SURGERY FOR CONGENITAL HEART DISEASE

COAGULATION FACTOR ABNORMALITIES AFTER THE FONTAN PROCEDURE AND ITS MODIFICATIONS

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Objective: Recently we reported the prevalence of thromboembolism in patients who underwent the Fontan procedure and its modifications. Although hemodynamic factors may well contribute to thromboembolism, recent evidence suggests that coagulation factor abnormalities may also play a role. We therefore set out to investigate the coagulation status in a group of patients who had undergone the Fontan procedure. **Methods:** The study population consists of 20 children who had undergone the Fontan procedure and its modifications. They were examined for coagulation factor abnormalities. Concentrations of serum albumin, total protein, and liver enzymes were also measured. The median age at the time of the operation was 6.2 years (17 months to 8 years) with a male/female ratio of 2.3:1. The median time from the Fontan repair was 4.9 years (18 to 76 months). **Results:** Protein C ($p < 0.001$), protein S ($p < 0.02$), and factor VII ($p < 0.001$) were significantly lower than the normal range. The changes in serum albumin and total protein and factors II, IX, and X were not significant. **Conclusions:** It is possible that deficiency in protein C, protein S, and factor VII partly account for the prevalence of thromboembolism after Fontan-type repairs. The risk of long-term anticoagulation should be weighed against the best palliative procedure for these patients. We suggest that reduced protein C, protein S, and factor VII levels in this group of patients should be regarded as risk factors and that such patients should be treated with anticoagulants. (J Thorac Cardiovasc Surg 1997;113:989-93)

The Fontan operation was first reported in 1971 to provide correction of the circulation in patients with tricuspid atresia.¹ Atriopulmonary or cavopulmonary anastomoses are now used as definitive palliation in a variety of complex congenital heart

defects including double-inlet ventricle, pulmonary atresia with intact ventricular septum, and hypoplastic left heart syndrome. Common to all these conditions is that only one ventricle of adequate size or function is available to be useful. After the Fontan procedure or one of its modifications, the systemic venous return reaches the pulmonary circulation without being pumped by a ventricle. This highly abnormal circulation may be complicated by increased right atrial pressure, protein-losing enteropathy with ascites, and thromboembolism. Thromboembolism is a widely recognized complication of the Fontan procedure and its modifications. Recently, we² reported the frequency of thromboembolism in 64 patients who underwent a Fontan type of procedure between 1987 and 1992. Ten cases of thromboembolic episodes were identified in the follow-up period, which ranged from 6 to 55 months. The episodes occurred 7 days to 4.5 years after the

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Table I. Coagulation factor abnormalities in 20 patients who underwent the Fontan-type operation

	Normal range (%)	Below normal range		Above normal range	
		No.	<i>p</i> Value	No.	<i>p</i> Value
Protein C	63-144	15	<0.001	0	0.6
Protein S	66-144	4	0.02	0	0.6
Antithrombin III	84-131	0	0.6	0	0.6
Factor II	50-150	2	0.3	0	0.6
Factor VII	57-165	11	<0.001	0	0.6
Factor IX	50-150	1	1.0	0	0.6
Factor X	50-150	2	0.3	0	0.6

The normal range for all values represents the 90% confidence interval.

Fontan repair. Seven of these were on the systemic venous or pulmonary aspect of the circulation, and three were on the systemic arterial aspect. In addition, several other reports of thromboembolism after the Fontan procedure have been published.³⁻⁵ Although hemodynamic factors including a low cardiac output and a less pulsatile pulmonary circulation than normal may contribute to thromboembolism, Cromme-Dijkhuis and colleagues⁶ have evidence to suggest that coagulation abnormalities may also play a role. We have therefore examined coagulation status in a group of patients who were in stable condition in the postoperative period.

Patients and methods

The study population includes 20 patients who were examined for coagulation factor abnormalities and liver function tests. The number of patients who have undergone the Fontan procedure and its modifications in our institute is considerably larger. Some patients, however, were not able to attend follow-up or did not consent to participate in this study. In addition, in the case of patients receiving warfarin, it was considered inappropriate to stop and then recommence warfarin for the purpose of the study. For this reason, patients receiving warfarin were excluded from the study. In our institute all patients with a history of thromboembolic episodes receive warfarin unless contraindicated; therefore these patients were also excluded.

All patients had undergone a Fontan-type operation. The median age at the time of the operation was 6.2 year (17 months to 8 years) with a male/female ratio of 2.3:1. The median time from the Fontan repair was 4.9 years (18 to 76 months). Of the 20 patients, 11 had an anastomosis constructed between the right atrium and the pulmonary artery. A direct anastomosis was used in seven of these, in two patients a roof of polytetrafluoroethylene was used, and in four a nonvalved pulmonary homograft was interposed between the right atrium and the pulmonary artery. Nine patients underwent total cavopulmonary connection, usually carried out by anastomosing the superior vena cava end to side to the right or left pulmonary artery and creating an intraatrial tunnel to conduct inferior vena caval blood to the superior vena caval orifice by means of a tunnel of polytetrafluoroethylene ($n = 6$) or pericardium ($n = 3$), with the right atrial free wall forming the posterior aspect. In five patients fenestration of the infe-

rior caval baffle was performed with a 4 mm aortic punch. All patients were treated with aspirin and were asked to stop taking aspirin 1 week before the study. None of the patients were receiving diuretics or clinically had protein-losing enteropathy. Ethical committee approval was obtained and informed consent was given by all patients and their parents. Venous blood was obtained for coagulation studies. Protein C activity was measured by the chromogenic substrate method of Behring Biochemical Company. Protein S antigen was measured by means of enzyme-linked immunosorbent assay. Factors II, VII, IX, and X were measured by means of a clotting assay, and antithrombin III was measured by means of a chromogenic assay. Levels of serum alkaline phosphatase, alanine transaminase, aspartate transaminase, total bilirubin, total protein, and albumin were measured with the use of an automatic clinical analyzer. Concentrations of these procoagulant and anticoagulant factors were expressed as percentages of the concentration in pooled normal plasma set at 100%.

The normal range is 90% confidence interval for normal samples. The *p* values are from a two-sided exact binomial test comparing the observed proportion of patients above and below the normal range with the expected proportion of 5%.⁷ That is to test whether the observed proportion of patients with values below the normal range or above the normal range is significantly different from 5%. For total bilirubin, alkaline transaminase, and aspartate transaminase concentrations, where the upper limit of the normal range is given, one would expect to see 10% of patients above the upper limit rather than 5%. Statistical analysis was performed with the use of the Stata statistical software package, version 5 (Clariscworks, Apple; London, United Kingdom).

Results

The coagulation factor abnormalities are shown in Table I. Protein C, protein S, and factor VII values are significantly lower than the normal range, whereas other values are not. The four patients with protein S deficiency all had reduced protein C levels.

No significant difference in coagulation factor abnormalities was observed between those patients who had a right atrial-pulmonary anastomosis and those who had a total cavopulmonary connection.

Furthermore, no relation was seen between the

Table II. Liver function tests in 17 patients who underwent the Fontan-type of operation

	Normal range (%)	Below normal range		Above normal range	
		No.	p Value	No.	p Value
Total bilirubin	<18	—	—	9	<0.001
Alkaline phosphatase	280-640 IU/L	2	0.2	1	0.6
Alkaline transaminase	<40 IU/L	—	—	1	1.0
Aspartate transaminase	<50 IU/L	—	—	10	<0.001
Total protein	62-82 gm/L	1	0.6	1	0.6
Albumin	34-48 gm/L	2	0.2	0	1.0

coagulation factor abnormalities, the type of heart defect, and the time of follow-up.

The values for liver function tests are shown in Table II. The same method of analysis applied to the coagulation factors was applied to the liver function tests. Seventeen complete sets were obtained. The samples for three patients were mislaid. Concentrations of total bilirubin and aspartate transaminase were significantly elevated, and the total protein and serum albumin levels were within the normal range.

Discussion

Recently, we² reported a high frequency of thromboembolic complications after the Fontan procedure and its modifications. Unpublished data reported in the World Congress of Paediatric Cardiology and Cardiac Surgery in 1993 indicated that the real frequency of thromboembolic complications may be even higher than reported owing to subclinical occurrence of pulmonary emboli. Having the Virchow's triad in mind, thromboembolism after the Fontan procedure could be due to stasis, the presence of abnormal surfaces, and change in coagulation. The aim of the Fontan operation is to produce a circulation in which blood is transmitted from the right atrium to the pulmonary artery. In this highly abnormal circulation, where no ventricle is present to pump the blood, stasis and areas of sluggish flow can predispose to the formation of a venous thrombus. Previously, we² showed no relation between the occurrence of thromboembolism and the use of foreign material, although the numbers were not large. The fact that thromboembolic episodes occur both on the pulmonary venous and on the systemic arterial aspect of the circulation led us to believe that a coagulation disorder may partly be responsible for thromboembolism after the Fontan procedure.

Protein C is a natural anticoagulant synthesized in the liver as a vitamin K-dependent protein.⁸ After activation by thrombin, protein C is a potent inhibitor of the coagulation cascade and stimulates fibrinolysis. Protein S acts as a cofactor in this pathway, and it

further stimulates fibrinolysis.⁹ Protein C deficiency with or without protein S deficiency, either inherited or acquired, has been associated with increased thrombotic activity.^{10,11} In this report we have demonstrated a significant decrease in protein C and protein S concentrations after the Fontan repair. This confirms the findings of Cromme-Dijkhuis and colleagues,⁶ who reported protein C deficiency as the most common and most pronounced abnormality in patients who had undergone the Fontan operation. In a similar study, they¹² reported normalization of protein C levels in patients who underwent the Fontan operation. The significance of this finding remains to be explained. In the present study we failed to show any recovery of the protein deficiencies.

Factor VII is a coagulation factor and is part of the extrinsic pathway. Factor VII interacting with tissue factor activates the extrinsic mechanism. In this study, we showed a deficiency of factor VII in 55% of the patients, which theoretically should predispose to bleeding and not coagulation. However, experimental evidence suggests that very low concentrations of factor VII activity can support tissue factor-induced coagulation in pathologic states.¹³ Furthermore, the risk for thromboembolism is apparently increased in patients with hereditary factor VII deficiency.¹⁴

Abnormalities of liver function tests in patients who have had the Fontan operation have previously been reported.¹⁵ In this report, concentrations of aspartate transaminase and total bilirubin were raised. However, no clinical evidence of hepatic dysfunction was observed. Total protein and serum albumin concentrations were not significantly reduced. We showed no correlation between liver function tests and coagulation abnormalities. This suggests that the overall synthesizing function of the liver in this group of patients was normal. It is difficult to explain the deficiency of protein C, but it may be due to a selective defect in liver synthesis.

The deficiency in protein C may partly account for the occurrence of thromboembolism after the Fontan procedure. One practical implication of this finding is

that long-term anticoagulation should be administered after the operation. However, the risks of long-term anticoagulation, especially in children, should be weighed against the benefits of the best palliative operation available for their complex congenital heart disease. We suggest that a postoperative decrease in protein C and protein S concentrations should be regarded as risk factors, and patients deficient in these proteins should be administered anticoagulants selectively.

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REFERENCES

- Fontan F, Baudet E. Surgical repair of tricuspid atresia. *Thorax* 1971;26:240-61.
- 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.
- Dobell ARC, Trusler GA, Smallhorn JF, Williams WA. Atrial thrombi after the Fontan operation. *Ann Thorac Surg* 1986;42:664-7.
- Kirklin JK, Blackstone EH, Kirklin JW, Pacifico AD, Barger LM. The Fontan operation. *J Thorac Cardiovasc Surg* 1986;92:1049-64.
- Shannon FL, Campbell DN, Clarke DR. Right atrial thrombosis: rare complication of the modified Fontan procedure. *Pediatr Cardiol* 1986;7:209-12.
- Cromme-Dijkhuis AH, Henkens CM, Bijleveld CMA, Hilleggen HL, Bom VJ, Van Der Mee J. Coagulation factor abnormalities as possible thrombotic risk factors after the Fontan operation. *Lancet* 1990;336:1087-90.
- Armitage P, Berry G. Statistical methods in medical research. 3rd ed. Oxford: Blackwell Science; 1994. p. 118-9.
- Stenflo J. A new vitamin K dependent protein: purification from bovine plasma and preliminary characterization. *J Biol Chem* 1976;281:355-63.
- Walker FJ. Protein S and the regulation of activated protein C. *Thromb Haemost* 1984;10:131-8.
- Griffin JH, Evatt B, Zimmerman TS, Kleiss AJ, Wideman C. Deficiency of protein C in congenital thrombotic disease. *J Clin Invest* 1981;68:1370-3.
- Manucci AM, Vigaro S. Deficiencies of protein C, an inhibitor of blood coagulation. *Lancet* 1982;11:463-7.
- Cromme-Dijkhuis AH, Hess J, Hahlen K, Henkens MD, Bink-Boelkens MTE, Eygelaar AA, et al. Specific sequelae after Fontan operation at mid and long-term follow-up. *J Thorac Cardiovasc Surg* 1993;106:1126-32.
- Zivelin A, Tao LVM, Rapaport SI. Mechanism of the anticoagulant 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.
- Rapaport SI, Rao MV. The time factor pathway: How it has become a "Prima Ballerina." *Thromb Haemost* 1995;74:7-17.
- Girard AD, Fontan F, Deville C, Ottenjamp J, Choussat A. Long-term results after the Fontan operation for tricuspid atresia. *Circulation* 1987;75:605-10.

Discussion

Dr. Richard A. Jonas (*Boston, Mass.*). The invited discussant for this paper was my colleague, Dr. John

Mayer, who had to return to Boston. He passed on to me some of his thoughts and questions.

We have long been concerned about the problem of thromboembolic stroke after the Fontan procedure. We have encountered this complication ourselves in Boston and have reported on this problem in a paper published, I believe, in the *Annals of Neurology*. We applaud you for addressing what we consider to be an important topic. I hope you will help us to pinpoint exactly what the predisposing factors might be in this problem.

Dr. Mayer's questions are as follows: First, have you made any attempt to correlate the changes in coagulation factors with either early or late hemodynamics, particularly right atrial pressure, duration of chest tube drainage, or length of hospital stay?

Second, have you seen any correlation with the technique of operation or the type of material used in the partition between the pulmonary and systemic venous return? In Boston we seemed to have an epidemic of systemic thromboemboli 3 or 4 years ago. When we changed from the tubular graft polytetrafluoroethylene, which had an external wrap, to the polytetrafluoroethylene patch material, this problem seemed to decrease in frequency.

Third, you recommended that patients with a low protein C or protein S concentration should receive anticoagulants. Inasmuch as protein C is dependent on vitamin K, what do you measure to ensure that you have tipped the balance of prothrombotic versus anti-thrombotic systems in the direction of opposing thrombosis?

Miss Jahangiri. Thank you very much for your comments and your questions, Dr. Jonas. Unfortunately, I do not have data on the coagulation factors and hemodynamic variables, and we have not attempted to correlate them, but that is a very good idea.

The length of hospital stay was not significantly different from that of the other patients having the Fontan procedure. However, the patients with thromboembolic episodes were not included in this study.

As for the correlation with the techniques and the type of material, none of these patients had a history of thromboembolism. The only correlation we found was in the previous study, in which 10 of 64 patients were identified with thromboembolic episodes. Patients who had a fenestration and residual fenestration in the follow-up period seemed to be at increased risk.

We monitor adequate anticoagulation by measuring the international normalized ratio.

Dr. Leonard L. Bailey (*Loma Linda, Calif.*). The one thing that seems missing from your report is any sort of a control set. Did you consider assessing for these proteins before the Fontan operation in the same group of patients, so that they could be their own controls, or could you select another set of controls to examine these proteins and to see whether it is unique to children having the Fontan procedure?

Miss Jahangiri. Preoperative samples were not taken. The controls were obtained from a collection of pooled plasma from age-matched patients. However, this is an ongoing study, and we are currently measuring the preoperative and postoperative coagulation status of our patients.

Dr. Bailey. If I were to do a routine ventricular septal defect operation today and measure these proteins during the coming week or so, would I expect to see any sort of abnormality?

Miss Jahangiri. You shouldn't. The only study I am aware of in which a preoperative assessment was made of the coagulation status of patients with congenital

heart disease of various types is a study by Dr. Turner-Gomes and Dr. Williams from Toronto. They evaluated thrombin regulation and showed that the levels were basically normal; and some of those children were cyanotic.

Dr. Bailey. I look forward to continued feedback from your investigations.

Notice of correction

In the March 1997 issue of the Journal, in the article by Sawant and associates titled "St. Jude Medical Cardiac Valves in Small Aortic Roots: Follow-up to Sixteen Years" (1997;113:499-509), an incorrect copy of Fig. 1 was published. The correct copy of Fig. 1 is reproduced below.

Fig. 1. Preoperative and follow-up NYHA functional class presentation. *Pts*, Patients.