Cardiopulmonary Bypass Without Systemic Heparinization for 24 Hours

Ludwig von Segesser, MD and Marko Turina, MD

Clinic for Cardiovascular Surgery
University Hospital, Zürich, Switzerland

Key words: Cardiopulmonary bypass, prolonged cardiopulmonary bypass, cardiopulmonary bypass without systemic heparinization, heparin surface coating for cardiopulmonary bypass

ABSTRACT

Cardiopulmonary bypass without systemic heparinization was realised by means of heparin surface COATED oxygenators and tubing sets and analysed in comparison to UNCOATED oxygenators and tubing sets with systemic heparinization (ACT>400s). Seven dogs were perfused for up to 24 hours (when perfusion was electively terminated) with a pumpflow of 50 ml/min/kg bodyweight and either heparin surface COATED equipment (34±5 kg) or UNCOATED equipment (40±7 kg) by cavo-aortic cannulation after median sternotomy. Besides continuous monitoring of hemodynamics, blood samples for blood gas, biochemical and hematological analyses were taken before, FIVE minutes after beginning of cardiopulmonary bypass and at regular intervals thereafter (see chart on page 82).

Mean duration of perfusion was 23±2 hours for COATED versus 20±5 hours for UNCOATED. Adequate gas exchange was obtained with COATED and UNCOATED equipment throughout the perfusion. Plasma hemoglobin production was significantly lower with COATED equipment which allowed open-chest cardiopulmonary bypass without return of shed blood for 13±1 hours.

INTRODUCTION

Heparin continues to be an essential drug in clinical cardiopulmonary bypass. This is mainly due to the poor biocompatibility of today's oxygenators and tubing sets, which are built from materials primarily suitable for industrial production. Despite the fact that new, more biocompatible materials are under development,[1] the fully thromboresistant cardiopulmonary bypass equipment is not yet available. In the meantime, heparin surface coating[2] appears to be a valid approach for improved biocompatibility of existing oxygenating devices. We have previously demonstrated that open chest, high flow cardiopulmonary bypass without systemic heparinization can be realized in dogs by the means of heparin surface coated equipment.[3,4] These experiments showed unaffected gas-exchange capacity of heparin surface coated membrane oxygenators during six hours of perfusion. Furthermore, the heparin surface coating effectively prevented clotting of oxygenators and tubing sets despite the absence of systemic heparinization.

The present study was designed to evaluate prolonged open chest cardiopulmonary bypass without systemic heparinization by means of heparin surface coated cardiopulmonary bypass equipment.

MATERIALS AND METHODS

Heparin surface COATED oxygenators and tubing sets

All blood exposed surfaces of standard hollow-fiber membrane oxygenators[a] and standard tubing sets were COATED with Bentley Duraflo II as reported previously.[4,5,6] The water insoluble complex was made from heparin (porcine intestinal mucosa) and the complex agent alkylbenzyldimethylammonium chloride of the formula (C_6 H_5 CH_2 N (CH3) 2 R) CL, in which R is a precisely defined C18 chain length alkyl. The heparin surface COATED tubing sets included a flexible venous reservoir[b] and an arterial filter.[c]

UNCOATED control oxygenators and tubing sets

UNCOATED, but otherwise identical heart lung packs including a flexible venous reservoir,[b] a hollow fiber membrane oxygenator,[a] and an arterial filter[c] were used for perfusion in the control group.

ANIMALS

The study included seven mongrel dogs. Three animals were assigned to the group COATED (mean body weight: 34±5 kg) and four animals were assigned to the group UNCOATED (mean body weight: 40±7 kg). All animals were premedicated with morphine sulfate. General anesthesia was started with pentothal (thiopental sodium) and maintained thereafter with volatile anesthetics.

CARDIOPULMONARY BYPASS

After a midline sternal splitting incision, heparin was given systemically (Liquemin Roche: 300 I.U./kg bodyweight) for UNCOATED and activated clotting time (Hemochron Technidyne: ACT) was maintained at 400 seconds throughout

Address correspondence to: Ludwig von Segesser, M.D., Clinic for Cardiovascular Surgery, University Hospital, CH-8091 Zurich, Switzerland

a., b. and c. American Bentley Inc., Irvine, CA

bypass. No heparin at all was given for COATED. Ascending aorta and right atrium were cannulated in standard fashion and connected to the respective tubing sets and oxygenators which were primed previously with 2000 ml of crystalloid priming solution (Ringers Lactate). Cardiotomy suction was used throughout perfusion for UNCOATED with systemic heparinization while it was avoided as long as possible for COATED without systemic heparinization. Gasflows were adjusted with a gas blender.[d] Pumpflow was started at 50 ml/min/kg bodyweight and maintained as long as possible. Cardiopulmonary bypass was electively terminated after 24 hours.

MEASUREMENTS

EKG, central venous pressure (microtip pressure transducer), arterial pressure (microtip pressure transducer), core temperature, arterial and venous temperatures were recorded continuously. The microtip pressure transducers[e] were used to avoid heparin drip to keep the blood pressure monitoring lines patent. A standard battery of blood samples, including hematocrit, total hemoglobine, plasma hemoglobin, red and white blood cell count, thrombocytes, arterial and venous blood gas analyses (AVL), Na, K and activated clotting time was performed beforehand, five minutes after onset of cardiopulmonary bypass, and every hour therafter.

DATA ANALYSES

For plasma hemoglobin, the results were corrected for hemodilution by changes in hematocrit. Mean and standard deviation was derived for each parameter of the two groups. Students t-test and GLM-ANOVA (Solo BMDP software) were used where applicable to analyze data for statistical significance ($p<0.05$).

RESULTS

In accordance with the protocol, open chest perfusion was maintained as long as possible and electively terminated after 24 hours. Mean duration of perfusion was 23±2 hours for COATED versus 20±5 hours for UNCOATED.

Mean arterial pH values could be maintained in physiologic ranges in both groups (**Figure 1**). The mean pH values were 7.4±0.1 at eight hours and 7.4±0.0 at 16 hours for COATED without systemic heparinization versus 7.4±0.1 and 7.4±0.1 respectively for UNCOATED with systemic heparinization (NS). Similar values were achieved in the two groups for $PaCO_2$ pressures which are depicted in **Figure 2**. The mean $PaCO_2$ was 3.9±0.5 kPa at eight hours and 3.9±0.4 kPa at 16 hours for COATED versus 4.0±0.6 kPa and 4.1±0.4 respectively for UNCOATED (NS). The curves for PaO_2 pressures are somewhat different as shown in **Figure 3**. The mean PaO_2 pressures for COATED were 32±10 kPa at eight hours and 38±8 kPa at 16 hours versus 28±8 kPa and 26±6 kPa respectively for UNCOATED. The lower values in the latter group are mainly due to one fully heparinized animal in which adequate oxygenation was not possible after 12 hours of perfusion when venous oxygen saturation dropped from 41% to 23% at 14 hours, despite increased pumpflow (100 ml/min/kg bodyweight). Hematocrit (**Figure 4**) dropped from 37.6±3.2% to 26.0±4.5% after five minutes of perfusion for COATED versus 39.5±6.1% to 24.7±3.8% for UNCOATED (NS). Hematocrit during perfusion was 18±1% after eight hours and 17±2% after 16 hours for COATED without systemic heparinization versus 22±5% and 20±3% respectively for UNCOATED with systemic heparinization (**Figure 4**). Return of shed blood was not necessary during 13±1 hours of open chest perfusion for COATED whereas it was necessary throughout the perfusion for UNCOATED. Plasma hemoglobine levels (**Figure 5**) were 0.2±0.0 before bypass and 0.3±0.0 at 8 hours for COATED versus 0.2±0.0 and 1.3±0.4 respectively for UNCOATED ($p<0.005$). ACT levels (**Figure 6**) were 140±10 before, 164±12 after eight hours and 215±65 at 16 hours for COATED wheras they were kept at 400s for UNCOATED. At the end of perfusion, the devices were disconnected and gently rinsed. There were no macroscopic clots in the hollow fiber oxygenating section of the surface coated oxygenators perfused for 24 hours. However some clots were observed in the heat exchanger section (**Figure 7**) as well as in the venting area of the flexible venous reservoir. No macroscopic clots were observed on the arterial side of the oxygenator.

DISCUSSION

Prolonged cardiopulmonary bypass (up to 24 hours) can be realized in an open chest dog model without systemic heparinization by means of heparin surface coated equipment. Gas exchange of the heparin surface coated oxygenators is similar to the uncoated control oxygenators. Throughout perfusion, pH, $PaCO_2$, and PaO_2 could be maintained in adequate ranges for animals perfused by the means of heparin surface COATED equipment without systemic heparinization. This is in contrast to the problems observed with oxygenation in 1/4 animals of the control group after 10 hours of perfusion by UNCOATED equipment with systemic heparinization in spite of increased pumpflow.

The absence of systemic heparinization in the group perfused with COATED equipment and maintenance of relatively low ACT levels reduces bleeding so that open chest cardiopulmonary bypass could be maintained over 13±1 hours without return of shed blood and without transfusion of homologous blood components. The fact that there is no recirculation of shed blood via a cardiotomy reservoir is reflected by the reduced plasma hemoglobin production in the heparin surface COATED group perfused. For similar baseline values in the two groups, plasma hemoglobin levels were after eight hours of perfusion 0.3±0.0 g/l for COATED versus 1.3±0.4 g/l for UNCOATED. This difference is highly significant ($p<0.005$) and further increases up to the 12th hour of perfusion before transfusion of shed blood is started. Despite the absence of systemic heparinization, there is no evidence of clotting in the oxygenating section of the oxygenator and on its arterial side. Some degree of clotting occurred, however, in the heat exchanger section of the oxygenator (**Figure 7**) and in the venous reservoir.

d. Sechrist, Anaheim, CA
e. Millar, Houston, TX

These findings are in contrast to our previous findings with high flow perfusion without systemic heparinization for 6 hours in canine experiments.[3,4] In the earlier series, which was performed with identical surface coated equipment and mean pumpflow of 4.1 l/min, there were no macroscopic clots after rinsing the coated devices, despite even lower ACT levels during at least four hours of perfusion. In the present series lasting over 24 hours, mean pumpflow was 1.7 l/min and therefore only 41% of the previous series. The low blood velocity in the large flexible venous reservoir resulting in stagnant flow may be responsible for the clots found not only in the venous reservoir and in the heat exchanger section of the oxygenator. Similar observations have been previously reported for heparin surface coated equipment used in partial veno-venous bypass for extracorporeal carbon dioxide elimination.[7] This localized problem, however, may be solved by improved design of the stagnant flow areas in today's cardiopulmonary bypass equipment. The surface coating leads to an efficient antithrombotic surface as shown previously in canine experiments where heparin surface coated equipment was replaced after six hours of perfusion with uncoated equipment which clotted immediately.[5]

In conclusion, surface coating of cardiopulmonary bypass equipment leads to improved biocompatibility and allows prolonged perfusion without systemic heparinization in open chest canine experiments with improved results.

REFERENCES

1. Connolly RJ, Anderson JM, Kambic HE, Greisler H, Merril EW.: Small diameter vascular prostheses. *Trans Am Soc Artif Intern Organs* 34: 1043-1046, 1988.
2. Gott VL, Whiffen JD, Datton RC.: Heparin bonding on colloidal graphite surfaces. *Science* 142: 1297-1298, 1963.
3. von Segesser L. Determination of significant differencies in performance of the Bentley BOS-CM 40 hollow fiber membrane oxygenator and the Polystan VT5000 venotherm bubble oxygenator. Perfusion 2: 289-295, 1987.
4 von Segesser LK, Turina M.: Heparin coated hollow-fiber membrane oxygenator without systemic heparinization in comparison to classic bubble and membrane oxygenators. *Proceedings AmSECT* (Anaheim March 11-14, 1988): 76-80.
5. von Segesser LK, Turina M.: Cardiopulmonary bypass without systemic heparinization: Performance of heparin coated oxygenators in comparison to classic bubble and membrane oxygenators. *J. Thorac Cardiovasc Surg*: 98: 386-396, 1989.
6. Balding D, Clarke RC.: An analysis of performance characteristics for the AF1040 C and AF 1025 Duraflo heparin coated arterial filters Abstract-book: 11è *Journèes du CECEC*, Paris, June 20-21,1986: 26.
7. Bindslev L, Eklund J, Norlander O, Swedenborg J, Olsson P, Nilsson E, Larm O, Gouda I, Malmberg A, Scholander E.: Treatment of acute respiratory failure by extracorporeal carbon dioxide elimination performed with a surface heparinized artificial lung. *Anesthesiology* 67: 117-120, 1987.

FIGURE 1 - Mean arterial pH values ± standard deviation before and throughout 24 hours cardiopulmonary bypass

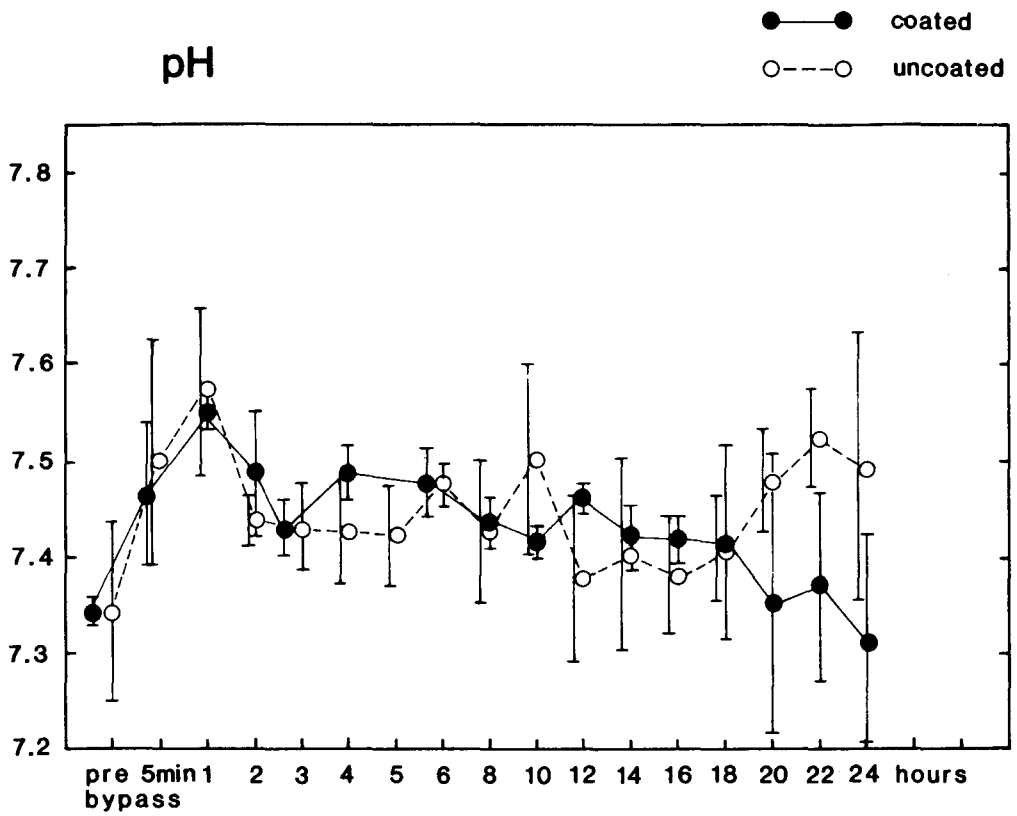

FIGURE 2 - Mean partial arterial CO2 pressures ± standard deviations before and throughout 24 hours cardiopulmonary bypass in kPa

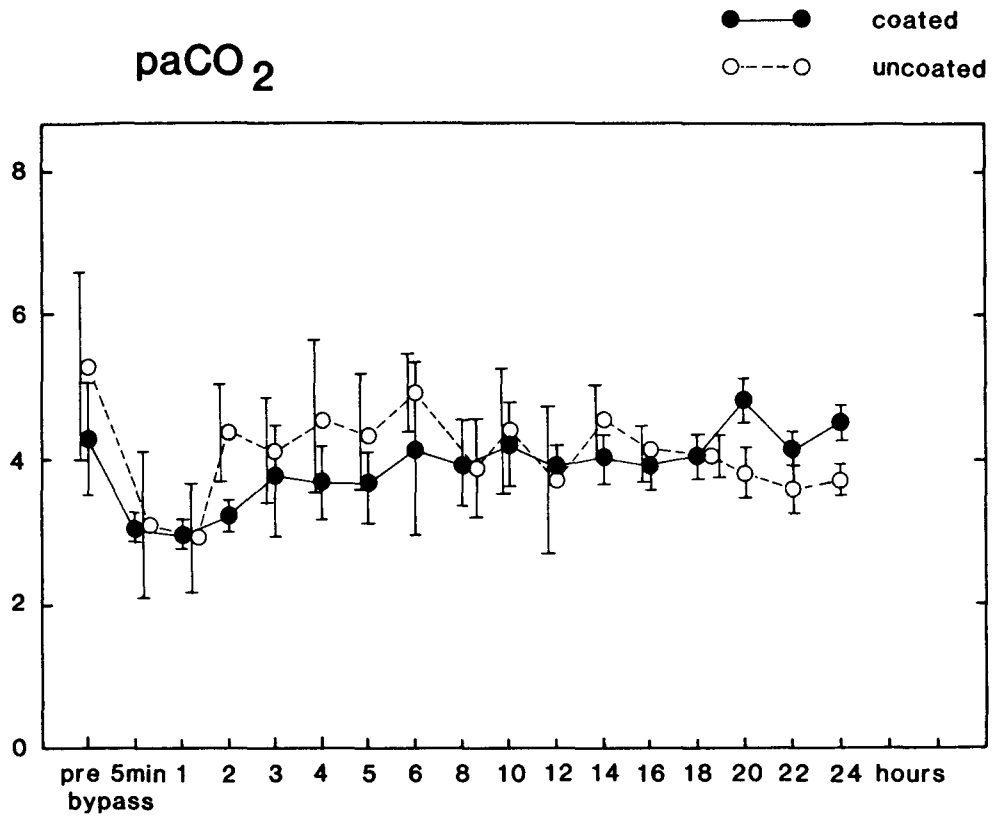

FIGURE 3 - Mean partial arterial O2 pressures ± standard deviations before and throughout cardiopulmonary bypass in kPa

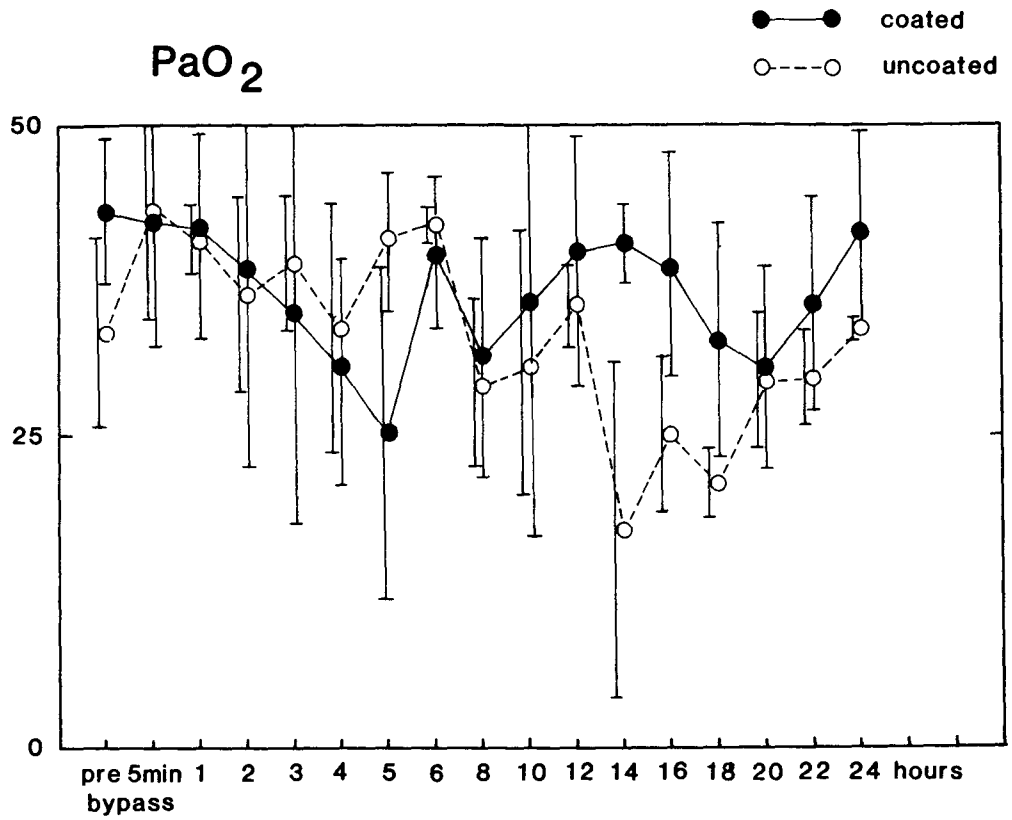

FIGURE 4 - Mean hematocrit ± standard deviations before and throughout cardiopulmonary bypass in %.

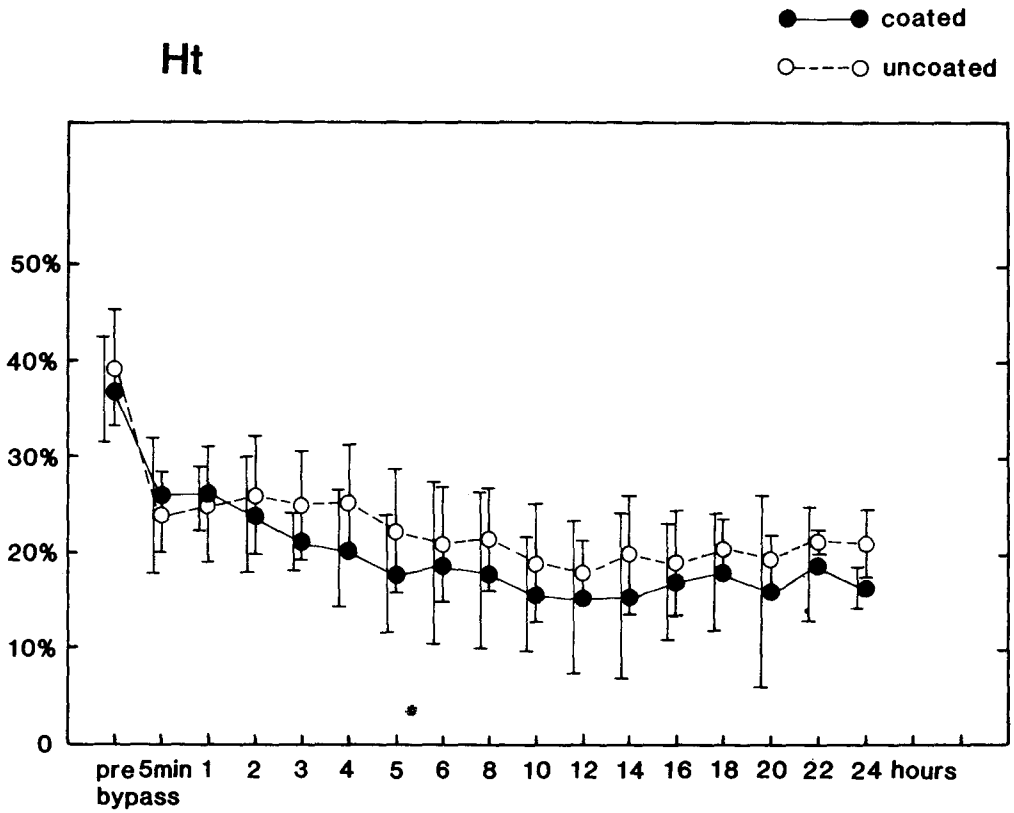

FIGURE 5 - Plasma hemoglobine production in g/l during cardiopulmonary bypass before onset of cardiotomy suction in group COATED. Values ± standard deviations are corrected for hemodilution by prebypass hematocrits.

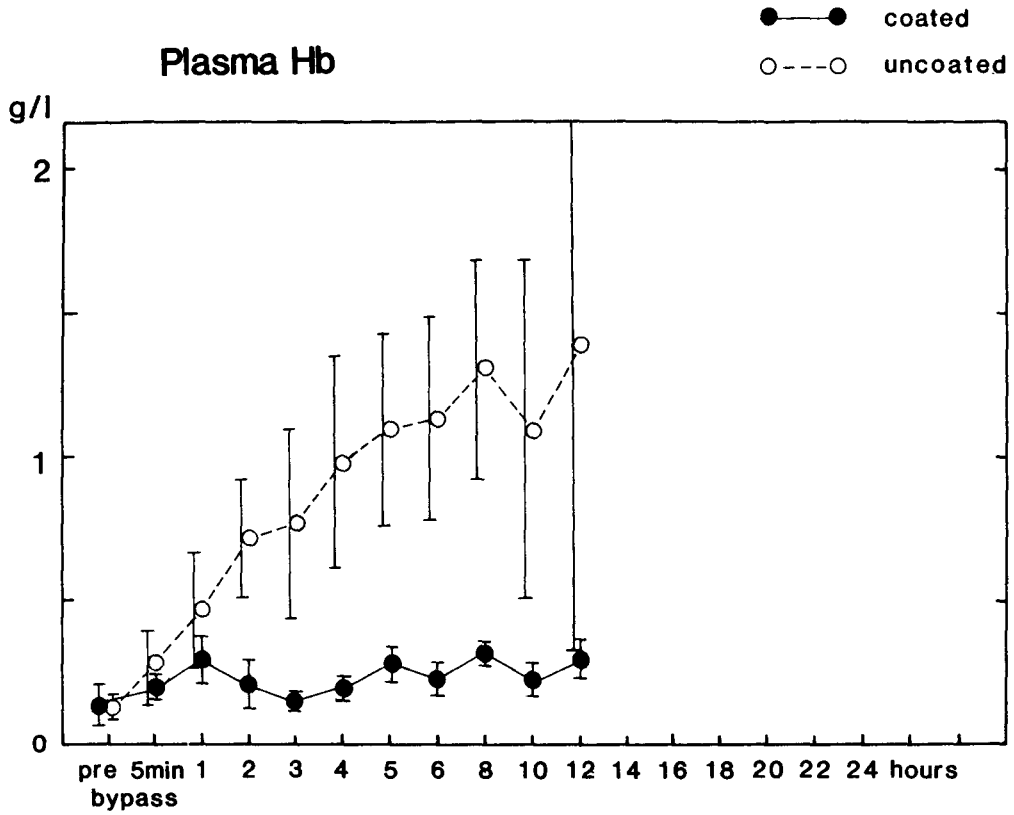

FIGURE 6 - ACT levels ± standard deviations in seconds for COATED before and during 16 hours of cardiopulmonary bypass.

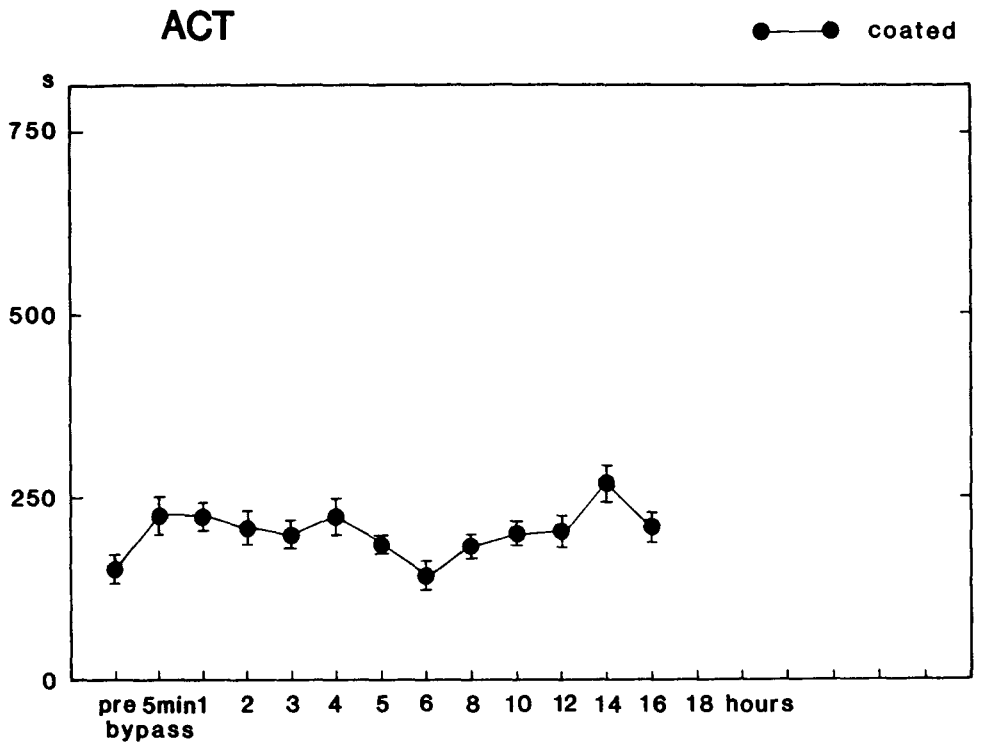

FIGURE 7 - Heparin surface coated hollow fiber membrane oxygenator rinsed after 24 hours cardiopulmonary bypass without systemic heparinization. Note clean oxygenating section (no dark occluded hollow fibers) and clots in heat exchanger section of the device.

	5 Minutes		8 Hours		16 Hours	
	Coated	**Uncoated**	**Coated**	**Uncoated**	**Coated**	**Uncoated**
pH	7.5±0.1	7.5±0.1	7.4±0.1	7.4±0.1	7.4±0.0	7.4±0.1
paCO2 kPa	3.1±0.0	3.2±0.1	3.9±0.5	4.0±0.6	3.6±0.4	4.1±0.4
paO2 kPa	43±11	44±7	32±10	28±8	38±8	26±6
Plasmahe-moglobine g/l	0.2±0.0	0.2±0.0	0.3±0.0	1.3±0.4	p<0.005	