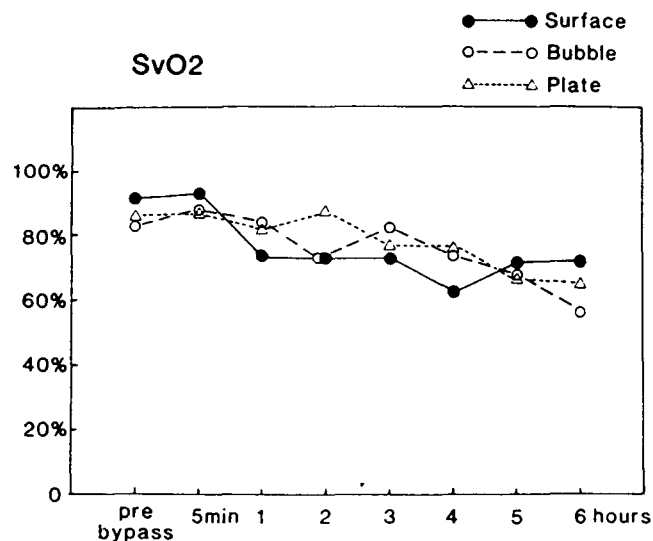


Figure 4: Mean venous O<sub>2</sub> saturation before and throughout the perfusion

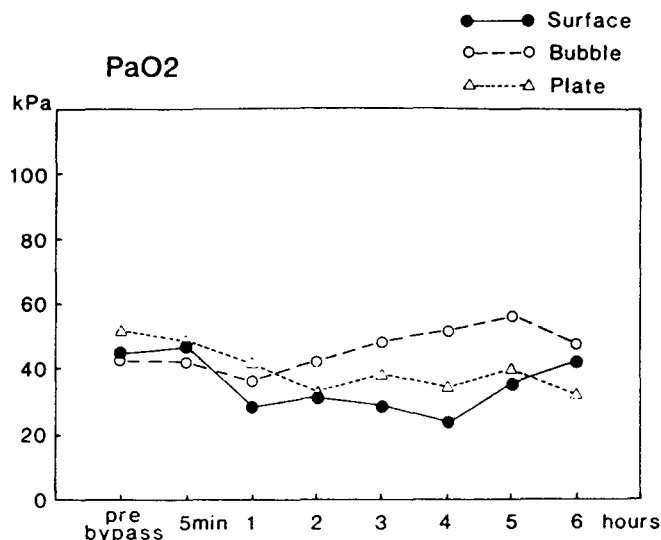


Figure 3: Mean partial arterial O<sub>2</sub> pressure before and throughout the perfusion

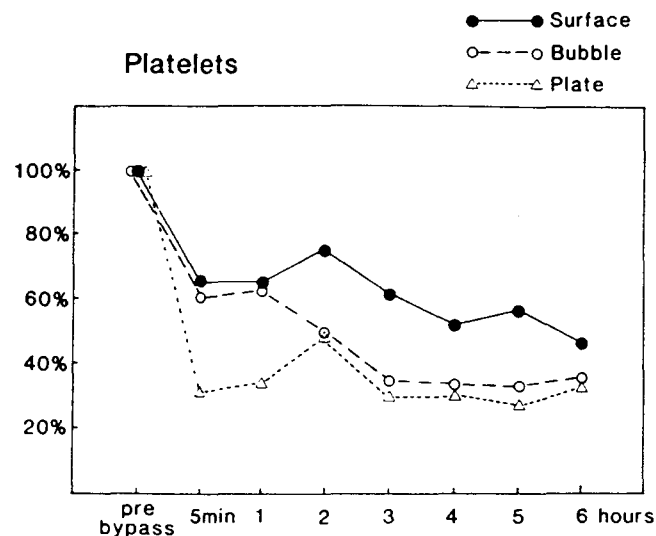


Figure 5: Mean platelet levels before and throughout the perfusion (values are corrected by hematocrit for hemodilution and normalized to prebypass values of 100%)

tion is depicted in Figure 5. All values are corrected for hemodilution and normalized by prebypass values. Thrombocyte depletion is significantly higher for bubble and plate with systemic heparinization versus surface without systemic heparinization. After 3 hours of perfusion, mean thrombocyte level for surface is  $62.0 \pm 8.1\%$  versus  $35.7 \pm 6.5\%$  for bubble ( $p < 0.005$ ) and  $29.3 \pm 10.8$  for plate ( $p < 0.005$ ). There is no significant difference between bubble and plate between 2 and 6 hours of perfusion.

During perfusion, hematocrit passed from  $36 \pm 3\%$  to  $19 \pm 2\%$  for surface,  $38 \pm 7\%$  to  $17 \pm 2\%$  for bubble,

and  $34 \pm 4\%$  to  $15 \pm 5\%$  for plate (Figure 6). Mean free plasma hemoglobin values are depicted in Figure 7. After 2 hours of perfusion there is a significant difference between surface without systemic heparinization versus bubble with systemic heparinization and plate with systemic heparinization (Figure 7). Free plasma hemoglobin levels after 2 hours are for surface  $0.22 \pm 0.08$  g/l versus  $1.00 \pm 0.34$  g/l for plate ( $p < 0.01$ ) and  $1.43 \pm 0.38$  for bubble ( $p < 0.005$ ). The differences increased with time and remained statistically significant. Activated clotting time (ACT) was  $148 \pm 61$  s before,  $179 \pm 6$  s at 1 hour, and  $123 \pm 17$  at 4 hours of

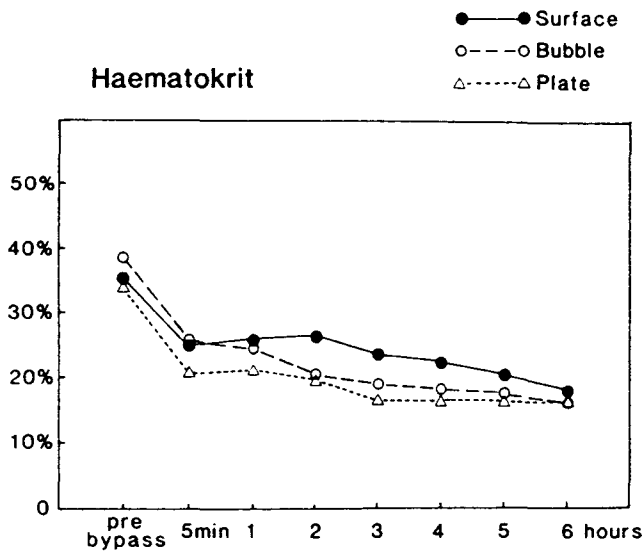


Figure 6: Mean hematocrit before and throughout perfusion

perfusion for surface without systemic heparinization, whereas it was kept above 400 s for plate with systemic heparinization as well as bubble with systemic heparinization.

At the end of perfusion the devices were disconnected and gently rinsed with saline. There were no macroscopic clots in the heparin surface coated hollow fiber membrane oxygenators and heparin surface coated tubing sets which have been used without systemic heparinization and near normal ACT values during perfusion. Bubble oxygenators used with systemic heparinization, and plate membrane oxygenators used with systemic heparinization were also clean at rinsing after perfusion.

## Discussion

Cardiopulmonary bypass without systemic heparinization can be realized by the means of heparin surface coated membrane oxygenators and tubing sets. In the present study, gas exchange of heparin surface coated membrane oxygenators was similar to the one achieved with classic bubble oxygenators and standard plate membrane oxygenators used with systemic heparinization. Throughout perfusion, pH,  $\text{paCO}_2$ ,  $\text{paO}_2$  and  $\text{SvO}_2$  could be maintained in physiologic ranges. There were no significant differences in gas exchange between the three systems tested whether they were heparin surface coated or not (Figure 1-4).

The absence of systemic heparinization and maintenance of near normal activated clotting times (ACT) reduces bleeding during cardiopulmonary bypass so far that the latter can be performed for several hours with open chest but without return of shed blood. The

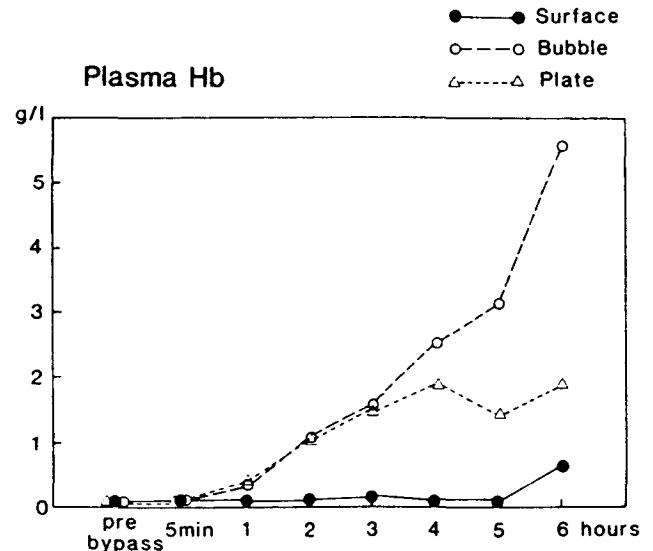


Figure 7: Mean free plasma-hemoglobin levels before and throughout the perfusion (values are corrected by hematocrit for hemodilution)

fact that there is no recirculation of shed blood via the cardiotomy reservoir is reflected by reduced plasma hemoglobin production and platelet depletion in the heparin surface coated group without systemic heparinization.

After 3 hours of perfusion, the thrombocyte level for surface was  $62.0 \pm 8.1\%$  or nearly the double of bubble ( $35.7 \pm 6.5\%$ ;  $p < 0.005$ ) and more than the double of plate ( $29.3 \pm 10.8\%$ ;  $p < 0.005$ ). In a similar way, mean free plasma hemoglobin level after 2 hours was for surface  $0.22 \pm 0.08$  g/l or 22% of plate ( $1.00 \pm 0.34$ ;  $p < 0.01$ ), and 15% of bubble ( $1.43 \pm 0.38$  g/l;  $p < 0.005$ ) (Figure 7).

Despite the absence of systemic heparinization, there was no evidence of clotting in the heparin surface coated oxygenators and tubing sets. Throughout perfusion gas exchange remained unaffected. And after perfusion, the rinsed devices were completely clean without any macroscopic clot in the collapsible venous reservoir, heat exchanger, oxygenator, arterial filter or tubing sets. These results in the heparin surface coated group were achieved with Bentley BOS-CM 40 hollow fiber oxygenators and tubing sets which were coated with the Bentley Duraflo II heparin coating<sup>5</sup>. The Bentley Duraflo II (patent pending) is a water insoluble complex between heparin and the complex agent alkylbenzyltrimethylammonium chloride of the formula  $(\text{C}_6\text{H}_5\text{CH}_2\text{N}(\text{CH}_3)_2\text{R})\text{Cl}$ , in which R is a precisely defined C18 chain length alkyl.

The resulting complex is insoluble in water and crystalloid prime solution and has superior retention on surfaces exposed to blood. The complex agent is retained on the surface as active heparin is slowly

released. The source of the heparin is porcine intestinal mucosa. The Duraflo II coating has to be classified in the group of ionic heparin coatings in accordance to Gott<sup>8</sup> and Kim.<sup>9</sup> However, Duraflo II has solubility and surface absorption properties uniquely different from other described ionic heparin coatings. For example benzalkonium heparin coating (originally described for the Gott shunt<sup>3</sup>) is soluble in crystalloid prime solutions, whereas Duraflo II is not.

Duraflo II coated components for cardiopulmonary bypass are already available for clinical application, as e.g. the Bentley Duraflo II coated arterial filters AF 1025 and AF 1040. The total heparin bound ionically in these filters is about 1000 U per filter, an amount below significance during cardiopulmonary bypass.

In the present study, ACT levels appeared to be near normal for the surface group without systemic heparinization during the first 4 hours of cardiopulmonary bypass. Measurements of free plasma heparin did not show significant heparin washout from the bypass equipment throughout perfusion. To avoid any contamination with heparin, all pressure transducers used were of the microtip type (Millar) which operate without heparin drip. Furthermore all stopcocks and sampling lines were also heparin-coated.

There is a wide range of clinical applications with potential benefits of heparin coated cardiopulmonary bypass equipment not requiring systemic heparinization. Most promising appears the warming-up of hypothermic patients with traumatic lesions. Actually warming-up of severely hypothermic patients by the means of cardiopulmonary bypass<sup>10</sup> is only feasible in absence of major traumatic lesions because of otherwise uncontrollable bleeding after systemic heparinization. Cardiopulmonary bypass without systemic heparinization could be "the" solution for these otherwise non-resuscitable patients.

Furthermore ECMO,<sup>11</sup> and its more recent modifications as LFPPV and ECCO<sub>2</sub>,<sup>12</sup> and mechanical circulatory support by cardiopulmonary bypass<sup>13</sup> could appear to have a very different outcome in the absence of systemic heparinization. Finally, there is cardiac surgery in general which could be quite different if cardiopulmonary bypass without systemic heparinization became available on a large scale. We conclude

that cardiopulmonary bypass with heparin surface coated equipment can be realized without systemic heparinization in dogs. There is no evidence of clotting in the used oxygenators and tubings. Gas exchanges can be maintained throughout perfusion in normal ranges. Further studies are necessary to establish the safety of the heparin surface coated material for clinical application with reduced anticoagulation.

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## Questions from the Audience

*Question:* What is the dissolution rate of the heparin coating off of the bypass circuit? And, have you planned further studies where you will actually be comparing two hollow fiber membrane oxygenators, one coated and one non-coated?

*Answer:* ACT levels measured during perfusion are slightly elevated at the beginning of the bypass. Afterwards, there are longer ACT levels which are not related to heparin washout.