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Original Article

Soluble endothelial adhesion molecules during paediatric cardiovascular surgery with or without cardiopulmonary bypass

Pavel Osmancik,[1] Jörg Hambsch,[2] Peter Schneider,[2] Wilfried Bellinghausen,[3] Attila Tarnok[2]

[1]Cardiac Centre, University Hospital Kralovske Vinohrady, Charles' University, Prague, Czech Republic; [2]Department of Paediatric Cardiology; [3]Clinic of Anaesthesiology, Cardiac Centre, University Leipzig, Germany

Abstract *Background:* Paediatric cardiovascular surgery with or without cardiopulmonary bypass induces a complex pattern of pro- and anti-inflammatory responses. It is suspected that they may contribute to changes on the vascular endothelium. The endothelial response to cardiosurgical trauma and cardiopulmonary bypass, especially in children, has yet to be well established. *Patients and methods:* We studied 29 children undergoing cardiovascular surgery with cardiopulmonary bypass, comparing them with 21 not undergoing bypass. The groups did not differ significantly with respect to age, sex, weight and preoperative parameters. Blood samples were drawn 24 h before surgery, after onset of anaesthesia, after onset of cardiopulmonary bypass and after rewarming in those undergoing bypass, or immediately after surgery in the control group, 4 h and 2 days after surgery, at discharge, and months after surgery during out-patient follow-up. Serum levels of soluble E-selectin, P-selectin and P-selectin glycoprotein ligand-1 were measured by enzyme-linked immunoassay. *Results:* Paediatric cardiovascular surgery leads perioperatively to the significant decreases of the serum levels of soluble P- and E-selectin, as well as of soluble P-selectin glycoprotein ligand-1 (all $p < 0.05$). The time course, and all concentrations, of these molecules were not significantly different with and without bypass. The decreases, however, were more pronounced with cardiopulmonary bypass. Preoperative baseline values were reached months after surgery. *Conclusion:* Endothelial activation of release of adhesion molecules is reduced during paediatric cardiovascular surgery. Endothelial activity is more perturbed with cardiopulmonary bypass and for a long time after surgery.

Keywords: E-selectin; P-selectin; PSGL-1; endothelium; coarctation of aorta; atrial septal defect

The trauma of cardiovascular surgery, especially with the use of cardiopulmonary bypass, induces distinct pro- and anti-inflammatory responses which are characterised by activation of inflammatory pathways and alterations of the mediators of the immune system such as cytokines, growth factors and complement.[1] This complex inflammatory cascade may contribute to the development of postoperative complications, including pulmonary or renal dysfunction, bleeding disorders, neurologic dysfunction, and altered hepatic function. It can ultimately lead to failure of multiple organs. Leukocytic extravasation is held responsible to be one of the causes of these events.[2–5]

Selectins are a family of three adhesion molecules (L-, E- and P-selectin) specialised in capturing leukocytes from the bloodstream. This initial contact with cells is selectin-mediated rolling of leukocytes on the endothelial cell surface. It represents the first step in a cascade of molecular interactions that lead to leukocytic activation, extravasation, and transmigration into the extravascular tissue.[6,7] All three selectins

Correspondence to: Dr Attila Tarnok, Paediatric Cardiology, Cardiac Centre Leipzig, Russen Str. 19, D-04289 Leipzig, Germany. Tel: +49 (0)341 8652430; Fax: +49 (0)341 8651143; E-mail: tarnok@medizin.uni-leipzig.de

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are responsible for rolling, but only E-selectin and P-selectin are expressed on endothelial cells.[7,8]

E-selectin mediates adhesion of neutrophils distinct from that mediated through integrins, and is of considerable importance for binding the neutrophils to the endothelium.[6,9] The increase in expression of E-selectin on the endothelium, and the release of its soluble form into the serum, are indicators of endothelial activation.[9] High concentrations of soluble E-selectin are found in a broad range of inflammatory processes, such as sepsis or systemic inflammatory disease.[10] P-selectin is stored in the α-granule of resting platelets, and in the Weibel-Palade bodies of endothelial cells. It can rapidly reach the surface of the cell upon activation.[11,12] P-selectin supports binding of leukocytes to platelets and endothelium through P-selectin glycoprotein ligand-1 expressed on circulating leukocytes.[13,14]

Although both endothelial selectins are very alike in their molecular structure, their kinetics of expression are quite different. P-selectin is synthesised constitutively, and is translocated to the platelet surface within minutes after stimulation by a variety of mediators, such as thrombin, histamine, complement components, hydrogen peroxide, and proinflammatory cytokines.[7] It promotes the immediate attachment and rapid rolling of circulating leukocytes.[15,16] Its expression on the cell surface is short lived and declines substantially within minutes.[17] E-selectin is transcriptionally regulated and appears on the activated endothelium within hours after activation. It produces slower rolling of leukocytes, which is important for their subsequent firm attachment.[16] After stimulation by interleukin-1α or tumour necrosis factor-α expression of E-selectin peaks within 4–6 h, declines to basal levels by 1–2 days, and then requires new synthesis of messenger ribonucleic acid and protein.[18] In contrast to different kinds of stimulation of the selectins, the inhibition of their expression on the membrane is similar. The most potent inhibitor of expression is interleukin-10. Other anti-inflammatory cytokines, such as the antagonist to the interleukin-1 receptor, nonetheless, can also inhibit their expression.[19]

A number of glycans with both small and large molecular weights bind to the selectins via an epitope displayed by the sialyl Lewis(x) tetrasacharide and related structures. This is a physiologically relevant component of recognition which is common to all three members of the selectin family.[20] Structurally diverse ligands, such as E-selectin ligand-1, or P-selectin glycoprotein ligand-1, bind the selectins with apparent high affinity. P-selectin glycoprotein ligand-1 is perhaps the best characterised of these ligands, with the highest affinity for both E- and P-selectin. It is expressed by almost all subsets of leukocytes.[15,21] Mice deficient for P-selectin glycoprotein ligand-1 exhibit a severe reduction in the rolling of cells mediated by P-selectin, demonstrating the importance of this ligand during life.[22]

Most studies that tried to understand the adverse postoperative outcome of patients undergoing cardiac surgery with cardiopulmonary bypass when compared to patients undergoing surgery without bypass have been focused on the role of neutrophils and their activation or deactivation.[23–26] The findings are controversial. Fewer studies have focused on the endothelium and changes of its activity during cardiovascular surgery.[27,28] The changes of circulating soluble adhesion molecules have been documented in adults, where the concentration of soluble E-selectin has been shown to decrease during cardiovascular surgery with cardiopulmonary bypass.[27] In children, different changes of soluble adhesion molecules during surgery with cardiopulmonary bypass have been documented,[2,29] but no study compared the endothelial response to cardiac surgery with and without cardiopulmonary bypass. The aim of the present study, therefore, was to investigate and compare the sequels of soluble endothelial adhesion molecules in children undergoing cardiovascular surgery with and without cardiopulmonary bypass.

Patients, materials and methods

Patients and surgery

The ethical committee of the University of Leipzig approved the study and written informed consent was obtained from the parents of all patients. We studied 50 children who underwent elective cardiovascular surgery to repair congenital heart defect in the Cardiac Centre Leipzig between 1995 and 1999. Criterions for inclusion were surgery for atrial or ventricular septal defect, coarctation of aorta or persistent arterial duct, and age greater than 3 years. Criterions for exclusion were any severe genetic defect such as trisomy 21, or absence of obtained informed consent from the parents.

We analysed 29 children who underwent a cardiovascular operation with bypass. The group included 22 undergoing correction of atrial, and 7 of ventricular septal defects. The other 21 children had surgery without cardiopulmonary bypass, 16 for correction of coarctation of the aorta, and 5 for closure of a persistent arterial duct.

During admission before surgery, no anaesthetic premedication was used. The children received only weight-related doses of crystalloid and glucose solutions. Induction and maintenance of anaesthesia was comparable for all patients with respect to weight-related doses of midazolam, fentanyl, etomidate and pancuronium. All those undergoing bypass received

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methylprednisolone intraoperatively, 125 mg being given about 40 min after onset of the anaesthesia. No child received any histamine-1 or histamine-2 receptor blockers. The extracorporeal circuit was managed in a standardised manner. Cardiopulmonary bypass was performed with a roller pump (Stoeckert-Shiley, Munich, Germany) and hollow-fibre oxygenator (DIDECO, Mirandola, Italy). Mild hypothermia, to about 32°C body temperature, was induced by cooling the priming solution of crystalloid solution, mannitol, and Iono-lactate in the extracorporeal circuit, and the circulating blood with the heat exchanger. Haemodilution during surgery was to approximately 30% as judged by the decrease of blood haematocrit levels. The utilisation of blood was based on the haematocrit. During the period of cooling, all patients received nitroglycerol for vasodilation. Bretschneider's cardioplegic solution was used for myocardial perfusion. Anticoagulation was obtained with an initial dose of sodium heparin of 300 U/kg before cannulation of the caval veins, and was monitored by activated clotting time. At the end of cardiopulmonary bypass, heparin was neutralised by protamine, giving 1 mg for each 100 units of heparin.

Postoperative care

In those undergoing bypass, median stay in the intensive care unit was 1 day, with a range from 1 to 4 days. All patients received immediately postoperatively dopamine at a dose of 2–3.5 ug/kg/min. Dobutamine or adrenalin in weigh-dependent doses were given to 20 children. In those not having bypass, the median stay in the intensive care unit was again 1 day, with a range from 1 to 3 days. Three patients with postoperative hypertension received weight-dependent doses of sodium, nitropruside, urapidil, or clonidinhydrochloride. No catecholamine support was needed in those not undergoing bypass.

Collection of blood samples

Blood samples were drawn into coagulation tubes one day before surgery and any medication as a baseline, after onset of anaesthesia, 10–30 min after the onset of the cardiopulmonary bypass, at the end of rewarming before administration of protamine, and 4–6 h after the end of surgery. Further samples were taken 1 and 2 days after the completion of surgery, at discharge and postoperatively at the out-patient follow-up. In those not undergoing bypass, samples were drawn at similar time intervals except for the beginning of bypass. A sample was simply drawn immediately at the end of surgery. Samples were sedimented at 2800×*g*, and supernatants were frozen at −80°C in aliquots within 1 h of sampling. The serum concentrations of the soluble adhesion molecules soluble E- and P-selectin and soluble P-selectin glycoprotein ligand-1 were quantified by enzyme-linked immunoassay (soluble E- and P-selectin: R&D Systems, Oxon, UK; soluble P-selectin glycoprotein ligand-1: Biozol, Eching, Germany). From the same blood samples, haematocrit values were determined. The time courses of haematocrit values were significant in both groups up to discharge. A volume correction for all adhesion molecules was made to eliminate haemodilution effect according to the formula: sample concentration × (baseline haematocrit/sample haematocrit). Only corrected data are displayed, and only the follow-up concentrations were not corrected for baseline haematocrit.

Statistics

Data are presented as mean values ±1 standard deviation or standard error of means, as indicated. Changes with time were analysed by the non-parametric Friedman test. Analysis of variances for repeated measures was used for comparison of those with or without bypass. Single data sets were compared by Students t-test or the non-parametric Wilcoxon test, as appropriate, using the SPSS program package version 10 (Knowledge Dynamics, Canyon Lake, TX, USA). P values of less than 0.05 were considered significant.

Results

Clinical results

The anthropometric, surgical and basal laboratory data are summarised in the Tables 1 and 2. The groups did not differ significantly with respect to age, sex, weight and duration of surgery and basal laboratory characteristics. Mild postoperative complications

Table 1. Anthropometrical and surgical characteristics of the patients undergoing surgery with and without cardiopulmonary bypass. Data are displayed as mean ± standard deviation.

	With bypass (n = 29)	Without bypass (n = 21)	P value
Age (yrs)	7.7 ± 2.8	7.9 ± 3.2	NS*
Weight (kg)	25.9 ± 12.0	26.8 ± 12.0	NS*
Sex (male/female)	11/18	14/9	NS†
Surgery (min)	154.7 ± 54.4	147.6 ± 56.6	NS*
Duration of bypass (min)	45.4 ± 22.6		
Cross-clamp (min)	18.8 ± 18.3		
Hypothermia (°C)	32.3 ± 3.0		
Hypothermia (min)	104.4 ± 51.2		

*Compared by unpaired Student's t-test; †compared by Fisher exact test

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were detected in eight children undergoing bypass. Pericardial effusions were diagnosed by echocardiography up to 3 days after surgery in three patients, postoperative pneumothorax (diagnosed by X-ray) occurred in three patients, fever without additive symptoms of infection in one patient, and fever with anaemia without signs of infection in the final patient. Mild postoperative complications were detected in five patients not having bypass. Pericardial effusions were seen in two patients, and postoperative hypertension in three patients. None of the patients with pericardial effusion fulfilled the criterions of postpericardiotomy syndrome.[29] The later intrahospital and follow-up outcome was good for all patients.

Serum concentrations of soluble adhesion molecules

Soluble E-selectin: The time course of soluble E-selectin is shown in Figure 1. No significant differences were found between those with and without bypass, although a more pronounced tendency was seen for their decrease in those undergoing bypass. In this group, soluble E-selectin changed with time ($p < 0.05$, Friedman test). In contrast, the time course was not significant in those undergoing surgery without bypass. In those having bypass, the concentration of soluble E-selectin decreased rapidly after anaesthesia (−9% compared to baseline, $p < 0.05$) and reached the lowest value at the end of bypass (−18% compared to baseline, $p < 0.001$). Return to baseline values did not occur until during the period of follow-up. In those not having bypass, no significant differences were found between the measured values and their baseline comparisons.

Table 2. The preoperative haematological and biochemical parameters on the day prior to surgery of those about to undergo correction with and without cardiopulmonary bypass. Data are displayed as mean ± standard deviation.

	With bypass (n = 29)	Without bypass (n = 21)	P value
Haemoglobin (mmol/l)	7.5 ± 0.9	7.9 ± 0.7	NS
Haematocrit (%)	35.2 ± 6.4	37.7 ± 4.1	NS
Erythrocyte count ($\times 10^{12}$/l)	4.7 ± 1.45	4.7 ± 0.5	NS
Leukocyte count ($\times 10^{9}$/l)	7.5 ± 1.7	6.6 ± 1.8	NS
Platelet count ($\times 10^{9}$/l)	266.9 ± 89.5	258.2 ± 50.9	NS
C-reactive protein (mg/l)	0.29 ± 0.14	0.20 ± 0.13	NS
Kreatinin (mmol/l)	60.7 ± 8.8	60.3 ± 8.5	NS

Statistical analysis was performed using unpaired Student's t-test

Soluble P-selectin: The time course of soluble P-selectin is shown in Figure 2. The time course was statistically significant for both groups, $p < 0.001$ for bypass, $p < 0.05$ without bypass, but no statistical differences were found between the groups, although the concentrations were slightly lower in those undergoing bypass during and after surgery. The concentration of soluble P-selectin decreased immediately after anaesthesia to a level of −18% as compared to baseline for those undergoing bypass ($p < 0.01$), and −16% for those without bypass ($p < 0.05$). The latter value was the lowest measured in those not having bypass. In contrast, in those undergoing bypass, the lowest value was reached at the beginning of the perfusion, −29% when compared to baseline ($p < 0.001$). Return to the baseline values occurred very quickly in both groups, 4 h after surgery in those having bypass, and at the end of surgery in those without bypass.

Soluble P-selectin glycoprotein ligand-1: The time course during surgery was significant with time in each group ($p = 0.01$; Fig. 3). It decreased after anaesthesia to a level of −5% compared to baseline in both groups. The lowest values were reached at the beginning of bypass, −17% compared to baseline in those undergoing bypass ($p = 0.003$), and

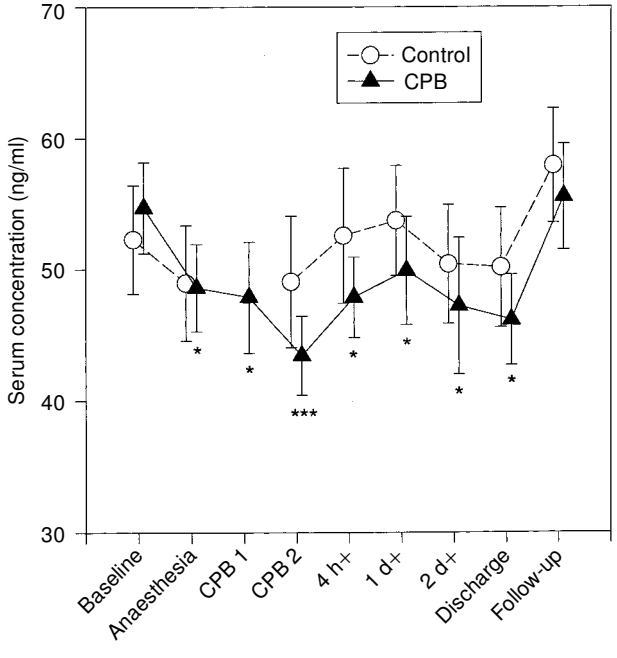

Figure 1.
*The concentrations of soluble E-selectin in the serum before, during and after surgery. The concentration is displayed as original values in ng/ml. Data show mean ±1 standard error of mean of those undergoing correction with (closed triangles, n = 29) or without cardiopulmonary bypass (open circles, n = 21). The results were significant when compared to baseline values in those undergoing bypass: *p < 0.05, **p < 0.01, ***p < 0.001.*

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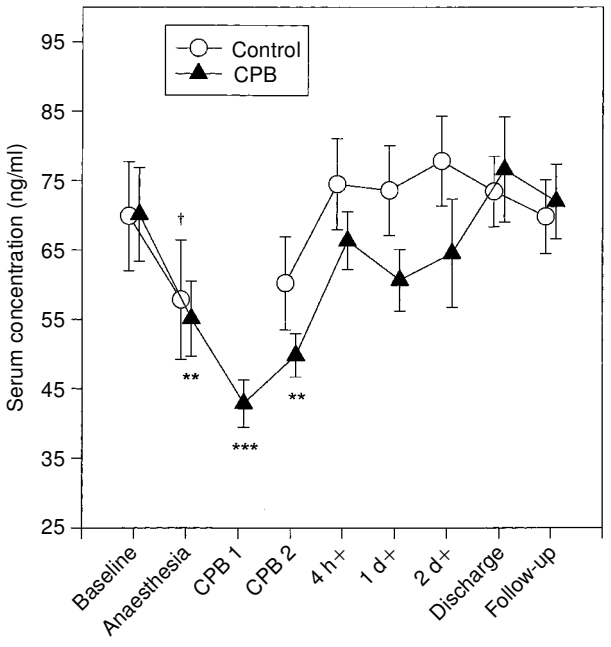

Figure 2.
*Concentrations of soluble P-selectin in the serum before, during and after surgery. The concentrations are displayed as original values in ng/ml. Data show mean ±1 standard error of mean for those undergoing correction with (closed triangles, n = 29) or without cardiopulmonary bypass (open circles, n = 21). The values were significant compared to baseline values in those having bypass (*p < 0.05, **p < 0.01, ***p < 0.001) and in those undergoing surgery without bypass (†p < 0.05).*

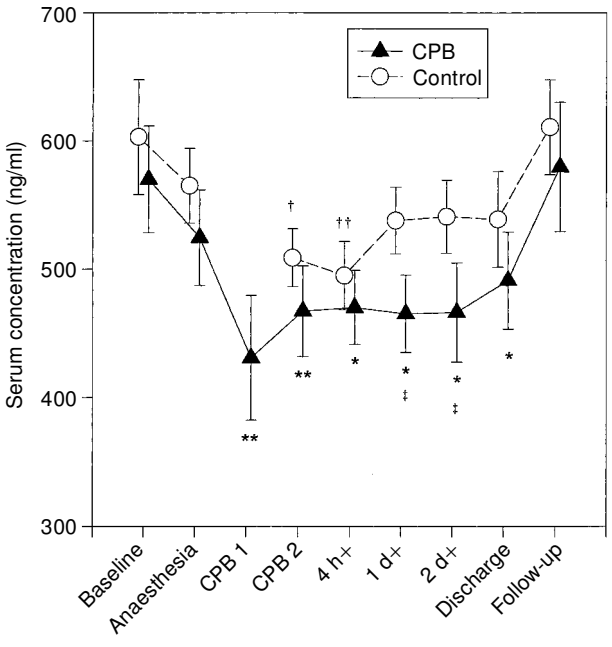

Figure 3.
*Concentrations of soluble P-selectin glycoprotein ligand-1 in the serum before, during, and after surgery. The concentrations are displayed as original values in ng/ml. Data show mean ± standard error of mean for those undergoing surgery with (closed triangles, n = 29) or without cardiopulmonary bypass (open circles, n = 21). Significance was achieved, when compared to baseline values, both in those undergoing bypass (*p < 0.05, **p < 0.01) and for those having surgery without bypass (*†p < 0.05, ††p < 0.01). The difference between the groups was also significant (‡p < 0.05).*

4 h after surgery in those not having bypass, the level being −19% (p = 0.005). In the group having bypass, return to the baseline values had not occurred at discharge, but during the period of follow-up. In those not having bypass, the values had returned to baseline 1 day after surgery. The only difference in values measured between the groups was observed on the first and second days after surgery (both, p < 0.05), but the overall time course was not statistically significant between the groups.

Postoperative complications and soluble adhesion molecules: The early postoperative outcome of three patients having bypass, and two patients not, was complicated by the development of pericardial effusion. Levels of soluble E-, P-selectin and soluble P-selectin glycoprotein ligand-1 were compared in these five patients to the patients without pericardial effusion. There were no statistically differences in the concentrations of all three adhesion molecules in the serum. The statistical analysis of patients who suffered from other postoperative complications was not possible due to their low incidence.

Discussion

The major findings of our study are that cardiovascular surgery induces a pronounced endothelial response, and that this response is sustained after surgery involving cardiopulmonary bypass. The results demonstrate a decrease in endothelial activation that occurs after induction of anaesthesia, with a return to baseline levels occurring only at discharge, or even at follow-up, in other words, months after surgery.

Blume et al.[30] had already described a decrease of soluble P- and E-selectin after cardiopulmonary bypass in children undergoing cardiovascular surgery, followed immediately by an increase up to 42 h postoperatively. As their baseline, these authors used the values obtained after induction of anaesthesia. Our data are partly in agreement with Blume et al., in that we found that levels of soluble P-selectin, but not E-selectin, had already increased during cardiopulmonary bypass. We now demonstrate that the initial effect on these molecules is during the induction of anaesthesia. This interpretation is in agreement with that of Boldt and co-workers,[2] who

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similarly observed a decrease of soluble E- and P-selectin during cardiovascular surgery in children undergoing cardiopulmonary bypass. They compared intraoperative results to preoperative baseline values. As in our study, they also corrected their results for haemodilution. The decrease of soluble E- and P-selectin, therefore, seems to start after anaesthesia, and is farther excacerbated by cardiopulmonary bypass.

An important aspect of our study is the obtaining of data long after surgery. This is an improvement on earlier studies, and is the more important for E-selectin because the kinetics of this agent is slow. After shedding of E-selectin, new synthesis is needed.[18] This may be the reason why, in our study, the measured values had not returned to baseline at discharge, but only late postoperatively. A similar intraoperative time course was found for soluble P-selectin glycoprotein ligand-1, but no other reports about the activity of this molecule during cardiovascular surgery have yet been published.

Our data show that it is the induction of anaesthesia which has the initial effect on decreased endothelial activity. Perhaps surprisingly, only a few reports have addressed the influence of anaesthetics on the endothelium and the adhesion of neutrophils via the action of adhesion molecules or their regulatory cytokines. The most effective activators of endothelial cells, in particular of E-selectin expression, are interleukin-1α and tumor necrosis factor-α.[18] Midazolam was reported to reduce the secretion of tumor necrosis factor-α and interleukin-1α. Additionally, sufentanyl combined with propofol and atracurium was reported not to induce secretion of these pro-inflammatory cytokines.[32] Our patients received a combination of midazolam, fentanyl, and etomidate. The effect of the combination of these anaesthetics remains unclear. As we showed earlier,[4] this combination led to depressed levels of tumor necrosis factor-α in the serum, and did not induce secretion of interleukin-1α. Decreased secretion of tumor necrosis factor-α during surgery with cardiopulmonary bypass in children, albeit using other anaesthetics, was recently observed by Carvalho and co-workers.[33] Concurrently, the activity of monocytes, one of the major sources of both cytokines as shown by our earlier study, was massively depressed.[34] The combination of these anaesthetics with intraoperative administration of corticoids, followed by cardiopulmonary bypass, seems not to lead to the secretion of pro-inflammatory cytokines that may activate endothelium and induce upregulation and release of E-selectin. The behaviour of E-selectin is particularly interesting because it is found only on activated endothelium. This is in contrast to P-selectin, which has a wider distribution in the tissues.[11,12] A considerable role in the enhancement of expression of P-selectin is played by thrombin, histamine, and complement.[7] In a previous study,[5] a greater release of complement was shown during surgery undertaken using cardiopulmonary bypass. This could lead to faster recovery from anaesthesia and surgical trauma of P-selectin compared to E-selectin.

Postoperative levels of soluble E-selectin and P-selectin glycoprotein ligand-1 in the serum seem to be reduced more sustainedly when surgery is carried out using cardiopulmonary bypass than without. As we and others showed, interleukin-10 is released at the end of cardiopulmonary bypass.[4,35] Release of this agent seems to be specific for cardiopulmonary bypass surgery in children.[36] Interleukin-10 was recently reported experimentally to inhibit upregulation of E-selectin.[37] Although the differences in levels of selectins were not significantly different with and without cardiopulmonary bypass, the return to baseline was slower in those having bypass. This slower recovery subsequent to cardiopulmonary bypass may also be the effect of secretion of interleukin-10 at the end of the period of bypass.[4,35,36]

Nowadays, according to new knowledge about pronounced anti-inflammatory response to cardiopulmonary bypass, with substantially higher production of interleukin-10 compared to surgery without cardiopulmonary bypass,[36] it remains questionable if the standard use of corticoids in children is advisable. Very recently, standard use of corticoids was found to be ineffective in children in preventing the development of the postpericardiotomy syndrome. Indeed, the routine administration of methylprednisolone even complicated the treatment of this syndrome.[38] Further studies are needed precisely to evaluate the clinical benefit of corticoids, and to make cardiac anaesthesia in children truly evidence-based.

None of our patients suffered extensive complications. But we did not study very young patients with an immature immune system, nor those with cyanosis, which might have altered the haematological parameters, nor any with severe genetic defects. So we probably showed the "physiological" response of endothelial selectins and their ligands to cardiovascular surgery and to cardiopulmonary bypass. Furthermore, the concentrations of selectins in patients with and without postoperative complications, above all those with pericardial effusion, were not different compared to other patients without complications.

The limitation of our study is that the patients we studied are not completely comparable. Those not undergoing bypass were children with different diagnoses from those undergoing bypass. It is

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impossible, however, to find two groups of children with comparable congenital cardiac malformations undergoing surgical correction with or without cardiopulmonary bypass. Confronted by this insuperable problem, we tried to make our groups as comparable as possible with respect to their anthropometrical characteristics, the duration of surgery, the anaesthetic regime, and so on. But it remains the fact that the groups are not completely identical. Furthermore, we could not directly show the response of endothelium, but only make indirect interpretations based on the measured levels of soluble adhesion molecules. Although scientifically important, ethically it is not feasible to accomplish endothelial biopsy in children.

Our study has shown, therefore, that cardiovascular surgery suppresses the activity of endothelial cells. This suppression is initiated by anaesthesia, and substantially enhanced by cardiopulmonary bypass. A long period is needed for the endothelium to recover. This understanding is important further to facilitate the improvement in the clinical management of children undergoing surgical correction of congenital cardiac malformations.

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