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Coagulation abnormalities and liver function after hemi-Fontan and Fontan procedures — the importance of hemodynamics in the early postoperative period☆

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Abstract

Introduction: The causes of coagulation abnormalities and thromboembolic complications during staged Fontan approach in patients with single ventricle remain unclear. This study was designed to evaluate the coagulation profile in the early postoperative period after hemi-Fontan and Fontan procedures with relationship to liver function and hemodynamic variables. **Materials and methods:** The prospective study on 43 patients after hemi-Fontan (group 1) and 37 patients after Fontan procedure (group 2) was carried out. Coagulation profile (factor VII, factor VIII, ATIII, fibrinogen, prothrombin), liver function (total serum protein, albumin, AST, ALT, bilirubin), and hemodynamic variables were assessed on postoperative day 1 and 5 and compared to preoperative measures. **Results:** Factor VIII concentration was significantly higher on first postoperative day in both groups. On postoperative day 5 the concentration of factor VIII was significantly decreased in group 1 whereas constant in group 2. The concentration of factor VII, ATIII, fibrinogen, and prothrombin was significantly decreased on first and increased on fifth postoperative day after both hemi-Fontan and Fontan procedures. The increase in bilirubin concentration was more distinctive after Fontan operation ($p = 0.003$) with lower AST in this group ($p < 0.0001$). The single ventricle function, $pO2$ and central venous pressure had significant influence on factor VIII ($p = 0.034$), factor VII ($p = 0.012$), ATIII ($p = 0.006$), and prothrombin ($p = 0.024$) concentrations in group 2 with no significant influence in group 1. **Conclusions:** The distinctive causes of coagulation abnormalities during staged Fontan approach are hemodynamic changes and temporary liver dysfunction. Elevated concentration of factor VIII and significant influence of hemodynamics on coagulation profile could contribute to postoperative thromboembolic complications.

Keywords: Fontan operation; Coagulation abnormalities; Liver dysfunction; Thromboembolic complications

1. Introduction

The Fontan operation since its first performance [1] has gone through many modifications with the improvement in mortality rate of 25—30% in the early reports to less then 5% in current studies [2]. Despite the constant evolution in the outcome of patients after Fontan operation, factors still contributing to mortality and morbidity are pleural effusions, arrhytmias, thromboembolic complications, protein-losing entheropathy, and ventricular dysfunction [3—6]. Thromboembolic complications are represented by venous, arterial, intracardiac thrombus formation, and cerebrovascular accidents with the occurrence up to 20% [3]. Risk factors associated with thrombosis in patients after Fontan operation are increased venous pressure, change in blood flow pattern, arrhythmias, hypoxia, single ventricle dysfunction, and coagulation abnormalities [2].

There has been many reports demonstrating both pro- and anticoagulant abnormalities in the late postoperative period in patients undergoing Fontan operation, but no study evaluating the status of coagulation profile and liver function in patients during staged Fontan approach in the early postoperative period [7—9]. The study was designed to assess the coagulation profile in children with functionally single ventricle in the early postoperative period after hemi-Fontan and Fontan procedures with the relationship to liver function and the influence of the hemodynamics on the coagulation status of blood.

2. Materials and methods

Between the years of 2003 and 2005 a consecutive 80 children with functionally single ventricle who were qualified

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for staged Fontan procedure (hemi-Fontan or Fontan operation) in a single institution were enrolled to a study. The study was approved by the Ethics Committee on Human Research of the Jagiellonian Univerisity and the informed consent for the study was obtained from the patients' parents.

All the data were derived from medical records, cardiac catheterization reports, and postoperative echocardiographic assessment. Most of the patients (97.5%) underwent previous palliative procedure suitable for the child's physiology (Norwood procedure, systemic-to-pulmonary shunt, pulmonary artery banding).

Group 1 consisted of 43 children who were qualified to the hemi-Fontan operation. The mean age of patients at the operation was 5.9 ± 3.1 months and the mean weight 6.0 ± 1.5 kg. In group 2 consisting of 37 patients, the Fontan operation was performed in the mean age of 23.2 ± 8.7 months and the mean weight of 12.5 ± 2.4 kg. Children from group 2 had previously undergone the hemi-Fontan operation in the mean age of 6.1 months. The anatomy of the congenital heart disease of children is presented in Table 1. The hemi-Fontan operation was based on the technique described by Douville et al. [10]. The children from group 2 underwent the Fontan operation by the mean of lateral intra-atrial tunnel with the fenestration. After the hemi-Fontan and Fontan procedures all children received acetylsalicylic acid in a dose of 2–5 mg/kg per day from day 1 after the surgery. No patient received oral anticoagulation therapy during the time of the study. No thromboembolic event occurred in any of the patients from group 1 and 2 during the time of the study. The pleural effusions requiring drainage occurred in 7% of patients from group 1 and 46% of children from group 2.

The postoperative two-dimensional and Doppler echocardiographic examination consisted of the assessment of ventricular function (1, normal; 2, mildly depressed; 3, severely depressed) and atrioventricular valve regurgitation (0, none; 1, trivial; 2, moderate; 3, severe). The data from echocardiographic examination are presented in Table 2.

Cardiac catheterization was performed in 39% of patients before hemi-Fontan and all patients before Fontan procedure. The following data (Table 3) were obtained from the cardiac catheterization reports: pulmonary artery pressure, pulmonary vascular resistance, superior vena cava pO_2 and saturation, right atrial pressure, pO_2 and saturation, single ventricle pO_2 and saturation, single ventricle systolic and end-diastolic pressure, aortic pO_2 and saturation, Qp:Qs, and cardiac index.

The data derived from medical records (hematocrit, heart rate, arterial or capillary pO2, oxygen saturation, and systemic venous pressure) are listed in Table 4.

For the assessment of coagulation profile and liver function blood samples were obtained from patients before the surgery in the operative room after induction of anesthesia, 24 h after the surgery, and on the fifth postoperative day. For the assessment of liver function, serum concentration of total protein, albumin, total bilirubin, aspartate aminotransferase, and alanine aminotransferase were measured with an automatic chemical analyzer (Johnson & Johnson Vitros 905 Chemical Analyzer). For the evaluation of coagulation profile, the concentration of prothrombin (factor II), factor VII, factor VIII, fibrinogen, antithrombin III, and International Normalized Ratio (INR) were measured. Prothrombin, INR, fibrinogen, and antithrombin III were assessed immediately after obtaining blood samples. The prothrombin was determined using Thromborel S human thromboplastin reagent (Dade Behring Marburg GmbH, Germany), fibrinogen using Multifibren U reagent (Dade Behring Marburg GmbH, Germany), antithrombin III was measured by chromogenic assay (Sysmex CA 560, Dade

Table 1
Anatomy of the cardiac malformations, n (%)

	Group 1	Group 1
Single ventricle morphology		
RV	29 (67)	30 (81)
LV	14 (33)	7 (19)
Anatomy of the congenital heart disease		
HLHS	24 (56)	23 (62)
Heterotaxy syndrome	6 (14)	1 (2.7)
TA	3 (7)	1 (2.7)
PA	2 (4.6)	2 (5.4)
TA/PA	2 (4.6)	1 (2.7)
DORV	1 (2.3)	3 (8.1)
Other	5 (11)	6 (16.2)

RV, right ventricle; LV, left ventricle; HLHS, hypoplastic left heart syndrome; TA, tricuspid atresia; PA, pulmonary atresia; DORV, double outlet right ventricle.

Table 2
Postoperative echocardiographic data, n (%)

Variable	Group 1 (n = 43)	Group 2 (n = 37)
Ventricular function		
Normal	30 (70)	28 (76)
Mildly depressed	11 (26)	9 (24)
Severely depressed	2 (4)	0 (0)
AVVR		
None to trivial	22 (51)	14 (40)
Moderate	17 (39)	21 (56)
Severe	4 (9)	2 (4)

AVVR, atrioventricular valve regurgitation.

Table 3
Preoperative cardiac catheterization data, mean ± SD

Variable	Group 1 (n = 17)	Group 2 (n = 37)
PAP (mmHg)	13.4 ± 2.8	11.0 ± 2.5
PVR (Wood units)	1.7 ± 0.6	1.8 ± 0.6
SVC-Sat O_2 (%)	51.5 ± 12.5	59.3 ± 8.0
SVC-pO_2 (mmHg)	29.1 ± 6.2	33.3 ± 4.7
RAP (mmHg)	7.3 ± 2.3	6.3 ± 1.9
RA-Sat O_2 (%)	62.2 ± 13.8	74.4 ± 9.0
RA-pO_2 (mmHg)	34.3 ± 7.6	41.1 ± 7.1
SV-Sat O_2 (mmHg)	71.8 ± 14.9	81.6 ± 6.2
SV-pO_2 (mmHg)	44.2 ± 17.6	47.6 ± 6.8
SVSP (mmHg)	97.5 ± 19.6	97.0 ± 14.3
SVEDP (mmHg)	9.3 ± 4.2	7.8 ± 2.6
Ao-Sat O_2 (%)	75.3 ± 10.3	83.5 ± 5.6
Ao-pO_2 (mmHg)	40.5 ± 6.9	50.8 ± 8.5
Qp:Qs	0.9 ± 0.4	0.65 ± 0.2
CI (l/min/m^2)	3.4 ± 1.0	3.5 ± 0.7

PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; SVC, superior vena cava; RAP, right atrial pressure; RA, right atrium; SV, single ventricle; SVSP, single ventricle systolic pressure; SVEDP, single ventricle end-diastolic pressure; Ao, aorta; Qp:Qs, pulmonary-to-systemic blood flow ratio; CI, cardiac index; pO_2, partial oxygen tension; Sat O_2, oxygen saturation.

Table 4
Perioperative data, mean ± SD

Variable	Group 1			Group 2		
	I	II	III	I	II	III
Hct (%)	49.3 ± 6.3	34 ± 3.9	38.9 ± 3.5	47.8 ± 5.5	34.8 ± 4.3	37 ± 3.7
HR (beats/min)	117.6 ± 13.2	105.6 ± 15	115.6 ± 14.8	99.2 ± 17.9	97.5 ± 16.9	104 ± 15.7
pO_2 (mmHg)	35.8 ± 4.5	42.5 ± 6.5	37 ± 5.2	38.7 ± 7.5	63.4 ± 13.5	53 ± 6.5
Sat O_2 (%)	67.4 ± 13.2	78.3 ± 6.9	73 ± 6.5	76.3 ± 6.6	90.5 ± 6.6	86.4 ± 3.8
CVP (mmHg)	NA	11.1 ± 2.3	NA	NA	11.9 ± 2.8	NA

Hct, hematocrit; HR, heart rate; pO_2, arterial or capillary oxygen tension; Sat O_2, systemic oxygen saturation; CVP, systemic venous pressure; I, before the operation; II, 24 h after the surgery; III, postoperative day 5; NA, not assessed.

Behring, Kobe, Japan). For the factors VII and VIII the citrated plasma was separated by centrifugation and stored at −80 °C until assayed. Factor VII and VIII were measured by clotting method using specific factor-deficient plasma (Fibrintimer BFT II, Dade Behring, Marburg GmbH, Germany). The concentration of coagulation factors (factor VII, VIII, antithrombin III, and prothrombin) is expressed as a percentage of activity. The concentration of fibrinogen is expressed in g/l.

2.1. The statistical analysis

Standard statistical methods were used. The data are expressed as mean ± standard deviation (SD). The differences between the groups concerning quantitative data were assessed using Mann–Whitney's test or Student's *t*-test as appropriate. Repeated measures ANOVA was used for the assessment of differences in coagulation factors concentration and liver function parameters. Chi-square test and its variants were used to determine the differences between the groups concerning categorical data. The relationship between coagulation factors activity and preoperative cardiac catheterization data (Table 3), postoperative variables (Table 4), liver function tests (Table 5), and postoperative echocardiographic measurements (Table 2) was determined using multiple regression. At a *p*-value of <0.05 differences were considered as significant. All statistical analyses were performed using Statistica software (StatSoft, Inc., 2003, STATISTICA data analysis software system, version 6).

3. Results

3.1. Liver function

The results of liver function tests are summarized in Table 5. Patients from both groups had significantly higher aspartate aminotransferase level on postoperative day 1 when compared to preoperative value (group 1, $p = 0.0019$; group 2, $p = 0.009$). The concentration of this enzyme decreased on postoperative day 5 and was not different from the measure done before the surgery in both groups. There was also a significant decrease in total serum protein concentration 24 h after the surgery in both groups (group 1, $p = 0.0039$; group 2, $p < 0.0001$) compared to preoperative value. On the fifth postoperative day the total serum protein concentration regained preoperative level in group 1 whereas in group 2 it continued to be significantly decreased when compared to preoperative rate ($p < 0.0001$). The concentration of bilirubin in group 2 was slightly increased on postoperative day 1 but dropped significantly on postoperative day 5 ($p < 0.0001$). In the first group, the bilirubin concentration remained without significant changes in concentration throughout the perioperative period.

When liver function data were compared between the two groups, patients from group 1 had significantly higher aspartate aminotransferase ($p < 0.0001$) and patients from group 2 had significantly higher bilirubin concentration ($p = 0.03$) on postoperative day 1. These differences were not observed on the fifth day after the surgery. Patients from group 2 also had significantly lower total serum protein

Table 5
Liver function tests, mean ± SD

Variable	I	II	III	*p*-value		
				I versus II	II versus III	I versus III
Group 1						
Total serum protein (g/l)	63.9 ± 9.9	58.2 ± 6.2	61.9 ± 7.7	0.0039	NS	NS
Albumin (g/l)	32.7 ± 6.9	33.5 ± 5.3	36.1 ± 5.8	NS	NS	NS
AST (U/l)	56.0 ± 19.9	155 ± 119	62.3 ± 44.6	0.0019	0.0049	NS
ALT (U/l)	32.5 ± 12.9	51.6 ± 31.2	51.3 ± 37	NS	NS	NS
Bilirubin (μmol/l)	12.4 ± 8.4	14.1 ± 7.4	8.4 ± 3.7	NS	NS	NS
Group 2						
Total serum protein (g/l)	68.8 ± 8.4	52.9 ± 8.3	58.5 ± 7.0	<0.0001	0.0065	<0.0001
Albumin (g/l)	32.9 ± 2.9	32.8 ± 4.5	35.4 ± 5.2	NS	NS	NS
AST (U/l)	50.0 ± 17.5	109.7 ± 70.1	89.3 ± 57.6	0.009	NS	NS
ALT (U/l)	25.5 ± 10.1	56.2 ± 32.3	55.0 ± 30.7	NS	NS	NS
Bilirubin (μmol/l)	15.6 ± 8.3	21.7 ± 14.4	8.4 ± 3.7	NS	<0.0001	NS

I, before the operation; II, 24 h after the surgery; III, postoperative day 5; AST, aspartate aminotransferase; ALT, alanine aminotransferase; NS, non-significant.

Table 6
Prevalence of patients with abnormal values of coagulation factors, *n* (%)

Variable	Group 1 (*n* = 43)			Group 2 (*n* = 37)		
	I	II	III	I	II	III
Prothrombin ↓	28 (65)	34 (79)	13 (30)	20 (54)	37 (100)*	27 (73)*
Factor VII ↓	14 (32)	28 (65)	3 (7)	11 (30)	28 (76)	11 (30)*
Factor VIII ↑	4 (9)	21 (49)	14 (32)	5 (13)	13 (35)	13 (35)
Factor VIII ↓	13 (30)	0 (0)	2 (7)	5 (13)	0 (0)	1 (3)
Fibrinogen ↓	12 (28)*	4 (9)	7 (16)	0 (0)	14 (38)*	12 (32)
Antythrombin III ↓	10 (23)	18 (42)	10 (23)	10 (27)	27 (73)*	9 (24)
INR ↑	25 (58)	36 (83)	14 (32)	20 (54)	37 (100)*	27 (73)*

I, before the operation; II, 24 h after the surgery; III, postoperative day 5; ↓, value below normal range for age; ↑, value above normal range for age. Hemostatic pediatric reference intervals obtained from the literature [12].
* Statistically significant.

Table 7
Coagulation profile, mean ± SD

Variable	I	II	III	*p*-value		
				I versus II	II versus III	I versus III
Group 1						
Factor VII (%)	60.9 ± 36.7	37.8 ± 18.9	88.9 ± 33.8	0.0005	<0.0001	<0.0001
Factor VIII (%)	88.9 ± 54.1	166.5 ± 82.3	131.6 ± 64.9	<0.0001	0.005	0.031
Fibrinogen (g/l)	1.7 ± 0.5	2.7 ± 0.8	2.6 ± 1.1	<0.0001	NS	<0.0001
Antithrombin III (%)	87.7 ± 19.1	82.9 ± 16.9	97.8 ± 28.2	0.025	0.0001	NS
Prothrombin (%)	61. 4 ± 17	54.5 ± 20.6	76.9 ± 31	NS	<0.0001	0.0028
INR	1.4 ± 0.3	1.6 ± 0.5	1.2 ± 0.4	0.009	<0.0001	0.012
Group 2						
Factor VII (%)	60.3 ± 35.3	28.0 ± 17.8	57.1 ± 28.1	<0.0001	0.0001	NS
Factor VIII (%)	105 ± 69.9	142.2 ± 75.0	145.5 ± 80.4	0.002	NS	0.008
Fibrinogen (g/l)	2.5 ± 0.9	1.7 ± 0.7	2.1 ± 1.3	0.01	NS	NS
Antithrombin III (%)	91.1 ± 14.5	68.6 ± 18.1	94.9 ± 17.7	<0.0001	<0.0001	NS
Prothrombin (%)	64.2 ± 19.2	39.6 ± 14.8	57.6 ± 23.2	<0.0001	0.0004	NS
INR	1.3 ± 0.3	2.1 ± 1.1	1.6 ± 0.6	<0.0001	<0.0001	NS

I, before the operation; II, 24 h after the surgery; III, postoperative day 5; INR, international normalized ratio.

concentration throughout the postoperative course (postoperative day 1, $p = 0.002$; postoperative day 5, $p = 0.04$).

3.2. Coagulation studies

The coagulation factors abnormalities were analyzed with respect to hemostatic pediatric reference intervals [11]. The results are presented in Table 6 and Table 7, and summarized on Fig. 1.

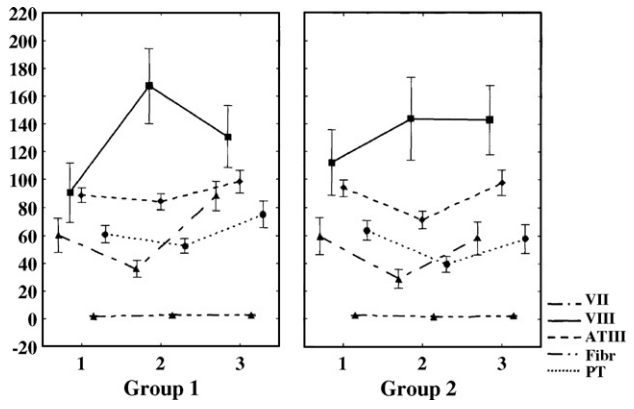

Fig. 1. Coagulation profile in patients after the surgery. VII, factor VII; VIII, factor VIII; AT III, antithrombin III; Fibr, fibrinogen; PT, prothrombin; 1, before surgery; 2, 24 h after the surgery; 3, postoperative day 5.

Decreased activity of prothrombin, factor VII, VIII, and antithrombin III was observed in numerous patients in the preoperative period before both hemi-Fontan and Fontan operations as detailed in Table 6. In the multiple regression, taking into the model the hemodynamic data listed in Table 3, there was a significant direct relation of saturation in the ventricle ($p = 0.006$) and saturation in the pulmonary veins ($p = 0.023$) to the activity of factor VII in the preoperative period in the hemi-Fontan group. There was no such influence in the Fontan group.

In the same model of multiple regression linking preoperative catheterization data with the postoperative disturbances of coagulation profile, higher preoperative aortic oxygen saturation was a predictor of higher postoperative activity of factor VIII ($p = 0.037$) and higher preoperative single ventricle end-diastolic pressure was a predictor of lower postoperative concentration of factor VII ($p = 0.03$) in the Fontan group with no such influence in the hemi-Fontan group.

In the early postoperative period the general tendency was the significant decrease in the activity of prothrombin, factor VII, and antithrombin III on postoperative day 1 and the significant increase on postoperative day 5 in both groups when compared to the preoperative measure. When

comparing the prevalence of coagulation factors deficiency between groups 1 and 2, significantly more patients from group 2 had a prothrombin ($p = 0.0001$), factor VII ($p = 0.008$), antithrombin III ($p = 0.0048$), and fibrinogen ($p = 0.0025$) deficiency on the first and fifth postoperative day.

In the multiple regression model taking into account postoperative hemodynamic data (heart rate, pO_2, oxygen saturation, systemic venous pressure, single ventricular function, atrioventricular valve regurgitation) the concentrations of antithrombin III ($p = 0.006$) and factor VII ($p = 0.01$) were inversely related to systemic venous pressure, and prothrombin concentration ($p = 0.024$) was directly related to systemic pO_2 in post-Fontan patients. None of the variable influenced postoperative coagulation profile in the hemi-Fontan group in this model.

As opposed to above-mentioned hemostatic parameters the concentration of factor VIII was significantly higher on postoperative day 1 in both groups compared to preoperative value (group 1, $p < 0.0001$; group 2, $p = 0.002$). On the fifth day after the surgery the concentration of factor VIII decreased significantly in patients from group 1 ($p = 0.005$), whereas in patients from group 2 it continued to increase. In the multiple regression there was an inverse proportion between the function of the single ventricle and the activity of factor VIII ($p = 0.034$) in second group with no such influence in first group.

The concentration of fibrinogen in group 1 was significantly higher on postoperative day 1 ($p < 0.0001$) and 5 ($p < 0.0001$) when compared to preoperative measure. In patients from group 2 the concentration of fibrinogen decreased significantly 24 h after the surgery ($p = 0.01$) and remained unchanged on postoperative day 5. In the multiply regression the fibrinogen concentration was directly related to total serum protein concentration in both hemi-Fontan ($p = 0.003$) and Fontan ($p = 0.0002$) groups.

4. Discussion

Thromboembolic complications are one of the major causes of mortality and morbidity after the Fontan operation [2,3]. Hemostatic abnormalities in patients during staged Fontan approach play an important role when assessing risk factors for thrombosis [7–9]. In this study we have attempted to determine whether changes in coagulation profile are present in the early postoperative period in patients after the hemi-Fontan and Fontan operation and to assess the possible influence of liver function and hemodynamics on hemostatic profile.

The observed abnormality in liver function was an increase in aspartate aminotransferase on first postoperative day in both groups with significant dominance in the hemi-Fontan group. No serious hepatocellular damage occurred because the concentration of alanine aminotransferase was not increased significantly (Table 5) and the concentration of total serum protein and albumin was within the normal range although its significant changes throughout the perioperative period were noted. The transient increase of aspartate aminotransferase concentration observed in children after the cardiac operations in our study can be caused by cardiopulmonary bypass, myocardial damage, or stress response [12].

The bilirubin concentration was slightly increased in post-Fontan patients on postoperative day 1. This is a similar finding to other studies in which signs of mild cholestasis without serious liver dysfunction were observed in patients after Fontan operation [8,13]. The increased bilirubin level in the early postoperative period may be as well as a result of hemolysis, hypothermia, or anesthetic agents [12]. The liver function tests within normal range on postoperative day 5 in both groups without any distinction between them indicate that overall synthesizing function of the liver is preserved in spite of transient hepatic damage shortly after the surgery which may affect the coagulation profile.

The changes in total serum protein concentration and directly related to it alternations of fibrinogen content during the early postoperative period were noted in both groups. The confusing propensity of the fibrinogen to increase in the hemi-Fontan group opposite to total serum protein concentration shortly after surgery can reflect the synthesis of this protein in the liver due to acute phase reaction [21] and confirm preserved function of the liver. It was not a case in the Fontan group in which more patients had pleural effusions and an extensive loss of proteins to pleural cavities [4] with persistently lower protein concentration on the postoperative day 5 compared to previous repeated measurements as well as to the appropriate rates in the hemi-Fontan group.

We found coagulation factor abnormalities in both groups in the preoperative period, generally characterized by deficiency in factor VII, VIII, antithrombin III, and prothrombin. Those abnormalities observed also in previous studies [14,15] may result from the delayed maturation of the hemostatic system due to hypoxia, low cardiac output, or genetic disorder in patients with congenital heart disease who undergo single-ventricle palliation, but the true impact of those abnormalities on coagulation status of children remains unclear. In multiple regression linking the coagulation profile and the data from pre-hemi Fontan cardiac catheterization, patients with higher oxygen saturation in the single ventricle and pulmonary veins had a higher concentration of factor VII before the surgery. In addition, in postoperative period the concentration of prothrombin was directly related to systemic pO_2 in patients after the Fontan operation. These findings confirm the important role of systemic oxygen saturation in determination of the hemostatic system function [16].

The evaluation of the hemostatic system on the first postoperative day may be difficult because of the possible changes in the concentration of coagulation factors as a consequence of acute-phase response, hemodilution, consumption coagulopathy, and blood products transfusion. Nevertheless, when comparing the coagulation profile before and after the surgery, the overall tendency in both groups was the decrease of factor VII, prothrombin, and antithrombin III 24 h after the surgery. It can suggest the global decrease of coagulation proteins concentration directly after the surgery may lead to hemorrhagic rather than thrombophilic tendency also observed in other coagulation studies [17,18].

In most patients the concentration of factor VII, antithrombin III, and prothrombin returned to normal value

on the postoperative day 5. However, there were still some abnormalities in coagulation profile that could contribute to hemostatic imbalance. The concentration of factor VII was below normal values in 30% of patients after Fontan operation on postoperative day 5. It can theoretically predispose to bleeding. However, previous studies have reported that low concentration of factor VII may in fact support tissue-factor inducing coagulation in pathologic states [19]. Also there is evidence of an increased risk of thromboembolism in patients with hereditary factor VII deficiency [20]. In our study, higher single ventricle end-diastolic pressure before the Fontan operation was a predictor of lower activity of factor VII postoperatively. Also, decreased factor VII and antithrombin III concentration was observed in patients with higher systemic venous pressure after the Fontan operation. These relationships indicate that hemodynamic factors are the main reason impairing the liver synthesizing function and coagulation proteins activity which is emphasized by the fact that they were detected only in the Fontan group.

As opposed to other hemostatic parameters the concentration of factor VIII was increased 24 h after the surgery in the hemi-Fontan and Fontan patients. Also, a higher pre-Fontan aortic oxygen saturation was a predictor of higher factor VIII concentration in the postoperative period. The immediate increase in activation of factor VIII in the early postoperative period likewise activity of fibrinogen in our patients may reflect an acute-phase reaction and cause hypercoagulable state [17,21]. Patients in the Fontan group in contrast to hemi-Fontan group still had increased factor VIII concentration on postoperative day 5. This finding is similar to earlier reports in which increased factor VIII was observed in patients after the Fontan operation [22,23]. Factor VIII was found to be an independent risk factor for thromboembolic complications in the Leiden Thrombofilia Study with a five- to sixfold increased risk when the concentration is above 150% [24]. In addition, a study of Hollestelle et al. found that mostly non-parenchymal cells (liver sinusoidal endothelium), not hepatocytes, play a major role in factor VIII synthesis [25]. In our report the concentration of factor VIII above 150% occurred in more than one-third of post-Fontan patients on the first and fifth postoperative day (Table 6) and children with decreased ventricular function had a higher concentration of factor VIII. The immediate increase in systemic venous pressure after the Fontan operation could contribute to increased factor VIII concentration which is apparent in the early postoperative period. This agrees with a study of Odegard et al. who found that systemic venous pressure was strongly related to factor VIII concentration [22].

Decreased antithrombin III and factor VII concentration with a significant increased factor VIII concentration in addition to other risk factors (increased venous pressure, change in the pattern of blood flow, temporary hepatic injury, hypoxia, and single ventricle dysfunction) in patients after Fontan operation can contribute to increased incidence of thromboembolic complications in the early postoperative period. These findings agree with previous reports that imbalance of both pro- and anticoagulant factors after Fontan operation predispose to thrombosis [7—9,15,22,23].

4.1. The limitations of the study

In our study we did not have the age-matched control group to compare the coagulation profile of patients with the values assessed in a control cohort, but we used hemostatic pediatric references intervals from a study of Andrew et al. [11] to evaluate the abnormalities of coagulation profile in our patients.

There is no consensus about the prophylactic antithrombotic strategy in children undergoing Fontan operation [2,3]. In the study all of the patients were taking aspirin as the antiplatelet therapy from the postoperative day 1. We do not routinely use the oral anticoagulation and we did not find any evidence of thromboembolic complications throughout the whole hospital stay in our patients. This might result from a short follow-up, small number of patients, or demonstrate that aspirin is sufficient in prophylactic antithrombotic therapy. On the other hand, based on our results, we could identify a group of children with perioperative factors associated with coagulation abnormalities and possible higher risk for thrombosis and consider the option of changing aspirin to more aggressive anticoagulation therapy. In the future studies it should be assessed weather observed coagulation abnormalities in post-Fontan patients coexist with the higher incidence of thrombosis in the late postoperative period and if adjusting the prophylactic anticoagulation strategy brings the desirable effect.

In conclusion, our study demonstrated a high incidence of both procoagulant and anticoagulant factors abnormalities in patients during staged Fontan approach in the early postoperative period. The transient hepatic damage in the early postoperative period may contribute to coagulation profile abnormalities. The decreased antithrombin III, factor VII, and increased factor VIII concentrations combined with the influence of unique hemodynamics on hemostatic parameters in patients after Fontan operation can contribute to increased risk of thromboembolic complications in the early postoperative period.

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References

[1] Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax 1971;26:240—8.
[2] Jacobs ML. The Fontan operation, thromboembolism, and anticoagulation: a reappraisal of the single bullet theory. J Thorac Cardiovasc Surg 2005;129:491—5.
[3] Monagle P, Cochrane A, McCrindle B, Benson L, Williams W, Andrew M. Thromboembolic complications after Fontan procedure — the role of prophylactic anticoagulation. J Thorac Cardiovasc Surg 1998;115:493—8.
[4] Gupta A, Daggett C, Behera S, Ferraro M, Wells W, Starnes V. Risk factors for persistent pleural effusions after the extracardiac Fontan procedure. J Thorac Cardiovasc Surg 2004;127:1664—9.
[5] Mertens L, Hagler DJ, Sauer U, Somerville J, Gewillig M. Protein-losing enteropathy after the Fontan operation: an international multicenter study. J Thorac Cardiovasc Surg 1998;115:1063—73.

[6] Fontan F, Kirklin JW, Fernandez G, Costa F, Naftel DC, Tritto F, Blackstone EH. Outcome after a "perfect" Fontan operation. Circulation 1990;81: 1520–36.
[7] Cromme-Dijkhuis AH, Henkens CM, Bijleveld CM, Hillege HL, Bom VJ, van der Meer J. Coagulation factor abnormalities as possible thrombotic risk factors after Fontan operation. Lancet 1990;336(8723):1087–90.
[8] Jahangiri M, Kreutzer J, Zurakowski D, Bacha E, Jonas RA. Evaluation of hemostatic and coagulation factor abnormalities in patients undergoing the Fontan operation. J Thorac Cardiovasc Surg 2000;120:778–82.
[9] Jahangiri M, Shore D, Kakkar V, Lincoln C, Shinebourne E. Coagulation factor after Fontan procedure and its modifications. J Thorac Cardiovasc Surg 1997;113:989–93.
[10] Douville EC, Sade RM, Fyfe DA. Hemi-Fontan operation in surgery for single ventricle: a preliminary report. Ann Thorac Surg 1991;51:893–9.
[11] Andrew M, Vegh P, Johnston M, Bowker J, Ofosu F, Mitchell L. Maturation of the hemostatic system during childhood. Blood 1992;80:1998–2005.
[12] Mitchell IM. Liver function after cardiopulmonary bypass in children. J Thorac Cardiovasc Surg 1995;110(1):284–6.
[13] van Nieuwenhuizen RC, Peters M, Lubbers LJ, Trip MD, Tijssen JGP, Mulder BJM. Abnormalities in liver function and coagulation profile following the Fontan procedure. Heart 1999;82:40–6.
[14] Odegard KC, McGowan FX, DiNardo JA, Castro RA, Zurakowski D, Connor CM, Hansen DD, Neufeld EJ, del Nido PJ, Laussen PC. Coagulation abnormalities in patients with single-ventricle physiology precede the Fontan procedure. J Thorac Cardiovasc Surg 2002;123:459–65.
[15] Odegard KC, McGowan FX, Zurakowski D, DiNardo JA, Castro RA, del Nido PJ, Laussen PC. Coagulation factor abnormalities in patients with single-ventricle physiology immediately prior to the Fontan procedure. Ann Thorac Surg 2002;73:1770–7.
[16] Cheung EW, Chay GW, Ma ES, Cheung YF. Systemic oxygen saturation and coagulation factor abnormalities before and after the Fontan operation. Am J Cardiol 2005;96(11):1571–5.
[17] Chan AK, Leaker M, Burrows FA, Williams WG, Gruenwald CE, Whyte L, Adams M, Brooker LA, Adams H, Mitchell L, Andrew M. Coagulation and fibrinolytic profile of paediatric patients undergoing cardiopulmonary bypass. Thromb Haemost 1997;77(2):270–7.
[18] Turner-Gomes SO, Mitchell L, Williams WG, Andrew M. Thrombin regulation in congenital heart disease after cardiopulmonary bypass operations. J Thorac Cardiovasc Surg 1994;107(2):562–8.
[19] Zivelin A, Tao LVM, Rapaport SI. Mechanism of the anticoagulation effect of warfarin as evaluated in rabbits by selective depression of individual procoagulant vitamin k-dependent clotting factors. J Clin Invest 1993;92:2131–40.
[20] Rapaport SI, Rao MV. The time factor pathway: How it has become a "Prima Ballerina". Thromb Haemost 1995;74:7–17.
[21] O'Donnell J, Tuddenham EG, Manning R, Kemball-Cook G, Johnson D, Laffan M. High prevelance of elevated factor VIII levels in patients referred for thrombophilia screening: role of increased synthesis and relationship to the acute phase reaction. Thromb Haemost 1997;77: 825–8.
[22] Odegard KC, McGowan FX, Zurakowski D, DiNardo JA, Castro RA, del Nido PJ, Laussen PC. Procoagulant and anticoagulant factor abnormalities following the Fontan procedure: increased factor VIII may predispose to thrombosis. J Thorac Cardiovasc Surg 2003;125:1260–7.
[23] Rauch R, Ries M, Hofbeck M, Buheitel G, Singer H, Klinge J. Hemostatic Changes following the modified Fontan operation (total cavopulmonary connection). Thromb Haemost 2000;83:678–82.
[24] Koster T, Blann AD, Briet E, Vanderbroucke JP, Rosendaal FR. Role of clotting factor VIII in effect of von Willebrand factor on occurrence of deep-vein thrombosis. Lancet 1995;345:152–5.
[25] Hollestelle MJ, Thinnes T, Crain K, Stico A, Kruijt JK, van Berkec TJC, Loskutoff DJ, van Mourik JA. Tissue distribution of factor VIII gene expression in vivo – a closer look. Thromb Haemost 2001;86:855–61.

Appendix A. Conference discussion

Dr R. Jonas (*Washington, D.C., USA*): What are the clinical implications of your work? Fenestration thrombosis early after surgery can frequently have a serious hemodynamic impact. And thrombus formation within a baffle or extracardiac conduit also can be a serious early postoperative problem. What are your recommendations regarding reversal of heparin after a Fontan operation, regarding the use of aprotinin during the Fontan operation, and what are your recommendations regarding long-term management of anticoagulation particularly with reference to aspirin and warfarin or Coumadin?

Dr Procelewska: We didn't use aprotinin in any patient after the Fontan operation. According to the prophylactic anticoagulation therapy, after stopping the bleeding shortly after the surgery in the ICU, we used the continuous infusion of heparin in all our patients, which was followed on the postoperative day 1 by a low dose aspirin of 2 to 5 mg/kg. We didn't use in any patient the oral anticoagulation therapy.

Concerning the first question, the clinical implications, I think that based on our studies we could define a subgroup of patients, in whom those hemodynamic changes, both in the preoperative period and also postoperatively, exist. In those patients we could measure the profile of coagulation abnormalities. If those abnormalities persist, we might think about changing the anticoagulation therapy into the oral anticoagulation.

Mr S. Zaefs (*Princeton, N.J., USA*): What's your hypothesis about the correlation between central venous pressure and coagulation? What's your hypothesis, why this is connected, the parameters of venous pressure and the concentration of coagulation factors?

And the second question, you didn't show it in your presentation, but maybe you have some pilot data. What's going on with factor XIII in this category of patients?

Dr Procelewska: We didn't measure factor XIII in our study, unfortunately.

Regarding the first question, in the hemi-Fontan group I think that single ventricle function is the only factor contributing to the changes in hepatic circulation. In post-Fontan patients, the change in the function of the ventricle is another associating factor that contributes to increase in PA pressure and increased venous pressure. So maybe the changes in the hemodynamics after Fontan procedure may influence significantly the changes in coagulation protein synthesis.

We think that increased venous pressure causing hepatic congestion causes the disturbances in coagulation protein synthesis by decreased synthesis of factors which are synthesized in the cells, and increase in factor VIII which is synthesized not in the cells of the liver but they are produced by the lining cells of the sinuses of the livers.