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Ethnic Differences in Coagulation Factor Abnormalities After the Fontan Procedure

Y.-F. Cheung,[1] G.W. Chay,[1] E.S.K. Ma[2]

[1]Division of Paediatric Cardiology, Department of Paediatrics and Adolescent Medicine, Grantham Hospital, The University of Hong Kong, 125, Wong Chuk Hang Road, Aberdeen, Hong Kong, People's Republic of China

[2]Division of Haematology, Department of Pathology, Queen Mary Hospital, The University of Hong Kong, Pokjulam Road, Hong Kong, People's Republic of China

Abstract. We tested the hypothesis that Chinese patients have a coagulation profile that is less prothrombotic than that of Caucasian counterparts after the Fontan procedure by determining the type and prevalence of anticoagulant and procoagulant deficiencies in Chinese patients and comparing the findings to those previously reported in Caucasian series. The liver function and coagulation factors were assessed in 21 ethnic Chinese patients, aged 17.0 ± 5.6 years, at 10.7 ± 4.0 years after the Fontan procedure. The results were compared to those of 21 age-matched Chinese controls with minor congenital heart disease. The prevalence of coagulation factor deficiencies in our patients was further compared to that reported in Caucasian patients. When compared with controls, patients had significantly lower protein C ($p = 0.014$), factors II ($p = 0.024$), V ($p < 0.001$), VII ($p < 0.001$), IX ($p = 0.036$), and X ($p < 0.001$), and higher bilirubin ($p = 0.001$) levels. The prevalence of protein C deficiency was 9.5%, whereas those of factor II, V, VII, IX, and X deficiencies were 0, 66.7, 9.5, 0, and 57.1%, respectively. When compared with Caucasian data, our data showed a significantly lower prevalence of protein C, total protein S, antithorombin III, factor II, and factor VII deficiencies. Furthermore, the previously reported increase in factor VIII levels was not found. In contrast, the prevalence of factor X deficiency was higher in our patients. This study provides the first evidence of ethnic differences in coagulation factor abnormalities after the Fontan procedure. The imbalance between procoagulant and anticoagulant pathways in Chinese patients favors a bleeding, rather than a thrombotic, tendency.

Key words: Fontan procedure — Ethnic difference — Coagulation

Correspondence to: Y.-F. Cheung, *email:* xfcheung@hkucc.hku.hk

The Fontan procedure is effective in the management of complex cyanotic congenital heart diseases with a single functional ventricle. However, this proves to be more of a palliative than curative procedure [8, 10, 12]. Among the long-term complications, thromboembolic complications have been reported to occur in Caucasian patients with an incidence as high as 20 to 33% [1, 11, 13]. Coagulation factors abnormalities, notably protein C and protein S deficiencies, have been reported in these patients [7, 8, 21, 23] that may predispose them to increased risk of thrombosis. In light of these findings, a number of authorities have recommended long-term anticoagulation therapy after the Fontan procedure [9, 13, 15, 18]. Nonetheless, given the well-documented ethnic differences in the risk of venous thrombosis [3, 4], it remains controversial whether similar recommendation is valid for ethnic Chinese patients after the Fontan procedure.

The low incidence of venous thrombosis in ethnic Chinese may in part be related to ethnic differences in anticoagulant levels and activated protein C resistance [3, 5, 17]. We hypothesized that Chinese post-Fontan patients have a coagulation profile that is less prothrombotic than that of the Caucasian counterparts. To test the hypothesis, we determined the prevalence of anticoagulant and procoagulant deficiencies in Chinese post-Fontan patients and compared the findings to those previously reported in Caucasian series [7, 14, 23].

Materials and Methods

Subjects and Design

Patients who were ethnic Chinese and had undergone Fontan procedures were recruited from the pediatric cardiac clinic of Grantham Hospital. Those on warfarin therapy were excluded. In our institution, warfarin was given empirically for 6–12 months

Table 1. Liver function test results in patients and control subjects

	Patients (n = 21)	Controls (n = 21)	p	Laboratory reference values	No. of patients with abnormal values of the parameters
Albumin	37.4 (2.69)	36.1 (2.66)	0.12	36–48	6 (28.6%) (<normal)
Total bilirubin	17.9 (9.48)	9.95 (4.27)	0.001*	0–17	6 (28.6%) (>normal)
ALT	35.4 (8.98)	36.3 (21.9)	0.88	0–58	0 (0%)
AST	28.9 (12.0)	22.4 (13.6)	0.11	14–64	0 (0%)
Alkaline phosphatase	213.0 (161.7)	162.6 (97.7)	0.24	Age dependent	1 (4.8%) (> normal)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.
* Statistically significant.

after the Fontan procedure and for long-term to patients with a history of thromboembolism and to those with impaired ventricular function and significant atrioventricular valve regurgitation. Age-matched subjects with hemodynamically insignificant cardiac lesions and a biventricular circulation were recruited as controls. The clinical records of all subjects were reviewed and the following data were collected: demographic data, cardiac diagnosis, history of thromboembolic complications, current cardiac medications, and anticoagulant use. The institutional ethics committee approved the study and patients or parents of minors gave written, informed consent.

Blood Investigations

Venous blood was obtained for liver function tests and coagulation studies. For assessment of liver function, serum concentrations of total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and albumin were measured with an automatic chemical analyzer (Dimension, Dade Behring, Deerfield, IL, USA). For the coagulation studies, the activated partial thromboplastin time (APTT) was determined using Thrombosil I activated PTT reagent (Hemoliance, Instrumentation Laboratory, Milan, Italy), the prothrombin time (PT) was determined using Thromborel S human thromboplastin reagent (Dade Behring), and fibrinogen was determined by the Clauss method using human thrombin (Sigma). For the factor assays, the citrated plasma was separated by centrifugation and stored at −80°C until assayed. Protein C and antithrombin III were measured by chromogenic assay (Diagnostica Stago, AsnieAres, France), whereas total protein S and free protein S were determined by enzyme-linked immunosorbent assay (Diagnostica Stago) Factors II, V, VII, VIII, IX, and X were measured by clotting method using specific factor-deficient plasma (Diagnostica Stago and Dade Behring).

Statistical Analysis

Data are presented as mean (standard deviation) unless otherwise stated. The liver function and coagulation parameters of patients and control subjects were compared using Student's t-test. Likewise, the parameters in control subjects who had and those who had not undergone previous cardiac surgery were compared. The normal reference range of the various parameters was derived from control subjects based on the empirical 95% confidence intervals (2.5–97.5 percentiles) [24]. The prevalence of abnormally low (<2.5 percentile) or high (>97.5 percentile) values beyond the reference range in patients was compared to that reported in Caucasian series [7, 14, 23] using Fisher's exact test. Pearson correlation analysis was used to assess for possible relationships between liver function indices and coagulation factor levels and, in the patient cohort, follow-up duration since the Fontan procedure and coagulation factor levels. A p value of < 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS version 10.0 software (SPSS, Chicago, IL, USA).

Results

Subjects

A total of 21 patients (12 males), aged 17.0 ± 5.6 years, were studied at 10.7 ± 4.0 years after the Fontan procedure. All of the patients were in New York Heart Association functional class I and free of cardiac arrhythmias at the time of study. None had history of thromboembolism. The cardiac diagnoses were tricuspid atresia in 10 patients, double-inlet right ventricle in 4, double-inlet left ventricle in 3, and 1 each with pulmonary atresia and intact ventricular septum, right isomerism with a double-inlet indeterminate ventricle, and left isomerism with a double-inlet indeterminate ventricle. The type of Fontan procedure was atriopulmonary anastomosis in 15 and total cavopulmonary connection in 6. Four of the patients were on oral aspirin at the time of study. Twenty-one control subjects, aged 16.9 ± 5.4 years (p = 0.95), were recruited. Of these, 13 had undergone cardiac operations 8.3 ± 5.9 years prior to this study: 8 had surgical repair of left-to-right shunts, 3 had surgical repair of tetralogy of Fallot, and 2 had arterial switch operation for transposition of great arteries; none had significant residual cardiac lesions. Of the remaining 8 subjects, 4 had a structurally normal heart, 2 had a small ventricular septal defect, 1 had mild mitral regurgitation, and 1 had mitral valve prolapse without mitral regurgitation.

Liver Function

The results of liver function tests are summarized in Table 1. When compared with control subjects, pa-

tients had a significantly higher total serum bilirubin level ($p = 0.001$). Of the 21 patients, 6 (29%) had a bilirubin level exceeding the upper limit of normal. On the other hand, the serum albumin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels did not differ between patients and controls. None of the patients had protein-losing enteropathy.

Coagulation Factor Abnormalities

The serum levels of anticoagulant and procoagulant factors are summarized in Table 2. Coagulation factor abnormalities that predispose to thrombosis were noted in only 2 of the 21 patients (9.5%), and both had decreased protein C levels. None of the patients had deficiency of free protein S or antithrombin III. As previously mentioned, none had a history of thromboembolism.

In contrast, abnormalities that may potentially increase the risk of bleeding were prevalent. Factor II, V, VII, IX, and X levels were significantly lower in patients than control subjects (Table 2). When individual results were analyzed, the level of factor II, V, VII, VIII, IX, and X fell below the lower limit of normal in 0, 66.7, 9.5, 4.8, 0 and 57.1% of patients, respectively. Furthermore, the prothrombin time was prolonged in 76% of patients.

Of the various liver function parameters, only bilirubin and alkaline phosphatase showed significant correlations with the coagulation factor levels, Bilirubin correlated negatively with factor V ($r = -0.35$, $p = 0.025$) and factor VII ($r = -0.36$, $p = 0.021$) levels and positively with prothrombin time ($r = 0.39$, $p = 0.01$). Alkaline phosphatase correlated negatively with protein C ($r = -0.52$, $p < 0.001$), factor II ($r = -0.56, p < 0.001$), factor VII ($r = -0.42$, $p = 0.09$), and factor X ($r = -0.43$, $p = 0.005$) levels and positively with prothrombin time ($r = 0.53, p < 0.001$).

Ethnic Differences

The prevalence of deficiencies of the various coagulation factors in this Oriental series was compared to that reported in Caucasian patients (Table 3). The prevalence of protein C, protein S, antithrombin, factor II, and factor VII deficiencies was lower in our patients compared to one or more of the Caucasian series [7, 14, 23]. On the other hand, factor X deficiency was more prevalent. An increased level of factor VIII, a risk factor predisposing to thrombosis, was reported to occur in 50% of 20 German post-Fontan patients [21]. However, in none of our patients was factor VIII found to be elevated ($p < 0.001$) (Table 2).

Discussion

The findings of the current study suggest important ethnic differences in coagulation factor abnormalities after the Fontan procedure. The prevalence of protein C deficiency in Chinese children after the Fontan procedure is low. Additionally, protein S deficiency, antithrombin III deficiency, and increased factor VIII level were not found in any of our patients. The ensuing prothrombotic risk attributable to the aforementioned factor abnormalities in our patients is therefore likely to be lower than that described in Caucasian post-Fontan patients.

Protein C deficiency has been incriminated as one of the most common factors predisposing to thrombosis in Caucasian patients after the Fontan procedure [7, 21, 23]. Although an increase in venous pressure after the Fontan procedure may have interfered with hepatic synthesis of anticoagulant factors, the fact that similar findings were observed after only cavopulmonary connection in Dutch patients suggests a possibility of alternative mechanisms [22]. However, the exact cause remains uncertain. The striking difference in the prevalence of protein C deficiency between ethnic Chinese and Caucasian cohorts (9.5 vs 24–75%) [7, 14, 23] is intriguing. A gradual reduction in the prevalence of protein C deficiency with an increase in follow-up interval since surgery has been observed [7, 23]. Nonetheless, the mean duration of follow-up in the current study did not differ from those reported previously. Notwithstanding a normal liver function in the majority of our patients, the degree of liver dysfunction is of minor predictive value for the previously reported coagulation abnormalities [23]. Thus, the difference in the prevalence observed may genuinely be ethnic in origin. Nonetheless, environmental factors, particularly dietary ones, probably also contribute to such a difference.

The reported parallel decrease in protein S and antithrombin III [7, 14, 21, 23] in Caucasian patients was likewise not observed in the current study. Apart from deficiencies of these naturally occurring anticoagulants, increased concentration of factor VIII has also been reported to be an independent risk factor for venous thromboembolism [16]. In two studies on hemostatic changes in post-Fontan Caucasian patients, a marked increase in factor VIII has been shown [20, 21]. Nonetheless, the current study failed to replicate these novel findings.

Although abnormalities predisposing to thrombus formation do not appear to be the predominant hemostatic disturbance in Chinese patients, those

Table 2. Levels of anticoagulant and procoagulant factors in patients and control subjects

				Reference values			
	Patients (p = 21)	Controls (n = 21)	p	Controls (2.5–97.5 percentile)	Laboratory adult-derived values	No. of patients with parameters below normal range (%)	No. of patients with parameters above normal range (%)
Protein C (IU/ml)	0.80 (0.12)	0.89 (0.12)	0.014*	0.69–1.10	0.7–1.3	2 (9.5)	0 (0)
Total protein S (IU/ml)	0.77 (0.10)	0.86 (0.10)	0.003*	0.62–1.03	0.67–1.13 (Male) 0.57–1.12 (Female)	1 (4.8)	0 (0)
Free protein S (IU/ml)	0.29 (0.04)	0.26 (0.04)	0.015*	0.18–0.33	0.21–0.39 (Male) 0.19–0.36 (Female)	0 (0)	3 (14.3)
AT III (IU/ml)	1.12 (0.09)	1.12 (0.14)	0.86	0.93–1.38	0.8–1.2	0 (0)	0 (0)
Coagulation factors (IU/ml)							
II	0.88 (0.10)	0.97 (0.14)	0.024*	0.64z–1.31	0.5–1.5	0	0 (0)
V	0.89 (0.19)	1.23 (0.23)	< 0.001*	0.97–1.74	0.5–1.5	14 (66.7)	0 (0)
VII	0.71 (0.11)	0.92 (0.19)	< 0.001*	0.57–1.31	0.5–1.5	2 (9.5)	0 (0)
VIII	1.07 (0.27)	1.06 (0.36)	0.87	0.61–2.17	0.5–1.5	1 (4.8)	0 (0)
IX	0.78 (0.09)	0.87 (0.18)	0.036*	0.61–1.26	0.5–1.5	0 (0)	0 (0)
X	0.86 (0.13)	1.08 (0.18)	< 0.001*	0.88–1.66	0.5–1.5	12 (57.1)	0 (0)
Fibrinogen (g/L)	2.38 (0.28)	2.56 (0.50)	0.15	1.84–3.42	1.46–3.38	0 (0)	0 (0)
PT (sec)	13.9 (0.93)	12.6 (0.92)	< 0.001*	—	11.3–13.2	0 (0)	16 (76)
INR	1.19 (0.07)	1.09 (0.09)	< 0.001*	—			
APTT (sec)	30.7 (2.62)	31.4 (8.66)	0.73	—	27.6–37.6	0 (0)	0 (0)

APTT, activated partial thromboplastin time; AT, antithrombin; INR, international normalized ratio; PT, prothrombin time.
* Statistically significant.

Table 3. Deficiencies in naturally occurring anticoagulants and coagulation factors in post-Fontan patients: comparison between Oriental and Caucasian series

	Current study (%)	Cromme-Dijkhuis et al. [7] (%)	van Nieuwenhuizen et al. [23] (%)	Jahangiri et al. [14] (%)
Protein C	9.5 (2/21)	57 (21/37)†	24 (5/21)	75 (15/20)†
Total protein S	4.8 (1/21)	57 (21/37)†	0 (0/21)	20 (4/20)
Free protein S	0 (0/21)	—	0 (0/21)	—
Antithrombin III	0 (0/21)	19 (7/36)*	0 (0/24)	0 (0/20)
Factor II	0 (0/21)	39 (14/36)†	—	10 (2/20)
Factor V	66.7 (14/21)	—	80 (16/20)	—
Factor VII	9.5 (2/21)	—	85 (17/20)†	55 (11/20)
Factor VIII	4.8 (1/21)	—	—	—
Factor IX	0	—	—	5 (1/20)
Factor X	57.1 (12/21)	38 (14/37)	—	10 (1/20)*

* $p < 0.05$.
† $p < 0.001$.

predisposing to prolonged bleeding are evident. The prothrombin time was prolonged, albeit slightly, in 76% of our patients, with concomitant decrease in coagulation factors of the extrinsic pathway (Table 2). These findings corroborate those reported previously [23]. Although these findings may reflect reduced gastrointestinal absorption of vitamin K, normal enteric absorption of lipid soluble vitamins after Fontan operation has been reported [7]. Furthermore, none of our patients had symptoms or signs of protein losing enteropathy. Alternatively, the lower levels of these coagulation factors may reflect impaired synthetic capacity of the liver. In keeping with previous findings [23], mild cholestasis is the predominant abnormality of the liver function test. Indeed, serum bilirubin level correlates negatively with factors V and VII and positively with prothrombin time in our patients.

The imbalance between procoagulant and anticoagulant pathways in Chinese patients thus favors a bleeding, rather than a thrombotic, tendency. Prolonged bleeding has been reported in post-Fontan patients undergoing noncardiac surgery [23], although the prevalence of bleeding complications requires further clarification. Therefore, it seems reasonable to speculate that when compared to Caucasians, ethnic Chinese patients are less predisposed to thrombotic complications. Indeed, we have reported a 4.5% prevalence of thromboembolic complications in our 88 long-term Fontan survivors [19], in contrast to a prevalence of 3–33% in Caucasians [1, 6, 11, 13]. Although this is only a crude comparison, it is tempting to speculate that ethnic difference in the incidence of thromboembolic complications may indeed be present as a result of differences in postoperative coagulation factor abnormalities.

The need for long-term anticoagulation treatment after the Fontan procedure is controversial [2]. The theoretical increase in thrombotic risk in Caucasian patients, due to deficiencies of protein C, protein S, and antithrombin III and an increase in factor VIII, has prompted a number of authors to recommend long-term anticoagulation therapy after the Fontan procedure [9, 13, 15, 18]. Nonetheless, the findings of our study do not support such a strategy in Chinese patients. In fact, the use of anticoagulants may further increase the risk of bleeding in this cohort. However, it is worthwhile to bear in mind that alteration of coagulation is only one of the three elements constituting the Virchow's triad. In considering the necessity for long-term anticoagulation, other risk factors intrinsic to the Fontan circulation that may promote stasis of blood or cause damage to the vessel surface also have to be taken into account.

A number of limitations deserve comments. First, we did not determine post-Fontan hemodynamic data by cardiac catheterization, although it may have been useful to explore the relations between central venous pressure and the levels of coagulation factors. Nonetheless, there was no clinical evidence of Fontan circuit malfunction or a significantly elevated central venous pressure in any of our patients. Second, the control group that comprises both pre- and postoperative subjects may appear relatively heterogeneous. However, inclusion of the latter may help to exclude potential confounding influence related to open-heart surgery. The fact that the control-derived references are similar to laboratory ones (Table 2) further supports the legitimacy of our control group. Third, we did not examine the influence of different Fontan modifications on coagulation factor abnormalities. It would be interesting to explore this aspect further in light of the variations in blood flow dynamics between these modifications.

In conclusion, this study provides the first evidence of ethnic differences in coagulation factor

abnormalities after the Fontan procedure. The findings may account for the differences in thrombotic risk and have implications for the need for long-term anticoagulation treatment in patients of different ethnicity.

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References

1. Balling G, Vogt M, Kaemmerer H, et al. (2000) Intracardiac thrombus formation after the Fontan operation. *J Thorac Cardiovasc Surg 119*:745–751
2. Bull K (1998) The Fontan procedure: lessons from the past. *Heart 79*:213–214
3. Chan KY, Yuen ST, Ng TH, Ng WF (1991) An autopsy study of pulmonary thromboembolism in Hong Kong Chinese. *Pathology 23*:181–184
4. Chan KY, Yuen ST, Wong MP (1997) Clinicopathological pattern of pulmonary thromboembolism in Chinese autopsy patients: comparison with Caucasian series. *Pathology 29*:263–266
5. Chan LC, Bourke C, Lam CK, et al. (1996) Lack of activated protein C resistance in healthy Hong Kong Chinese blood donors–correlation with absence of Arg 506–Gln mutation of Factor V gene. *Thromb Haemost 75*:522–523
6. Cheung YF, Chay GW, Chiu CS, Cheng LC (2005) Long-term anticoagulation therapy and thromboembolic complications after the Fontan procedure. *Int J Cardiol*, 19 July 2005; Epub
7. Cromme-Dijkhuis AH, Henkens CMA, Bijleveld CMA, et al. (1990) Coagulation factor abnormalities as possible thrombotic risk factors after Fontan operations. *Lancet 336*:1087–1090
8. Cromme-Dijkhuis AH, Hess J, Hählen K, et al. (1993) Specific sequelae after Fontan operation at mid- and long-term follow-up. *J Thorac Cardiovasc Surg 106*:1126–1132
9. Dobell AR, Trusler GA, Smallhorn JF, Williams WG (1986) Atrial thrombi after the Fontan operation. *Ann Thorac Surg 42*:664–667
10. Driscoll DJ, Offord KP, Feldt RH, et al. (1992) Five- to fifteen-year follow-up after Fontan operation. *Circulation 85*: 469–496
11. Fletcher SE, Case CL, Fyfe DA, Gillette PC (1991) Clinical spectrum of venous thrombi in the Fontan patient. *Am J Cardiol 68*:1721–1722
12. Fontan F, Kirklin JW, Fernandez G, et al. (1990) Outcome after a "perfect" Fontan operation. *Circulation 81*:1520–1536
13. Jahangiri M, Ross DB, Redington AN, Lincoln C, Shinebourne EA (1994) Thromboembolism after the Fontan procedure and its modifications. *Ann Thorac Surg 58*:1409–1414
14. Jahangiri M, Shore D, Kakkar V, Lincoln C, Shinebourne E (1997) Coagulation factor abnormalities after the Fontan procedure and its modifications. *J Thorac Cardiovasc Surg 113*:989–993
15. Kaulitz R, Luhmer I, Bergmann F, Rodeck B, Hausdorf G (1997) Sequelae after modified Fontan operation: postoperative haemodynamic data and organ function. *Heart 78*:154–159
16. Koster T, Blann AD, Briet E, Vandenbroucke JP, Rosendaal FR (1995) Role of clotting factor VIII in effect of von Willebrand factor on occurrence of deep-vein thrombosis. *Lancet 345*:152–155
17. Lao TT, Yuen PM, Yin JA (1989) Protein S and protein C levels in Chinese women during pregnancy, delivery and the puerperium. *Br J Obstet Gynaecol 96*:167–170
18. Manning PB, Mayer JE, Wernovsky G, Fishberger SB, Walsch EP (1996) Staged operation to Fontan increased the incidence of sinoatrial node dysfunction. *J Thorac Cardiovasc Surg 111*:833–840
19. Monagle P, Cochrane A, McCrindle B, et al. (1998) Thromboembolic complications after Fontan procedures — the role of prophylactic anticoagulation. *J Thorac Cardiovasc Surg 115*:493–498
20. Odegard KC, McGowan FX, Zurakowski D, et al. (2002) Coagulation factor abnormalities following the Fontan procedure: factor VIII is increased and may predispose to thrombosis. *J Am Coll Cardiol 106*:II–523
21. Rauch R, Ries M, Hofbeck M, et al. (2000) Hemostatic changes following the modified Fontan operation (total cavopulmonary connection). *Thromb Haemost 83*:678–682
22. Ravn HB, Hjortdal VE, Stenbog EV, et al. (2001) Increased platelet reactivity and significant changes in coagulation markers after cavopulmonary connection. *Heart 85*:61–65
23. van Nieuwenhuizen RC, Peters M, Lubbers LJ, et al. (1999) Abnormalities in liver function and coagulation profile following the Fontan procedure. *Heart 82*:40–46
24. Wright EM, Royston P (1999) Calculating reference intervals for laboratory measurements. *Stat Methods Med Res 8*:93–112

Procoagulant and anticoagulant factor abnormalities following the Fontan procedure: Increased factor VIII may predispose to thrombosis

Kirsten C. Odegard, MD[a]
Francis X. McGowan, Jr, MD[a]
David Zurakowski, PhD[c]
James A. DiNardo, MD[a]
Robert A. Castro, MT[a]
Pedro J. del Nido, MD[b]
Peter C. Laussen, MBBS[a]

CHD

Objective: Using age-matched controls, this study prospectively evaluated coagulation factor abnormalities and hemodynamic variables in children who had undergone the Fontan operation.

Methods: Coagulation factors were assayed in 20 children (mean age 6.4 ± 2.9 years), at a mean 3.7 ± 2.3 years after the Fontan procedure; 24 healthy children (mean age 6.8 ± 2.8 years) were assayed as controls. Concentration of factors II, V, VII, VIII, IX, X; ATIII; plasminogen; proteins C and S; fibrinogen; serum albumin; and liver enzymes were measured. Normal reference intervals based on the control patients were determined using 95% confidence limits. Patient demographic, hemodynamic variables, and elapsed time after the Fontan procedure were evaluated as possible predictors of coagulation abnormalities.

Results: Concentrations of protein C; factors II, V, VII, X; plasminogen; and ATIII were significantly lower in Fontan patients compared with age-matched controls ($P < .01$); factor VIII was significantly elevated in 6 patients (35%), 2 of whom had a thromboembolic event. A higher superior vena cava pressure was predictive of an elevated factor VIII level ($P = .003$). No other specific hemodynamic variables were predictive of a procoagulant or anticoagulant abnormality.

Conclusion: Procoagulant and anticoagulant factor levels were significantly lower in patients after the Fontan operation independent of hemodynamic variables peculiar to the Fontan circulation. Increased factor VIII level requires further evaluation as a cause of thrombosis in patients with Fontan physiology and may also indicate a subset of these patients in whom anticoagulation is indicated.

From the Departments of Anesthesia, Cardiac Surgery, and Biostatistics, Children's Hospital, Boston, and Harvard Medical School, Boston, Mass.

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Address for reprints: Kirsten C. Odegard, MD, Cardiac Anesthesia Service, 300 Longwood Avenue, Children's Hospital, Boston, MA 02115 (E-mail: kirsten.odegard@tch.harvard.edu).

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Since the original Fontan operation was described, several modifications have been undertaken that have improved early and late morbidity and mortality. Survival following the fenestrated lateral tunnel Fontan procedure of 93% at 5 years and 91% at 10 years has recently been reported.[1] Nevertheless, complications including ventricular dysfunction, thromboembolic events, dysrythmias, and protein losing enteropathy may compromise longer-term function and outcome.[2]

The incidence of thromboembolic events in patients with Fontan physiology is uncertain but has been reported to be as high as 20% to 33%.[3-6] Abnormal coagulation parameters following the Fontan procedure involving both pro- and anticoagulant factors have been described.[7-10] These studies suggested that the alterations in the coagulation factors found in some Fontan patients are a direct

consequence of the anatomic and physiologic changes that result from the Fontan operation. The nature of the "Fontan" circulation with elevated central venous pressure, low flow with possible stasis through the atrial baffle and pulmonary circulation, atrial dysrhythmias, hepatic dysfunction, and increased resting venous tone are some of the suggested factors. However, we recently reported that pro- and anticoagulant factor abnormalities occur earlier in the course of staged surgical palliation for single ventricle disease.[11,12] Whether this is due to other physiologic derangements such as cyanosis, low cardiac output, venous congestion, or perhaps a genetic predisposition is unknown.

Previous studies have evaluated only a small number of coagulation factor abnormalities after the Fontan operation, have not used age-matched controls, and have not undertaken a detailed analysis of hemodynamic variables that could alter coagulation factor levels. In this single-center, prospective, cohort study, coagulation factor abnormalities after the Fontan operation were evaluated, along with hemodynamic variables peculiar to the Fontan circulation that could contribute to coagulation abnormalities.

Materials and Methods

After obtaining institutional review board approval and informed parental consent, 20 children who had undergone a prior Fontan operation were enrolled in this prospective study. Patients were excluded if they had preexisting hematological disorders, concurrent coagulopathies, or if they were anticoagulated with coumadin; 16 (80%) patients had been receiving aspirin but this was discontinued 7 to 10 days prior to blood draw.

All patients underwent general anesthesia; 13 patients for cardiac catheterization, 5 patients for permanent pacemaker placement/revision, 1 patient for aortic valvuloplasty, and 1 patient for elective noncardiac surgery. Blood samples from all patients (8 mL) were obtained from a venous catheter or an indwelling arterial catheter after induction of general anesthesia. Measured parameters included hemoglobin (Hgb), hematocrit (Hct), platelet count, prothrombin time (PT), and activated partial prothrombin time (APTT). Inhibitors of coagulation measured included protein C, protein S, plasminogen, and antithrombin III; the procoagulant factors measured were II, V, VII, VIII, IX, X, and fibrinogen.

The Coulter T 660 (Beckman Coulter, Inc, Miami, Fla, USA) automated hematology analyzer was used to measure Hgb, Hct, and platelets; coefficients of variation (%) within and between assays 3 different Hgb levels were: 1.8, 1.0, 0.9; for Hct: 1.8, 1.2, 1.5; and for platelets: 4.8, 2.7, 1.8, respectively.

The ACL 3000 plus (Automated Coagulation Laboratory, Beckman Coulter Inc, Miami, Fla) was used to assay individual procoagulant and anticoagulant factors as well as the PT and APTT. The ACL contains two measuring systems: (1) nephelometry, which is used to detect clot formation as the endpoint, and (2) photometry, which is used for chromogenic substrate assays. Blood for these assays was collected in citrated plasma (3.2% buffered sodium citrate) from an indwelling cannula from which 10 mL of blood had been aspirated to remove residual heparin. The blood was immediately centrifuged at 13,000 rpm for 5 minutes and the plasma layer removed. The PT, APTT, and fibrinogen were measured immediately using nephelometry (coefficients of variation [%] respectively: PT: 1.2, 2.3; APTT: 2.1, 4.8; fibrinogen: 3.1, 5.5). Remaining plasma was stored at −70°C in 200 μL aliquots for batch performance of the other coagulation assays, as described below.

Protein C and S activity were both measured using functional clotting assays. Protein C activity was determined based on the prolongation of the APTT using the Staclot Protein C kit (Diagnostica Stago, Asnieres-Sur-Seine, France) according to the manufacturer's directions. In this assay, activated protein C inhibits factor V and VIII activity, thus prolonging the APTT of a system in which all the factors with the exception of protein C are present in excess; protein C is derived from the sample being tested (coefficients of variation [%]: 1.8 and 2.4).

Protein S activity was determined based on the principle of factor Va inhibition using the Staclot Protein S kit (Diagnostica Stago, Asnieres-Sur-Seine, France). The principle of the test is based upon the cofactor activity of protein S, which enhances the anticoagulant action of activated protein C. This enhancement is reflected by the prolongation of the clotting time of a system enriched with factor Va (coefficients of variation [%]: 7.9 and 3.8).

Extrinsic coagulation factors (factors II, V, VII, and X) were each determined by performing a modified prothrombin time assay. Intrinsic coagulation factors (factors VIII and IX) were determined by performing a modified activated partial thromboplastin time. In these assays, correction of the clotting time of plasma specifically deficient in the factor being tested is proportional to the concentration (activity %) of that factor in the patient plasma, interpolated from a calibration curve (control plasma deficient in factors II, V, VII, VIII, IX, or X was obtained from Instrument Laboratory, Lexington, Mass; coefficient of variation [%] respectively: II: 2.3, 2.7; V: 3.3, 2.3; VII: 2.5, 2.2; VIII: 4.9, 3.7; IX: 3.2, 3.1; X: 3.0, 2.0).

Antithrombin III activity was determined using a synthetic chromogenic substrate assay that is based upon factor Xa inactivation (Antithrombin III, Instrument Laboratory, Lexington, Mass, USA; coefficients of variation [%]: 4.3 and 2.8). Plasma plasminogen was activated through reaction with an excess of streptokinase in the presence of fibrinogen. Plasminogen content was then determined based on a synthetic chromogenic substrate assay according to the manufacturer's directions (Plasminogen, Instrument Laboratory, Lexington, Mass; coefficients of variation [%]: 4.5 and 3.7).

Because altered hepatic dysfunction can contribute to coagulation factor abnormalities, serum alkaline phosphatase, gamma-glutamyl transferase, alanine transaminase, aspartate transaminase, total bilirubin, albumin, and total protein were measured in all patients and compared with normal values for our laboratory.

Age-Matched Control Coagulation Parameters

Coagulation factor levels vary with age and maturation of the coagulation system, as well as with the reagents used to perform the different tests. To adjust for this, after informed written parental consent was obtained, 24 healthy children (9 females, 15 males), mean age 6.8 ± 2.8 years (range 3.0 to 13.5 years), undergoing minor day surgery procedures were also studied. Blood was taken from each patient after induction of anesthesia and

TABLE 1. Cardiac diagnoses of patients after the Fontan procedure

Diagnoses	n	Prior surgery
Morphologic LV		
DILV/MA	1	BTS, BDG, FenFon
DILV	1	PAB, BDG, FenFon
DILV/TGA	3	1 St1, FenFon, PPM/1 BDG, PPM, FenFon/1 BDG, Ex.FenFon
TA/PS	1	BTS, FenFon
TGA/PA	1	BTS, FenFon
Morphologic RV		
DORV/VSD	2	1 PAB, BDG, FenFon/1 PAB, FenFon
DORV/MA	1	PAB, BDG, FenFon
DORV/PS/MS	1	BDG, FenFon
TA/PS	1	BTS, FenFon
TGA/PA	1	BTS, FenFon
HLHS	8	8 St1, BDG/7, FenFon/1 Ex. FenFon/1 PPM
Heterotaxy	1	BTS, BDG, FenFon

BDG, Bidirect Glenn procedure; *BTS,* Blalock-Taussig shunt; *DILV,* double inlet left ventricle; *DORV,* double outlet right ventricle; *FenFon,* Fenestrated Fontan procedure; *Ex.FenFon,* extracardiac fenestrated Fontan procedure; *HLHS,* hypoplastic left heart syndrome; *MA,* mitral stenosis; *MS,* mitral stenosis; *PA,* pulmonary atresia; *PAB,* pulmonary artery band; *PPM,* permanent pacemaker; *PS,* pulmonary stenosis; *St1,* stage 1 procedure (Norwood); *TA,* tricuspid atresia; *TGA,* transposition of great arteries; *VSD,* ventricular septal defect.

placement of an intravenous catheter and collected into citrated plasma tubes (3.2% buffered sodium citrate). Blood samples were immediately centrifuged at 13,000 rpm for 5 minutes and the plasma stored at −70°C for subsequent batch analyses. Proteins C and S, plasminogen, fibrinogen, ATIII, and factors II, V, VII, VIII, IX, X were analyzed as described above.

Potential Hemodynamic Factors

Ventricular morphology (morphologic right or left systemic ventricle), ventricular function, and atrioventricular valve and semilunar valve function were assessed by preoperative echocardiography. Superior vena cava O_2 saturation (SvO_2), the ratio of pulmonary to systemic blood flow (Qp/Qs), superior vena cava pressure (SVCp), pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), and systemic ventricular end-diastolic pressure (EDP) were all assessed by cardiac catheterization, either the day of data collection or within 3 months prior to the procedure. The length of time following the Fontan operation was also examined as a potential variable contributing to coagulation abnormalities.

Statistical Analysis

Normal ranges for each of the 11 coagulation variables and proteins were determined using the empirical 95% confidence intervals. Controls and Fontan patients were compared using the 2-sample Student *t* test after testing for normality (Kolmogorov-Smirnov test). The sample sizes of 24 controls and 20 Fontan patients provided 85% power (at an α level of 0.05, effect size = 1) to detect a significant difference between the groups for each of the coagulation factors (version 4.0, nQuery Advisor, Statistical Solutions, Boston, Mass). Univariate and multivariate logistic regression using maximum likelihood estimation was performed to identify potential predictors of a coagulation abnormality. Variables evaluated included age, weight, gender, ventricle morphology (left or right), EDP, SvO_2, SVCp, Qp/Qs ratio, PAP, PVR, ventricular function, atrioventricular valve regurgitation, and time since Fontan operation. Mean coagulation levels in patients with and without fenestration closure were assessed using Student *t* tests. Multiple linear regression was used to develop a prediction equation for coagulation levels with adjusted R^2 as the measure of goodness-of-fit. Statistical analysis was conducted using the SPSS software package (version 11.0, SPSS Inc, Chicago, Ill). Values are given as mean ± SD unless otherwise stated. Significance was set at $P < 0.05$ for 2-tailed comparisons.

Results

The mean age for the 20 patients (3 girls and 17 boys) was 6.4 ± 2.9 years (range 2.6 to 14.5 years) and mean weight was 19.8 ± 9.8 kg. Patient diagnoses and prior procedures are summarized in Table 1. Eighteen patients had undergone a fenestrated intra-atrial lateral tunnel Fontan operation. Two patients had undergone an extracardiac Fontan operation, one of which was fenestrated at the time of surgery and the other fenestrated in the catheterization laboratory because of protein losing enteropathy (PLE). Three patients (15%) had signs of PLE with hypoproteinemia and ascites; 2 of these patients had elevated SVCp (20 and 20 mm Hg) and EDP (12 and 14 mm Hg), respectively. The follow-up period between the Fontan operation and inclusion in our study was 3.7 ± 2.3 years (range 8.5 months to 9.5 years).

Thirteen patients had a morphologic right ventricle and 7 had a morphologic left ventricle. There were no differences in measured hemodynamics based on ventricular morphology. Hemodynamic variables as assessed either by echocardiography or cardiac catheterization are shown in Table 2.

Normal Ranges

For the 24 control subjects (9 girls, 15 boys), the mean age was 6.8 ± 2.8 years (range 3.5 to 13.5 years). The normal reference ranges for coagulation factors are shown in Table 3. Normal ranges were based on the empirical 95% confidence intervals derived from the 2.5 and 97.5 percentile confidence limits.

Coagulation Abnormalities

The comparison between coagulation factors in Fontan patients and healthy controls is summarized in Table 4. Significant reductions in the levels of both procoagulant factors and inhibitors of coagulation were detected in all 20 Fontan patients. Concentration of protein C; factors II, V, VII, X; plasminogen; and ATIII were significant lower in Fontan patients compared with age-matched controls ($P < .01$). Using univariate and multivariate logistic regression, no significant relationship between these coagulation abnormalities and gender, weight, prior procedure, serum albu-

TABLE 2. Hemodynamic characteristics in Fontan patients

Variable	n (%)
Ventricular function	
Normal	13 (69%)
Mildly depressed	5 (26%)
Moderately severely depressed	1 (5%)
AVVR	
No regurgitation	4 (21%)
Trivial	3 (16%)
Mild–moderate	12 (63%)
EDP (mean mm Hg)	8.2 ± 3.7
SVCp (mean mm Hg)	12.9 ± 4.3
TPG (mean mm Hg)	5.4 ± 1.7
PVR (Wood units)	1.9 ± 0.6
Qp/Qs	0.85 ± 0.2
Pao_2 mm Hg	59.5 ± 8.2
Svo_2 (%)	66 ± 0.1
Spo_2 (%)	88 ± 0.1

Data expressed as number (%), and mean ± standard deviation. *AVVR,* Atrioventricular valve regurgitation; *CVP,* superior vena cava pressure; *EDP,* end-diastolic pressure; *PAP,* pulmonary artery pressure; PO_2, oxygen tension; *PVR,* pulmonary vascular resistance; *Qp/Qs,* pulmonary to systemic blood flow; SpO_2, oxygen saturation; SvO_2, superior vena cava O_2 saturation; *TPG,* transpulmonary gradient.

TABLE 3. Normal ranges for coagulation factors and protein levels

Variable	Median	Mean ± SD	Normal range*
Fibrinogen (mg/L)	321	315 ± 107	104-570
Factor II (%)	92	97 ± 17	71-130
Factor V (%)	107	106 ± 23	76-160
Factor VII (%)	92	97 ± 24	67-172
Factor VIII (%)	99	98 ± 25	43-143
Factor IX (%)	78	81 ± 22	52-136
Factor X (%)	91	94 ± 17	66-126
Antithrombin III (%)	109	107 ± 16	50-127
Plasminogen (%)	102	100 ± 14	77-134
Protein C (%)	97	98 ± 23	56-147
Protein S (%)	83	87 ± 17	69-133

*Normal ranges were based on the empirical 95% confidence intervals derived from the 2.5 and 97.5 percentile limits (n = 24), except fibrinogen (n = 21). *SD,* Standard deviation.

min, the hemodynamic variables previously listed (diagnosis, right or left ventricle morphology, ventricular function, AVVR, PVR, oxygen saturation, SVo_2, Qp/Qr ratio, Po_2, SVCp, transpulmonary gradient, and EDP) or the time period after the Fontan procedure could be identified (all $P >$ .20).

In contrast, factor VIII was significantly elevated in Fontan patients compared with controls ($P < .04$; Figure 1). Six patients (35%) had markedly elevated factor VIII levels (>150% activity) compared with the controls. Multiple linear regression analysis indicated that SVCp was a strong predictor of factor VIII levels and this relationship was maintained after controlling for all other hemodynamic and laboratory variables (adjusted $R^2 = 0.74$, $P = .003$). The relationship between SVCp and factor VIII is illustrated in Figure 2. The predictive equation derived from this model was: Factor VIII (%) = 12.7 × SVCp − 28.

No significant correlations were detected between time since the Fontan operation and any of the 11 coagulation factors or proteins (all $P > .2$).

Hemostatic Variables and Liver Function

The mean Hct, platelet count, PT, APTT, and liver function tests (LFTs) for Fontan patients are shown in Table 5. Partial thromboplastin time (PTT) was abnormally elevated in 29% of the patients. In all but three patients, abnormal PT and/or PTT values corrected when calibration plasma (Instrumentation Laboratory Company, Lexington, Mass) was added in a 50:50 ratio to patient's plasma. Calibration plasma is obtained from healthy donors and is processed to maintain the characteristics of normal plasma. Normalization by calibration plasma indicates one or more factor deficiencies as the cause of the PT or PTT prolongation (as opposed to circulating anticoagulants such as heparin). Three patients did not normalize with calibration plasma for PTT, which was interpreted as heparin contamination; these patients were excluded from PTT evaluation. Three patients failed to normalize with calibration plasma; because protein C and factor VIII and IX assays are also based upon prolongation of the PTT, their protein C and factor VIII and factor IX data were excluded from analysis.

Liver function tests are also shown in Table 5. Several patients had small elevations of aspartate aminotransferase and alanine aminotransferase, but mean values were within the normal range; gammaglutamyl transpeptidase was elevated in 9 patients (45%), and 5 patients (25%) had signs of hypoproteinemia (albumin <3 g/dL), including the 3 patients who carried the clinical diagnosis of PLE. There were no correlations between abnormal liver function tests, hemodynamic variables such as elevated SVCp, or coagulation factor abnormalities.

Thromboembolic Events

Two patients in our series had a history of significant thromboembolic events. Factor VIII levels for these 2 patients were significantly higher than the other 15 patients (239 ± 30% versus 116 ± 58%, respectively, $P = .01$, Student t test). One 5-year-old male with PLE was admitted with severe ventricular dysfunction 2.5 years after his Fontan operation. Thrombus in his common atrium and superior vena cava was detected. He was ultimately placed on extracorporeal membrane oxygenation for low cardiac output state and underwent successful orthotopic cardiac transplant. This patient's coagulation profile measured 5 months prior to the event mentioned above was significant for a low normal protein S level, elevated factor V and IX levels

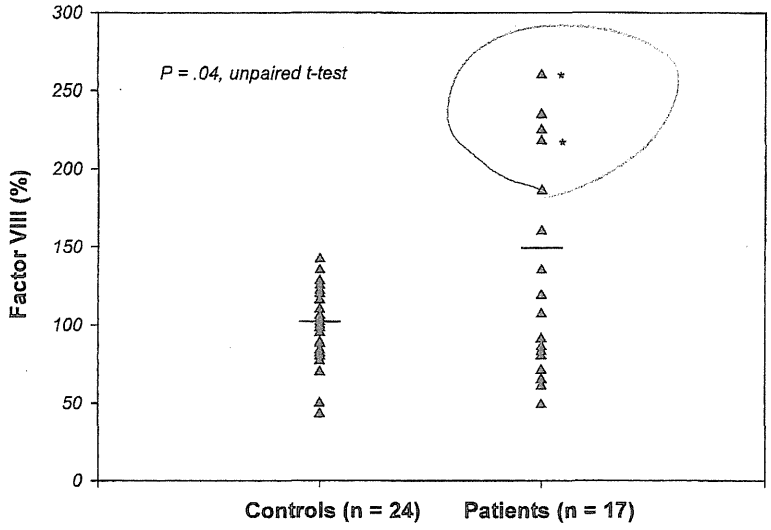

Figure 1. Factor VIII activity in Fontan patients and age-matched controls. Mean factor VIII levels were significantly higher in patients than controls (131 ± 68% versus 98 ± 25%, *P* = .04. *Asterisks* (*) indicate the 2 patients who clotted. The mean factor VIII level for each group is marked by a *small horizontal bar*.

TABLE 4. Coagulation variables for controls and post-Fontan patients

Variable	Controls (n = 24)	Post-Fontan (n = 20)	*P* value*	No. (%) below normal range	No. (%) above normal range
Fibrinogen (mg/L)	315 ± 107	254 ± 74	<.05	0 (0)	0 (0)
Factor II (%)	97 ± 17	72 ± 10	<.01	8 (40)	0 (0)
Factor V (%)	106 ± 23	72 ± 28	<.01	10 (50)	0 (0)
Factor VII (%)	97 ± 24	53 ± 19	<.01	17 (85)	0 (0)
Factor VIII (%)	98 ± 25	131 ± 68	.04	0 (0)	6 (35)
Factor IX (%)	81 ± 21	72 ± 31	.28	4 (24)	0 (0)
Factor X (%)	94 ± 17	73 ± 15	<.01	5 (25)	0 (0)
Antithrombin III (%)	107 ± 16	84 ± 24	<.01	2 (10)	1 (5)
Plasminogen (%)	100 ± 14	83 ± 18	<.01	6 (30)	0 (0)
Protein C (%)	98 ± 22	66 ± 15	<.01	3 (18)	0 (0)
Protein S (%)	87 ± 17	80 ± 14	.17	4 (22)	0 (0)

**P* values were determined by the 2-sample Student *t* test. All variables are expressed in terms of the mean ± SD. n = 24 for controls, except for fibrinogen (n = 21); n = 20 for Fontan patients except for factor VIII, factor IX, and protein C (n = 17) and for protein S (n = 18).

(138% and 132%, respectively), and a markedly elevated factor VIII level of 260%. LFTs were within normal levels except an albumin level of 1.2 g/dL.

The second patient was a 8-year-old boy who had previously undergone an extracardiac nonfenestrated Fontan procedure. He developed progressive PLE and ascites and was admitted for creation of a fenestration in the Fontan baffle. Within hours of the procedure the fenestration became obstructed by thrombus and he was treated with fibrinolytic agents and heparin. He was subsequently discharged home on coumadin. This patient's coagulation profile on the morning of the procedure (prior to thrombus formation) revealed a normal PT, APTT, and protein C and S levels but markedly elevated factor VIII level (218%) and elevated factor IX (125%). LFTs were within normal levels with an albumin of 2.1 g/dL.

No other patients demonstrated clinical evidence of thromboembolic events, and no intracardiac thrombus was detected by transthoracic echocardiography. The majority of the patients (16/20) were discharged home on aspirin alone; 1 patient was discharged on Coumadin; and 3 patients were not given any antiplatelet or anticoagulant therapy.

Discussion

In this prospective study of coagulation profiles in children with complex single ventricle congenital heart disease who had undergone a prior Fontan operation, abnormalities of

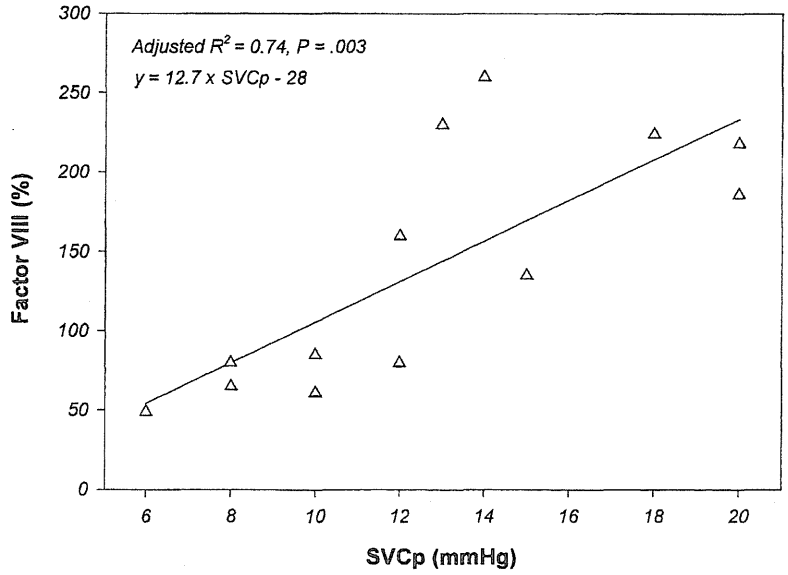

Figure 2. Scatter diagram of the empirical data showing the positive correlation between factor VIII activity as a function of SVC pressure in Fontan patients. The fitted model showed a good linear fit ($R^2 = 0.74$) for the regression equation: $y = 12.7x - 28$ (*solid line*).

TABLE 5. Laboratory values for Fontan patients

Variable	n	Mean ± SD	Normal range	Number (%) above or below normal range
Hematocrit (%)	19	39 ± 5	33-55	2 (11)
Platelet count ($\times 10^3$)	19	221 ± 59	130-400	1 (5)
PT (seconds)	19	12.9 ± 1.4	11-13	6 (32)
PTT (seconds)	17	38.6 ± 22	27-37	5 (29)
Albumin (g/dL)	20	3.2 ± 0.7	3.0-4.6	5 (25)
AST (U/L)	20	38 ± 11	2-40	9 (45)
ALT (U/L)	20	24 ± 12	0-35	2 (10)
GGTP (U/L)	19	46 ± 30	5-40	9 (47)
Bilirubin (mmol/L)	20	0.8 ± 0.7	0.3-1.2	1 (5)

SD, Standard deviation; *PT*, prothrombin time; *PPT*, partial thromboplastin time; *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase; *GGTP*, gammaglutamyl transpepsidase.

procoagulant factors and inhibitors of coagulation were demonstrated in all children. Although there was no correlation between the significantly low levels of various factors with hemodynamic variables or liver function tests, the significant elevation in factor VIII, and its correlation with an increased SVC pressure, could suggest a prothrombotic relationship in patients with Fontan physiology.

The cause of thromboembolic events after the Fontan procedure seems to be multifactorial, and no consistent predisposing risk factors have been identified. Several authors have previously described coagulation factor abnormalities involving both pro- and anticoagulant proteins as a cause of a hypercoagulable state in children who have previously undergone the Fontan operation, with specific emphasis on low levels of the naturally occurring inhibitors of coagulation, protein C, protein S and, ATIII.[7-10] These earlier studies suggested that an imbalance between procoagulant factors and inhibitors of coagulation favors thrombus formation and that one or more aspects of the Fontan physiology may be responsible for the imbalance. However, these studies did not examine a full complement of coagulation factors and did not employ age-matched control subjects, nor did they undertake detailed hemodynamic evaluation.

The use of age-matched controls is important because the hemostatic system matures over the first several years of life,[13] leading to important differences in factor activity measurements in children compared with adults. In general, values of most pro- and anticoagulant factors are lowest in neonates and infants and increase toward adult values at

varying rates, some not reaching adult levels until relatively late in the teenage years. Despite the observed differences there is no evidence that infants are at greater risk for hemorrhagic or thrombotic problems compared with adults, suggesting that the neonatal and infant system is in "functional balance" at lower concentrations of most factors. Whether the overall coagulation factor abnormalities (compared to age-matched controls) we measured in our patients are due to delayed maturation in the Fontan patient is speculative.

Hepatic synthetic dysfunction (eg, reduced albumin) or evidence of hepatocellular dysfunction (eg, bilirubin, transaminase) did not appear to be associated with coagulation abnormalities in our patients, an important observation given the prominent role of the liver in the synthesis of procoagulants and inhibitors of coagulation and the potential for altered liver blood flow and oxygen delivery in Fontan patients. We were unable to relate specific hemodynamic variables, including an elevated SVCp or poor ventricular function, with altered hepatic synthetic function.

We have previously reported that abnormalities in coagulation factor levels may occur earlier in the staged palliation of complex single ventricle disease.[11,12] The changes after the Fontan procedure found in our present study are qualitatively and quantitatively similar to those found in patients *prior* to the Fontan operation, with the important exception of factor VIII. In contrast to the two prior stages of single ventricle repair (pre-Glenn and pre-Fontan) where factor VIII concentrations were lower than age-matched controls, it appears that Fontan physiology is associated with a specific tendency to increase factor VIII; in 6 patients the level was significantly above the normal range. A similar finding was recently reported by Rauch and colleagues in 20 patients 4 to 63 months following the total cavopulmonary connection.[14]

The importance of an elevated factor VIII level as an independent risk factor for venous thrombosis in patients without cardiac defects has been reported.[15-19] Factor VIII levels >150% are associated with a five- to sixfold increased risk for venous thrombosis when compared with levels below 100%.[20] The overall prevalence of an elevated factor VIII appears to be relatively high, having been reported in one study to be elevated in 25% of patients with a first episode of venous thrombosis and 11% of the healthy population.[18] In a prospective study by Kyrle and colleagues of 360 adult patients, the risk of recurrence of thromboembolism was almost 7 times as great among patients with factor VIII levels above the 90th percentile (>234%),[15] and it was speculated that prolonged anticoagulation therapy may be indicated in this subset of patients.

The cause of increased factor VIII levels in patients with Fontan circulation is unknown. The apparent conversion from a state of relatively low factor VIII earlier in the course of single ventricle repair suggests an acquired disturbance related directly to Fontan physiology. This is supported in our study by the significant relationship demonstrated between factor VIII activity and the higher SVC pressure. Factor VIII is expressed by multiple tissues. A recent report by Hollestelle and colleagues[21] showed that the liver and kidney especially express high levels of factor VIII mRNA compared with the level of expression of other hemostatic proteins in these organs. Further analysis indicated that most of the VIII mRNA expression was detected in the endothelial lining of the liver sinusoids; a significantly lower signal was detected in hepatocytes. Although speculative, it is possible that the Fontan circulation with elevated central and hepatic venous pressure may contribute to an increase in factor VIII production from liver sinusoidal endothelium. This could also explain the lower factor VIII levels detected in patients with bidirectional Glenn physiology who have lower atrial and hepatic venous pressure.

In view of the potential risk of thromboembolic events in post-Fontan patients and evidence that high levels of factor VIII may be an independent risk factor for both early and late thromboembolic events, quantifying factor VIII may identify a subset of Fontan patients who would benefit from anticoagulant treatment. Further work is clearly necessary to determine whether there may be a critical factor VIII plasma concentration associated with thromboembolic risk in these patients and also whether, analogous to adult venous thrombosis events, there is an interaction with low levels of native circulating inhibitors of coagulation (eg, proteins C and S and ATIII) or prothrombotic genetic mutations.

References

1. Stamm C, Friehs I, Mayer JE, Zurakowski D, et al. Long-term results of the lateral tunnel Fontan operation. *J Thorac Cardiovasc Surg.* 2001;121:28-41.
2. Cromme-Dijkhuis AH, Hess J, Hahlen K, et al. Specific sequelae after Fontan operation at mid- and long-term follow-up. Arrhythmia, liver dysfunction, and coagulation disorders. *J Thorac Cardiovasc Surg.* 1993;106:1126-32.
3. Rosenthal DN, Friedman AH, Kleinman CS, Kopf GS, Rosenfeld LE, Hellenbrand WE. Thromboembolic complications after Fontan operations. *Circulation.* 1995;92(Suppl II):287-93.
4. Jahangiri M, Ross DB, Redington AN, Lincoln C, Shinebourne EA. Thromboembolism after the Fontan procedure and its modifications. *Ann Thorac Surg.* 1994;58:1409-14.
5. Balling G, Vogt M, Kaemmerer H, Eicken A, Meisner H, Hess J. Intracardiac thrombus formation after the Fontan operation. *J Thorac Cardiovasc Surg.* 2000;119:745-52.
6. Monagle P, Cochrane A, McCrindle B, Benson L, Williams W, Andrew M. Editorial: thromboembolic complications after the Fontan procedures—the role of prophylactic anticoagulation. *J Thorac Cardiovasc Surg.* 1998;115:493-8.
7. Jahangiri M, Shore D, Kakkar V, Lincoln C, Shinebourne E. Coagulation factor abnormalities after the Fontan procedure and its modifications. *J Thorac Cardiovasc Surg.* 1997;113:989-93.
8. 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 operations. *Lancet.* 1990;336:1087-90.
9. van Nieuwenhuizen RC, Peters M, Lubbers LJ, Trip MD, Tijssen JG, Mulder BJ. Abnormalities in liver function and coagulation profile following the Fontan procedure. *Heart.* 1999;82:40-6.

10. 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.
11. Odegard KC, McGowan FX, DiNardo JA, et al. Coagulation factor abnormalities in patients with single ventricle physiology precede the Fontan operation. *J Thorac Cardiovasc Surg.* 2002;123:459-65.
12. Odegard KC, McGowan, FX, Zurakowski D, et al. Coagulation factor abnormalities in patients with single ventricle physiology immediately prior to the Fontan procedure. *Ann Thorac Surg.* 2002;73:1770-7.
13. Andrew M, Vegh P, Johnston M, Bowker J, Ofosu F, Mitchell L. Maturation of the hemostatic system during childhood. *Blood.* 1992; 80:1998-2005.
14. 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.
15. Kyrle PA, Minar E, Hirschl M, et al. High Plasma levels of factor VIII and the risk of recurrent venous thromboembolism. *N Engl J Med.* 2000;343:457-62.
16. O'Donnell J, Tuddenham EG, Manning R, Kemball-Cook G, Johnson D, Laffan M. High prevalence 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.
17. Kamphuisen PW, Eikenboom JC, Vos HL, et al. Increased levels of factor VIII and fibrinogen in patients with venous thrombosis are not caused by acute phase reaction. *Thromb Haemost.* 1999;81:680-3.
18. Kraaijenhagen RA, in't Anker PS, Koopman MM, et al. High plasma concentration of factor VIIIc is a major risk factor for venous thrombembolism. *Thromb Haemost.* 2000;83:5-9.
19. Kamphuisen PW, Eikenboom PW, Bertina RM. Elevated factor VIII levels and the risk of thrombosis. *Arterioscler Thromb Vasc Biol.* 2001;21:731-8.
20. Koster T, Blann AD, Briet E, Vandenbroucke 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.
21. Hollestelle MJ, Thinnes T, Crain K, et al. Tissue distribution of factor VIII gene expression in vivo-a closer look. *Thromb Haemost.* 2001; 86:855-61.

Prophylaxis of thromboembolic complications after the Fontan operation (total cavopulmonary anastomosis)

Renate Kaulitz, MD[a]
Gerhard Ziemer, MD[b]
Ralf Rauch, MD[a]
Monika Girisch, MD[a]
Harald Bertram, MD[a]
Armin Wessel, MD[a]
Michael Hofbeck, MD[a]

See related editorial on page 491.

Objectives: Thrombotic events have been reported as a major cause of morbidity after the Fontan procedure. There is no consensus concerning the postoperative mode and duration of anticoagulation prophylaxis. In a retrospective study, we evaluated the results of a prophylactic regimen on the basis of the surgical technique, potentially predisposing risk factors, and specific sequelae.

Methods: We evaluated 142 surviving patients after total cavopulmonary anastomosis (mean follow-up was 91.1 ± 43.9 months). Prophylactic antithrombotic treatment was initiated in 86 patients with partial prosthetic venous pathway with acetylsalicylic acid; 45 patients with complete autologous tissue venous pathway or partial prosthetic venous pathway received no anticoagulation, and 11 patients received warfarin sodium (Coumadin). During long-term follow-up, 22 patients (12 after acetylsalicylic acid medication) crossed over to warfarin.

Results: Thrombotic events occurred in 10 patients (7%), with systemic venous thrombus formation in 8 (5.6%), stroke in 2 (1.4%), and a peak incidence during the first postoperative year. Eight of 10 patients were receiving heparin therapy mainly for prolonged postoperative immobilization. During follow-up, none of the 74 patients receiving acetylsalicylic acid and 1 of 40 patients without medication presented with thrombus formation. Under warfarin medication, 1 of 28 patients had an asymptomatic thrombus. Expected freedom from a thromboembolic event was 92% at 5 years and 79% at 10 years. There was no association with coagulation factor abnormalities. Protein-losing enteropathy was present in 4 of 10 patients.

Conclusion: A prophylactic anticoagulation strategy that considers the surgical technique and potential predisposing circumstances proved effective in the prevention of late thrombotic complications after total cavopulmonary anastomosis. There is no need for routine anticoagulation during long-term follow-up after Fontan-type surgery in pediatric patients.

From the Department of Pediatric Cardiology and Pediatric Intensive Care Medicine,[a] Tuebingen University Hospital and Hannover Medical School, and the Department of Thoracic, Cardiac and Vascular Surgery,[b] Tuebingen University Hospital, Tuebingen, Germany.

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Address for reprints: Renate Kaulitz, MD, Department of Pediatric Cardiology and Pediatric Intensive Care Medicine, Tuebingen University Hospital, Hoppe-Seyler Str 3, D-72076, Tuebingen, Germany (E-mail: renate.kaulitz@med.uni-tuebingen.de).

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Late morbidity and long-term prognosis after the Fontan operation are mainly determined by atrial dysrhythmia, systemic ventricular dysfunction, protein-losing enteropathy, hepatic dysfunction, and thromboembolic complications.[1-3] Few data are available that analyze the time course of thromboembolism and that demonstrate a persistent implied risk throughout the time of follow-up.[4] Systemic venous thromboembolic complications have been described in 3% to 20%.[4-6] The incidence of arterial thromboembolic events ranged from 3% to 19% in one of the earliest publications.[7] The large variance in the incidence of thrombus formation

TABLE 1. Patient data (n = 142)

	n (%)
Diagnosis	
Tricuspid atresia	30 (21.1)
Double-inlet ventricle	30 (21.1)
Complex univentricular heart	82 (57.7)
Heterotaxy syndrome	14 (9.8)
Fontan procedure	
Total cavopulmonary anastomosis (with fenestration n = 38) (with autologous intra-atrial tunnel n = 16)	121 (85.2)
Extracardiac conduit	21 (14.7)
Age at Fontan procedure	Mean ± SD(range)
Total	66.3 ± 57.9 (6-393 mo 5)
Total cavopulmonary anastomosis	67.8 ± 52.1 (7-393 mo)
Extracardiac conduit	49.5 ± 3 9.7 (6-151 mo)
Follow-up	Mean ± SD (range)
Total	91.1 ± 43.9 (12-177 mo)
Total cavopulmonary anastomosis	91.8 ± 34.1 (18-129 mo)
Extracardiac conduit	48.3 ± 21.7 (12-81 mo)

might reflect the results of different modifications of the Fontan procedure, the various durations of postoperative follow-up, and the diagnostic method used to identify intracardiac thrombi in the majority of asymptomatic patients.[5,6,8,9] Liver dysfunction or protein-losing enteropathy may result in changes of synthesis of procoagulant and anticoagulant factors, influencing the balance of the coagulation and fibrinolytic system.[3,10-12]

The optimum type and duration of postoperative anticoagulation therapy is still a matter of discussion because no controlled studies comparing different strategies preventing thromboembolic complications are available yet. Initial anticoagulation with warfarin sodium (Coumadin) has been recommended by some authors for all patients after Fontan-type surgery irrespective of the individual situation.[5,12,13]

In this study we analyzed the initial intention to treat and assessed the results of a long-term risk-stratified prophylactic treatment depending on the potential predisposing circumstances in our patients after a total cavopulmonary anastomosis.

Patients and Methods

This is a retrospective study on 142 surviving patients who underwent a total cavopulmonary anastomosis between 1988 and 2002 performed by 1 surgeon at 2 institutions (Table 1). Ethical committee approval was obtained, and informed consent was given by all patients and their parents.

A total cavopulmonary anastomosis was accomplished by a lateral partial prosthetic tunnel procedure in 121 patients (including 38 patients with tunnel fenestration). In 16 of these patients, the lateral tunnel was created with only autologous tissue. An extracardiac conduit procedure was performed in 21 patients. A patent pulmonary valve was closed at the annulus level during the Glenn or Fontan procedure in all patients except one. The age at operation varied from 6 to 393 months (mean 66.3 ± 57.9 months). The early postoperative period was defined as the time before discharge or the first 30 postoperative days. The duration of follow-up was 91.1 ± 43.9 months (range 12-177 months) with 46 patients (32.3%) followed up for more than 10 years. Data on postoperative cardiac catheterization were available for 97 patients. Yearly outpatient follow-up examinations included transthoracic echocardiography with a Hewlett-Packard (Palo Alto, Calif) ultrasound system (2.5-5 MHz transducer). Transthoracic echocardiography was followed by transesophageal evaluation in patients with a clinical suspicion of thrombus formation, a questionable finding on transthoracic echocardiography, or an increased level of D-dimer as a potential marker of fibrinolysis. Transesophageal echocardiography was also performed routinely before cardiac catheterization. Thrombus formation at the atrial, ventricular, or vascular level was defined as an echogenic mass adherent to cardiac structures and described with regard to localization and size. Laboratory investigations were performed for hereditary thrombophilia and coagulation factor analysis on a cross-sectional basis including screening for prothrombotic state with imbalance of procoagulation and anticoagulation factors and liver dysfunction. Late dysrhythmia was defined as sinuatrial dysfunction or intra-atrial reentry tachycardia (IART) with the need for antiarrhythmic medication.[14] Protein-losing enteropathy was diagnosed in patients with clinical symptoms related to hypoproteinemia; when indicated, the a_1-antitrypsin clearance was calculated.[15]

The initial antithrombotic treatment was based on the surgical method and influenced by preoperative parameters and early postoperative functional result. It was modified during long-term follow-up when thromboembolic complications occurred or sequelae such as atrial tachydysrhythmia, symptomatic protein-losing enteropathy, polycythemia, or ventricular dysfunction associated with systemic venous slow blood flow phenomenon on echocardiogram developed. This resulted in 22 cross-overs to warfarin during follow-up.

After the early postoperative period, 85 patients with a partial prosthetic venous pathway (including patients with tunnel fenestration) were treated with acetylsalicylic acid (ASA; 3-5 mg/kg per day). No anticoagulation was administered to 16 patients with autologous tissue venous pathways and 29 patients with partial prosthetic venous pathways and an uncomplicated early postoperative period. Six patients received warfarin as initial treatment because of borderline preoperative hemodynamic parameters or related to surgical technique. Eight patients received heparin for prolonged pleural effusions or immobilization and crossed over to ASA or warfarin during follow-up (Figure 1).

Statistical Analysis

When appropriate, data were expressed as mean ± standard deviation. All data were analyzed using SPSS statistical software (SPSS Inc, Chicago, Ill). Numeric data were analyzed with the unpaired *t* test; categorical data were analyzed with chi-square analysis.

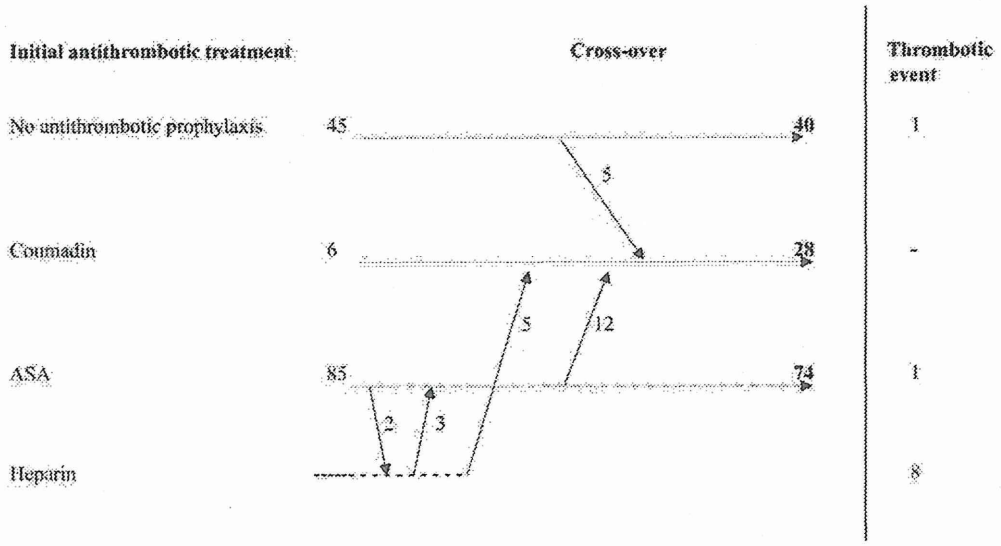

Figure 1. Antithrombotic treatment.

Results

Incidence of Thrombus Formation and Thromboembolic Events

A total of 142 survivors were assessed (none of the patients who died during the early or late postoperative period died of a thromboembolic event or thrombus formation). Thrombus formation and thromboembolic events occurred in 10 patients (7%). Eight of these patients (5.6%) presented with systemic venous thrombus formation, whereas arterial emboli resulted in a stroke in 2 patients (1.4%) (Table 2). Six of 8 patients with right-sided thrombi were asymptomatic; 2 patients (patients 1 and 5) had symptoms of supraventricular tachycardia and venous congestion, respectively. In 3 additional patients (patients 6, 7, and 9), venous thrombus formation was detected on the routine postoperative echocardiogram during the early postoperative period. Potential predisposing factors were postoperative immobilization or a central venous line. Late asymptomatic systemic venous thrombi were detected in 3 patients (patients 2, 3, and 4); symptomatic protein-losing enteropathy had already developed in 2 patients.

A stroke was the first symptom of a thromboembolic complication in 2 patients (patients 8 and 10). This occurred before discharge in the presence of prolonged postoperative immobilization and protein-losing enteropathy in 1 patient. The second patient was admitted 20 months after the Fontan-type procedure with neurologic signs of a stroke; 6 weeks before, he had been placed on high molecular weight heparin (5000 U/m^2 bovine serum albumin subcutaneously) for treatment of recurrent symptomatic protein-losing enteropathy. Altogether, 8 of 10 patients with thromboembolic events received heparin (administered intravenously in 7 patients [maintenance dosage 15-25 U kg^{-1} · h^{-1}] and subcutaneously in 1 patient) at the time of thrombus formation, mainly for postoperative immobilization (Table 2), and presented with a partial thromboplastin time of 50 to 60 seconds or more (except for patient 6). The Kaplan-Meier estimate for freedom from a thrombotic or thromboembolic event (systemic venous or arterial) is 91.6% at 5 years and 78.8% at 10 years (Figure 2).

Risk-Stratified Anticoagulant Prophylaxis During Long-Term Follow-up

According to initial management, 45 patients (including 16 patients with autologous venous pathway) received no anticoagulation. During long-term follow-up, 5 patients crossed over to warfarin (Figure 1) because of complications or functional sequelae in 3 and a thromboembolic event in 1. One patient crossed over to warfarin because of a patent pulmonary valve with residual pulmonary artery stump, as recommended in recent studies.[16,17] None of the remaining 40 patients had specific sequelae of the Fontan circulation during long-term follow-up; so far, 38 patients have undergone cardiac catheterization confirming an adequate morphologic and hemodynamic result. A total of 85 patients were initially treated with ASA; 74 patients who remained on long-term ASA medication (Figure 1) crossed over to warfarin because of functional sequelae of the Fontan circulation or a thromboembolic event. None of these patients presented with clinical symptoms of thromboembolic events or suspicious findings on transthoracic echocardiogram; 45 patients had undergone cardiac catheterization combined with transesophageal echocardiography to exclude any tunnel obstruction.

The number of patients who received warfarin increased from 6 to 28 during follow-up. Cross-over to warfarin was

TABLE 2. Patients with thromboembolic events

	Patient 1	Patient 2	Patient 3
Anatomy	PA/IVS	DORV, MGA,	DILV, TGA, coarctation
Surgery	TCPA	TCPA	TCPA
Age at operation	135 mo	57 mo	114 mo
Thrombus formation			
Localization	iT	iT	iT
Interval to surgery	12 d	108 mo	3 mo
Symptoms	SVT	—	—
Prophylaxis of thrombus at diagnosis	Heparin	—	Warfarin
Potential predisposing circumstances	Anastomosis stenosis	—	Ventricular dysfunction, PLE
Thrombus therapy	Reoperation (anastomosis revision)	Warfarin	rt-PA
Long-term prophylaxis	ASA for the first postop year; beginning warfarin 12 y postop	Warfarin	Warfarin

	Patient 4	Patient 5
Anatomy	HLHS	DORV, MGA
Surgery	TCPA	Fenestrated TCPA
Age at operation	27 mo	9 mo
Thrombus formation		
Localization	iT	Fenestration
Interval to surgery	49 mo	3 d
Symptoms	—	Increased systemic venous pressure
Prophylaxis of thrombus at diagnosis	Heparin	Heparin
Potential predisposing circumstances	Postop immobilization (pacemaker revision), PLE	Venous stasis, increased PAP
Thrombus therapy	Warfarin	Reoperation (refenestration)
Long-term prophylaxis	Warfarin	ASA

	Patient 6	Patient 7	Patient 8
Anatomy	Heterotaxy syndrome, SV, SA, TAPVD, SPS	Heterotaxy syndrome, CAVSD, TGA, PA, PAPVD, bilateral SVC	TA Ic
Surgery	TCPA	Extracardiac CPC	TCPA
Age at operation	132 mo	52 mo	68 mo
Thrombus formation			
Localization	iT	SVC	Not detected
Interval to surgery	25 d	6 d	2 mo
Symptoms	—	—	
Cerebrovascular accident			
Prophylaxis of thrombus at diagnosis	Heparin	Heparin	Heparin
Potential predisposing circumstances	Postop immobilization (pleural drainage)	Central venous line	Postop immobilization PLE (cholelithiasis, drainage)
Thrombus therapy	rt-PA	Heparin	Heparin
Long-term prophylaxis	ASA, beginning warfarin 3 y postop	ASA	Warfarin

	Patient 9	Patient 10
Anatomy	DORV, TGA, SPS, PS	TA IIc
Surgery	TCPA	Fenestrated TCPA
Age at operation	7 mo	20 mo
Thrombus formation		
Localization	iT	Not detected
Interval to surgery	21 d	10 mo >

TABLE 2. Continued

	Patient 9	Patient 10
Symptoms	—	Cerebrovascular accident
Prophylaxis of thrombus at diagnosis	Heparin	Heparin SC (PLE)
Potential predisposing circumstances	Postop immobilization	PLE, fenestrated occclusion
Thrombus therapy	Warfarin for 3 mo	Warfarin
Long-term prophylaxis	ASA	Warfarin

ASA, Acetylsalicylic acid; *CAVSD,* common atrioventricular septal defect; *DILV,* double inlet left ventricle; *DORV,* double outlet right ventricle; *CPC,* cavopulmonary connection; *HLHS,* hypoplastic left-heart syndrome; *iT,* intra-atrial tunnel; *MGA,* malposition of the great arteries; *PA/IVS,* pulmonary atresia/intact ventricular septum; *PAPVD,* partial anomalous pulmonary venous drainage; *PLE,* protein-losing enteropathy; *PS,* pulmonary stenosis; *rt-PA,* recombinant tissue-type plasminogen activator; *SA,* single atrium; *SC,* subcutaneous; *SPS,* subpulmonary stenosis; *SV,* single ventricle; *SVC,* superior vena cava; *SVT,* supraventricular tachycardia; *TA,* tricuspid atresia; *TAPVD,* total anomalous pulmonary venous drainage; *TCPA,* total cavopulmonary anastomosis; *TGA,* transposition of the great arteries.

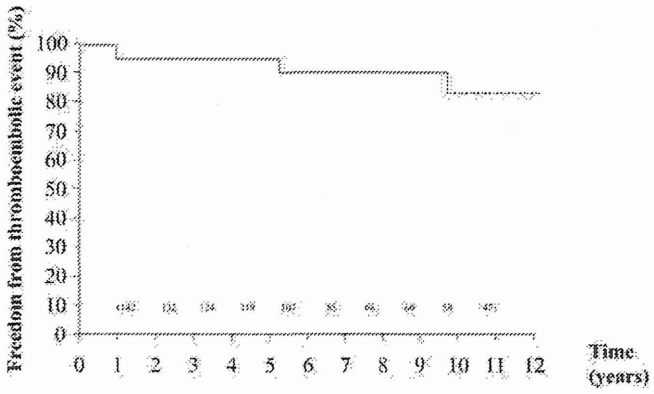

Figure 2. Kaplan-Meier estimate for freedom from thrombotic or thromboembolic events.

TABLE 3. Special indications for anticoagulant treatment with warfarin (25/142 patients)

Prior thrombus formation/thromboembolic event (including 4 patients with PLE)	7
Tunnel-fenestration	2
Residual PA trunk	1
Atrial dysrhythmia/IART	6
Slow blood flow phenomenon on TTE	3
Ventricular dysfunction	4
Polycythemia	3
Venous congestion/elevated PA pressure	1
After transcatheter intervention (fenestration closure)	1

IART, Intra-atrial reentry tachycardia; *PA,* pulmonary artery; *PLE,* protein-losing enteropathy; *TTE,* transthoracic echocardiography.

initiated because of a thromboembolic event in 7 patients or the development of potential predisposing causes for thromboembolic complications (Table 3); prophylactic anticoagulation was begun 16 to 110 months (mean 56.2 ± 32.2 months) postoperatively. None of these patients had bleeding complications. Patients without any antithrombotic prophylaxis had significantly longer mean follow-up (123.8 ± 32.3 months) compared with patients who received warfarin (101.4 ± 46.6 months; $P = .04$) or ASA (69.7 ± 34.8 months; $P = .005$).

Atrial dysrhythmia defined as IART occurred in 18 patients (12.6%); 6 of these patients who required antiarrhythmic medication received warfarin (Table 3). Evidence of protein-losing enteropathy was found in 9 patients (6.3%). Four of these patients had a history of thromboembolic complications with or after the onset of symptoms of protein-losing enteropathy and were subsequently placed on warfarin. Two additional patients had symptomatic protein-losing enteropathy and received prophylactic anticoagulation treatment 23 and 60 months postoperatively. Slow blood flow phenomenon and ventricular dysfunction documented on echocardiographic follow-up studies led to prophylactic warfarin medication in 7 adolescent patients (aged 136-245 months) 40 to 110 months postoperatively. After transcatheter procedures (closure of residual interatrial communications/fenestrations in 11 patients and device closure of a reopened left superior caval vein draining into the coronary sinus in 3 patients), patients continued to receive ASA, except for 3 patients who remained on warfarin (2 patients with a history of thromboembolic complication or protein-losing enteropathy). None of these patients had a late thromboembolic event during follow-up.

Discussion

The number of reports on thrombotic and thromboembolic complications after the Fontan operation is increasing, reflecting longer postoperative survival and duration of follow-up. Recent studies reported an incidence as high as 20% for systemic venous and arterial thrombosis with an unknown ratio of asymptomatic patients.[4-6,18] Therefore, the true incidence of cardiac thrombi is unknown.

Anticoagulation strategies have been considered with various ideas concerning the indication and type and duration of therapy.[8,13,16] Some of these suggestions, however, were based on the experience of patients undergoing previous types of univentricular palliation. These included a high

proportion of patients with atriopulmonary anastomosis or total cavopulmonary anastomosis and a blind pouch left after main pulmonary artery ligation/division. Because of a high incidence of late thromboembolic complications in these patients, long-term anticoagulant therapy with warfarin was recommended for all patients undergoing a Fontan procedure irrespective of the surgical technique or additional predisposing factors.[9,13] On the basis of the assumption that potential risk factors may exist and can be used as a rationale to decide on different anticoagulation treatment regimens, we assessed the relationship between individualized treatment and outcome, that is, thromboembolic problems in patients after total cavopulmonary anastomosis. Our results show that the surgical technique is relevant in 2 aspects. None of the 16 patients with an autologous tunnel procedure had thrombus formation, although they did not receive any anticoagulation medication as part of our strategy. This may be related to the nonturbulent systemic venous flow dynamics with the preservation of a somewhat pulsatile flow by atrial contraction and less respiratory-dependent venous return.[19] Thrombus formation in the residual pulmonary trunk after pulmonary artery ligation or division with the risk of arterial embolization and cerebral infarction is not a rare event; it has been described in approximately 30% to 50% of patients with thrombus formation after univentricular palliation.[9,18] However, it was our policy to start to close any pulmonary trunk at the pulmonary valve annulus level. We succeeded in all but 1 patient, who was then administered anticoagulation treatment. Because of the potentially serious sequelae, diagnosis of a thrombus in the pulmonary stump should prompt urgent removal and closure of the pulmonary valve even in asymptomatic patients.[16]

As reported in the literature, the type of material used for creation of the lateral tunnel or the presence of fenestrations did not affect the risk of stroke.[7,17,18] After tunnel fenestration, a high proportion of spontaneous fenestration closures during follow-up has been described, limiting the potential risk of paradoxic thromboembolism.[20] In our study, patients with persistent tunnel fenestration were placed on ASA (except for 2 patients), although an increased risk of stroke has not been proven in these patients.[7]

Early experience in patients who underwent an extracardiac conduit procedure revealed a high incidence of thrombus formation,[5,21] but the number of patients under extended follow-up is still limited. None of the young patients who had recently undergone an extracardiac conduit procedure at our institution were placed on warfarin. However, we never used prosthetic tubes in the extracardiac Fontan procedure; we used as much autologous tissue (mainly in situ pericardium) as possible.

All patients with a history of thrombus formation in our study had at least 1 potential predisposing factor that might increase the risk of thromboembolic complications. The findings of other investigators[4,7,22] (ie, supraventricular tachycardia and IART may promote thrombus formation on an atrial level) prompted us to anticoagulate our patients with recurrent atrial tachydysrhythmia. Thrombus formation in association with the diagnosis of protein-losing enteropathy occurred in 4 of our 10 patients. This clinical observation had not been made in the literature. The potential risk of imbalance of the procoagulant and anticoagulant factors in patients with protein-losing enteropathy, resulting from similar molecular weights for albumin, protein C and S, antithrombin III, and factors II and X, had already been described by Cromme-Dijkhuis and associates.[10] Patients with protein-losing enteropathy and thrombus formation in our study did not show a uniform pattern of coagulation factor abnormalities. Under therapy with warfarin, none of these patients experienced further thrombosis during follow-up.

The follow-up in our patients was too short and the number of patients was too small to confirm the impression of other studies that the incidence of arrhythmias and thromboembolic events increases with the duration of follow-up, especially after 10 years.[2,13] On the other hand, patients with long-term follow-up and adult patients are at risk for systemic ventricular dysfunction; in this case, we believe that anticoagulation treatment is indicated especially when contrast echocardiograms demonstrate a slow blood flow situation, which is probably caused by spontaneous microcavitations within the cavopulmonary connection.[23] One major potential predisposing factor in our study was prolonged postoperative immobilization documented in 4 patients with thrombus formation. Postoperative heparinization was routinely started in all patients shortly after the Fontan procedure or noncardiac surgery (with prolongation of partial thromboplastin time to 50-60 seconds), as recommended in adults and adapted for children.[6] However, disease states might coexist that influence plasma concentrations of antithrombin or the anticoagulant capacity of heparin by an increase in acute phase proteins.[6,8] Coagulation factor abnormalities potentially predisposing to thromboembolic events have been described in recent reports in various constellations after the Fontan procedure, suggesting an unpredictable risk of imbalance in procoagulant and anticoagulant factors with the need for anticoagulation treatment.[24,25] However, there is presently no coagulation profile that can be used to identify patients at increased risk for thrombus formation or permanent abnormal consumption of coagulation factors.

Limitations of the Study

Transesophageal echocardiography has proven to be the method of choice to identify intracardiac thrombi in the majority of asymptomatic patients, especially older children