Coagulation Patterns in Perfusion with Low Systemic Heparinization

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Abstract

Cardiopulmonary bypass (CPB) with heparin coated perfusion equipment was realized in 13 patients undergoing myocardial revascularization with either low (ACT>180) or full systemic heparinization (ACT>480). Blood samples for coagulation and other studies were drawn before, after heparin, and at regular intervals during and after CPB.

We conclude, that low dose systemic heparinization (16% of full) resulted in adequate anticoagulation during perfusion with heparin coated equipment and in reduced blood loss.

Introduction

Improved biocompatibility and increased thromboreistance of heparin coated perfusion equipment has been shown in experimental cardiopulmonary bypass (CPB) (1-3) as well as in roller and centrifugal pump left heart bypass (LHBP) (4, 5). After successful clinical application of heparin coated perfusion equipment in surgery of thoraco-abdominal aortic aneurysms (6) we have evaluated heparin coated CPB equipment with low systemic heparinization during coronary artery revascularization procedures (7). This latter study showed reduced blood loss and transfusion requirements in patients perfused with low systemic heparinization. The present study was designed to evaluate the coagulation patterns during clinical perfusion with low systemic heparinization.

Patients and Methods

CPB with heparin coated equipment was realized in 13 patients undergoing elective myocardial revascularization. Standardized surgical techniques were used (8). Informed consent was obtained from the patients to be included in the study who were randomly assigned to two groups perfused either with low (activated coagulation time (ACT)>180) or with full systemic heparinization (ACT>480).

Cardiopulmonary bypass

Heparin coated CPB equipment (Duraflo II: Baxter, Bentley Division, Irvine, CA, USA) was used for both groups as follows: coated venous two stage cannula, coated venous line, coated flexible venous reservoir (Bentley BRM 1900), coated pump loop, coated heat exchanger oxygenator structure (Bentley BOS CM-50) coated arterial filter (Bentley AFC 1040), coated arterial line, and coated arterial cannula. An uncoated standard cardiotomy reservoir was installed in both groups. It was routinely used in the group perfused with full systemic heparinization (ACT>480 s) and kept ready for emergencies only in the group perfused with low systemic heparinization (ACT>180 s). All-crystalloid priming with Ringer's lactate solution was used in both groups. CPB was started and carried out in standard fashion. Moderate hyperthermia, pericardial cooling, and potassium rich cardioplegia were employed for myocardial protection. In the group receiving low systemic heparinization, the aortic root was vented directly into the venous line of the pump oxygenator avoiding cardiotomy suction. To avoid stagnation of the blood in the perfusion system, recirculation through a shunt in the operating field was started immediately after weaning. After perfusion, all oxygenators and tubing sets were gently rinsed and carefully inspected.

Group low: ACT>180 s

In patients perfused with heparin coated equipment and low systemic heparinization, the loading dose of hepa-
In patients perfused with heparin coated equipment and full systemic heparinization, a heparin loading dose of 300 IU/kg body weight and 5000 IU/L priming volume was employed. ACT was kept above 480 s during CPB. Routine cardiotomy suction and retransfusion of oxygenator sump blood were used. Protamin equivalent to 300 IU of heparin/kg body weight was given after CPB. Additional doses of Protamin were given if ACT did not return to preoperative levels.

### Group full: ACT > 480 s

In patients perfused with heparin coated equipment and full systemic heparinization, a heparin loading dose of 300 IU/kg body weight and 5000 IU/L priming volume was employed. ACT was kept above 480 s during CPB. Routine cardiotomy suction and retransfusion of oxygenator sump blood were used. Protamin equivalent to 300 IU of heparin/kg body weight was given after CPB. Additional protamin was given if ACT did not return to the preoperative level.

### Anesthesia, monitoring and analyses

Standard anesthetic (flunitrazepam, fentanyl, pancuronium) and monitoring techniques (electrocardiogram, central venous and arterial catheters, urinary catheter and temperature probes) were used in both groups of patients. Perfusion pressure was monitored before and after the heat-exchanger/oxygenator structure. Blood samples were drawn for routine blood gas analyses, hematological, biochemical and the coagulation studies before CPB, 5 min after heparin administration, 10 min after beginning of cardiopulmonary bypass (including first dose of cardioplegic solution = mixing), 60 (45) min after the beginning of CPB, after protamin administration, and 60 minutes later. Blood samples for coagulation studies were transferred without delay in citrated, silicone coated tubes on ice and processed immediately. Standard clinical tests were used for determination of coagulation patterns including measurement of activated coagulation time (ACT: Hemochron, International Technidyne, Edison, NJ, USA), thrombin time (TT: first dilution was performed with 4 U of thrombin/mL: Roche, Basel, Switzerland), prothrombin time (PT: Thromborel S, Behringwerke, Marburg, Germany), read on a standard curve established with serial dilutions made from a pool of normal human plasma), activated partial thromboplastin time (PTT reagent, Behringwerke AG, Marburg, Germany), fibrinogen levels (chronometric method), ethanol test and D-dimer levels (latex agglutination test with a monoclonal antibody: Boehringer Mannheim GmbH, Germany).

### Data analyses

Quantitative data are presented as mean ± standard deviation. Students t-test for paired and unpaired variables and analysis of variance (GLM-ANOVA) were used where applicable for determination of statistical significance (p<0.05).

### Results

Similar base line characteristics were observed in the two groups for age (63±10 years for low versus 59±6 years for full: NS), body weight (69±11 kg for low versus 72±5 kg for full: NS), body surface area (1.81±0.14 m² for low versus 1.82±0.12 m² for full: NS), hypothermia (28±3 °C for low versus 29±1 °C for full: NS), duration of CPB (69±19 min for low versus 62±13 min for full: NS), crossclamp time (40±14 min for low versus 35±8 min for full: NS), mean number of bypasses (3.0±0.8 for low versus 3.1±0.6 for full: NS) and mean number of internal thoracic artery (ITA) anastomoses (1.0±0.6 for low versus 0.9±0.3 for full: NS). All patients survived the procedure and are well. Mean ACT measured before, during and after CPB are depicted in figure 1. The prebypass ACT was 118±6 s for low versus 112±13 s for full (NS). After heparin the ACT moved to 249±26 s for low versus 412±71 s for full and the first value on bypass was 251±31 for low versus 436±54 for full (p<0.05 in accordance to the protocol). In the group perfused with low systemic heparinization the ACT remained fairly constant throughout perfusion and reached 230±19 s after 60 min without additional heparin dose whereas additional heparin doses were necessary in the group perfused with full systemic heparinization and the final ACT on bypass was 594±287 s. Sixty minutes after protamin the ACT was 110±11 s for low versus 109±7 s for full (NS). The heparin dose given for low totalized 8029±1580 IU versus 51100±8863 IU for full (p<0.001) whereas the protamin dose given for low totalized 6840±970 IU versus 29500±3740 IU for full (p<0.001).

Mean PTT measured are depicted in figure 2. The baseline value was 38±4 s for low versus 35±2 s for full (NS). After heparin, PTT moved to 44±4 s for low versus 45±4 s for full. Whereas the highest for low was observed after mixing (64±8 s for low versus 63±8 s for full) the peak occurred for full after 60 minutes of CPB (56±9 s for low versus 94±3 s for full (NS)). After protamin, 47±7 s were measured for low versus 49±6 s for full (NS). Evolution of TT is shown in figure 3. Similar baseline TT (14±1 s for low versus 14±1 s for full: NS) was followed by 200 s for low versus 200 s for full from the onset of systemic heparinization till at the end of perfusion. After protamin, TT was 32±15 for low versus 12±90 for full (p<0.05). The final TT was 19±6 for low versus 19±6 for full (NS).

Mean PT is depicted in figure 4. The baseline value was 99±4 % for low versus 99±2 % for full. After heparin, 74±5 % was measured for low versus 71±2 % for full (NS). After mixing, 47±4 % was observed for low versus 50±10 % for
full (NS) whereas it was 51±6 % for low versus 37±13 % for full (p<0.05) after 60 min of CPB. Following protamin, 63±7 % was measured for low versus 53±9 % for full (p<0.05) and the final value was 74±5 % for low versus 71±11 % for full.

Mean fibrinogen levels are depicted in figure 5. The baseline levels measured were 3.1±0.3 g/L for low versus 3.0±0.4 g/L for full (NS). During CPB, 1.4±0.1 g/L was measured for low versus 1.3±0.3 g/L for full after mixing and 1.6±0.2 g/L for low versus 1.2±0.2 g/L for full (p<0.01) after 60 min. After protamin, the fibrinogen level was 1.8±0.2 g/L for low and 1.4±0.2 g/L for full (p<0.01).

All ethanol tests performed during and after CPB were negative. Mean D-dimer levels are depicted in figure 6. Baseline values were below 0.5 mg/L for low and full (NS) and remained fairly constant up to 60 min of CPB (<0.5 mg/L for low versus <0.5 mg/L for full: NS). After protamin, the mean D-dimer level measured was 0.6±0.5 mg/L for low versus 1.1±0.6 mg/L for full (NS).

Blood loss on day one totaled 0.3±0.1 L/m² for low versus 1.1±1.0 L/m² for full (p<0.05).

No device failure occurred and no increase in oxygenator gradient was documented during cardiopulmonary bypass.

At inspection, there were no macroscopic clots in the oxygenating compartments. Isolated hollow fibers were occluded in both groups at a similar degree. All arterial filters were clean.

Comments

Cardiopulmonary bypass for clinical coronary artery revascularization can be realized with heparin coated perfusion equipment and low systemic heparinization. The protocol selected for low systemic heparinization (heparin priming dose 1000 IU/L, loading dose 100 IU/kg body weight, ACT>180 s) appears to result in adequate anticoagulation during perfusion with heparin coated cardiopulmonary bypass equipment as documented by the measured coagulation patterns. In the group with low systemic heparinization, ACT was maintained above 180 s in accordance to the protocol throughout the perfusion whereas it was maintained above 480 s in the group with full systemic heparinization (fig. 1). No additional heparin was necessary for low.

PTT showed similar values after low and full dose of heparin as well as at the beginning of perfusion. After 60 min of CPB however, mean PTT measured for low was 56±9 s versus 94±63 s for full (p<0.1). This difference is not significant because of to important scatter in the group perfused with full systemic heparinization. However, important scatter of PTT is typical in measurements of high values. In both groups the TT was 200 s or longer for the first dilution throughout cardiopulmonary bypass. This finding documents significant anticoagulation for full as well as for low systemic heparinization. After protamin however, the group perfused with low systemic heparinization showed a significantly lower TT as compared to full (32±15 s for low versus 126±90 s for full: p<0.05). This finding in conjunction with ACT returning to the baseline level, higher PT values, and higher fibrinogen levels documents the superior hemostatic potential after perfusion with low systemic heparinization. Considering the lower total heparin (16% of full) and protamin (23% of full) doses the significantly lower blood loss observed in the group perfused with low systemic heparinization (0.3±0.1 L/m² for low versus 1.1±1.0 L/m² for full: p<0.05) is no surprise.

Despite the increased hemostatic potential in the group perfused with low systemic heparinization all devices remained functional during and after the procedure. There was no oxygenator failure, increase in oxygenator gradient or decrease in gas or heat exchange detected. Obstruction of isolated hollow fibers of the oxygenators can be observed after perfusion with low as well as with full systemic heparinization. It can be the result of repairs of the device. The latter are routine during hollow fiber oxygenator manufacturing (exclusion of leaking fibers by occlusion of their end). Absence of subclinical coagulation in the blood path of the patient and the perfused devices was documented by normal ethanol tests and normal D-dimer levels for the group perfused with low systemic heparinization (fig. 6). The fact that the D-dimer levels measured are slightly higher in the group perfused with full systemic heparinization is probably due to the routine use of the cardiotomy reservoir in this group, which is a known challenge for formed and unformed elements of the blood. Interestingly the values observed in both groups were well below those observed by Moretz et al. (9) who reported peak values of 8 mg/L and higher. However there was only a weak correlation between low ACT and rise in D-dimers in their study. Reduction of systemic heparinization during CPB was also suggested by Metz and Keats (10) who concluded, that the adequate ACT level for perfusion with standard equipment is probably below 400 s.

We conclude from our study, that acceptable coagulation patterns occur during cardiopulmonary bypass with heparin coated perfusion equipment and low systemic heparinization. The selected approach allows to achieve a significant reduction of systemic heparin and protamin application resulting in a marked reduction of postoperative blood loss. However, several rules have to be respected very strictly during cardiopulmonary bypass with low systemic heparinization:

1. Standard, not heparin coated, elements in the perfusion circuit have to be avoided.
2. Close monitoring of perfusion system, perfusion parameters and ACT is necessary throughout the procedure.
3. Cannulas must be vented just before onset of perfusion.
4. Stagnant blood has to be avoided during and after the procedure (this includes immediate recirculation after weaning from CPB).
References


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Questions and Comments

Steve Raskin, Houston, Texas
Q. Did you notice any problem of leaching of the heparin off the materials? What about any prolonged cardiopulmonary bypass due to a leaching later on, because I notice your pump runs are about 60 minutes? What if you have an extended period like two to two and one-half hours?
A. Well, we have animal data using the same equipment for 24 hours and it works too, but we have no human data for the moment and I am not so keen to get them.

Ace Adams, Mobile, Ala.
Q. You said you heparinized your circuity. What technique did you use to do this and did you have any way of measuring what the uptake was on the equipment?
A. Well, this circuit here is a commercially available circuit from Bentley. You can order it and get it coated. Everything is coated.

Q. Do you have any way of knowing how much heparin is in the equipment? Do they publish anything in that regard?
A. Well, I don’t know for the whole circuit; I know for the arterial filter the amount given is less than 1,000 units, but that’s what is on the circuit. That’s not what’s going to go into your perfusion. We have measured previously in a number of other studies the potential of leaking of heparin and that was not measurable in quantity. But, it is true this coating is an ionic coating where you have some wash out of the heparin that is there but for short applications — let’s say six hours — in our point of view that doesn’t matter.

Q. The fact that the system was heparinized when you bought it means you have no way of knowing how much was left after the bypass was finished?
A. We have performed a lot of animal studies with this equipment and therefore we know the heparin washout that you can get from the system is not significantly measureable.

Gary Stems, Providence, R.I.
Q. My question is in regard to you mentioning there was no system failure. First of all, I would like to know how you determine that, and second, how you measured the delta across your lung. Was there any increase delta in the low heparinized patients?
A. We have measured gradients over the perfusion and we have not found any increase in trans-oxygenater gradient. We know from previous (not human) studies that gas exchange remains constant over 24 hours.

Victor Carcipolo, Cleveland, Ohio
Q. I noticed on one slide you have post-60 minutes into bypass the ACT range seemed to be quite different from that of the linear effect of the previous ACT. Could that be from the heparin slough or washout and what are your platelet survival on these particular heparin coated circuits?
A. The ACT in the group that used low systemic heparinization starts at a mean value of about 230 or something like that. For one hour of perfusion you have a small drop to maybe 210 or something like that for the mean value. The ACT is decreasing, not increasing. We have done bleeding tests in other studies and we found that the bleeding time is reduced; we found that the platelet numbers are better preserved than when you do not have full systemic heparinization, but we didn't do specific platelet activity tests.

Q. Can you comment on a wonder drug now being used in the European community clinically: the proteinase inhibitor aprotinin, and its possible application either toward coating the circuit or in some way treating concurrently with patients who have gotten heparin coated circuits? Following up on hemostasis whether you believe that this may or may not affect blood loss from cardiac surgery, there is just phenomenal data that's out.

A. At our institution it is routine to use aprotinin. We are going on to study the combination of coated equipment and aprotinin. We have done some animal tests which show that it is feasible to do both things together. What we don't know yet is if there is any benefit to combining these, because if one imagines that both treatments act through surface interaction, you might see no difference. What we can say now is that you can use heparin coated equipment and aprotinin in the animal model without any problem.

Bill Watson, Houston, Texas

Q. Could you comment a little on your suction techniques? You'd mentioned that you use a passive drainage for your low heparinization patients. Could you elaborate a little more on that, please?

A. The problem in cardiopulmonary bypass for cardiac surgery with low systemic heparinization is that there is no functional cardiotomy reservoir available yet that you can use safely with low systemic heparinization. You have at this time to use some alternative methods for blood recovery. We use the cell saver or autotrans equipment. For left venting, you must have some solution, too, and we use gravity drainage for the study group instead of cardiotomy suction.

Q. You use gravity drainage back into your venous line?

A. Yes. Gravity drainage is connected directly to the venous line. The only problem is that you should try to avoid getting air in there.

Craig Vocelka, Seattle, Wash.

Q. First, can you address the cost effectiveness issue using this tubing, and second, one of your last recommendations was full heparinization if necessary — what is your indication to fully heparinize the patient during bypass?

A. At this time the cost was no issue. What we want to know is if you can perfuse with low systemic heparinization as we believe the amount of heparin we give today is no good for the patients and the protamin required afterward is worse, so cost was no issue. We think if we can show and others can show that you can improve perfusion as it was shown with membranes, the industry will find a way to produce these devices at a reasonable price. Cardiac surgeons are used to having cardiotomy suctions ready so if they get into trouble with cannulation they should not hesitate to heparinize the patient immediately and to use standard techniques.
Figure 3. Thrombin time (s) before, during and after CPB (mean ± standard deviation)

Figure 4. Prothrombin time (%) before, during, and after CPB (mean ± standard deviation)

Figure 5. Fibrinogen (g/L) before, during and after CPB (mean ± standard deviation)

Figure 6. D-dimer levels (mg/L) before, during and after CPB (mean ± standard deviation)