Monitoring of coagulation and platelet function in paediatric cardiac surgery

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To all children with
congenital heart disease

Abstract

Background: Paediatric cardiac surgery has developed dramatically during the last decades. Today, a wide range of patients is operated on-from premature neonates to grown up children with congenital heart disease. Excessive bleeding during and after cardiac surgery is still common, and it is one of the most serious complications. In this thesis, we consider different aspects of monitoring of coagulation and platelet function during and after paediatric cardiac surgery. The aims were to determine (1) whether thromboelastometry analyses can be accelerated, (2) whether routine use of intraoperative thromboelastometry reduces perioperative transfusions, (3) whether platelet inhibition can be monitored with impedance aggregometry in children with systemic-to-pulmonary shunts, (4) how platelet count and function varies perioperatively, (5) whether ultrafiltration influences coagulation and platelet function, and (6) whether thromboelastometry detects clinically significant platelet dysfunction.

Methods: Paediatric patients undergoing cardiac surgery were included in five prospective studies. Coagulation was assessed with standard laboratory tests and thromboelastometry while platelet function was assessed with impedance aggregometry.

Results: Thromboelastometry can be accelerated by performing the analysis before ultrafiltration and weaning of cardiopulmonary bypass, and by analyzing clot firmness after 10 minutes. Routine use of intraoperative thromboelastometry reduces the overall proportion of patients receiving transfusions (64% vs. 92%, $p < 0.001$). Impedance aggregometry can be used to monitor anti-platelet effects of acetyl salicylic acid after shunt implantation in paediatric patients. A substantial proportion of the patients are outside the therapeutic range 3-6 months after surgery. There are substantial reductions both in platelet count and platelet function during and immediately after surgery. Platelet function, but not platelet count, recovers during the first 24 hours after surgery. Ultrafiltration has no or limited effect on platelet count, platelet function, and thromboelastometry analyses. Thromboelastometry has acceptable ability to detect intraoperative but not postoperative ADP-induced platelet dysfunction.

Conclusion: Monitoring of coagulation and platelet function gives important information about haemostatic disturbances during and after paediatric cardiac surgery. Routine monitoring of the coagulation markedly reduces transfusion requirements in paediatric cardiac surgery. After surgery, more specific platelet tests are necessary to assess platelet function.

Key words: paediatric cardiac surgery, haemostasis, platelet, coagulation, thromboelastometry, impedance aggregometry, coagulopathy, haemoconcentration

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Original papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:

I. Romlin BS, Wåhlander H, Synnergren M, Baghaei F, Jeppsson A. **Earlier detection of coagulopathy with thromboelastometry during pediatric cardiac surgery: a prospective observational study.** *Paediatr Anaesth. 2013;23:222-227.*

II. Romlin BS, Wåhlander H, Berggren H, Synnergren M, Baghaei F, Nilsson K, Jeppsson A. **Intraoperative thromboelastometry is associated with reduced transfusion prevalence in pediatric cardiac surgery**. *Anesth Analg. 2011;112:30-36.*

III. Romlin BS, Wåhlander H, Strömvall-Larsson E, Synnergren M, Baghaei F, Jeppsson A. **Monitoring of acetyl salicylic acid-induced platelet inhibition with impedance aggregometry in children with systemic-to-pulmonary shunts.** *Cardiol Young. 2013;23:225-232.*

IV. Romlin BS, Söderlund F, Wåhlander H, Nilsson B, Baghaei F, Jeppsson A. **Platelet count and function in paediatric cardiac surgery: A prospective observational study.** *Submitted.*

V. Romlin BS, Wåhlander H, Hallhagen S, Baghaei F, Jeppsson A. **Perioperative monitoring of platelet function in paediatric cardiac surgery: Thromboelastometry, platelet aggregometry or both?** *Manuscript.*

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Abbreviations

AA	arachidonic acid
ACT	activated clotting time
ADP	adenosine diphosphate
APTT	activated partial thromboplastin time
ASA	acetylsalicylic acid
AUC	area under the concentration curve
AT	anti-thrombin
ATP	adenosine triphosphate
CI	confidence interval
CFT	clot formation time
COX	cyclo-oxygenase
CT	clotting time
CHD	congenital heart disease
CPB	cardiopulmonary bypass
FDP	fibrin degradation products
FFP	fresh frozen plasma
Hb	haemoglobin
Hct	haematocrit
ICU	intensive care unit
INR	international normalized ratio
IU	international unit
MCF	maximum clot firmness
MUF	modified ultrafiltration
PT	prothrombin time
RBC	red blood cell
TAT	thrombin-anti-thrombin complex
TEG	thromboelastography
TEM	thromboelastometry
TFPI	tissue factor pathway inhibitor
t-PA	tissue-plasminogen activator
TRALI	transfusion-related acute lung injury
TXA_2	thromboxane A_2
vWF	von Willenbrand factor

Introduction

Paediatric cardiac surgery

Congenital cardiac anomalies have been recognized for centuries. In the fourth century BC, Aristotele studied the embryology of the chick, noting the beating of the foetal heart. The discovery of the ductus arteriosus and foramen ovale was made in the sixteenth century, and in 1888 Etienne-Louis-Arthur Fallot described his comprehensive account in tetralogy. During the late 1870s, the origin and nature of congenital septal and interventricular septal defects were described, and in 1897 Eisenmenger described the complex that bears his name. However, few or no treatments were available until the twentieth century. The cornerstones during this period were the closure of patent ductus arteriosus in 1939, subclavian to pulmonary artery shunt to improve pulmonary blood flow reported by Blalock and Taussig in 1945 (Fig. 1), and a successful cardiopulmonary bypass using a pump oxygenator reported by Gibbon in 1953. In the 1970s, one of the most important advances was the use of prostaglandins to maintain ductal patency and pulmonary blood flow.

This decade also saw the start of the use of echocardiography in children. In 1981, Norwood described a successful palliation of hypoplastic left heart syndrome, and by the end of the 1980s nearly all congenital cardiac lesions could be repaired or at least palliated by surgical procedures.

During the modern era from 1990, paediatric cardiac surgery has developed dramatically and today a wide range of patients is operated on, from premature neonates to grown up children with congenital heart disease. One of the reasons for this fast development is the improvement of cardiopulmonary bypass with miniaturization of the oxygenator, heat exchanger, and other components, leading to reduced priming volume and resulting in less haemodilution. Also, the introduction of ultrafiltration contributed to reduced levels of inflammatory mediators and optimal fluid balance (1).

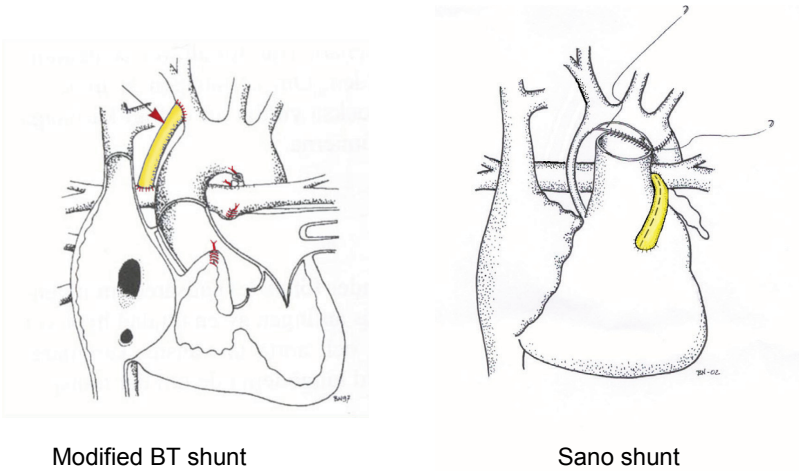

Figure 1: Modified Blalock-Taussig shunt and Sano shunt.

Congenital heart disease affects approximately 1% of children. Moreover, worldwide, many children born with a normal heart develop some form of acquired heart disease, usually as a result of rheumatic fever. Without corrective surgery, many of these children die prematurely or become permanently disabled (1).

Risk factors for bleeding

Excessive bleeding during and after cardiac surgery is still a great challenge. Bleeding is common, and it is associated with increased morbidity and mortality. Internationally, more than 90% of children undergoing cardiac surgery are transfused with blood products (2). Many studies have been performed to give us a better understanding of risk factors associated with excessive bleeding in cardiac surgery. In paediatric cardiac surgery, weight and age are two important factors. Neonates experience greater postoperative blood loss than children older than 5 years (3). In one study, children weighing less than 8 kg had more blood loss and transfusions than those above 8 kg (4). Transfusions were avoided in only 2% of patients weighing less than 8 kg as compared to 25% in those greater than 8 kg. In another study, almost 60% of neonates received platelets, as compared to only 14% of infants between 4 weeks and 1 year (5). One possible explanation might be differences in maturation of the coagulation system (6). Risk factors for bleeding may also vary between different age groups. Lower body tempera-

ture during CPB was found to be highly associated with blood loss in infants, whereas re-sternotomy, preoperative congestive heart failure, and prolonged duration of CPB were significant factors for bleeding and transfusion in children over 1 year (7). High preoperative haematocrit and low platelet count during cardiopulmonary bypass are two other important risk factors that have been shown to be significantly associated with bleeding and transfusions (7). Platelet count and function and fibrinogen concentration contribute to clot strength after surgery. Low platelet count and/or impaired platelet function increase the risk of bleeding in paediatric cardiac surgery (8,9) yet the minimum number and minimal function of platelets to achieve sufficient haemostasis remain unclear (4).

Another factor that contributes to bleeding complications is the complexity of the surgical procedure. More complex procedures may involve longer suture lines, longer CPB times, re-sternotomy, and significant hypothermia, which all results in increased bleeding (4). Several studies have demonstrated that modified ultrafiltration (MUF) improves haemostasis after CPB in paediatric cardiac surgery with beneficial effects on postoperative bleeding, chest drainage, and the need for blood transfusions (10,11). Other possible risk factors for bleeding are excessive thrombin generation during CPB, inadequate heparin reversal, excessive administration of protamine, low levels of calcium, and low pH (12,13).

Transfusions

The first well-documented blood transfusion was performed in 1818, by James Blundell, an obstetrician at the United Hospital of St Thomas's and Guy's in London. Blundell performed ten blood transfusions, five of which were successful (14,15). Since then, transfusion therapy has contributed to many of the medical and surgical advances that benefit patients (16). Since excessive bleeding during and after cardiac surgery is common, transfusions will continue to be an integral part of the practice. Today, more than 90% of paediatric cardiac surgery patients receive blood transfusions during or after surgery, and more than 50% receive fresh frozen plasma and platelets (17,18,2).

Transfusion of red blood cells

The primary goal of red blood cell (RBC) transfusion is to increase the oxygen-carrying capacity of blood and to improve tissue oxygen delivery. The

challenge is to discern the haemoglobin level at which red blood cells (RBCs) should be administered. For example, the brain and heart extract large amounts of oxygen even at rest, as indicated by large differences in arterio-venous oxygen content across their vascular beds. Thus, delivery of oxygen to these organs may be affected by even small changes in haemoglobin (19). In one study comparing low haematocrit levels (mean hematocrit 21.5%) and high haematocrit levels (mean 27.8%) in infants during hypothermic low-flow CPB, the authors found worse perioperative outcomes (lower cardiac index 3 h after removal of the aortic clamp, higher serum lactate levels 1 h after CPB, and a greater increase in total body water on the first postoperative day) including psychomotor development index scores at 1 year in the group with low haematocrit (20). Red blood cells also play an essential role in the autoregulation of tissue blood flow: upon deoxygenation, haemoglobin reduces nitrite to nitric oxide, which in turn increases regional tissue blood flow (21).

Platelet transfusion

Initial treatment for bleeding following CPB is generally aimed at correcting low platelet count and function. Thus, platelet transfusions are very common in this patient group, especially in neonates and infants (22). One thing to be aware of is a difference in preparation of platelets. The concentrate can either be prepared from buffy coats from several donors (generally four) or by apheresis technique from a single donor. In addition, there can be differences in concentration and the amount of plasma in the concentrate. These factors are important since increased donor exposure increases the risk of unfavourable outcome after transfusion (23).

Transfusion of plasma, cryoprecipitate, and fibrinogen

The use of plasma is based on the observation that the concentration of clotting factors is often low immediately after by-pass, and plasma has been administered from elevated results of PT and APTT (> 1.5 times). However, these tests are often also significantly prolonged in the absence of bleeding and, when analyzed after by-pass, correlate poorly with excessive bleeding (24). Meta-analysis regarding the use of FFP to treat acquired coagulopathy failed to demonstrate any benefit (25). In another study, a number of patients had coagulopathic bleeding after transfusion of platelets; if these patients were then given FFP, bleeding increased-but if cryoprecipitate was

given, bleeding decreased (4). Not all coagulation factors are of equal importance during bleeding (8). Fibrinogen is normally present in much higher concentrations than other clotting factors, and while other factors are mainly involved in initiating or amplifying thrombin formation, fibrinogen is a substrate for the production of fibrin. Low levels of fibrinogen are reflected by reduced strength of the clot and they are associated with increased bleeding (8). Fibrinogen can be administered in two different ways, either as cryoprecipitate which contains fibrinogen, von Willenbrand factor (vWF), FVIII, and F XIII or as virally inactivated and pasteurized fibrinogen concentrates. Both of these agents are effective in controlling bleeding after either paediatric or adult cardiac surgery (26-30).

Negative effects of transfusion

Unfortunately, transfusion of blood products also has unfavourable effects. It is expensive, and recruitment of donors to meet the demand remains a complicated task. Historically, the main concern regarding red blood cell transfusion has been the risk of transmission of blood-related infectious diseases. Today, there is improved donor screening and there are new technologies to test donor blood; these have resulted in significantly reduced risk for transmission of infection diseases (31). Instead, non-infectious complications are the most common problem today (31). The most common complication is transfusion of the wrong unit into the wrong individual.

Blood transfusions are associated with substantial changes in the immune system (32). It has been suggested that leukocytes present in the transfused blood are primarily responsible for these effects, including febrile reactions, transfusion-related immunomodulation, and the transmission of cell-associated pathogens such as cytomegalovirus. Consequently, leukocyte reduction defined as $< 5 \times 10^6$ white blood cells per unit is now performed by most blood collection centres.

Storage time is also important for reducing complications. With increasing storage time, adenosine triphosphate (ATP) levels decline, resulting in changes in membrane lipid content and in RBC shape and rigidity; these changes may contribute to micro-circulatory occlusion in certain tissue beds, further promoting tissue ischaemia (33) 2,3 DPG, the phosphate that binds deoxygenated haemoglobin and facilities the release of oxygen in the tissue, also declines over time and is undetectable after 1 week of storage (34). Concerns have therefore been raised that RBCs stored for longer than 1 week have a reduced ability to unload oxygen to hypoxic tissue.

There is currently a dispute about whether transfusion of fresh whole blood or packed red blood cells is preferable. In a review by Guzzetta (16), the author concluded that transfusion of fresh whole blood to infants after CPB may be beneficial in reducing postoperative bleeding, owing to persevered platelet function (35). However, it does not appear to achieve the same goal when used in CPB prime (36). In addition, whole blood that is less than 48 h old is not readily available at all paediatric cardiac centres, and when it is, it has usually been stored at 4ºC, a factor known to be responsible for depressing platelet function (35).

In recent years, several prospective and retrospective studies have found that RBC transfusion is independently associated with increased morbidity and mortality in a variety of surgical situations (37). In a large retrospective, single-centre investigation published in 2007 of 295 critically ill children admitted to the paediatric ICU, an independent association between RBC transfusion and ICU mortality was seen, despite the use of leukocyte-depleted erythrocytes (38). The investigators also observed an increase in the number of vasoactive infusions, in the duration of mechanical ventilation, and in the length of ICU stay in those children who received the most RBC transfusions. This study, together with several others (39,40), suggest that a dose-outcome relationship may exist between the number of RBC transfusions and mortality. There has been a lack of investigations examining the effect of RBC transfusion on morbidity and mortality in children after cardiac surgery; such studies have been hindered by the small and heterogeneous populations represented by these children.

There is some recent evidence to support a more conservative approach regarding transfusions in paediatric cardiac surgery (41,42,16), particularly in children undergoing repair of simple cardiac defects. Conversely, there are certain situations where a higher haematocrit is indicated, e.g. neonates and infants undergoing low-flow hypothermic CPB, where a higher hematocrit is indicated (20).

Haemostasis

The theory in this part of the thesis is described in three current textbooks on haemostasis: Kolde (43), Blombäck (44), Blanchette (45).

Haemostasis is classically divided into three parts: primary haemostasis, coagulation (secondary haemostasis), and fibrinolysis (Fig. 2). These systems balance the opposing forces of coagulation and anti-coagulation to protect

the vasculature from uncontrolled bleeding on the one hand and excessive clotting on the other.

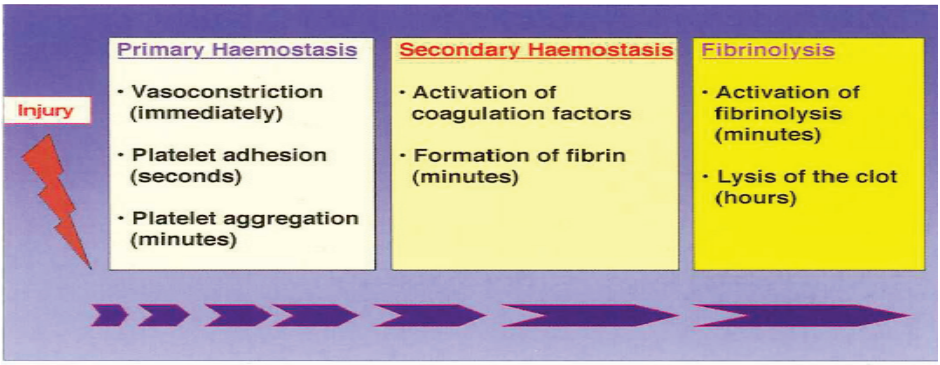

Figure 2: Timing of events in haemostasis (reproduced with permission from Pentapharm).

Another factor that influences haeamostasis is rheology. Under conditions of a normal haematocrit, RBC flow is maximal at the centre of the vessel, and platelets are marginalized toward the periphery close to the site of injury, thus promoting platelet-endothelial interaction (46). This rheological effect of RBCs can increase platelet concentration near the injured vessel wall by as much as seven times normal, and can therefore enhance thrombus formation.

Primary haemostasis

The first step in primary haemostasis is an immediate vasoconstriction, mediated by the autonomous nerve system and local factors in the endothelium of the injured vessel, followed by adhesion of platelets to the site of injury. Adhesion of platelets to sub-endothelial collagen is promoted by vWF; during high shear forces, vWF will be stretched out over a large area and in this way give more time for platelets to adhere. Receptor GP Ib on the platelets connects to vWF, which is in turn connected to endothelium (Fig. 3). Once adherent, platelets become activated by strong agonists present at the site of injury, primarily collagen, thrombin, and ADP. Upon activation, platelets undergo a change in morphology and expose negatively charged phospholipids, previously unexpressed, on their surface membrane (Fig. 4). These negatively charged phospholipids play an important role in the adhesion of vari-

ous coagulation factors to the activated surface. Platelet activation also results in release of dense granules (ADP,Ca and serotonin) and alpha granules (vWF,FV,FXIII,fibrinogen, and thromboxane A2). These substances promote aggressive platelet aggregation, vasoconstriction, and activation of the coagulation system. In their activated form, platelet receptors GPIIb/IIIa will be exposed, which gives fibrinogen the chance to link platelets to each other, the so-called aggregation. Platelet aggregation occurs in conjunction with activation of coagulation factors on the platelet surface, to support generation of thrombin and the formation of a fibrin clot. The formation of a platelet plug is tightly controlled, and it is limited to areas of vascular injury by intact endothelial cells producing powerful inhibitors of platelet aggregation and vasodilators.

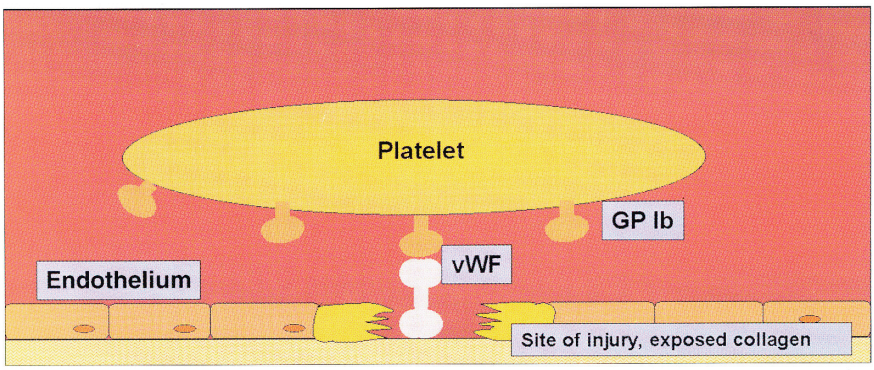

Figure 3: Platelet adhesion mediated by vWF and platelet GPIb (reproduced with permission from Pentapharm).

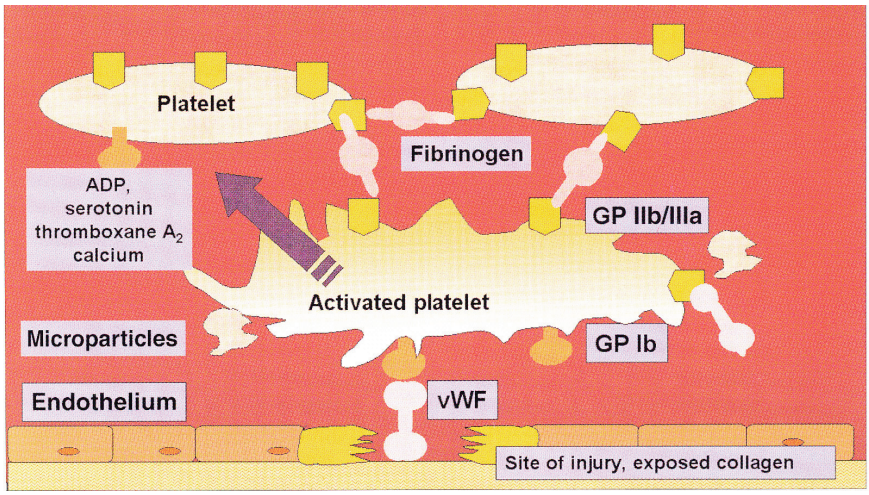

Figure 4: Platelet adhesion and aggregation (reproduced with permission from Pentapharm).

Coagulation

The coagulation system is a complex web of interactions (Fig. 5) and is usually divided into two pathways: the intrinsic (contact XIIa) pathway and the extrinsic (tissue factor) pathway. These two pathways come together into a common pathway, which activates FX to FXa. The FXa/FVa complex then converts prothrombin to thrombin. Thrombin has many different roles in the coagulation system, and is the strongest activator of coagulation. One of its most important roles is to convert fibrinogen to fibrin. Fibrinogen plays a significant role in primary haemostasis-linking platelets together-and in the coagulation system where it is converted to fibrin, which in turn forms the stable clot.

In 2001, Hoffman and Monroe described the cell-based model of coagulation (47). In this model, coagulation is initiated when there is damage to the vessel wall, allowing binding of circulating FVIIa to tissue factor- (TF-) bearing cells in the extravascular space. Hoffman and Monroe divided the process into three phases: initiation, propagation, and termination. The cell-based model provides an adequate explanation for clinical observations; for example, patients with severe congenital FXII deficiency do not show abnormal bleeding, and patients with congenital FXII deficiency are capable of generating as much thrombin as normal patients during CPB.

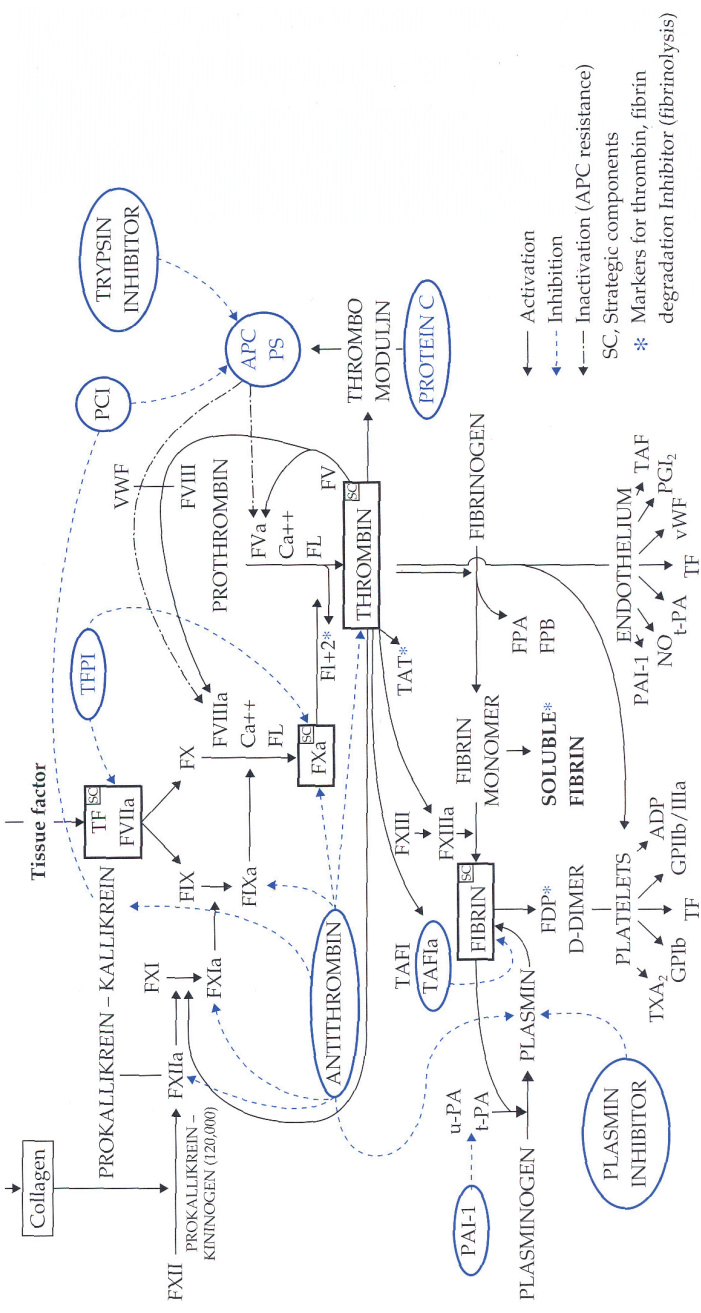

Figure 5: The coagulation system, and cell and tissue injury.
(Taken with permission from Nils Egberg, Essential Guide to Blood Coagulation, Wiley-Blackwell)

Fibrinolysis

This system is responsible for the balance between clot formation and clot lysis. Plasminogen is produced in the liver and binds to fibrin. In this position (plasminogen bound to fibrin), it is activated to plasmin by t-Pa and the activated plasmin cleaves fibrin to fibrin degradation products. This system with activation at the site allows for local fibrinolysis.

Differences between children and adults

Small infants and neonates have an immature but balanced coagulation system with lower levels (approximately 50% compared to adults) of coagulation factors VII, IX, X, XI, XII, and prothrombin. On the other hand, the levels of vWF, (V), VIII, and XIII are somewhat higher than those in adults. Also, the levels of inhibitors of coagulation (AT, Protein C, and protein S) are 50% of those in adults (45, chap 4) (9). The newborn coagulation system matures to adult concentrations and functions for six months (45, chap 4). Neonatal platelet counts and mean volumes do not differ from those in adults. However, neonatal platelets show a notable decrease in function for the first 2-4 weeks after birth. When examined *in vitro*, platelets show reduced responses to a variety of standard agonists (epinephrine, ADP, collagen, and thrombin) (48). This reduced responsiveness is evident as a decrease in platelet granule secretion, a decrease in the expression of fibrinogen binding sites on the platelet surface, and reduced platelet aggregation (49). However, most *in vivo* assays of platelet function do not show platelet dysfunction in neonates (50). In fact, bleeding time and platelet function analyzer closure times (PFA-100 Dade Behring, Miami FL, USA) are all shorter in neonates than adults, suggesting that under physiological conditions neonatal platelets are at least as efficient as adult platelets in achieving primary haemostasis (51). The explanation might be the prominent role that vWF plays in neonatal haemostasis, with higher concentrations and a greater percentage of large vWF multimers, the molecules most effective in promoting platelet-vessel wall adhesiveness (50).

Coagulation abnormalities in children with congenital heart disease

Approximately 50% of infants with congenital heart defects (CHDs) have depressed clotting factor levels (52). Severe heart failure can lead to liver impairment and reduced production of coagulation factors, especially fibrinogen and prothrombin. However, reduced levels of factor II, IX, and X,

reduced plasma volume, and low levels of vWF have been observed especially in children with cyanotic CHD (53). Beyond clotting factor deficiency, thrombocytopenia and platelet dysfunction is common, especially in cyanotic CHD (54). The occurrence and severity of thrombocytopenia show a direct relationship with the severity of polycythaemia (55) and arterial desaturation (56). Similarly, platelet dysfunction, represented by platelet aggregation, correlates with the extent of cyanosis and polycythaemia (57).

Cardiopulmonary bypass and haemostasis

The linings of artificial cardiopulmonary bypass (CPB) circuits differ from endothelium in two major respects: proteins will bind freely to their surface and they lack any inhibitory effect on coagulation (58). Adherent platelets undergo activation, encouraging further adhesion and release of procoagulants. Heparin dramatically reduces thrombin formation, but it does not prevent initial protein binding or activation of coagulation or platelets (60). In the majority of cardiac centres, the heparin dose administered prior to CPB is 300-400 U/kg with additional bolus doses being given as required to maintain activated clotting time (ACT) values above 480 s. One problem is that ACT values do not correlate with the plasma heparin concentration, and are also influenced by haemodilution and hypothermia (61). The optimal heparin dose during CPB is still debatable: some studies have found that higher heparin doses during CPB reduce thrombin activation and fibrinolysis, and result in higher levels of FV, FVIII, fibrinogen, and AT-and as a consequence, less postoperative bleeding (62). On the other hand, Gravlee et al. found a positive correlation between plasma heparin concentration during CPB and blood loss (63). Protamine sulphate is the most common agent used to reverse heparin-induced anti-coagulation at the end of CPB. However, protamine sulphate has a number of limitations. The most important in this context is the contribution to the haemostatic defect associated with cardiac surgery. Platelet reactivity and aggregation induced by thrombin are markedly inhibited by protamine sulphate (64), and protamine sulphate also alters the interactions between platelet glycoprotein GPIb and vWF, especially when the protamine sulphate levels are in excess of heparin (64). Thus, optimization of the dose of protamine sulphate is essential to minimize its potential adverse side effects (65). This indicates that extra protamine sulphate doses should not be routinely administered when prolonged ACTs are measured following CPB, unless there is evidence that there is a high plasma level of heparin-since the prolonged ACT could reflect heparin-independent

coagulopathy (65). Recent data suggests that re-transfusion of cardiotomy suction blood impairs platelet function and clot formation (66). These findings were confirmed in a study showing that platelet activation and inflammation are reduced in patients when re-infusion of blood aspirated from the pericardium and pleural space is avoided, or is processed in a cell saver before re-transfusion (67,68). CPB induces intensive activation of the inflammatory system (69). The link between the activation of the coagulation and the inflammatory system during CPB is complex, and may in part be related to the generation of acute-phase reactions similar to those seen in sepsis (70).

The haemodilution during CPB will reduce the concentration of clotting factors, RBCs, and platelets (52). Modified ultrafiltration is added to the CPB circuit to remove excess fluid and produce haemoconcentration. Several studies have shown that modified ultrafiltration (MUF) improve homeostasis after CPB in paediatric cardiac surgery, with beneficial effects on postoperative bleeding, chest drainage volume, and the need for blood transfusions (10). Friesen et al. have reported significantly increased haematocrit, fibrinogen levels, and total plasma protein levels, but no effect on platelet count (71). Last but not least, hypothermia influences coagulation by slowing down enzymatic reactions (43, chap 14).

Monitoring of coagulation and platelet function

Perioperative coagulation tests are performed to identify the coagulation abnormalities that are most likely to contribute to bleeding or thrombosis. If the results of these tests can be available to the clinician in a short time, therapy can be directed more effectively to the specific cause of bleeding or thrombosis, leading to more rapid correction of the coagulopathy and avoidance of unnecessary therapy. Tests can be divided between those conducted primarily in haematology laboratories and those available at the patient's bedside (point-of-care devices). The objective with point-of-care tests is to make the results available to clinicians more rapidly. All tests available have their own advantages and limitations.

Laboratory–based coagulation tests

The coagulation system could be investigated in a systemic way, screening the function of either the extrinsic or the intrinsic pathway. This will give an overview of the enzymes, co-factors, and inhibitors involved in the respective

pathway. The test also monitors influences of drugs or auto-antibodies (43, chap 12). Activated partial thromboplastin time (APTT) assesses the intrinsic pathway, and the test is also often used for monitoring of heparin effect. Prothrombin time (PT, (INR)) assesses the extrinsic pathway, and the test is also used to monitor the effects from oral-anticoagulants (vitamin K antagonists). Interpretation of the PT test can be complicated. First, PT is prolonged in a number of situations despite functionally normal coagulation, including healthy neonates and patients with moderate hepatic disease (72). In these patients, the long PT reflects low concentrations of coagulation factors which, *in vivo*, are balanced by low concentrations of inhibitors. A long PT is also common in the absence of abnormal bleeding after paediatric heart surgery, and this may reflect a similar situation. Basing treatment on PT may not lead to optimal correction of bleeding. This was also confirmed in studies that found that abnormal preoperative routine coagulation results (PT, APTT) were not predictive of excessive bleeding in children undergoing CPB (24, 73).

Fibrinogen

The most frequently used method of measuring fibrinogen concentration is the Clauss assay (74). The test can interfere with heparin and fibrinogen degradation products (FDP), which might lead to falsely low values.

Platelet tests

Platelet aggregation tests measure the ability of various agonists to induce *in vitro* activation and platelet-to-platelet aggregation. Classically, Born aggregometry uses platelet-rich plasma. The method is challenging, time consuming, and is only performed in specialized labs by experienced technicians; also, the quality of the sample is critical.

Point-of-care tests

Thromboelastometry/thromboelastography

These methods monitor haemostasis in a low-shear environment as a whole dynamic process, instead of revealing information on isolated parts of the different pathways (Fig. 6). The method yields qualitative and quantitative data that characterize clot formation, its physical strength and stability, and its retraction (43, chap 9). The method was first described in 1948 by Har-

tert, and even though the method provided interesting analytical information, it was initially difficult to use in routine clinical practice (75). At the beginning of 1990s, the principle of thromboelastometry (ROTEM®; Pentapharm, Munich, Germany) was developed (76,77). In contrast to classical thromboelastography, thromboelastometry is insensitive to vibration and has automated pipetting.

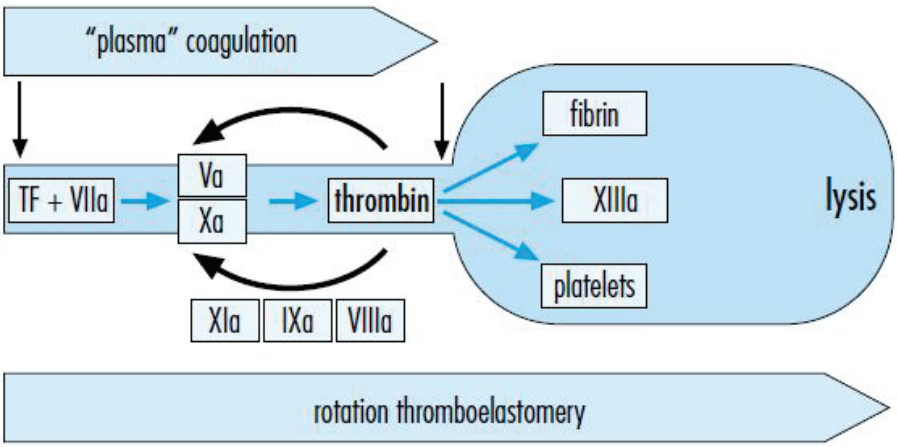

Figure 6: Physiological coagulation during thromboelastometry/thromboelastography.

To examine different pathways in the coagulation process, different assays are available: INTEM (activation of clot formation via the contact phase; assessment of factors XII, XI, IX, VIII, X, V, II, I, platelets, and fibrinolysis); EXTEM (activation of clot formation by thromboplastin (tissue factor); assessment of factors VII, X, V, II, I, platelets, and fibrinolysis); FIBTEM (activation as in EXTEM with addition of cytochalasin D, a platelet-blocking substance. In the FIBTEM assay, fibrinogen levels and fibrin polymerization can be assessed in a functional way); and HEPTEM (activation as in INTEM, with the addition of heparinase). Heparinase degrades heparin. When HEPTEM results are compared to INTEM results, heparin-related coagulation disturbances can be specifically detected (76,77). All extrinsic activated tests include a heparin inhibitor, which is able to eliminate the effect of up to 6 international units (IU) of heparin per mL of blood (77,78). The time elapsed between the activator being added and the onset of clot formation is defined as the clotting time (CT), which is dependent on the activator (this corresponds to the clotting time measured by

APTT or PT). Clot formation time (CFT) is the interval between the onset of coagulation and the curve reaching an amplitude of 20 mm. This value provides information on the rate of clot formation.

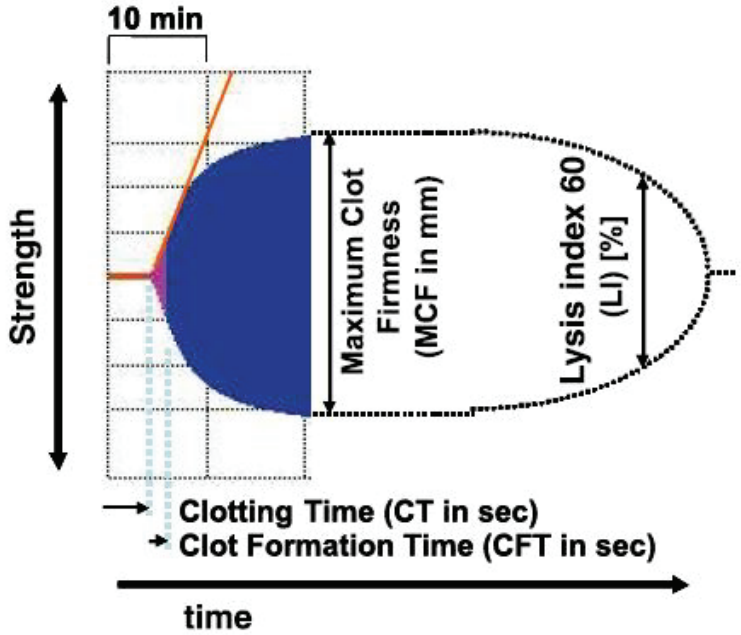

Figure 7: Thromboelatometry parameters.

The maximum amplitude is a measure of the maximum strength of the clot, referred to as maximum clot firmness (MCF). The strength of a clot is affected by a few factors, the most important being fibrinogen, platelets, and FXIII (Fig. 7). Maximum clot firmness in the FIBTEM analysis is inhibited by pharmacological means with cytochalasin D, and the clot firmness corresponds to the plasma component-mainly fibrinogen (79).

Hyperfibrinolysis poses a considerable differential diagnostic problem in perioperative bleeding. In this situation, TEM/TEG is considered the gold standard for diagnosis of hyperfibrinolysis or premature clot lysis (77,80).

Important limitations of TEM and TEG include that they completely ignore flow dynamics and are insensitive to diagnosis of vWD syndrome and disorders of primary haemostasis. Pharmaceutical platelet inhibition cannot be detected.

Platelet function tests

A number of different platelet function tests are commercially available, including PFA-100, Verify Now, and impedance aggregometry (81). Recently, impedance aggregometry has gained widespread use. The method was developed by Cardinal and Flower, and it has been used since the 1980s for the assessment of platelet function in whole blood (81,82). Aggregometry is based on the principle that blood platelets are non-thrombogenic in their resting state, but that they expose receptors on their surface when they become activated, which allow them to attach to sites of vascular injury and to artificial surfaces. In the multiple-electrode impedance aggregometry analyzer (Multiplate®; Roche Diagnostics, Basel, Switzerland), analysis takes place in a single-use test cell, which incorporates a dual sensor unit and a coated stirring magnet. When platelets stick to the sensor wires, they enhance the electrical resistance between them, which is continuously recorded-resulting in an aggregation curve (83). The area under the aggregation curve is a measure of platelet aggregation, and is measured in (AU × min) (which is then converted to units (U), for simplicity (Fig. 8). The most important differences between classical Born aggregometry and impedance aggregometry are that impedance aggregometry uses whole blood instead of platelet-rich plasma (PRP), and it uses hirudin or heparin as anti-coagulant instead of citrate.

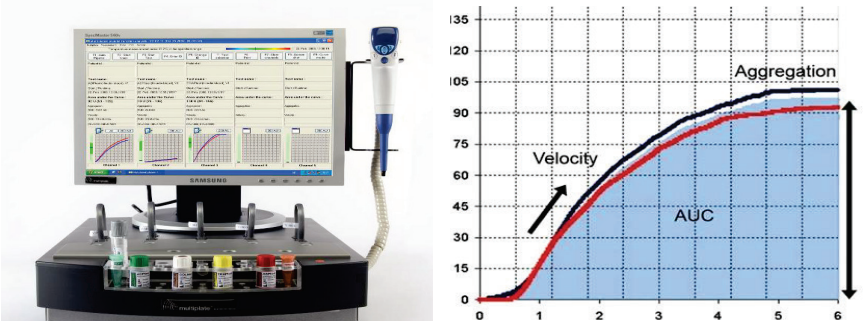

Figure 8: Impedance aggregometry monitor and impedance aggregometry result curve.

Several specific test reagents are available for stimulation of different receptors or activation of signal transduction pathways of platelets, in order to detect changes induced by drugs and by acquired or hereditary platelet disorders. The tests include:

- ASPI test: arachidonic acid (AA) is the substrate for cyclo-oxygenase (COX), which forms thromboxane A2 (TXA2). Thromboxane A2 is a potent platelet agonist. COX is inactivated irreversibly by ASA and reversibly by several anti-inflammatory drugs.
- ADP test: adenosine diphosphate (ADP) activates platelets by stimulation of ADP receptors. The most important ADP receptor ($P2Y_{12}$) is blocked by clopidogrel, prasugrel, and ticagrelor for example.
- TRAP test: thrombin receptor-activating peptide-6 (TRAP-6) stimulates the thrombin receptors PAR 1 and PAR 4 on the platelet surface. Thrombin is the most potent platelet activator. Its action is not blocked by ASA or clopidogrel. TRAP test also allows detection of the effect of GpIIb/IIIa receptor inhibitors in blood samples from patients treated with ASA or clopidogrel.

Impedance aggregometry has been tested in different clinical settings, including anti-platelet therapy in patients with acute coronary syndrome (84,85), prediction of platelet transfusion in adult cardiac surgery (86), and prediction of both bleeding complications and thrombosis after off-pump coronary artery by-pass surgery (87). Important limitations of impedance aggregometry include the fact that there are limited data concerning sensitivity of the method for analysis of von Willenbrand's disease (82), and data on its diagnostic power are also limited.

Aims

- To investigate whether thromboelastometry analysis in paediatric cardiac surgery can be accelerated by analyzing thromboelastometry at cardiopulmonary bypass and by analyzing clot firmness at 10 minutes instead of at maximum firmness (paper I).

- To determine whether routine use of intraoperative thromboelastometry reduces the number of perioperative transfusions and influences transfusion patterns in paediatric cardiac surgery (paper II).

- To determine whether the effects of acetyl salicylic acid medication on platelet aggregation can be monitored with impedance aggregometry in children with systemic-to-pulmonary shunts (paper III).

- To describe changes in platelet count and platelet function during and after paediatric cardiac surgery, and their potential associations (paper IV).

- To determine whether modified ultrafiltration influences coagulation and platelet function in paediatric cardiac surgery (paper I and paper IV).

- To determine whether thromboelastometry can detect clinically significant platelet dysfunction before, during, and after paediatric cardiac surgery (paper V).

Materials and methods

Patients

The Human Research Ethics Committee of the Sahlgrenska Academy at the University of Gothenburg approved all the studies. All the patients in studies I, III, IV, and V were included after obtaining written informed consent from caregivers. The studies were performed at the Department of Paediatric Anaesthesia and Intensive Care at Sahlgrenska University Hospital, Gothenburg, Sweden. Patients with a known coagulation defect or severe renal or hepatic disorder were excluded. All patients were operated on and anaesthetized by the same group of surgeons and anaesthesiologists.

Paper I

Fifty-six paediatric cardiac patients undergoing surgery with CPB were included in this prospective observational study. Twenty-three patients (41%) had a body weight of < 5 kg. Patient characteristics and types of congenital heart defects are given in Table 1.

Table 1. Patient characteristics, diagnoses, and intraoperative variables in paper I.

Age, months	
Mean ± SD	21± 33
Median (range)	5.8 (0.1–124)
Weight, kg	
Mean ± SD	9.5 ± 8.0
Median (range)	5.8 (2.3–42)
Girls, n (%)	21 (38%)
Diagnoses, n (%)	
ASD	3 (5%)
VSD	13 (23%)
AS	3 (5%)
AVSD	9 (16%)
CoA	2 (4%)
Fallot	4 (7%)
HLHS	7 (13%)
TGA	4 (7%)
Others	11 (20%)
CPB time, min	132 ± 72
Aortic clamp time, min	66 ± 45

Key: ASD, atrial septal defect; AS, aortic stenosis; AVSD, atrial-ventricular septal defect; Coa, coarctation; CPB, cardiopulmonary bypass; HLHS, hypoplastic left heart syndrome; TGA, transposition of the great arteries; VSD, ventricular septal defect.

Mean ± standard deviation, median (range), or number (percentage)

Paper II

Informed parental consent for the control group was waived by the Ethics Committee. Fifty patients were prospectively included in the study group after obtaining written informed consent from caregivers. The study group was compared with a procedure- and age-matched control group. Patient characteristics are given in Table 2.

Table 2: Patient demography and baseline characteristics in paper II

	STUDY GROUP n = 50	**CONTROL GROUP n = 50**	**p-value**
Age, months	5 (0.1 - 135)	6 (0.1 - 175)	0.94
Female gender	26 (52%)	22 (44%)	0.42
Weight, kg	5.7 (2.2 - 42)	5.8 (2.9 - 41)	0.43
Preoperative			
Haemoglobin, g/L	126 ± 21	127 ± 28	0.83
Haematocrit, %	38.2 ± 6.3	38.5 ± 8.3	0.86
Platelet count, $x10^9$/L	366 ± 145	327 ± 115	0.25
PT, INR	1.28 ± 0.18	1.24 ± 0.17	0.31
ECC time, min	118 (27- 383)	96 (23 - 302)	0.20
Aortic clamp time, min	58 (0 -169)	58 (0 - 224)	0.97
Tranexamic acid	29 (58%)	29 (58%)	1.0

Key: INR, international normalized ratio; PT, prothrombin time; ECC, extracorporeal circulation.

Mean ± standard deviation, median (range), or number (percentage).

Paper III

Fourteen patients were included in a prospective observational study. A Sano shunt was implanted in eight children, a modified Blalock-Taussig shunt in five, and a central shunt in one child. Patient demographics and surgical procedures are presented in Table 3.

Table 3. Patient characteristics, diagnosis, procedures, and ASA dose in paper III

Patient	Gender	Age, (days)	Weight, (kg)	Diagnosis	Operation	ASA 1, mg/kg	ASA 2, mg/kg
1	M	8	3.7	PA	BT	5.4	–
2	F	13	4.6	AV	S (ND)	4.3	–
3	F	21	2.2	PA	BT	4.5	4.5
4	F	5	3.5	HL	S	5.7	7.1
5	M	12	3.0	HL	S (ND)	5.0	5.0
6	F	3	3.4	HL	S (ND)	4.4	–
7	F	11	3.5	HL	S(ND)	4.3	4.3
8	M	12	3.6	HL	S (ND)	5.6	6.9
9	M	11	3.9	HL	S (ND)	5.1	5.1
10	M	12	3.3	HL	BT (ND)	4.5	4.6
11	M	31	2.7	AV	C	5.6	5.6
12	F	6	3.7	PA	BT	4.1	4.1
13	M	100	4.6	DO	S	4.3	5.4
14	M	12	3.5	PA	BT	5.7	7.1

Key: ASA 1, initial ASA dose; ASA 2, adjusted ASA dose after 3-6 months of treatment; BT, modified Blalock-Taussig shunt; S, Sano shunt; C, central shunt; ND, Norwood procedure; PA, pulmonary atresia; HL, hypoplastic left heart syndrome; DO, double- outlet right ventricle; AV, atrial-ventricular septal defect; M, male, F, female

Papers IV and V

Fifty-seven patients undergoing paediatric cardiac surgery with CPB were included in a prospective observational study. The patient characteristics and the types of congenital heart defects are given in Table 4.

Table 4. Patient characteristics, operative variables, and preoperative laboratory analyses in paper IV and V.

Age, months	5 (0.1 - 90.2)
Weight, kg	5.8 (2.4 - 23)
Girls, n (%)	24 (42%)
Diagnosis	
ASD	1
VSD	13
AVSD	11
Tetralogy of Fallot	8
TGA	3
AS	3
HLHS, DORV, hypoplastic aortic arc	7
Truncus arteriosus	2
Others	9
CPB time, min	124 ± 69
Aortic clamp time, min	67 ± 48
Haemoglobin, g/L	130 ± 22
Prothrombin time, INR	1.2 ± 0.2

Key: AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrial-ventricular septal defect; CPB, cardiopulmonary bypass; DORV, double-outlet right ventricle; HLHS, hypoplastic left heart syndrome; INR, international normalized ratio; SD, standard deviation; TGA, transposition of the great arteries; VSD, ventricular septal defect.

Mean ± standard deviation, median (range), or number (percentage).

Anaesthesia and cardiopulmonary bypass

Anaesthesia

Intravenous midazolam and ketamine were used for induction of anaesthesia. Maintenance of anaesthesia included inhaled isoflurane before and during CPB, iv fentanyl (25–75 μg/kg), iv midazolam (0.1–0.3 mg/kg), iv pancuronium (0.1–0.3 mg/kg) or atracurium (0.5–0.7 mg/kg), supplemented with iv propofol in patients older than 1 year and weighing > 10 kg, and we aimed for early tracheal extubation. The anaesthesia procedure remained the same during the study period and was identical to that used for the matched controls in paper II.

Cardiopulmonary bypass

Heparin (Leo Pharma A/S, Ballerup, Denmark) was used as anti-coagulation and repeatedly controlled with activated clotting time (ACT) (Hemocron Jr II ACT+; ITC, Edison, NY, USA) during by-pass. Reversal of heparinization was achieved with protamine (Leo Pharma A/S).

Cardiopulmonary bypass was conducted with a hard-shell reservoir and a patient size-adapted membrane oxygenator. The total pump prime volume ranged from 350 to 700 mL, depending on the tubing and the oxygenator. The prime consisted of crystalloid fluid, packed red blood cells, mannitol, heparin, and Tribonat® (Fresenius Kabi AB, Uppsala, Sweden). Myocardial protection was achieved with cold intermittent blood cardioplegia.

Modified ultrafiltration was performed after weaning from CPB.

Study design and analyses

Modified rotational thromboelastometry (TEM)

Whole blood coagulation was analyzed by modified rotational thromboelastometry (ROTEM®, Pentapharm GmbH, Munich, Germany) (76,77). Technical details and evaluation of the method have been reported previously (22,78,88). Whole blood (900 μL) was drawn from the non-heparinized arterial line and collected in a tube containing citrate (Minicollect; Greiner Bio-One GmbH, Badhaller, Austria). Samples of 300 μL each were analyzed at 37°C using INTEM (contact pathway activation), HEPTEM (heparinase

added for heparin-insensitive analysis), and FIBTEM. Clotting time (CT), clot formation time (CFT), and maximum clot firmness (MCF) were measured in the INTEM and HEPTEM channels. The specific importance of the fibrin polymerization for the MCF was evaluated in the FIBTEM analysis.

Platelet aggregometry

Whole blood samples were collected in heparinized tubes (Vaccuette LH Lithium Heparin; Greiner Bio-One, Kremsmynster, Austria) for aggregometry. Platelet aggregation was analyzed by multiple-electrode impedance aggregometry (Multiplate® Roche Diagnostics, Basel, Switzerland), as described previously (83,89). The analysis is performed in the test cell with 300 μL pre-heated saline (37°C) and 300 μL heparin anti-coagulated whole blood. The test kits used were ADP test kit (final ADP concentration: 6.5 μmo/L), ASPI test kit (final arachidonic acid (AA) concentration: 0.5 mmo/L), and TRAP test kit (final concentration of thrombin receptor-activating peptide-6: 32 μmo/L).

Study design

Paper I

Haemoglobin (Hb), haematocrit (Hct), and platelet count were analyzed with routine methods before surgery, immediately after surgery, and on the first postoperative morning. Thromboelastometry with HEPTEM clotting time (CT), HEPTEM clot formation time (CFT), HEPTEM clot firmness after 10 min (A10) and at maximum (MCF), and FIBTEM clot firmness after 10 min and at maximum were analyzed at five pre-set time points: (1) after induction of anaesthesia, (2) at the end of CPB, after rewarming, (3) after modified ultrafiltration (after weaning from by-pass but before protamine administration), (4) on arrival at the ICU after surgery, and (5) on the first postoperative day.

Measurements of TEM variables before and after weaning and ultrafiltration were compared. In addition, HEPTEM and FIBTEM clot firmness values after 10 min and at maximum firmness were compared.

Paper II

The study group was compared with an age-, weight-, and procedure-matched control group regarding transfusion prevalence, number of transfusions and the transfusion pattern of packed red blood cells (PRBCs), FFP, platelets, and fibrinogen intraoperatively and in the ICU. After weaning from by-pass and protamine administration, bleeding was clinically evaluated by observation of the operating field for the presence of oozing without visible clots. In addition, haemodynamic derangements and repeated analyses of Hb and Hct were evaluated. In the study group, but not in the control group, transfusions were guided by thromboelastometry according to the following schedule.

1 Insignificant bleeding - normal TEM ⇒ no transfusions
2 Insignificant bleeding - abnormal TEM ⇒ no transfusions
3 Significant bleeding - normal TEM ⇒ surgical re-evaluation
4 Significant bleeding - abnormal TEM ⇒ transfusion of blood products as indicated by:
   a. HEPTEM MCF < 50 mm ⇒ platelets
   b. FIBTEM MCF < 9 mm ⇒ fibrinogen concentrate
   c. HEPTEM CT > 240 s ⇒ fresh frozen plasma
   d. HEPTEM CFT > 110 s ⇒ fibrinogen and/or platelets, depending on MCF

Total postoperative bleeding was defined in both groups as the total drain loss until 06.00 on the first postoperative morning. Transfusion volumes of PRBCs, fresh frozen plasma (FFP), platelets, and fibrinogen concentrate intraoperatively and in the ICU until 06.00 on the first postoperative morning were registered. Transfusions in the ICU were not guided by thromboelastometry.

Paper III

Once oral feeding was established, acetyl salicylic acid treatment was started with a dose of 4-5 mg/kg once daily.

Routine laboratory analyses and haemostatic test (APTT, PT, factor V activity, concentration of fibrinogen, D-dimer, anti-thrombin, protein C, protein S) were performed at three time points: (1) before the primary shunt operation, (2) before the first acetyl salicylic acid dose (postoperative day 1-3), and (3) after 3-6 months of acetyl salicylic acid treatment. Platelet aggre-

gation and platelet count were analyzed at five time points: (1) before the primary shunt operation; (2) before the first acetyl salicylic acid dose; (3) 5 h after the first acetyl salicylic acid dose; (4) 24 h after the first acetyl salicylic acid dose, and (5) after 3-6 months of acetyl salicylic acid treatment. The immediate response to acetyl salicylic acid was calculated as being the difference between measurement number 2 (before acetyl salicylic acid) and measurement number 3 (5 h after acetyl salicylic acid).

Paper IV

Platelet count, platelet aggregometry, and haematocrit were analyzed in all patients at five pre-set time points: (1) after induction of anaesthesia, (2) at the end of CPB (after rewarming), (3) after modified ultrafiltration (after weaning from by-pass but before protamine administration), (4) on arrival at the ICU, and (5) on the first postoperative day. In paper IV, impaired platelet function during CPB and on arrival at the ICU was defined as ADP-initiated aggregation of ≤ 30 Units. The correlation between platelet count and function was calculated at the different time points. Platelet count and platelet function before and after ultrafiltration was calculated, and factors associated with impaired platelet function were determined. Finally, the associations between platelet function and transfusion requirements were assessed.

Paper V

Sampling was performed at the same time points as in paper IV.

The correlation between platelet aggregometry and platelet-dependent thromboelastometry variables (CFT and MCF) were calculated at the different time points. Sensitivity, specificity, and positive and negative predictive values for the ability of thromboelastometry tests to reveal platelet dysfunction as measured with platelet aggregometry were determined. After preliminary analyses, CFT ≥ 220 s and MCF ≤ 40 mm were chosen as cut-off values. Platelet dysfunction was defined as platelet aggregation ≤ 30 Units, measured with ADP as initiator (90, 91).

Statistics

For all five studies, any p-value of < 0.05 was considered statistically significant. Statistical analyses were performed with SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL, USA) or Statistica (StatSoft Scandinavia AB, Uppsala, Sweden).

Paper I

The results are presented as mean and standard deviation (SD) or mean and 95% confidence interval. Paired t-test was used to compare continuous variables before and after ultrafiltration, and clot firmness after 10 min and at maximum firmness. Correlation was calculated with Pearson's test. No formal sample size calculation was performed.

The study was observational and explorative and the analyses were meant to be mainly descriptive. The number of study subjects was based on previous publications on the subject and was chosen for practical reasons.

Paper II

The primary outcome variable was the proportion of patients receiving any perioperative transfusion (intraoperatively and in the ICU) in the study group and in the control group. The other analyses were meant to be mainly descriptive. No power calculation was performed. For continuous variables, Student's t-test or Mann-Whitney U test was used to compare the groups, as appropriate. The Chi-square test was used for categorical variables. No corrections for multiplicity were made.

Paper III

Paired Student's t-test was used to compare the postoperative measurements with the preoperative measurement. No sample size calculation was performed. The study was descriptive and longitudinal, and the patients served as their own controls. All eligible patients at our institution between 2007 and 2009 were included in the study.

Paper IV

Paired t-test was used to compare continuous variables before and after ultrafiltration. In group comparisons, Student's t-test was used to compare normally distributed continuous variables and Mann-Whitney U test was used to compare continuous variables that were not normally distributed. Categorical variables were compared with the Chi-square test. Correlation was assessed with Pearson's test. Due to the exploratory nature of the study, no power calculation was performed.

Paper V

In group comparisons, Student's t-test was used to compare normally distributed continuous variables, Mann-Whitney U test was used to compare non-normally distributed continuous variables, and categorical variables were compared with Chi-square test. Correlation was assessed with Pearson's test. Sensitivity, specificity, and positive and negative predictive values were calculated with standard methods. A power calculation has not been performed because of the exploratory study design.

Results

Paper I

Earlier detection of coagulopathy with thromboelastometry during paediatric cardiac surgery: A prospective observational study.

TEM variables before and after haemoconcentration

Modified ultrafiltration with haemoconcentration increased haematocrit from 28 ± 3% to 37 ± 4%, ($p < 0.001$). There were limited differences when absolute values of TEM variables were compared before and after haemoconcentration. Only the differences in HEPTEM-CT and HEPTEM-MCF were statistically significant ($p = 0.036$ and $p = 0.038$, respectively). The correlation coefficients between variables on CPB and after modified ultrafiltration were all statistically significant ($r = 0.61$ to 0.82, all $p < 0.001$) (Table 5).

Clot firmness after 10 min and at maximum

There were excellent correlations between HEPTEM A10 and MCF before surgery (r=0.94), during CPB (r=0.95), after weaning and haemoconcentration (r=0.93), after surgery (r=0.93), and on postoperative day 1 (r=0.91) (all $p < 0.001$). In FIBTEM also, the correlations between A10 and MCF were excellent (r=0.98 before surgery, r=0.96 on CPB, r=0.95 after weaning and haemoconcentration, r=0.95 after surgery, and r=0.97 on postoperative day 1 (all $p < 0.001$).

The differences between A10 and MCF during surgery were highly predictable, both during CPB (with narrow confidence intervals: HEPTEM -8.2 mm (-8.9 to -7.5) and FIBTEM -0.5 mm (-0.7 to -0.3)) (Fig. 1), and after weaning and haemoconcentration (HEPTEM -8.5 mm (-9.2 to -7.8) and FIBTEM -0.5 mm (-0.8 to -0.3). (Fig. 9).

Table 5. Correlations and absolute and relative differences between thrombo-elastometric measurements during CPB and after weaning and haemoconcentration

	Correlation coefficient	p-value (correlation)	Absolute difference (95% CI)
HEPTEM			
CT, s	0.61	< 0.001	29 (2 to 57)
CFT, s	0.73	< 0.001	-26 (-53 to 1)
A10, mm	0.74	< 0.001	1.2 (-0.3 to 2.7)
MCF, mm	0.77	< 0.001	1.5 (0.1 to 2.9)
FIBTEM			
A10, mm	0.79	< 0.001	0.2 (-0.2 to 0.7)
MCF, mm	0.82	< 0.001	0.2 (-0.3 to 0.6)

Key: A10, clot firmness after 10 min; CFT, clot formation time; CI, confidence interval; CT, clotting time; MCF, maximum clot firmness.

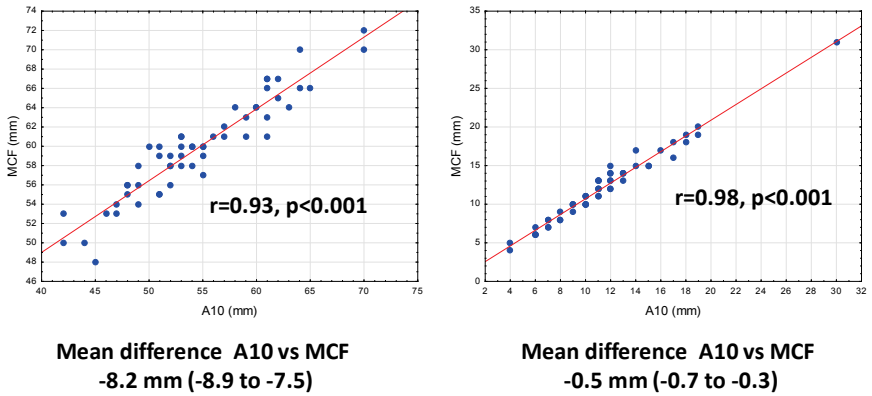

Figure 9: Correlation between HEPTEM and FIBTEM A10 and maximum clot firmness during cardiopulmonary bypass.

Paper II

Intraoperative thromboelastometry is associated with reduced transfusion prevalence in paediatric cardiac surgery.

Intraoperative and postoperative transfusions

The proportion of patients receiving any intraoperative or postoperative transfusion of PRBCs, fresh frozen plasma, platelets, or fibrinogen concentrate was significantly lower in the study group than in the control group (32/50 (64%) vs. 46/50 (92%), $p < 0.001$), as shown in Figure 10. Significantly fewer patients in the study group received transfusions of PRBCs (58% vs. 78%, $p = 0.032$) and plasma (14% vs. 78%, $p < 0.001$), while significantly more patients in the study group received transfusions of platelets (38% vs. 12%, $p = 0.002$) and fibrinogen concentrate (16% vs. 2%, $p = 0.015$) (Table 6).

Thromboelastometry

In the intraoperative TEM, analyzed during CPB, 29/50 (58%) of the patients had a HEPTEM CT value of > 240 s, 43/50 (86%) had a HEPTEM CFT of > 110 s, 37/50 (74%) had a HEPTEM MCF of < 50 mm, and 45/50 (90%) had a FIBTEM MCF of < 9 mm.

Three patients in the study group had insignificant bleeding and normal TEM. None of these patients received any intraoperative or postoperative transfusions. Twenty patients had insignificant bleeding and abnormal TEM. None of these received intraoperative transfusions, while seven received PRBCs in the ICU but not plasma or platelets. One patient had significant bleeding and normal TEM and underwent surgical re-evaluation before the sternum was closed, and did not receive any transfusions-either intraoperatively or in the ICU. Twenty-six patients had significant bleeding and abnormal TEM.

Bleeding

The postoperative blood loss and the postoperative haemoglobin levels were not significantly different in the study group and the control group.

Table 6. Proportion of patients receiving PRBCs, FFP, platelets, fibrinogen concentrate, and any transfusion intraoperatively and in the ICU.

	STUDY GROUP N=50	CONTROL GROUP N=50	p-value (Chi-square test)
Packed red blood cells (PRBCs)			
Intraoperatively	17 (34%)	34 (68%)	< 0.001
ICU	18 (36%)	25 (50%)	0.16
Total	29 (58%)	39 (78%)	0.032
Plasma			
Intraoperatively	4 (8%)	33 (66%)	< 0.001
ICU	5 (10%)	27 (54%)	< 0.001
Total	7 (14%)	39 (78%)	< 0.001
Platelets			
Intraoperatively	19 (38%)	5 (10%)	< 0.001
ICU	1 (2%)	1 (2%)	1.0
Total	19 (38%)	6 (12%)	0.003
Fibrinogen			
Intraoperatively	8 (16%)	1 (2%)	0.015
ICU	0	0	1.0
Total	8 (16%)	1 (2%)	0.015
Any transfusion			
Intraoperatively	25 (50%)	44 (88%)	< 0.001
ICU	22 (44%)	40 (80%)	< 0.001
Total	32 (64%)	46 (92%)	< 0.001

Key: ICU, intensive care unit.

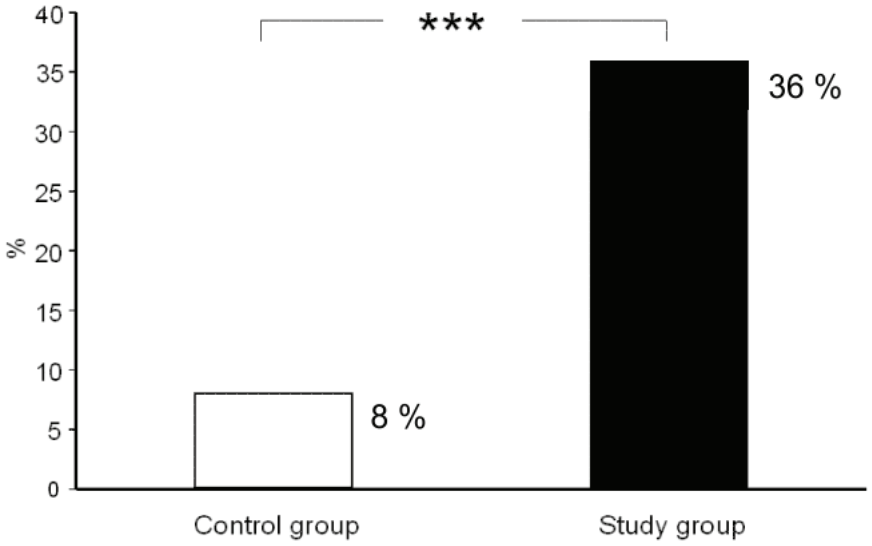

Figure 10: The proportion of patients who did not receive any transfusion in the control group and in the study group. *** $p < 0.001$ between groups (Chi-square test).

Paper III

Monitoring of acetyl salicylic acid-induced platelet inhibition with impedance aggregometry in children with systemic-to-pulmonary shunts.

ASPI test (Fig. 11A)

Acetyl salicylic acid reduced the immediate salicylic acid-dependent platelet aggregation in all but one patient (from mean 86 ± 21 to 35 ± 13 units; $p < 0.001$). When compared to preoperative levels, the first postoperative measurement ASPI test results did not differ significantly ($p = 0.13$) but were significantly lower at all the later time points (5 h, 24 h, and 3-6 months after surgery) (Fig. 11). Thirteen of 14 patients (93%) were in the therapeutic range for acetyl salicylic acid treatment (ASPI test < 60 units) 5 h after the first dose of acetyl salicylic acid, 12 of 14 (86%) after 24 h, and 7 of 11 (64%) after 3-6 months of acetyl salicylic acid treatment (Fig. 12).

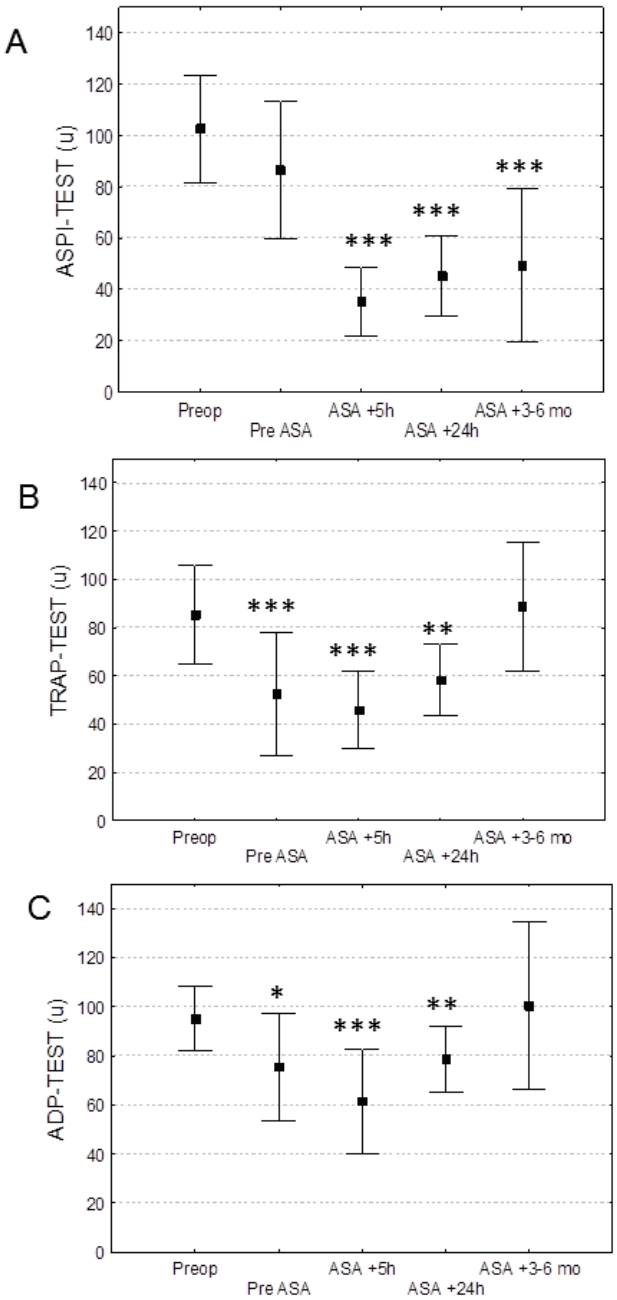

Figure 11: Impedance aggregometry with ASPI test (A), TRAP test (B), and ADP test (C) before and after acetyl salicylic acid medication in children who were operated upon with systemic-to-pulmonary shunts. Mean ± SD. *p < 0.05 vs. preoperatively, **p < 0.01 vs. preoperatively, ***p < 0.001 vs. preoperatively.

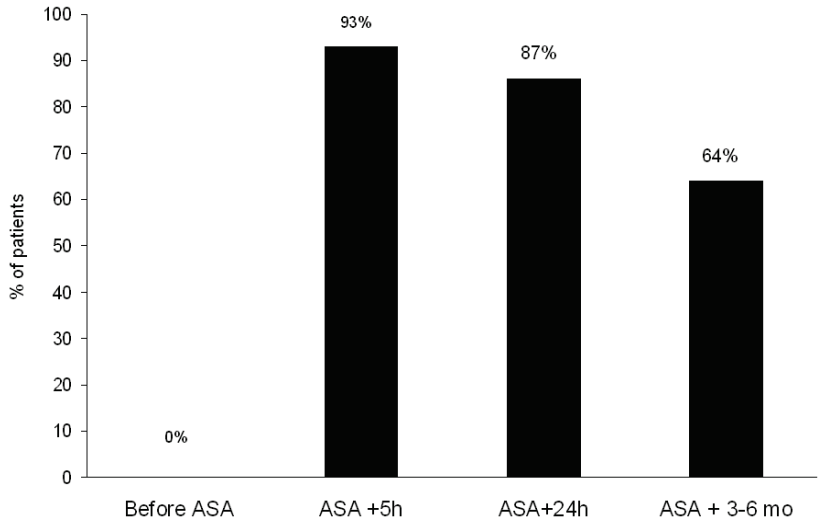

Figure 12: Percentage of patients within the therapeutic range for acetyl salicylic acid treatment (arachidonic acid (ASPI) test < 60 units).

Paper IV

Platelet count and function in paediatric cardiac surgery: A prospective observational study.

Platelet count and function

Platelet counts and all aggregation tests were significantly reduced during surgery in comparison to preoperative levels, with the greatest reduction at the end of CPB (Table 7 and Fig. 13). The reduction in ADP-induced aggregation was greatest, followed by platelet count. On postoperative day 1, platelet count was reduced by 47 ± 30% while platelet aggregation had returned to or was above preoperative levels (Table 7 and Fig. 13).

There were moderate correlations between platelet count and platelet aggregation at all time points, except for TRAP-induced aggregation preoperatively. Ultrafiltration increased haematocrit from 28% to 36% ($p < 0.001$) but had no significant influence on platelet count or ADP- and TRAP-induced aggregation (Table 7).

Age, weight, and aortic clamp time were intraoperative factors associated with platelet dysfunction. Factors associated with platelet dysfunction on

arrival at the ICU were age, weight, preoperative haemoglobin, and preoperative platelet count.

Intraoperatively, 27 of 57 patients (47%) received transfusions of blood products, 18 (32%) with red blood cell concentrate, 9 (16%) with platelets, and 17 (30%) with fibrinogen concentrate. None of the patients received plasma transfusion. Impaired intraoperative platelet function was highly associated with the prevalence of intraoperative transfusion (Fig. 14).

Table 7. Platelet aggregometry variables at five pre-set time points. Mean ± SD.

	Before surgery	**On CPB**	**After CPB and modified ultrafiltration**	**Arrival at ICU**	**Day 1 after surgery**
Platelet count (x 10^9)	369 ± 137	152 ± 53***	155 ± 50***	162 ± 63***	185 ± 124***
Haematocrit (%)	39 ± 7	28 ± 2***	36 ± 4**$^{\#\#\#}$	36 ± 5*	38 ± 5
Platelet aggregometry (Units, U)					
ADP	71 ± 19	27 ± 20***	29 ± 22***	41 ± 21***	61 ± 22**
AA	73 ± 21	34 ± 25***	40 ± 28***$^{\#}$	55 ± 29***	83 ± 31**
TRAP	86 ± 16	49 ± 35***	53 ± 33***	68 ± 31***	87 ± 28

Key: AA, arachidonic acid; ADP, adenosine diphosphate; CPB, cardiopulmonary bypass; ICU, intensive care unit; TRAP, thrombin receptor-activating peptide. *$p < 0.05$ vs. baseline, **$p < 0.01$ vs. baseline, ***$p < 0.001$ vs. baseline,
$^{\#}p < 0.05$ vs. on CPB, $^{\#\#\#}$ $p < 0.001$ vs. on CPB.

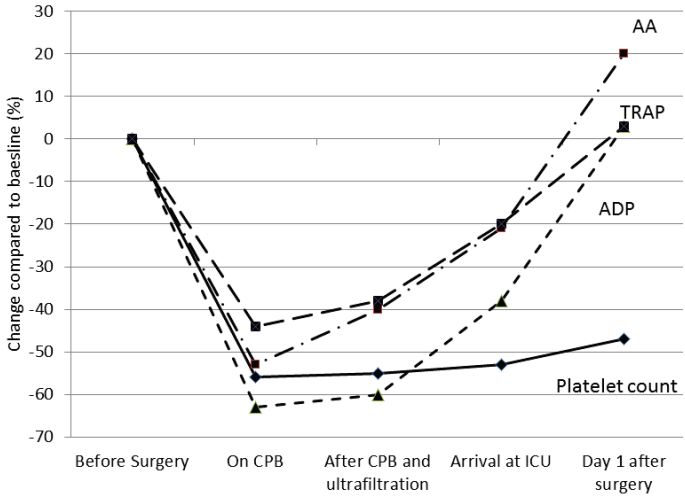

Figure 13: Percentage change in platelet count and platelet aggregation from baseline during and after paediatric cardiac surgery. For absolute values, standard deviations, and statistical analyses, see Table 2.

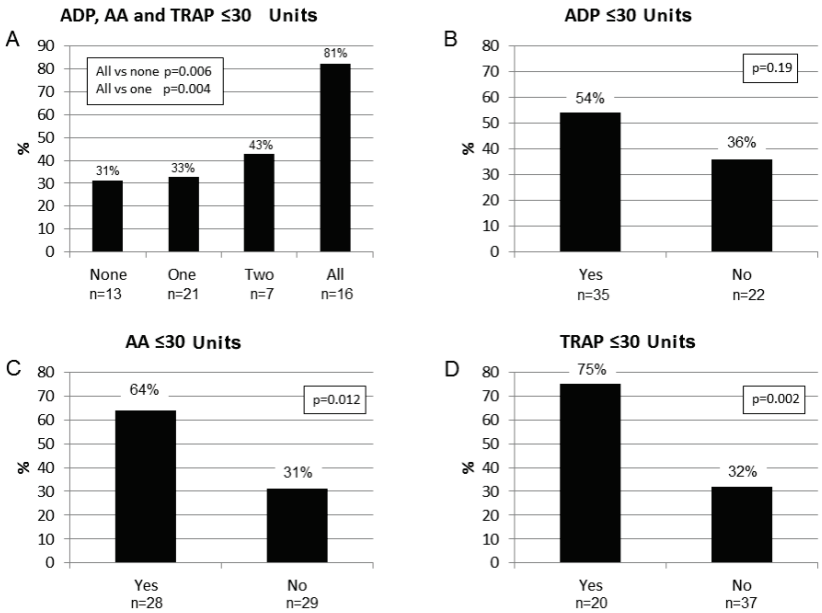

Figure 14: Panel A: Prevalence of intraoperative transfusions for patients with none, one, two, or three of the ADP-, AA-, and TRAP-induced aggregation measurements ≤ 30 Units. Panels B-D: Prevalence of intraoperative transfusions in patients with ADP-induced (panel B), AA-induced (panel C), or TRAP-induced (panel D) aggregation ≤ or >30 Units.
Key: ADP, adenosine diphosphate; AA, arachidonic acid; TRAP, thrombin receptor-activating peptide.

Paper V

Perioperative monitoring of platelet function in paediatric cardiac surgery: Thromboelastometry, platelet aggregometry, or both?

The correlations between ADP-, AA-, and TRAP-induced aggregation and MCF and CFT thromboelastometry before, during, and after CPB were moderate at all time points except on arrival at the ICU. The best correlations were seen during CPB. Accordingly, ADP-, AA-, and TRAP-induced platelet aggregation was significantly lower in children with CFT ≥ 220 s than in children with CFT < 220 s, as shown in Fig. 15 (all $p < 0.001$).

During CPB, both CFT and MCF had a high sensitivity (87% and 95%, respectively), a high negative predictive value (82% and 95%), acceptable specificity (62% and 60%), and positive predictive value (69% and 60%) for revealing platelet dysfunction (Table 8). After ultrafiltration and weaning from CPB, the predictive values were less accurate and on day 1, TEM did not identify any of the six children with platelet dysfunction.

The relationship between CFT and MCF on CPB and the prevalence of intraoperative transfusions are shown in Fig. 16. The prevalence was significantly higher in children with CFT ≥ 220 s ($p < 0.001$) (Fig. 16. A) and in children with MCF ≤ 40 mm ($p = 0.002$) (Fig. 16 B).

Table 8. Specificity, sensitivity, and positive and negative predictive value for the ability of thromboelastometry variables to predict platelet dysfunction* during and immediately after paediatric surgery, and on the first postoperative day

	On CPB	After CPB and modified ultrafiltration	On arrival at ICU
Sensitivity			
HEPTEM-CFT > 220 s	87	75	27
HEPTEM-MCF < 40 mm	95	74	9
Specificity			
HEPTEM-CFT > 220 s	62	55	63
HEPTEM-MCF < 40 mm	60	47	91
Positive predictive value			
HEPTEM-CFT > 220 s	69	62	27
HEPTEM-MCF < 40 mm	60	41	40
Negative predictive value			
HEPTEM-CFT > 220 s	82	69	63
HEPTEM-MCF < 40 mm	95	78	60

Key: CFT, clot formation time; CPB, cardiopulmonary bypass; ICU, intensive care unit; MCF, maximum clot firmness.

* Platelet dysfunction was defined as ADP-induced aggregation ≤ 30 Units.

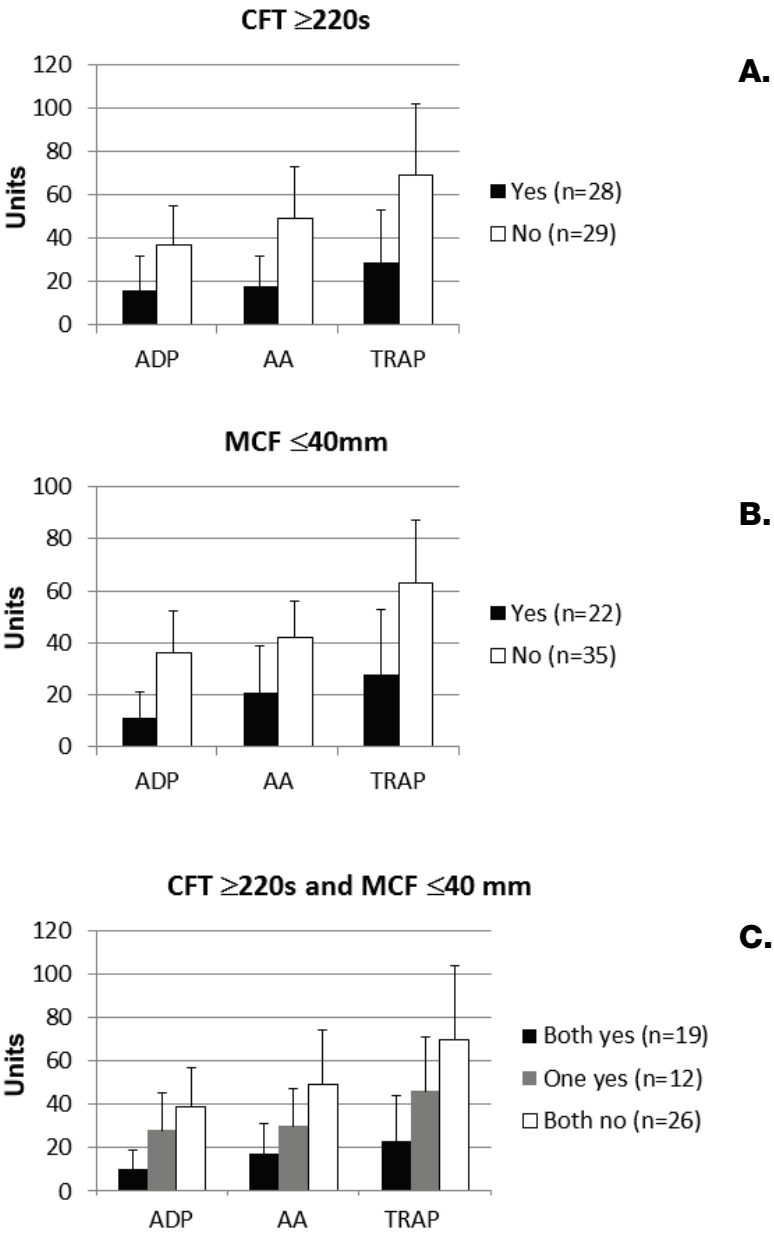

Figure 15. ADP-, AA-, and TRAP-induced platelet aggregation during CPB in children with CFT ≥ or < 220 s (panel A), in children with MCF ≤ 40 or > 40 mm (panel B), and in children with both, one, or none of CFT ≥ 220 s and MCF ≤ 40 mm (panel C).
Key: AA, arachidonic acid; ADP, adenosine diphosphate; CFT, clot formation time; CPB, cardiopulmonary bypass; MCF, maximum clot firmness; TRAP, thrombin receptor-activating peptide.

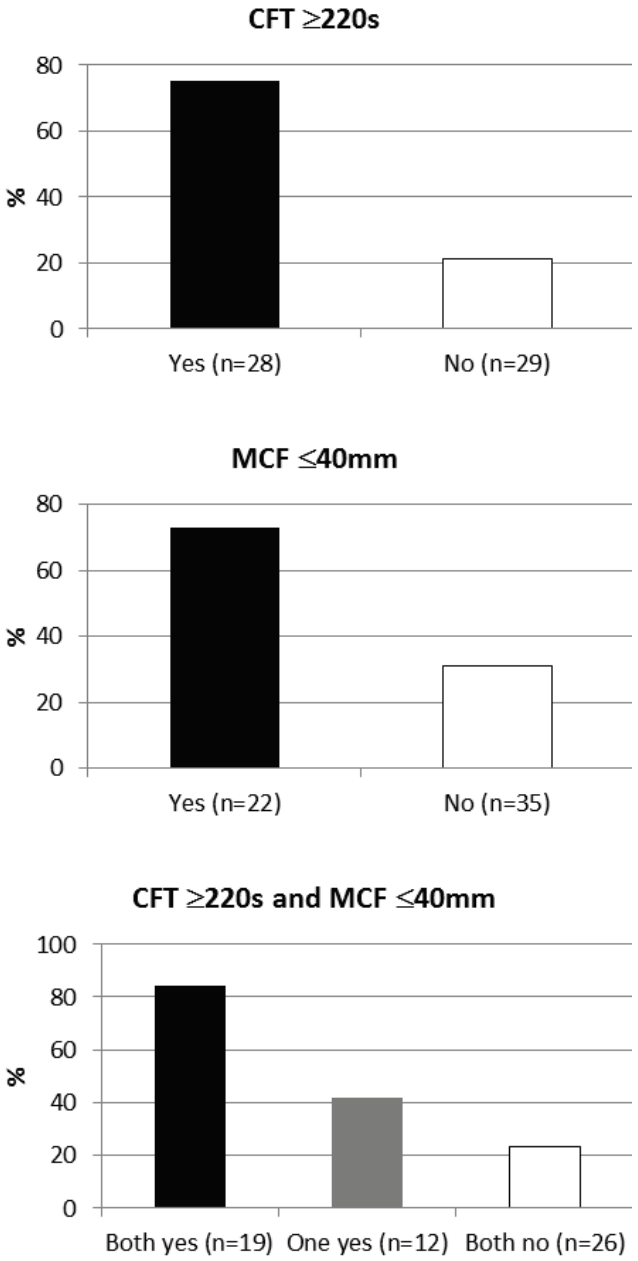

Figure 16: Prevalence of intraoperative transfusions in children with CFT ≥ or < 220 s (panel A), in children with MCF ≤ 40 or > 40 mm (panel B), and in children with both, one, or none of CFT ≥ 220 s and MCF ≤ 40 mm (panel C).
Key: CFT, clot formation time; CPB, cardiopulmonary bypass; MCF, maximum clot firmness; TRAP, thrombin receptor-activating peptide.

Discussion

Paper I

Earlier detection of coagulopathy with thromboelastometry during paediatric cardiac surgery: a prospective observational study.

We investigated whether there was any correlation between measurements performed during CPB and measurements performed after weaning CPB and haemoconcentration. A systematic difference between the two measurements would indicate that it is necessary to wait until after weaning and haemoconcentration to perform the analysis. However, we could not detect any clear systematic variation. The correlations between the two measurements were statistically significant (r-values between 0.61 and 0.82), and in the only two variables where absolute values differed significantly (HEPTEM-CT and HEPTEM-MCF), the mean differences were small (29 seconds in CT and 1.5 mm in MCF). The results therefore suggest that TEM analyses with heparinase allow measurements during CPB after rewarming. However, in some patients the differences were greater. As a method, rotational thromboelastometry analysis has acceptable repeatability, with an intra-assay coefficient of variation for FIBTEM MCF of 6–13% and of < 5% for EXTEM MCF (92). Thus, the results suggest that there are individual differences in alterations of haemostasis in response to haemoconcentration.

Our second aim was to determine whether the assessment of intraoperative coagulation could be evaluated already after 10 min instead of at maximum firmness, which normally takes about 30 min. We found that the correlation between A10 and MCF was excellent (Fig. 9) and the difference was statistically significant. The confidence interval was, however, narrow and it is possible to directly predict the MCF intraoperatively from the A10 values by adding 8 mm to the HEPTEM analysis and 0.5 mm to the FIBTEM analysis. The close association between A10 and MCF has been found before in liver transplant and trauma patients (93,94), but not in children undergoing cardiac surgery.

Paper II

Intraoperative thromboelastometry is associated with reduced transfusion prevalence in paediatric cardiac surgery.

In paper II, we investigated whether routine monitoring of intraoperative haemostasis with thromboelastometry influences transfusion prevalence in paediatric cardiac surgery. A number of previous studies have shown an association between TEM/TEG variables and bleeding and transfusion requirements in adult and paediatric cardiac surgery (95-98), but the impact of routine intraoperative TEM/TEG on bleeding and transfusions in paediatric cardiac surgery had not been determined previously. We found a marked reduction in RBC and plasma transfusions in the TEM group while transfusions of platelets and fibrinogen increased.

This study did not define explicit TEM cut-off values as the sole trigger for transfusions. Instead, TEM values together with clinical observations guided transfusions in the immediate post-CPB period. Clinical observation of post-CPB bleeding was thus a prerequisite for transfusion, and the TEM results were additional factors for deciding the appropriate therapy. In study II, the patients in the study group were divided into four groups based on clinical observations (significant or insignificant bleeding) and TEM variables (normal or abnormal TEM). The results of the study indicated three groups that were straightforward: patients with insignificant bleeding and normal TEM do not need transfusion, and in patients with significant bleeding and normal TEM, a surgical cause of the bleeding is plausible. None of these patients received intraoperative transfusions in the study. The patients with insignificant bleeding and abnormal TEM were not transfused intraoperatively in this study, since on-going bleeding was a prerequisite for transfusion. Finally, there was a group with significant bleeding and abnormal TEM. All the patients in the study group who were transfused intraoperatively belonged to this subgroup. In these patients, TEM readings guided the decisions for transfusions, resulting in a tailored, individualized treatment.

A notable difference between the groups in study II was the lower prevalence of plasma transfusions in the TEM group (14% vs. 78%). This is of particular interest, since recent data suggest that plasma transfusion is associated with acute lung injury, both in adult and paediatric patients (99-101). Platelet transfusion was significantly more common in the study group, a finding that was probably caused by a low prevalence of platelet transfusions

in the control group (2). This result may have been due to concerns in our institution that platelet transfusion may compromise extra-anatomical shunts. Another interesting finding was that not only were intraoperative transfusions reduced in the study group, but also postoperative transfusions, despite the fact that TEM was used only to guide intraoperative transfusions. There are two potential explanations for this finding. First, the children in the study group may have arrived at the ICU less coagulopathic, making further transfusion unnecessary. Alternatively, the transfusion policy in the ICU may be biased by the intraoperative use of TEM, resulting in a more restrictive transfusion policy.

The study had important limitations. The study design was not sufficient to prove a direct causality between routine use of intraoperative TEM and transfusion prevalence. The reduced transfusion prevalence may instead have been caused by increased vigilance regarding transfusions, resulting in a changed transfusion policy (102). To prove causality, a randomized controlled trial (RCT) would be needed. The definition of abnormal TEM in study II was based on cut-off levels from adult values (92). This is a limitation, since children with congenital cardiac defects have a larger age-dependent variability in their haemostatic system, as has been demonstrated previously (88,103).

Paper III

Monitoring of acetyl salicylic acid-induced platelet inhibition with impedance aggregometry in children with systemic-to-pulmonary shunts.

Treatment with acetyl salicylic acid is generally recommended in children with systemic-to-pulmonary shunts because of the increased risk of thrombotic events (104). This recommendation is based on a large observational multicentre study by Li et al. where reduced prevalence of shunt thrombosis and improved survival was observed when acetyl salicylic acid was used (105). However, the effect of acetyl salicylic acid is rarely monitored despite evidence that a significant percentage of children may have an impaired response to acetyl salicylic acid (106-108). In study III, acetyl salicylic acid reduced the immediate arachidonic acid-induced platelet aggregation in all but one patient. The response varied considerably, with acetyl salicylic acid-dependent platelet inhibition ranging from 20% to79%, which supports the concept that acetyl salicylic acid response might be monitored. The variation in response

was in accordance with previous studies (106,107). It is, however, difficult to compare the immediate platelet inhibition in the present study with previous observations since the pre-acetyl salicylic acid values were influenced by the surgical procedure. A proportion of children were outside the therapeutic range after the immediate postoperative period, which cannot be ignored. Our results therefor indicate that the current recommended dose of acetyl salicylic acid (1-5 mg/kg) may be insufficient in some patients after the early postoperative period and that either a higher dose of acetyl salicylic acid or a combination of platelet inhibitors may be necessary. It may also be speculated that monitoring of the effect of platelet inhibition can be used to tailor individual doses and thereby ensure sufficient platelet inhibition in all patients.

In study III, platelet aggregation was monitored with multi-electrode impedance aggregometry. Impedance aggregometry has been shown to correlate with other established platelet aggregation tests (89,109,110). However, there are two important issues to discuss. First, the reference ranges used in this study came from adult patients, since no study has established reference values in children using heparin as anti-coagulant. Secondly, the therapeutic range for acetyl salicylic acid with impedance aggregometry is not well defined. The manufacturer of the test recommends that acetyl salicylic acid-treated patients should have an ASPI test result below 60 units with heparin tubes, and this range was used in the present study. Others have suggested that the lower normal limit for heparin tubes is 51 units (111). Irrespective of definition, the study showed that a large proportion of the patients were outside the therapeutic range, especially after 3-6 months.

The main limitation of this study was the sample size. The study should be regarded as a pilot investigation, and the results interpreted with caution. Larger multi-centre studies are warranted to further determine the value of monitoring acetyl salicylic acid response after systemic-to-pulmonary shunt implantation in children with congenital heart disease.

Paper IV

Platelet count and function in paediatric cardiac surgery: a prospective observational study.

The low platelet count during and after surgery confirm previous observations in paediatric cardiac surgery (7,8). In contrast, studies of perioperative platelet function have given conflicting results. Guay and co-workers and Ranucci and co-workers reported increased platelet reactivity (112,113) whereas Hofer and co-workers and Ichinose and co-workers reported reduced function (114,115) during and after paediatric cardiac surgery. The divergent results may be consequences of the multifaceted paediatric cardiac surgery in patients with immature coagulation systems, of complex surgical procedures, and of the range of patients (cyanotic-acyanotic, neonates and older children, etc.) but may also be related to differences in study design and analysis. The only moderate correlations between platelet count and aggregation found in study IV (Table 3) lend further support to the idea that measurements of platelet count alone are insufficient for estimation of platelet function during and after paediatric cardiac surgery.

Modified ultrafiltration did not influence platelet count and ADP- and TRAP-induced platelet aggregation. Ultrafiltration has previously been shown not to significantly affect thromboelastography and thromboelastometry for the assessment of intraoperative coagulation (116,117). Monitoring of platelet count, platelet function, and coagulation could therefore be performed at the end of CPB instead of waiting until after weaning from bypass. This approach might accelerate the diagnosis of platelet dysfunction and coagulation disturbances and improve tailored treatment. Impaired intraoperative platelet function, as measured with impedance aggregometry during CPB, was significantly associated with the total intraoperative transfusion prevalence (Fig. 14). Since impedance aggregometry results were not available for the physicians who prescribed transfusions, this would indicate that clinical observations, platelet count, and intraoperative thromboelastometry can identify the majority of patients with impaired intraoperative platelet function. It is, however, possible that routine perioperative platelet aggregometry would improve our ability to identify patients with clinically significant platelet dysfunction, and consequently help tailor specific transfusion therapy, but this requires further studies to be fully elucidated.

Paper V

Perioperative monitoring of platelet function in paediatric cardiac surgery: Thromboelastometry, platelet aggregometry, or both?

We investigated whether routine TEM detects clinically significant platelet dysfunction at different time points during and after paediatric cardiac surgery. We also measured platelet function with multiple-electrode aggregometry and defined platelet dysfunction as ADP-initiated aggregation ≤ 30 Units. With this definition, approximately 60% of the children had platelet dysfunction during and immediately after CPB

With TEM, platelets mainly influence CFT and MCF (118). However, these variables are not specific for platelet function, since other factors also, such as fibrin polymerization, may affect the results. In addition, impaired platelet function and impaired fibrin polymerization often occur simultaneously during and after CPB (8,119,120), which complicates the picture further. This makes interpretation of the perioperative TEM results difficult regarding platelet function. In study V, we first calculated the correlation between CFT, MCF, and platelet aggregometry and found only moderate correlations, which was to be expected given the discussion above. The best correlation was achieved during and immediately after CPB, while postoperative correlation was low or absent. We then tested the predictive values for CFT ≥ 220 s and MCF ≤ 40 mm to detect platelet dysfunction and found the same pattern-acceptable prediction during and immediately after CPB but not on arrival at the ICU or on the first postoperative day. Taken together, these results indicated that TEM has acceptable ability to detect intraoperative platelet dysfunction but no or low predictive value after the operation. The results therefore suggest that after paediatric cardiac surgery, specific platelet tests are needed to reliably assess platelet function.

The limitations of this study were the same as in Paper IV, i.e. Multiple-electrode impedance aggregometry is a new method to assess platelet dysfunction, limited study population, and lack of clear definitions of platelet dysfunction.

Summary

- Thromboelastometry results in paediatric cardiac surgery can be accelerated by analyzing before ultrafiltration and weaning cardiopulmonary bypass and by analyzing clot firmness after 10 minutes instead of at maximum.

- Routine use of intraoperative thromboelastometry reduces the overall proportion of patients receiving transfusions of blood products and alters the transfusion pattern, resulting in fewer children receiving packed red blood cells and fresh frozen plasma and more children receiving platelets and fibrinogen concentrate.

- Impedance aggregometry can be used to monitor effects of acetyl salicylic acid after shunt implantation in paediatric patients. A considerable proportion of the children are outside the therapeutic range after the immediate postoperative period.

- There are substantial reductions both in platelet count and platelet function during and immediately after paediatric cardiac surgery. Platelet function, but not platelet count, recovers during the first 24 hours after surgery. The association between count and function is moderate.

- Ultrafiltration has no or limited effects on platelet count, platelet function, and thromboelastometry analysis.

- Thromboelastometry has acceptable ability to detect intraoperative but not postoperative ADP-dependent platelet dysfunction in paediatric cardiac surgery.

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Populärvetenskaplig sammanfattning

Mätning av koagulation och trombocyt funktion under barnhjärtkirurgi

Barnhjärtkirurgin har utvecklats dramatiskt under de senaste decennierna, idag opereras allt från för tidigt födda barn till ungdomar som vuxit upp med ”medfödda” hjärtfel. Blödning under och efter hjärtkirurgi är fortfarande vanligt och en av de allvarligaste komplikationerna. Stora mängder transfusioner av blodprodukter kan också bidra till att öka sjukligheten och dödligheten i denna patientgrupp. Åtgärder för att begränsa blödning och transfusioner av blodprodukter har idag hög prioritet både inom barn- och vuxen hjärtkirurgi. En del av patienterna har också en ökad risk för blodproppsbildning efter operationen. I avhandlingen har vi undersökt om man kan: 1. Minska blödning och transfusioner genom att mäta blodets koagulationsförmåga (levringsförmåga) hos barn som hjärtopereras. 2. Tidigarelägga diagnosen av eventuell koagulationsrubbning genom att göra mätningarna redan under operationen, när patienten fortfarande är på hjärtlungmaskin. 3. Om det är möjligt att följa effekten av läkemedel som hämmar blodplättarna (acetylsalicylsyra) då vissa patientgrupper behöver denna medicin för att inte bilda blodproppar efter operation. 4. Kartlägga blodplättarnas funktion under operationen. För att besvara dessa frågeställningar har fem prospektiva studier genomförts på barn som hjärtopererats. Vi kontrollerade koagulationen och blodplättarnas funktion med patientnära metoder (tromboelastometri och aggregometri) före, under och efter hjärtkirurgi. Dessutom analyserades koagulationen med sedvanliga laboratorieprover.

Studierna visar att rutinmässig mätning av koagulationsförmågan, i kombination med klinisk bedömning av blödningsstatus under barnhjärtkirurgi, dramatiskt minskade både andelen transfunderade barn och mängden blodprodukter. Mätningen gjorde det också möjligt att bedöma varje barns specifika behov av eventuella blodprodukter. Studierna visar också att det går att få fram analysresultaten snabbare genom att mäta koagulation och funktionen hos blodplättarna redan under tiden på hjärtlungmaskin och genom att analysera koagelstyrka efter 10 minuter i stället för efter 30 minuter. Detta gör att man får tidig information om eventuell försämring i barnets koagulationsförmåga och då kan vidta åtgärder i tid. Vi fann också att det är möjligt att mäta effekten av läkemedel som hämmar blodplättarna och hindrar uppkomst av blodproppar och det visade sig att en stor andel av de behandlade barnen hade otillräcklig effekt av läkemedlet. Vidare fann vi att blodplättarnas funktion är kraftigt reducerad under och direkt efter operationen men att funktionen återhämtar sig under första dygnet efter operationen.