Cardiology in the Young

cambridge.org/cty

Preoperative heart failure is not associated with impaired coagulation in paediatric cardiac surgery

Fredrik Söderlund[1,5], Håkan Wåhlander[2,6], Emma C. Hansson[3,4] and Birgitta S. Romlin[1,4]

[1]Department of Paediatric Anaesthesiology and Intensive Care; [2]Department of Cardiology, Queen Silvia's Children and Youth Hospital, Gothenburg, Sweden; [3]Department of Cardiothoracic Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden; [4]Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [5]Department of Anaesthesiology and Intensive Care Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden and [6]Department of Paediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Original Article

Cite this article: Söderlund F, Wåhlander H, Hansson EC, and Romlin BS (2021) Preoperative heart failure is not associated with impaired coagulation in paediatric cardiac surgery. *Cardiology in the Young* **31**: 979–984. doi: 10.1017/S1047951120005004

Received: 1 December 2020
Accepted: 26 December 2020
First published online: 8 February 2021

Keywords:
Congenital heart defect; cardiac surgery; heart failure; paediatric; brain natriuretic peptide; thromboelastometry

Author for correspondence:
Dr F. Söderlund, Department of Paediatric Anaesthesiology and Intensive Care, Sahlgrenska Academy Queen Silvia's Children Hospital, Sahlgrenska University Hospital University of Gothenburg, Gothenburg, 41685, Sweden. Tel: +46-31-3434000;
Fax: +46-31-343 58 80.
E-mail: fredrik.soderlund@vgregion.se

Abstract

Objective: The objectives of the present study were to determine whether there was any association between the grade of heart failure, as expressed by preoperative levels of brain natriuretic peptide and Ross score, and the preoperative coagulation status in patients with non-restrictive ventricular shunts and determine whether there were any postoperative disturbances of the coagulation system in these patients, as measured by thromboelastometry and standard laboratory analyses of coagulation. *Design:* Perioperative coagulation was analysed with laboratory-based coagulation tests and thromboelastometry before, 8 hours after, and 18 hours after cardiac surgery. In addition, brain natriuretic peptide was analysed before and 18 hours after surgery. *Patients:* 40 children less than 12 months old with non-restrictive congenital ventricular or atrio-ventricular shunts scheduled for elective repair of their heart defects. *Results:* All coagulation parameters measured were within normal ranges preoperatively. There was a significant correlation between brain natriuretic peptide and plasma fibrinogen concentration preoperatively. There was no statistically significant correlation between brain natriuretic peptide and INTEM-MCF, FIBTEM-MCF, plasma fibrinogen, activated partial thromboplastin time, prothrombin time, or platelet count at any other time point, either preoperatively or postoperatively. Postoperatively, fibrinogen plasma concentration and FIBTEM-MCF decreased significantly at 8 hours, followed by a large increase at 18 hours to higher levels than preoperatively. *Conclusions:* There was no evidence of children with non-restrictive shunts having coagulation abnormalities before cardiac surgery. Brain natriuretic peptide levels or Ross score did not correlate with coagulation parameters in any clinically significant way.

The management of coagulopathy and bleeding during paediatric cardiac surgery is an integral part of the intraoperative patient care. Ideally, patients at risk of excessive bleeding would be identified before the surgery starts, to enable appropriate prophylactic measures. So far, the attempts to find these patients using analysis of the coagulation system in blood have shown promising results in adults[1] but have mostly been disappointing in pediatric patients. One of the reasons for this may be that most study populations in paediatric cardiac surgery are relatively heterogenous, comprising patients of various ages and with different diagnoses.[2,3] An alternative approach to identify risk patients would be to look at the type of cardiac malformations that are thought to compromise the coagulation system even before surgery has begun.[4,5] One group of patients whose cardiac condition may impair their coagulation are those with defects that cause some degree of heart failure. Several mechanisms have been suggested for an impaired coagulation in these children. Inappropriate platelet activation and endothelial dysfunction through inflammatory pathways are possible mechanisms.[6] Another plausible factor is an imbalance or lack of coagulation factors due to liver impairment, in turn caused by increased systemic venous pressure transmitted from a right ventricle suffering from volume overload.[7] To investigate whether this hypothesis – that children with heart failure have a limited coagulation capacity – is tenable, we chose a rather narrow patient population, consisting of infants 3–8 months old, who had an elective surgical correction of either an atrio-ventricular septal defect or a ventricular septal defect, with an anatomical potential for heart failure before surgery in the form of a non-restrictive intracardiac shunt. The degree of heart failure in these children was quantified using brain natriuretic peptide, a hormone that is secreted in excess in both paediatric and adult patients with cardiac decompensation, and that is used clinically to monitor these patients.[8] The Ross score, a clinical scoring tool for assessing heart failure,[9] was also recorded, as were the height and weight of the patients, compared to expected age-corrected values.

CAMBRIDGE UNIVERSITY PRESS

The aims of this prospective, observational study were to investigate the coagulation system preoperatively in this patient population with significant shunts and search for correlations between brain natriuretic peptide levels and coagulation tests and to determine the changes in platelet count and rotational thromboelastometry caused by open heart surgery with cardio-pulmonary bypass in patients with non-restrictive shunts.

Materials and method

Study population

Forty children scheduled for elective open surgery using cardio-pulmonary bypass for congenital heart defects were enrolled. The inclusion criterion were the diagnoses of either a ventricular septal defect or an atrio-ventricular septal defect with concomitant signs of heart failure, defined as having a non-restrictive intracardial shunt diagnosed using echocardiography, with a Ross score of at least 3. The exclusion criteria were coagulation disorders or other conditions affecting coagulation, treatment with anticoagulant drugs, and hepatic or renal failure. The study was performed according to the Helsinki Declaration, with permission being granted from the regional ethics committee, and informed written consent was obtained from all the parents.

Anaesthesia

Ketamine (2–5 mg/kg), midazolam (0, 1 mg/kg), fentanyl (5–10 μg/kg), and atracurium (0, 5 mg/kg) were used for induction of anaesthesia. Intraoperative anaesthesia was provided with isoflurane or sevoflurane, fentanyl, and propofol (during cardio-pulmonary bypass). The anaesthetic regimen was unchanged during the study.

Anticoagulation and reversal

Before cardio-pulmonary bypass cannulation, an intravenous bolus of unfractionated heparin (Leo Pharma A/S, Ballerup, Denmark), 350 U/kg, was administered. ACT analysis, with kaolin as initiator, was used to monitor the level of anticoagulation during cardio-pulmonary bypass. Heparin reversal was achieved with protamine (Leo Pharma A/S), 1 mg per unit of total heparin given. Additional protamine was administered when the ACT remained high in combination with relevant clinical signs.

Cardio-pulmonary bypass technique

Cardio-pulmonary bypass was accomplished with a hard-shell reservoir and a membrane oxygenator adapted to patient size (Terumo, Tokyo, Japan). The priming solution consisted of crystalloid fluid, allogeneic blood, mannitol (1 mg/kg), heparin, and Tribonat buffer (Fresenius Kabi, Uppsala, Sweden). Packed red blood cells were added to the priming solution to achieve a haematocrit during cardio-pulmonary bypass of 27–30%. Target rectal patient temperature was decided by the surgeon, based on the type of surgery, (and in this study group ranged from 30 to 36°C). Extra heparin doses were given when the ACT fell below 480 seconds. Cold intermittent blood cardioplegia was used for cardiac protection. After weaning from cardio-pulmonary bypass, but with cannulae in place, modified ultrafiltration was used to attain a patient haematocrit of 35–40%. For elective reoperations, expected complicated surgery, or for children weighing < 3 kg, tranexamic acid was given before (50 mg/kg) and after (30 mg/kg) initiation of cardio-pulmonary bypass. Aprotinin was not used for any of the patients.

Study protocol

Platelet count, activated partial thromboplastin time, prothrombin time, plasma fibrinogen concentration, and rotational thromboelastometry were measured at three time points: immediately before surgery, 8 hours after surgery was finished, and 18 hours after surgery. Transfusions and coagulation products given perioperatively and postoperatively were recorded. All postoperative blood samples were taken after the patients were warmed to 37°C. The Ross score was also recorded, as were the height and weight of the patients, compared to expected age-corrected values.

Laboratory analyses

Platelet count, activated partial thromboplastin time (Dade Actin FSL reagent; Siemens Healthcare Diagnostics, Marburg, Germany), and plasma fibrinogen (using the previously described Clauss method[10] with Dade thrombin reagent; Siemens Healthcare Diagnostics) were analysed at an accredited university hospital laboratory facility (Sahlgrenska Universitetssjukhuset, Göteborg, Sweden). ACT analysis was done using the Hemochron Jr analyser (ITC, Edison, NY, United States of America). Samples for rotational thromboelastometry were collected in MiniCollect citrate tubes (Greiner Bio-One, Kremsmünster, Austria) and analysed using a rotational thromboelastometry delta machine (Tem Innovations GmbH, Basel, Switzerland). Details of this method have been described in detail previously.[11] Three different analysis channels were used: INTEM (measuring global coagulation), HEPTEM (containing heparinase, removing any residual heparin activity), and FIBTEM (containing cytochalasin D, a platelet inhibitor), thus measuring clot strength without the contribution of platelets. Age-specific reference ranges for these analyses were used.[12]

The degree of heart failure in these children was quantified using brain natriuretic peptide, a hormone that is secreted in excess in both paediatric and adult patients with cardiac decompensation, and that is used clinically to monitor these patients.[8] Brain natriuretic peptide was analysed at an accredited university hospital laboratory facility (Sahlgrenska Universitetssjukhuset, Göteborg, Sweden). Venous blood samples of 2 ml were drawn and collected in tubes containing disodium ethylene diamine tetraacetic acid and aprotinin. Brain natriuretic peptide was then measured using solid-phase immunoradiometric assays (Shionoria, Shionogi & Co. Ltd., Osaka, Japan).

Statistical analysis

Results are shown as mean and standard deviation (SD) or median and range, and with 95% confidence intervals (95% CI). Any p value < 0.05 was considered to be statistically significant. All variables were continuous. Repeated-measures analysis of variance was used for comparisons between different time points, and Pearson tests were used to calculate correlations between variables. Spearman's test for correlation was used for data that were not normally distributed. Statistical calculations were done using the statistical software package SPSS version 25 (IBM Corp., Armonk, NY, United States of America).

https://doi.org/10.1017/S1047951120005004 Published online by Cambridge University Press

Results

Clinical course

All the patients completed the study, and there was no in-study mortality. All 40 patients were included in the analysis of the results.

Baseline variables

The patient characteristics are summarised in Table 1. Median age was 160 (range 133) days, and median weight was 5.6 (range 4.3) kg. There were 14 female and 26 male patients, and 24 had Down's syndrome (trisomy 21). Mean preoperative Ross score was 6.1 (SD 2.0). 23 patients had a Ross score between 3 and 6, indicating mild heart failure, and 17 had a score between 6 and 9, indicating moderate heart failure. When compared to Swedish standard growth curves, the patients were found to be lagging in both weight (mean −1.2 SD) and height (mean −0.5 SD) compared to expected values. Medical treatment of the non-restrictive shunt included furosemide (30 patients), spironolactone (11 patients), enalapril (7 patients), and digoxin (4 patients). There was a significant correlation between the Ross score and the number of drugs the patients were taking for their heart failure ($r = 0.54$, $p < 0.01$).

Mean preoperative platelet count was 336 x 10^9/L (SD 96), mean activated partial thromboplastin time was 41 seconds (SD 5.4), and mean fibrinogen plasma concentration was 1.90 (SD 0.40). Median preoperative brain natriuretic peptide was 86 ng/L (range 10–1480). Preoperative INTEM-CT, INTEM-CFT, INTEM-MCF and FIBTEM-MCF were all within the previously suggested reference ranges for healthy children of the same age.

Effect of Down's syndrome

Children with Down's syndrome had a significantly lower activated partial thromboplastin time and Intem-MCF preoperatively. See Table 2 for details. However, there were no significant discrepancies between the groups in any of the variables postoperatively.

Effect of preoperative heart failure

There was a significant but modest correlation between preoperative brain natriuretic peptide and preoperative fibrinogen plasma concentration ($r = 0.40$; $p = 0.04$) and between the preoperative plasma fibrinogen concentration and the number of heart failure drugs the patients were taking ($r = 0.33$; $p = 0.043$). There was no significant correlation between Ross score and preoperative fibrinogen concentration. There was no statistically significant correlation between brain natriuretic peptide and INTEM-MCF, FIBTEM-MCF, plasma fibrinogen, activated partial thromboplastin time, or platelet count at any other time point, either preoperatively or postoperatively.

Postoperative changes in platelet count and INTEM-MCF

Mean INTEM-MCF decreased from baseline by 18% (SD 11%), from 60 to 49 mm (SD 6.30, 95% CI 9.11, 13.1; $p < 0.001$), at 8 hours and by 11% (SD 10%), from 60 to 53 mm (SD 6.12, 95% CI 4.69, 8.61; $p < 0.001$), at 18 hours. Mean platelet count preoperatively was 336 (SD 96) x 10^9/L and dropped significantly by a mean of 50% (SD 25%), from 336 to 166 (SD 84, 95% CI 142, 196; $p < 0.001$), at 8 hours and by 51% (SD 23%), from 336 to 170 (SD 78, 95% CI 141, 191; $p < 0.001$), at 18 hours.

Table 1. Patient characteristics.

	Study population	Reference range for healthy children
Mean age (days)	160 (SD 30)	n/a
Mean weight (kg)	5.6 kg (SD 0.97)	n/a
Female patients	14 (35%)	n/a
Diagnosis	AVSD 19 (48%), VSD 21 (52%)	n/a
Mean CPB time (minutes)	103 (SD 30)	n/a
Down's syndrome	30 (75%)	n/a
Mean platelet count	336 (SD 96)	170–400*
Mean plasma fibrinogen (g/L)	1.90 (SD 0.40)	2.31 (SD 0.57)†
Mean INTEM-CT (seconds)	177 (SD 108)	105–285**
Mean INTEM-CFT (seconds)	76 (SD 44)	27–88**
Mean INTEM-MCF (mm)	60 (SD 7)	54–73**
Mean FIBTEM-MCF (mm)	12 (SD 4)	8–23**
Mean BNP (ng/L)	179 (SD 186)	<18 ng/L*

*Local laboratory reference range.
**Published data.[13]
†Published data.[14]
AVSD = atrioventricular septal defect; BNP = brain natriuretic peptide; CFT = clot formation time; CPB = cardio-pulmonary bypass; CT = clotting time, MCF = maximum clot firmness; SD = standard deviation; VSD = ventricular septal defect.

Table 2. Comparison of baseline variables between children with and without Down's syndrome.

	Mean difference between Down's syndrome group and non-Down's syndrome group	p values
BNP (ng/L)	63.5 (95% CI 109, 236)	0.59
Ross score	−1.27 (95% CI -2.59, 0.54)	0.053
Platelet count	−50 (95% CI -117, 50)	0.12
Plasma fibrinogen (g/L)	−0.16 (95% CI -0.43, 0.11)	0.25
APTT	−3.8 (95% CI -7.2, -0.40)	0.030
PT	0.047 (95% CI 0.040, -0.035)	0.29
Intem-MCF (mm)	−5.1 (95% CI -9.4, -0.79)	0.022
Fibtem-MCF (mm)	1.9 (95% CI -0.7, 4.5)	0.14

APTT = activated partial thromboplastin time; BNP = brain natriuretic peptide, CI = confidence interval; PT = prothrombin time, MCF = maximum clot firmness.

Changes in plasma fibrinogen and FIBTEM-MCF

Both plasma fibrinogen and FIBTEM-MCF showed a similar pattern, decreasing to below baseline values after 8 hours, followed by an increase to above baseline (for plasma fibrinogen) or slightly below baseline (for FIBTEM-MCF) after 18 hours. Plasma fibrinogen decreased by a mean of 10% (SD 32%), from 1.9 to 1.7 g/L (SD 0.60, 95% CI 0.00, −0.38; $p = 0.051$), after 8 hours and increased by a mean of 22% (SD 34%), from 1.9 to 2.3 g/L (SD 0.64, 95% CI 0.21, 0.62; $p < 0.001$), after 18 hours. FIBTEM-MCF

https://doi.org/10.1017/S1047951120005004 Published online by Cambridge University Press

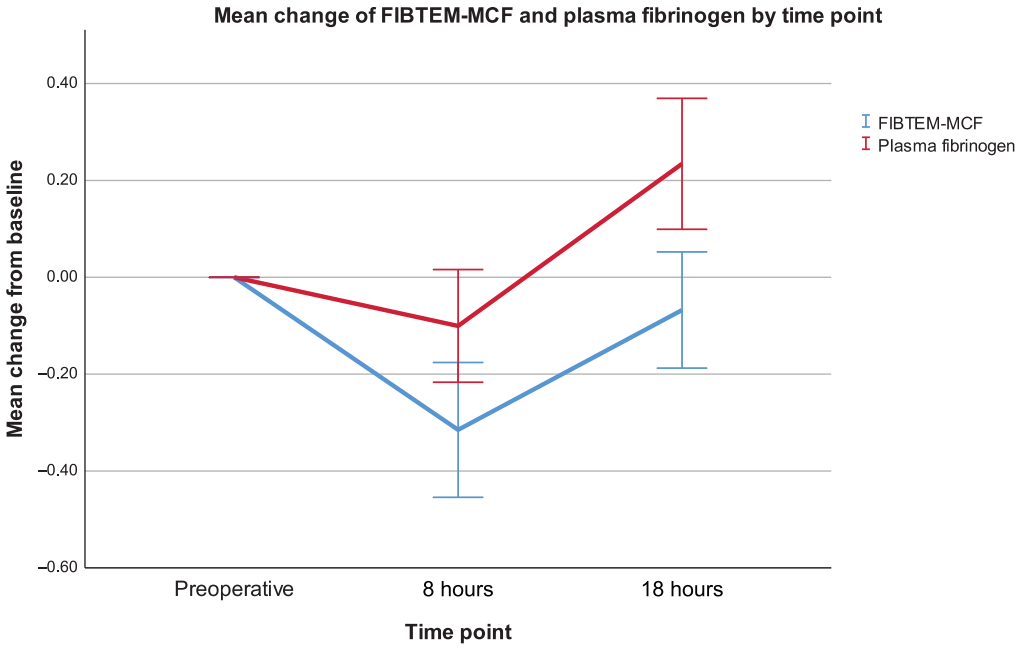

Figure 1. Mean change (as a fraction of the preoperative value, which has the value 0 in this figure) in plasma fibrinogen and FIBTEM-MCF. MCF = maximum clot firmness. Error bars show 95% confidence intervals.

decreased by a mean of 56% (SD 38%), from 11.7 to 6.5 (SD 4.37, 95% CI −6.73, −3.53; $p < 0.001$), after 8 hours, recovering by a mean of 83% (SD 32%), from 11.7 to 9.7 g/L (SD 3.78, 95% CI −0.55, 3.32; $p = 0.008$), still below the baseline value, after 18 hours. Figure 1 shows the same changes for plasma fibrinogen and FIBTEM-MCF but expressed as the fractional change from baseline.

Transfusions during surgery

Seven of the patients received a transfusion of packed red blood cells (median transfused volume = 70 ml, range 35–120 ml). In total, 12 received fresh frozen plasma (median 110 ml, range 25–200 ml), 5 received platelets (median 90 ml, range 40–160 ml), and 10 received fibrinogen concentrate (median 0.50 g, range 0.25–0.8 g). Treatment of coagulopathy was based on clinical signs of bleeding after reversal of heparin. No transfusions or coagulation products were given postoperatively.

Discussion

Preoperative heart failure

Except for a very modest positive correlation between preoperative plasma fibrinogen and brain natriuretic peptide, there were no signs that the level of pro-brain natriuretic peptide might act as a marker of an abnormal coagulation capacity. Furthermore, median preoperative FIBTEM-MCF was 12 mm (mean 11.7, SD 3.7) which is close to the median value of the reference range proposed by Oswald et al[13] for healthy children of the same age. This contrasts with a previous study by Osthaus et al[15], which found that mean Fibtem-MCF was lower in children with the same diagnoses as in our study, although still within the normal reference range. The mean Fibtem-MCF in the Osthaus study was, however, very similar to that in our study (13 as opposed to 12 mm), and the reason for our colleagues' conclusion that children with cardiac malformations had a lower FIBTEM-MCF appears to be that this value was higher in their control group of healthy children (18 mm). The Oswald study[13] presenting the reference values only supplied the median for FIBTEM-MCF, which makes it impossible to directly compare the healthy populations in the two studies. However, it appears likely that the perceived difference between healthy children and children with cardiac malformations in the Osthaus study was due to elevated Fibtem-MCF in the control group, rather than a lower value in the study group. Thus, based on the data available, we believe that there is no solid evidence for cardiac failure having an adverse effect on coagulation in children with cardiac malformations, when coagulation is analysed with functional tests. It is reasonable to assume that this may reflect the fact that children with cardiac lesions causing heart failure are well managed medically in our hospital before their surgery, which dampens the effects of their large shunts, including effects on the coagulation system.

Down's syndrome

There were subtle but significant differences in activated partial thromboplastin time and Intem-MCF between children with and without Down's syndrome before surgery. However, this seems not to have had much impact on later events, as no significant differences in the coagulation could be detected postoperatively. In this study population, there appears to be no reason to assume that children with Down's syndrome are at an increased risk of coagulopathy after cardiac surgery.

Changes in platelet count

We have previously shown, in a slightly older and more diverse patient group, how the initiation of cardio-pulmonary bypass and the accompanying haemodilution cause a rapid decrease in platelet count and aggregation, followed by a recovery – particularly of the aggregation.[16] It is not possible to directly confirm these findings in this study since no specific tests of platelet aggregation were used. The picture that emerges from the two studies is, however, similar. The partial recovery of INTEM-MCF between 8 and 18 hours, despite the platelet count remaining essentially the same, can possibly be explained by a combination of the large increase in plasma fibrinogen that occurs between 8 and 18 hours, and a rapid recovery of platelet aggregation. This hypothesis is also supported by the results of the study by Rahe-Meyer et al[17], in which a large

https://doi.org/10.1017/S1047951120005004 Published online by Cambridge University Press

dose of fibrinogen was associated with an increase in both INTEM-MCF and EXTEM-MCF, despite the patients having a low platelet count.

In the study mentioned above, we found that platelet aggregation recovers much faster than platelet count after paediatric cardiac surgery, which may therefore be part of the explanation as to why INTEM-MCF increases more than platelet count between 8 and 18 hours postoperatively.

Plasma fibrinogen and FIBTEM-MCF

Plasma fibrinogen had a decreasing trend after 8 hours, a finding that just failed to reach statistical significance. After 18 hours, there was a significant increase, however. This result is in accordance with the study by Moganasundram et al, in which plasma fibrinogen was found to increase during the first 24 hours after surgery.[18] Ten of the patients in the present study received fibrinogen towards the end of the surgery, but exclusion of these from the analysis of plasma fibrinogen did not change the result in any significant way. Of the patients who did not receive fibrinogen, 12 received fresh frozen plasma, and this too did not lead to any significant changes when the analysis was performed with them excluded. Also, none of the patients were administered any coagulation factors or fresh frozen plasma postoperatively, which means that the change in fibrinogen in the patients between 8 and 18 hours is entirely an endogenous reaction. Since no other coagulation factors were analysed separately in this study, we can only speculate why plasma fibrinogen recovers more quickly postoperatively than FIBTEM-MCF. One possibility might be a lack of other coagulation factors, which have previously been shown to be less prone to survive modified ultrafiltration than fibrinogen,[19] and the absence of which could have the effect of lowering FIBTEM-MCF. This does not, however, explain why the correlation between plasma fibrinogen and FIBTEM-MCF all but disappeared after 18 hours, even though the relative difference between fibrinogen level and FIBTEM-MCF remained unchanged. It is known that fibrinogen – being an acute phase reactant – increases during the postoperative phase, which often has an inflammatory component due to the cardio-pulmonary bypass and surgical trauma. This inflammatory response may have other simultaneous effects on the coagulation system – which could be the reason for FIBTEM-MCF failing to recover completely. Another explanation might be that the increase in plasma fibrinogen, being a by-product of an inflammatory response, cannot alone push the rest of the coagulation system to an equally large increase, possibly because other coagulation factors simply do not follow suit. One such factor could be factor XIII, which does not increase in response to an inflammatory reaction and has been shown to affect Fibtem-MCF in vitro.[20,21] Interestingly, in a study by Solomon et al, the correlation between plasma fibrinogen and Fibtem-MCF was found to be excellent after weaning from cardio-pulmonary bypass ($r = 0.71$–0.82, depending on which fibrinogen analysis method was used), but it decreased substantially after fibrinogen concentrate was given.[22] Perhaps a relative factor XIII deficiency occurs when plasma fibrinogen increases to high enough levels, which removes the correlation with Fibtem-MCF. Also, some data indicate that the factor XIII level and the bleeding tendency are not correlated throughout the range of factor XIII plasma concentrations.[23]

Limitations

The present study had important limitations. The most significant was the lack of a control group, which ideally would be composed of children of the same age and with the same cardiac defect, but without non-restrictive shunts. However, very few children with an atrio-ventricular septal defect have restrictive shunts, and those with a restrictive ventricular septal defect tend to be corrected at a different time point, if indeed at all. Also, the study would have benefitted from a higher number of children. The number of patients included was unfortunately limited by logistical constraints at our clinic.

In conclusion

We found no evidence of children with non-restrictive shunts having abnormalities in their coagulation before and after cardiac surgery. Brain natriuretic peptide levels did not correlate with coagulation parameters in any clinically significant way. Transfusion requirements were modest during surgery, and no transfusions were needed after transfer to the intensive care unit.

Acknowledgements. None.

Financial support. The study was partially funded by a grant by the Gothenburg Medical Society [grant number GLS-588461]. The Society had no influence over the study or the content of this article.

Conflicts of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards required by Swedish laws on experimental research involving humans, and with the Helsinki Declaration of 1975, as revised in 2008. The present study has also been approved by the Regional Ethics Committee of Gothenburg.

References

1. Petricevic M, Biocina B, Milicic D, et al. Bleeding risk assessment using whole blood impedance aggregometry and rotational thromboelastometry in patients following cardiac surgery. J Thromb Thrombolysis 2013; 36: 514–526.
2. Szekely A, Cserep Z, Sapi E, et al. Risks and predictors of blood transfusion in pediatric patients undergoing open heart operations. Ann Thorac Surg 2009; 87: 187–197.
3. Ignjatovic V, Than J, Summerhayes R, et al. The quantitative and qualitative responses of platelets in pediatric patients undergoing cardiopulmonary bypass surgery. Pediatr Cardiol 2012; 33: 55–59.
4. Shebl SS, El-Shehaby WAN, Said YS, Darwish AH, Elfadaly NH, Amer E. Thrombo-hemorrhagic liability in children with congenital heart diseases. Hematol Oncol Stem Cell Ther 2018; 11: 123–128.
5. Levin E, Wu J, Devine DV, et al. Hemostatic parameters and platelet activation marker expression in cyanotic and acyanotic pediatric patients undergoing cardiac surgery in the presence of tranexamic acid. Thromb Haemost 2000; 83: 54–59.
6. Kim JH, Shah P, Tantry US, Gurbel PA. Coagulation abnormalities in heart failure: pathophysiology and therapeutic implications. Curr Heart Fail Rep 2016; 13: 319–328.
7. Correale M, Tarantino N, Petrucci R, et al. Liver disease and heart failure: back and forth. Eur J Intern Med 2018; 48: 25–34.
8. Neves AL, Henriques-Coelho T, Leite-Moreira A, Areias JC. The utility of brain natriuretic peptide in pediatric cardiology: a review. Pediatr Crit Care Med 2016; 17: e529–e538.
9. Ross RD. The Ross classification for heart failure in children after 25 years: a review and an age-stratified revision. Pediatr Cardiol 2012; 33: 1295–1300.
10. Clauss A. Rapid physiological coagulation method in determination of fibrinogen. Acta Haematol 1957; 17: 237–246.
11. Whiting D, DiNardo JA. TEG and ROTEM: technology and clinical applications. Am J Hematol 2014; 89: 228–232.

https://doi.org/10.1017/S1047951120005004 Published online by Cambridge University Press

12. Lang T, Bauters A, Braun SL, et al. Multi-centre investigation on reference ranges for ROTEM thromboelastometry. Blood Coagul Fibrinolysis 2005; 16: 301–310.
13. Oswald E, Stalzer B, Heitz E, et al. Thromboelastometry (ROTEM) in children: age-related reference ranges and correlations with standard coagulation tests. Br J Anaesth 2010; 105: 827–835.
14. Miller BE, Tosone SR, Guzzetta NA, Miller JL, Brosius KK. Fibrinogen in children undergoing cardiac surgery: is it effective? Anesth Analg 2004; 99: 1341–1346.
15. Osthaus WA, Boethig D, Johanning K, et al. Whole blood coagulation measured by modified thrombelastography (ROTEM) is impaired in infants with congenital heart diseases. Blood Coagul Fibrinolysis 2008; 19: 220–225.
16. Romlin BS, Soderlund F, Wahlander H, Nilsson B, Baghaei F, Jeppsson A. Platelet count and function in paediatric cardiac surgery: a prospective observational study. Br J Anaesth 2014; 113: 847–854.
17. Rahe-Meyer N, Solomon C, Winterhalter M, et al. Thromboelastometry-guided administration of fibrinogen concentrate for the treatment of excessive intraoperative bleeding in thoracoabdominal aortic aneurysm surgery. J Thorac Cardiovasc Surg 2009; 138: 694–702.
18. Moganasundram S, Hunt BJ, Sykes K, et al. The relationship among thromboelastography, hemostatic variables, and bleeding after cardiopulmonary bypass surgery in children. Anesth Analg 2010; 110: 995–1002.
19. Ootaki Y, Yamaguchi M, Oshima Y, Yoshimura N, Oka S. Effects of modified ultrafiltration on coagulation factors in pediatric cardiac surgery. Surg Today 2002; 32: 203–206.
20. Nielsen VG, Gurley WQ, Jr., Burch TM. The impact of factor XIII on coagulation kinetics and clot strength determined by thrombelastography. Anesth Analg 2004; 99: 120–123.
21. Shams Hakimi C, Carling MS, Hansson EC, et al. The effect of ex vivo factor XIII supplementation on clot formation in blood samples from cardiac and scoliosis surgery patients. Clin Appl Thromb Hemost 2018; 24: 677–683.
22. Solomon C, Cadamuro J, Ziegler B, et al. A comparison of fibrinogen measurement methods with fibrin clot elasticity assessed by thromboelastometry, before and after administration of fibrinogen concentrate in cardiac surgery patients. Transfusion 2011; 51: 1695–1706.
23. Pitkanen HH, Jouppila A, Lemponen M, Ilmakunnas M, Ahonen J, Lassila R. Factor XIII deficiency enhances thrombin generation due to impaired fibrin polymerization - An effect corrected by Factor XIII replacement. Thromb Res 2017; 149: 56–61.

https://doi.org/10.1017/S1047951120005004 Published online by Cambridge University Press