Original Article

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Performance Characteristics of Hemofilters with Heparin Surface Coating: An Experimental Study

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Abstract

Heparin surface coated hemofilters and tubing sets were evaluated in comparison to identical but uncoated controls in 8 bovine experiments (74±6 kg). No heparin was given (neither systemically nor in the priming fluid). The hemofilters were primed with one liter of Ringer's lactate in both groups and the maximal filter performance (arterial line pressure 300 mmHg; transmembrane pressure (TMP) 500 mmHg) was measured over 6 hours or until filter occlusion. All coated and one control filter remained functional during the scheduled 6 hours. The mean filter patency was 360±0 minutes for coated versus 210±99 minutes for uncoated ($p<0.01$). Mean blood flow at 1 hour and 6 hours was 675±114 and 580±96 ml/min for coated versus 432±183 and 25±43 for uncoated (NS; $p<0.01$). Mean filter output during the 6th hour and total filter output over 6 hours was 4225±998 ml and 21779±4273 for coated versus 400±692 and 7717±9757 for uncoated ($p<0.01$; $p<0.01$). Mean lactatedehydrogenase (LDH) levels before and 30 minutes after hemofiltration were 1855±413 IU and 2007±635 for coated versus 2160±411 and 1945±500 for uncoated (NS; NS). The heparin coated hemofilters demonstrated improved thromboresistance resulting in superior filter performance. There was no evidence of increased blood trauma.

Introduction

Hemofiltration (1) during and following cardiopulmonary bypass has proven to be an efficient tool for hemoconcentration in patients undergoing open heart surgery (2). However, the standard hemofilters available today still require a significant degree of anticoagulation to remain functional. Hence, at this time, perfusion with low or no systemic heparinization (3-5) precludes efficient hemofiltration. The present study was designed to evaluate the performance characteristics of heparin coated hemofilters without systemic heparinization.

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Materials and Methods

Animals

Eight calves (74±6 kg bodyweight) were randomly assigned to two groups for hemofiltration either by heparin surface coated hemofilters and heparin coated tubing sets without systemic heparinization (coated) or standard uncoated hemofilters and tubing sets without systemic heparinization (uncoated). Following standardized premedication, general anesthesia was started with thiopenthal sodium and, after endotracheal intubation, maintained with nitrous oxide and halothane. All animals used in the study received humane

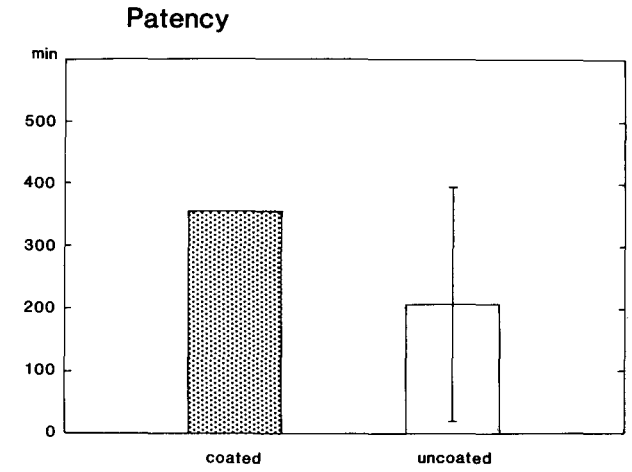

Figure 1
Mean duration of perfusion (± standard deviation) for heparin coated versus uncoated hemofilters ($p<0.01$)

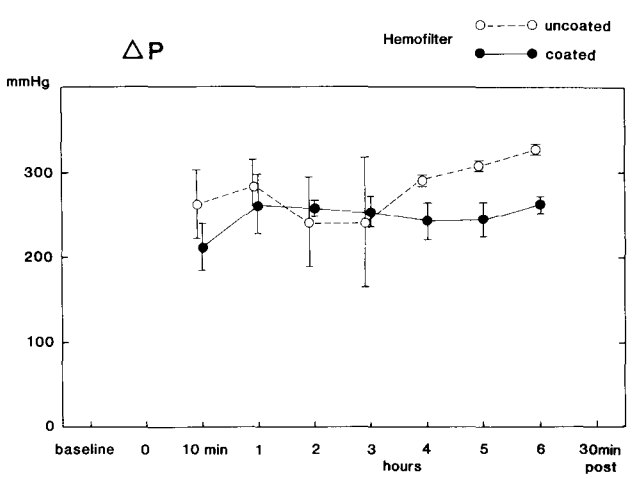

Figure 2
Pressure gradient of blood path measured between inlet and outlet of hemofilters (mean ± standard deviation)

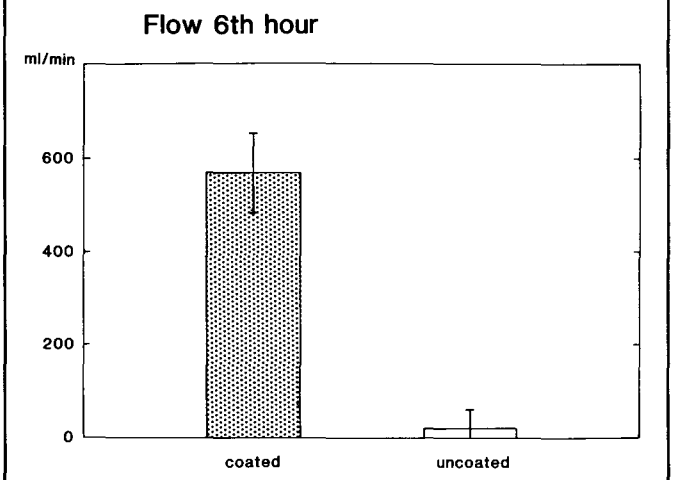

Figure 3
Blood flows (mean±standard deviation) measured after 6 hours for heparin coated hemofilters versus uncoated controls ($p<0.01$)

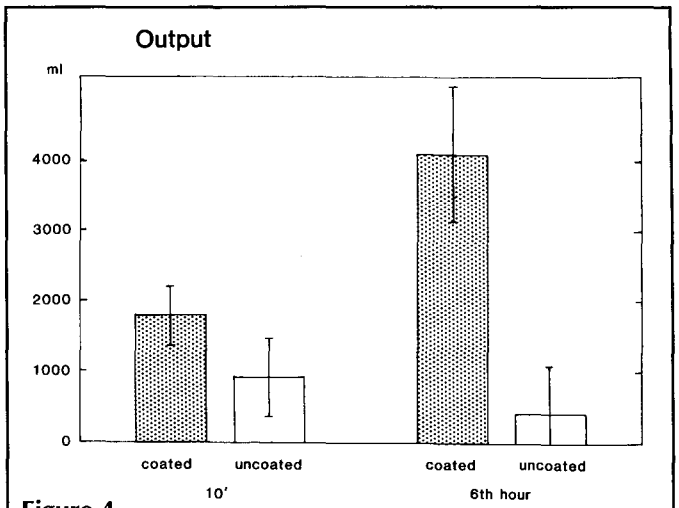

Figure 4
Hemofilter output (mean ± standard deviation) for the first 10 minutes and the 6th hour (coated versus uncoated: $p<0.01$

animal care in compliance with the "Guide for the Care and Use of Laboratory Animals," published by the National Institutes of Health (NIH Publication No. 85-23, revised 1985).

Perfusion Equipment

Hemofiltration equipment consisted of heparin surface coated[a] hemofilters[b] as well as heparin coated cannulas, PVC tubings, polycarbonate connectors and silicone pump loops for the study group (coated) whereas uncoated, but otherwise identical hemofilters and tubing sets were used for the control group (uncoated). A roller pump[c] was used for both groups.

Hemofiltration

Hemofiltration was initiated in standard fashion. No heparin was given systemically. The hemofilters and tubing sets were primed with 1 L of Ringer's lactate and 1000 IU of heparin[d]. Following cervicotomy, the carotid artery and jugular vein were isolated and cannulated. The cannulas were connected

a Duraflo II, Baxter Bentley, Irvine, CA 92714
b Diafilter 30, Amicon, W. R. Grace & Co, Beverly, MA
c Stockert, Munich, Germany
d Liquemin, Roche, Basel, Switzerland

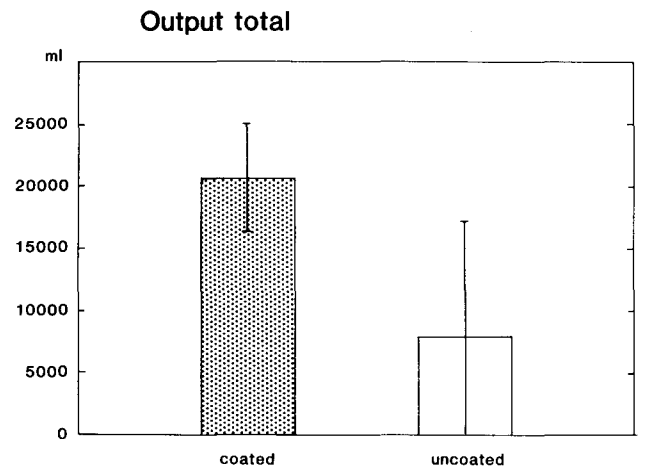

Figure 5
Total output (mean ± standard deviation) for heparin coated versus uncoated hemofilters ($p<0.05$)

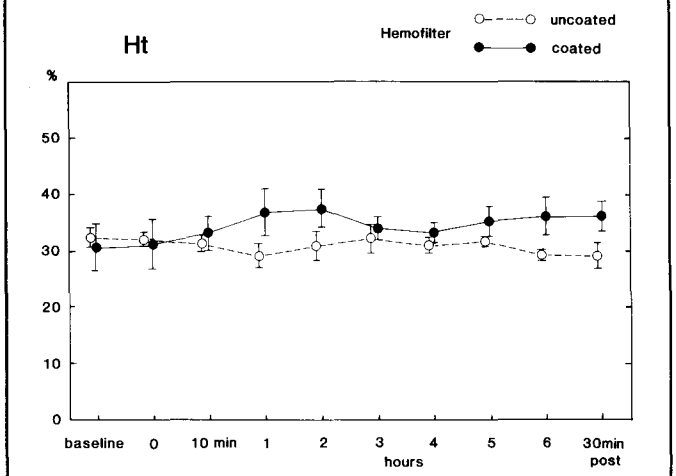

Figure 7
Hematocrit (mean ± standard deviation) for the group perfused with heparin coated hemofilters versus the group with uncoated hemofilters ($p<0.05$)

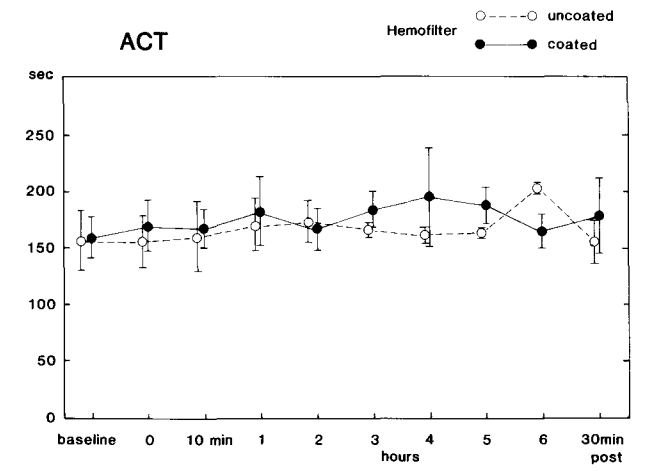

Figure 6
ACT (mean ± standard deviation) for the group perfused with heparin coated hemofilters versus uncoated hemofilters (baseline and 30 min. post: NS)

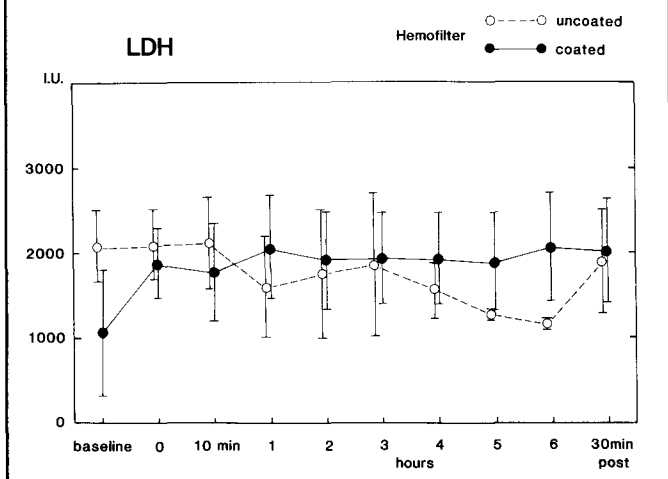

Figure 8
Lactadehydrogenase levels (mean ± standard deviation) for the group perfused with heparin coated hemofilters versus uncoated hemofilters (final value: NS)

to the tubing sets and hemofiltration was started. Arteriovenous hemofiltration with a roller pump proximal to the hemofilter was selected to achieve maximum blood flow (arterial line pressure 300 mmHg; transmembrane pressure (TMP) 500 mmHg). Filter performance under these conditions was measured over 6 hours or until filter occlusion. The following parameters were analyzed: patency, filter pressure gradient (blood path), TMP, blood flow, filter output, activated coagulation time (ACT), hematocrit, and lactatedehydrogenase (LDH)

Data Analyses

Mean and standard deviation was derived for each parameter analyzed in the two groups. Students t-test for unpaired variables was used where applicable to determine statistical significance of data: significance was defined at $p<0.05$.

Results

All coated hemofilters and one uncoated hemofilter remained functional during the scheduled 6 hour study period.

Hence 0/4 coated versus 3/4 control filters occluded completely resulting in a mean patency (Figure 1) of 360±0 min for coated as compared to 210±99 for uncoated ($p<0.01$). Mean filter gradient (blood path) is depicted in Figure 2. It remained below 270 mmHg for coated whereas it increased above 300 mmHg (before the pump was stopped) for uncoated. Mean blood flow at 10 min and one hour was 895±187 ml/min and 675±114 ml/min for coated versus 712±123 ml/min and 432±183 ml/min for uncoated (NS; NS). Mean blood flow at 6 hours is depicted in Figure 3 and accounted for 580±96 ml/min for coated versus 25±43 ml/min for uncoated ($p<0.01$). Hemofilter output is depicted in Figure 4. During the first 10 minutes, 1625±419 ml were filtered with coated hemofilters as compared to 900±555 ml with uncoated hemofilters. Mean filter output during the 6th hour was 4225±998 ml for coated versus 400±692 ml for uncoated ($p<0.01$). Total filter output (Figure 5) over the 6 hour measuring period was 21779±4273 ml for coated as compared to 7717±9757 ml for uncoated. The ACT is depicted in Figure 6. The baseline value was 164±21 sec for coated as compared to 159±25 sec for uncoated (NS). At 6 hours the mean ACT was 163±16 sec for coated as compared 261 sec for the only uncoated hemofilter still remaining patent. The evolution of the hematocrit is depicted in Figure 7. There is no difference between the two groups after cannulation: 31.7±4.9% for coated versus 32.6±1.3% for uncoated). However the value after 6 hours is significantly higher in the group perfused with heparin coated hemofilters (36.9±5.8% for coated versus 29.6±0.0% for uncoated: $p<0.05$). Mean lactatedehydrogenase (LDH) levels are given in Figure 8. The values measured before and after 6 hours were 1855±413 IU and 2007±635 IU for coated versus 2160±411 and 1945±500 IU for uncoated (NS; NS).

Discussion

Improved thromboresistance of heparin coated hemofilters results in superior filter performance. Improved thromboresistance of the heparin coated hemofilters is demonstrated in the present set-up by the absence of hemofilter occlusion during the 6 hour testing period with maximal blood flow. Only one filter of the control group remained patent for the full 6 hour test period. Thus mean duration of perfusion was significantly lower for uncoated devices (Figure 1). Progressive filter occlusion in the control group resulted also in an increasing filter gradient as measured for the blood path of the hemofilter (Figure 2). In contrast, the gradient for the heparin coated filters remained almost constant between 1 and 6 hours of perfusion. As a result of the increasing blood path gradient, the blood flow decreased in the control group and reached after 6 hours only 4.3% of the study group (Figure 3). Interestingly, hemofilter output was already superior for coated during the first 10 minutes when it reached 160% of uncoated (Figure 4). This finding suggests, that the heparin surface coating acted from the very beginning and that the protein layer built on the blood exposed heparin coated surfaces was different from uncoated devices. In the sixth hour, the output for coated hemofilters was tenfold that of uncoated controls. Hence filter output finally totaled after 6 hours, 21.8 L for coated as compared to 7.7 L for uncoated (Figure 5). This equalled over the 6 hour study period a mean filter output of 60 ml/min for coated as compared to 21 ml/min for uncoated. One can further speculate, that the not completely occluded uncoated hemofilter remained only patent because that specific animal had a prolonged activated coagulation time of more than 200 sec as shown in Figure 6. This could be due to contamination of the animal with a heparinized syringe used for blood gas sampling. The increased occlusion rate of uncoated hemofilters was not due to a difference of hematocrit for the two studied groups as shown in Figure 7. The hematocrit was even higher in the group perfused with heparin coated hemofilters that handled therefore successfully a larger cumulated blood cell mass with higher velocity. The constant LDH levels observed for the study group (Figure 8) demonstrate further that there was no major blood trauma despite maximized hemofiltration with blood flows above 500 ml/min for 6 hours in this group. The decrease of the LDH level observed for the control group after 5 hours can be attributed to increasing hemodilution which resulted from decreasing hemofiltration in this group. Hence, heparin coated hemofilters provide superior filter performance without measurable increase of blood trauma. Heparin coated hemofilters with improved thromboresistance and superior filter performance are a further step for development of extracorporeal life support with better biocompatibility. The potential benefits of thromboresistant perfusion equipment that have been shown in the experimental set-up with low or no systemic heparinization include superior hemostasis (3, 4), reduced blood loss (3,4), superior hemodynamics (4), better preservation of renal function and attenuated hormonal response (6). Improved thromboresistance of heparin coated perfusion equipment has been confirmed by other groups (7-9). However, a number of thromboresistant components are still lacking. Only recently, heparin coated cardiotomy reservoirs with improved thromboresistance became available (10). In the meanwhile, a number of clinical applications of heparin coated cardiopulmonary bypass equipment have been evaluated in selected cases with low systemic heparinization (5, 11). Under extreme conditions, i.e. accidental deep hypothermia with cerebral trauma, perfusion without systemic heparinization at all was successfully performed (12, 13). However, when the standard hemofilters used for reduction of serum potassium (14) were used with heparin coated cardiopulmonary bypass equipment without systemic heparinization, they had to be changed several times because of clotting. Hence, lack of

thromboresistant hemofilters, proved to be a major problem in this situation and triggered further research. The development of thromboresistant hemofilters for clinical application is therefore a necessity that will improve not only hemofiltration in patients undergoing cardiopulmonary bypass but also in patients with bleeding problems after cardiothoracic surgery, general surgery, major trauma or long term hemofiltration (15, 16) in general.

References

1. Henderson LW, Besarab A, Michels A, Bluemle Jr LW. Blood purification by ultrafiltration and fluid replacement (diafiltration). Trans Am Soc Artif Int Organs. 1967; 13: 216-226.
2. von Segesser LK, Garcia E, Lachat M, Turina M. A convertible cardiopulmonary bypass system for optimized hemofiltration. Proceedings 28th International Conference American Society of Extra-Corporeal Technology. Dallas, April 6-10, 1990: 68-71.
3. von Segesser LK, Turina MI. Cardiopulmonary bypass without systemic heparinization: Performance of heparin coated hollow fibre membrane oxygenators without systemic heparinization in comparison with classic membrane and bubble oxygenators. J Thorac Cardiovasc Surg. 1989; 98: 386-396.
4. von Segesser LK, Weiss BM, Turina MI. Perfusion with heparin coated equipment: Potential for clinical use. Seminars in Thoracic and Cardiovascular Surgery. 1990; 2: 373-380.
5. von Segesser LK, Weiss BM, Garcia E, Gallino A, Turina M. Reduced blood loss and transfusion requirements with low systemic heparinization: preliminary clinical results in coronary artery revascularization. Eur J Cardio-thorac Surg. 1990; 4: 639-643.
6. Weiss BM, von Segesser LK, Vetter W, Gautschi K, Pasch T. Heparin-coated left heart bypass: renal function and hormonal response. Int J Artif Organs. 1991; 14: 792-799.
7. Toomasian IM, Hsu LC, Hirschl LB, Heiss KF, Hultquist KA, Bartlett RH. Evaluation of Duraflo II heparin coating in prolonged extracorporeal circulation. ASAIO Trans. 1988; 34: 410-414.
8. Hsu LC. Heparin-coating of bypass circuits: principles of heparin coating techniques. Perfusion. 1991; 6: 209-219.
9. Tong SD, Rolfs MR, Hsu LC. Evaluation of Duraflo II heparin immobilized cardiopulmonary bypass circuits. ASAIO Trans. 1990; 36: 654-656.
10. von Segesser LK, Pasic M, Leskosek B, Garcia E, Turina M. Heparin coated cardiotomy reservoirs with improved thromboresistance: Experimental evaluation ex vivo. Les Cahiers du CECEC. 1991; 36: 9-16.
11. von Segesser LK, Weiss BM, Garcia E, Turina MI. Clinical application of heparin coated equipment with special emphasis on patients refusing homologous transfusions. Perfusion. 1991; 6: 227-233.
12. von Segesser LK, Garcia E, Turina M. Perfusion without systemic heparinization for rewarming in accidental hypothermia. Ann Thorac Surg. 1991; 52: 560-561.
13. von Segesser LK, Weiss BM, Garcia E, von Felten A, Turina MI. Reduction and elimination of systemic heparinization during cardiopulmonary bypass: Experimental basis and clinical application. J Thorac Cardiovasc Surg. 1992: in press.
14. Cross DA. The use of a hemoconcentrator for management of sudden acute hyperkalemia during hypothermic cardiopulmonary bypass. J Extra-Corp Technol. 1992; 24: 33-35.
15. Quellhorst E, Shunemann B, Hildebrand U. Morbidity and mortality in long-term hemofiltration. ASAIO Journal. 1983; 8: 185-191.
16. Baldamus C, Quellhorst E. Outcome of long-term hemofiltration. Kidney International. 1985; 17: 41-46.